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Antimicrobial Therapy for Acute Colonic Diverticulitis

Matthew C. Byrnes* and John E. Mazuski

Abstract

Background: Although guidelines and reviews have systematically evaluated diagnosis and surgical management of acute diverticulitis, they have focused only minimally on antibiotic selection for the treatment of this disease. We undertook a review of the literature to assess more clearly the use of specific antimicrobial agents in the treatment of patients with acute diverticulitis of the colon.

Methods: A MEDLINE search was conducted to identify original research, review papers, and guidelines on the use of antimicrobial agents for the treatment of acute diverticulitis.

Results: The general recommendation to use antibiotics with activity against common gram-negative and anaerobic pathogens has remained consistent. A number of single agents and combination regimens provide such activity. However, there is little evidence on which to base selection of specific antimicrobial regimens, and no regimen has demonstrated superiority. In general, episodes of diverticulitis severe enough to warrant hospitalization should be managed initially with intravenous antibiotics. Oral therapy can be used for outpatient treatment or when the patient's condition improves. There is a paucity of data regarding the optimal duration of antimicrobial therapy.

Conclusions: Careful clinical studies are needed to evaluate better the antibiotic regimens for the treatment of acute diverticulitis. Until such studies are conducted, we are forced to rely on tradition, in vitro analyses, pharmacokinetic profiling, and indirect evidence from studies of complicated intra-abdominal infections to determine appropriate therapy for this disease.

OVER THE PAST TWO DECADES, substantial advances have been made in the management of acute colonic diverticulitis. Improved diagnosis and staging have been facilitated by modern imaging techniques, particularly computed tomography (CT). The ability to temporize the acute disease through medical therapy alone has been extended by advances in interventional radiology (e.g., percutaneous drainage). Concomitantly, the indications for surgical intervention have been narrowed and defined more clearly, decreasing the need for emergency procedures.

During this period, numerous antimicrobial agents have been developed and marketed. Their use has been studied carefully for the management of many infectious diseases. However, even though antimicrobial therapy is integral to the management of acute diverticulitis, there is remarkably little clinical evidence regarding the optimal approach to such therapy. The general recommendation of providing coverage of gram-negative and obligate anaerobic bacteria has remained consistent [1–3], but recommendations re-

garding specific antimicrobial regimens have not been well delineated.

A number of important questions should be considered with regard to antimicrobial therapy for acute diverticulitis:

1. Among the many antibiotics available to treat this disease, is any single agent or combination regimen superior?
2. What is the appropriate duration of antimicrobial therapy when treating diverticulitis?
3. When should an antibiotic regimen be altered?
4. What clinical conditions or patient risk factors (e.g., age or disease severity) might prompt a change in the general approach to the provision of antibiotics for this disease?

Although guidelines and reviews have addressed diagnostic and surgical management of this disease process, they have not evaluated the aforementioned questions systematically [1–4]. In fact, no review has focused specifically on the

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selection of antibiotics for the treatment of acute diverticulitis. We reviewed the literature to define more clearly the use of antimicrobial agents in treating this disease.

Overview

The incidence of colonic diverticular disease increased in the Twentieth Century, in part because of lifestyle changes [5,6]. This disease process is a significant cause of morbidity and death in developed countries. The incidence is closely related to age: Diverticulosis can be found in 30% of the population aged 60 years or older, and in 60% of the population aged 80 years or older [4]. As the population continues to age, the prevalence of diverticular disease is likely to increase.

Pathophysiology

Diverticular disease is an acquired phenomenon, seen primarily in populations consuming a low-fiber diet, such as that of the United States [6]. Chronic elevation of intraluminal pressure leads to outpouching of the colonic mucosa [1,7]. This results in the formation of pseudodiverticula, which are composed only of the inner layer of the bowel wall. Diverticula tend to form near the vasa recta, which are sites of intrinsic weakness [8].

As many as 25% of persons with diverticulosis ultimately develop an infectious complication [9,10]. The inciting event leading to an episode of diverticulitis is believed to be obstruction of the diverticular neck, analogous to the pathophysiology of appendicitis. The diverticular mucosa continues to secrete mucus, which leads to distention of the diverticulum until it becomes ischemic and perforates. This colonic perforation is suspected to be a component of nearly all cases of clinically manifest diverticulitis. The opening may range from a microperforation to gross fecal spillage [11].

Clinical presentation

The hallmark of acute diverticulitis is left lower quadrant abdominal pain. Evacuation patterns are variable, and blood in the stool is uncommon [4,12,13]. Patients typically are febrile and anorexic. Laboratory abnormalities, such as leukocytosis, are consistent with an infectious etiology. Computed tomography and, to a lesser extent, sonography are used most widely for diagnosis and staging of the disease.

Diverticulitis can present as uncomplicated or complicated disease. The latter is characterized by overt perforation, obstruction, abscess formation, or fistulization. As the severity of the episode increases, patients typically develop more diffuse abdominal pain. Septic shock ensues occasionally. Approximately one-third of patients will experience a recurrence after an initial acute episode.

Clinical staging

The extent of perforation associated with diverticulitis has been described by the Hinchey classification [12,14]:

- I. Localized perforation with a pericolonic phlegmon. This perforation typically is contained by the mesocolon or epiploic appendages;
- II. Perforation with abscess formation;
- III. Perforation with purulent peritonitis;
- IV. Free perforation with feculent peritonitis.

There also is a subset of patients with radiographic evidence of mild colonic thickening and inflammatory changes in the surrounding fat who have no evidence of a pericolonic phlegmon. This condition sometimes is described as Hinchey class "0." However, a Hinchey classification of "0" also has been used to describe patients who have not had diagnostic imaging, so this nomenclature is not precise.

