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The Surgical Infection Society Guidelines on Antimicrobial Therapy for Intra-Abdominal Infections: Evidence for the Recommendations

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ABSTRACT

Revised guidelines for the use of antimicrobial therapy in patients with intra-abdominal infections were recently developed by the Therapeutic Agents Committee of the Surgical Infection Society (Mazuski et al., *Surg Infect* 2002;3:161–173). These were based, insofar as possible, on evidence published over the past decade. The objective of this document is to describe the process by which the Committee identified and reviewed the published literature utilized to develop the recommendations and to summarize the results of those reviews. English-language articles published between 1990 and 2000 related to antimicrobial therapy for intra-abdominal infections were identified by a systematic MEDLINE search and an examination of references included in recent review articles. If current literature with regard to a specific issue was lacking, relevant articles published prior to 1990 were identified. All prospective randomized controlled trials, as well as other articles selected by the Committee, were evaluated individually and collectively. Data with regard to patient numbers, types of infections, and results of interventions were abstracted. Studies were categorized according to their design, and all included trials were graded according to quality. On the basis of this evidence, the Committee formulated recommendations for antimicrobial therapy for intra-abdominal infections and graded those recommendations. After receiving comments from invited reviewers and the general membership of the Society, the guidelines were finalized and submitted to the Council of the Surgical Infection Society for approval. The final recommendations related to the selection of patients needing therapeutic antimicrobials, acceptable antimicrobial regimens, duration of antimicrobial use, and the identification and treatment of higher-risk patients. Although numerous publications pertaining to these topics were identified, but nearly all of the prospective randomized controlled trials represented comparisons of different antimicrobial regimens for the treatment of intra-abdominal infections. A few prospective trials evaluated the need for therapeutic antimicrobial therapy in patients with peritoneal contamination following abdominal trauma. The quality of these prospective trials was highly variable. Many did not limit enrollment to patients with complicated intra-

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abdominal infections, lacked blinding of treatment assignment, did not provide a complete description of the criteria used to determine therapeutic success or failure, failed to identify the reasons why patients were excluded from analysis, or did not include an intention-to-treat analysis. For many issues, no prospective randomized controlled trials were encountered, and guidelines had to be formulated using evidence from studies with historical controls or uncontrolled data, or on the basis of expert opinion.

INTRODUCTION

In 1992, the Antimicrobial Agents Committee (now the Therapeutic Agents Committee) of the Surgical Infection Society (SIS) published guidelines for the use of antimicrobial agents in patients with intra-abdominal infections [1]. These guidelines defined the types of infections that required antimicrobial therapy, characterized the bacteria likely to be involved in those infections, described the general principles for the use of antimicrobials, and recommended specific antimicrobial agents or combination regimens which were considered appropriate for treatment. The Therapeutic Agents Committee of the SIS has recently updated the original guidelines published in 1992, primarily using literature published since 1990 [2]. These revised guidelines represent an extension, but not a replacement of the original guidelines developed by Bohnen et al. [1].

In undertaking this revision, the Committee set as an additional goal the formal categorization of its recommendations according to current principles of evidence-based medicine. Although there is no universally accepted system for describing clinical evidence or recommendations [3], most authors employ terminology similar to that originally developed by the Canadian Task Force on the Periodic Health Evaluation [4]. Using this methodology, the published studies used to create recommendations are first categorized according to study design and quality, and then, in turn, the recommendations developed from these studies are graded according to the strength of evidence behind them.

In this article, we will first describe the processes by which the Committee selected and evaluated the literature relevant to these guidelines, and integrated these data to formulate the recommendations regarding antimicrobial therapy for patients with intra-abdominal infections. Then, the actual evidence used in developing the guidelines will be detailed separately with regard to the four major topics reviewed: (1) the selection of patients requiring therapeutic antimicrobials; (2) the duration of antimicrobial therapy; (3) appropriate antimicrobial regimens for treatment of patients with intra-abdominal infections; and (4) the identification and treatment of higher-risk patients for whom initial therapy of their infections is likely to fail.

GUIDELINE DEVELOPMENT

The initial impetus for the development of these revised guidelines came at the meeting of the Therapeutic Agents Committee in May 2000, following a directive from the Council of the SIS that the Committee undertake a formalized process of guideline development and review. The Committee proposed that a high priority be given to revising the previous position paper of the Society on the use of antimicrobial therapy for patients with intra-abdominal infections, since this document had not been revisited in nearly ten years, and was an issue of importance to the membership of the Society at large. The proposal to revise these guidelines was formally accepted by the Council in October 2000, with the Therapeutic Agents Committee directed to serve as the expert panel for this revision.

The initial deliberations of the Committee focused on the approach to be used in revising the previous guidelines. Over the past decade, the "science" of guideline development has undergone considerable evolution, and many organizations have produced guidelines related

to clinical issues. Among surgical organizations, the Eastern Association for the Surgery of Trauma (EAST) has been at the forefront in developing guidelines for the treatment of patients with surgical problems. Their approach to guideline development has been described in detail [5]. The Committee therefore selected this approach as its model for the preparation of these revised guidelines. The steps recommended by the EAST in guideline development are outlined in Table 1.

Scope of the guidelines

The Committee first sought to define the types of patients with intra-abdominal infections that would be covered by these guidelines, and then to identify specific questions to be addressed. In general, the Committee chose to restrict its focus to surgical patients with intra-abdominal infections, that is, those generally described as secondary or tertiary peritonitis, or intra-abdominal abscesses. Patients who would not be covered by these guidelines included those with primary peritonitis and infections associated with indwelling intra-abdominal catheters, and those with infections related to primary gynecological or genitourinary disorders. Patients with localized infections of an abdominal organ for which no primary source control procedure was performed, such as patients with acute diverticulitis or cholecystitis treated non-operatively, would also not be covered by the proposed recommendations. Thus, these guidelines would apply to patients described as having complicated intra-abdominal infections, that is, those requiring a surgical or radiologically guided procedure for control of the infection [6]. These restrictions are quite similar to those used previously by Bohnen et al. [1].

Table 1. Development of Clinical Practice Guidelines

Step	*Procedure*
1	Topic selection
2	Selection of a panel
3	Clarification of purpose and scope of the guidelines
4	Listing of goals and specification of questions
5	Assessment (grading) of scientific evidence
6	Establishing the recommendations
7	Drafting and validation of the document
8	Presentation
9	Implementation
10	Validation

Adapted from Pasquale [5].

In the initial discussions, the Committee also decided not to attempt a complete revision of the previous guidelines of Bohnen et al. [1]. Many of their descriptions, such as those related to the pathogenesis and microbiology of intra-abdominal infections, were still up to date and did not need revising. Instead, the Committee chose to focus on several treatment-related issues that had engendered discussion both in the published literature as well as at Society meetings during the past decade. Each issue was to be reviewed initially by a two- or three-member working group of the Committee, and then by the Committee as a whole. The issues and questions that were selected for discussion fell into four general areas:

Patient selection. Which patients should be treated with antimicrobials for intra-abdominal infections? What distinguishes intra-abdominal contamination from an established intra-abdominal infection? Are prolonged courses of antimicrobials warranted in patients who have contamination only? What constitutes prophylactic, as opposed to therapeutic, use of antimicrobials for intra-abdominal infections?

Duration of antimicrobial therapy. What is the optimal duration of antimicrobial therapy for patients with intra-abdominal infections? Can this be specified based on the type of intra-abdominal infection? Should clinical symptoms and signs be used to guide duration of antimicrobial therapy?

Recommended antimicrobial regimens. Which antimicrobial regimens can be recommended for the treatment of patients with intra-abdominal infections? Are any of these regimens of greater or lesser efficacy? Can oral antimicrobials be utilized in patients with intra-abdominal infections? How should aminoglycosides be utilized in these patients?

Identification and treatment of the higher risk patient. What risk factors identify patients likely

to experience failure of initial therapy? Can the antimicrobial regimen be intensified in such patients to decrease the risk of failure? Should higher–risk patients be treated empirically for enterococcal or fungal organisms? How should patients with tertiary peritonitis be treated?

Selection of the literature for review

In order to obtain the best evidence with which to address these questions, the Committee undertook a systematic search for all English-language articles on the use of antimicrobials for intra-abdominal infections published between 1990 and 2000. The 1990 limit was selected because the relevant literature up to 1990 had been available to the authors of the previous guidelines. The MEDLINE database was searched using multiple strategies, in which the names of specific antimicrobials or more general descriptors (e.g., cephalosporins) were paired with words and phrases indicating an intra-abdominal infection (e.g., peritonitis, intra-abdominal abscess, appendicitis). This initial search included studies that were in the MEDLINE database as of December 4, 2000.

At the outset, one goal of the Committee was to develop a database of all prospective randomized controlled trials published during this time period that related to the use of antimicrobial therapy for the treatment of intra-abdominal infections. These publications were believed to provide the best evidence for potential guidelines. Therefore, all abstracts obtained from this initial search strategy were screened in an effort to identify any publication that might feature this trial design. To uncover additional prospective randomized controlled trials missed by this screening process, the references of a number of authoritative review articles discussing treatment of intra-abdominal infections [7–19] were also examined. A search of the *Cochrane Database of Systematic Reviews* [20] was also performed, but this failed to identify additional relevant publications.

All articles identified by this initial screening process then received a preliminary review. Studies that were not prospective randomized controlled trials were excluded from the database. However, those publications could still be used for the development of specific recommendations if an individual working group believed that the study contained information relevant to the specific topic. In addition, prospective trials that examined prophylactic, but not therapeutic, use of antimicrobials, administered to patients who did not have established intra-abdominal infections were also eliminated from further consideration.

All remaining prospective randomized controlled trials were then reviewed by at least one member of the Committee to determine their suitability for inclusion in the database. Studies could be excluded from further consideration for several reasons established by the Committee. The decision to exclude any given prospective trial had to be confirmed by a consensus of the Committee as a whole. A few reports were excluded because they were found to be duplicate publications of the same trial. Under these circumstances, the publication that more thoroughly described the trial was included in the database. In addition, some trials enrolled patients with indications for antimicrobial use other than intra-abdominal infections. These other indications included pneumonia, bacteremia, and soft tissue infections. Generally, the Committee utilized such trials only if the clinical efficacy in patients with intra-abdominal infections was described separately from the overall group of patients, and there were at least 30 evaluable patients with intra-abdominal infections for whom data were available. A few studies permitted administration of additional antimicrobials on the basis of physician discretion, without any clear criteria for their use being specified in the protocol. These studies were excluded from the database if the final efficacy determination was obscured by the inclusion of such patients. Finally, some trials enrolled patients who did not undergo operative therapy of their intra-abdominal infections, and many studies included patients who did not need prolonged antimicrobial therapy for established infections, according to the previous criteria of Bohnen et al. [1] and the Infectious Disease Society of America (IDSA) guidelines [6]. Patients in this latter category included those with simple appendicitis or cholecystitis, and those with recent traumatic intestinal perforations or gastroduodenal perforations. Ultimately, the Committee chose to

include most of these studies in the database, as long as it appeared that the majority of evaluable patients had positive peritoneal cultures or diagnoses of complicated intra-abdominal infections requiring therapeutic antimicrobial therapy. However, studies in which most or all patients could have been treated with short-term antimicrobial therapy were excluded.

Not surprisingly, many facets of antimicrobial therapy for intra-abdominal infections were not addressed by prospective randomized controlled trials. Therefore, other studies that appeared relevant to the development of these guidelines were also selected from the body of literature identified during this screening process. Priority for review was given to epidemiological studies and investigations that utilized some type of controlled design, although articles expressing the opinions of experts in the field were also collected. The decisions to select additional studies for review was left to the working groups developing those areas of the guidelines, and ultimately approved by the Committee as a whole.

For some topics, there was a paucity of evidence published after 1990. Therefore, the individual working groups identified prospective randomized controlled trials and other studies published prior to 1990 that could be used to supplement the data obtained from later investigations. The prospective trials were included in the database, but a formal, systematic search to identify all such studies published prior to 1990 was not performed.

Evaluation of the evidence

The prospective randomized controlled trials selected for inclusion in the database, and all other studies judged to be relevant to the development of the guidelines were reviewed fully by at least one, and usually two members of the Committee. Details were abstracted with regard to the specific topic investigated, the study design, the types of patients entered and excluded from the study, and the results of the treatment interventions. The study design was classified using the nomenclature outlined by the EAST [5], and supplemented by descriptions utilized by the American Society for Parenteral and Enteral Nutrition [21] (Table 2). Essentially, Class I evidence was that obtained from prospective randomized controlled trials or meta-analyses of those trials, Class II evidence was that obtained from other prospective and retrospective controlled studies containing clearly reliable data, and Class III evidence was that obtained from uncontrolled studies, case reports, and expert opinion.

All prospective randomized controlled trials were further graded for quality using the system devised by Jadad et al. [22] (Table 3). This assessment assigns a quality score of 0–5 based on the adequacy of randomization, blinding, and description of patients excluded from the study. Reproducibility of the quality ratings was determined by having second members of the Committee, blinded to the first reviewers' scores, grade most studies. Replicate quality scores were nearly always within one point of each other, and no major discrepancies were identified. Minor discrepancies between the reviewers were resolved between the individual Committee members. Since no generally accepted system exists for assessing the quality of Class II and Class III evidence, these studies were not graded objectively.

The quality scores determined from these reviews proved to be quite low. Only about 20% of the trials received a score of 4 or 5; an additional 20% received a score of 3. The median quality score for all prospective trials was less than 2.

Among the individual components of the quality scores, randomization appeared to be adequate in nearly all the studies, and most trials were given 1 or 2 points toward the overall quality score. However, fewer than 30% of the trials were given any points for blinding, since most were not designed as double-blind trials. There were descriptions in some publications of attempts to obtain blinded assessments of outcome even though the study was designed as an open-label trial. Generally, these trials still did not meet the criteria specified by Jadad et al. [22] to ensure that they were free from bias.

The final point of the quality rating is determined by how the investigators have described patients excluded from the trial after randomization. Both the reasons for exclusions, and the

Table 2. Classification of Evidence

Class	Evidence
I	Prospective randomized controlled trials or meta-analyses of such trials.
II	Prospective studies without randomization or other studies in which data were collected prospectively, and retrospective analyses based on clearly reliable data. These include observational studies, cohort studies, prevalence studies, and retrospective case control studies.
III	Uncontrolled studies using retrospective data, such as clinical series or case reviews, and expert opinion.

Adapted from Pasquale [5] and Wolfe and Mathiesen [21].

numbers of patients excluded for each reason need to be detailed. The Committee identified this as a particular area of concern. Fully one-third of the publications provided an inadequate description of excluded patients. However, there were problems even among the studies that received credit for providing the necessary information. It became apparent that the criteria cited by the various investigators for excluding patients, that is, defining the clinically evaluable population, varied widely. Some of these criteria seemed quite arbitrary. In some trials, patients were excluded automatically if they were found subsequently to have a resistant organism isolated at the time of operative intervention, regardless of the results of initial empiric antimicrobial therapy. Others excluded patients who suffered adverse reactions to study drugs, even if they were switched to different antimicrobial agents because of the adverse reaction. In addition, some studies excluded patients who developed nosocomial infections outside of the abdominal cavity that required subsequent antimicrobial therapy. Although the final outcome in some of these patients is truly indeterminate, both the IDSA [6] and the SIS [23] guidelines for the design of these antimicrobial trials indicate that most of these patients can be considered evaluable, as long as success or failure of the therapy of the intra-abdominal infection is apparent at the time treatment of the nosocomial infection is initiated.

Many studies, as alluded to above, included patients in the final analysis who should have been excluded, because they did not have complicated intra-abdominal infections requiring antimicrobial therapy for greater than 24 h. Examples of such patients included those whose infections had not been confirmed with positive peritoneal cultures, those who had diagnoses not requiring prolonged antimicrobial therapy, such as non-perforated appendicitis, and those who had conditions such as recent gastroduodenal perforation suggestive of intra-abdominal contamination but not infection. In addition, a few studies included limited numbers of patients with gynecological, perirectal, or abdominal wound infections, or patients who were treated non-operatively for an intra-abdominal process such as acute diverticulitis. Unfortunately, the inclusions of such patients in the clinically evaluable populations limit the usefulness of these trials for determining optimal antimicrobial therapy of patients with complicated intra-abdominal infections.

Table 3. Quality Scoring of Prospective Randomized Controlled Trials

Randomization: Score one point if the study was described as randomized. Add one additional point if the method of randomization was described, and was appropriate (e.g., random number table, computer-generated list). Subtract one point if the method of randomization was inappropriate (e.g., alternate allocation, date of birth, hospital number).
Double blinding: Score one point if the study was described as double blind. Add one additional point if the method of double blinding was described and was appropriate (e.g., identical placebo, active placebo, dummy). Subtract one point if the method of blinding was inappropriate (e.g., no double dummy for comparison of an oral versus an injectable medication).
Withdrawals and dropouts: Score one point if the reasons why randomized patients were withdrawn from analysis were described, and the numbers of patients withdrawn for each reason were specified.

Adapted from Jadad et al. [22].

In reviewing all the evidence, the Committee attempted to apply a common descriptor of outcome to the data obtained from prospective trials. Most investigators reported a clinical success or clinical failure rate in evaluable patients. The Committee generally chose to use the investigators' reported clinical success rates, or recalculated clinical success rates when necessary, as its common measure of outcome.

For a number of reasons, however, the reported clinical success rates were not readily comparable across the various studies. As discussed above, investigators used different criteria to exclude patients from the final analysis, which changes the denominator used to calculate success rates. Of perhaps greater importance, investigators utilized different criteria to describe clinical successes and failures, which affects the numerator used in these calculations. Unfortunately, in some publications, the authors failed to specify exactly the criteria that were used to determine clinical success or failure. Moreover, many investigators did not utilize standards similar to those suggested by the IDSA and SIS [6,23] for evaluating clinical outcome in trials of antimicrobial therapy for intra-abdominal infections.

