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Overview
Resistant pathogens have been associated with an increased rate of in-hospital mortality, increased morbidity, and longer hospital stays. Because delays in administering appropriate therapy have been associated with excess mortality, it is essential to administer empiric therapy promptly in patients with infectious diseases. This educational activity will focus on management strategies for intra-abdominal infections and complicated skin and skin structure infections (cSSSIs).

Learning Objectives
At the conclusion of the activity, participants will be able to:
- Discuss Surgical Infection Society (SIS) and Infectious Diseases Society of America (IDSA) guidelines and their impact on selection and appropriate use of anti-infective agents for treating cSSSIs and intra-abdominal infections
- Review current antimicrobial treatment options to reduce morbidity and mortality in patients with cSSSIs and intra-abdominal infections
- Evaluate emergent clinical data on fluoroquinolones and their relevance in managing patients with cSSSIs and intra-abdominal infections
- Recognize the continued evolution of antimicrobial resistance and evaluate strategies to reduce health care costs, minimize antimicrobial resistance, and improve patient outcomes
- Discuss the various pharmacologic differences between anti-infective agents to optimize treatment

Audience
This program is intended for surgeons, physicians, surgical fellows, nurses, and other health care providers who select antibiotics for patients with infectious diseases.

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Contemporary Approaches to Complex Infections

Surgical and Antimicrobial Management

Intra-abdominal infection is a familiar problem to surgeons, with an average incidence of 3.5 million cases per year in the United States and mortality rates of approximately 60% in patients with well-established infection and resulting organ failure.[1,2] Serious skin infections also are common, accounting for approximately 10% of hospital admissions.[3]

The increasing prevalence of resistant pathogens and the mix of anaerobic and aerobic bacteria that is frequently observed in complicated infections are challenges to surgeons, despite the availability of numerous potent antibiotics. Because delays in administering appropriate therapy have been associated with excess mortality, prompt empiric treatment of serious infections is essential.

This supplement reviews the Surgical Infection Society and Infectious Diseases Society of America clinical guidelines for complicated infections. Emergent clinical trial data on newly approved antimicrobial agents including tigecycline and fluoroquinolones are discussed in relation to patient management.

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Treatment of Peritonitis: Source Control and Antimicrobial Therapy

Lena M. Napolitano, MD

Intra-abdominal infections remain a major source of morbidity and mortality despite the availability of numerous potent antibiotics. The causative bacteria vary depending on the source of the infection, and the bacteriology contributes to the infection's severity.

Peritonitis is the growth of pathogenic microorganisms in the peritoneum, normally a sterile region of the abdominal cavity. Characterized by inflammation of the peritoneum, peritonitis can be primary, secondary, or tertiary. Management of peritonitis and other intra-abdominal infections can involve both surgery and antibiotic therapy. Treatment of peritonitis specifically and guidelines for all intra-abdominal infections are described here.

Peritonitis: Causes and Bacteriology at Each Level

Primary Peritonitis

In primary peritonitis, no intra-abdominal source for the infection is evident. Primary peritonitis has been associated with ascites, cirrhosis, peritoneal dialysis, and systemic lupus erythematosus. Primary peritonitis is most often monobacterial and *Escherichia coli* is the most common pathogen.[1] Other Gram-negative bacteria, such as *Klebsiella*, are common in primary peritonitis, as are *Streptococcus* and *Enterococcus* species. Mortality can be as high as 50% in cases involving cirrhosis.

KEY POINTS

- Abdominal infections comprise numerous and wide-ranging clinical conditions from appendicitis to pancreatitis.
- The causative agent varies according to the severity and source of the infection.
- The principal treatment of secondary and tertiary peritonitis is appropriate surgical intervention to eliminate or control the source of the infection.
- The recommendations of the Infectious Diseases Society of America and the Surgical Infection Society should guide the selection of an antimicrobial agent for treatment of an intra-abdominal infection. No regimen has been consistently shown to be superior or inferior.

Secondary Peritonitis

Secondary peritonitis is predominantly related to bowel perforation and contamination with gut flora, and mortality varies with the organ involved and host factors. The microbial etiology depends on the level of disruption of the gastrointestinal tract.[1] Mechanical small-bowel obstruction or an ischemic segment due to any cause leads to microbial counts that are much higher than normal.[2]

Polymicrobial isolates are obtained in more than two thirds of cases of secondary peritonitis and intra-abdominal abscess[2]; *Bacteroides fragilis* and *E coli*, as well as *Clostridium*, *Klebsiella*, *Streptococcus*, *Enterococcus*, and *Pseudomonas* species are the most commonly implicated bacteria. In most clinical settings, 2 to 3 aerobic species and 1 to 2 anaerobic species are identified in patients with secondary peritonitis. Aerobic and anaerobic bacteria can synergistically enhance virulence; for example, aerobic bacteria can lower redox potential, thus favoring the growth of coexisting anaerobic bacteria.[2] Infection with *E coli* and *B fragilis*, especially in combination, can progress to intra-abdominal abscesses and substantial mortality.[2]

Secondary peritonitis associated with appendicitis or perforated duodenal ulcer has a mortality rate of about 5%. When other intraperitoneal organs, such as the colon or gall bladder are involved, mortality can be closer to 20% and can rise to 30% to 50% in postoperative secondary peritonitis.[3]

Tertiary Peritonitis

Tertiary peritonitis is uncommon and the most serious form of peritonitis. Mortality is approximately 30%, even when the patient receives expert care, and recovery in survivors can take months or years. Tertiary peritonitis evolves from secondary peritonitis when source control fails and an impaired host is unable to contain the infection; it is usually nosocomial.[4,5]

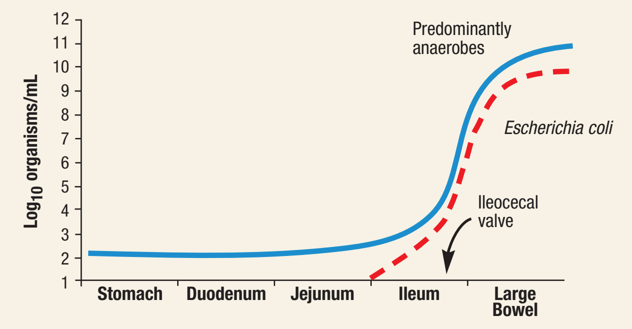
Tertiary peritonitis is characterized by persistent systemic inflammatory response syndrome and multiple-organ dysfunction syndrome. Patients with tertiary peritonitis can present with multiple intra-abdominal abscesses; they may also present without a discrete abscess or infection but with serosanguineous fluid containing resistant bacterial organisms and fungi. Involvement of nonendogenous microbes in tertiary infection is debatable, as tertiary peritonitis may represent failure of host defenses in the peritoneal cavity rather than invasive infection.[2] However, species of *Enterobacter*, *Enterococcus*, *Pseudomonas*, and *Candida*, *Staphylococcus epidermidis*, methicillin-resistant *Staphylococcus aureus* (MRSA), and vancomycin-resistant enterococci (VRE) may play a significant role in tertiary peritonitis.