The Hinchey classification has been used to stratify patients for operative vs. nonoperative therapy. In general, patients with Hinchey class 0 and I disease are treated nonoperatively initially, whereas patients with Hinchey III and IV disease typically undergo early operative intervention. Patients with Hinchey II disease can be temporized with antibiotics alone, percutaneous drainage, or operative intervention, with percutaneous drainage being selected most commonly as the initial measure. Regardless of the decision made with respect to source control, nearly all patients receive antimicrobial therapy.

Microbiology of Diverticulitis

The selection of appropriate antimicrobial agents for the treatment of diverticulitis should be based on an understanding of the microbiology of the disease process. Because diverticular infections originate from colonic perforations [1], the offending bacteria are components of the normal colonic flora, including anaerobic, gram-positive, and gram-negative organisms. Anaerobic bacteria outnumber aerobic and facultative organisms on the order of 1,000:1, with *Bacteroides fragilis* being the most common. The microbial load of stool is high, with 10^{10} – 10^{11} bacteria present per gram [15].

The microbiology of diverticulitis likely resembles that of other complicated intra-abdominal infections, which has been studied extensively. Intra-abdominal infections are characterized by bacterial growth in a normally sterile site in the abdominal cavity, usually resulting from a perforation of the gastrointestinal tract. Complicated intra-abdominal infections are those treated with a surgical procedure or percutaneous drainage. The usual finding is a polymicrobial infection, with an average of five organisms identified per patient [16,17]. *Escherichia coli* and *B. fragilis* are the facultatively aerobic and anaerobic species isolated most commonly.

Although the microbiology of complicated intra-abdominal infection may be a reasonable surrogate for that of diverticulitis, certain points need to be borne in mind. Complicated intra-abdominal infections result from many types of gastrointestinal perforations, not just the colonic perforations pathognomonic of diverticulitis. Moreover, in most studies of complicated intra-abdominal infections, many of the microbiologic specimens are obtained from patients with perforated appendicitis, who usually are much younger than patients with diverticular disease. Some change in the bacterial flora of the lower gastrointestinal tract attributable to aging cannot be excluded. Finally, these specimens are by definition obtained from patients who undergo a source control procedure; the microbiological results from these more disseminated infections may not be identical to those of earlier, more localized infections typical of diverticulitis managed nonoperatively. Thus, the microbiology of acute diverticulitis could differ to some extent from that observed with complicated intra-abdominal infections.

Brook et al. specifically evaluated patients with peritonitis related to diverticulitis [18]. One hundred ten patients with diffuse peritonitis and 27 patients with abdominal abscesses secondary to diverticulitis were studied over a 15-year period. About three-quarters of the specimens were polymicrobial, with an average of three species of bacteria isolated per patient. *E. coli* was cultured from 71% of patients. A sizable minority of patients (10–20%) were infected with gram-positive organisms. The most common of these were streptococci. About 10% of patients were infected with group D streptococci (likely *Enterococcus* spp.). *Bacteroides fragilis* was isolated from one-half of the clinical specimens. In addition to *Bacteroides* spp., the most common anaerobic bacteria were *Clostridium* spp. and *Fusobacterium* spp. These results provide reassurance that the microbiology of complicated diverticulitis resembles that of complicated intra-abdominal infection.

Complicated intra-abdominal infections can be characterized as community-acquired or hospital-acquired [19]. Hospital-acquired infections tend to be associated with more resistant organisms, such as *Pseudomonas* spp., *Enterobacter* spp., *Enterococcus* spp., and staphylococci. Patients with diverticulitis in whom initial medical management has failed may have infections caused by these more resistant organisms, because typically, they have received broad-spectrum antibiotics that select for such pathogens.

Antimicrobial Therapy for Acute Diverticulitis

As a general principle, an antimicrobial regimen for any disease process should have: 1) Activity against the offending bacteria; 2) minimal toxicity; 3) good penetration into the tissues being treated; and 4) clinical efficacy. This fourth point is of the greatest importance, as there are many examples of antibiotic regimens that are active in vitro, but fail in clinical trials. Conversely, there are regimens that do not

TABLE 1. SINGLE AGENT REGIMENS FOR ACUTE DIVERTICULITIS

Cephalosporin
Cefoxitin ^{a,b}
Penicillin/beta-lactamase inhibitor combinations
Ampicillin/sulbactam ^{b,c}
Ticarcillin/clavulanic acid ^b
Piperacillin/tazobactam ^d
Carbapenem
Imipenem/cilastatin ^b
Meropenem ^b
Doripenem ^b
Ertapenem ^b
Glycylcycline ^b
Tigecycline ^b
Fluoroquinolone ^b
Moxifloxacin ^b

^aNot recommended by some authorities because of increased resistance of *Bacteroides fragilis*.

^bFood and Drug Administration approved for intra-abdominal infections.

^cNot recommended as first-line therapy because of increased resistance of community-acquired *Escherichia coli*.

^dAccording to product labeling, FDA approved specifically for appendicitis and peritonitis.

TABLE 2. COMBINATION REGIMENS FOR ACUTE DIVERTICULITIS

Aminoglycoside ^a + an anti-anaerobic agent ^b
Tobramycin ^c
Gentamicin ^d
Cephalosporin + an anti-anaerobic agent ^b
Cefotaxime ^c
Ceftriaxone ^c
Ceftazidime ^c
Cefepime ^c
Monobactam + an anti-anaerobic agent ^b
Aztreonam ^c
Trimethoprin/sulfamethoxazole ^e + an anti-anaerobic agent ^b
Fluoroquinolone + an anti-anaerobic agent ^b
Ciprofloxacin ^f
Levofloxacin ^e

^aNot recommended as first-line therapy because of toxicity concerns.

