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# Empiric treatment options in the management of complicated intra-abdominal infections

## ■ ABSTRACT

Complicated intra-abdominal infections remain a major challenge for surgeons and internists because of their association with high morbidity and mortality. For optimal outcome, these infections require a combination of appropriate and timely surgical source control and adjunctive broad-spectrum antimicrobial therapy. This review discusses criteria for choosing empiric antimicrobial therapy, outlines available treatment options, and highlights new antimicrobial therapies for these infections.

## ■ KEY POINTS

Source control for complicated intra-abdominal infections remains the most important component of successful treatment. Proper selection of empiric antibiotic therapy is adjunctive but important in the overall treatment approach.

Selection of empiric antimicrobial therapy for complicated intra-abdominal infections depends on the severity of illness and how the infection was acquired.

The diverse bacteriology of complicated intra-abdominal infections and the emergence of bacterial resistance make the antimicrobial treatment of these infections an important clinical challenge.

Emerging resistance of many gram-negative enteric pathogens and *Bacteroides fragilis* continues to stimulate the search for effective new antimicrobials.

**B**ecause of their association with high rates of morbidity and mortality, intra-abdominal infections remain one of the major challenges facing surgeons and internists. Although approximately 80% of intra-abdominal infections are acquired outside of the health care setting,[1] the threat of infection with health care–associated pathogens is concerning, given the rapid colonization of hospitalized patients with resistant bacteria.

Source control (surgical measures to eradicate a focus of infection, prevent ongoing microbial contamination, and restore functional anatomy) is fundamental to the management of patients with complicated intra-abdominal infections. Empiric antimicrobial therapy, although adjunctive, is nevertheless important in the overall management plan, and the search for the optimal antimicrobial regimen continues. After beginning with an overview of intra-abdominal infections, this review focuses on criteria for choosing empiric antimicrobial therapy for complicated infections and on the available and emerging therapeutic options for these infections.

## ■ CAUSES AND CLASSIFICATION OF INTRA-ABDOMINAL INFECTIONS

More than a century ago, aerobic and anaerobic bacteria were each implicated as probable causes for the development of intra-abdominal infections. With the availability of advanced anaerobic culture techniques, it became firmly established by the mid-1970s that serious intra-abdominal infections involved synergistic mixtures of bacteria.[2]

Intra-abdominal infections generally occur because a normal anatomic barrier is disrupted. The most common disruptions occur in hollow viscera, allowing intraluminal bacteria to invade and proliferate in typically sterile regions such as the peritoneal cavity or the retroperitoneum.

### Peritonitis: Wide variations in presentation
Although the term *peritonitis* is often used synonymously for intra-abdominal infections, the degree of

## Peritonitis at a glance

**Primary bacterial peritonitis** refers to spontaneous bacterial peritonitis that arises without a breach in the peritoneal cavity. It is most commonly seen in infancy and early childhood and in patients with cirrhosis or compromised immune function.

**Secondary bacterial peritonitis** occurs secondary to spillage of gut organisms through a hole in the gastrointestinal tract. It may be community-acquired or health care–associated.

**Tertiary peritonitis** is characterized by persistent or recurrent infection that typically occurs at least 48 hours after apparently adequate management of primary or secondary peritonitis. It is most often seen in patients with significant comorbidities and in those with compromised immune function.

peritoneal involvement can vary greatly. Clinical presentation of intra-abdominal infections varies from localized appendicitis to diffuse inflammation of the abdominal cavity, characterized as generalized peritonitis. Intra-abdominal infections also can be described as primary, secondary, or tertiary peritonitis (see "Peritonitis at a glance" sidebar). Whereas primary infections usually do not involve a hollow viscus, secondary infections are associated with hollow viscus perforations. Tertiary infections are associated with immunocompromised patients and usually involve treatment failures.[3,4] Tertiary peritonitis is defined as the persistence or recurrence of intra-abdominal infection despite what appears to be have been adequate source control and appropriate antimicrobial therapy. It also may be associated with bacteria that are usually considered to have low virulence, such as enterococci and *Staphylococcus epidermidis*.[5]