Bacterial Flora of the Gastrointestinal Tract

The lower gastrointestinal tract contains hundreds of bacterial species, and concentrations of 10^{11} bacteria/gram of stool have been observed; anaerobic bacteria are 1000 times more common than aerobes. The upper gastrointestinal tract (stomach, duodenum, jejunum, and upper ileum) contains relatively few microorganisms, less than 10^4 bacteria/mL of intestinal secretions (**FIGURE 1**).[6] Organisms normally found in the large intestine are not usually seen in the small intestine or upper gastrointestinal tract.[7]

FIGURE 1

Concentration of Bacterial Flora in Regions of the Gastrointestinal Tract



Gorbach SL. Available at: http://gsbs.utmb.edu/microbook/ch095.htm. Accessed November 6, 2006.

Microbiologic Differences by Infection Origin

A broad spectrum of bacterial species is involved in both community-acquired and nosocomial peritoneal infections; however, depending on the origin of the infection, the microbial species vary substantially. Roehrborn and colleagues conducted a study to characterize the specific postoperative microbiologic characteristics of infection in patients with peritonitis.[8] Bacterial cultures were obtained from 67 patients with nosocomial postoperative peritonitis. The microbiologic findings from this population were compared with those of 68 patients with community-acquired peritonitis from another multicenter trial. The most common site of the primary surgical procedure in the nosocomial population was the colon (n = 27; 40%), followed by the stomach (n = 14; 21%), pancreas (n = 10; 15%), and small intestine (n = 9; 13%). The distribution of surgical sites in the group of patients with community-acquired peritonitis was similar to the distribution of surgical sites in the population with nosocomial peritonitis.

E coli was the most commonly isolated microbe among patients with community-acquired peritonitis, and the prevalence was significantly higher (*P* = .005) than that observed in patients with nosocomial peritonitis (36% vs 19%, respectively). In contrast, the incidence of enterococci was significantly lower in the community population (*P* = .001) than in the nosocomial population (5% vs 21%).

Significant between-group differences were also noted for isolates of *Enterobacter* species (3% community vs 12% nosocomial; *P* <.05), *S aureus* (1% community vs 6% nosocomial; *P* <.05), and streptococci (14% community vs 4% nosocomial; *P* = .005). There was also a significant difference in incidence of coagulase-negative streptococci between the 2 populations (1% community vs 5% nosocomial; *P* = .05).

Principles of Therapy in Peritonitis

The principal treatment of secondary and tertiary peritonitis is appropriate surgical intervention to eliminate or control the source of the infection. Source control entails removal of the infected organ (eg, appendix, gall bladder), debridement of necrotic tissue, resection of ischemic bowel, repair/resection of traumatic perforations, and operative or radiologic drainage of abscesses. Optimal management of secondary and tertiary peritonitis also includes resection of a diseased/perforated viscus to stop continued peritoneal contamination with bacteria. All recent studies in abdominal sepsis now include a separate surgical review panel to determine the adequacy of source control and of the initial surgical intervention. Interestingly, in the 359 patients with abdominal sepsis enrolled in the Recombinant Human

TABLE 1

Recommended Antimicrobial Regimens: IDSA and SIS

IDSA	SIS
Mild-to-moderate infections	**Lower-risk patient**
Single-agent regimen	
• Ampicillin-sulbactam* • Ticarcillin-clavulanic acid • Ertapenem	• Cefotetan • Cefoxitin • Ertapenem • Meropenem • Ampicillin-sulbactam • Imipenem-cilastatin • Piperacillin-tazobactam • Ticarcillin-clavulanate
Combination regimen	
• Cefazolin or cefuroxime + metronidazole • Fluoroquinolone-based therapy + metronidazole†	• Ciprofloxacin + metronidazole • Aminoglycoside + antianaerobe • Aztreonam + clindamycin • Cefuroxime + metronidazole • Third-/fourth-generation cephalosporin + antianaerobe
High-severity infections	**Higher-risk patients**
Single-agent regimen	
• Piperacillin-tazobactam • Imipenem-cilastatin • Meropenem	• Piperacillin-tazobactam • Imipenem-cilastatin • Meropenem
Combination regimen	
• Cefotaxime, ceftriaxone, ceftizoxime, ceftazidime, cefepime + metronidazole • Aztreonam + metronidazole • Ciprofloxacin + metronidazole	• Ciprofloxacin + metronidazole • Aminoglycoside + antianaerobe • Aztreonam + clindamycin • Third-/fourth-generation cephalosporin + antianaerobe

IDSA = Infectious Diseases Society of America; SIS = Surgical Infection Society.
*Because increasing resistance of *Escherichia coli* to ampicillin and to ampicillin-sulbactam has been reported, local susceptibility profiles should be reviewed before use.
†Fluoroquinolone = ciprofloxacin, levofloxacin, moxifloxacin, gatifloxacin.

Solomkin JS, et al. *Clin Infect Dis*. 2003;37:997-1005; Mazuski JE, et al. *Surg Infect (Larchmt)*. 2002;3:161-173.

Activated Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) study, 89 patients (24.8%) had inadequate source control.[9]

Recommended Antimicrobial Regimens: IDSA and SIS

The antimicrobials and combinations of antimicrobials listed in **TABLE 1** are recommended for the treatment of intra-abdominal infections by the Infectious Diseases Society of America (IDSA) and the Surgical Infection Society (SIS).[10,11] No regimen has been consistently shown to be superior or inferior.[10]

Patients with more-severe infections, as defined by accepted physiologic scoring systems, or patients deemed to have immunosuppression subsequent to medical therapy, or acute or chronic disease, might benefit from regimens with a broader spectrum of activity against facultative anaerobic Gram-negative organisms as listed in **TABLE 1**.

Nosocomial infections are caused by more-resistant flora; for these infections, complex multidrug regimens are recommended, because adequate empiric antimicrobial therapy is important in reducing mortality. Local nosocomial resistance patterns should also be considered in decisions regarding empiric antimicrobial treatment of intra-abdominal infection. Supported by clinical evidence for high-severity infections, ciprofloxacin in combination with metronidazole is the only recommended fluoroquinolone-based combination regimen.[10-12]

Determining Adequate and Appropriate Antibiotic Therapy

Appropriate antibiotic therapy covers all suspected pathogens, is administered promptly at the proper dose and dose interval, is well tolerated, penetrates the site of infection, takes prior antibiotic therapy into account, and does not increase selection pressure for antibiotic-resistant organisms.[10] Though the choice of initial empiric antibiotic therapy is important to improving patient outcomes, resistance and complex bacteriology can complicate the selection of a regimen.[13]

Covering All the Suspects: Selecting an Empiric Antibiotic Therapy

A prospective study in 20 German clinics isolated pathogens from 425 patients with community-acquired intra-abdominal infections within 2 days of surgery. Culture of the isolates revealed that 13% of the patients received empiric antibiotic therapy that did not cover the bacteria isolated or did not cover both anaerobic and aerobic species. The increase in organisms resistant to standard antibiotics accounts for much of the therapeutic failure in these cases. *E coli* was the predominant isolate as well as the species with the greatest number of resistant isolates (**TABLE 2**).[13]

The Study for Monitoring Antimicrobial Resistance Trends (SMART) researchers analyzed 3134 aerobic and facultative Gram-negative bacilli from the intra-abdominal infections of 2730 patients from 40 centers in 17 countries worldwide. *E coli* (45%) and *Klebsiella* species (17%) were the most common species isolated. Analysis of the samples clearly indicated an increasing resistance of *E coli* to ampicillin-sulbactam, which had become no more effective against *E coli* than aminoglycoside-based regimens. Only 56% of 1200 *E coli* isolates were susceptible to ampicillin-sulbactam, and only 60% of isolates obtained before 48 hours of hospitalization were susceptible, indicating the need for other antimicrobial agents for treatment of intra-abdominal infections.[14]

New Agents for Complicated Intra-abdominal Infections

Moxifloxacin

Moxifloxacin is one of the most recently approved antibiotic agents for treatment of intra-abdominal infection. It has activity against both aerobic and anaerobic pathogens commonly isolated from patients with complicated intra-abdominal infection. Moxifloxacin penetrates and accumulates in gastrointestinal mucosal tissue and therefore can be used as monotherapy for the treatment of complicated intra-abdominal infections.

