Intra-abdominal infections are generally the result of invasion and multiplication of enteric bacteria in the wall of a hollow viscus or beyond. When the infection extends into the peritoneal cavity or another normally sterile region of the abdominal cavity, the infection is described as a “complicated” intra-abdominal infection. Complicated intra-abdominal infections are usually treated with an invasive procedure for source control; this use of a source control procedure has been included as part of the operational definition of a complicated intra-abdominal infection. The term “uncomplicated” intra-abdominal infection is less well defined; usually, it refers to an inflammatory process or infection in the wall of an abdominal organ, which may result in the development of a complicated intra-abdominal infection if not treated expeditiously. Thus, pathologic processes such as acute appendicitis or cholecystitis have been considered examples of uncomplicated intra-abdominal infections.

The use of this terminology is problematic. For instance, acute appendicitis and cholecystitis are initially inflammatory disorders related to obstruction, and are not infectious in nature until later in their course. Moreover, even at the time of surgical treatment, most cases of acute cholecystitis are still sterile inflammatory processes rather than overt infections. The distinction between uncomplicated and complicated intra-abdominal infections becomes further muddled when one attempts to classify acute diverticulitis. Acute diverticulitis may be due to obstruction and bacterial multiplication within the diverticulum itself, in which case it could be considered an uncomplicated infection. However, it may also be due to a microperforation resulting in extension of the infection into the mesentery, and thus could be considered a complicated intra-abdominal infection. However, because most cases of diverticulitis are managed nonoperatively, without a source control procedure, they are considered uncomplicated according to the operational version of the definition. Thus, in
describing intra-abdominal infections, it is probably preferable to describe the source and extent of spread of the infection rather than rely on the nonspecific and confusing terms, “uncomplicated” and “complicated” intra-abdominal infections.

Most of the complicated intra-abdominal infections treated by surgeons involve peritonitis or intra-abdominal abscesses. Peritonitis is subdivided into primary, secondary, and tertiary varieties (Table 1). Primary peritonitis is a monomicrobial infection in which the integrity of the gastrointestinal tract has not been violated. The most common manifestation is “spontaneous bacterial peritonitis,” and is typically identified in patients who have ascites due to end-stage liver disease. Historically, primary streptococcal or pneumococcal infections of the peritoneal cavity were common, although these entities are rarely seen in the current era. Peritonitis may also develop in conjunction with the use of indwelling peritoneal catheters, such as peritoneal dialysis catheters; this type of peritonitis is sometimes considered a form of primary peritonitis, or may be described as a separate entity. Primary and catheter-associated peritonitis are usually monomicrobial infections treated medically, and are not considered further here.

Secondary peritonitis results from the perforation of a hollow viscus, and is the most common type of complicated intra-abdominal infection managed by surgeons. Tertiary peritonitis is a poorly defined entity. At a minimum, it is a diffuse infection developing after the failure of initial management of secondary peritonitis. However, it is generally recognized in patients who have failed several previous attempts at control of an intra-abdominal infection. Many of these patients have impaired host defenses because of ongoing infection or pre-existing comorbid conditions.

Intra-abdominal abscesses may develop following secondary peritonitis. In reality, intra-abdominal abscesses are the end result of the host’s response to secondary peritonitis, and represent the temporal evolution of that infection rather than a distinct pathologic process. Thus, following contamination of the peritoneal cavity as a result of perforation of a hollow viscus, normal host defense mechanisms are invoked, which serve to limit the development and spread of an infection. Bacteria and other particulate matter are rapidly removed from the peritoneal cavity through the process

<table>
<thead>
<tr>
<th>Type</th>
<th>Definition</th>
<th>Microbiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>A peritoneal infection developing in the absence of a break in the integrity of the gastrointestinal tract, as a result of hematogenous or lymphatic seeding, or bacterial translocation</td>
<td>Monomicrobial infection due to gram-negative Enterobacteriaceae or streptococci</td>
</tr>
<tr>
<td>Secondary</td>
<td>A peritoneal infection developing in conjunction with an inflammatory process of the gastrointestinal tract or its extensions, usually associated with microscopic or macroscopic perforation</td>
<td>Polymicrobial infection due to aerobic gram-negative bacilli, gram-positive cocci, and enteric anaerobes</td>
</tr>
<tr>
<td>Tertiary</td>
<td>A persistent or recurrent peritoneal infection developing after initial treatment of secondary peritonitis</td>
<td>Nosocomial organisms, including resistant gram-negativebacilli, enterococci, staphylococci, and yeast</td>
</tr>
</tbody>
</table>