^bMetronidazole or clindamycin have been used as anti-anaerobic agents. Many authorities question the utility of clindamycin because of increasing resistance of *Bacteroides fragilis* and the association of the drug with *Clostridium difficile* colitis.

^cFood and Drug Administration approved for intra-abdominal infections; combination agents not mentioned in the product labeling.

^dFDA approved for peritonitis; combination agents not mentioned in the product labeling.

^eNot FDA approved for intra-abdominal infections.

^fFDA approved for intra-abdominal infections when administered with metronidazole.

appear to have adequate in vitro activity against certain bacteria, yet have demonstrated clinical efficacy. With polymicrobial infections such as intra-abdominal infections, some microorganisms, such as enterococci, demonstrate limited pathogenicity. Provided the antimicrobial regimen reduces the burden of the major pathogens, in this case, gram-negative bacilli and anaerobes, the host defenses suffice to eradicate less pathogenic organisms.

For diverticulitis, many antimicrobial agents satisfy the first three requirements (Tables 1 and 2). However, there is relatively little information regarding the clinical efficacy of these regimens. In fact, although antimicrobial therapy generally is considered essential for the management of diverticulitis, even this point can be disputed. One retrospective study reported a 96% success rate in treating patients using restriction of oral intake only without antibiotics [20]. However, illness was mild, and it is unclear if these results are applicable to most patients with this disorder. Most authors, including those who have written guidelines, recommend antimicrobial therapy for the treatment of acute diverticulitis; it would not be prudent to withhold antibiotics from patients who show systemic signs of illness, such as fever or leukocytosis, in the absence of a well-designed prospective trial demonstrating the efficacy of this approach and identifying any subsets of patients from whom antimicrobial therapy could be withheld safely.

Our literature review revealed only one randomized controlled trial of different antimicrobial regimens specifically for the treatment of acute diverticulitis. In 1992, Kellum et al. reported clinical success rates of 90% and 86% for patients with acute diverticulitis randomized to receive cefoxitin alone or gentamicin + clindamycin, respectively (p > 0.05)

[21]. Otherwise, there are few class I data (i.e., data derived from adequately powered, randomized controlled trials) on which to base recommendations with regard to antimicrobial therapy of diverticulitis. As such, it is necessary to rely on indirect clinical evidence to develop recommendations. Such evidence comes from various clinical trials of antimicrobial efficacy in the treatment of patients with complicated intra-abdominal infections, and from *in vitro* data documenting the susceptibilities of common pathogens to various antimicrobial agents.

On the basis of the microbiology of complicated intra-abdominal infections and diverticulitis and the available clinical data on the treatment of these disorders, the use of antimicrobial regimens with activity against various gram-negative, gram-positive, and anaerobic pathogens has become standard practice. Mixed combinations of facultative aerobic and anaerobic microorganisms exhibit synergistic growth, so failure to cover one microorganism may lead to persistence of the infection [22]. Both animal and clinical studies have demonstrated higher failure and mortality rates when antibiotic coverage is inadequate [23,24]. In particular, anaerobic coverage appears to be essential, although there are no large prospective trials examining omission of anaerobic coverage for patients with diverticulitis or complicated intra-abdominal infection. Nearly all regimens that have activity against the usual gram-negative organisms found in these infections also cover the common anaerobic streptococci involved in this disease process; thus, the need for such coverage is rarely a consideration by itself. However, the need for enterococcal coverage is a much more controversial issue, which is considered later.

Published Guidelines

A number of guidelines and review papers have described generally accepted approaches to the diagnosis and management of acute diverticulitis. The American Society of Colorectal Surgeons and the American College of Gastroenterology have published recommendations on this topic [2,3]. Neither of these guidelines focuses solely on antibiotic selection. The limitation of all guidelines and reviews is that there is little high-quality clinical evidence on which to base recommendations. Thus, the sections of these guidelines that describe antibiotic selection generally rely on expert opinion and refer to review papers rather than to original studies as their justifications. There is an implicit assumption that regimens with similar *in vitro* activity will have equivalent therapeutic efficacy.

The American Society of Colon and Rectal Surgeons guidelines on practice parameters for diverticulitis were published in 2000 and subsequently revised in 2006 [2,25]. These guidelines recommend selecting antibiotics "to treat the most common bacteria found in the colon: Gram-negative rods and anaerobes." The guidelines also indicate that "single and multi-antibiotic regimens are equally effective." Although this point has been supported by numerous review papers, the conclusion actually is based on the single study described earlier, which compared gentamicin + clindamycin with cefoxitin [21]. It is unknown if this conclusion holds true for regimens in more common use today.

The American College of Gastroenterology guidelines on the diagnosis and treatment of diverticular disease were pub-

lished in 1999 [3]. The recommended antimicrobial regimens included cefoxitin or ampicillin/sulbactam as single agents, and an aminoglycoside, third-generation cephalosporin, or monobactam in combination with an anti-anaerobic agent as combination regimens. The guidelines indicated that these regimens were "based more on clinical consensus than on randomized trials."

A more extensive body of evidence was available for the development of guidelines on the use of antibiotics for patients with complicated intra-abdominal infection. The major guidelines were created by the Surgical Infection Society (SIS) in 2002 and by the Infectious Diseases Society of America (IDSA) in 2003 [19,26]. The IDSA guidelines recommend ampicillin/sulbactam, ticarcillin/clavulanic acid, or erapenem as monotherapy and cefuroxime, cefazolin, or a fluoroquinolone with metronidazole as combination therapy for mild-to-moderate complicated intra-abdominal infections. They recommend piperacillin/tazobactam, imipenem/cilastatin, or meropenem as monotherapy and a third- or fourth-generation cephalosporin, ciprofloxacin, or aztreonam with metronidazole as combination therapy for more severe intra-abdominal infections.