### Uncomplicated vs complicated infections

Intra-abdominal infections also can be categorized as uncomplicated versus complicated, although the distinction is not always clear. Complicated intra-abdominal infections are often defined as extending beyond the hollow viscus of origin into the peritoneal space with associated abscess formation or peritonitis.[1] These infections are potentially serious medical conditions that require an invasive procedure for source control.[1]

### ■ DESPITE PROGRESS, STILL A MAJOR BURDEN

The overall incidence of intra-abdominal infections is difficult to establish and varies with the underlying abdominal disease processes. The clinical significance of complicated intra-abdominal infections is often measured by the substantial burden they place on health care resources in terms of the need for emergency room services, hospital admission, imaging and laboratory diagnostics, and surgery (both initial and repeat interventions).[6] In addition, ineffective initial empiric antimicrobial therapy can significantly increase the cost of treating intra-abdominal infections, underscoring the need for prompt and appropriate interventions.[6]

Tremendous progress has been made over the past century in the management of intra-abdominal infections, as mortality rates have dropped from approximately 90% in 1900 to 23% in 2002.[7] However, mortality rates still can vary widely depending on the source of the infection, ranging from 0.25% for the appendix[8] to much higher rates for the stomach/duodenum (21%), pancreas (33%), small bowel (38%), large bowel (45%), and biliary tract (50%).[9]

Although outcomes have improved, complicated intra-abdominal infections still are associated with a high rate of mortality related to organ dysfunction in critically ill surgical patients. As a result, these infections require a combination of appropriate and timely surgical source control and broad-spectrum antimicrobial therapy for optimal outcomes. The ultimate treatment goals are to avoid invasive sepsis/bacteremia, local destructive effects of infection, and death.

### ■ RISK STRATIFICATION

Many factors can contribute to the severity of an intra-abdominal infection and to a patient's risk for a poor outcome. These include patient age, underlying comorbidities (eg, diabetes, cardiovascular disease, cancer), the extent of infection, where the infection was acquired (community vs health care setting), the presence of compromised organ function or sepsis, nutritional status, and the success of initial source control procedures.[1,10]

Dividing patients with intra-abdominal infections into lower and higher risk categories is not always straightforward, but attempting to assess a patient's risk of treatment failure and/or death is essential to optimizing a treatment plan. Proper risk stratification also is important when comparing treatment regimens and when introducing new antimicrobial agents.

Several types of patients with complicated intra-

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**TABLE 1**

**Independent risk factors for death or treatment failure in patients with intra-abdominal infections[10]**

| | |
|---|---|
| Higher APACHE II score | Liver disease |
| Advanced age | Malignancy |
| Hypoalbuminemia | Renal disease |
| Hypocholesterolemia | Corticosteroid therapy |
| Malnutrition | Unsuccessful operation |
| Preoperative organ impairment | |

APACHE II = Acute Physiology and Chronic Health Evaluation II

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**FIGURE 1.** Usual microflora of the gastrointestinal tract.

abdominal infections have been identified as being at higher risk for a poor outcome, including those with higher scores on the Acute Physiology and Chronic Health Evaluation (APACHE II) classification, poor nutritional status, hypoalbuminemia, significant cardiovascular disease, and unsuccessful surgical attempts to control the local infection.[11–16] Notably, many of these risk factors are not specifically related to intra-abdominal infection but more to the patient's physiologic status or underlying medical condition **(Table 1)**.[10]

Patients who acquire infection within the hospital also have a poorer prognosis. Several studies have demonstrated that the presence of resistant microorganisms is associated with higher rates of treatment failure.[17–19] Accordingly, the selection of empiric antimicrobial therapy is likely to influence, at least in part, clinical outcome. Stratifying patients according to the probability that they harbor health care–associated resistant pathogens is another approach that can be useful in selecting antimicrobial therapy.