Many different examples of the variable definitions of clinical success or failure were encountered. In a number of studies, clinical failure was defined as the persistence of symptoms or signs of infection after a limited time period, whether or not a different antimicrobial treatment regimen was implemented. The SIS and IDSA guidelines indicate that these patients should be considered clinical treatment failures if additional antimicrobial therapy is utilized or another source control procedure is necessary to treat ongoing infection. As indicated previously, patients who developed nosocomial infections outside of the abdomen were also variably described. In some studies, these patients were considered successfully treated, in others, they were counted as treatment failures, and in still others, they were excluded from the final analysis. Also, in a few studies, patients with adverse events requiring a change to other antimicrobial agents were reported as treated successfully or were excluded from the final analysis, although these patients should generally be reported as having failed the initial antimicrobial treatment regimen.

Another problem with the reported success rates was the lack of uniformity in the timing of outcome reporting. In general, final outcome should be determined several weeks after the end of antimicrobial therapy, and patients for whom there is incomplete follow-up data should be considered unevaluable. In a number of publications, however, there was no indication as to when success or failure was determined. Other authors reported success rates only at the end of therapy, or provided only incomplete follow-up data after the end of therapy. In a few studies, it was apparent that patient outcomes had changed during subsequent follow-up, and that success rates reported at the end of therapy had been overstated. Nevertheless, the incomplete follow-up information made it impossible to verify the accuracy of success rates determined at later time points. Therefore, success rates reported at the end of therapy were used as the final measure of outcome in these studies if they were the only ones available that were based on an assessment of the entire clinically evaluable population.

Although it might have been desirable to reclassify patient outcomes to bring them more into line with the SIS and IDSA criteria [6,23], this would rarely have been possible because of the limited descriptions of unsuccessful clinical outcomes provided in most publications. Ultimately, the Committee accepted most of the investigators' reported success rates at face value, and only modified them for a few selected reasons to improve uniformity. If the investigators had not already done so, patients who were given a final outcome of "improved" or some similar adjective were included among the successfully treated patients in recalculating clinical success rates. Patients designated as "improved" generally required no further antimicrobial therapy, although they might not have completely resolved all symptoms and signs of infection. The Committee also recalculated some success rates by excluding patients with indeterminate outcomes from the denominator, if this had not already been done. In a few studies, no clinical success or failure rate was reported, but a description of the adverse outcomes that occurred in patients enrolled in

the study was provided. For these studies, the success rate was calculated as best as possible using the available information.

Interpretations of outcome were also influenced strongly by the manner in which investigators reported surgical site infections ("wound infections"). Most studies counted such patients as therapeutic failures, which is consistent with the IDSA and SIS criteria [6,23]. In some trials, though, patients with superficial surgical site infections were considered to be treated successfully as long as no other complications occurred. Since the development and identification of superficial surgical site infections in patients with intra-abdominal infections may relate more to surgical decisions regarding wound closure than to the utility of a specific antimicrobial regimen, it has been recommended that adverse outcomes due only to superficial surgical site infections be reported separately from other failures [24].

In some of these studies, in fact, virtually all the clinical failures were due to "wound infections." In order to evaluate more serious failures apart from those due to superficial surgical site infections, when possible, the Committee determined the rates of these infections from the information available in the publications. Further, the Committee calculated additional clinical success rates in which patients with isolated superficial surgical site infections were not counted as treatment failures. For these calculations to be valid, however, the numbers of patients who failed therapy exclusively because of superficial surgical site infections had to be unambiguously stated. In calculating these additional success rates, patients with deep surgical site infections, and patients who had reasons aside from superficial surgical site infections for failing therapy were still considered as unsuccessfully treated. Although these recalculated success rates are clearly subject to interpretational error, they do provide an additional measure with which to compare different trials of antimicrobial therapy for intra-abdominal infections, particularly when superficial surgical site infections account for many of the reported adverse outcomes.

By considering the outcome in all patients, an intention-to-treat (ITT) analysis helps ensure that issues related to patient exclusions and indeterminate outcomes have not unduly biased study results. In a few of the trials of antimicrobials for intra-abdominal infections, an ITT analysis was provided. In other trials, a modified ITT analysis was performed. For these modified ITT analyses, patients might be excluded because they did not have an intra-abdominal infection identified at the time of surgical intervention, or they did not receive study medications for some reason. Unfortunately, most publications did not include the results of either an ITT or a modified ITT analysis. Many times, only the results obtained from the clinically evaluable patients were reported.

Other reviewers [24,25] have previously identified many of the same problems in trial design, implementation, and interpretation that were prevalent in the publications reviewed by the Committee. Overall, though, it appeared that trial quality had improved somewhat over the decade. Several recent large multi-institutional trials were conducted according to the principles outlined by the IDSA and SIS. Nevertheless, for the database as a whole, relatively poor quality data was the rule rather than the exception. Although potentially desirable, the Committee did not believe that it would be possible to rely exclusively on the larger, higher-quality studies for developing guidelines without limiting greatly the scope of the recommendations.

Ultimately, the Committee attempted to integrate the evidence in the database by using investigators' reported success rates in clinically evaluable patients as a means of comparing outcome across studies. Where available, the results of recalculated success rates excluding patients who failed therapy because of superficial surgical site infections and the results of ITT analyses were also utilized. However, the Committee recognizes that the interpretation of these success rates is problematic because of the numerous methodological issues described above. Therefore, these reported clinical success rates can only be used as a rough guide to the utility of various interventions, particularly when such interventions have not been compared directly in prospective trials.

Formulation and approval of the guidelines

Based on this and other evidence, the individual working groups drafted provisional guidelines in their particular area of investigation, and graded those recommendations. For grading, the Committee chose the relatively simple system outlined by the EAST [5], supplemented by descriptions employed by the American Society for Parenteral and Enteral Nutrition (Table 4) [21]. Although this grading system is less complex than others, it still allows a straightforward characterization of the evidence behind each recommendation. Level 1 guidelines are those having good research-based evidence to support the recommendation, which usually requires relatively homogeneous Class I evidence. Generally, the Committee required consistent evidence from at least two prospective randomized controlled trials to justify a Level 1 recommendation. Level 2 guidelines are based on reasonable research-based evidence, which may indicate some heterogeneity in the results of prospective randomized controlled trials, or the need to rely primarily on Class II evidence to support the recommendation. Level 3 guidelines are those based on Class III evidence and expert opinion. Although Level 1 guidelines can be considered standards of care, the evidence behind recommendations classified as Level 2 or Level 3 is insufficient for them to be so considered. Level 3 recommendations, in particular, identify issues that should be addressed by additional prospective randomized controlled trials or other rigorously-conducted studies.

The entire Committee then refined the recommendations drafted by each working group through a process of iterative consensus. A consensus on the grading of each recommendation was also reached. A preliminary draft of the guidelines and the evidence behind them was then submitted to two independent reviewers from the Society, who were not members of the Committee. The proposed guidelines were presented at the 21st Annual Meeting of the SIS (May 3–5, 2001, Snowbird, UT), following which the two discussants provided their in-depth critiques of the recommendations. An open forum was also held to allow the general membership of the Society to comment on the proposed guidelines.

These critiques and discussions were then used to modify the guidelines into their present form. After final consensus was achieved, the Committee submitted these guidelines along with supporting materials to the Council of the SIS. The Council has approved these guidelines as the official position of the SIS with respect to antimicrobial therapy for patients with intra-abdominal infections.

PATIENT SELECTION

Most patients undergoing abdominal procedures receive antimicrobials in the perioperative period. Much of this use is intended as prophylaxis, primarily to prevent surgical site infections. Prophylactic antimicrobials seldom should be used for longer than 24 h; a single dose of antibiotic is sufficient for most procedures. The use of prophylactic antimicrobials is not covered under these guidelines.

The decision to treat a patient with therapeutic (non-prophylactic) antimicrobials re-

Table 4. Rating Scale for Recommendations

Level	*Recommendation*
1	Recommendation based on good research-based evidence. Supported primarily by homogeneous, prospective, randomized controlled trials, although strong Class II data may be the basis of the recommendation when the issue is not amenable to study with a prospective randomized controlled trial.
2	Recommendation based on fair research-based evidence. Supported by limited data from prospective, randomized controlled trials, or from other prospective or retrospective analyses with good study design, and strongly supported by expert opinion.
3	Recommendation based primarily on limited or uncontrolled data and supported by expert opinion.

quires that an established intra-abdominal infection be present. Therapeutic antimicrobials are defined here as those that are given for greater than 24 h. To fulfill the diagnosis of an established intra-abdominal infection, not only must a normally sterile area of the abdominal cavity be contaminated with infectious material, but also an inflammatory focus must have become established because of that microbial inoculum. From the perspective of the surgeon, this corresponds to an infected site that cannot be eradicated completely with the primary source control procedure.

The presence of infectious material, which is a prerequisite for the development of an intra-abdominal infection, is usually apparent at the time of the initial source control procedure. An obvious bowel perforation or the presence of enteric fluid implies that contamination with infectious material has occurred. Occasionally, purulent peritoneal fluid without an obvious enteric source is identified, and it may be less clear that infectious material is actually present. Under these circumstances, Gram stain and culture of the fluid may be performed to determine if microorganisms are actually present, although these tests prove ambiguous on occasion.

Contamination of the abdominal cavity by microorganisms is not in itself synonymous with an established intra-abdominal infection. The duration of the contamination and the intensity of the reaction must be sufficient to allow for the development of an inflammatory focus. The abdominal cavity probably needs to be exposed to infectious material for at least 12–24 h to allow an intra-abdominal infection to become established. The source and quantity of the infectious material contaminating the abdomen influences greatly the size of the microbial inoculum, and thereby the rapidity with which an infection develops. Nonetheless, there are no absolute criteria for determining if intra-abdominal contamination has progressed to an established infection. Ultimately, the clinician must use the clinical history, radiographic examinations, and direct intra-operative observations to make this judgment.

The issue as to whether or not an established intra-abdominal infection is present generates much of the controversy regarding the selection of patients for therapeutic antimicrobial therapy. There are clearly patients who fall into the gray area between contamination and established infection. Such patients include those who sustained heavy intra-abdominal contamination before or during an operative procedure, and those who have an infected focus within the abdominal cavity confined to a specific organ that can be eradicated by an operative procedure. The need for therapeutic antimicrobials in such patients should be based, in as much as possible, on the results of prospective studies of antimicrobial therapy carried out in similar patients.

Summary of findings

By far the best evidence concerning which patients need therapeutic antimicrobials comes from studies of patients with traumatic bowel perforations. Based on studies available at the time, Bohnen et al. [1] recommended that patients with traumatic bowel perforations operated on within 12 h receive 24 h or less of antimicrobial therapy. Three large prospective randomized controlled trials published in the past decade have provided additional evidence to support that recommendation. These studies compared the use of short-term versus longer-term antimicrobial therapy in patients with penetrating abdominal trauma [26–28]. Two of these studies [26,28] were restricted to patients with hollow viscus injuries as a result of penetrating trauma. Nearly half of the patients in the third study also had such injuries [27]. In the three studies combined, 852 patients were evaluated who had been randomized to receive 24 h versus 5 days of perioperative antibiotics. There were no significant differences between the two study groups in any of the trials with respect to the numbers of patients developing intra-abdominal infections, which averaged 6–10% in both groups (Table 5). The total numbers of infections, including those outside the abdomen, also did not appear to be influenced by the duration of antimicrobial treatment. Thus, in patients with penetrating abdominal trauma and hollow viscus injury, there does not seem to be any benefit to the use of prolonged antimicrobial therapy, and prophylactic antibiotics administered for 24 h or less are appropriate for these patients.

Table 5. Prospective Randomized Controlled Trials of Antimicrobial Duration for Penetrating Abdominal Trauma

Reference	*Antimicrobial agents*	*Specified treatment duration*	*Number of patients enrolled*	*Number of evaluable patients*	*Reported success rate*	*Percentage of patients with sSSI*	*Success rate excluding isolated sSSI*	*ITT analysis*	*Mortality*	*Percentage of patients with hollow viscus injury*	*Quality score*	*APACHE II scoring?*
[26] Fabian, 1992	Cefoxitin 2 g q6h or Cefotetan 2 g q12h	1 day	NR	118	92%[1]	17%[2]	92%[3]	NR	3%	100%	4	No
		5 days		117	90%[1]	18%[2]	90%[3]		3%	100%		
[27] Bozorgzadeh, 1999	Cefoxitin 1 g q6h	1 day	314	148	84%[1]	10%	94%	NR	0%	41%	2	No
		5 days		152	83%[1]	11%	94%		0%	56%		
[28] Kirton, 2000	Ampicillin/sulbactam 3 g q6h[4]	1 day	158	NR[5]	NR[6]	1%	N/A	90%[1,7]	3%	100%	4	No
		5 days	159			0%		92%[1]	1%	100%		

[1]Only patients who had abdominal infections were considered treatment failures for these calculations of success rates.
[2]Rates of sSSI were determined only in patients who had their wounds closed.
[3]Patients with sSSI were not considered treatment failures.
[4]Ampicillin/sulbactam dosages were modified according to renal function.
[5]The numbers of excluded patients were not reported.
[6]Only an ITT analysis was reported.
[7]The success rate was 91% if a patient with an isolated sSSI was not considered a treatment failure.

It is important to note that all patients in these trials underwent surgical therapy fairly soon after the injury was sustained. Patients who were not operated on early or had missed injuries were excluded from these studies. The guidelines of Bohnen et al. [1] recommended short-term antimicrobial therapy only for those patients whose perforations had been treated surgically within 12 h. Although this time point was not directly ascertained on the basis of prospective data, it still represents a reasonable estimate of the time required for major contamination to evolve into an established infection.

Although these trials enrolled only patients with penetrating abdominal trauma, it seems reasonable to apply the results to other patient groups. Examples of such patients include those who have sustained hollow viscus injuries as a result of blunt trauma and those who have received an iatrogenic bowel injury, such as a colonoscopic perforation of the colon. Again, this consideration would apply only if the operative procedure was performed expeditiously. These results should also apply to patients who have inadvertent enteric contamination during elective abdominal procedures, since the short duration of contamination should not result in an established infection. In these additional patient groups it seems unlikely that prolonged exposure to antimicrobials would produce a clinical benefit that was not evident in patients who had sustained penetrating hollow viscus injury.

Because of the low numbers of bacteria normally found in the stomach and duodenum, perforations of the gastrointestinal tract above the ligament of Treitz generally result in much less intra-abdominal contamination than perforations of the distal small bowel or colon. Bohnen et al. [1] indicated that patients with gastroduodenal perforations less than 24 h old did not need to be treated with therapeutic antimicrobials. Although a definitive study of this has not been performed, very limited data and expert opinions indicate that gastroduodenal perforations repaired early require less than 24 h of antimicrobial therapy [29–31].

Patients who had an infected focus that could be eradicated fully at the time of surgical intervention also do not require therapeutic antimicrobials, according to the previous guidelines [1]. Examples of these patients include those with non-perforated appendicitis, acute or gangrenous cholecystitis, or bowel necrosis without perforation. Treatment of such patients with prophylactic antimicrobial therapy was examined in two series of patients. Andåker et al. [29] described 147 patients with acute or gangrenous appendicitis, 18 patients with cholecystitis, and 52 patients with small bowel or colonic obstructions who were treated with antimicrobials for 24 h or less. Clinical success rates in these three groups of patients were 98%, 100%, and 90%, respectively (Table 6). Schein et al. [30] described a series of 92 patients, among whom were 55 with acute or gangrenous appendicitis, 21 with acute or gangrenous cholecystitis, and four with small bowel necrosis without perforation. These patients were treated according to a protocol specifying a maximum of 24 h of perioperative antibiotics. There were no major intra-abdominal infectious complications in these patients, and only 4% of the patients developed superficial surgical site infections (Table 6). Overall, infection rates in both of these series were comparable to those found in contemporary literature. Thus, there is reasonable evidence that antimicrobial therapy can be limited to 24 h or less in patients with acute or gangrenous appendicitis, acute or gangrenous cholecystitis, and those with bowel obstruction or bowel necrosis due to a vascular accident or strangulation, in whom there is no evidence of perforation (Table 7). However, these recommendations do not apply to patients whose infection has extended beyond the initial anatomic focus and who have purulent, infected, peritoneal fluid. Since these patients have established intra-abdominal infections, therapeutic antimicrobial therapy is warranted. The guidelines regarding patient selection for use of therapeutic antimicrobials are summarized in Table 8.

DURATION OF ANTIMICROBIAL THERAPY

Although patients who do not have established intra-abdominal infections can be treated with antimicrobials for 24 h or less, the

TABLE 6. STUDIES IN WHICH DURATION OF ANTIMICROBIAL THERAPY WAS LIMITED ACCORDING TO DIAGNOSIS

Reference	*Antimicrobial agents*	*Diagnosis*	*Specified treatment duration*	*Number of patients treated*	*Reported success rate*	*Percentage of patients with sSSI*	*Success rate excluding isolated sSSI*	*Mortality*	*Quality score*	*APACHE II scoring?*
[29] Andåker, 1987	Gentamicin 160 mg, then 80 mg q8h[1] or Fosfomycin 4 g q6h + Metronidazole 500 mg q8h	Acute appendicitis	Perioperative only	55	98%	NR[3]	N/A	NR	N/A	NR
		Gangrenous appendicitis	24 h	92	98%					
		Gangrenous cholecystitis		18	100%					
		Small or large bowel obstruction		52	90%					
		Perforated appendicitis	5 days	53	94%					
		Gastroduodenal perforation		17	88%					
		Small bowel necrosis		3	100%					
		Peritonitis (any source)		84[2]	93%					
[30] Schein, 1994	Ampicillin 1 g[4] + Gentamicin 120 mg[4] + Metronidazole 500 mg[4] or	Acute appendicitis	Perioperative only	34	97%	3%	100%	0%	NA	No
		Acute diverticulitis		2						
		Acute cholecystitis		10						
		Bowel necrosis without perforation		4						
		Early (<12 h) gastroduodenal perforation		5						
		Early (<12 h) traumatic bowel perforation		5						
		Gangrenous appendicitis	24 h	32	94%	6%	100%	3%		
		Gallbladder necrosis		21						
		Gallbladder empyema		11						
		Perforated appendicitis[6]	48 h	23						
		Perforated cholecystitis[6]		14						

TABLE 6. STUDIES IN WHICH DURATION OF ANTIMICROBIAL THERAPY WAS LIMITED ACCORDING TO DIAGNOSIS (CONT'D)

Reference	*Antimicrobial agents*	*Diagnosis*	*Specified treatment duration*	*Number of patients treated*	*Reported success rate*	*Percentage of patients with sSSI*	*Success rate excluding isolated sSSI*	*Mortality*	*Quality score*	*APACHE II scoring?*
	Ceftriaxone 1 g[4] + Metronidazole 500 mg[4,5]	Perforated diverticulitis[6]	48 h	2	88%	10%	98%	2%		
		Perforated colon cancer[6]		4						
		Late (>12 h) gastroduodenal perforation[6]		3						
		Late (>12 h) traumatic bowel perforation[6]		1						
		Strangulated small bowel[6]		1						
		Perforated appendicitis[7]	3–5 days	8	83%	13%	96%	4%		
		Perforated cholecystitis[7]		6						
		Gastroduodenal perforation[7]		3						
		Strangulated small bowel[7]		4						
		Perforated colon cancer[7]		2						

[1]Gentamicin dosing was modified according to serum drug concentrations.
[2]This value includes the patients listed above with perforated appendicitis, gastroduodenal perforation, or small bowel necrosis, as well as a few patients with other conditions.
[3]All patients who failed had sSSI; some patients failed because of unspecified additional reasons.
[4]Dosing intervals were not specified.
[5]The ceftriaxone plus metronidazole regimen was used for patients with renal dysfunction.
[6]Patients in this group had localized peritonitis only.
[7]Patients in this group had diffuse, generalized peritonitis.