Table 1  
Classification of peritonitis
of mechanical clearance, in which peritoneal fluid circulates within the peritoneal cavity as a result of diaphragmatic contractions and is absorbed into the lymphatic system through specialized stomata on the undersurface of the diaphragm. This process results in the elimination of a significant portion of the bacterial inoculum. In addition to mechanical clearance, an inflammatory reaction is rapidly generated within the peritoneal cavity to aid in removal of infective material. This reaction involves recognition of pathologic microbial molecules by pattern recognition receptors on resident macrophages within the peritoneal cavity, and the triggering of signals that promote the rapid ingress of polymorphonuclear leukocytes and subsequently mononuclear cells into the peritoneal cavity. These phagocytic cells further eliminate pathogenic organisms from the peritoneal cavity. Finally, the process of sequestration results in limitation of the infection. Microscopic sequestration results from the generation of fibrin and other macromolecules that trap populations of microorganisms and may also seal small gastrointestinal tract perforations. These adhesive molecules also promote adherence of the omentum, loops of bowel, the mesentery, and the abdominal wall to each other, which results in macroscopic restriction of the infectious process. Overall, these mechanisms result in either complete clearance of the infection or in the formation of a localized infection, now recognized as an intra-abdominal abscess. In this sense, then, an intra-abdominal abscess represents a success of the usual host defense mechanisms. In contrast, the poorly localized, diffuse infections characteristic of tertiary peritonitis represent a failure of these normal host defenses.

In addition to primary and catheter-associated peritonitis, certain types of infections found in the abdominal region are usually excluded from consideration in descriptions of intra-abdominal infections. Many of these infections arise from the genitourinary tract, including gynecologic infections such as tubo-ovarian abscesses, and perirenal infections, extending into the surrounding tissues from an infected kidney. Abscesses in solid organs such as the liver and spleen, which develop as a result of hematogenous seeding, are also generally considered apart from other types of intra-abdominal infections. These infections are not the focus of this discussion, which will be restricted to the pathologic processes arising from the gastrointestinal tract and its appendages.

**MICROBIOLOGY**

The resident gastrointestinal flora are the cause of most intra-abdominal infections. Because the microbiology of the gastrointestinal tract changes markedly with location, the types of microorganisms isolated in these infections may also vary, depending on the source of the infecting inoculum. As one progresses down the gastrointestinal tract in the normal individual, the number of microorganisms increases and their character changes. Few microorganisms are found in the normal stomach and proximal small intestine, typically less than $10^3$ to $10^4$ organisms per gram of contents. Most of these are gram-positive cocci, particularly streptococci, or lactobacilli. These microorganisms are considered by many to represent “transients” from the oral cavity, and not true colonizers of the upper gastrointestinal tract. In the more distal small intestine, gram-positive cocci continue to be present, but enteric gram-negative aerobic/facultative anaerobic bacilli begin to make an appearance. In the terminal ileum, bacterial counts may reach $10^8$ organisms per gram of contents, and many anaerobic organisms are present in addition to the aerobic organisms. In the colon, $10^{10}$ to $10^{11}$ microorganisms are present per gram of contents, and obligate anaerobic microorganisms predominate by as much as 100 to 1000 fold over the aerobic and facultative anaerobic microorganisms.
Most intra-abdominal infections resulting from perforations of the gastrointestinal tract or its appendages are polymicrobial. Enteric gram-negative bacilli, gram-positive cocci, and anaerobic microorganisms are the predominant pathogens. Only a few of these microorganisms are typically identified by most clinical laboratories. In research studies, five to ten bacterial isolates may be isolated from each clinical sample, with anaerobic species predominating over aerobic ones. However, clinical laboratories may report only one or two organisms per sample, with 25% to 50% of the samples showing no growth; full characterization of anaerobic isolates is typically not done by most clinical laboratories.

*Escherichia coli* is the most common organism isolated from patients who have intra-abdominal infections. Usually, 50% or more of patients are found to be infected with this organism. Several other enteric gram-negative bacilli may also be isolated, including *Klebsiella* sp, which is probably the next most common isolate, and *Enterobacter* sp, although these are generally encountered much less frequently. Noncoliform gram-negative bacilli, particularly *Pseudomonas aeruginosa*, may also be isolated from some of these infections.

Gram-positive cocci are frequently components of intra-abdominal infections. The most common gram-positive organisms isolated are streptococci, predominately of the viridans type. *Enterococcus* sp is isolated much less frequently than streptococci, being reported in 10% to 20% of patients. Most of the enterococcal strains isolated from patients who have community-acquired intra-abdominal infections are penicillin-susceptible strains of *Enterococcus faecalis*. The role of *Enterococcus* in intra-abdominal infections, particularly those acquired in the community, remains controversial.

