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Clinical Challenges and Unmet Needs in the Management of Complicated Intra-abdominal Infections

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ABSTRACT

Background: **Management of complicated intra-abdominal infections involves invasive procedures for control of the source of the infection and antimicrobial therapy directed against gram-negative and anaerobic pathogens. Application of these management principles to the individual patient is essential to optimize the patient's chances for recovery, while also avoiding unnecessary therapy that may have no clinical benefits, or that may carry risk.**

Methods: **Based on a review of the literature, treatment guidelines, and expert opinion, the challenges of managing patients with complicated intra-abdominal infections are summarized using a patient stratification approach: "Lower risk" of treatment failure and death vs. "higher risk."**

Results: **Risk factors for treatment failure and death can be grouped into several categories, including the patient's pre-existing medical comorbidities and physiological response to the infection, the extent of the intra-abdominal infection, and the presence of specific pathogenic microorganisms. These latter factors may be more useful than the Acute Physiology and Chronic Health Evaluation (APACHE) II score in evaluating specific management strategies for patients with complicated intra-abdominal infections. The principal goal of treatment in lower-risk patients is to avoid morbidity related to source control procedures and antimicrobial therapy. Limitation of the scope of source control procedures and utilization of short-duration, narrow-spectrum, low-toxicity antimicrobial regimens is advisable to avoid adverse drug reactions and selection of resistant organisms. For higher-risk patients, the goal is to develop improved management modalities, so that morbidity and mortality are reduced. The recommended approach for higher-risk patients is to identify the most appropriate source control procedure and antimicrobial therapy, as dictated by the patient's specific risk factors, and to utilize the optimal tools of critical care medicine to treat these critically ill, septic patients. The emergence of bacterial resistance also must be considered when selecting antimicrobial therapy for both low risk and high risk patients with intra-abdominal infections. Because aminoglycoside regimens are becoming less favored, and optimal therapeutic strategies have not been standardized, the use of new treatment options (e.g., tigecycline) may be valuable when managing patients with intra-abdominal infections. especially for resistant isolates.**

Conclusions: **The management of lower-risk patients with intra-abdominal infections is distinct compared with patients at higher risk due to compromised physiological status, extent of intra-abdominal infection, or presence of nosocomial pathogens associated with higher-**

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risk patients. Carefully designed, multidisciplinary-sponsored, clinical trials in patients with specific clinical risk factors are needed to better assess the role of various antimicrobial regimens in the treatment of higher-risk patients with intra-abdominal infections.

INTRA-ABDOMINAL INFECTIONS result from the growth of bacteria in sterile regions of the abdomen such as the peritoneal cavity, the retroperitoneum, or solid organs, or from the uncontrolled overgrowth of microorganisms within the hollow viscera, where the normal resident flora coexists in a commensal relationship with the host. These infections ordinarily occur in association with an inflammatory process as either cause or consequence of the infection. As such, there is a wide variety of disparate pathological processes that can be called intra-abdominal infections, ranging from localized appendicitis to the diffuse inflammation of the abdominal cavity characterized as tertiary peritonitis [1,2].

The term "complicated" intra-abdominal infections is used to distinguish infections that require an invasive procedure for source control from "uncomplicated" infections, which can be treated medically without an invasive intervention [1]. This distinction is most applicable when there is a clear dichotomy in the pathophysiology and microbiology of the infections. Disorders such as secondary peritonitis and intra-abdominal abscesses generally arise from the resident intestinal flora and are polymicrobial in nature; these infections are generally treated with an invasive procedure. In contrast, disorders such as primary peritonitis and peritoneal catheter-associated infections are not usually due to enteric pathogens, and are usually monomicrobial; such infections are usually treated medically. However, this distinction, having been based on operational rather than pathophysiological differences, becomes somewhat artificial when applied to certain disorders, particularly those characterized by localized perforation of a hollow viscus. Thus, perforated diverticulitis or a peri-appendiceal phlegmon would be classified as uncomplicated if treated non-operatively by one practitioner, but as complicated if treated surgically by another. The lines between complicated and uncomplicated infections are also blurred by the use of percutaneous, radiologically-guided procedures for both diagnostic and therapeutic purposes. For instance, would the diagnostic "fine-needle" aspiration of a pancreatic phlegmon to ascertain the presence of infection suffice for that infection, if present, to be classified as "complicated?" Alternatively, would a drain have to be left in place for that distinction to be made? This review does not adhere to a strict separation of intra-abdominal infections into uncomplicated and complicated varieties. The discussion will focus on those intra-abdominal infections treated typically by surgeons, whether or not an initial surgical intervention is performed.