Table 7. Conditions for which Therapeutic Antimicrobials (>24 h) Are Not Recommended

Traumatic and iatrogenic enteric perforations operated on within 12 h.
Gastroduodenal perforations operated on within 24 h.
Acute or gangrenous appendicitis without perforation.
Acute or gangrenous cholecystitis without perforation.
Transmural bowel necrosis from embolic, thrombotic, or obstructive vascular occlusion without perforation or established peritonitis or abscess.

optimal duration of antimicrobial therapy for patients with established intra-abdominal infections remains controversial. There is very little Class I evidence that can be used to evaluate this topic, and expert opinions vary widely. In many prospective trials, duration of therapy has been left to the discretion of the investigator. Thus, antimicrobial therapy has been permitted for 3–14 days or more, and few criteria have been specified for eventual discontinuation of antimicrobials.

There is little agreement even with regard to the clinical determinants that should be used in establishing optimal duration of treatment. Some recommend that a fixed duration of antimicrobial therapy be designated at the time of the initial surgical intervention, based on the specific pathological findings. Others advocate continuation of antimicrobial therapy until the patient's symptoms and signs of infection have resolved. Still others promote a combined approach.

One difficulty in determining the optimal duration of therapy is that a remarkably diverse number of conditions are described as intra-abdominal infections. These vary from relatively minor infections, such as a peri-appendiceal abscess, to severe infections, such as a massive retroperitoneal infection associated with extensive peri-pancreatic necrosis. Patients with the former conditions might be treated adequately with very short courses of antimicrobials, whereas patients with the latter conditions might need more prolonged therapy. In fact, it may be impossible to achieve adequate source control in patients with these latter conditions, and antimicrobial therapy may ultimately be unsuccessful, regardless of its duration.

One potential approach to the diversity of conditions described as intra-abdominal infections would be to utilize systems that stratify patients according to the type and source of infection, such as that outlined by Meakins et al. [32]. Such systems could define cohorts of patients for investigations of optimal duration of antimicrobial therapy. Unfortunately, such stratification schemes have not been used widely in clinical trials up to now.

Thus, there has not yet been a sufficiently powered, prospective randomized controlled clinical trial performed that has evaluated adequately the duration of antimicrobial therapy for patients with intra-abdominal infections. This lack of data may be explained by the logistical difficulties of studying this complex population of patients, as well as the lack of a commercial incentive to carry out such trials, whose results might lead to decreased use of antimicrobials. The evidence that can be used to formulate recommendations on this topic, therefore, is limited to that obtained from small prospective studies, retrospective studies, and expert opinions.

Summary of findings

There is a growing consensus that prolonged courses of antimicrobial agents are not necessary for many patients with intra-abdominal infections. In the previous guidelines, Bohnen et al. [1] recommended 5–7 days of antimicrobial ther-

Table 8. Guidelines for Selection of Patients who Require Therapeutic (>24 h) versus Prophylactic Antimicrobials (<24 h)

1. Patients with peritoneal contamination due to traumatic or iatrogenic bowel injuries repaired within 12 h (Level 1), and those having gastroduodenal perforations less than 24 h old (Level 3) are not considered to have established intra-abdominal infections, and should be treated with prophylactic antimicrobials for 24 h or less.
2. Patients with a fully removable focus of inflammation, such as those with acute or gangrenous, but non-perforated appendicitis or cholecystitis, and those with bowel necrosis or obstruction without perforation or peritonitis, should be treated with prophylactic antimicrobials for 24 h or less (Level 2).
3. Patients with more extensive conditions than those noted above should be treated as having established infections, and given therapeutic antimicrobials for greater than 24 h (Level 3).

apy for most patients. More recently, Wittmann and Schein [31] proposed even shorter durations of therapy. Although there are no Class I studies addressing this issue specifically, some evidence supporting shorter duration of antimicrobial use can be gleaned from reports of protocols that limited the duration of therapy based on the initial operative findings. In the study described previously by Andåker et al. [27], antimicrobials were limited to 5 days in a cohort of 84 patients with intra-abdominal infections. Similarly, in the study by Schein et al. [28] antimicrobials were limited to 48 h in 48 patients with localized peritonitis, and to three to five days in 23 patients with diffuse peritonitis. In both studies, the reported success rates for these patients ranged from 83%–100% (Table 6). These success rates are comparable to those reported in contemporary literature for patients with similar disease processes, who generally received longer courses of antimicrobials.

As an alternative to a fixed duration of therapy, antimicrobials could be discontinued when the patient's symptoms and signs of infection resolve. The risk of treatment failure appears to be quite low in patients who have no clinical evidence of infection at the time of cessation of antimicrobial therapy [33,34]. This usually implies that the patient's temperature and white blood cell count has normalized, and bowel function has returned. In a Class II study by Smith et al. [35], patients with peritonitis from appendiceal and non-appendiceal sources had antimicrobials discontinued after four days of therapy if clinical evidence of infection had abated. Compared to historical controls, these patients received fewer doses of antibiotics and had no increase in infectious complications (Table 9). In a prospective randomized controlled trial, Taylor et al. [36] evaluated the need for prolonged antimicrobial therapy in two groups of patients with complicated appendicitis. In one group, all patients received a minimum of 5 days of intravenous antibiotics, but in the second group, no minimum duration of antibiotic therapy was specified. Eventual discontinuation of antibiotics in both groups was based on clinical criteria. The duration of antibiotic use was significantly longer in the group assigned to a minimum of 5 days of antimicrobial therapy, but there was no difference between the two groups in the numbers of infectious complications. Thus, limiting the duration of antimicrobial therapy on the basis of clinical signs and symptoms seems reasonable according to the evidence provided by these studies. Unfortunately, this conclusion is clouded somewhat because many of the patients in these studies did not need prolonged antimicrobial therapy, as they had gangrenous appendicitis or intra-abdominal contamination only.

Although these data suggest that antimicrobial therapy can be limited in patients with intra-abdominal infections who show improvements in their clinical signs and symptoms, they do not address the problematic patient who does not show similar improvements after a prescribed course of antimicrobials. Several investigators have determined that patients with persistent clinical evidence of infection at the time of discontinuation of antimicrobials are likely to develop subsequent infectious complications. Studies by Lennard et al. [33,34], among others, identified persistent fever and leukocytosis as predictors of clinical failure.

When patients have persistent clinical signs of infection, the tendency of many clinicians is to prolong the course of antimicrobial therapy, using the same or different agents. However, there are few, if any data demonstrating that this approach improves patient outcome. In fact, Lennard et al. [33,34] did not advocate such an approach. In their studies, most of the patients with persistent clinical signs of infection were eventually found to have a new or recurrent intra-abdominal infection. Thus, they felt that a search for the source of the persistent clinical signs, along with an appropriate procedure to adequately control that source, would have ultimately been much more beneficial than either prolongation of the same antimicrobial therapy or a change to other agents.

However, there is some evidence that a more prolonged course of antimicrobials is warranted in certain highly selected patients. Visser et al. [37] analyzed retrospectively a series of patients managed using an open abdominal technique because of refractory peritonitis. Decreased duration of antimicrobial treatment was identified as a risk factor for failure in these patients. The authors recommended that antimicrobials not be discontin-

TABLE 9. STUDIES IN WHICH DURATION OF ANTIMICROBIAL THERAPY WAS LIMITED ACCORDING TO CLINICAL FINDINGS

Reference	*Antimicrobial agents*	*Diagnosis*	*Specified treatment duration*	*Number of evaluable patients*	*Reported success rate*	*Percentage of patients with sSSI*	*Success rate excluding isolated sSSI*	*Mortality*	*Duration of antimicrobial therapy*	*Quality score*	*APACHE II scoring?*
[35] Smith, 1985	Tobramycin 1.5 mg/kg q8h + Metronidazole 500 mg q8h	Gangrenous or perforated appendicitis	4 days, then discontinuation per protocol[1]	24	96%[2]	4%	100%[2]	0%	12.7 doses	N/A	NR
		Other intra-abdominal infections		23	70%[2]	30%	100%[2]	4%	21.4 doses[3]		
		Gangrenous or perforated appendicitis	Discontinuation per physician discretion	21	95%[2]	5%	100%[2]	0%	16.4 doses		
		Other intra-abdominal infections		21	77%[2]	23%	100%[2]	6%	28.1 doses[3]		
[36] Taylor, 2000	Ampicillin/ sulbactam[4]	Gangrenous or perforated appendicitis	No minimum treatment duration[5]	48[6]	88%	8%	96%	0%	4.3 days[7,8]	2	NR
			Minimum 5 days of intravenous antibiotics[5]	46[6]	87%	4%	91%	0%	5.9 days[7,8]		

[1]The protocol criteria for discontinuation of antibiotics included a temperature of less than 38°C orally or 38.5°C rectally during the preceding 24 h, a reduction of the white blood cell count by 10% or more, the passage of flatus, and two of four minor criteria (absence of rebound tenderness, absence of wound infection, negative blood culture, and absence of clinical or radiological evidence of an abscess).

[2]The only complications reported were sSSI. It is uncertain if other therapeutic failures occurred.

[3]In patients with non-appendiceal disease, the duration of antimicrobial therapy was significantly shorter ($p < 0.001$) in the group treated according to the protocol.

[4]The antimicrobial regimen in most patients was ampicillin/sulbactam preoperatively and postoperatively followed by oral cephalexin after cessation of intravenous therapy. Dosages were not reported.

[5]Discontinuation of antibiotics in both groups was based on clinical criteria including resolution of fever, improved abdominal symptoms and signs, return of bowel function, and, in some patients, a decrease in leukocytosis.

[6]One patient enrolled in the group with no minimum duration specified, and two patients enrolled in the group specifying a minimum of 5 days of therapy were excluded from the analysis.

[7]These are days of intravenous antibiotic therapy, and do not include days of oral antibiotics.

[8]The duration of antimicrobial therapy was significantly shorter ($p = 0.014$) in the group with no specified minimum treatment duration.

ued in such patients if there was ongoing clinical evidence of infection. It seems reasonable to utilize a longer course of antimicrobial therapy in similar patients in whom it is difficult or impossible to achieve primary source control. However, such considerations apply to only a small number of patients, such as those with infected peri-pancreatic necrosis, in whom an adequate primary source control procedure may not be feasible, or those with tertiary peritonitis, who have repeatedly failed previous therapeutic efforts.

Based on the limited data and the opinions of members of the SIS, therefore, the Committee recommends that antimicrobial therapy be limited to no more than five to seven days for most patients with complicated intra-abdominal infections (Table 10). It seems reasonable to base the maximum duration of antimicrobial therapy on the extent of the infection identified at the time of the initial source control procedure, and to discontinue therapy when clinical symptoms and signs of infection abate. In patients with persistent clinical evidence of infection after the completion of a predetermined course of antimicrobial therapy, an attempt should be made to determine the source of that problem. Patients with persistent or recurrent intra-abdominal infections are unlikely to respond just to prolongation of antibiotic therapy with the same or a modified regimen, but rather will likely require additional therapeutic efforts to achieve definitive source control. Patients with nosocomial infections at extra-abdominal sites will need appropriate antimicrobial therapy directed at those problems. If a patient has persistent clinical symptoms and signs, but no evidence of a new or persistent infection is uncovered after a careful investigation, a trial observation off all antimicrobial therapy is warranted, since the persistent clinical symptoms and signs may be the result of ongoing sterile tissue inflammation or drug-induced hyperthermia, and not due to infection [31]. However, it is prudent to monitor carefully such patients for recurrent intra-abdominal infection, which could still develop.

Table 10. Guidelines for the Duration of Antimicrobial Therapy for Established Intra-Abdominal Infections

1. Antimicrobial therapy of most established intra-abdominal infections should be limited to no more than 5 (Level 2) to 7 days (Level 3). The duration of antimicrobial therapy for intra-abdominal infections can be based on the intra-operative findings at the time of initial intervention (Level 3). Antimicrobial therapy can be discontinued in patients when they have no clinical evidence of infection such as fever or leukocytosis (Level 2).
2. Continued clinical evidence of infection at the end of the time period designated for antimicrobial therapy should prompt appropriate diagnostic investigations rather than prolongation of antimicrobial treatment (Level 3).
3. If adequate source control cannot be achieved, a longer duration of antimicrobial therapy may be warranted (Level 3).

ANTIMICROBIAL REGIMENS FOR INTRA-ABDOMINAL INFECTIONS

The fundamental principles of antimicrobial therapy for intra-abdominal infections were outlined over 25 years ago, and have not changed substantially in the interim. These principles were based on experimental models of intra-abdominal infections and subsequent clinical studies, which demonstrated that antimicrobial regimens should cover common aerobic/facultatively anaerobic Enterobacteriaceae such as *Escherichia coli*, and anaerobic organisms, particularly *Bacteroides fragilis* [38,39]. Although the initial regimens shown to be efficacious included an aminoglycoside, such as gentamicin, combined with an antianaerobic agent, such as clindamycin, the repertoire of antimicrobial agents has expanded greatly over the past two decades, and many single agents or combination regimens are now available for the treatment of patients with intra-abdominal infections.

In the previous guidelines, Bohnen et al. [1] identified second-generation cephalosporins with anaerobic coverage (cefoxitin, cefotetan, cefmetazole), ticarcillin/clavulanic acid, and imipenem/cilastatin as acceptable single-agent therapy. Appropriate combination regimens included an aminoglycoside (gentamicin, tobramycin, netilmicin, or amikacin) plus an antianaerobic agent (clindamycin or metronidazole), a third-generation cephalosporin (cefotaxime, ceftizoxime, ceftazidime, or ceftriax-

one) plus an antianaerobic agent, and aztreonam plus clindamycin for the treatment of patients with intra-abdominal infections. Over the past decade, a number of prospective randomized controlled trials have evaluated further these agents, as well as others such as ampicillin/sulbactam, piperacillin/tazobactam, meropenem, ertapenem, and cefuroxime, cefepime, ciprofloxacin combined with metronidazole, for which little definitive information was available prior to 1990. The results of these and selected earlier trials are summarized individually in Table 11, to which the reader is referred during the subsequent discussions of specific antimicrobial regimens. The Committee used this body of Class I data, supplemented by limited amounts of Class II and Class III data, to expand the list of acceptable antimicrobial regimens for the treatment of patients with complicated intra-abdominal infections.

Ideally, these data would identify those antimicrobial agents most effective for treating intra-abdominal infections. The Committee could then designate those agents as preferred or first-line therapy for this indication. However, the Committee found it impossible to make such determinations on the basis of therapeutic superiority. Few trials reported a statistically significant difference in outcome between treatment arms, and those that did so tended to be smaller, lower-quality studies. Moreover, in several studies, the observed differences in outcome were related primarily to rates of superficial surgical site infections, and not to more serious infectious complications. In general, the larger, higher-quality studies demonstrated few statistically significant differences in outcome between different regimens.

A further problem with designating preferred antimicrobial regimens was that very few of the trials were actually designed to detect therapeutic superiority. Many investigators did not include a power analysis in their descriptions of trial design, that is, there was no estimate of the number of patients that would be needed to detect a specific difference between the treatment groups. Among those that did provide this information, the trials were usually powered only to detect therapeutic equivalence, or more correctly, non-inferiority, and not therapeutic superiority. Thus, many of these trials were only designed to detect a true difference of greater than 10–15% between treatment arms.

The technique of meta-analysis can be used to combine the results of studies that individually are powered insufficiently to detect measurable differences in outcome. In actuality, however, the Committee found that very few meta-analyses related to antimicrobial therapy for patients with intra-abdominal infections. Although the Committee did utilize the reported and calculated clinical success rates as a rough guide to compare the results of different therapeutic regimens, this was done without undertaking a formal meta-analytic review. In any case, the results of such meta-analyses would have to have been interpreted with extreme caution, since the component trials had such widely varying design and quality.

In the end, the Committee concluded that the information from the database could be used to identify effective antimicrobial regimens for the treatment of patients with intra-abdominal infections, but not to specify therapeutically superior regimens. Preference for one regimen over another would need to be based on criteria other than the therapeutic efficacies reported in the published literature.