Obligate anaerobic organisms are important components of most intra-abdominal infections, even though clinical laboratories may not recover or report these organisms. The most prevalent anaerobic organism in intra-abdominal infections is *Bacteroides fragilis*, likely present in one third to one half of these infections. Other members of the *B fragilis* group, including *B thetaiotaomicron*, *B distasonis*, *B vulgatus*, *B ovatus*, and *B uniformis*, can probably be found in an equivalent percentage of patients. Anaerobic microorganisms that also contribute to these infections include *Peptostreptococcus*, *Peptococcus*, *Eubacteria*, *Fusobacterium*, and *Clostridia* sp, among others.

The microbiology of intra-abdominal infections is significantly altered in patients who have been exposed to the health care setting. This alteration may be due to the acquisition of nosocomial pathogens or may reflect prior antimicrobial therapy that has selected for resistant organisms. Even the normal gastrointestinal flora is altered significantly in patients who have been hospitalized. Reddy and colleagues found gastric colonization with *Enterobacteriaceae* and *Candida* in 16% and 31% of unselected patients undergoing surgical procedures. Marshall and colleagues demonstrated near universal colonization of the upper gastrointestinal tract in critically ill surgical patients; the pathogenic organisms encountered included *Enterobacteriaceae*, gram-positive cocci, and yeast.

Thus, compared with patients who have community-acquired intra-abdominal infections, patients who have acquired their intra-abdominal infections postoperatively have a shift in the relative frequency of the gram-negative isolates, with *E coli* being isolated less often, and *Enterobacter* and *Pseudomonas* more often. Similarly, isolation of streptococci is decreased, whereas isolation of *Enterococcus* is increased in these patients. Fungal organisms, predominantly *Candida albicans*, are also encountered with some frequency in hospitalized patients who have intra-abdominal infections.
This shift toward a more resistant group of microorganisms reaches its zenith in patients who have tertiary peritonitis, who have likely been treated with multiple courses of antibiotics.\(^6,7\) These patients may have intra-abdominal infections due to multiply-resistant gram-negative pathogens, such as *Pseudomonas* and *Acinetobacter*; enterococci, particularly the more resistant *E. faecium*, with strains of vancomycin-resistant *E. faecium* occasionally surfacing; staphylococci, including coagulase-negative staphylococci and *Staphylococcus aureus*, most of which are resistant to methicillin; and yeast, including some non-*C. albicans* species.\(^24-26\)

**SOURCE CONTROL**

Source control is the general term for the interventional procedures used to control or eliminate the focus of an intra-abdominal infection. Marshall\(^1\) has described source control as “drainage of abscesses or infected fluid collections, debridement of necrotic infected tissue, and definitive measures to control a source of ongoing microbial contamination and to restore anatomy and function.” Source control of uncomplicated intra-abdominal infections, such as nonperforated appendicitis or cholecystitis, should serve to eliminate the infective focus completely and thereby prevent dissemination of pathogenic microorganisms into the peritoneal cavity. With complicated intra-abdominal infections, however, source control procedures by themselves cannot completely eliminate all infected material, although the goal should be to reduce the infective inoculum sufficiently such that additional anti-infective therapy will lead to complete resolution of the infection. Given the importance of source control in the management of intra-abdominal infections, the failure or inability to achieve adequate source control is associated with a worse clinical outcome in terms of increased rates of treatment failure and increased mortality.\(^27,28\)

Despite the perceived primacy of source control in the management of intra-abdominal infections, there has been a trend toward the use of less aggressive forms of source control or even deferral or avoidance of source control procedures altogether under selected circumstances. Thus, minimally invasive surgical procedures are widely used for managing acute appendicitis and cholecystitis, and percutaneous, image-guided drainage procedures are the standard for treatment of most intra-abdominal abscesses.\(^29,30\) Initial nonoperative management has long been the standard for most patients who have localized acute diverticulitis. Many patients who have perforated appendicitis who present with an inflammatory phlegmon or small abscess can be managed nonoperatively in an analogous fashion. These less invasive approaches have the potential to reduce the complications associated with major surgical procedures. Nonetheless, avoiding operative complications will have little benefit if the patient ultimately succumbs to an inadequately treated intra-abdominal infection. Therefore, carefully performed research studies are needed to identify the appropriate patients for management using this approach, and to further delineate the relative risks and benefits of deferral or elimination of definitive source control as part of their overall therapy.