The optimal treatment of patients with intra-abdominal infections includes a source control procedure for drainage or control of the infectious focus, and adjuvant antimicrobial therapy to treat residual infecting organisms [2–5]. In some patients with uncomplicated intra-abdominal infections, the definitive source control procedure is deferred, and there is sole reliance on antimicrobial agents and the host response to control the infection. This latter approach applies to the patients described above, who are treated nonoperatively for a phlegmon resulting from acute diverticulitis or appendicitis. Another crucial element in the care of these patients is physiological support of organ function during the acute phase. This includes appropriate fluid resuscitation and other interventions needed to maintain critical perfusion of organs being pushed to their physiological limits by the host response to the infection [2].

Overall, the treatment paradigm of appropriate source control and antimicrobial therapy has produced generally satisfactory results. One epidemiological survey of patients with complicated intra-abdominal infections found an overall mortality rate of 6.0%, a postoperative abscess rate of 10.2%, and a re-operation rate of 12.5% [6]. Nonetheless, these data reflect the outcome of a heterogeneous group of patients at variable risks of treatment failure and death. Thus, the generally good results obtained in lower-risk patients, such as the young

patient with complicated appendicitis, contrasts with the much poorer results observed in higher-risk patients, such as the elderly individual with multiple medical comorbidities who develops generalized peritonitis following disruption of a colonic anastomosis.

Although stratifying the population of patients with intra-abdominal infections into lower-risk and higher-risk patients is a simplification, it is helpful in discussing their respective, differing management challenges. The central concept adhered to in this review is that the management approach should reflect the expected outcome, and that the issues in management differ between patients at lower risk and those at higher risk. Thus, clinical investigations should address different questions in lower-risk and higher-risk patients.

The topics that will be discussed can be grouped into three general areas: Distinguishing lower-risk from higher-risk patients, and understanding how distinct risk factors might influence therapeutic decision-making; minimizing the morbidity of the specific procedures employed and simplifying the type of antimicrobial therapy used for lower-risk patients with expected good clinical outcomes; and determining how to utilize different invasive strategies appropriately for source control and to tailor antimicrobial therapy to the likely pathogens that will be present in higher-risk patients, in whom mortality is substantial.

CHARACTERIZING PATIENT RISK

Before describing separate management strategies for lower-risk and higher-risk patients with intra-abdominal infections, it is necessary to consider how to stratify patients into these different risk categories. Stratification can best be based on specific clinical risk factors that predict adverse clinical outcomes, identified through the use of multivariate analyses. For patients with complicated intra-abdominal infections, a number of studies have identified risk factors that are associated with treatment failure or death.

A question that might arise is which clinical endpoint, treatment failure or death, is more appropriate for risk stratification. There are advantages and disadvantages to the use of either endpoint. At first glance, mortality might seem to be the most logical endpoint. However, death is a relatively infrequent outcome for patients with intra-abdominal infections, especially for low risk infections, and may ultimately be influenced more by factors related to the patient's underlying physiological condition than by factors related to the infection itself. Conceivably, stratification on the basis of risk factors that predict treatment failure might be more likely to identify a group of patients for whom altered therapeutic interventions would impact outcome favorably. However, treatment failure can be a somewhat nebulous endpoint, and needs to be described carefully. For example, if adverse outcomes such as superficial surgical site infections are included as treatment failures in the analyses, then the identified risk factors may pertain primarily to these minor complications, and not to major complications such as an intra-abdominal abscess or a need for re-operation.