Another issue that proved problematic for the Committee was the applicability of these antimicrobial recommendations to different groups of patients with intra-abdominal infections. To evaluate this, the Committee reviewed the diagnoses of the clinically evaluable patients enrolled in the various trials. Overall, it appeared that most of the patients had relatively easy-to-treat community-acquired infections, such as complicated appendicitis. In fact, in ten trials, enrollment was limited to such patients, and in many others, the majority of the evaluable patients had an appendiceal source of infection. The conclusion that most patients enrolled in these studies were less severely ill was confirmed by the relatively low mortality rates found in most trials, as will be discussed subsequently. Therefore, the recommendations outlined in this section pertain primarily to the treatment of lower-risk patients with community-acquired intra-abdominal infec-

TABLE 11. PROSPECTIVE RANDOMIZED CONTROLLED TRIALS OF ANTIMICROBIAL REGIMENS FOR PATIENTS WITH INTRA-ABDOMINAL INFECTIONS

Reference	*Antimicrobial agents*	*Number of patients enrolled*	*Number of evaluable patients*	*Reported success rate*	*Percentage of patients with sSSI*	*Success rate excluding isolated sSSI*	*ITT analysis*	*Mortality*	*Percentage of patients with appendicitis*	*Quality score*	*APACHE II scoring?*	*Complicated infections per IDSA criteria?*
[40] Malangoni, 1985	Cefoxitin 3 g q6h	82	59	83%	3%	86%	NR	8%	22%	5	Yes[2]	Probably not
	Tobramycin 1.5 mg/kg q8h[1] + Clindamycin 600 mg q6h	88	53	79%	4%	83%		6%	17%			
[41] Yellin, 1985	Ampicillin/ sulbactam 3 g q6h	197	67	88%[3]	6%	94%	NR	0%	100%	4	No	No
	Gentamicin 1.5 mg/kg q8h[1] + Clindamycin 600 mg q6h		38	100%[3]	0%	100%		0%	100%			
[42] Study Group, 1986	Ampicillin/ sulbactam 3 g q6h	62	46[4]	87%[5]	NR	N/A	NR	NR	NR	4	No	No
	Gentamicin 1.5 mg/kg q8h[1] + Clindamycin 600 mg q6h	61	37[4]	97%[5]								
[43] Kooi, 1990	Ceftazidime 20 mg/kg tid + Metronidazole 7.5 mg/kg tid	NR[6]	50	98%[7]	0%	98%	NR	0%	100%	1	No	No
	Netilmicin 2 mg/kg tid + Metronidazole 7.5 mg/kg tid		50	82%[7]	18%[8]	98%		0%	100%			

[44] Jauregui, 1990	Cefoperazone/ sulbactam 3 g q12h	100	76[9]	93%[5,10]	NR	N/A	NR	NR	NR	3	No	No
	Gentamicin 1.5–2 mg/kg q8h[1] + Clindamycin 600–800 mg q6–8h	52	34[9]	74%[5,10]								
[45] Swedish Study Group, 1990	Pefloxacin 800 mg, then 400 mg q12h + Metronidazole 500 mg q8h	136	104[11]	90%[5]	NR	N/A	NR	0%	61%	1	No	No
	Gentamicin 1.5 mg/kg q8h[1] + Metronidazole 500 mg q8h	135	78[11]	82%[5]				3%	65%			
[46] Bubrick, 1990	Ceftazidime 2 g q8h + Clindamycin 900 mg q8h	47	34	91%[5]	6%	97%	NR	NR	NR	1	No	No
	Tobramycin 1.5–2 mg/kg[12] + Clindamycin 900 mg q8h	47	34	91%[5]	9%	100%						
[47] Poenaru, 1990	Imipenem/cilastatin 500 mg q6h	52	48[13]	85%[13]	NR	N/A	NR	8%[14]	NR	1	11.2	Yes
	Tobramycin 1.5–2 mg/kg q8h[1] + Clindamycin 600 mg q6h or Metronidazole 500 mg q6h	52	46[13]	76%[13]				17[14]			12.1	

TABLE 11. PROSPECTIVE RANDOMIZED CONTROLLED TRIALS OF ANTIMICROBIAL REGIMENS FOR PATIENTS WITH INTRA-ABDOMINAL INFECTIONS (CONT'D)

Reference	*Antimicrobial agents*	*Number of patients enrolled*	*Number of evaluable patients*	*Reported success rate*	*Percentage of patients with sSSI*	*Success rate excluding isolated sSSI*	*ITT analysis*	*Mortality*	*Percentage of patients with appendicitis*	*Quality score*	*APACHE II scoring?*	*Complicated infections per IDSA criteria?*
[48] Solomkin, 1990	Imipenem/ cilastatin 500 mg q6h[15]	148	81	83%[16]	4%	86%	NR	14%	28%	2	Yes[17]	Yes
	Tobramycin 1.5 mg/kg q8h[1] + Clindamycin 600 mg q6h[15]	142	81	70%[16]	2%	73%		17%	20%			
[49] Sirinek, 1991	Ticarcillin/ clavulanic acid 3.1 g q6h (75 mg/kg q6h)[18]	NR[19]	56	86%	5%	91%	NR	0%	100%	1	No	No
	Gentamicin 1.5 mg/kg q8h (2 mg/kg q8h)[1,18] + Clindamycin 600 mg q6h (10 mg/kg q6h)[18]		43	84%	14%	98%		0%	100%			
[50] Schropp, 1991	Cefotaxime 25 mg/kg q6h + Clindamycin 10 mg/kg q8h	154[21]	50	96%	0%	96%	NR	NR	100%	5	No	No
	Gentamicin 2–2.5 mg/kg q8h[20] + Clindamycin 10 mg/kg q8h + Ampicillin 50 mg/kg q6h		47	89%	2%	91%			100%			

[51] Williams, 1991	Aztreonam 3–8 g/day[22] + Clindamycin 1.8–4.8 g/day[22,23]	155	104	85%	NR	N/A	NR	4%	50%	2	No	Probably not
	Tobramycin 3–5 mg/kg/day[1,22] + Clindamycin 1.8–4.8 g/day[22,23]	161	105	85%				2%	42%			
[52] Luke, 1991	Ceftriaxone 1 g qd[24] + Metronidazole 1.5 g qd[24]	99[25]	94	94%[26]	1%	95%	NR	4%	47%	2	No	No
	Netilmicin 150 mg bid[24] + Metronidazole 1.5 g qd[24] + Ampicillin 2 g bid[24]	102[25]	96	81%[26]	9%	91%		5%	33%			
[53] Meller, 1991	Cefoxitin[27]	59[28]	29	93%	3%	97%	NR	NR	100%	1	No	No
	Gentamicin,[1,27] + Clindamycin[27]		27	78%	7%	85%			100%			
[54] Eckhauser, 1992	Imipenem/cilastatin 500 mg q6–8h[22,29]	66	53	96%[5]	NR	N/A	NR	3%[14]	11%	1	No	Probably not
	Gentamicin or Tobramycin 1 mg/kg q8h[1] + Clindamycin 600 mg q6h	79	64	92%[5]				5%[14]	25%			

TABLE 11. PROSPECTIVE RANDOMIZED CONTROLLED TRIALS OF ANTIMICROBIAL REGIMENS FOR PATIENTS WITH INTRA-ABDOMINAL INFECTIONS (CONT'D)

Reference	*Antimicrobial agents*	*Number of patients enrolled*	*Number of evaluable patients*	*Reported success rate*	*Percentage of patients with sSSI*	*Success rate excluding isolated sSSI*	*ITT analysis*	*Mortality*	*Percentage of patients with appendicitis*	*Quality score*	*APACHE II scoring?*	*Complicated infections per IDSA criteria?*
[55] Berne, 1993	Cefepime 2 g q12h + Metronidazole 500 mg q8h	156	50	94%	0%	94%	NR	0%	100%	2	No	No
	Gentamicin 1.5 mg/kg q8h[1] + Clindamycin 900 mg q8h		46	83%	4%	87%		0%	100%			
[56] Polk, 1993	Piperacillin/ Tazobactam 3.375 g q6h	217	104	88%[5]	NR	N/A[30]	88%	3%[5]	56%	1	No	Probably not
	Gentamicin 2.5–5 mg/kg/day divided q8–12h[1] + Clindamycin 600 mg q6h	114	43	77%[5]			81%	4%[14]	49%			
[57] Barboza, 1994	Aztreonam 2 g q8h + Clindamycin 900 mg q8h	33	31	100%[5]	13%	100%[30]	NR	3%	58%	2	No	Probably not
	Amikacin 5 mg/kg q8h + Clindamycin 900 mg q8h	34	31	94%[5]	6%	94%[30]		3%	58%			

[58] Greenberg, 1994	Cefoperazone/ sulbactam 3 g q12h[22]	87	47	NR[31]	NR	N/A[30]	70%[32]	13%[33]	34%	3	No	No
	Gentamicin[1] + Clindamycin 900 mg q8h		29				52%[32]	10%	28%			
[59] Hopkins, 1994	Cefotetan 2 g q12h	58	40	90%	8%	98%	NR	NR	100%	4	No	No
	Amikacin 500 mg, then 7.5 mg/kg q12h + Clindamycin 600 mg q6h	55	36	86%	0%	86%			100%			
[60] Dougherty, 1995	Ticarcillin/ clavulanic acid 3.1 g q4–6h (200–300 mg/kg/ day)[18,22]	640[19]	204	86%[5]	3%	89%	83%	2%	NR	1	No	Probably not
	Gentamicin (2–2.5 mg/kg q8h)[1,18] + Clindamycin 1200–2700 mg/day (25–40 mg/kg/day) + Ampicillin (12.5 mg/kg q6h)[18]	346[19]	137	84%[5]	5%	89%	77%	2%				
[61] Shyr 1995	Piperacillin/ tazobactam 4.5 g q8h	47	46	98%	NR	N/A	NR	0%	30%[34]	3	No	No
	Gentamicin 2.5–5 mg/kg/day divided q8–12h[1] + Clindamycin 600 mg q6h	30	30	97%				0%	23%[34]			

TABLE 11. PROSPECTIVE RANDOMIZED CONTROLLED TRIALS OF ANTIMICROBIAL REGIMENS FOR PATIENTS WITH INTRA-ABDOMINAL INFECTIONS (CONT'D)

Reference	*Antimicrobial agents*	*Number of patients enrolled*	*Number of evaluable patients*	*Reported success rate*	*Percentage of patients with sSSI*	*Success rate excluding isolated sSSI*	*ITT analysis*	*Mortality*	*Percentage of patients with appendicitis*	*Quality score*	*APACHE II scoring?*	*Complicated infections per IDSA criteria?*
[62] Condon, 1995	Meropenem 1 g q8h	88	64	92%	0%	92%	70%	2%	34%	4	Yes[2]	No
	Tobramycin 1.67 mg/kg q8h[1] + Clindamycin 900 mg q8h	89	63	89%	2%	90%	65%	2%	38%			
[63] Berne, 1996	Meropenem 1 g q8h	118	63	92%	0%	92%	NR	0%	100%	4	No	No
	Tobramycin 1.67 mg/kg q8h[1] + Clindamycin 900 mg q8h	110	66	91%	0%	91%		0%	100%			
[64] Wilson, 1997	Meropenem 1 g q8h	215	97	96%[5]	NR	N/A	96%	1%	73%	5	Yes[2]	Probably not
	Tobramycin 1.67 mg/kg q8h[1] + Clindamycin 900 mg q8h	212	94	93%[5]			94%	1%	72%			
[65] Ciftci, 1997	Tobramycin 1.33 mg/kg tid + Clindamycin 10 mg/kg qid + Penicillin 25,000 units/kg q3h	NR[35]	50	92%[11]	4%	96%	NR	0%	100%	2	No	No
	Tobramycin 1.33 mg/kg tid +											

	Ornidazole 10 mg/kg bid + Penicillin 25,000 units/kg q3h		50	92%	4%	96%		0%	100%			
	Piperacillin 67 mg/kg tid		50	92%	8%	100%		0%	100%			
	Ceftriaxone 25 mg/kg bid + Ornidazole 10 mg/kg bid		50	96%	4%	100%		0%	100%			
[66] Torres, 2000	Cefminox 2 g q12h	80	76	99%[13]	11%	99%[30]	94%	0%	53%		3.7	No
	Gentamicin 80 mg q8h + Metronidazole 500 mg q8h	80	73[1]	96%[13]	18%	96%[30]	88%	1%	66%		3.2	
[67] Leal del Rosal, 1995	Isepamicin 15 mg/kg qd + Metronidazole[27]	178	135	96%[5]	NR	N/A	95%	1%	NR	1	No	Probably not
	Amikacin 7.5 mg/kg bid + Metronidazole[27]	89	70	94%[5]			94%	0%				
[68] Cometta, 1994	Imipenem/ cilastatin 500 mg qid	313[36]	39	79%[37]	NR	N/A	NR	NR[38]	0%	3	Yes[39,40]	Probably not
	Imipenem/ cilastatin 500 mg qid + Netilmicin 150 mg bid		39	92%[37]					0%			

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Reference	*Antimicrobial agents*	*Number of patients enrolled*	*Number of evaluable patients*	*Reported success rate*	*Percentage of patients with sSSI*	*Success rate excluding isolated sSSI*	*ITT analysis*	*Mortality*	*Percentage of patients with appendicitis*	*Quality score*	*APACHE II scoring?*	*Complicated infections per IDSA criteria?*
[69] Hoogkamp-Korstanje, 1995	Ciprofloxacin 300 mg bid[41] + Metronidazole 500 mg tid	NR	40	78%[5,43]	NR	N/A	NR	20%	4%	0	No	Probably not
	Cefotaxime 1 g qid + Gentamicin 120 mg bid[42] + Metronidazole 500 mg tid		39	56%[5,43]				13%				
[70] Dupont, 2000	Piperacillin/ tazobactam 4 g qid	241	81	51%	NR	N/A	44%	19%[14]	9%[34]	3	No	Yes
	Piperacillin/ tazobactam 4 g qid + Amikacin 7.5 mg/kg bid[1]		78	51%			48%	21%[14]	9%[34]			
[72] Hollender, 1989	Netilmicin 4.5 mg/kg qd[1,44] + Metronidazole 500 mg tid[45,46]	58	57	100%[5]	2%	100%[30]	NR	0%	75%	3	No	No
	Netilmicin 1.5 mg/kg tid[1,44] + Metronidazole 500 mg tid[45,46]	56	55[47]	98%[5]	4%	98%[30]		2%	80%			

[73] de Vries, 1990	Netilmicin 6 mg/kg qd[1] + Tinidazole 800 mg qd[48]	211	80	93%[5]	15%	93%[30]	NR	NR	41%	3	7.5	No
	Netilmicin 2 mg/kg tid[1] + Tinidazole 800 mg qd[48]		76	96%[5]	9%	96%[30]			31%		7.9	
[74] Walker, 1993	Cefoxitin 2 g q6h[29]	191	101	78%	0%	78%	NR	NR	35%	4	No	Probably not
	Ampicillin/ sulbactam 3 g q6h[29]	194	96	86%	1%	87%			33%			
[75] Allo, 1999	Imipenem/cilastatin 1 g q6h	128[49]	73	96%[5]	NR	N/A	95%	NR	100%	2	No	Probably not
	Ticarcillin/ clavulanic acid 3.1 g q6h[29]	122[49]	64	97%[5]			96%		100%			
[76] Brismar, 1992	Imipenem/cilastatin 1 g q8h	65	58	69%[5,50]	2%	71%	68%[51]	6%[14]	57%[34]	2	No	No
	Piperacillin/ tazobactam 4.5 g q8h	69	55	93%[50]	0%	93%	84%[51]	0%[14]	52%[34]			
[77] Niinikoski, 1993	Imipenem/ cilastatin 1 g q8h	39	26	77%[5]	NR	N/A	NR	3%[14]	15%[34]	1	No	No
	Piperacillin/ tazobactam 4.5 g q8h	47	30	87%[5]				4%[14]	30%[34]			
[78] Jaccard, 1998	Imipenem/ cilastatin 500 mg qid[29]	371[52]	83[53]	93%[37]	NR	N/A	NR	2%[54]	17%	2	7.3	No
	Piperacillin/ tazobactam 4.5 g tid[29]		76[53]	95%[37]				1%[54]	12%		8.3	

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Reference	*Antimicrobial agents*	*Number of patients enrolled*	*Number of evaluable patients*	*Reported success rate*	*Percentage of patients with sSSI*	*Success rate excluding isolated sSSI*	*ITT analysis*	*Mortality*	*Percentage of patients with appendicitis*	*Quality score*	*APACHE II scoring?*	*Complicated infections per IDSA criteria?*
[79] Ohlin 1999 [55]	Cefuroxime 1.5 g q8h + Metronidazole 1.5 g q24h	129	91	91%[55]	1%	92%	70%	3%[14]	67%	2	No	No
	Piperacillin/ tazobactam 4.5 g q8h	140	102	90%[55]	2%	92%	74%	2%[14]	74%			
[80] Cohn, 2000	Ciprofloxacin 400 mg q12h + Metronidazole 500 mg q6h[56]	235	134	74%[57]	11%	77%[57]	75%	6%[14]	31%	3	9.6	No
	Piperacillin/ tazobactam 3.375 g q6h	224	116	63%[57]	19%	67%[57]	69%	4%[14]	38%		9.5	
[81] Röhrborn, 2000	Cefotaxime[27,58] or Ceftriaxone[27,58] + Metronidazole[27]	62	55	80%	11%	N/A	NR	9%	25%	2	Yes[2]	No
	Piperacillin/ tazobactam[27,58] or Mezlocillin[27,58] + Metronidazole[27]	60	55	64%	13%			7%	24%			

[82] Paakkonen, 1991	Cefuroxime 1.5 g q8h + Metronidazole 500 mg q8h	85	45	64%	9%	N/A	NR	4%	33%	1	No	No
	Piperacillin 4 g q6h		38	71%	11%			8%	29%			
[83] Scheinin, 1994	Aspoxicillin 4 g qd[59]	111	50	90%[13]	4%	N/A	NR	6%	33%	1	No	No
	Piperacillin 4 g qid[59]		53	91%	8%			4%	38%			
[85] Yoshioka, 1991	Ciprofloxacin 200 mg q12h + Metronidazole 500 mg q12h[60]	40	38	97%[5]	NR	N/A	NR	NR	NR	2	No	No
	Amoxacillin/ clavulanic acid 1.2 g q8h[61] + Metronidazole 500 mg q12h[62]	40	40	90%[5]								
[86] Donahue, 1998	Alatrofloxacin 300 mg qd[63]	414	156	83%[5]	1%	84%	NR	5%[14]	52%	3	6.4	No[65]
	Imipenem/ cilastatin 1 g q8h[64]		152	84%[5]	1%	85%		5%[14]	47%		7.0	
[87] Lewis, 1988	Cefotetan 1–2 g q12h[22]	122	95	98%[5]	0%	98%	NR	2%[14]	25–26%[66]	1	No	No
	Cefoxitin 1–2 g q6h[22]	66	43	95%[5]	0%	95%		0%[14]	26–33%[66]			
[88] Wilson, 1988	Moxalactam 2 g q8h	271	56	91%[5]	NR	N/A	NR	NR	48%	1	No	Probably not
	Cefotetan 2 g q12h		109	94%[5]					47%			