**Source Control for Appendicitis**

Treatment of appendicitis represents a good example of a potential paradigm shift in the approach to source control. Appendicitis is the most common intra-abdominal infection treated by surgeons. For at least the past century, early appendectomy has been considered essential for the treatment of this disease. In part, this practice was based on the view that there was inexorable progression from obstruction of the appendiceal lumen with an appendicolith, through subsequent distention and
bacterial overgrowth within the lumen of the appendix, to gangrene or perforation of
the appendix with the development of severe peritonitis. However, this concept of
the pathophysiology of appendicitis has been challenged, and the results of recent
clinical trials question whether the natural history of the disease is truly inevitable
progression to perforation and potentially fatal peritonitis.31,32

Deferral of appendectomy for acute appendicitis has been intermittently described
in the surgical literature as an option for treatment of acute appendicitis, although
generally in the context of a treatment to be used under extraordinary circumstances.
A commonly cited reference refers to a case series of nine military patients who had
acute appendicitis who were successfully managed nonoperatively using antibiotic
therapy alone.33 Subsequently, a small prospective randomized pilot study demonstrat-
ated that most patients who had acute appendicitis could be managed nonopera-
tively with antibiotic therapy only, although late recurrence of the disease was
frequent.34 A follow-up prospective randomized controlled trial of nonoperative
management of appendicitis was reported in 2005.35 This trial enrolled 252 Swedish
male patients who had acute appendicitis, who were not believed to have perforated
appendicitis based on clinical findings. This study compared immediate surgical
management in 124 patients with initial nonoperative therapy in 128; the latter patients
received 2 days of intravenous antibiotic therapy followed by 10 days of outpatient oral
antibiotic therapy, and only underwent operative management if their clinical picture
had not improved 24 hours after admission. Overall, 15 patients (12%) of those
randomized to initial non operative therapy underwent early appendectomy. Seven
patients in this group (5% of the overall group) were found to have perforated appen-
dicitis at the time of the operation. In the patients randomized to undergo immediate
operation, six (5%) had perforated appendicitis. Therefore, perforation did not appear
to increase dramatically as a result of a 24-hour delay in undertaking operative
management in nonresponding patients. By the time of the 1-year follow-up, 16 addi-
tional patients (15%) randomized to initial nonoperative management had undergone
appendectomy because of recurrent appendicitis; this procedure occurred an
average of 4 months after initial enrollment in the study. Thus, at 1 year, nonoperative
management had been successful in 76% (97/128) of the patients randomized to initial
nonoperative management.

Although these data suggest that nonoperative management of acute appendicitis
is safe, extensive data also document that appendectomy is a safe procedure for
patients who have this disease. In the Swedish population, the overall mortality rate
was 0.8 per 1000 for patients who underwent appendectomy for nonperforated
appendicitis; this rate was greater than 10 per 1000 (1%) only in patients 70 years
of age or older.36 For patients aged 20 to 59, mortality was increased 1.8 fold
compared with the general population, but this increase was not statistically
significant. The incidence of operatively managed small bowel obstruction after
appendectomy was examined using a case-control design in another study of the
Swedish population.37 At the 30-year time point, an operation for small bowel obstruc-
tion had only been noted in 0.75% of the patients who had undergone appendectomy
for nonperforated appendicitis; in matched control patients who had not undergone
appendectomy, the corresponding rate was 0.21%. The corresponding rate in
patients being managed nonoperatively for acute appendicitis is unknown. These
data suggest, then, that the traditional operative approach and the initial nonoperative
approach are viable options for treating patients who have acute nonperforated
appendicitis.

The therapy of perforated appendicitis is also undergoing evolution. Traditionally,
appendectomy had been recommended for all patients who had perforated
appendicitis, except for those who had a periappendiceal abscess; in those patients, treatment with antimicrobial therapy and drainage of the abscess, with subsequent interval appendectomy, was recommended. Many aspects of this treatment approach have now been questioned, particularly for patients who have perforated appendicitis who develop a periappendiceal phlegmon or inflammatory mass in the region of the appendix.

In a recent meta-analysis by Andersson and Petzold, this pathology was estimated to occur in 3.8% of patients who had appendicitis. Usually, such patients have had symptoms for several days, and do not present acutely. Because of extensive inflammation around the cecum, operative therapy of such patients may necessitate a more complicated procedure than simple appendectomy (eg, an ileocectomy or right hemicolectomy). Therefore, interest has grown in treating such patients with antibiotics alone, in a manner analogous to that used for acute diverticulitis, in the hope of avoiding a more morbid and difficult operative procedure.