Malangoni and colleagues compared the safety and efficacy of sequential intravenous and oral moxifloxacin with piperacillin-tazobactam and amoxicillin-clavulanate in a prospective, double-blind, randomized trial of patients with complicated intra-abdominal infections.[15] The majority of patients had polymicrobial infections (84%, moxifloxacin group, and 78%, comparator group). *E coli* and *B fragilis* were the most common pretherapy pathogens isolated in this pivotal study. The rates of clinical cure, defined as the disappearance of acute signs and symptoms related to the infection, or sufficient improvement such that additional antimicrobial therapy was not required, at the test-of-cure visit were 80% for moxifloxacin and 78% for comparator groups (**FIGURE 2**). Bacterial eradication rates for *E coli* were approximately 77% in both treatment groups. For *B fragilis* organisms, moxifloxacin had an 85% eradication rate whereas the comparator had eradicated 72% of the organism; this was not statistically significant.

Tigecycline

Tigecycline, a novel glycylcycline, is another recently approved antibiotic for complicated intra-abdominal infections. Tigecycline has exhibited expanded broad-spectrum antibacterial activity against resistant pathogens including MRSA and VRE, and it can be used as monotherapy in complicated intra-abdominal infections. This was shown in a pooled analysis of 2 phase 3, double-blind, randomized trials that compared the safety and efficacy of tigecycline and imipenem-cilastatin in 1642 patients with complicated intra-abdominal infec-

TABLE 2

Pathogens Isolated From Patients With Community-Acquired Intra-abdominal Infections

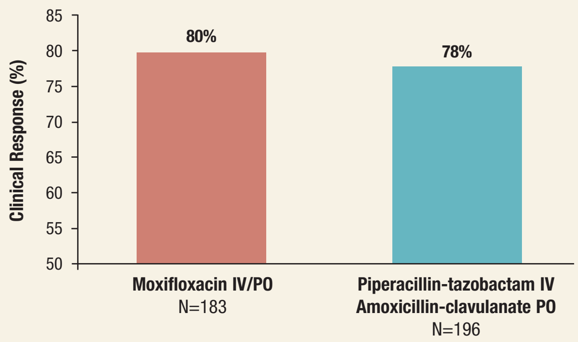
Pathogen Isolated	Total Isolates, N (%)[a]	Resistant Isolates, N (%)[b]
Gram-negative bacilli		
Escherichia coli	147 (47)	32 (40)
Klebsiella spp	22 (7)	5 (6)
Proteus spp	19 (6)	6 (7)
Enterobacter spp	13 (4)	6 (7)
Pseudomonas aeruginosa	13 (4)	7 (9)
Haemophilus spp	1 (<1)	—
Morganella morganii	1 (<1)	—
Gram-positive bacilli		
Streptococcus spp	22 (7)	7 (9)
Enterococci	19 (6)	8 (10)
Anaerobes		
Bacteroides spp	19 (6)	2 (3)
Bacteroides fragilis	6 (2)	1 (1)
Other anaerobes[c]	6 (2)	1 (1)
All others[d]	25 (8)	6 (7)
All	**313 (100)**	**81 (100)**

[a] Isolates obtained from 183 patients.
[b] Isolates obtained from 43 patients.
[c] Other anaerobes included *Fusobacterium* spp, *Clostridium* spp, *Peptostreptococcus* spp, and *Lactobacillus* spp.
[d] Unclassified pathogens.

Adapted with permission from Krobot K, et al. *Eur J Clin Microbiol Infect Dis*. 2004;23:682-687.

FIGURE 2

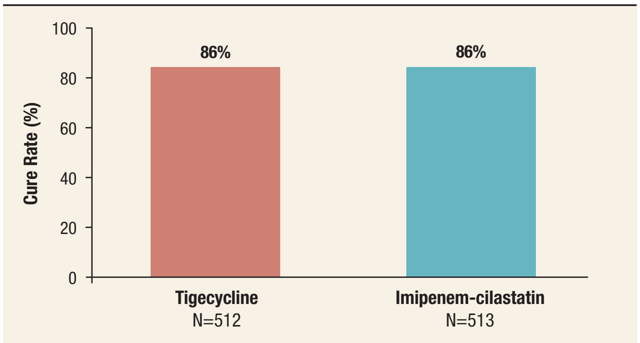
Test-of-Cure Results With Moxifloxacin vs Standard Antibiotic Regimen



P = NS; 95% confidence interval, -7.6 to 9.2.
Malangoni MA, et al. *Ann Surg*. 2006;244:204-211.

FIGURE 3

Clinical Cure Rates: Tigecycline vs Imipenem-Cilastatin



Cure = the course of tigecycline or imipenem-cilastatin and initial intervention (operative and/or radiographically-controlled drainage procedures) resolved the intra-abdominal infectious process.

Babinchak T, et al. *Clin Infect Dis*. 2005;41(suppl 5):S354-S367.

tions.[16] The primary end point was the clinical response at the test-of-cure visit (12-42 days after therapy). Clinical cure was considered to be the resolution of intra-abdominal infection after the initial intervention (operative and/or radiographically controlled drainage procedures) and subsequent treatment with tigecycline or imipenem-cilastatin. The clinical cure rate among patients receiving tigecycline was comparable to the cure rate observed in patients receiving imipenem-cilastatin (approximately 86% in both treatment groups) (**FIGURE 3**).

Duration of Antibiotic Therapy: Knowing When to Stop

Excessive duration of treatment is probably the main inappropriate use of antibiotics in surgical practice and the intensive care unit. Antibiotic therapy for the treatment of complicated intra-abdominal infection should be discontinued when signs and symptoms of infection have resolved.[17]

The reasons for inappropriate duration of antibiotic therapy are numerous. One major reason is that clinicians fail to distinguish between infection and contamination. For contamination caused by acute perforation, usually a single prophylactic dose of an antibiotic is sufficient, and postsurgical antibiotics are not needed. For resectable infection (eg, appendectomy for gangrenous appendicitis), 24 hours of postoperative antibiotic therapy are sufficient. For mild infections with localized pus formation, 48 hours of therapy will suffice. In more advanced yet still moderate infection (ie, an abscess), treatment is required for 2 to 5 days. When infections are not easily controllable owing to failure of source control, much longer than 5 days of antibiotic therapy may be required for resolution.[17]

Contrary to traditional practice, postsurgical antibiotic therapy should not be administered to patients solely because their temperature or white blood cell count is elevated. Such symptoms could indicate an inflammatory response rather than infection.[17] If patients continue to manifest signs and symptoms of infection, this usually indicates ongoing infection that should probably be treated with further surgical intervention rather than a longer course of antibiotics.[11] ■

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CONTEMPORARY SURGERY

General Guidelines for the Management of Intra-abdominal Infections

Robert G. Sawyer, MD

Several medical societies concerned with the treatment of infection have recommended guidelines for selecting anti-infective agents to treat intra-abdominal infections. In 2002, the Surgical Infection Society published guidelines that focused on issues facing the clinician in 4 important areas[1]:

1. Distinguishing intra-abdominal contamination requiring only prophylactic antimicrobial therapy from established infection requiring therapeutic administration of antibiotic agents.
2. Determining which agents, if any, provide optimal efficacy for the individual patient.
3. Optimizing the duration of therapeutic antibiotic therapy.
4. Risk factors that predict the failure of antimicrobial therapy.