A number of studies [7–12] analyzing risk factors for death and treatment failure were reviewed as part of the revised Surgical Infection Society (SIS) guidelines on antimicrobial therapy for intra-abdominal infections [3,4]. These risk factors are summarized in Table 1. To a first approximation, these data suggest that the same general types of risk factors influence both treatment failure and death, few of which relate directly to the infection itself or to the treatment modalities utilized. The Acute Physiology and Chronic Health Evaluation (APACHE) II score was associated with an adverse outcome in all of the studies, and was the most powerful marker of both treatment failure and death. The APACHE II score is based on the patient's age, acute physiological derangements, and the chronic health problems as determined within 24 h of the reference time point. As such, the APACHE II score reflects a compilation of the severity of the infection, the host response to the infection, and the patient's underlying comorbid medical conditions. Several other risk factors identified in these studies also pertained primarily to the patients' comorbidities. For instance, hypoalbuminemia was found to be a risk factor for a poor outcome in patients with intra-abdomi-

Table 1. Independent Risk Factors for Mortality or Treatment Failure

Mortality (five studies)	*Treatment failure (two studies)*
APACHE II Score[#]	APACHE II Score*
Age*	Age
Hypoalbuminemia*	Hypoalbuminemia
Hypocholesterolemia	Prolonged pre-study length of hospitalization
Malnutrition	
Preoperative Organ Impairment	
NYHA Functional Class	
Liver Disease	
Malignant Disease	
Renal Disease	
Corticosteroid Therapy	
Mannheim Peritonitis Index	
Unsuccessful Operation	

[#]Identified in five studies.
*Identified in two studies.
Adapted from [4], based on [7–12].

nal infections, and is, in fact, a factor for identifying patients at risk for an adverse outcome following any surgical procedure [13]. Nonetheless, these other risk factors are reflected to some extent in the APACHE II score, and this score proved to be a more consistent predictor of outcome than any marker of the patient's underlying medical condition considered separately.

There are several difficulties related to the use of the APACHE II score for stratifying patients with intra-abdominal infections. It is somewhat cumbersome to use, and is subject to inter-observer variability. Furthermore, if this score is calculated after a patient has first been resuscitated in the emergency department or operating room, as occurs frequently in the patient with an intra-abdominal infection, the score is artifactually lowered. However, the major issue is whether or not the APACHE II score provides information that is unique to patients with intra-abdominal infections, and can be used to guide specific therapy for these patients. Given that the APACHE II score is a general marker of critical illness, it seems possible that this score would be more useful in determining the general treatment approach to be followed in the intensive care unit than in delineating specific source control procedures or antimicrobial regimens to be used in a given patient.

In the studies cited, a few risk factors pertained more to the infection, and to the treatments utilized, than to the patient's physiological status or underlying medical condition. These risk factors might have more direct applicability to specific therapies selected for patients with intra-abdominal infections. It is interesting that the source of the infection is not found to be an independent risk factor in these analyses. Thus, the lower mortality rate of patients with complicated appendicitis [6] may be related to their younger age and healthier condition as to the extent of peritoneal contamination, compared to patients with other types of intra-abdominal infections.

The source of the infection may contribute indirectly to risk, however, as an influence on the extent of the infection. In one of the risk factor analyses, the Mannheim Peritonitis Index, a parameter describing the extent of the intra-abdominal infection, was found to be an independent risk factor [10]. One observational trial suggested limiting the duration of antimicrobial therapy based on the extent of the peritoneal infection [14], even though it did not use the Mannheim Peritonitis Index. The use of repeat laparotomy or multiple reoperations has

also been based, at least to some degree, on the extent of the peritoneal infection [2]. Thus, stratifying patients through the use of a reproducible system to describe the extent of the intra-abdominal infection could have direct utility for future investigations into their management.