In their meta-analysis reviewing nonsurgical management of perforated appendicitis with appendiceal abscess or phlegmon, Andersson and Petzold found that 19.7% of these patients underwent drainage of an abscess associated with the process, but that more than 80% were treated without any source control procedure, in many cases because no abscess existed or it was too small or inaccessible for drainage. Nevertheless, the failure rate for this initial nonoperative approach was only 7.2% in the combined series. In studies that compared use of an initial nonoperative approach with immediate operation, the former was associated with a nearly threefold decrease in morbidity compared with the latter (13.5% versus 35.6%). Thus, these results suggest that the nonoperative approach is appropriate and may be preferable for patients who have perforated appendicitis presenting with an abscess or phlegmon.

In the meta-analysis by Andersson and Petzold, centers that practiced routine interval appendectomy reported a morbidity of that procedure of 11%. However, in those centers that did not schedule routine interval appendectomy, recurrent appendicitis developed in 7.4% of the non–surgically managed patients; most of these recurrences occurred within 6 months. Thus, the low risk for recurrent appendicitis and the morbidity of interval appendectomy argue against the use of routine interval appendectomy in most patients following successful nonoperative management of a periappendiceal abscess or phlegmon.

**Source Control for Severe, Diffuse Peritonitis**

At the opposite end of the spectrum from good-risk patients who have a localized process such as appendicitis are patients who have severe, diffuse peritonitis. Such patients should undergo emergency abdominal exploration to control the source of their infection. Increasingly, though, a “damage control” approach has been advocated for such patients, with a plan for subsequent relaparotomy. Thus, if the patient has septic shock or other significant physiologic derangements, placement of anastomoses or ostomies may be deferred to a later operation. Additionally, with aggressive fluid resuscitation, some of these patients are at risk for developing abdominal compartment syndrome, and definitive closure of the abdomen might be delayed for this reason. Finally, for patients who have questionable bowel viability, a second-look laparotomy may be advisable. Thus, performing a limited initial operation with a plan for relaparotomy may be a useful approach for some severely ill patients who have intra-abdominal infections. Much more controversial, however, is the use of scheduled relaparotomy for patients who have diffuse peritonitis but who lack any of these indications for relaparotomy. Van Ruler and colleagues recently...
reported the results of a prospective trial comparing scheduled relaparotomy every 36 to 48 hours with repeat laparotomy based on clinical indications in 232 patients who had secondary peritonitis and an Acute Physiology and Chronic Health Evaluation (APACHE)-II score greater than 10. Scheduled relaparotomy did not result in decreased mortality or major morbidity, and was associated with increased costs and use of health care resources. Thus, mandatory relaparotomy does not appear to be beneficial for most patients who have diffuse, secondary peritonitis in the absence of a clear indication for the procedure.

ANTIMICROBIAL THERAPY

Antimicrobial therapy is generally considered an adjunct to the use of appropriate source control in the treatment of intra-abdominal infections. However, in patients in whom source control is deferred, antimicrobial therapy plays a more definitive role.

The general principle underlying antimicrobial therapy for patients who have intra-abdominal infections is to use agents effective against the aerobic/facultative anaerobic gram-negative bacilli, aerobic gram-positive cocci, and obligate anaerobic organisms commonly encountered with these infections. The importance of anaerobic coverage has been verified in two recent studies, which found higher failure rates when patients were treated with regimens lacking anaerobic coverage. Several single antimicrobial agents or combinations of agents have reasonable activity against common aerobic and anaerobic enteric bacteria, and can potentially be used for this indication. Regimens that have this activity and have been used for the treatment of intra-abdominal infections are listed in Box 1.

Several factors should be taken into account when selecting specific antimicrobial regimens for the treatment of patients who have intra-abdominal infections, including considerations of efficacy, toxicity, prevention of “collateral damage,” and cost. The most important of these is efficacy. However, despite numerous prospective trials comparing various antimicrobial regimens, little evidence indicates that any particular regimen is more effective than any other for the treatment of patients who have intra-abdominal infections.

The inability to identify superior regimens could reflect the limited power of these prospective trials to detect true differences in efficacy. Generally, the subjects enrolled in clinical trials have a low acuity of illness and a good prognosis and the trials themselves are designed as “noninferiority” trials, which makes it unlikely that significant differences in efficacy between regimens can be uncovered. Nonetheless, the similarity in the efficacy of various antimicrobial regimens does not appear to be simply a question of inadequate data. A recent large multi-institutional database study of 6056 patients who had complicated intra-abdominal infections also revealed little difference in efficacy among different regimens, with the exception of those that lacked effective anaerobic coverage.