## ■ BACTERIOLOGY

The bacteria that cause intra-abdominal infections are derived from the endogenous flora of the gastrointestinal tract. An appreciation of the normal microflora within the gastrointestinal tract is key to understanding the spectrum of intra-abdominal infections that may ensue. **Figure 1** lists bacteria commonly found in various segments of the gastrointestinal tract.[20]

### Polymicrobial isolates are the hallmark

Polymicrobial isolates remain the hallmark of intra-abdominal infections.

The most commonly isolated aerobe is *Escherichia coli,* and the most commonly isolated anaerobe is *Bac-*
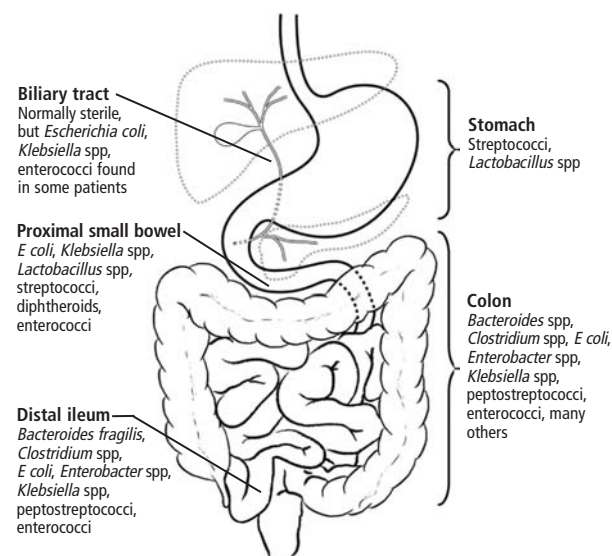
*teroides fragilis.*[1,4,10] Other *Bacteroides* isolates include *Bacteroides distasonis, Bacteroides ovatus, Bacteroides thetaiotaomicron,* and *Bacteroides vulgatus.*

The role of enterococci in intra-abdominal infections remains controversial, but treatment failure attributable to these organisms appears to be common in high-risk patients.[21–23] When enterococci are isolated, *Enterococcus faecalis* and *Enterococcus faecium* account for 90% and 10% of episodes, respectively.[24]

*Pseudomonas aeruginosa* and other enteric gram-negative bacteria (eg, *Acinetobacter* species) are other potential pathogens of concern because they are increasingly resistant to many antimicrobials. Infection with *P aeruginosa* is typically observed in high-risk patients such as those with late-onset nosocomial infection and those who have received previous antimicrobial therapy, undergone recurrent surgeries, or both. In constrast, patients with early-onset health care–associated or community-acquired infections have a low prevalence of *P aeruginosa.*[10]

*Staphylococcus aureus* is also a potential pathogen with inherent antibiotic resistance issues.[25]

### Type/site of infection and acquisition mode indicate likely pathogens

The likely etiology of intra-abdominal infections can be predicted based on the type of peritonitis, the site of infection, and the mode of acquisition.[1,4,10] In general, primary (spontaneous) bacterial peritonitis is typically monomicrobial (eg, streptococci, *E coli,* staphylococci), whereas secondary and tertiary peritonitis are polymicrobial mixtures of aerobic and anaerobic bac-