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[89] Holloway, 1989	Cefmetazole 2 g q8h[67]	52	73[69]	92%[70,71]	NR	N/A	NR	3%[14]	47%[34]	1	No	No
	Cefoxitin 2 g q6h[68]	27							48%[34]			
[90] Christou, 1996	Imipenem/ cilastatin 1 g q6h	104	74	88%	0%	88%	83%	3%	25%[34]	3	8.9	Yes
	Cefoxitin 2 g q6h	109	80	84%	0%	84%	82%	3%	28%[34]		7.7	
[91] Angerås, 1996	Imipenem/ cilastatin 1.5–2.0 g/day	258	161	87%[5]	NR	N/A	83%	7%[14]	45%	2	Yes[2]	Probably not
	Cefuroxime 3.0–4.5 g/day + Metronidazole 1.0–1.5 g/day	257	145	91%[5]			86%	5%[14]	46%			
[92] Huzinga, 1995	Meropenem 2 g q8h[29]	77	70	91%[5,72,73]	NR	N/A	NR	3%[14]	27%	1	Yes[2]	No
	Cefotaxime 2 g q8h[29] + Metronidazole 500 mg q8h	83	78	100%[5,72,73]				1%[14]	40%			
[93] Kempf, 1996	Meropenem 1.0 g q8h	48	43	95%[5,74]	0%	95%	NR	2%[75]	40%	1	Yes[2]	No
	Cefotaxime 1 g q8h + Metronidazole 500 mg q8h	46	40	75%[5,74]	0%	75%		4%[75]	35%			

[94] Mehtar, 1997	Meropenem 1 g tid[29]	81[76]	51[77]	96%[78]	0%	96%	NR	NR	NR	2	Yes[2]	No
	Cefotaxime 1 g tid + Metronidazole 500 mg tid	80[76]	46[77]	96%[78]	0%	96%						
[95] Barie, 1997	Imipenem/ cilastatin 500 mg q6h	159	122	76%[79]	2%[80]	78%	76%	7%	33%	4	9.3[82]	Yes
	Cefepime 2 g q12h + Metronidazole 500 mg q6h or 7.5 mg/kg q6h	164	95	88%[79]	0%	88%	82%	2%	33%		7.8[82]	
[96] de Groot, 1993	Imipenem/ cilastatin 1 g q6h[29]	104	38	76%	16%	92%	NR	3%	53%[83]	2	7[84]	Probably not
	Aztreonam 1 g q8h[29] + Clindamycin 600 mg q8h		42	71%	17%	88%		5%	24%[83]		11[84]	
[97] Solomkin, 1996	Ciprofloxacin 400 mg q12h + Metronidazole 500 mg q6h[85]	222	111	84%	3%	86%	82%	5%	24%	4	9.2	Yes
	Ciprofloxacin 400 mg q12h[86] + Metronidazole 500 mg q6h[85,86]	219	106	86%	2%	88%	84%	11%	36%		9.2	
	Imipenem/ cilastatin 500 mg q6h[85]	230	113	81%	1%	81%	81%	9%	25%		10.5	

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[98] Kanellakopoulou, 1993	Meropenem 1 g q8h	30	28	100%[5]	0%	100%	NR	NR	47%[34]	2	No	Probably not
	Imipenem/ cilastatin 1 g q8h	32	31	100%[5]	0%	100%			38%[34]			
[99] Brismar, 1995	Meropenem 500 mg q8h	132	99	98%	NR	N/A	94%[87]	1%	67%[34]	3	Yes[2]	No
	Imipenem/ cilastatin 1 g q8h	117	90	96%			85%[87]	4%	66%[34]			
[100] Geroulanos, 1995	Meropenem 1 g q8h[29]	116	82	96%[5]	NR	N/A	NR	5%[14]	34%	2	No	Probably not
	Imipenem/ cilastatin 1 g q8h[29]	116	88	94%[5]				3%[14]	33%			
[101] Basoli, 1997	Meropenem 1 g q8h[29]	148	100	95%	NR	N/A	NR	NR	39%	2	5.9	Probably not
	Imipenem/ cilastatin 500 mg q8h[29]	139	101	98%					33%		6.4	
[102] Zanetti, 1999	Meropenem 500 mg q8h[29]	82	71[88]	92%[5]	NR	N/A	82%	6%[14]	18%	3	5.8	No
	Imipenem/ cilastatin 500 mg q6h[29]	79	64[88]	94%[5]			86%	6%[14]	23%		6.4	
[103] Brismar, 1996	Biapenem 500 mg q8h	58	43	65%	NR	N/A	62%	3%[14]	67%	3	Yes[2]	Yes
	Imipenem/ cilastatin 1 g q6h	60	40	68%			62%	5%[14]	78%			

[104] Solomkin, in press	Ertapenem 1 g qd[85]	323	203	87%	3%	90%	79%[83]	6%[14]	61%	4	Yes[2]	Yes
	Piperacillin/ tazobactam 3.375 g q6h[85]	310	193	81%	4%	85%	76%[83]	4%[14]	59%			
[108] Collins, 1998	Gentamicin or Tobramycin 6–7.5 mg/kg/day + Ampicillin/ Sulbactam 150–300 mg/kg/day	131[89]	75	97%[5]	NR	N/A	NR	NR	NR[90]	2	No	Probably not
	Gentamicin or Tobramycin 6–7.5 mg/kg/day + Clindamycin 20–40 mg/kg/day + Ampicillin 200 mg/kg/day	64[89]	39	97%[5]								
[109] Yellin, 1993	Gentamicin 1.5 mg/kg q8h[1] + Clindamycin 900 mg q8h	NR	80	93%	3%	95%	NR	NR	100%	1	No	No
	Gentamicin 1.5 mg/kg q8h[1] + Clindamycin 600 mg q6h		46	91%	7%	98%			100%			

[1]Aminoglycoside dosing was modified according to renal function or serum drug concentrations.
[2]Distributions of APACHE II scores were provided.
[3]Significantly different ($p = 0.03$) in favor of gentamicin plus clindamycin.
[4]Four patients in the clinically evaluable population had soft tissue infections.
[5]Success rates include patients reported as cured or improved.
[6]All patients enrolled were children 12 years of age or younger.
[7]Significantly different ($p = 0.001$) in favor of ceftazidime plus metronidazole.
[8]Cultures from four of nine patients with superficial surgical site "infections" revealed no growth.
[9]Five patients in the clinically evaluable population had soft tissue infections.
[10]Significantly different ($p = 0.006$) in favor of cefoperazone/sulbactam.

[11]Three patients in the clinically evaluable population had soft tissue infections.
[12]After the initial dose, subsequent tobramycin dosing was based on pharmacokinetic calculations and serum drug concentrations.
[13]Success rates were calculated after excluding patients with indeterminate outcomes.
[14]Mortality rates were based on all patients enrolled in the study.
[15]Use of vancomycin was permitted for patients thought to have resistant Gram-positive organisms.
[16]Significantly different ($p = 0.04$) in favor of imipenem/cilastatin.
[17]Median APACHE II scores were provided for different diagnoses.
[18]Pediatric dosing.
[19]Patients enrolled included children 2 years of age or older and adult patients.
[20]Children 10 years of age and younger received the higher gentamicin dose.
[21]All patients enrolled were children 18 years of age and younger.
[22]Higher doses and/or shorter dosing intervals were used for patients with serious or life-threatening infections.
[23]Use of vancomycin, nafcillin, or metronidazole was permitted for patients with Gram-positive organisms resistant to clindamycin.
[24]Pediatric doses were adjusted according to weight.
[25]Patients enrolled included children 3 years of age or older and adult patients.
[26]Significantly different ($p = 0.02$) in favor of ceftriaxone plus metronidazole.
[27]Dosage not reported.
[28]All patients enrolled were children between 2 and 15 years of age.
[29]Dosage was modified according to renal function.
[30]Patients with superficial surgical site infections were not necessarily considered failures.
[31]Only an intention-to-treat analysis was reported.
[32]Failures included patients who received additional antibiotics for any reason, even if unrelated to the intra-abdominal infection.
[33]Mortality rate includes patients who died more than 35 days after completion of therapy.
[34]Percentages of patients with appendicitis were based on all patients enrolled in the study.
[35]All patients enrolled were between 1 and 16 years of age.
[36]Patients were enrolled for nosocomial pneumonia, sepsis, or severe diffuse peritonitis.
[37]Success rates refer only to clinically evaluable patients with peritonitis.
[38]The mortality rate was not reported separately for patients with peritonitis. The mortality rate due to infection in all enrolled patients was 13% in patients treated with imipenem/cilastatin and 9% in patients treated with imipenem/cilastatin plus netilmicin.
[39]The mean APACHE II score for patients with peritonitis was not reported. The mean APACHE II scores for all enrolled patients were 9.8 for patients treated with imipenem/cilastatin and 9.6 for patients treated with imipenem/cilastatin plus netilmicin.
[40]Patients with peritonitis in the imipenem/cilastatin group had higher APACHE II scores.
[41]After 3 days of treatment, oral ciprofloxacin (500–750 bid) could be substituted for intravenous ciprofloxacin.
[42]Gentamicin was discontinued after 3 days in 51% of patients whose organisms were sensitive to cefotaxime.
[43]Significantly different ($p = 0.02$) in favor of ciprofloxacin plus metronidazole.
[44]Netilmicin could be administered intramuscularly or intravenously.
[45]Oral administration of metronidazole was permitted.
[46]Metronidazole was not given to 28% of patients receiving once daily netilmicin and to 32% of patients receiving thrice daily netilmicin.
[47]One patient in the clinically evaluable population had a soft tissue infection.
[48]Oral tinidazole (1 g qd) could be substituted for intravenous tinidazole.
[49]Patients enrolled included children 12 years of age and older and adults.
[50]Significantly different ($p = 0.001$) in favor of piperacillin/tazobactam.
[51]Significantly different ($p = 0.02$) in favor of piperacillin/tazobactam.
[52]Patients were enrolled for nosocomial pneumonia or peritonitis.
[53]Of the 159 clinically evaluable patients with peritonitis, 29 did not undergo a surgical procedure.
[54]Only mortality attributable to infection was reported.

[55]Success rates were calculated after excluding patients with incomplete follow-up or indeterminate outcomes.
[56]After 2 days, patients could be switched to blinded therapy with oral ciprofloxacin and oral metronidazole. Dosages not reported.
[57] Significantly different ($p = 0.047$) in favor of ciprofloxacin plus metronidazole.
[58]Amikacin, 15 mg/kg/day, could be added at the investigator's discretion for additional coverage of *Pseudomonas*.
[59]Twelve patients randomized to receive aspoxicillin and 13 patients randomized to receive piperacillin were given an additional antimicrobial, usually an aminoglycoside.
[60]After the start of therapy, patients could be switched to oral ciprofloxacin 750 mg q12h plus oral metronidazole 200 mg q12h.
[61]Contains 1 g of amoxacillin and 200 mg of clavulanic acid.
[62]After the start of therapy, patients could be switched to oral amoxacillin/clavulanic acid 875 mg q8h plus metronidazole 200 mg q12h.
[63]After the start of therapy, patients could be switched to oral trovafloxacin, 200 mg qd, at the investigator's discretion.
[64]After the start of therapy, patients could be switched to oral amoxacillin/clavulanic acid 50 mg q8h.
[65]All patients had diagnoses consistent with IDSA criteria, but patients with negative peritoneal cultures were considered clinically evaluable.
[66]The source of the infection was not fully explained in patients having bacteremia associated with an appendiceal or colonic perforation.
[67]Dosage of cefmetazole could be increased to 8 g per day at the investigator's discretion.
[68]Dosage of cefoxitin could be increased to 12 g per day at the investigator's discretion.
[69]The numbers of clinically evaluable patients were not reported for the two study groups.
[70]The numbers of successfully treated patients were not reported for the two study groups.
[71]The authors stated that there were no statistically significant differences in success rates comparing cefmetazole and cefoxitin.
[72]Significantly different ($p = 0.008$) in favor of cefotaxime plus metronidazole.
[73]At later, follow-up, success rates were 98% for 54 patients treated with meropenem, and 97% for 64 patients treated with cefotaxime plus metronidazole.
[74]Significantly different ($p = 0.008$) in favor of meropenem.
[75]Mortality rates were reported at the end of therapy for all patients enrolled in the study. During subsequent follow-up, mortality increased to 6% for patients treated with meropenem and to 11% for patients treated with cefotaxime plus metronidazole.
[76]Patients were enrolled for intra-abdominal infections and other indications.
[77]These values represent the numbers of clinically evaluable patients who had intra-abdominal infections. Some patients may have had other infections as well.
[78]Success rates for clinically evaluable patients with intra-abdominal infections were estimated from data provided in the article. Success rates include patients reported as cured or improved.
[79]Significantly different ($p = 0.02$) in favor of cefepime plus metronidazole. After adjustment for differences in prognostic factors between the two groups, the difference was no longer significant ($p = 0.06$).
[80]Only wound infections associated with fever were reported as failures.
[81]Mortality rates were based on the ITT populations. The difference in mortality significantly favored patients treated with cefepime plus metronidazole ($p = 0.03$).
[82]Mean APACHE II scores were significantly higher among patients treated with imipenem/cilastatin.
[83]The percentage of patients with appendicitis was significantly higher in the imipenem/cilastatin group.
[84]Mean APACHE II scores were significantly higher among patients treated with aztreonam plus clindamycin.
[85]Use of vancomycin was permitted for patients with methicillin resistant *Staphylococcus aureus* or enterococcal infections; the use of antifungal therapy was permitted.
[86]After 3 days, patients could be switched to blinded therapy with oral ciprofloxacin, 500 mg q12h plus oral metronidazole, 500 mg q6h. Patients in the other arms of the study received intravenous antimicrobials only.
[87]Significantly different ($p = 0.014$) in favor of meropenem.
[88]A surgical procedure was not performed in 46% of patients in the meropenem group and in 28% of patients in the imipenem/cilastatin group.
[89]All patients enrolled were children 3 months to 11 years of age.
[90]Intra-abdominal infections were primarily due to perforated appendicitis.

tions. Recommendations regarding higher-risk patients will be discussed in the subsequent section.

Summary of findings

Aminoglycosides. The combination of an aminoglycoside and an antianaerobic agent was considered the mainstay of antimicrobial therapy for intra-abdominal infections until newer agents were found to be equally effective. Thus, this combination was extensively used as a comparator in many trials of newer antimicrobials. The committee reviewed 27 studies, including three published prior to 1990, in which the combination of an aminoglycoside plus an antianaerobic agent was compared to other regimens [40–66]. One additional study compared the efficacy of two different aminoglycosides in combination with an antianaerobic agent [67]. There were also three studies in which an aminoglycoside was tested in combination with other agents having extended spectrum gram-negative coverage [68–70]. These latter studies will be considered more fully in the subsequent discussion of therapy for higher risk patients with intra-abdominal infections.

A total of 1,786 clinically evaluable patients were treated with aminoglycoside-based regimens in the 28 studies reviewed. The aminoglycosides tested included gentamicin, tobramycin, netilmicin, amikacin, and isepamicin. Either clindamycin or metronidazole were utilized as the antianaerobic agents in all studies, and in one study [65] ornidazole was also tested. This regimen was compared to a variety of other single agents or combination regimens, including an extended-spectrum penicillin alone or combined with a beta-lactamase inhibitor [41,42,49,56,60,61,65], a second-generation cephalosporin with intrinsic anaerobic coverage [40,53,59,66], a third- or fourth-generation cephalosporin in combination with an antianaerobic agent or a beta-lactamase inhibitor [43,44,46,50,52,55,58,65] aztreonam plus clindamycin [51,57], a carbapenem alone [47,48,54,62-64], or the combination of a fluoroquinolone plus metronidazole [45]. In one study, the aminoglycosides, isepamicin and amikacin were compared [67]. In six of these studies, antibiotics effective against *Enterococcus* or other gram-positive organisms were permitted or required along with the aminoglycoside and the antianaerobic agent [48,50–52,60,65].

Many of these 28 studies involved patients with relatively low–acuity infections. Nine studies enrolled patients with appendicitis only [41,43,49,50,53,55,59,63,65]. Mortality among aminoglycoside-treated patients was greater than 5% in only four of these studies [40,47,48,58]. Many of these studies were published toward the beginning of the decade, and tended to be of relatively lower quality than later studies.

Success rates using aminoglycoside-based regimens ranged from 70% to 100% in these studies except for one trial in which only the results of an ITT analysis were presented [58]. The overall success rate was 86% for all 1,786 clinically evaluable patients who received aminoglycosides. The individual and overall success rates were comparable to those obtained with other antimicrobial regimens used for treating intra-abdominal infections. Most of the studies demonstrated no significant differences in patient outcome between the aminoglycoside-based and comparator regimens, but in five studies the differences in success rates were statistically significant. Success rates were lower with an aminoglycoside-based regimen compared to a third-generation cephalosporin plus an antianaerobe in two studies, compared to a third-generation cephalosporin/beta-lactamase inhibitor combination in one study, and compared to carbapenem in one study [43,44,48,52]. In two of these studies, the higher failure rates observed in aminoglycoside-treated patients were due entirely to an increase in superficial surgical site infections [43,52]. In contrast to these studies, an earlier study found an aminoglycoside-based regimen to be superior to ampicillin/sulbactam for patients with complicated appendicitis [41].

In analyzing the results of their trial comparing imipenem/cilastatin with tobramycin plus clindamycin, Solomkin et al. [48] suggested that a delay in achieving therapeutic tobramycin concentrations contributed to the higher failure rate observed in patients who received the aminoglycoside-based regimen. Among the other studies that described lower success rates with aminoglycoside-based therapy, one did not report any monitoring of serum aminogly-

coside concentrations [52], and the other two did not comment on the time required to achieve therapeutic aminoglycoside concentrations [43,44]. Thus, if aminoglycoside-based regimens are utilized, it would seem prudent to direct attention toward prompt attainment of therapeutic concentrations of these agents, perhaps by using a once-daily dosing strategy.