The guidelines for antimicrobial therapy of complicated intra-abdominal infections pertain indirectly to the treatment of most patients with diverticulitis. They are applicable specifically only to those patients who undergo operative procedures or percutaneous drainage. Even in this patient group, it is unclear if the guidelines are entirely appropriate. The studies of antimicrobial therapy for complicated intra-abdominal infections generally have been performed in patients with a heterogeneous group of infections, including those developing after perforations of the appendix, gastroduodenal ulcers, and various lesions of the small and large bowel. In nearly all these studies, the most frequent diagnosis has been perforated appendicitis. Diverticulitis patients have constituted a minority of those enrolled in most trials.

Aside from the source of infection, a fundamental difference between treatment of diverticulitis and that of complicated intra-abdominal infections is that most patients with diverticulitis are managed nonoperatively initially, whereas patients with complicated intra-abdominal infections are required to have undergone a source control procedure. Thus, in patients with complicated intra-abdominal infections, the role of antibiotics is primarily as an adjunct to source control, whereas in most patients with diverticulitis, there is complete reliance on the antimicrobial regimen and the host response to eradicate the infection. In actuality, treatment of nonoperatively managed intra-abdominal infections, such as diverticulitis, may be a more rigorous test of antimicrobial efficacy than is treatment of the usual complicated intra-abdominal infection, in which a source control procedure eliminates most of the microbial inoculum.

Specific Regimens

Aminoglycosides

Aminoglycoside antibiotics were used extensively in the past to treat complicated intra-abdominal infections. They have broad gram-negative and some gram-positive coverage; however, because they have no appreciable anti-anaerobic activity, they are combined with an anti-anaerobic agent when treating intra-abdominal infections. Several aminogly-

cosides are available, including gentamicin, tobramycin, netilmicin, and amikacin, with gentamicin being the most commonly used agent in the class. Aminoglycosides are bactericidal and exhibit concentration-dependent killing. Once-daily dosing is as efficacious as traditional dosing, and potentially associated with less nephrotoxicity [27]; this approach has not been validated thoroughly with respect to intra-abdominal infections, however. Aminoglycosides distribute into the extracellular fluid but have questionable tissue penetration. In individual trials, aminoglycoside-based regimens appeared to have efficacy similar to that of other antimicrobials for the treatment of complicated intra-abdominal infections [28–31]. However, a recent meta-analysis suggested that aminoglycoside-based regimens were inferior to other agents for this indication [32]. Moreover, given the nephrotoxicity and ototoxicity of these agents, many clinicians now view this class of antibiotics as a second-line option for the treatment of complicated intra-abdominal infections [33].

These considerations likely apply to the treatment of patients with diverticulitis. Although results of the randomized trial [21] suggest that these drugs can be used for this indication, their toxicity and poor tissue penetration probably should relegate them to second-line therapy. Their requirements for intravenous administration and pharmacokinetic monitoring make them a poor choice for outpatient use.

Cephalosporins

There are at least 25 cephalosporins available for clinical use; they are grouped into four “generations” with different spectra of activity. Although the general rule is increasing gram-negative activity and decreasing gram-positive activity with increasing generation, this rule is inexact. First-generation cephalosporins are used primarily for gram-positive coverage, although they have activity against many of the common *Enterobacteriaceae* in complicated intra-abdominal infections, such as *E. coli* and *Klebsiella*. Second-generation cephalosporins are more difficult to characterize. Some, such as cefoxitin, have anti-anaerobic activity, whereas others, such as cefuroxime, have a wider spectrum of gram-negative coverage but little anti-anaerobic activity. Third-generation cephalosporins have better gram-negative coverage, heterogeneous gram-positive coverage, and unreliable anaerobic coverage. The fourth-generation cephalosporin, cefepime, has broad gram-positive and gram-negative coverage, but lacks activity against *Bacteroides* spp.

These agents are bactericidal and act by inhibiting cell wall synthesis, leading to bacterial lysis. Pharmacokinetic profiles differ, but all cephalosporins achieve good concentrations in peritoneal fluid. Adverse effects are uncommon and include allergic reactions and, rarely, anaphylaxis. However, pseudomembranous colitis caused by *Clostridium difficile* is a concern with the use of these agents.

Cefoxitin is the primary second-generation cephalosporin with anti-anaerobic activity that is available for monotherapy of complicated intra-abdominal infections [34,35]. In older trials, cefoxitin performed similarly to other comparators in the treatment of these infections. For treatment of diverticulitis, cefoxitin was tested directly against an aminoglycoside-based regimen in a randomized trial, and appeared to be therapeutically equivalent [21]. However,

concern has been raised about its efficacy because of increasing in vitro resistance of anaerobic bacteria, particularly *B. fragilis*, to the agent [19]. The clinical significance of this finding remains unclear.

Multiple studies have evaluated the use of third- or fourth-generation cephalosporins in combination with an anti-anaerobic agent for the treatment of complicated intra-abdominal infections. Clinical success rates have been 75–100% [36,37]. These regimens appear to be superior to aminoglycoside-based regimens [32], and have performed similarly to other comparators.