**TABLE 2**
**Pathogens associated with peritonitis**

| Type/site of infection | Common aerobes | Common anaerobes |
|---|---|---|
| Primary bacterial peritonitis | | |
| Children (spontaneous) | *Streptococcus pneumoniae*, group A streptococci | — |
| Cirrhosis | *Escherichia coli*, *Klebsiella* spp, *S pneumoniae* | — |
| Peritoneal dialysis | Staphylococci, streptococci | — |
| Secondary bacterial peritonitis | | |
| Gastroduodenal | Streptococci, *E coli* | — |
| Biliary tract | *E coli*, *Klebsiella* spp, enterococci | *Clostridium* spp or *Bacteroides* spp (both infrequent) |
| Small or large bowel | *E coli*, *Klebsiella* spp, *Proteus* spp | *B fragilis* and other *Bacteroides* spp, *Clostridium* spp |
| Appendicitis | *E coli*, *Pseudomonas* spp | *Bacteroides* spp |
| Abscesses | *E coli*, *Klebsiella* spp, enterococci | *B fragilis* and other *Bacteroides* spp, *Clostridium* spp, anaerobic cocci |
| Liver | *E coli*, *Klebsiella* spp, enterococci, staphylococci | *Bacteroides* spp (rare) |
| Spleen | Staphylococci, streptococci | — |
| Tertiary bacterial peritonitis | | |
| | All of the above, but more likely to involve resistant *Pseudomonas aeruginosa*, *Enterobacter* spp, enterococci, MRSA, coagulase-negative staphylococci, and *Candida* spp | All of the above |

MRSA = methicillin-resistant *Staphylococcus aureus*

teria (and occasionally fungi in cases of tertiary peritonitis). In community-acquired secondary peritonitis, gram-positive and gram-negative facultative and aerobic organisms often are implicated in infections derived from the stomach, duodenum, biliary system, and proximal small bowel.

When bacteria are present with cholecystitis, the most commonly isolated organisms are *E coli*, *Klebsiella* species, and enterococci. Infections arising from perforations in the distal small bowel are typically caused by gram-negative aerobic and facultative bacteria as well as by anaerobes. For infections beyond the proximal small bowel, a variety of anaerobes must also be considered. A wide range of bacteria also may cause colon-derived intra-abdominal infections, but facultative and obligate anaerobic organisms outnumber aerobic bacteria (eg, streptococci, enterococci, gram-negative coliforms) by a ratio of 10,000:1.[26]

In health care–associated intra-abdominal infections, which typically encompass tertiary peritonitis, nosocomial isolates particular to the site of previous surgery and to the specific hospital and unit may determine which organisms are responsible.[1] Most patients with tertiary peritonitis require treatment with multiple antimicrobials, and fungal infection, especially with *Candida* species, must always be considered. The organisms most commonly associated with primary, secondary, and tertiary peritonitis are outlined in **Table 2**.

### ■ GENERAL TREATMENT APPROACH

Fluid resuscitation, source control (ie, surgical debridement, drainage, and repair), and appropriate systemic antibacterial therapy are paramount to the successful treatment of complicated intra-abdominal infections.[1,4,10] While antimicrobial agents should not be discounted in any treatment regimen for a patient with peritonitis, source control must be considered paramount. Without source control, antibiotics will not successfully treat a patient with secondary or tertiary peritonitis.

Once the diagnosis of complicated intra-abdominal infection is suspected (ie, due to presence of a systemic and local inflammatory response), it is appropriate to plan which methods will be needed for source control and to begin antimicrobial therapy immediately. Therapy need not be delayed until an exact diagnosis is established or the results of appropriate cultures are available.[1] Withholding antimicrobials or using inadequate empiric antimicrobial therapy can result in increased failure rates and increased mortality.[27–31]

### ■ ISSUES IN ANTIMICROBIAL SELECTION AND USE

#### Avoid inappropriate use
Routine use of full-course antimicrobial therapy is not appropriate for all patients with intra-abdominal infections. Patients with bowel injuries due to pene-

trating, blunt, or iatrogenic trauma that are repaired within 12 hours should receive only short-course (perioperative) antimicrobial therapy, as should patients with intraoperative contamination of the operative field by enteric contents under other circumstances.[1] Likewise, patients with acute perforations of the stomach, duodenum, or proximal jejunum in the absence of antacid therapy or malignancy require only perioperative antimicrobial therapy, as do patients with acute appendicitis without evidence of gangrene, perforation, abscess, or peritonitis.[1] Appropriate perioperative antimicrobial therapy in these cases is no more than 24 hours in duration.