One risk factor identified as a predictor of mortality is an unsuccessful initial operation [12]. It is often uncertain if the initial failure is due to technical error or due to the widespread nature of infection. In any case, these data provide some validation for the concept that an optimal source control procedure is crucial to achieving a good outcome in patients with complicated intra-abdominal infections. The challenge, then, is in determining how to achieve successful initial source control, considering the multiplicity of technical approaches that are available, the lack of data regarding comparative efficacy of operative procedures, and the major influences of experience and opinion in clinical surgical practice.

There is increasing recognition that patients with intra-abdominal infections due to organisms acquired in health care institutions (i.e., nosocomial intra-abdominal infections) are at higher-risk for treatment failure and death. Although not noted in the other multivariate analyses, the study of Barie et al. [11] identified a prolonged pre-study duration of hospitalization as a risk factor for treatment failure. This clinical parameter may be a surrogate for the acquisition of resistant flora. Several studies have affirmed a role of resistant microorganisms in treatment failure [15–17]. In particular, Montravers et al. [17] used a multivariate analysis to show that the presence of organisms resistant to the empiric antimicrobial regimen chosen is an independent predictor of mortality in patients with postoperative peritonitis. The choice of empiric antimicrobial therapy may therefore play a role in determining clinical outcome. Thus, stratifying patients according to their likelihood of harboring resistant pathogens acquired nosocomially could be an approach to guiding the selection of specific antimicrobial therapy.

In summary, challenges remain in developing risk stratification of patients with complicated intra-abdominal infections. Although the APACHE II score is a powerful marker of treatment failure and death, factors describing the extent of the intra-abdominal infection and the likelihood of resistant pathogens could potentially be more useful than the APACHE II score in evaluating specific management strategies for these patients.

MANAGEMENT OF LOWER-RISK PATIENTS

Lower-risk patients with community-acquired intra-abdominal infections can usually be managed successfully using the standard approach of an appropriate source-control procedure and adjuvant antimicrobial therapy directed against gram-negative *Enterobacteriacae* and anaerobic pathogens. The outcome of lower-risk patients can be inferred from the results of antibiotic registration trials carried out in patients with complicated intra-abdominal infections. In many of these trials, lower-risk patients with community-acquired infections were predominately or exclusively enrolled and evaluated. With the exception of a few trials emphasizing higher-risk patients, mortality was nearly always less than 5% in these trials, and was often zero. Typically, success (clinical cure) rates ranged from 85–100% [4]. Many of the treatment failures recorded were relatively minor, such as the development of a superficial surgical site infection in a patient whose surgical incision was closed primarily. Although substantive treatment failures do occur occasionally in these lower-risk patients, the low incidence of these complications would make it unlikely that major changes in the standard treatment approach would be rewarded by significant improvements in outcome.

If the standard approach remains valid for lower-risk patients with community-acquired intra-abdominal infections, what then are the unmet needs in managing this group of patients? Conceivably, these could be the patients for whom less aggressive interventions might be warranted under selected circumstances, in order to minimize morbidity. Thus, with regard to source control procedures, the challenge would be to determine if less invasive procedures could be used, or if it is possible to defer a definitive source control procedure en-

tirely in selected patients. Obviously, this could only be done if there is no compromise to the generally good overall outcome of this group of patients. With regard to antimicrobial therapy, the goal would be to utilize a regimen that is not only effective, but also as safe as possible. Within this context, safety applies not only to the patient, in avoiding a potentially toxic regimen, but also to the community at large, in avoiding a regimen likely to encourage the development of resistant pathogens. The ideal regimen would also be simple to administer and perhaps amenable for use in the outpatient setting. The challenges of providing appropriate source control and antimicrobial therapy to lower-risk patients with community-acquired infections will be discussed separately.