Penicillin/beta-lactamase inhibitor combinations

Three intravenous penicillin/beta-lactamase inhibitor combinations were recommended in the SIS and IDSA guidelines for use in patients with complicated intra-abdominal infections: ampicillin/sulbactam, ticarcillin/clavulanic acid, and piperacillin/tazobactam. In addition, an oral formulation, amoxicillin/clavulanic acid, was recommended for continuation of antimicrobial therapy. All of these agents have activity against gram-positive, gram-negative, and anaerobic bacteria. With regard to gram-negative bacteria, ampicillin/sulbactam has the narrowest spectrum of activity and piperacillin/tazobactam the broadest. Ticarcillin/clavulanic acid lacks activity against *Enterococcus faecalis*, whereas the other agents typically cover this microorganism. These antibiotics distribute well into most tissues as well as the peritoneal fluid. They are bactericidal and act by inhibiting cell wall synthesis, leading to bacterial lysis. There is a low incidence of adverse effects; potential side effects include anaphylaxis, other allergic reactions, pseudomembranous colitis, and thrombocytopenia.

The intravenous penicillin/beta-lactamase inhibitor combinations generally have shown good efficacy when used as monotherapy for complicated intra-abdominal infections. Recently, however, the use of ampicillin/sulbactam has come under scrutiny [19]. In older clinical trials, this agent appeared to perform similarly to comparators, with success rates of 86–89% [23,38]. However, a recent study of bacterial isolates from patients with intra-abdominal infections in 40 countries demonstrated a 45% rate of resistance of *E. coli* to ampicillin/sulbactam [39]. In another recent study, Krobot et al. identified “inappropriate” antimicrobial therapy as a risk factor for treatment failure in patients with community-acquired intra-abdominal infections; a significant proportion of this “inappropriate” therapy was attributable to resistant *E. coli* [40]. Accordingly, unless local resistance patterns demonstrate better susceptibility profiles, ampicillin/sulbactam probably should not be considered a first-line agent for intra-abdominal infections. Ticarcillin/clavulanic acid appeared to be equivalent to comparator regimens in clinical trials, with success rates of approximately 88% in complicated intra-abdominal infections [41]. Piperacillin/tazobactam is one of the agents used most extensively for complicated intra-abdominal infections. It performed similarly to imipenem/cilastatin, ciprofloxacin + metronidazole, various cephalosporins + metronidazole, and ertapenem in clinical trials [42–44].

Carbapenems

Four carbapenem agents are approved for use in the United States: imipenem/cilastatin, meropenem, doripenem,

and ertapenem. Imipenem/cilastatin and meropenem generally are considered to have the broadest spectra of any antimicrobial agents, with activity against gram-positive, gram-negative, and anaerobic organisms. Doripenem was recently approved by the FDA for treatment of complicated intra-abdominal infections and has a similar broad spectrum of activity. Ertapenem has a somewhat narrower range of activity, with coverage of many gram-positive, gram-negative, and anaerobic organisms but limited activity against *Pseudomonas*, *Acinetobacter*, and *Enterococcus*. Because of its long half-life, once-daily dosing can be used for patients with complicated intra-abdominal infections. Carbapenems have good tissue penetration and distribute well into peritoneal fluid. They inhibit cell wall synthesis and are bactericidal. Adverse effects are uncommon and include seizures (imipenem/cilastatin), anaphylaxis, pseudomembranous colitis, and agranulocytosis.

Many prospective trials have evaluated carbapenems against other classes of antibiotics as well as against each other for the treatment of complicated intra-abdominal infections. Success rates have ranged from 70–100% and generally have been similar to those of comparators [31,45–47].

Monobactams

Aztreonam is the only antibiotic in the monobactam class that has been released by regulatory authorities. It is a synthetic beta-lactam antibiotic for intravenous administration only. It is bactericidal and acts by inhibiting cell wall synthesis. It penetrates most body tissues well; high concentrations are found in peritoneal fluid. It is highly active against most gram-negative organisms but has no significant gram-positive or anaerobic activity. Accordingly, it must be used with an anti-anaerobic agent when treating intra-abdominal infections. In addition, given the lack of gram-positive coverage, there is a theoretical concern about inadequate streptococcal activity if it is used in combination with metronidazole instead of clindamycin. There is a low incidence of adverse effects with this agent; possible effects are anaphylaxis, toxic epidermal necrolysis, and pseudomembranous colitis. Of note, most patients with penicillin allergies can be treated safely with this agent. A theoretical problem with aztreonam is that it induces beta-lactamase production; when exposed to this agent, bacteria may begin expressing the enzyme, which could make ultimate eradication of the infection more difficult [48].

Several prospective trials have evaluated aztreonam + clindamycin against either gentamicin + clindamycin or imipenem/cilastatin for complicated abdominal infections [30,49,50]. The success rate of aztreonam + clindamycin was 71–100%. No significant differences were noted between this regimen and the comparators.

Trimethoprim/sulfamethoxazole

Trimethoprim/sulfamethoxazole is a sulfa drug combination with activity against some gram-positive and gram-negative organisms, including most *Enterobacteriaceae*. It lacks enterococcal and pseudomonad coverage. It is bactericidal and acts by inhibiting sequential enzymes required for folic acid synthesis. It distributes well into most body tissues and peritoneal fluid. Hypersensitivity reactions are somewhat more common with this class of drugs than with various an-

tibiotics; Stevens-Johnson syndrome is an uncommon but devastating complication.

Trimethoprim/sulfamethoxazole lacks anti-anaerobic activity, so it must be combined with metronidazole when treating intra-abdominal infections. It has been suggested as a treatment for diverticulitis [47], particularly as it can be administered orally. It also is indicated for certain forms of enterocolitis. Although its spectrum of action seems appropriate for intra-abdominal infections, one international study indicated that only 69% of urinary isolates of *E. coli* were, in fact, susceptible to this drug combination in vitro [51]. Thus, the utility of this regimen in the treatment of patients with diverticulitis remains unclear.