Considerations in each of these areas are discussed here.

Contamination vs Established Infection

More than 300 species of microbes compose the normal flora in the colon, yet few actually participate in active infections.[2] Thus, not all colonic contamination leads to infection. Whether an infection becomes established depends on other factors such as host defenses, inoculum size, and local environmental factors such as oxygen tension, organism symbiosis or antagonism, duration of exposure, and previous treatment. In the case of secondary peritonitis, the presence of blood, enteric contents, bile, necrotic tissue, and inert materials can encourage infection.

The Surgical Infection Society guidelines on antimicrobial therapy for intra-abdominal infections state that patients whose peritoneum has been contaminated as a result of bowel injuries that have been surgically repaired within 12 hours are not considered to have established intra-abdominal infections. Patients with gastroduodenal perforations of less than 24 hours duration also are considered to have contamination, not established infection. These patients should be treated prophylactically with antimicrobials for no more than 24 hours.[1]

The Surgical Infection Society also states that patients who have a fully removable focus of inflammation, such as acute or gangrenous but nonperforated appendicitis or cholecystitis, and those with bowel necrosis or obstruction not accompanied by perforation or peritonitis should be treated prophylactically with antimicrobials for no more than 24 hours.[1]

Patients with more serious conditions, for example, those that include bowel perforation, should be treated as having established infections and given antimicrobial agents for longer than 24 hours.[1]

Optimal Antibiotic Selection

Critical factors that influence the choice of antibiotic regimen are whether the infection is community acquired or nosocomial, underlying medical conditions, and illness severity.

Recommended Agents for Nosocomial Infections

Infections acquired in the hospital or other health care sites are often caused by organisms resistant to one or

KEY POINTS

- Not all intra-abdominal contamination becomes an established infection; therapeutic antibiotic regimens should be reserved only for established infection.
- Factors that influence the selection of an empiric antibiotic regimen for established infections are whether the infection is community acquired or nosocomial, underlying medical conditions, and illness severity.
- Antimicrobial therapy of most established intra-abdominal infections should be limited to no more than 7 days.
- Use of a standard scoring system determines the infection's severity and can inform the selection of an antibiotic regimen.

TABLE 1

Recommended Agents for Treating Community-Acquired Complicated Intra-abdominal Infections

Type of Therapy	Mild-to-Moderate Infections	High-Severity Infections
Single-agent regimen		
β-lactam/β-lactamase inhibitor combinations	Ampicillin-sulbactam, ticarcillin-clavulanic acid	Piperacillin-tazobactam
Carbapenems	Ertapenem	Imipenem-cilastatin, meropenem
Combination regimen		
Cephalosporin based	Cefazolin or cefuroxime plus metronidazole	Third-/fourth-generation cephalosporin (cefotaxime, ceftriaxone, ceftizoxime, ceftazidime, cefepime) plus metronidazole
Fluoroquinolone based	Ciprofloxacin, levofloxacin, moxifloxacin or gatifloxacin, each in combination with metronidazole	Ciprofloxacin in combination with metronidazole
Monobactam based		Aztreonam plus metronidazole

Solomkin JS, et al. *Clin Infect Dis*. 2003;37:997-1005.

more antibiotics. Common nosocomial pathogens include species of *Pseudomonas*, *Enterococcus*, *Candida,* and, infrequently, anaerobes.

Inadequate initial treatment of intra-abdominal infections is associated with increased mortality and treatment failure. Therefore, the Surgical Infection Society recommends that patients with hospital-acquired infections and other higher-risk patients receive a broad-spectrum antibiotic regimen that has activity against most Gram-negative aerobic/facultative anaerobic organisms.[1] Such regimens would include extended-range beta-lactam/beta-lactamase agents, carbapenems, third- or fourth-generation cephalosporins plus an antianaerobic agent, aztreonam plus clindamycin, and ciprofloxacin plus metronidazole. Patients with tertiary peritonitis are likely to be infected with organisms that are difficult to eradicate, such as coagulase-negative staphylococci, enterococci (including vancomycin-resistant enterococci), and multiple drug-resistant Gram-negative bacteria. Enterococcal antibiotic coverage is indicated when enterococci are isolated from a nosocomial infection.[3]

Local sensitivity patterns should be used to determine the optimal antibiotic therapy. The optimal antibiotic therapy may be a regimen of multiple drugs, including the possible addition of a quinolone or aminoglycoside.[1]

Recommended Agents for Community-Acquired Infections

Patients with community-acquired, mild-to-moderate intra-abdominal infections should be treated with antibiotics with a narrower spectrum of activity than those recommended for nosocomial infections and with less risk of adverse effects. These could include ampicillin-sulbactam, cefazolin or cefuroxime plus metronidazole, ticarcillin-clavulanate, ertapenem, and quinolones plus metronidazole.

Immunocompromised patients or patients who have more-severe infection defined by accepted severity scoring systems should receive broader-spectrum antibiotics (**TABLE 1**).[3] The antibiotics selected should be active against facultative and aerobic Gram-negative organisms; these agents may include meropenem, imipenem-cilastatin, a third- or fourth-generation cephalosporin (cefotaxime, ceftriaxone, ceftizoxime, ceftazidime, and cefepime) plus metronidazole, ciprofloxacin plus metronidazole, and piperacillin-tazobactam.

The need for enterococcal coverage in antibiotic therapy for community-acquired infections is still being debated. In community-acquired infection, enterococcal therapy has not been found to alter outcomes and is generally not appropriate.[3]

Newly Approved Antibiotics: Moxifloxacin and Tigecycline

Moxifloxacin is one of the most recently approved antibiotic agents for treatment of intra-abdominal infection. Moxifloxacin was equivalent to piperacillin-tazobactam in a study of 379 patients with intra-abdominal infection.[4]

The 2 most common pretherapy pathogens isolated in this study were *Escherichia coli* and *Bacteroides fragilis*; importantly, 84.0% of patients in the moxifloxacin group and 78.2% in the comparator group had polymicrobial infections. Bacterial eradication rates for *E coli* were similar between the 2 treatment groups: moxifloxacin had microbiologic success in 77.0% of patients and the comparator was successful in 76.7% of patients (P = NS). Moxifloxacin microbiologic success for *B fragilis* organisms was 85.4%, in contrast to the comparator at 72%; this was not statistically significant.

Tigecycline was shown to be equivalent in clinical cure rates to imipenem-cilastatin in studies of 1642 patients with intra-abdominal infection.[5] Clinical cure was considered to be the resolution of intra-abdominal infection after initial intervention (operative and/or radiographically-controlled drainage procedures) and treatment with tigecycline or imipenem-cilastatin. Pooled data from the 2 double-blind, randomized, multicenter studies indicated clinical cure rates of 86% in both tigecycline- and imipenem-cilastatin–treated patients in the microbiologically evaluable population (95% CI, 82.8-89.0 for tigecycline-treated patients, and 95% CI, 82.9-89.0 for imipenem-cilastatin–treated patients).