Source control for lower-risk patients with community-acquired intra-abdominal infections

The optimal source-control procedure for patients with intra-abdominal infections has been characterized by Marshall [2] as "*drainage* of abscesses or infected fluid collections, *debridement* of necrotic infected tissue, and *definitive measures* to control a source of ongoing microbial contamination and to restore anatomy and function." Although source control is considered central to the treatment of complicated intra-abdominal infections, and is included as a necessary component in this definition, there are clearly patients with intra-abdominal infections who are managed successfully without an initial source control procedure. For instance, many patients with acute diverticulitis have traditionally been managed non-operatively, as have some patients with perforated duodenal ulcers. In addition, some patients with complicated appendicitis are being treated with a less invasive approach, or even an initial non-operative approach. Some of the trends in the management of patients with appendicitis will now be detailed, as an example of how the approach to source control in lower-risk patients with community-acquired intra-abdominal infections might be altered in order to decrease morbidity.

Appendicitis is probably the most common intra-abdominal infection treated by surgeons. The pathophysiology of acute appendicitis has long been assumed to be obstruction of the appendiceal lumen, with subsequent distention and bacterial overgrowth within the lumen, which eventually results in gangrene or perforation of the appendix. Some would argue that acute appendicitis is not an intra-abdominal infection until there is actual spread of bacteria beyond the appendiceal wall through perforation. For purposes of this discussion, however, all aspects of source control for appendicitis will be considered, although issues related to perforated and non-perforated appendicitis will be discussed separately.

The therapy of perforated appendicitis is undergoing evolution, in part because modern imaging tools allow the extent of the infection to be characterized as part of diagnosis. Traditionally, appendectomy had been recommended for all patients with perforated appendicitis, except for those with a palpable mass presumed due to a mature peri-appendiceal abscess; those patients were treated with antimicrobial therapy and drainage of the abscess, with subsequent interval appendectomy. However, many patients with perforated appendicitis are now being diagnosed radiographically; these patients do not have a palpable mass or a mature abscess. Rather, they have a peri-appendiceal phlegmon or, at most, a small abscess in the region of the appendix.

How should a patient with a peri-appendiceal abscess or phlegmon be treated now that the diagnosis can be made accurately? The standard operative approach may necessitate a large procedure (e.g., right hemicolectomy) due to extensive inflammation around the cecum. Initial non-operative management might allow inflammation to subside sufficiently, such that appendectomy would become feasible after an appropriate interval.

A number of studies have evaluated this approach to management of patients with complicated appendicitis. Oliak et al. [18] reported a series of 77 patients with perforated appendicitis and no palpable mass. These patients were initially treated nonoperatively, in many cases without drainage of a radiologically-confirmed abscess. Overall, there was no difference in outcome between these patients and a historical group of patients without a palpable mass who were treated with an immediate op-

erative procedure. Nonoperative management was successful in 95% of the patients; 12% of the patients had major complications, some of which were the result of an interval appendectomy performed subsequently. These data parallel those from an earlier series reported by Hoffmann et al. [19], as well as a recent small prospective randomized study by Kumar and Jain [20]. However, Samuel et al. [21] published a series of 48 children treated nonoperatively, and found that 21% required early operative intervention because of a failure of medical management. They concluded that early operative management was associated with fewer complications than was initial medical therapy. Thus, the appropriate role of nonoperative management of patients with perforated appendicitis is still being debated.

If non-operative management for perforated appendicitis is utilized, what is the role of interval appendectomy, which is recommended by many surgeons, particularly pediatric surgeons [22]? Again, a definitive answer is not available, due to the lack of large-scale, prospective trials. Several authors suggest that this procedure is superfluous because the incidence of recurrent appendicitis in these patients is actually quite low, less than 20% [20,23–27]. It has also been suggested that recurrent appendicitis, when it does occur, has a more benign presentation than when it was diagnosed originally [24,27]. Moreover, interval appendectomy has complications associated with its use [18,26,28]. An argument in favor of interval appendectomy has been made based on the fact that important pathological findings are often found in the resected specimen and that an underlying tumor or other important lesion might still be present even with negative diagnostic imaging studies [21,29,30].