Tetracyclines and glycylicyclines

Tetracyclines have not been tested extensively for the treatment of complicated intra-abdominal infections, although they were used in the past for these infections. The recent release of tigecycline has led to renewed interest in these agents for this indication. Tigecycline is a glycylicycline that has a broad spectrum of activity against anaerobic bacteria and many resistant gram-positive and gram-negative organisms, with the exception of *Pseudomonas*. Tigecycline proved to be non-inferior to imipenem/cilastatin in prospective trials in patients with complicated intra-abdominal infections, and it has been approved for this indication [52]. It is concentrated actively in tissues, including the colon. Given its spectrum of activity and tissue concentration, it likely would be useful for the treatment of acute diverticulitis. However, because no oral formulation is available, tigecycline is not a good choice for outpatient therapy.

Fluoroquinolones

Two fluoroquinolone agents currently in use have been evaluated formally and approved for the treatment of patients with complicated intra-abdominal infections: Ciprofloxacin (in combination with metronidazole) and moxifloxacin (as monotherapy). Fluoroquinolones are bactericidal and act by inhibiting DNA gyrase. They exhibit concentration-dependent killing and have a prolonged post-antibiotic effect. They are distributed widely in tissues and achieve higher concentrations in intraperitoneal organs than in serum. They are available in oral and parenteral formulations. Ciprofloxacin has broad gram-negative activity, limited gram-positive activity, and no anti-anaerobic activity. Accordingly, it is used with metronidazole when treating intra-abdominal infections. Moxifloxacin has activity against common gram-positive, gram-negative, and anaerobic organisms, and thus can be used as monotherapy for complicated intra-abdominal infections. Moxifloxacin has less activity against resistant gram-negative organisms, such as *Pseudomonas*, and probably is suited better to community-acquired than nosocomial intra-abdominal infections.

Several clinical trials have compared the use of ciprofloxacin + metronidazole with other agents for complicated abdominal infections [43,53–55]. Success rates have been 74–97%, similar to those of comparator regimens. One of these trials prospectively evaluated a change to oral formulations of ciprofloxacin + metronidazole after initial intravenous therapy with these agents, and concluded that such a switch could be made without sacrifice of efficacy.

Ciprofloxacin + metronidazole probably has become the regimen used most commonly for the management of acute diverticulitis, especially in the outpatient setting.

Levofloxacin, in combination with metronidazole, has been prescribed widely for the treatment of complicated intra-abdominal infections, as well as for the treatment of acute diverticulitis. However, levofloxacin has not been approved in the United States for the treatment of complicated intra-abdominal infections. Because levofloxacin and ciprofloxacin have similar activities against enteric gram-negative organisms, it generally has been assumed that levofloxacin + metronidazole would be equivalent to ciprofloxacin + metronidazole for this indication, but no published studies have verified this assumption. The optimal dosing of levofloxacin for complicated intra-abdominal infection or diverticulitis is not known.

Moxifloxacin was evaluated recently for complicated intra-abdominal infections in a randomized controlled trial [56]. Intravenous moxifloxacin with an option for oral conversion was compared with piperacillin/tazobactam, with the option of conversion to oral amoxicillin/clavulanic acid. About 15% of the patients had perforations of the large or small bowel. The clinical cure rates were similar in the two groups. No studies have evaluated the efficacy of moxifloxacin specifically for the treatment of diverticulitis. In view of the clinical efficacy of ciprofloxacin + metronidazole, the antibacterial profile of moxifloxacin, and its concentration in target tissues [57], it probably is suitable for this indication. Potential advantages of moxifloxacin for acute diverticulitis include the availability of an oral formulation, the option of using this agent as monotherapy, its once-daily dosing, and the absence of a need for dosing adjustments for renal failure [58].

The side effect profiles of fluoroquinolones generally are favorable, with relatively few severe adverse reactions. However, the potential association of fluoroquinolone use with epidemics of *C. difficile*-associated disease has been the subject of several recent reports [59-64]. In the past, *C. difficile*-associated disease was linked epidemiologically to a variety of antibiotics, including clindamycin, cephalosporins, and ampicillin and ampicillin/sulbactam. Thus, it is difficult to ascertain the clinical importance of these findings. In fact, a recent study of epidemic *C. difficile*-associated disease in Québec found no association with the use of any specific antibiotic [65]. Careful attention to infection control practices rather than arbitrary changes in antibiotic prescribing practices was believed to be the most important measure in decreasing the spread of this pathogen.

Anti-anaerobic agents

It generally is accepted that antibiotic regimens aimed at treating diverticulitis should include anaerobic coverage when the gram-negative agents lack intrinsic activity against anaerobes. Regimens with inadequate anaerobic coverage have been associated consistently with higher failure rates in patients with complicated intra-abdominal infections. The two agents that have been used most often to provide supplemental anti-anaerobic coverage are clindamycin and metronidazole. Traditionally, these agents were considered equally efficacious, a concept supported by data from older prospective trials. However, more recent in vitro data have

demonstrated increasing resistance of *B. fragilis* and other anaerobic bacteria to clindamycin [66,67]. Although there have been no studies demonstrating that these changes in resistance have led to poorer clinical outcomes, this possibility remains a concern for some practitioners. In addition, the association of clindamycin with *C. difficile* colitis has led some to shy away from its use in intra-abdominal infections. Currently, most authorities reserve this antibiotic for situations in which metronidazole should not or cannot be used. Single agent and combination regimens that can be considered for the treatment of acute diverticulitis are listed in Tables 1 and 2, respectively.

Treatment of Higher Risk Patients

Certain clinical considerations relevant to the management of higher risk patients with complicated intra-abdominal infections may apply also to higher risk patients with diverticulitis. Because infections in these patients are many times characterized by the presence of difficult-to-treat pathogens, such as resistant gram-negative bacteria, *Enterococcus*, and *Candida*, antimicrobial therapy may need to be modified or extended.