Antifungal Therapy for Select Patients

Antifungal therapy is recommended for patients receiving immunosuppressive therapy or those who have postoperative or recurrent infection. In such cases, fluconazole is generally used for *Candida albicans* and voriconazole or caspofungin for other *Candida* species.[6,7] With time, even newer antifungal agents may be useful for this indication. Antifungal therapy should not be used for otherwise healthy patients if fungi are isolated as part of a mixed culture.

Duration of Antimicrobial Therapy for Established Intra-abdominal Infections

There are few quality studies on the optimal duration of antibiotic therapy. For most established intra-abdominal infections, the Surgical Infection Society recommends that antibiotics not be given for more than 7 days.[1] It also advises that the findings during the initial surgical intervention guide the physician on how long to administer an antibiotic regimen. Empiric therapy should be aimed at the pathogens that are most likely to be the infectious agents, taking into account the patient's previous antibiotic use and community patterns of infectious microorganisms and antimicrobial resistance.[1]

Debatable Value of Peritoneal Fluid Cultures

Although there is a consensus that peritoneal fluid cultures should be obtained in tertiary peritonitis, the value of routine cultures in secondary peritonitis is still under debate as most of the normal colonic flora are nonpathogenic.[8] Positive cultures for simple perforated appendicitis, for example, do not affect outcomes. However, more complicated infections (especially in the colon) have higher failure rates if empiric therapy is inadequate, and culture results can aid in choosing a more appropriate antibiotic regimen. Changing the antibiotic regimen based on the results of such cultures improves outcomes.[9]

TABLE 2

Peritonitis Severity Score: Severity Assessment by Physiopathologic and Surgical Factors

	PSS		
	1	2	3
Age (y)	<70	>70	—
ASA grade	I-II	III	IV
Preoperative organ failure	None	—	1 or more organs
Immunocompromised	No	Yes	—
Ischemic colitis	No	Yes	—
Peritonitis stage	1-2	3-4	—

ASA = American Society of Anesthesiologists; PSS = Peritonitis Severity Score.
Biondo S, et al. *Br J Surg*. 2006;93:616-622.

TABLE 3

Mannheim Peritonitis Index: Calculate Infection Severity During Surgery

Risk Factor	Score
Age >50 y	5
Female sex	5
Organ failure	7
Malignancy	4
Preoperative duration of peritonitis >24 h	4
Origin of sepsis not colonic	4
Diffuse generalized peritonitis	6
Exudate	
Clear	0
Cloudy, purulent	6
Faecal	12

Biondo S, et al. *Br J Surg*. 2006;93:616-622.

Discontinuing Antibiotic Therapy

Antimicrobial therapy can be discontinued when a patient has no clinical evidence of infection such as fever or leukocytosis. If the patient continues to show signs of infection at the time that antimicrobial therapy is scheduled to end, the patient may require further surgical intervention. If source control fails, the patient may need a longer period of antimicrobial therapy.[1]

Illness Severity Calculation: Factors That Predict Antibiotic Failure

A standard scoring system is used to determine the severity of a patient's infection. Several systems are in use, including the Acute Physiology and Chronic Health Evaluation (APACHE) II, the Peritonitis

Severity Score (PSS), and the Mannheim Peritonitis Index (MPI) (**TABLES 2, 3**).[10]

The APACHE II score is not specific for peritonitis, but it can correlate mortality rate with the severity of disease. A drawback of this score is that it can only be calculated after the patient has been in the intensive care unit for 24 hours. The MPI is specific for peritonitis and easier to calculate, even during surgery. The PSS is specific for colonic perforation and is based on physiopathologic and surgical factors.[10]

Some of the factors included in these scoring systems that increase morbidity and mortality in patients with intra-abdominal infection are advanced age, hypoalbuminemia, poor nutrition, poor source control, immunosuppression, chemotherapy, transplantation, inflammatory bowel disease, malignant disease, and concomitant corticosteroid therapy.[11] Other factors that predict a poor outcome in patients include prolonged hospitalization before therapy, and infection with nosocomial pathogens (especially species of *Enterococcus*) or pathogens resistant to the initial empiric antimicrobial regimen. Higher mortality rates have been associated with preoperative organ impairment; heart, liver, or renal disease; malignancy; and corticosteroid therapy.[12]

Medical Management

Besides antibiotic therapy, medical management of the patient with intra-abdominal infection should include fluid resuscitation, adequate nutrition/glucose control, and support of failing organ systems.[13] The use of other adjunctive agents in septic patients, such as activated protein C and glucocorticoids, may be warranted. ■

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CONTEMPORARY SURGERY

Surgical Intervention and Treatment of Complicated Skin Infections

Dennis L. Stevens, MD, PhD

Skin and skin structure infections (SSSIs) are among the most common bacterial infections, as well as some of the most common indications for the use of antibiotic agents. Serious skin infections account for approximately 10% of hospital admissions.[1]

Whereas uncomplicated skin infections do not require surgical treatment, surgical intervention is the standard treatment for complicated skin infections. These serious infections can include secondary infections of diseased skin; acute wound infections resulting from trauma, bites, or surgery; chronic wound infections such as diabetic foot infections, venous stasis ulcers, and pressure sores; and perianal cellulitis with or without abscess. SSSIs also are managed by wound care and antimicrobial therapy. This article focuses on infections that often require surgical intervention.[2,3]

Management of Common SSSIs

SSSIs are frequently encountered in the hospital: up to 30% of nosocomial infections are wound infections, which also account for up to 57% of extra hospital days and 42% of excess hospital costs.[4]

Surgical Site Infections

Surgical wound infections take various forms: suture-line infections, abscesses, endocarditis following valve replacement, and prosthetic-device infection. These infections usually do not appear immediately after surgery. It generally takes 48 hours for the patient to develop clinical signs of infection, most often fever. Usually the fever does not warrant the administration of antibiotic therapy, provided the temperature is below 38.5 °C and the patient has not developed tachycardia; dressing changes or opening the incision site is usually sufficient for infection control. A temperature above 38.5 °C or tachycardia faster than 100 beats/min usually indicates the need for adjunctive antibiotic therapy (**FIGURE 1**).[2,3]

Pressure Ulcers

Pressure ulcers are most common among the elderly and those confined to bed or a wheelchair for long periods: pressure ulcers stage II or higher have a 1.2% to 11.3% prevalence among nursing home residents. In acute care hospitals, the prevalence is 11.2% among patients aged 70 to 79 years and 34% among patients older than 90 years. The mortality rate among patients with bacteremia due to infected pressure ulcers approached 50% by 2002. Treatment of infected pressure ulcers may include surgical debridement to remove necrotic tissue, appropriate dressing selection, surgical repair, antibiotics, and measures to relieve pressure such as air or fluid mattresses.[5]