If deferring or abandoning a source control procedure for perforated appendicitis is a potentially viable option, what should be the role of appendectomy for the larger group of patients who have non-perforated appendicitis? Clearly, the disease process is less severe in these patients than it is in patients who have had a perforation; yet, much of the interest in utilizing less aggressive therapy for source control has focused only on patients who have perforated appendicitis. The reluctance to consider nonoperative management for patients with acute, non-perforated appendicitis may reflect the longstanding concept that this pathological process inevitably progresses to perforation and potentially fatal peritonitis. However, this concept is likely based more on surgical lore than on the actual natural history of the disease process [31].

Thus, there are few data available with regard to the nonoperative management of acute, non-perforated appendicitis. The most-cited reference is a retrospective review of successful nonoperative management in nine military patients [32]. Additionally, a small prospective, randomized trial by Eriksson and Granstrom demonstrated initial success with nonoperative management in 95% of patients with acute appendicitis, but subsequent recurrence of appendicitis in 35% [33]. Although these data suggest that nonoperative management of acute appendicitis is reasonably safe, there are extensive data documenting that appendectomy for acute, non-perforated appendicitis is also safe. The overall mortality over a ten-year period in the Swedish population was 0.8/1,000 appendectomies performed [34]. The mortality rate approached 1% only in elderly patients. Another study from Sweden documented that only 1.3% of patients who had undergone appendectomy underwent a subsequent surgical procedure for adhesive small bowel obstruction after 30 years of follow-up [35]. Although this rate was six-fold higher than that of the control population, the increased risk was lowest among patients who had undergone appendectomy because of non-perforated appendicitis. It is not known what the risk of subsequent small bowel obstruction would be in patients with acute appendicitis managed nonoperatively.

Given these data, the traditional operative approach to patients with acute appendicitis seems an excellent option. What would be the benefit of testing an option of nonoperative management? Given that mortality and morbidity related to the operative procedure is already quite low, it is likely that only outcomes such as the cost of therapy or the time to full recovery could be addressed feasibly. Nonetheless, further examination of the issue may be worthwhile. In the United States, there has

been a widespread increase in the use of diagnostic imaging techniques, particularly the use of computerized tomographic (CT) imaging of the abdomen, to evaluate patients with abdominal pain. This use may be triggering an operation in patients with fairly mild acute appendicitis, who, in the past, were observed clinically and ultimately treated nonoperatively. Obviously, additional data are needed to determine whether or not this conjecture is true. However, this increased use of abdominal imaging may improve knowledge of the natural history of early appendicitis and thereby allow objective identification of lower-risk patients who might be treated appropriately using a nonoperative approach.

Antimicrobial therapy for lower-risk patients with intra-abdominal infections

The standard principle of antimicrobial therapy for intra-abdominal infections is that the agents used should be active against both the aerobic/facultative anaerobic, gram-negative bacilli and obligate anaerobic organisms that are found as a component of the normal gut flora, and that account for most of these polymicrobial infections [2,3,5]. A number of agents have been shown to be effective for treating patients with complicated intra-abdominal infections in prospective, randomized, controlled trials. Indeed, this is one area in which there are sufficient Class I data to develop firm recommendations. Although there are far fewer prospective data evaluating antimicrobial therapy for patients with intra-abdominal infections treated non-operatively, presumably these same agents would be effective for treating patients with uncomplicated intra-abdominal infections.