## Factors that influence antimicrobial selection

Antimicrobial therapy poses an important clinical challenge because of the diverse bacteriology of complicated intra-abdominal infections and the emergence of bacterial resistance. In general, selection of an empiric agent or combination regimen must be directed at providing reliable activity against *E coli*, other gram-negative facultative bacteria, and *B fragilis*.[1,4,10] Consideration also must be given to whether the infection was community-acquired or health care–associated **(Table 3)**. The continuing emergence of antimicrobial resistance among some gram-negative enteric pathogens and *B fragilis* has become concerning.[32–34]

Many other factors influence the selection of an antimicrobial agent, including its potential to induce bacterial resistance, its risk of hypersensitivity, its overall tolerability, its dosing frequency, and its cost. Accordingly, the search continues for an effective antimicrobial regimen that has activity against resistant pathogens, a minimal risk of side effects, a convenient dosing schedule, and potential cost benefits.

## Available antimicrobial options

Several intravenous antibiotics have been investigated, as monotherapy or as part of a combination regimen, for the management of patients with intra-abdominal infections. The old standard of care involved double- or triple-antimicrobial therapy (eg, aminoglycoside/ beta-lactam/clindamycin) to provide coverage against an array of potential pathogens. In recent years, monotherapy with imipenem/cilastatin (Primaxin) has become the new gold standard because of its broad spectrum of activity against anticipated pathogens and its relative safety and ease of use. In addition to imipenem/cilastatin,[29,35,36] contemporary agents with documented efficacy include cefoxitin,[37,38] ampicillin/sulbactam,[39] ticarcillin clavulanate (Timentin),[40] and piperacillin/tazobactam (Zosyn).[41–44] More recently, meropenem (Merrem),[45–47] ertapenem (Invanz),[48] and

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**TABLE 3**
**Considerations in antimicrobial selection**

**For patients with community-acquired secondary peritonitis**

Choose agents active against enteric gram-negative aerobic and facultative bacilli and against beta-lactam–susceptible gram-positive cocci

For distal small bowel and colon-derived infections and more proximal gastrointestinal perforation with obstruction, choose agents with activity against anaerobes

Avoid agents used to treat nosocomial infection in the intensive care unit, except for high-risk patients

Inclusion of agents with enterococcal coverage provides no benefit in outcomes for patients with community-acquired infections

For high-risk patients (ie, with high APACHE II score, poor nutritional status, significant cardiovascular disease, immunosuppression, or inability to obtain adequate source control), use agents with a wider spectrum of antibacterial activity

**For patients with tertiary and health care–associated peritonitis**

More resistant flora are routinely encountered in this setting

Organisms are similar to those in other nosocomial infections

Treatment is based on local nosocomial flora and their resistance patterns

Agents that offer enterococcal coverage are appropriate for health care–associated infections

Consider fungal infections based on the patient's history of prior antimicrobial use and underlying risk factors

APACHE II = Acute Physiology and Chronic Health Evaluation II

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tigecycline (Tygacil)[49] have been shown to be effective as monotherapy.

The use of oral antibiotics (eg, ciprofloxacin, amoxicillin/clavulanate) as step-down therapy for patients with intra-abdominal infections is a relatively recent advance that can be considered in most patients.

## ■ ANTIMICROBIAL TREATMENT GUIDELINES

Antimicrobial agents and regimens currently recommended by the Infectious Diseases Society of America, the Surgical Infection Society, the American Society for Microbiology, and the Society of Infectious Disease Pharmacists are outlined in **Table 4**.[1,10] The overall evidence suggests that no regimen has been shown to be superior to another.