Other data, however, suggest that some caution should be paid to the use of certain antimicrobial agents. For instance, the use of aminoglycoside-based regimens, the historic “gold standard” for the treatment of patients who have intra-abdominal infections, was called into question in a meta-analysis, which suggested that these regimens were actually inferior to most other comparator regimens. The increased development of resistance in bacteria, including those acquired in the community, might also lead one to avoid the use of certain antimicrobials. In vitro resistance of E coli to this antibiotic was identified in 45% of the isolates obtained worldwide from patients who had intra-abdominal infections; this high level of resistance was also present in patients who likely had community-acquired intra-abdominal
### Box 1

**Antimicrobial agents for patients who have intra-abdominal infections**

**Single agents**

- β-lactam/β-lactamase inhibitor combinations
  - Ampicillin/sulbactam\(^a,b\)
  - Piperacillin/tazobactam\(^c\)
  - Ticarcillin/clavulanic acid

- Carbapenems
  - Doripenem\(^c\)
  - Ertapenem
  - Imipenem/cilastatin\(^c\)
  - Meropenem\(^c\)

- Anaerobic cephalosporins
  - Cefotetan\(^b\)
  - Cefoxitin\(^b\)

- Fluoroquinolone
  - Moxifloxacin

- Glycylcycline
  - Tigecycline

**Combination regimens**

- Cephalosporin-based regimens
  - First- or second-generation cephalosporin (cefazolin or cefuroxime) plus metronidazole
  - Third- or fourth-generation cephalosporin (cefotaxime, ceftriaxone, ceftazidime,\(^c\) cefepime\(^d\)) plus metronidazole or clindamycin\(^b\)

- Monobactam-based regimens
  - Aztreonam\(^d\) plus clindamycin\(^b\) or aztreonam plus metronidazole plus vancomycin

- Fluoroquinolone-based regimens
  - Ciprofloxacin\(^c\) or levofloxacin plus metronidazole

- Aminoglycoside-based regimens\(^e\)
  - Amikacin, gentamicin, netilmicin, or tobramycin plus metronidazole or clindamycin\(^b\)

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\(^a\) This agent may not be optimal because of increasing resistance of *E coli*.

\(^b\) Increased resistance of *B fragilis* and other anaerobes has been observed with this agent.

\(^c\) This broad-spectrum agent is most appropriate for use in patients who have higher severity infections.

\(^d\) Because aztreonam lacks appreciable activity against gram-positive organisms, it should be used in conjunction with an agent with such activity (clindamycin or vancomycin).

\(^e\) Because of toxicity and possible lower efficacy, these are no longer considered first-line agents for treatment of intra-abdominal infections.
infections. Increasing resistance of *E coli* to ciprofloxacin was also documented in this study, although this issue may not be as important in North America and Europe as it is in other parts of the world.\(^48\) Emergence of gram-negative isolates with high-level resistance to several antibiotics is frequently observed in patients who have nosocomial intra-abdominal infections, but these problematic organisms are also being encountered with community-acquired infections in certain locales.\(^48,49\) In vitro resistance of *B fragilis* to several agents, such as clindamycin and anaerobic cephalosporins, also appears to be widespread, although the clinical importance of this is still debated.\(^46,50,51\)

Retrospective studies have identified bacterial resistance as a risk factor for treatment failure and mortality in patients who have complicated intra-abdominal infections. Krobot and colleagues\(^52\) found that 26% of all isolates, 26% of gram-negative isolates, and 22% of *E coli* isolates from patients who had community-acquired infections were resistant to some commonly used antimicrobial agents. Moreover, the use of an empiric regimen that did not cover these resistant bacteria was associated with a greater than twofold increase in the risk for treatment failure, although it did not result in any increase in mortality. In an older study of critically ill patients who had postoperative infections, however, Montravers and colleagues\(^53\) found that mortality increased twofold when the initial empiric regimen was determined retrospectively to be “inadequate” (ie, it failed to have in vitro activity against some of the microbial pathogens eventually isolated). This twofold increase in mortality with inadequate therapy is similar to that observed in studies monitoring the efficacy of empiric antimicrobial regimens for other indications, particularly for ventilator-associated pneumonia.\(^54\)

Thus, the data regarding the importance of antimicrobial selection seem at first glance to be contradictory. Many of the studies suggest little influence of the antimicrobial regimen on the ultimate outcome of patients who have intra-abdominal infections, whereas others indicate that an inadequate initial empiric antimicrobial regimen can have a deleterious effect on outcome. This contradiction may be explained to some extent by considering the dichotomous nature of these infections. At first approximation, two groups of patients who have intra-abdominal infections exist. One group includes many patients who have a localized disease process, such as perforated appendicitis. These patients typically have community-acquired intra-abdominal infections. The bacteria involved in these infections are generally susceptible to most antimicrobial agents, with the exception of certain resistant bacterial strains already established in the community, such as ampicillin/sulbactam–resistant *E coli*. These patients are at a low risk for treatment failure and mortality. For these patients, the selection of specific antimicrobial agents is likely to play a minor role in the ultimate success or failure of the overall therapeutic program.\(^55\)