Patient stratification

Most of the patients enrolled in trials of treatment for complicated intra-abdominal infections have had community-acquired infections, and have not been particularly compromised thereby. Usually, these patients can be treated successfully with an adequate source control procedure and an appropriate antimicrobial regimen. However, certain patients clearly are at higher risk for an adverse outcome. Multivariable analyses have identified a number of risk factors that predict treatment failure and death. The Acute Physiology and Chronic Health Evaluation (APACHE) II score, a measure of the degree of physiological derangement induced by the disease process and of the patient's pre-morbid characteristics, consistently has been the best predictor of outcome [33]. However, this and many other risk factors are not under the control of the clinician.

Risk factors that portend infection with more resistant or difficult-to-treat organisms are more likely to be relevant to the selection of specific antimicrobial therapy. Patients likely to harbor resistant pathogens are those with nosocomially acquired intra-abdominal infections or who already have received antimicrobial therapy. Patients who have recently undergone a surgical procedure and or who reside in a long-term care facility also are at risk of harboring resistant organisms [68]. It has been hypothesized that such higher risk patients should receive a broader-spectrum antimicrobial regimen [69]. Although this approach has not been tested directly, a higher mortality rate has been found in seriously ill patients with intra-abdominal infections treated with an "inadequate" empiric regimen, "inadequate" being defined as lacking activity against one or more of the microorganisms isolated from definitive cultures [70].

Gram-negative coverage

The SIS and IDSA guidelines recommended use of broader-spectrum gram-negative antimicrobial agents when treating higher risk patients or those with more severe intra-

abdominal infections. This approach could be applicable to some patients with diverticulitis, particularly those in whom initial antimicrobial therapy for their disease has failed. Such patients might be suspected of having relatively resistant gram-negative organisms as a result of prior antimicrobial therapy.

Enterococcal coverage

Although *Enterococcus* spp. normally are part of the colonic flora and are isolated from a certain percentage of patients with complicated intra-abdominal infections, the routine use of antimicrobial regimens that provide enterococcal coverage is not beneficial clinically [71]. However, there are some patients for whom enterococcal coverage has been advocated [19,33]; this recommendation is based primarily on the observation that patients whose cultures reveal *Enterococcus* are at higher risk for an adverse outcome [71]. Patients at risk for enterococcal infection include those with postoperative intra-abdominal infection, those with recurrent gastrointestinal perforation, those with high APACHE II scores, and those receiving immunosuppressive medications [71]. In addition, it seems reasonable that patients with significant prior antibiotic exposure would be more likely to have *Enterococcus* infections and should be considered for routine empiric anti-enterococcal coverage [72]. Among the regimens described previously, imipenem/cilastatin, ampicillin/sulbactam, piperacillin/tazobactam, and moxifloxacin provide reliable enterococcal coverage. Vancomycin or ampicillin can be added when it is believed to be necessary to provide additional enterococcal coverage. Vancomycin-resistant enterococci are only rarely identified in intra-abdominal infections, usually in the setting of tertiary peritonitis and substantial prior antimicrobial exposure. If this pathogen is cultured, linezolid or another antibiotic to which the organism is sensitive can be added.

Fungal coverage

Antifungal therapy generally is not recommended for patients with community-acquired intra-abdominal infections, a consideration that would apply to most patients with diverticulitis. Fungal peritonitis is encountered primarily in patients whose infections developed while they were receiving broad-spectrum antibiotics [19]. As such, empiric antifungal therapy could be considered in patients in whom a long course of medical therapy has failed and who require operative intervention. If not already given, antifungal therapy should be initiated in these patients if peritoneal cultures are positive for *Candida* [73]. Fluconazole is an appropriate agent for most patients with peritonitis caused by *C. albicans*, although some authorities have suggested that fungicidal agents such as echinocandins or amphotericin B have better efficacy. For patients with infections attributed to *C. glabrata* or *C. krusei*, which are resistant to standard doses of fluconazole, either voriconazole or an echinocandin can be used.

Duration of Therapy

For patients with complicated intra-abdominal infections, an unanswered question is the optimal duration of antimicrobial therapy. The current approach is for shorter

courses of therapy, especially in patients exhibiting a satisfactory clinical response. For patients with complicated intra-abdominal infections, treatment longer than five to seven days usually is not recommended [19,33].

At present, practice patterns with regard to the duration of antimicrobial therapy for diverticulitis remain highly variable. An approach similar to that used for complicated intra-abdominal infections would seem as appropriate as any other. Antibiotic therapy could be limited to five to seven days, as was recommended in the SIS and IDSA guidelines for complicated intra-abdominal infections [19,33]. Another option would be to stop antibiotics once the patient has defervesced, abdominal pain has resolved, and leukocytosis has improved [74]. Patients who do not respond to initial antimicrobial therapy should be re-evaluated with imaging studies to ensure there is no focus of infection necessitating intervention to achieve adequate source control. Arbitrary changes in the antibiotic regimen without a necessary source control procedure cannot be expected to be successful according to experience in patients with complicated intra-abdominal infections.

No published evidence indicates that treatment duration should be based on the extent of diverticulitis. It could be argued that patients with Hinchey III or IV diverticulitis have more extensive disease and therefore require longer antibiotic therapy. However, these patients usually are treated through a source control procedure, and the duration of antibiotic therapy should be the same as that recommended for patients with complicated intra-abdominal infections. Paradoxically, patients with Hinchey I diverticulitis could theoretically require longer treatment than those with Hinchey III or IV disease because typically, they do not undergo a source control procedure, which eliminates most of the infecting organisms. Thus, for patients with acute diverticulitis, it would seem reasonable to employ either a fixed duration of five to seven days of antimicrobial therapy or a clinically determined duration based on resolution of symptoms and signs of inflammation, regardless of the extent of disease.