Cutaneous Abscesses and Carbuncles

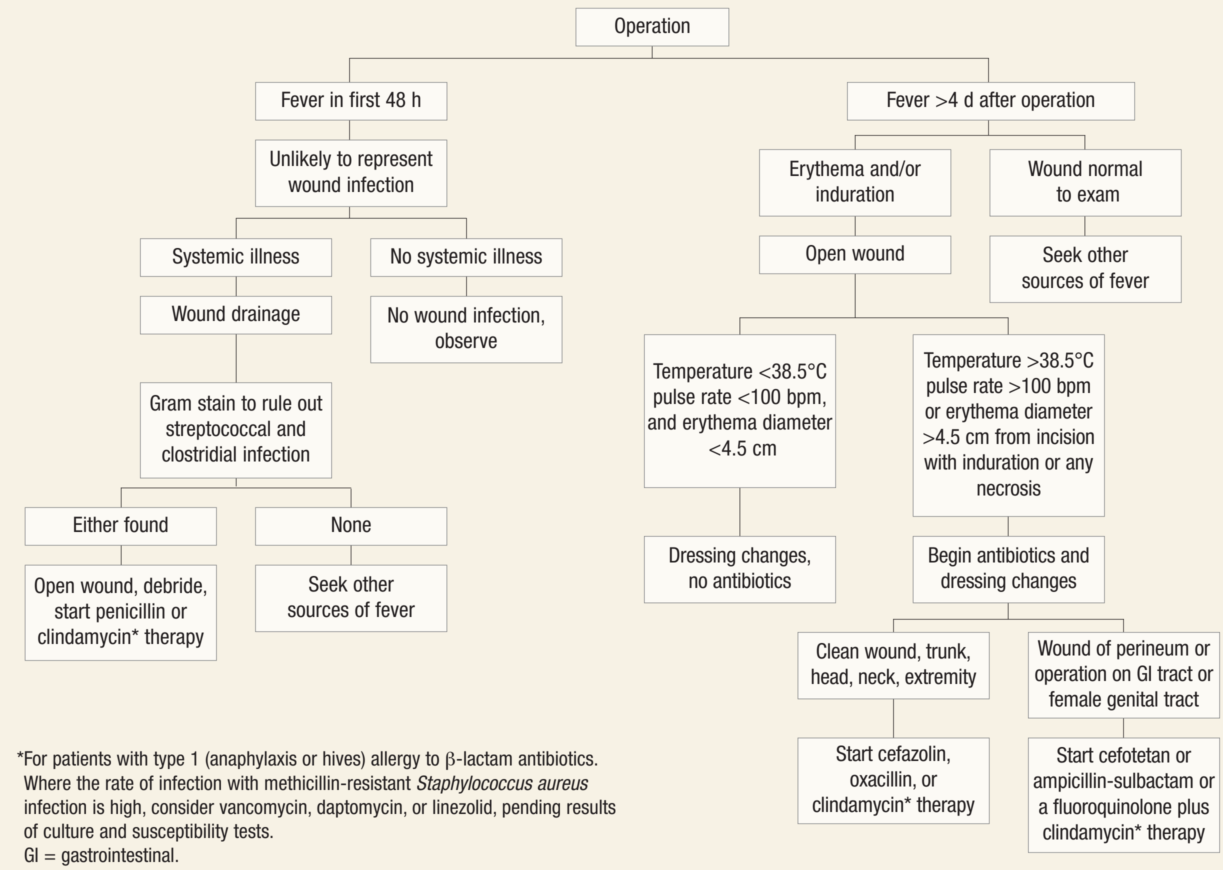
Cutaneous abscesses are painful pus-containing infections within the dermis that extend to deeper skin

KEY POINTS

- Surgical intervention is the standard treatment for complicated skin infections.
- Antibiotic therapy is required to treat serious skin and skin structure infections (SSSIs).
- Choosing an empiric antibiotic therapy for an SSSI can be challenging; the Infectious Diseases Society of America guidelines offer specific recommendations.
- Later-generation fluoroquinolones are more active than early-generation agents against clinically important Gram-positive cocci and atypical pathogens. They also have potent broad-spectrum activity against Gram-negative organisms as well as antianaerobic activity.
- Early diagnosis and surgical debridement are essential to establish a diagnosis and reduce the often extensive morbidity and mortality in cases of clostridial myonecrosis and other forms of necrotizing fasciitis.

FIGURE 1

Algorithm for the Management and Treatment of Surgical Site Infections



*For patients with type 1 (anaphylaxis or hives) allergy to β-lactam antibiotics. Where the rate of infection with methicillin-resistant *Staphylococcus aureus* infection is high, consider vancomycin, daptomycin, or linezolid, pending results of culture and susceptibility tests.
GI = gastrointestinal.

Adapted and modified with permission from Dellinger EP. In: Wilmore DW, et al, eds. *ACS Surgery: Principles and Practice.* New York, NY: WebMD Professional Publishing, 2002.

structures. They appear as erythematous nodules that are often topped by a pustule and encircled by swollen red skin. Unless there are signs of serious systemic involvement, such as high fever or the presence of gangrene or multiple lesions, it is usually sufficient to incise the infection site, drain the pus, and cover the site with a dry dressing. Antibiotics are not usually necessary.

Infection of more than 1 hair follicle can produce a carbuncle, an inflamed pustular mass. Carbuncles also require incision and drainage but seldom require antibiotics unless the erythema is 74.5 cm in circumference or the patient is febrile.[2]

Cellulitis/Erysipelas

Cellulitis and erysipelas are diffuse, spreading skin infections for which antibiotic treatment alone is usually effective. However, when a patient is slow to respond to an antibiotic regimen, it may signal the presence of a deeper infection that requires surgical intervention or an underlying condition such as diabetes, chronic venous insufficiency, or lymphedema.[2]

Necrotizing Skin and Soft Tissue Infections

A necrotizing SSSI is any monomicrobial or polymicrobial bacterial infection that rapidly destroys skin, subcutaneous tissue, fascia, or muscle. Life-threatening sequelae often become evident within a few hours after the patient is infected. The seriousness of the infection depends on the depth of invasion. Mortality has been reported to range as high as 76%.[6] Fortunately, these infections are uncommon, with a prevalence of 500 to 1500 cases in the United States annually.[7] Type 1, the most common type of necrotizing fasciitis,[7] is caused by a mixture of aerobic or anaerobic bacteria as sometimes seen in diabetic foot infections, abdominal or genitourinary complications, Fournier's gangrene, and Ludwig's angina. Type 2 necrotizing fasciitis is a monobacterial infection caused by streptococci (especially, *Streptococcus pyogenes*), *Vibrio vulnificus*, *Aeromonas hydrophila*, *Bacillus* species, *Clostridium* species, or methicillin-resistant *Staphylococcus aureus* (MRSA).[2,8]

Clostridial Infections

Clostridial myonecrosis, more commonly known as gas gangrene, is a necrotizing infection caused by *Clostridium perfringens* in 80% of cases. It often is a result of trauma such as a penetrating or crushing injury that interrupts local blood supply and provides an anaerobic niche for the clostridia. Clostridial myonecrosis can occur spontaneously without prior trauma as the result of intra-abdominal radiation, disorders such as neutropenia (congenital or cyclical), or gastrointestinal malignancy. Spontaneous infection is initiated by hematogenous translocation of intestinal *Clostridium septicum,* which is aerotolerant, to deep soft tissues. Recurrent clostridial myonecrosis also occurs, mainly caused by *C septicum* and *C perfringens*.[9]

A Surgical Emergency

Clostridial myonecrosis and other forms of necrotizing fasciitis are fulminant infections associated with high mortality and extensive morbidity. Early diagnosis and surgical debridement are essential to reduce morbidity and mortality. Surgical inspection reveals a lack of contraction or bleeding in affected muscle and no inflammatory response in tissues. Studies have found that amputation and mortality increase when debridement is delayed more than 12 hours.[6] Patient survival improves when treatment includes reexploration of surgical wounds, antibiotics, nutritional support, pressure relief (every 2 hours), moisture control, and an appropriately selected dressing. Other supportive measures that may be needed include intravenous fluids (both crystalloid and colloid), blood transfusion (to normalize blood in which hemolytic toxins are present), dialysis, and ventilator support.[5,6] Passive immunization with fasciitis-specific antitoxins is not currently available; however, intravenous gamma globulin may also be helpful in necrotizing fasciitis caused by *S pyogenes*.[2] Some studies suggest that hyperbaric oxygen treatment improves outcome, but double-blind controlled studies