In contrast to these lower-risk patients, a few higher-risk patients typically have severe, diffuse peritonitis, postoperative peritonitis, or tertiary peritonitis. These patients are much more likely to have an adverse outcome as a result of their infection. Multivariate analyses have attempted to identify the risk factors that characterize this group of higher-risk patients. In these analyses, however, the most important risk factors are usually related to the patient’s underlying medical conditions and to his or her physiologic response to the infection.\(^46,56\) Thus, APACHE II-scores, which are based on both of these components, have generally been the most reproducible markers of treatment failure and death in patients who have intra-abdominal infections.\(^46\) Unfortunately, this score provides little information as to how treatment might be altered in the higher-risk patient. However, the recognition that higher-risk patients who have intra-abdominal infections are much more likely to have infections due to resistant organisms, and that
these resistant organisms place these patients at higher risk for treatment failure and death, suggest that altering empiric antimicrobial therapy to better cover these potentially resistant organisms may prove advantageous.52,53,57–60

Published guidelines have therefore recommended different approaches to antimicrobial therapy for the lower and higher-risk patients who have intra-abdominal infections. For patients who have community-acquired intra-abdominal infections who are considered to be at mild-to-moderate risk for treatment failure, the guidelines recommend using narrower-spectrum antimicrobial agents as first-line therapy. The selected regimen should satisfy the principle of providing coverage of the typical aerobic and anaerobic pathogens involved in these infections, such as *E. coli* and *B. fragilis*. In addition, if a bacterial pathogen resistant to a certain antibiotic is frequently isolated in the local community, that antibiotic should be avoided for initial empiric therapy. The goal of using narrower-spectrum agents for this group of patients is to preserve the usefulness of the broader-spectrum agents listed in Box 1 for the higher-risk patients who are more likely to have resistant and difficult-to-treat pathogens.40,41

For these higher-risk patients, the recommended approach is to use an agent or agents with activity against a wide range of gram-negative bacilli and anaerobic organisms. These regimens include piperacillin/tazobactam; broad-spectrum carbapenems, including imipenem/cilastatin, meropenem, and doripenem; third- or fourth-generation cephalosporins plus metronidazole; and ciprofloxacin plus metronidazole. This regimen may be further broadened in selected patients to provide coverage of *Enterococcus*, yeast, and resistant gram-positive cocci.40,41

Empiric treatment of *Enterococcus* sp is not routinely recommended for the patients who have community-acquired intra-abdominal infections. However, isolation of *Enterococcus* is more common in patients who have hospital-acquired intra-abdominal infections, and is a risk factor for treatment failure and death in those patients.15,21,53,61,62 Thus, coverage of *Enterococcus* sp should be considered for higher-risk patients, particularly those who have postoperative infections and those who have had recent exposure to broad-spectrum antimicrobial agents.40,41,63

Postoperative patients, especially those who have been treated with broad-spectrum antibiotics, are also at risk for the development of invasive infections due to *Candida*.64 Patients at a particularly high risk for *Candida* peritonitis include those who have recurrent gastrointestinal perforations and those who have surgically treated pancreatitis.22,23 Empiric use of fluconazole was shown to be of benefit in one prospective trial performed in such higher-risk patients.65 In general, empiric antifungal therapy is unnecessary in patients who have community-acquired intra-abdominal infections40,41 but can be considered in patients whose underlying medical conditions and history of prior infections and antimicrobial exposure place them at significant risk for a nosocomial intra-abdominal infection secondary to *Candida*.

Finally, patients who develop tertiary peritonitis may have infections due to highly resistant organisms, including methicillin-resistant coagulase-negative and coagulase-positive staphylococci, vancomycin-resistant enterococci, multiply-resistant gram-negative bacteria, and non-–*C. albicans* candidal species. Such patients typically need multiple drug regimens. Agents should be selected empirically, based on knowledge of the likely nosocomial organisms present in the local setting.40,41,60 A reasonable approach in such patients is to provide broad-spectrum empiric antimicrobial therapy initially but then to de-escalate or narrow that therapy based on definitive culture results.56