**Low-risk patients.** The general consensus is that for low-risk patients with community-acquired intra-abdominal infections (most cases of secondary peri-

**TABLE 4**
**Recommended empiric antimicrobial regimens for treatment of intra-abdominal infections[1,10]**

| Type of infection | Monotherapy regimens | Combination regimens |
|---|---|---|
| Low-risk, community-acquired secondary peritonitis | • Ampicillin/sulbactam (various)<br>• Ticarcillin/clavulanate (Timentin)<br>• Ertapenem (Invanz)<br>• Cefotetan (Cefotan)<br>• Cefoxitin (various) | • Cefazolin (various) or cefuroxime (various) **plus** clindamycin (various) or metronidazole (various)<br>• Ciprofloxacin (various), levofloxacin (Levaquin), or gatifloxacin (Tequin) **plus** clindamycin or metronidazole |
| High-risk or health care-associated secondary peritonitis and all tertiary peritonitis* | • Imipenem/cilastatin (Primaxin)<br>• Meropenem (Merrem)<br>• Piperacillin/tazobactam (Zosyn) | • Aminoglycoside,† aztreonam (Azactam), ciprofloxacin, or third/fourth-generation cephalosporin‡ **plus** clindamycin or metronidazole |

*Regimen may need to be modified based on need to provide coverage for methicillin-resistant *Staphylococcus aureus*, coagulase-negative staphylococci, enterococci, and *Candida* species.
†Once-daily administration recommended.
‡Cefepime (Maxipime), cefotaxime (various), ceftazidime (various), ceftizoxime (Cefizox), ceftriaxone (various)

tonitis), narrow-spectrum agents such as antianaerobic cephalosporins or ampicillin/sulbactam are preferable to more costly broad-spectrum agents as well as to those with a greater risk of toxicity. Specific enterococcal coverage, although not routinely warranted for these patients, is a benefit of penicillin derivatives.

**High-risk patients.** Patients who are at high risk for failure (ie, with health care–associated secondary peritonitis or any form of tertiary peritonitis) should be treated with a broad-spectrum regimen with adequate coverage against gram-negative aerobic/facultative anaerobic organisms. Addition of empiric coverage for enterococci and *Candida* species should be considered on a patient-by-patient basis. Both monotherapy (eg, imipenem/cilastatin, meropenem, piperacillin/tazobactam) and combination therapy (eg, an aminoglycoside, aztreonam, ciprofloxacin, or a third-/fourth-generation cephalosporin plus an antianaerobe) are appropriate options.

**Special considerations.** Special consideration is required for patients with tertiary peritonitis who are likely to be infected with difficult-to-treat organisms, such as coagulase-negative staphylococci, enterococci (including vancomycin-resistant strains), multidrug-resistant gram-negative bacilli, or yeasts. Empiric therapy in these cases must consider the patient's history of previous antimicrobial therapy and local (ie, in the hospital or unit) patterns of organisms and resistance.

■ **NEWER THERAPEUTIC OPTIONS**

**Tigecycline**

Subsequent to the publication of the most recent guidelines for treatment of intra-abdominal infections,[1,10] tigecycline was approved by the US Food and Drug Administration (FDA) for use in patients with complicated intra-abdominal infections. Tigecycline is a glycylcycline antibiotic with expanded broad-spectrum activity in vitro against bacteria commonly associated with intra-abdominal infections. Its overall spectrum of activity includes aerobic and facultative gram-positive and gram-negative bacteria and anaerobic bacteria.[50–53] While tigecycline exhibits greater activity against many gram-negative bacteria compared with earlier-generation tetracycline compounds, it lacks reliable activity against *P aeruginosa*.[54,55] It has a distinct mechanism of action that is not affected by resistance mechanisms that are common in response to beta-lactam, tetracycline, and aminoglycoside antibiotics.

**Direct comparison with imipenem/cilastatin.** Tigecycline's efficacy was compared with that of imipenem/cilastatin in 1,642 patients with complicated intra-abdominal infections in two double-blind, randomized phase 3 trials whose results were reported in a pooled analysis in 2005.[49] All patients had known or suspected complicated intra-abdominal infection and underwent appropriate source control. The most common infection diagnoses were complicated appendicitis (51%) and complicated cholecystitis (14%).