FIGURE 2

SSSI Clinical Assessment: 2005 IDSA Guidelines

Presentation	• Fever or hypothermia • Tachycardia (HR >100 bpm) • Hypotension (SBP <90 mm Hg or 20 mm Hg below baseline)
Laboratory tests	• Blood culture and drug susceptibility testing • Complete blood count with differential • Creatinine, bicarbonate, CPK, C-reactive protein
Hospitalization criteria	• Hypotension • Elevated creatinine • Low serum bicarbonate • Elevated CPK (2-3x upper limit of normal) • Marked left shift • C-reactive protein >13 mg/L Pursue definitive etiologic diagnosis

CPK = creatine phosphokinase; HR = heart rate; IDSA = Infectious Diseases Society of America; SBP = systolic blood pressure; SSSI = skin and skin structure infection.
Stevens DL, et al. *Clin Infect Dis*. 2005;41:1373-1406.

of this therapy are lacking.[2] However, supplemental perioperative oxygen administration seems to be effective in reducing surgical wound infection.[10,11]

Antibiotic Treatment of SSSIs Requiring Surgery

Choosing an empiric antibiotic therapy for an SSSI can be challenging; the Infectious Diseases Society of America guidelines offer specific recommendations (**FIGURE 2**),[2] and data from the SENTRY Antimicrobial Surveillance Program provide additional guidance. Between October and December 2000, 1404 bacterial species were isolated from hospitalized patients with SSSIs in 29 sites in the United States and 5 Canadian medical centers, and the prevalence of various causative organisms was established (**FIGURE 3**).[12]

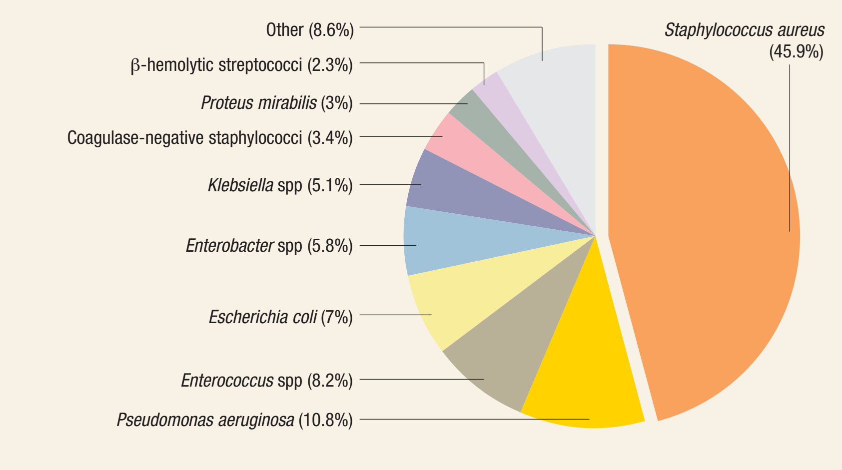
In choosing an antimicrobial agent for an individual patient, the clinician should be guided by infection type and severity, the most common local/nosocomial pathogens, local susceptibility data, and patient compatibility.

Mixed Aerobic and Anaerobic Infections

Infections that contain a mixture of aerobic and anaerobic bacteria require combination antibiotic therapy to cover all the infecting organisms. Such therapy could include the following:

FIGURE 3

Prevalence of Causative Pathogens In SSSIs



Rennie RP, et al. *Diagn Microbiol Infect Dis*. 2003;45:287-293.

- Ampicillin is usually effective against aerobic and Gram-positive organisms.
- Clindamycin covers most anaerobic organisms and usually covers aerobic Gram-positive cocci.
- Metronidazole is most effective against anaerobic enteric Gram-negative bacteria; it is less effective against Gram-positive anaerobic cocci.
- Gentamicin, fluorinated quinolone, ticarcillin-clavulanate, piperacillin-sulbactam, or penem antibiotics are good choices for coverage against resistant Gram-negative rods.

The emergence of MRSA has complicated treatment of staphylococcal infections with methicillin and cephalosporins.

The selected antimicrobial regimen should be continued until repeated surgical intervention is no longer needed and the patient has improved clinically and is without fever for 48 to 72 hours.[2]

Fluoroquinolones in Skin Infections

Early-generation fluoroquinolones (ciprofloxacin, ofloxacin, levofloxacin) have potent, broad-spectrum activity against aerobic Gram-negative bacilli but are not very active against clinically important Gram-positive cocci or anaerobic organisms. Ciprofloxacin is, however, the most potent fluoroquinolone against *Pseudomonas aeruginosa*. Later-generation fluoroquinolones (gatifloxacin, moxifloxacin, trovafloxacin) are more active than early-generation agents against clinically important Gram-positive cocci and atypical pathogens (*Mycoplasma*, *Chlamydia*). They also have potent broad-spectrum activity against Gram-negative organisms as well as antianaerobic activity.[13]

Several studies support the use of several fluoroquinolones for uncomplicated and complicated SSSIs. Levofloxacin (750 mg) and the newer fluoroquinolones, moxifloxacin and gatifloxacin, have been more effective in eradicating *S aureus* than penicillin and cephalosporins.[14,15] Blondeau and colleagues[13] tested the in vitro activity of 6 fluoroquinolones against more than 4000 aerobic organisms. The minimum inhibitory concentration to eradicate 90% of the organisms associated with skin and soft tissue infections showed that moxifloxacin, gatifloxacin, and levofloxacin were the most potent fluoroquinolone agents:

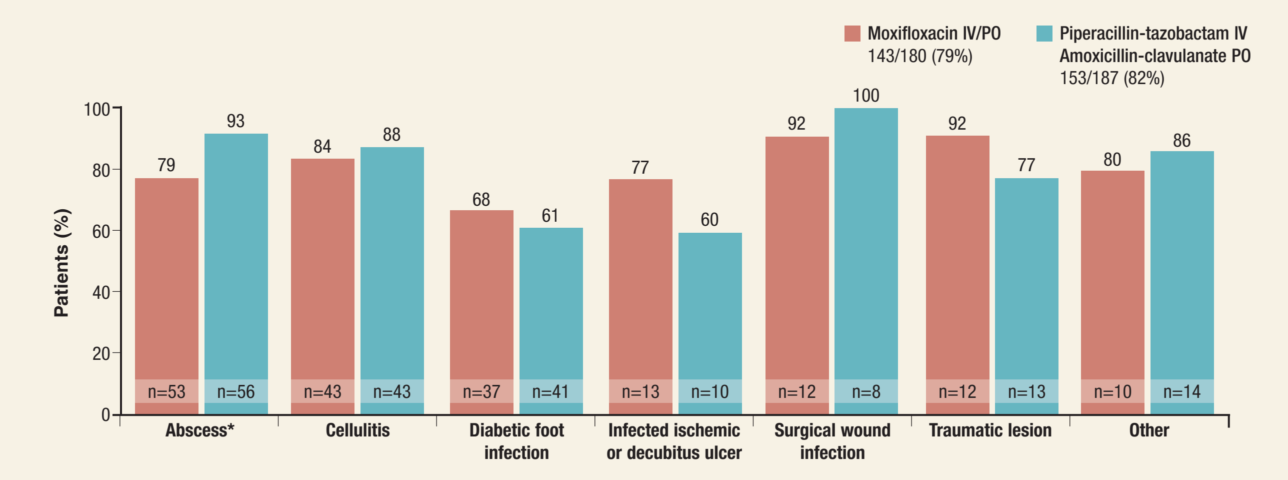
- *S aureus* (methicillin-susceptible): moxifloxacin, 0.125 mcg/mL > gatifloxacin, 0.25 mcg/mL > levofloxacin, 0.5 mcg/mL
- *S aureus* (methicillin-resistant): moxifloxacin, 2 mcg/mL > gatifloxacin, 4 mg/mL = levofloxacin, 4 mcg/mL
- *S pyogenes* and *Streptococcus agalactiae*: gatifloxacin, 0.25 mcg/mL = moxifloxacin, 0.25 mcg/mL > levofloxacin, 0.5 mcg/mL
- *Enterococcus* species: gatifloxacin, 16 mcg/mL = moxifloxacin, 16 mcg/mL = levofloxacin, ≥ 16 mcg/mL.[13]