Once-daily administration of aminoglycosides is an alternative that simplifies the use of these agents, and potentially avoids problems of underdosing. In a large meta-analysis of patients treated with aminoglycosides for any indication, once-daily aminoglycoside dosing was associated with similar efficacy and possibly decreased toxicity compared to multiple daily dose regimens [71]. Two prospective randomized controlled trials have compared once-daily with multiple daily dose regimens of netilmicin in patients with intra-abdominal infections [72,73]. Success rates were greater than 90% in the treatment arms of both studies, and no significant differences in therapeutic efficacy or toxicity were detected. However, many of the evaluable patients in these studies had relatively mild infections, and it is uncertain if these results apply to a more severely ill population of patients receiving aminoglycosides.

Based on these studies using aminoglycoside-based regimens, the Committee continues to include the combination of an aminoglycoside with an antianaerobic agent in the list of recommended agents for the treatment of intra-abdominal infections. However, given the equivalent performance of other regimens and the nephrotoxicity and ototoxicity of aminoglycosides, these drugs should not necessarily be considered first-line agents for therapy. They may be of greater use for patients who have failed therapy with other agents or for patients with severe allergic reactions to other antimicrobials.

Penicillin/beta-lactamase inhibitor combinations. In the previous guidelines [1], ticarcillin/clavulanic acid was the only recommended agent in this class for the treatment of patients with intra-abdominal infections. However, ampicillin/sulbactam has been employed frequently for this indication. The Committee identified at least three prospective randomized controlled trials that evaluated use of this agent, two of which were published prior to 1990. In these studies, ampicillin/sulbactam was compared against gentamicin plus clindamycin [41,42] or cefoxitin [74]. One study enrolled only patients with complicated appendicitis [41]. Mortality in all studies appeared to be low.

A total of 209 clinically evaluable patients received ampicillin/sulbactam in these trials. The reported success rates were 86–88% in the individual trials; among all 209 patients who received ampicillin/sulbactam, the success rate was 87%. In one trial, limited to patients with complicated appendicitis [41], the failure rate was significantly higher with ampicillin/sulbactam than with gentamicin and clindamycin. However, one-half of these failures were due to superficial surgical site infections. In addition, there was an imbalance in randomization, such that fewer patients with gangrenous appendicitis and more patients with perforated appendicitis received ampicillin/sulbactam than received gentamicin plus clindamycin. In the other two studies, there were no significant differences in therapeutic efficacy comparing ampicillin/sulbactam to the other agents. Based on these limited data and the relatively widespread clinical use of this agent, the Committee has included ampicillin/sulbactam in the list of acceptable single agents for the treatment of patients with intra-abdominal infections.

The use of ticarcillin/clavulanic acid for the treatment of intra-abdominal infections was described further in three trials published between 1990 and 2000 [49,60,75]. This agent was compared to gentamicin-containing regimens in two studies [49,60] and to imipenem/cilastatin in one [75]. Two of these trials enrolled only patients with complicated appendicitis [49,75], and mortality in all studies appeared to be low. Overall, these trials included 324 clinically evaluable patients treated with ticarcillin/clavulanic acid. Success rates in these trials ranged from 86% to 97%. The overall success rate among all patients treated with ticarcillin/clavulanic acid was 88%. There were no statistically significant differences in outcome in any of the studies. The Committee continues to recommend ticarcillin/clavulanic acid for antimicrobial therapy of intra-abdominal infections.

The use of piperacillin/tazobactam for treatment of patients with intra-abdominal infections was examined in eight trials published over the

past decade [56,61,76-81], and the use of piperacillin alone was evaluated in another three [65,82,83]. Comparator regimens included an aminoglycoside plus an antianaerobic agent [56,61,65], imipenem/cilastatin [76–78], cefuroxime plus metronidazole [79,82], a third-generation cephalosporin plus an antianaerobic agent [65,81], ciprofloxacin plus metronidazole [80], and another extended-range penicillin, aspoxicillin [83]. Only one of these trials [65] was restricted to patients with appendicitis. Mortality was greater than 5% in two trials [81,82].

In these studies, 571 clinically evaluable patients were treated with piperacillin/tazobactam, and an additional 141 patients were treated with piperacillin alone. Success rates with piperacillin/tazobactam or piperacillin alone ranged from 63% to 98% in individual trials, and the overall success rate for all clinically evaluable patients was 85%. Success rates were equivalent to the comparators in all trials except two. In one trial, piperacillin/tazobactam appeared to be superior to imipenem/cilastatin [76]. However, patients treated with the carbapenem had an unexpectedly low success rate compared to that observed in other trials with this agent [84]. In another study, treatment with piperacillin/tazobactam appeared to be less efficacious than treatment with ciprofloxacin plus metronidazole when the analysis was based on clinically evaluable patients, but this difference was not statistically significant in a modified ITT analysis [80]. Based on these data, the Committee has included piperacillin/tazobactam in the list of recommended regimens for the treatment of patients with intra-abdominal infections. The use of piperacillin alone also appears to be acceptable for the treatment of these patients, but the use of piperacillin alone seems to have been greatly curtailed since piperacillin/tazobactam became available. The Committee therefore has made no separate recommendation with regard to the use of piperacillin alone.

The extended spectrum penicillin/beta lactamase regimens described here, particularly ampicillin/sulbactam and piperacillin/tazobactam, cover most isolates of *Enterococcus* recovered from patients with community-acquired intra-abdominal infections. In three studies evaluating ampicillin/sulbactam [41,42,74] and six studies evaluating piperacillin/tazobactam or piperacillin alone [56,61,79–82], the comparator regimen would not have had similar coverage. The trial of Röhrborn et al. [81] was designed specifically to study the need for enterococcal coverage in patients treated for community-acquired intra-abdominal infections. None of these trials demonstrated any advantage to the extended spectrum penicillin/beta-lactamase regimen. Thus, these data suggest that routine coverage of *Enterococcus* is not necessary for most patients with community-acquired intra-abdominal infections.

In two studies, oral amoxicillin/clavulanic acid was used to complete a course of intravenous amoxacillin/clavulanic acid or imipenem/cilastatin [85,86]. Utilization of the oral agent was at the investigator's discretion, however, and not according to a specific protocol. A prospective trial of an obligatory intravenous regimen compared to one permitting conversion to oral amoxicillin/clavulanic acid has not been conducted. Based on the limited evidence from these two trials, the use of oral amoxicillin/clavulanic acid to complete a course of intravenous antimicrobials appears to be an acceptable option for selected patients with intra-abdominal infections who are able to tolerate an oral diet.

Cephalosporins. In the previous guidelines, Bohnen et al. [1] recommended second-generation cephalosporins with anaerobic coverage, specifically cefoxitin, cefotetan, and cefmetazole, as acceptable monotherapy for the treatment of patients with intra-abdominal infections of mild to moderate severity. The use of these agents has been examined in at least eight prospective randomized controlled trials, four of which have been published since 1990 [40,53,59,74,87–90]. Two of these trials [53,59] were restricted to patients with appendicitis. In only one study was mortality greater than 5% [40].

Cefoxitin was compared to an aminoglycoside plus clindamycin [40,53], ampicillin/sulbactam [74], cefotetan [87], cefmetazole [89], or imipenem/cilastatin [90] in six studies enrolling an estimated 337 clinically evaluable patients. Reported success rates ranged from 78% to 97% in these trials. The overall success rate among all cefoxitin-treated patients was 85%. Cefotetan was compared to amikacin plus clindamycin [59], cefoxitin [87], or moxalactam [88]

in 244 clinically evaluable patients. Success rates in the cefotetan-treated patients ranged from 90% to 98% in these three trials. The success rate among all patients treated with cefotetan was 95%. Among clinically evaluable patients who received either cefoxitin or cefotetan, the overall success rate was 89%. There were no statistically significant differences in outcome in any of the trials which utilized cefoxitin or cefotetan.

The Committee could identify only a single prospective randomized controlled trial that examined the use of cefmetazole for the treatment of patients with intra-abdominal infections [89]. This small study enrolled 52 patients treated with cefmetazole and 27 treated with cefoxitin. An overall success rate of 92% was described, but the success rates using each agent were not described unambiguously. The authors stated that there were no statistically significant differences in clinical outcome comparing cefmetazole to cefoxitin.

Based on these data, the Committee continues to recommend cefoxitin and cefotetan as acceptable agents for the empiric treatment of patients with intra-abdominal infections. Although the spectrum of activity of cefmetazole is similar to cefoxitin and cefotetan, the Committee does not believe that there is adequate evidence to make a specific recommendation with respect to this agent, particularly since it has not been widely used for treating patients with intra-abdominal infections following its initial evaluation.

The efficacy of another second-generation cephalosporin, cefuroxime, in combination with metronidazole, was compared to that of piperacillin/tazobactam [79], piperacillin alone [82], or imipenem/cilastatin [91] in three clinical trials, including 281 clinically evaluable patients. None of these studies was restricted to patients with appendicitis, and none had a mortality rate of greater than 5%. Cefuroxime plus metronidazole was equivalent to the comparator in each study, with success rates ranging from 64% to 91% in individual studies. The overall success rate was 87% for all clinically evaluable patients treated with this regimen. Based on these data, the combination of cefuroxime plus metronidazole has been added to the recommended list of regimens for the treatment of patients with intra-abdominal infections.

Bohnen et al. [1] included combinations of a third-generation cephalosporin (cefotaxime, ceftizoxime, ceftazidime, or ceftriaxone) with an antianaerobic agent in their list of recommended regimens for the treatment of patients with intra-abdominal infections. Since 1990, additional trials of cefotaxime [50,81,92–94], ceftazidime [43,46], and ceftriaxone [52,65,81], have been published. The fourth-generation cephalosporin, cefepime, was also evaluated in two published trials [55,95]. Metronidazole was the antianaerobic agent used along with the cephalosporin in most of these trials [43,52,55,81,92–95], although clindamycin was used in two trials [46,50] and ornidazole in one other [65]. The comparator regimens included an aminoglycoside plus an antianaerobic agent [43,46,50,52,55,65], an extended spectrum penicillin with or without a beta-lactamase inhibitor or metronidazole [65,81], or a carbapenem [92–95]. Four of these trials were restricted to patients with appendicitis [43,50,56,65]. Mortality was greater than 5% in three trials, all of them relatively recent [81,93,94].

In these eleven trials, 642 evaluable patients received the combination of a third- or fourth-generation cephalosporin with an antianaerobic agent. Overall success rates using the cephalosporin-based regimens ranged from 75% to 100%, with the rate being 92% for all patients treated with this regimen. In five of these trials, success rates with the cephalosporin-based regimens differed significantly from those of the comparators. In two of these trials, as indicated previously, outcome was significantly better with a cephalosporin-based regimen compared to an aminoglycoside-based regimen [43,52]. In two other trials, the cephalosporin-based regimen was significantly favored over a carbapenem [92,95], but the opposite was found in one additional trial [93]. In the largest of these trials [95], the combination of cefepime and metronidazole appeared to be superior to imipenem/cilastatin in an unadjusted analysis. However, the authors noted that there was an imbalance in randomization; patients who received imipenem/cilastatin had higher mean APACHE II scores than patients who received cefepime plus metronidazole. After using a multivariate analysis to adjust for differences in clinical risk factors, the statistical advantage in favor of cefepime plus metronidazole was lost. In ad-

dition, no statistically significant differences were found in an ITT analysis.

Based on the aggregate data, the Committee continues to include the combination of a third- or fourth-generation cephalosporin with an antianaerobic agent in the list of recommended agents for the treatment of patients with intra-abdominal infections. The previous guidelines of Bohnen et al. [1] included cefotaxime, ceftazidime, ceftriaxone, and ceftizoxime as acceptable third-generation cephalosporins, to which the fourth-generation cephalosporin, cefepime, can be added. It should be noted, however, that the data in support of some of these individual agents are limited, and no new publications supporting the use of ceftizoxime were identified. Thus, it is uncertain if these agents are actually all of equivalent therapeutic efficacy.

Monobactams. Aztreonam plus clindamycin was listed previously as an acceptable regimen for the treatment of patients with intra-abdominal infections [1]. Three additional prospective trials, including 177 clinically evaluable patients treated with this regimen, have been published since 1990 [51,57,96]. Aztreonam plus clindamycin was compared to an aminoglycoside plus clindamycin in two studies [51,57] and to imipenem/cilastatin in one [96]. None of these trials was restricted to patients with appendicitis, and none had a mortality rate of greater than 5%. The success rates with aztreonam plus clindamycin ranged from 71% to 100% in the individual trials. The overall success rate was 84% among all patients treated with this regimen. There were no statistically significant differences between aztreonam plus clindamycin and the comparators in any of the trials. The Committee continues to recommend this regimen for the treatment of patients with intra-abdominal infections.

Carbapenems. Imipenem/cilastatin was also included previously in the list of recommended agents for the treatment of intra-abdominal infections [1]. In studies published between 1990 and 2000, both imipenem/cilastatin and another carbapenem, meropenem, were evaluated extensively as single agents for the treatment of patients with intra-abdominal infections. In 13 trials, imipenem/cilastatin was compared to agents in other antimicrobial classes [47,48, 54,75–78,86,90,91,95–97], and in six studies meropenem was compared to other therapeutic agents [62–64,92–94]. In five additional studies, imipenem/cilastatin and meropenem were compared with each other [98–102], and in one study, imipenem/cilastatin was compared to another carbapenem, biapenem [103].

In all, imipenem/cilastatin was used in 1,496 clinically evaluable patients, compared against an aminoglycoside plus an antianaerobic agent [47,48,54], ticarcillin/clavulanic acid [75], piperacillin/tazobactam [76–78], cefoxitin [90], cefuroxime [91] or cefepime [95] plus metronidazole, aztreonam plus clindamycin [96], ciprofloxacin plus metronidazole [97], alatrofloxacin [86], meropenem [98–102], or biapenem [103]. Completion of therapy with oral amoxacillin/clavulanic acid was permitted in one study [86]. Only one of these studies [75] was limited to patients with an appendiceal source of infection. Mortality rates greater than 5% were observed in six of the studies comparing imipenem/cilastatin against other agents [47,48,76,91,95,97] and in one study comparing imipenem/cilastatin with meropenem [102].

Success rates using imipenem/cilastatin ranged from 69% to 100% in the individual trials. The success rate among all 1,496 clinically evaluable patients who received imipenem/cilastatin was 87%. In three studies [48,76,95], discussed previously, statistically significant differences in success rates were observed between imipenem/cilastatin and the other agents. One of these trials favored imipenem/cilastatin [48] and two favored the comparators [76,95]. There were no statistically significant differences in outcome in any of the studies comparing imipenem/cilastatin and meropenem.

Meropenem was tested in 768 clinically evaluable patients, and it was compared against tobramycin plus clindamycin [62–64], cefotaxime plus metronidazole [92–94], and imipenem/cilastatin [98–102]. One of these studies [63] included only patients with appendicitis. Mortality rates were greater than 5% in three studies [93,94,102]. In individual trials, the clinical success rates using meropenem ranged from 91% to 100%. The success rate in all patients treated with meropenem was 95%. One trial comparing

meropenem to cefotaxime plus metronidazole found the success rate to be significantly higher with meropenem [93], but the opposite was found in another trial [92].

A meta-analysis by Chang and Wilson [84] further supported the use of carbapenems for the treatment of patients with intra-abdominal infections. This study summarized the results of ten trials comparing imipenem/cilastatin or meropenem against non-carbapenem comparators. Overall, there were no significant differences in success rates comparing the carbapenems against other regimens. There were also no significant differences in outcome in separate assessments of imipenem/cilastatin and meropenem against their respective comparators. Based on this large body of evidence, the Committee continues to recommend imipenem/cilastatin for the treatment of patients with intra-abdominal infections, and has added meropenem to the list of acceptable agents.

As with the extended spectrum penicillin/beta lactamase inhibitor combinations, both imipenem/cilastatin and meropenem cover routine isolates of *Enterococcus faecalis*. In many of the studies cited above, the non-carbapenem comparator would not have been expected to provide reliable enterococcal coverage [47,48,54,62–64,90–97]. However, there was no evidence that the enterococcal coverage provided by the carbapenems improved clinical outcome in any of these trials. These data, along with the data from studies of extended spectrum penicillin/beta-lactamase inhibitor combinations, support the conclusion that routine coverage of *Enterococcus* is unnecessary for most patients with community-acquired intra-abdominal infections.

Recently, a newer carbapenem, ertapenem, was tested against piperacillin/tazobactam in a large prospective randomized controlled trial reported at the Annual Meeting of the SIS in 2001 [104]. Overall, 203 clinically evaluable patients were treated with ertapenem, of whom 61% had perforated appendicitis. The mortality rate in this study was 6%. The success rate in patients treated with ertapenem was 87%, which was equivalent to the 81% success rate observed in patients treated with piperacillin/tazobactam. Based on the data from this large trial, the Committee has added ertapenem to the list of acceptable therapeutic agents for the treatment of patients with intra-abdominal infections. However, clinical experience with this agent is limited at present, so its overall usefulness for this indication has yet to be defined fully.

Fluoroquinolones. The role of fluoroquinolones in treating patients with intra-abdominal infections was investigated increasingly over the past decade. Four trials compared the combination of ciprofloxacin plus metronidazole with amoxacillin/clavulanic acid plus metronidazole [85]; piperacillin/tazobactam [80]; cefotaxime, gentamicin, and metronidazole [69]; or imipenem/cilastatin [97]. None of these studies was restricted to patients with appendicitis. Mortality rates over 5% were observed in three of the four trials [69,80,97].

These four studies included 429 clinically evaluable patients who received ciprofloxacin plus metronidazole. Success rates using this regimen ranged from 74% to 97%, and the success rate among all clinically evaluable patients was 82%. In two trials, there was a statistically significant difference in success rates favoring the ciprofloxacin plus metronidazole regimen [69,80], although this advantage was not observed in an ITT analysis performed as part of one trial [80].

In a carefully designed study, Solomkin et al. [97] examined the efficacy of oral ciprofloxacin and metronidazole in patients with intra-abdominal infections. In this study, there were two separate arms that involved treatment with ciprofloxacin plus metronidazole. In one arm, patients received only intravenous ciprofloxacin and metronidazole, whereas in the other, patients could receive blinded oral therapy with the same agents after 3 days of intravenous therapy. Approximately 47% of the patients in this trial were switched to oral medications or placebos. Success rates were similar among patients who received only intravenous therapy and patients who were allowed to receive oral therapy.