Among microbiologically evaluable patients, clinical cure rates were 86.1% (441/512) with tigecycline and 86.2% (442/513) with imipenem/cilastatin (95% CI for the difference, –4.5% to 4.4%; $P < .0001$ for noninferiority).[49] Tigecycline's efficacy was noninferior to that of imipenem/cilastatin across a variety of intra-abdominal infection diagnoses **(Figure 2)**. In both treatment groups, clinical cure rates varied by the type of infection and were lower, for instance, in patients with intra-abdominal abscess and higher in patients with compli-

## Cure rates by clinical diagnosis in patients with complicated intra-abdominal infections
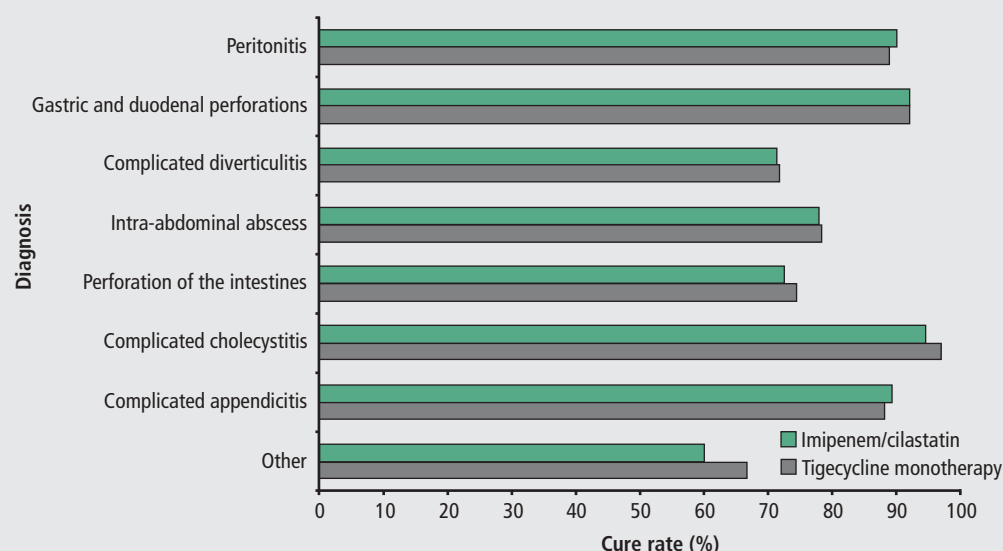


**FIGURE 2.** Clinical cure rates at the test-of-cure visit after treatment with imipenem/cilastatin or tigecycline in 1,025 microbiologically evaluable adults with complicated intra-abdominal infections. Data are from a pooled analysis of two randomized phase 3 trials.[49]

cated appendicitis. Not unexpectedly, patients in both treatment groups who had polymicrobial infections had a lower rate of successful outcomes compared with those who had monomicrobial infections.

Both tigecycline and imipenem/cilastatin were well tolerated in these pooled studies, with a similar frequency and distribution of treatment-emergent adverse events.[49] Gastrointestinal events were the most frequently reported adverse events in both treatment groups. Overall, the three most commonly reported adverse events were nausea (24.4% incidence with tigecycline vs 19.0% with imipenem/cilastatin; $P$ = .010), vomiting (19.2% and 14.3%, respectively; $P$ = .008), and diarrhea (13.8% and 13.2%, respectively; $P$ = .719). Despite the statistically significantly higher incidence of nausea and vomiting with tigecycline, rates of premature discontinuation due to an adverse event did not differ between the two groups.