Oral Antimicrobial Therapy

Patients who are hospitalized for acute diverticulitis should be given intravenous antibiotics initially, as oral absorption may be sporadic in the face of localized peritonitis. However, patients who respond to intravenous therapy may be candidates for oral therapy to facilitate hospital discharge (Table 3). In addition, a large number of patients are treated as outpatients with oral therapy alone.

A number of oral drugs are potentially useful as single agents or in combination regimens for treating patients with

TABLE 3. ORAL REGIMENS FOR ACUTE DIVERTICULITIS

Moxifloxacin ^a
Amoxicillin/clavulanic acid ^b
Ciprofloxacin ^c + metronidazole
Trimethoprim/sulfamethoxazole ^b + metronidazole

^aFood and Drug Administration approved for intra-abdominal infections.

^bNot FDA approved for intra-abdominal infections.

^cFDA approved for intra-abdominal infections when administered with metronidazole.

diverticulitis. The best evidence for the efficacy of an oral regimen comes from the study of Solomkin et al. [53], in which a switch to the use of oral ciprofloxacin + metronidazole was found to be as effective as continued intravenous therapy in the treatment of patients with complicated intra-abdominal infections. In other trials for complicated intra-abdominal infections, oral moxifloxacin was used as continuation therapy after intravenous moxifloxacin [56], and amoxicillin/clavulanic acid was used as continuation therapy after piperacillin/tazobactam or a carbapenem [33]. No prospective studies have investigated the use of oral antibiotics specifically for the treatment of diverticulitis.

In addition to ciprofloxacin, metronidazole, moxifloxacin, and amoxicillin/clavulanic acid, oral formulations of trimethoprim/sulfamethoxazole and clindamycin are available. Moxifloxacin and amoxicillin/clavulanic acid could be used as monotherapy for outpatient management of diverticulitis; the other agents would have to be combined to provide a regimen effective against both common gram-negative bacteria and anaerobes. The selection of a specific oral regimen can be based on several factors, including cost and convenience and the patient's tolerance. In addition, if a patient's condition improves on a given intravenous regimen, it might be desirable to use that same regimen as continuation oral therapy; however, this is applicable only to those agents that have both oral and intravenous formulations. No data indicate that switching to an oral regimen from another class of drugs has any adverse impact on outcome in the individual patient.

Summary

This review was undertaken to investigate a few questions regarding the use of antimicrobial agents in the management of acute diverticulitis. Unfortunately, a review of the literature indicates that these questions must remain mostly unanswered, at least according to current principles of evidence-based medicine.

- (1) Among the many antibiotics available to treat this disease, is any single agent or combination regimen superior?

No regimen has demonstrated superiority. Certainly, carbapenems and piperacillin/tazobactam have the broadest spectrum of activity, but there is no evidence that this translates into a clinical benefit. The use of some previously recommended agents, such as ampicillin/sulbactam and clindamycin, has been questioned because of changes in the susceptibilities of the bacterial species commonly involved in these infections. Other considerations in antibiotic selection are toxicity and ease of use. With regard to toxicity, in the absence of a specific patient reaction to a given agent, there seems little to differentiate most of the commonly used antibiotics; however, aminoglycosides would be less desirable because of their toxicity. With regard to ease of use, agents that can be given as monotherapy and can be administered once daily would seem advantageous. In addition, easy conversion to oral therapy might be desirable. Among the various agents, only fluoroquinolones offer the advantage of conversion to oral therapy without having to change the antibiotic. Finally, cost may be important, al-

though such data often are applicable only to a specific institution, and may vary according to specific insurance coverage for individual patients undergoing outpatient therapy.

- (2) What is the appropriate duration of antimicrobial therapy when treating diverticulitis?

There is no clinical evidence with which to answer this question properly. An approach similar to that employed for complicated intra-abdominal infections—limiting antimicrobial therapy to five to seven days—seems reasonable. Another option is to determine duration of therapy on the basis of resolution of the symptoms and signs of the infection.

- (3) When should antibiotic regimens be altered?

Again, there is little evidence to evaluate this issue specifically. A reasonable approach is to re-evaluate the patient after five to seven days, or sooner if there are signs of clinical deterioration. If initial management is deemed to have failed, further evaluation should include imaging or other clinical studies to determine whether the patient remains a candidate for nonoperative management or should undergo a source control procedure. Clearly, a failure to provide adequate source control, when needed, places the patient at high risk for an adverse outcome, irrespective of any changes in the antimicrobial regimen. For a patient receiving continued nonoperative management, the potential risk of resistant pathogens should be borne in mind when selecting further antimicrobial therapy.

- (4) What clinical conditions or patient risk factors (e.g., age or disease severity) might prompt a change in the general approach to the provision of antibiotics for this disease?

Certain patients are at higher risk for treatment failure because of co-morbid conditions and the severity of their septic complications. However, expanded antimicrobial therapy probably is most important in those patients who are at risk of harboring resistant pathogens. Patients who have had antimicrobial therapy or who are likely for other reasons to be colonized with resistant organisms may benefit from the selective use of regimens with expanded gram-negative coverage, and possibly anti-enterococcal and antifungal activities.

Overall, given the paucity of data directly applicable to antimicrobial therapy for diverticulitis, careful clinical studies to evaluate antibiotic regimens for this disease are warranted. Until such data are available, we are forced to rely on tradition, *in vitro* analyses, pharmacokinetic profiling, and indirect evidence from studies of complicated intra-abdominal infections to determine appropriate antimicrobial therapy for patients with acute diverticulitis.

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