Overall, the Committee believes that the evidence justifies inclusion of the regimen of ciprofloxacin plus metronidazole in the list of recommended agents for the treatment of intra-abdominal infections. There is also reason-

able evidence that oral ciprofloxacin and metronidazole can be used to complete an initial intravenous course of these agents for patients able to tolerate oral medications.

The role of other fluoroquinolones for the treatment of intra-abdominal infections remains to be determined. There is particular interest in newer agents that are active against anaerobic as well as aerobic gram-negative organisms, and thus could be used as single agents for these infections. In one large study, a regimen using intravenous alatrofloxacin followed by oral trovafloxacin was found comparable to a regimen of imipenem/cilastatin followed by oral amoxicillin/clavulanic acid [86]. However, because of its hepatic toxicity, use of alatrofloxacin and trovafloxacin was subsequently curtailed sharply, and this regimen cannot be recommended at present. Additional fluoroquinolones, such as moxifloxacin and others still in clinical development, are currently being tested as monotherapy for patients with intra-abdominal infections. Such agents may provide additional therapeutic alternatives for these patients in the future.

Antianaerobic agents. The previous guidelines recommended clindamycin and metronidazole as acceptable antianaerobic agents in combination regimens for the treatment of patients with intra-abdominal infections. These guidelines did not recommend the use of chloramphenicol because of its risk of side effects [1]. The Committee uncovered very little recent data with which to evaluate further these recommendations.

In several studies, a trend toward increasing *in vitro* resistance of *B. fragilis* and other anaerobes to several antianaerobic agents was observed. However, this did not appear to be occurring with metronidazole [105–107]. This led some authors to question the use of antimicrobials such as cefoxitin and clindamycin for patients with intra-abdominal infections [107]. Although an occasional clinical failure in prospective trials has been attributed to resistant anaerobic bacteria, the overwhelming majority of prospective trials provide little indication that success rates are influenced significantly by the antianaerobic component of the regimen, as long as anaerobic coverage is present. Thus, the clinical relevance of the changing resistance patterns of anaerobic organisms remains uncertain.

A few reports published between 1990 and 2000 evaluated the efficacy of the antianaerobic agents used to treat patients with intra-abdominal infections. One small prospective study compared 75 pediatric patients who received a regimen of ampicillin/sulbactam and gentamicin against 39 similar patients who received a regimen of ampicillin, gentamicin and clindamycin [108]. Success rates for both study groups were 97%, suggesting that ampicillin/sulbactam had adequate anaerobic efficacy. Another prospective trial randomized patients with perforated appendicitis to receive clindamycin, 900 mg given every 8 h or clindamycin, 600 mg given every 6 h; all patients also received gentamicin to cover aerobic/facultative anaerobic gram-negative organisms [109]. Success rates were 93% and 91% in 80 and 46 clinically evaluable patients, respectively. In some studies, a lower dose of clindamycin, 600 mg given every 8 h, has been used. Rovers et al. [110] compared patient outcomes in three series that used this dosing regimen with outcomes in three other series that used a higher dose of 900 mg q8h. These authors concluded that the lower dose of clindamycin was less efficacious for the treatment of patients with intra-abdominal infections. However, since none of the studies included in the analysis by these authors directly compared these two regimens, this conclusion seems questionable.

Overall, the Committee does not believe that the available data justify any change in the previous recommendations regarding antianaerobic agents. Thus, clindamycin or metronidazole continue to be recommended as acceptable antianaerobic components of combination regimens used for the treatment of patients with intra-abdominal infections.

Selection of antimicrobial agents. The recommended antimicrobial agents for the treatment of patients with intra-abdominal infections are listed in Table 12. As discussed previously, the Committee did not designate preferred or first-line regimens, because the available evidence did not prove that any specific regimen was superior. Thus, for the treatment of most patients, particularly those with mild-to-moderate community-acquired infections, selection of spe-

Table 12. Recommended Antimicrobial Regimens for Intra-Abdominal Infections

Single agents
Ampicillin/sulbactam
Cefotetan
Cefoxitin
Ertapenem
Imipenem/cilastatin
Meropenem
Piperacillin/tazobactam
Ticarcillin/clavulanic acid
Combination regimens
Aminoglycoside (amikacin, gentamicin, netilmicin, tobramycin,) plus antianaerobe (clindamycin or metronidazole)
Aztreonam plus clindamycin
Cefuroxime plus metronidazole
Ciprofloxacin plus metronidazole
Third/fourth-generation cephalosporin (cefepime, cefotaxime, ceftazidime, ceftizoxime, ceftriaxone) plus antianaerobe

cific antimicrobials must be based on criteria other than clinical efficacy.

One property that could potentially guide selection of an initial empiric regimen is the activity of the antimicrobial agents against the common bacterial organisms that cause intra-abdominal infections. In actuality, all the recommended regimens are active against the typical aerobic and anaerobic pathogens observed in patients with community-acquired infections. The various antimicrobial agents differ with respect to their coverage of *Enterococcus* and their breadth of gram-negative coverage.

As discussed previously, there is little indication that routine enterococcal coverage is necessary for most patients with community-acquired intra-abdominal infections, therefore this should not be a consideration. With regard to activity against gram-negative organisms, some agents such as second-generation cephalosporins or ampicillin/sulbactam provide less coverage of organisms such as *Enterobacter* and *Pseudomonas* than do broader-spectrum agents in their classes. Nonetheless, these antimicrobials have generally performed as well as others in clinical trials. Thus, the expanded gram-negative spectrum of many recommended antimicrobial agents is not necessarily advantageous for patients with community-acquired intra-abdominal infections, who are at relatively low risk for failure. In fact, since one of the guiding principles of antimicrobial therapy is to use an agent with a narrower spectrum of activity when possible, it might even be preferable to use an agent such as cefoxitin, cefotetan, ampicillin/sulbactam, or ticarcillin/clavulanate for the initial empiric treatment of lower-risk patients with intra-abdominal infections. However, this would not apply to patients likely to harbor more resistant organisms, such as those already in health care institutions or those who have recently been treated with antimicrobial agents.

Another relevant consideration to the selection of specific antimicrobials for the treatment of intra-abdominal infections is the toxicity of different agents. Because of their narrow therapeutic ranges and associated problems of ototoxicity and nephrotoxicity, aminoglycosides are generally considered higher-risk agents. Fear of toxicity may actually lead to underdosing of these agents, and thereby result in therapeutic failure [48]. It would seem reasonable to use these agents primarily for patients with allergies to other antimicrobial agents or when necessary to treat resistant organisms.

Cost considerations could play a role in the selection of the initial empiric antimicrobial therapy. However, determining the actual costs of different regimens is problematic. The acquisition costs of different antimicrobial agents may be quite specific to a particular institution, and differ substantially from national averages. Costs of administration may add appreciably to acquisition costs, but are difficult to estimate. These may differ substantially for different regimens according to how many antimicrobial doses must be given. In addition, the relatively low acquisition costs of certain agents, such as aminoglycosides, may be offset by costs incurred with laboratory monitoring. Finally, the use of oral antimicrobials might allow for outpatient therapy, and thereby substantially decrease overall costs of treatment, notwithstanding the expense of the antimicrobial agents themselves.

An additional issue related to the use of antimicrobials for intra-abdominal infections is whether or not to alter the initial empiric regimen according to the results of intraoperative cultures. There is substantial controversy regarding the usefulness of intraoperative cultures for most patients with intra-abdominal infections, particularly those with community-acquired infections. Several authors believe that the routine use of such cultures is unwar-

ranted [111,112], while others still advocate their use [90]. If peritoneal cultures are obtained, however, it is common for the final results to reveal one or more organisms resistant to the initial empiric antimicrobial regimen. The consensus of the Committee is that if the patient is showing an adequate clinical response, there is little justification for changing antimicrobial agents on the basis of culture results alone. Although this approach might be considered in a patient who is not showing signs of clinical improvement, there is also a real possibility that such a patient has either a persistent intra-abdominal infection requiring further efforts at source control, or a nosocomial infection outside the abdomen requiring different types of antimicrobials altogether. Under either of these circumstances, alteration of the antimicrobial regimen based on the intraoperative culture results may not be successful in treating the patient. The guidelines developed regarding the use of antimicrobial regimens for the treatment of patients with intra-abdominal infections are listed in Table 13.

ANTIMICROBIAL THERAPY FOR THE HIGHER-RISK PATIENT

Up to now, the guidelines have focused primarily on antimicrobial therapy for lower risk patients with common community-acquired intra-abdominal infections. Most of these patients are expected to make an uncomplicated recovery following a primary source control procedure and appropriate antimicrobial treatment. However, there are some patients with intra-abdominal infections for whom an uncomplicated postoperative course seems less likely. This impression may be due to the overwhelming nature of the infection itself, the patient's severely limited physiological reserves, or the failure of previous attempts at therapy.

Table 13. Guidelines for Antimicrobial Regimens for Intra-Abdominal Infections

1. Antimicrobial regimens for intra-abdominal infections should cover common aerobic and anaerobic enteric flora. The following antimicrobials or combinations of antimicrobials are effective for the treatment of intra-abdominal infections. No regimen has been demonstrated to be superior to another (Level 1).

   Single agents:
   - Ampicillin/sulbactam
   - Cefotetan
   - Cefoxitin
   - Ertapenem
   - Imipenem/cilastatin
   - Meropenem
   - Piperacillin/tazobactam
   - Ticarcillin/clavulanic acid

   Combination regimens:
   - Aminoglycoside (amikacin, gentamicin, netilmicin, tobramycin) plus antianaerobe (clindamycin or metronidazole)
   - Aztreonam plus clindamycin
   - Cefuroxime plus metronidazole
   - Ciprofloxacin plus metronidazole
   - Third/fourth-generation cephalosporin (cefepime, cefotaxime, ceftazidime, ceftizoxime, ceftriaxone) plus antianaerobe

2. For patients with mild-to-moderate community-acquired infections, agents having a narrower spectrum of activity, such as antianaerobic cephalosporins, ampicillin-sulbactam, or ticarcillin-clavulanic acid are preferable to more costly agents having broader coverage of gram-negative organisms and/or greater risk of toxicity (Level 3).
3. Completion of the antimicrobial course with oral forms of ciprofloxacin plus metronidazole (Level 2) or with oral amoxacillin/clavulanic acid (Level 3) is acceptable in patients able to tolerate an oral diet.
4. Once-daily administration of aminoglycosides is the preferred dosing regimen for patients receiving these agents for intra-abdominal infections. Careful attention should be paid to prompt attainment of therapeutic antibiotic concentrations when aminoglycosides are used (Level 2).
5. Regimens providing enterococcal coverage are not routinely necessary in the treatment of most patients with intra-abdominal infections (Level 2).
6. The routine use of intra-operative cultures is controversial. However, altering the antimicrobial regimen on the basis of culture results does not improve outcome in patients having a satisfactory clinical response (Level 3).

The selection of appropriate antimicrobial therapy for higher-risk patients would be facilitated greatly by the identification of objective criteria for recognizing such patients. Several analyses, in fact, have identified specific risk factors that predict mortality in patients with intra-abdominal infections. However, many of these risk factors are the same as those that predict perioperative mortality in any patient undergoing a surgical procedure, whether or not an intra-abdominal infection is present. Such risk factors relate primarily to patients' underlying comorbidities, such as preexisting cardiac disease or other medical problems. These risk factors are probably of little relevance in selecting specific antimicrobial regimens to be used in the treatment of higher risk patients with intra-abdominal infection. However, risk factors for treatment failure rather than postoperative mortality, particularly those that pertain to the pathogenic organisms involved in the infection, might be more germane to the selection of antimicrobial therapy for higher risk patients. Unfortunately, relatively few analyses have focused on the infection-related parameters that predict treatment failure.

Even if patients at higher risk for treatment failure can be identified, the development of specific recommendations is difficult because relatively little Class I evidence pertains to these higher-risk patients. As discussed previously, prospective randomized controlled trials comparing different antimicrobials primarily enrolled patients with community-acquired intra-abdominal infections, such as perforated appendicitis, who were likely at lower risk for treatment failure and death. Many trials specifically excluded higher risk patients.

To characterize further the studies comprising the database, the Committee examined mortality rates as crude indicators of the inclusion of higher-risk patients in the trials. Notably, three-quarters of the trials reported a mortality of 5% or less, with a number reporting no mortality at all. This contrasts with mortality rates ranging from 17% to 32% in several series evaluating risk factors for treatment failure and death in patients with intra-abdominal infections [113–118], and a mortality rate of 6% in an epidemiological survey that was broadly representative of patients with intra-abdominal infections and included substantial numbers of patients with complicated appendicitis [119]. The lower mortality rates found in clinical trials compared to broader surveys of patients with intra-abdominal infections support the conclusion that most patients enrolled in clinical trials were at relatively low risk for therapeutic failure, and that relatively few higher-risk patients were enrolled in most of these studies.

Therefore, the Committee believes it is inappropriate to apply the results of most clinical trials to higher-risk patients. There were a few clinical trials that specifically focused on higher-risk patients, and these trials did provide some Class I evidence suitable for developing recommendations. However, in the end, many of these recommendations for higher-risk patients had to be based primarily on expert opinion.

Summary of findings

Identification of risk factors. For patients with intra-abdominal infections, treatment failure and death are likely related both to the severity of the infectious process as well as to the patient's intrinsic physiological capacity to respond to that infection. In a number of studies that utilized multivariate analyses to identify risk factors for treatment failure or death [95,113–117], this latter capacity proved to be of paramount importance in determining the likelihood of an adverse outcome. The independent risk factors identified in these studies included higher APACHE II scores, advanced age, malnutrition, hypoalbuminemia, hypocholesterolemia, the presence of medical conditions such as cardiovascular disease, renal disease, and malignancy, and the use of corticosteroid medications (Table 14). Advanced age and significant hypoalbuminemia were identified as risk factors in more than one study, but a higher APACHE II score was identified as an independent risk factor in all the studies examined. Thus, the APACHE II score appears to be the best predictor of treatment failure or death in patients with intra-abdominal infections, a conclusion that has been echoed by Ohmann and Hau [120].

Higher APACHE II scores primarily identify

Table 14. Independent Risk Factors for Mortality or Treatment Failure Identified by Multivariate Analyses

Reference	*Mortality*	*Treatment failure*
[95] Barie, 1997	NR	APACHE II score Prolonged prestudy length of hospitalization
[113] Dellinger, 1985	APACHE II score Malnutrition Age	NR
[114] Christou, 1993	APACHE II score Hypoalbuminemia NYHA functional class	APACHE II score Hypoalbuminemia Age
[115] Bohnen, 1994	APACHE II score Corticosteroid therapy	NR
[116] Pucelli, 1996	APACHE II score Mannheim peritonitis index Hypoalbuminemia Hypocholesterolemia Preoperative organ impairment	NR
[117] Wacha, 1999	APACHE II score Unsuccessful operation Age Liver disease Malignant disease Renal disease	NR

patients with acute physiological changes induced by infection and chronically impaired physiological reserves. It is unclear how the selection of antimicrobial therapy might be expected to impact clinical outcome in higher-risk patients designated on this basis. It seems more likely that the choice of antimicrobial therapy would influence outcome if higher-risk patients were selected on the basis of the severity of the intra-abdominal infection itself or, particularly, on the basis of the specific organisms involved in the infection.

Traditionally, the source of the intra-abdominal infection was believed to influence the risk of treatment failure and death, as exemplified by the low mortality rates of patients with perforated appendicitis [113,114,116,119]. However, in multivariate analyses, the source of the infection has not proved to predict outcome independently. The lower risk of treatment failure and death in patients with perforated appendicitis probably reflects the relatively young age and lack of comorbid conditions typical of patients with this disorder.

There is evidence, however, that the susceptibility patterns of the organisms involved in the intra-abdominal infection influence the success or failure of empiric antimicrobial therapy. In a trial by Christou et al. [90], all patients having at least one resistant organism isolated at the time of initial intervention experienced treatment failure. In another trial, Barie et al. [95] found that a prolonged prestudy length of hospitalization was an independent predictor of failure. This risk factor may have identified patients who had previous antimicrobial exposure or who had postoperative peritonitis, and would therefore be more likely to harbor organisms resistant to commonly used antimicrobials. In a retrospective review of five antibiotic trials, Hopkins et al. [121] found that the susceptibility of peritoneal isolates to the initial empiric regimen also predicted treatment success or failure. Finally, Montavers et al. [122] reached a similar conclusion based on a retrospective review of patients with postoperative peritonitis, and showed by multivariate analysis that the presence of organisms resistant to the empiric regimen was an independent predictor of mortality. It is important to note that none of these studies provided direct evidence that any specific antimicrobial regi-

men would improve outcome in the higher-risk patients defined by these criteria. However, these results do suggest that a common feature of higher-risk patients is the presence of resistant organisms. The Committee would speculate that many of these resistant organisms are of nosocomial origin.

One final risk factor for failure that has been increasingly emphasized in recent trials is an inadequate initial source control procedure. An unsuccessful operation was, in fact, found to be a risk factor for death in the multivariate analysis carried out by Wacha et al. [117]. Clearly, no antimicrobial regimen can be expected to be successful if there is ongoing contamination or an uncontrolled infectious source within the abdomen.

Selection of antimicrobial regimens. Considering that higher-risk patients with intra-abdominal infections are more likely to fail because of resistant organisms, it seems reasonable to recommend antimicrobial regimens with broader coverage of gram-negative aerobic/facultatively anaerobic organisms for use in these patients. However, as discussed previously, this recommendation was not made on the basis of convincing Class I evidence demonstrating that this approach improves outcome. In the previous guidelines, Bohnen et al. [1] recommended imipenem/cilastatin, a third-generation cephalosporin plus an antianaerobic agent, an aminoglycoside plus an antianaerobic agent, or aztreonam plus clindamycin for the treatment of patients with more serious infections. To this list, the Committee has added piperacillin/tazobactam, meropenem, the fourth-generation cephalosporin cefepime plus an antianaerobic agent, and ciprofloxacin plus metronidazole (Table 15). Depending on the likelihood of infection due to *Pseudomonas* in these higher risk patients, the doses of some antimicrobial agents, such as piperacillin/tazobactam, may need to be increased to provide adequate anti-pseudomonal coverage. An aminoglycoside plus an antianaerobic agent is still included in the list of recommended regimens, but it is important that the aminoglycoside be dosed adequately to ensure rapid attainment of therapeutic serum concentrations in higher risk patients. Further, these patients may be at increased risk for nephrotoxicity and ototoxicity due to these agents.