Guidelines for the use of antimicrobial agents for intra-abdominal infections have been promulgated by both the SIS [3,4], and the Infectious Diseases Society of America (IDSA) [5] (Table 2). The IDSA recommendations specified a set of antimicrobials for the treatment of patients with mild-to-moderate infections. In contrast, the SIS guidelines did not specify which agents to use in lower-risk patients with community-acquired infections, but suggested that agents with a narrower spectrum of activity, lower toxicity, and lower cost were preferable for these patients. Examples cited included anti-anaerobic cephalosporins, ampicillin/sulbactam, and ticarcillin/clavulanic acid, but were not limited to those agents.

Table 2. Recommended Antimicrobial Agents for Patients with Intra-Abdominal Infections

SIS Guidelines [3]	*IDSA Guidelines [5] (mild-to-moderate severity community-acquired infections)*
Ampicillin/sulbactam	Ampicillin/sulbactam
Piperacillin/tazobactam	Ticarcillin/clavulanic acid
Ticarcillin/clavulanic acid	Ertapenem
Ertapenem	Cefazolin or cefuroxime plus metronidazole
Imipenem/cilastatin	Ciprofloxacin, levofloxacin, moxifloxacin, or gatafloxacin plus metronidazole
Meropenem	
Cefotetan	
Cefoxitin	
Gentamicin, tobramycin, netilmicin, or amikacin plus an anti-anaerobe (clindamycin or metronidazole)	
Cefuroxime plus metronidazole	
Third/fourth-generation cephalosporin (cefotaxime, ceftriaxone, ceftizoxime, ceftazidime, cefepime) plus an anti-anaerobe	
Ciprofloxacin plus metronidazole	
Aztreonam plus clindamycin	

Beyond these general guidelines, it is difficult to derive more specific recommendations. The available evidence only identifies antimicrobial regimens that are effective for the treatment of patients with intra-abdominal infections, but does not provide much information as to which agents are preferred. Given the large number of agents available, there have been relatively few direct comparisons. Moreover, because most registration trials have been powered to demonstrate non-inferiority rather than superiority, such comparisons can usually not be made. The use of meta-analysis might provide some insight when individual trials are powered inadequately to detect significant differences. For example, a recent meta-analysis re-analyzed the role of an aminoglycoside, used in conjunction with an anti-anaerobic agent, for the therapy of intra-abdominal infections [38]. This study concluded that aminoglycosides were less effective than newer agents, a finding that contradicts the concept that these agents are the "gold standard" of antimicrobial therapy for intra-abdominal infections. Further, there was poor documentation of the side effects of aminoglycosides, particularly ototoxicity. A drawback to any meta-analysis, however, is that it is dependent on the quality of the individual studies included for analysis. In this particular analysis, it was found that many of the studies included in the meta-analysis, particularly those conducted one to two decades ago, were of low quality, thus compromising any conclusions that could be drawn. Moreover, single-daily-dose administration of aminoglycosides has not been evaluated prospectively for therapy of intra-abdominal infections, because comparator regimens used in registration trials of new agents (which comprise the bulk of the Class I data) must be approved by the U.S. Food and Drug Administration (FDA). Nonetheless, a primary role for aminoglycosides in the treatment of intra-abdominal infections could be questioned on the basis of these results.

The development of bacterial resistance is another challenge to be faced in selecting antimicrobial therapy for lower-risk patients with intra-abdominal infections. Although it is of considerable importance in patients with nosocomial intra-abdominal infections, which will be considered later, this issue is also germane to patients with community-acquired infections. Increasing resistance of *Bacteroides fragilis* to a number of agents has been well documented, including clindamycin and anaerobic cephalosporins, although its clinical importance is still debated [4,5]. Of more concern is the increasing resistance of many gram-negative pathogens in general and of *Escherichia coli* in particular. In a recent study from Germany, Krobot et al. [36] found that 26% of all isolates, 26% of gram-negative isolates, and 22% of *E. coli* isolates from patients with community-acquired infections were resistant to some commonly-used antimicrobial agents. This resulted in at least some patients receiving potentially ineffective empiric antimicrobial therapy, which was a risk factor for treatment failure. Thus, even with community-acquired infections, there is no room for complacency with regard to emerging bacterial resistance.