The US Food and Drug Administration has approved moxifloxacin for the treatment of uncomplicated SSSIs caused by methicillin-sensitive *S aureus* or *S pyogenes* in adults.

A prospective, double-blind, multicenter study, randomized adults with complicated SSSIs to receive sequential intravenous/oral moxifloxacin (400 mg once daily) or a control regimen of intravenous piperacillin-tazobactam (3.0/0.375 g every 6 hours for at least 3 days) followed by oral amoxicillin-clavulanate (800 mg every 12 hours), for a 7- to 14-day course of treatment (**FIGURE 4**).[16] Clinical cure rates at the test-of-cure visit (10 to 42 days after therapy) for the efficacy-valid population were 79% (143/180) for the moxifloxacin-treated group and 82% (153/187) for the control group (95% confidence interval, -12.04% to -3.29%). Bacteriologic eradi-

FIGURE 4

Moxifloxacin in Complicated Skin and Skin Structure Infections: Clinical Cure Rates



**P* = .04. Efficacy-valid population.

Giordano P, et al. *Int J Antimicrob Agents*. 2005;26:357-365.

cation rates for *S aureus*, the most prevalent organism, were 78% for moxifloxacin and 80% for the control group. The incidence of drug-related adverse events was approximately 30% in both groups. The researchers concluded that sequential intravenous/oral moxifloxacin was as effective and well tolerated as intravenous piperacillin-tazobactam followed by oral amoxicillin-clavulanate in treating patients with complicated SSSIs. ■

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ASSESSMENT

To receive credit, you must score 70% or above on the assessment. Please complete the assessment and evaluation form and mail or fax the completed form to:

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• PLEASE ALLOW 6 TO 8 WEEKS FOR PROCESSING.

1. Which of the following are true regarding gas gangrene caused by *Clostridium* species?

a. Gas gangrene caused by *Clostridium perfringens* is most commonly associated with trauma that interrupts the blood supply.
b. Spontaneous gas gangrene of the soft tissues is most commonly caused by *Clostridium septicum* in association with gastrointestinal malignancies and cyclic neutropenia.
c. Hyperbaric oxygen treatment should be administered even before surgical debridement in order to preserve viable tissue adjacent to the site of infection.
d. Answers A and B
e. Answers A, B, and C

2. Which of the following disease states is considered to be only contamination rather than an established infection?

a. A stab wound to the colon treated 4 hours after injury
b. Infected necrotizing pancreatitis
c. A peridiverticular abscess
d. Perforated appendicitis

3. Which of the following is not an important consideration in the choice of empiric antibiotic treatment for intra-abdominal infection?

a. Whether the infection is nosocomial or community-acquired
b. Underlying medical conditions
c. Patient gender
d. Severity of illness
e. All of the above

4. Necrotizing soft tissue infections can be caused by which of the following?

a. Mixed aerobic/anaerobic bacteria
b. *Streptococcus pyogenes*
c. *Vibrio vulnificus*
d. *Aeromonas hydrophila*
e. MRSA
f. All of the above

5. An acceptable treatment option for community-acquired intra-abdominal infection is

a. Levofloxacin alone
b. Gentamicin and ampicillin
c. Vancomycin and metronidazole
d. Moxifloxacin

6. How long should antibiotics be continued for treatment of an established intra-abdominal infection with good source control and eradication of the focus?

a. 14-21 days
b. 24 hours
c. 5-7 days
d. Until the patient is seen in follow-up as an outpatient

7. Which of the following are true regarding antimicrobial treatment of skin and soft tissue infections?

a. Moxifloxacin is as effective as piperacillin-tazobactam for treatment of complicated soft tissue infections.
b. Incision and drainage (no antibiotics) are all that is necessary for treatment of cutaneous abscesses and carbuncles unless the surrounding erythema is >74.5 cm in circumference or the patient has a fever.
c. Due to the recent rapid spread of hospital- and community-acquired MRSA, serious infections presumed to be staphylococcal should be empirically treated with a first-line antibiotic with proven efficacy against MRSA (daptomycin, linezolid, tigecycline, or vancomycin).
d. Answers A and B
e. Answers A, B, and C

PROGRAM EVALUATION

So that we may assess the value of the self-study program, we ask that you please fill out the evaluation form.

Circle the appropriate response
(1 = Strongly disagree; 2 = Disagree; 3 = Neutral; 4 = Agree; 5 = Strongly agree)

Please indicate your level of agreement with the following statements:					
a. The program met my informational needs.	1	2	3	4	5
b. The program met my practice needs.	1	2	3	4	5
Please indicate your level of agreement with how well the program met each of the following objectives:					
a. Discuss Surgical Infection Society and Infectious Diseases Society of America guidelines and their impact on selection and appropriate use of anti-infective agents for treating cSSSIs and intra-abdominal infections	1	2	3	4	5
b. Review current antimicrobial treatment options to reduce morbidity and mortality in patients with cSSSIs and intra-abdominal infections	1	2	3	4	5
c. Evaluate emergent clinical data on fluoroquinolones and their relevance in managing patients with cSSSIs and intra-abdominal infections	1	2	3	4	5
d. Recognize the continued evolution of antimicrobial resistance and evaluate strategies to reduce health care costs, minimize antimicrobial resistance, and improve patient outcomes	1	2	3	4	5
e. Discuss the various pharmacologic differences between anti-infective agents to optimize treatment	1	2	3	4	5
Please indicate your level of agreement with the following statements:					
a. I will apply the knowledge I learned to my clinical/managed care practice.	1	2	3	4	5
b. The program was free of commercial bias.	1	2	3	4	5

Please provide recommendations or suggestions to improve future continuing education programs.

EVALUATION FORM *(Please print clearly)*

I certify that I have completed this educational activity and posttest and claim full credit.

SIGNATURE DATE

TYPE OF CREDIT REQUESTED (PLEASE CHECK ONLY ONE): ❏ CME OR ❏ CNE

FIRST NAME, MI

LAST NAME, DEGREE

TITLE

AFFILIATION

SPECIALTY

ADDRESS (NO P.O. BOXES, PLEASE)

CITY, STATE, ZIP

DAYTIME TELEPHONE

FAX

EMAIL