Beyond efficacy considerations, other factors that play a role in antimicrobial selection include the toxicity of a given regimen and its propensity for creation of
“collateral damage.” Concerns regarding the ototoxicity and nephrotoxicity of aminoglycosides have led to limitations in their use for the treatment of patients who have intra-abdominal infections. In the case of an individual patient, a history of a reaction to an antibiotic of a certain class, such as a penicillin, should lead to the use of an alternative agent. The question of “collateral damage,” referring to the development of resistant or superinfecting bacteria in the patient and the institution, is more difficult to evaluate. Emergence of resistant bacteria and epidemics of *Clostridium difficile*–associated disease have been attributed to overuse of certain antibiotics but these may be specific to an individual institution or locale. Nonetheless, if epidemiologic evidence indicates that a given antimicrobial agent is associated with the spread of resistant organisms or the development of significant superinfections, it would be prudent to limit its use at that site.

One of the most important ways to limit “collateral damage” is to curtail the unnecessary use of antibiotics. For most patients who have intra-abdominal infections, evidence is increasing that prolonged antimicrobial therapy is unnecessary. One approach to limiting antibiotics is to discontinue them once the patient has defervesced, has a normalizing white blood cell count, and has had return of gastrointestinal activity. An alternative approach is to set the maximum duration of therapy to no more than 4 days, rather than the traditional 7 or more days. Prospective trials have indicated that this approach also allows for a reduction in the days of antibiotic therapy without impacting clinical outcome. Thus, expeditious discontinuation of antimicrobial therapy may contribute to an improvement in the outcome of patients who have intra-abdominal infections by limiting the “collateral damage” associated with excessive antimicrobial therapy.

**CLINICAL OUTCOMES**

Treatment of patients who have complicated intra-abdominal infections using a combination of adequate source control and appropriate antimicrobial therapy has generally been thought to produce satisfactory results. Contemporary clinical trials have demonstrated cure in 78% to 86% of patients who were considered clinically evaluable, with an overall mortality of 2% to 3% among all enrolled patients. However, results from published clinical trials are not representative of the true morbidity and mortality of these infections. Patients who have perforated appendicitis are usually overrepresented in clinical trials. Mortality from perforated appendicitis is low compared with that observed in patients who have intra-abdominal infections from other sources. The patient enrolled in a clinical trial who has an infection from a source other than the appendix also likely has a better prognosis than the typical patient who has that intra-abdominal infection. After excluding patients who have perforated appendicitis, Merlino and colleagues found that the cure rate among patients who had intra-abdominal infections and were enrolled in clinical trials was much higher than that of patients who were not enrolled (79% versus 41%) and that the mortality rate was much lower (10% versus 33%). Epidemiologic studies of patients who have intra-abdominal infections that include severely ill patients have demonstrated mortality rates of 17% to 32%. A statewide survey of patients who had complicated intra-abdominal infections in New Mexico found an overall mortality rate of 6%, a postoperative abscess rate of 10%, and a reoperation rate of 13%; mortality was 1% among patients with perforated appendicitis, but 13% among patients who had a non-appendiceal source of their intra-abdominal infection. Thus, despite the seemingly good results identified in clinical trials, complicated intra-abdominal infections are still responsible for considerable morbidity and
mortality, particularly among patients who have a nonappendiceal source of infection and other risk factors contributing to a poorer prognosis.

SUMMARY

“Intra-abdominal infection” is a term that is applied to various infections usually described as peritonitis or intra-abdominal abscess. The prognosis of these infections varies widely, depending on the source of the infection, the patient’s underlying physiologic reserves, and the extent of prior treatment. The principles of therapy remain restoration of systemic perfusion through fluid resuscitation and adjunctive measures for managing sepsis, source control to prevent ongoing microbial contamination, and the use of appropriate antimicrobial therapy directed against enteric bacteria. In recent years, few changes have been made to this treatment paradigm, although nonoperative management for highly selected patients who have a well-controlled focus of infection is gaining favor. Antimicrobial therapy should be stratified to the individual patient. Patients who have community-acquired intra-abdominal infections should receive narrower-spectrum agents that provide coverage against the common gram-negative and gram-positive aerobic and obligate anaerobic microorganisms typically found with these infections. In contrast, higher-risk patients, especially those who have nosocomial intra-abdominal infections, may benefit from a broader-spectrum empiric regimen, which includes selective use of agents effective against resistant gram-negative organisms, Enterococcus sp, and Candida sp. Such a regimen can be de-escalated once definitive culture results are available. Antimicrobial therapy should generally be limited to no more than 4 to 5 days in most patients who have a satisfactory clinical response, to lower the risk for superinfection and the emergence of highly resistant bacteria.

REFERENCES