This large pooled analysis demonstrated that tigecycline was similarly efficacious and well tolerated when compared with imipenem/cilastatin in patients with complicated intra-abdominal infections.[49] No economic analysis of these agents was performed, but for a patient with normal renal function, the cost of a course of tigecycline monotherapy, based on average wholesale price,[56] is similar to that of imipenem/cilastatin for the duration of therapy used in these pooled studies (5 to 14 days). Actual drug acquisition costs and patient variables, however, would influence a formal economic evaluation.

**Role in therapy.** Where does tigecycline fit into clinical practice, given that many good options for treating patients with complicated intra-abdominal infections are currently available? There are a number of situations in which tigecycline might be a reasonable option, as outlined below.

• The logical patient of choice for tigecycline therapy would be one with a complicated intra-abdominal infection caused by a known resistant organism.

• Empiric therapy with tigecycline might be appropriate if local bacterial isolates from intra-abdominal infections demonstrated a resistance pattern that would make tigecycline a reasonable choice in a specific patient population based on a risk-stratification system. This would clearly be a local decision that would need to be based on objective data.

• Empiric therapy with tigecycline for a patient with tertiary peritonitis would be appropriate as long as *P aeruginosa* were not a concern. In such cases, this empiric therapy should be coupled with antifungal therapy until culture results can be obtained.

It is doubtful that tigecycline will become a first-line choice for most patients with complicated intra-abdominal infections unless an economic advantage over other regimens can be shown in future studies.

### Doripenem and other investigational antimicrobials
New antibiotics for intra-abdominal infection are hard to come by these days, but a few investigational agents are on the horizon.

Doripenem is an investigational carbapenem with broad-spectrum coverage that promises to have activity against extended-spectrum beta-lactamase (ESBL)-producing gram-negative organisms.[57] A phase 3 trial comparing doripenem with an active control in patients with complicated intra-abdominal infections was recently completed[58] but has not yet been reported. A New Drug Application for doripenem was submitted to the FDA in December 2006 for indications including complicated intra-abdominal infections.

Other investigational antibiotics that do not currently appear to have a role in the therapy of abdominal infections include iclaprim, ceftobiprole, ceftaroline, and garenoxacin. As bacterial resistance rises, we can hope that the search for new antibiotics will continue.

## DURATION OF ANTIMICROBIAL THERAPY

A final issue of importance to the use of antibiotics for any condition is the duration of treatment. Excessive or prolonged therapy is considered to be one driver of bacterial resistance.[59] A common problem in clinical practice is the temptation to provide extended treatment regimens to patients with intra-abdominal infection. An antimicrobial regimen for intra-abdominal infection should be continued until all presenting clinical signs and symptoms are resolved, including normalization of body temperature and white blood cell count and return to baseline gastrointestinal function.[1,4] When source control is adequate, the antimicrobial course can be restricted to 5 to 7 days.

## SUMMARY AND CONCLUSIONS

Source control remains the most important component in the successful treatment of complicated intra-abdominal infections. Proper selection of empiric antibiotic therapy is adjunctive but is still important to the overall treatment plan. Selection of empiric antimicrobial therapy for complicated intra-abdominal infections depends on the severity of the illness and how the infection was acquired. Knowledge of bacterial resistance in the hospital and community must be available to inform selection of the optimal regimen. Patients with community-acquired intra-abdominal infections producing mild to moderate disease should not routinely receive extended-spectrum antibiotic regimens. Excessive use of these regimens in this population has the potential to increase bacterial resistance.[1]

A number of antibiotics have demonstrated efficacy in treating complicated intra-abdominal infections, and treatment guidelines offer specific recommendations.[1,10] However, rising rates of antibiotic-resistant bacteria in community and hospital settings highlight the need for new therapeutic options. Newer agents such as tigecycline and possibly doripenem, when available, have a potential role in the empiric treatment of complicated intra-abdominal infections when coverage is needed against gram-positive (including methicillin-resistant *S aureus* and enterococci) and gram-negative bacteria as well as aerobic and anaerobic bacteria.

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