Table 15. Recommended Antimicrobial Regimens for Higher-Risk Patients with Intra-Abdominal Infections

Single agents
Imipenem/cilastatin
Meropenem
Piperacillin/tazobactam
Combination regimens
Aminoglycoside (amikacin, gentamicin, netilmicin, tobramycin) plus an antianaerobe
Aztreonam plus clindamycin
Ciprofloxacin plus metronidazole
Third/fourth-generation cephalosporin (cefepime, cefotaxime, ceftazidime, ceftizoxime, ceftriaxone) plus an antianaerobe (clindamycin or metronidazole)

Another potential approach to treatment of higher risk-patients with intra-abdominal infections is to utilize two agents effective against gram-negative aerobic/facultative anaerobic organisms. The usual combination is an aminoglycoside plus an extended spectrum beta-lactam antibiotic. This approach was tested directly in several prospective randomized controlled trials. In the largest comparison, Dupont et al. [70] compared piperacillin/tazobactam alone against the combination of piperacillin/tazobactam with amikacin in patients with severe community-acquired intra-abdominal infections and hospital-acquired intra-abdominal infections. The overall mortality rate in this trial was 20%, attesting to the high acuity of the patients enrolled. Although the success rate with piperacillin/tazobactam (51%) was lower than that observed in other studies of intra-abdominal infections, it was equivalent to that seen in the group receiving combination therapy (51%). In another study, imipenem/cilastatin alone was compared to imipenem/cilastatin plus netilmicin in 78 patients with severe, diffuse peritonitis [68]. Patients with peritonitis due to appendicitis or upper gastrointestinal perforations were excluded from this study. The success rate with imipenem/cilastatin alone was 79% as compared to the success rate of 92% using imipenem/cilastatin plus netilmicin. This difference in outcome was of borderline significance ($p = 0.09$), and was likely explained by an imbalance in the numbers of severely ill pa-

tients in the two groups. Many more of the patients who received imipenem/cilastatin alone had high APACHE II scores compared to those who received the combination regimen. Finally, one additional study of 79 clinically evaluable patients found that patients treated with ciprofloxacin plus metronidazole had a significantly better clinical outcome than patients treated with the combination of cefotaxime, gentamicin, and metronidazole [69]. Mortality was also relatively high in this study, suggesting that a higher-risk group of patients had been enrolled. Overall, these studies did not demonstrate that the routine addition of an aminoglycoside to another agent effective against aerobic/facultative anaerobic gram-negative organisms improves outcome, and the Committee recommends against this approach in higher-risk patients with intra-abdominal infections.

Enterococcal coverage. Depending on the etiology and severity of the infection, *Enterococcus* is isolated from 5–20% of patients with intra-abdominal infections. Its importance as a pathogen and the need for its routine treatment remain controversial [74,80,81,90,95]. As described previously, prospective trials did not demonstrate any improvement in outcome comparing antimicrobial regimens that covered this organism with those that did not. Therefore, the Committee did not recommend routine use of regimens providing enterococcal coverage for most patients with intra-abdominal infections.

However, it is not clear that this recommendation should be extrapolated to higher-risk patients, particularly those with hospital-acquired infections. As emphasized repeatedly, prospective trials have primarily enrolled less severely ill patients. Further, the incidence of enterococcal infections among enrolled patients has tended to be low. For instance, in the study by Röhrborn et al. [81], which was designed specifically to test the need for routine enterococcal coverage in patients with community-acquired intra-abdominal infections, only 5% of the patients actually had *Enterococcus* isolated at the time of the initial laparotomy.

Enterococcal infections may be more common in higher risk patients, and, as with other resistant organisms, isolation of *Enterococcus* may also identify patients at higher risk for treatment failure. In the retrospective review by Hopkins et al. [121], isolation of Group D *Streptococcus*, presumably enterococci, was associated with the likelihood of failure, although it was not clear that this was an independent predictor of failure. However, in another multivariate analysis of data obtained from a prospective trial, Burnett et al. [123] found that the isolation of *Enterococcus* was indeed an independent predictor of failure. In this study of 330 patients, of whom 21% had positive cultures for *Enterococcus*, the failure rate was 28% among patients who had this organism, but was 14% among patients who did not. These authors also found that patients at risk for enterococcal infections were those who were of advanced age, had higher APACHE II scores, had longer hospital lengths of stay prior to developing the infection, had a postoperative infection, or had a colonic or small bowel source of infection. Enterococci did not tend to be isolated from patients with infections resulting from appendicitis. Thus, the risk factors for having enterococcal infections were quite similar to those that described higher-risk patients in general.

Although there is no Class I evidence that treatment of higher-risk patients with antimicrobials providing enterococcal coverage improves outcome, the Committee believes that this may be a reasonable approach, given the correlation that exists between enterococcal isolation and increased risk of treatment failure. Thus, for higher-risk patients with intra-abdominal infections, the Committee recommends that consideration be given to the use of a regimen covering *Enterococcus*, particularly when patients are likely to harbor this organism because of a previous failure of antimicrobial therapy. The choice of the specific antimicrobial regimen would depend in part on the enterococcal resistance patterns specific to the particular institution.

Treatment of Candida. Intra-abdominal infections due to fungal organisms, particularly *Candida albicans*, primarily occur in higher-risk patients. Many of these infections develop in

postoperative patients, and almost all develop in patients who have already been heavily treated with broad-spectrum antibiotics [124]. Invasive candidal infections in the abdominal cavity are associated with high mortality rates, despite utilization of antifungal agents. Unfortunately, there are only limited prospective data with which to evaluate different approaches to the prevention and management of intra-abdominal infections due to *Candida*.

Early initiation of antifungal therapy appears to be an important determinant of outcome in patients with intra-abdominal candidal infections. Solomkin et al. [124] described 55 patients with *Candida* peritonitis, and noted a progression of disease from infection of the peritoneal cavity only, to colonization and infection of multiple sites, to the eventual development of candidemia and widespread, diffuse candidiasis. Patients who did not receive antifungal therapy until they developed positive blood cultures were likely to fail treatment and to die of the infection.

Although patients with *Candida* peritonitis clearly have an established infection requiring antifungal therapy, *Candida* is also isolated from the peritoneal cultures of patients who are colonized, but not infected with this organism. Calandra et al. [125] examined a series of 49 patients with positive peritoneal cultures for *Candida*, to determine what clinical characteristics predicted the need for antifungal therapy. These authors found that patients with recurrent gastrointestinal perforations and those with postoperative infections following surgical management of acute pancreatitis were at high risk for having an invasive candidal infection requiring treatment. Patients with heavy or increasing growth of *Candida* in semiquantitative cultures of peritoneal fluid were also likely to need systemic antifungal therapy.

Based on these clinical findings, Eggiman et

Table 16. Summary of Prospective Randomized Controlled Trials of Antifungal Agents for the Treatment of Patients with Intra-Abdominal Infections

Reference	*Antifungal agents*	*Number of patients enrolled*	*Number of evaluable patients*	*Reported success rate*	*ITT analysis*	*Mortality*	*Quality score*	*APACHE II scoring?*
[126] Eggiman, 1999	Prophylactic fluconazole 400 mg qd	25	23	96%[1,2]	NR[3]	30%	4	13
	No prophylactic antifungal agent	24	20	65%[1,2]		50%		13
[127] Abele-Horn, 1996	Fluconazole 400 mg, then 200 mg qd	NR	8[4]	25%[5,6]	NR	63%	1	21
	Amphotericin B 1–1.5 mg/kg qod + 5-Flucytosine 2.5 g tid		9[4]	56%[5,6]		33%		20

[1]Patients who failed therapy were those who developed *Candida* peritonitis. Success rates were 83% in the fluconazole group and 65% in the placebo group if any candidal infection was considered a treatment failure.

[2]The difference between the groups was statistically significant ($p = 0.02$), in favor of the fluconazole group. The difference between groups was not statistically significant for the development of any candidal infection.

[3]No data were provided, but the result of the ITT analysis was stated to confirm the significant difference between the groups with respect to the development of *Candida* peritonitis.

[4]The values represent the numbers of patients enrolled because of *Candida* peritonitis. A total of 36 patients were enrolled in each group because of any type of candidal infection.

[5]Success rates are based only on patients reported as clinically cured of *Candida* peritonitis. Additional patients with *Candida* peritonitis were considered improved, and could have been considered successfully treated, but their numbers were not reported.

[6]Success rates in all treated patients, not just those with *Candida* peritonitis, were 67% in the fluconazole group and 69% in the amphotericin B plus 5-flucytosine group.

al. [126] undertook a prospective randomized controlled trial of empiric fluconazole therapy to prevent the development of invasive intra-abdominal candidal infections in higher-risk patients. The study population was restricted to critically ill patients with recurrent gastrointestinal perforations or other postoperative infections. Candidal peritonitis developed in only one of the 23 clinically evaluable patients treated with fluconazole, but in seven of the 20 clinically evaluable patients who received a placebo. This difference was statistically significant. Overall, 30% of the patients randomized to empiric therapy with fluconazole died, as opposed to 50% of those in the placebo group. Although this difference was not statistically significant, four of the 10 deaths in the latter group were directly attributed to complications of *Candida* peritonitis (Table 16).

There is some controversy regarding the antifungal agent of choice for patients with confirmed intra-abdominal candidal infections. The efficacy of fluconazole for the treatment of these infections was fortuitously demonstrated in the data of Eggiman et al. [126], since 40% of the patients who received fluconazole already had a candidal infection, as evidenced by isolation of *Candida* from cultures of peritoneal fluid obtained at the time of study entry. Nonetheless, another trial questioned the use of fluconazole for the treatment of candidal peritonitis. This prospective randomized controlled trial compared fluconazole with amphotericin B and 5-flucytosine for the treatment of critically ill patients with candidiasis from any source. Seventeen of the 72 evaluable patients in this trial had *Candida* peritonitis. Two of the eight patients (25%) treated with fluconazole were cured, as compared to five of the nine (56%) treated with amphotericin B and 5-flucytosine (Table 16). These results did not reach statistical significance because of the

Table 17. Guidelines for Antimicrobial Therapy for the Higher-Risk Patient

1. In patients with intra-abdominal infections, treatment failure and death is associated with patient-related risk factors such as advanced age, poor nutritional status, a low serum albumin, and preexisting medical conditions, especially cardiovascular disease. A higher APACHE II score is the most consistently recognized risk factor for both death and treatment failure (Level 1).
2. Disease- and treatment-related risk factors, including a nosocomial origin of infection, the presence of resistant pathogens, and the lack of adequate source control, are associated with treatment failure and death (Level 2).
3. Patients at higher risk for failure (particularly from non–community-acquired organisms) should be treated with an antimicrobial regimen having a broader spectrum of coverage of gram-negative aerobic/facultative anaerobic organisms (Level 3):
   Single agents:
   - Imipenem/cilastatin
   - Meropenem
   - Piperacillin-tazobactam

   Combination regimens:
   - Aminoglycoside plus antianaerobe
   - Aztreonam plus clindamycin
   - Ciprofloxacin plus metronidazole
   - Third/fourth generation cephalosporin plus antianaerobe
4. Routine addition of an aminoglycoside to other effective gram-negative agents such as imipenem/cilastatin, piperacillin/tazobactam, or third- or fourth-generation cephalosporins, is not recommended (Level 2).
5. High-risk patients likely to fail due to *Enterococcus*, such as those of advanced age, with higher APACHE II scores, a colonic or small bowel source of infection, a postoperative infection, or a nosocomial origin of infection, may benefit from the use of a regimen covering this organism (Level 3).
6. Addition of empiric antifungal therapy with fluconazole is reasonable for patients with postoperative intra-abdominal infections at high risk for candidiasis (Level 2). For patients with established *Candida* peritonitis, antifungal therapy with amphotericin B may be preferable to use of fluconazole, but the choice of therapy must be influenced by the risk of toxicity in a given patient (Level 3).
7. Patients with tertiary peritonitis are likely to harbor difficult to eradicate organisms, such as coagulase-negative staphylococci, enterococci (including vancomycin resistant enterococci), multiply-resistant gram-negative bacilli, and yeast (Level 2). Empiric therapy should be directed at organisms likely to be present based on the patient's history of previous antimicrobial therapy and local patterns of infectious organisms and resistance. Empiric therapy should be modified according to definitive culture results (Level 3).

small number of patients in this subset analysis, but they raised some concern with regard to the efficacy of fluconazole in a particularly severely ill population of patients with intra-abdominal candidal infections.

Overall, based on this limited evidence, the Committee recommends empiric use of fluconazole in patients who are at high risk for failure due to candidal infections in the abdomen. Examples of such patients include those with recurrent gastrointestinal perforations or anastomotic leaks, and those who develop or have persistent infections after operative management of acute pancreatitis. For critically ill patients with established candidal peritonitis, there is a suggestion that amphotericin B may be preferable to fluconazole. However, additional considerations, particularly the risks of toxicity in a given patient, must also be factored into the decision to select a specific antifungal agent.

Tertiary peritonitis. Patients who have persistent intra-abdominal infections after multiple therapeutic attempts are described as having tertiary peritonitis. There are relatively few data to guide treatment decisions in this group of patients. Typically, these patients are infected with resistant organisms such as coagulase–negative *Staphylococcus*, enterococci, including those resistant to vancomycin, multiply resistant gram-negative bacilli, and fungal organisms, including many that are resistant to fluconazole [128,129]. Open abdominal techniques have been used in some of these patients as a means of achieving source control, but the efficacy of such methods has not been proved definitively.

The consensus of the Committee is that antimicrobial therapy needs to be individualized for patients with tertiary peritonitis. Empiric antimicrobial therapy should be directed at the nosocomial organisms likely to be causing the infection, based on individual and institutional experience. The choice of agents should also reflect the resistance patterns of likely pathogens, the patient's history of prior antimicrobial exposure, and the results of the Gram stain of infected peritoneal fluid, when available. Empiric therapy is adjusted subsequently according to the final culture results.

Patients suffering from tertiary peritonitis have an overwhelming failure of host defense mechanisms [128–130]. Treatment failure is common, and many of these patients eventually succumb to the effects of multiple organ failure, whether or not the intra-abdominal infection has been controlled. This has led some to speculate that antimicrobial therapy should not be used in patients with tertiary peritonitis. However, in the absence of data establishing a benefit of not treating pathogenic microorganisms, the Committee concurs with the opinion of Solomkin [130] that specific antimicrobial therapy is warranted for these very challenging patients. Guidelines for the identification and treatment of higher-risk patients with intra-abdominal infections are listed in Table 17.

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APPENDIX: EXPLANATIONS OF HEADINGS AND ABBREVIATIONS FOUND IN TABLES 3–8

Headings

Antimicrobial agents or antifungal agents. Only the initial doses of antimicrobials are indicated. If aminoglycoside dosing was subsequently modified according to monitoring of serum aminoglycoside concentrations, this is indicated in the footnotes. Dosing modifications of other agents are also indicated in the footnotes.

Number of patients enrolled. These numbers represent all patients randomized to study treatment. If patients were enrolled for diagnoses other than intra-abdominal infections, this is indicated in the footnotes. The inclusions of patients less than 14 years of age are indicated in the footnotes.

Number of evaluable patients. These numbers represent the number of clinically evaluable patients actually used in determining success rates. Inclusions of patients in the clinically evaluable population who did not have complicated intra-abdominal infections, that is, those who did not undergo primary source control procedures, are indicated in the footnotes.

Reported success rate. Success rates are based on clinically evaluable patients with intra-abdominal infections. In studies reporting treatment results other than success or failure, success rates were calculated after counting all patients classified as "improved" as successfully treated, and excluding patients classified as having indeterminate outcomes. If several success rates were reported, the rates indicated are those determined at the latest time point for which follow-up was complete. If the investigators did not report an overall success rate, it was calculated as best as possible using the data provided in the publication. Except for these exceptions, the success rates reported by the investigators were accepted as final, regardless of the criteria used to define success and failure.

Percentage of patients with sSSI. If information was provided in the publication, the percentages of patients who developed sSSI were determined, whether or not these infections were considered to represent a failure of therapy.

Success rate excluding isolated sSSI. The reported success rates were recalculated after counting patients who failed therapy only because of isolated sSSI as successfully treated. N/A indicates that the calculation could not be performed because the number of patients who failed therapy because of isolated sSSI could not be determined.

ITT analysis. Only analyses reported by the authors are included.

Mortality. These values were based on the clinically evaluable populations unless otherwise indicated.

Percentage of patients with hollow viscus injury and percentage of patients with appendicitis. These values were based on the clinically evaluable populations unless otherwise indicated.

Quality score. These values were determined according to the procedure of Jadad et al. [22]. N/A is indicated for class II studies, which were not graded.

APACHE II scoring? "Yes" indicates that scoring was performed. If mean APACHE II scores were reported, they are included in the table.

Specified treatment duration. The duration of treatment specified by the protocol.

Duration of antimicrobial therapy. The average length of time patients actually received antimicrobial therapy.

Complicated infection per IDSA criteria? "Yes" indicates that the authors used the criteria of Solomkin et al. [6] or similar criteria to determine enrollment and inclusions of patients in the clinically evaluable populations. "No" indicates that patients who did not have intra-abdominal infections or did not undergo primary source control procedures were considered clinically evaluable, or that patients with negative peritoneal cultures were included in the clinically evaluable populations. "Probably not" indicates that all patients had intra-abdominal infections and positive peritoneal cultures, but that some patients may have had localized infections or intra-abdominal contamination not requiring therapeutic antimicrobial therapy. Examples of such patients include those with localized, non-perforated appendicitis and those with recent gastroduodenal or traumatic enteric perforations.

Abbreviations

ITT	Intention-to-treat
NR	Not reported
N/A	Not applicable
IDSA	Infectious Disease Society of America
NYHA	New York Heart Association
sSSI	Superficial surgical site infection