Certainly, it is hoped that antimicrobials under development may aid in the struggle against resistant organisms. However, there have been few new developments in therapeutic agents for gram-negative pathogens, although some newer fluoroquinolones and carbapenems are now available or undergoing clinical study. An agent which may soon be available is tigecycline, which is the first in a new class of antibiotics known as glycylcyclines. This agent exhibits *in vitro* activity against a variety of gram-positive, gram-negative, and anaerobic bacteria, including a number of resistant pathogens [37]. Dartois et al. recently demonstrated non-inferiority (i.e., therapeutic equivalence) of tigecycline compared to imipenem-cilastatin for the treatment of patients with complicated intra-abdominal infections. Definitive recommendations cannot be made until the data have been published in peer-reviewed manuscript form, but tigecycline could represent the first new agent from a novel antimicrobial class to be introduced in recent years that can be used as monotherapy for the treatment of patients with intra-abdominal infections. This agent might be useful in the treatment of patients who are allergic to penicillin and other beta-lactam agents, and those more likely to harbor resistant pathogens because of its broad amtibacterial spectrum of activity.

Although newer bacterial agents may aid temporarily in the treatment of resistant organisms, the real key is avoiding, or at least curtailing, the development of these organisms. Raymond et al. [39] have outlined a series of steps to be taken to decrease the development of resistant organisms in surgical patients. As indicated previously, the choice of antimicrobial agents for lower-risk patients with community-acquired organisms is important in this regard, because a narrower-spectrum agent would be less likely to induce resistance than would a broad-spectrum agent. Moreover, although it is important that the agents are active against the common gram-negative and anaerobic organisms typically associated with intra-abdominal infections, additional antimicrobial therapy directed against *Enterococcus* or against fungal organisms is of no apparent benefit for the lower-risk patient with a community-acquired infection [3,5]. Thus, the use of an extended-spectrum antimicrobial agent or the addition of another antimicrobial agent to provide such coverage will likely only lead to the development of further resistance.

Another approach to curtailing resistance emphasized by Raymond et al. [39] is to stop antimicrobials once the infection is cured. Unfortunately, there is relatively little data available with regard to an adequate duration of therapy for patients with intra-abdominal infections. Schein et al. [14] recommended that duration of therapy should be limited, with the most serious infections being treated for only three to five days, and more localized infections (such as perforated appendicitis) being treated for only 24–48 h. Their data indicated that such a strategy was associated with few treatment failures. A recent study by Gleisner et al. [40] verified that a longer duration of antimicrobial therapy for patients with intra-abdominal infections was not associated with a decrease in infectious complications. Both the SIS and IDSA guidelines support limiting duration of therapy to no more than five to seven days. Despite this, prolonged use of antimicrobial therapy remains common. A common provision in clinical trials in intra-abdominal infections is a minimum five-day course of antimicrobial therapy, allowing up to 14 days of therapy. Thus, the belief that prolonged antimicrobial therapy is somehow beneficial seems to be particularly persistent.

Another concept that seems to have persisted despite evidence to the contrary is that intravenous antimicrobial therapy is essential for patients with intra-abdominal infections. An oral regimen of ciprofloxacin plus metronidazole is as efficacious as an intravenous regimen of the same agents once the patient is able to tolerate oral medications [4]. Oral amoxicillin/clavulanic acid is another agent that has been utilized in several trials, although its use has not been studied as rigorously [4]. Greater utilization of oral antimicrobial regimens would simplify the care of patients with intra-abdominal infections and facilitate outpatient treatment. However, regardless of whether oral or intravenous antimicrobials are used, it is still important to limit the overall duration of antimicrobial exposure. The total course of therapy must not be lengthened by the reflexive writing of prescriptions for a certain number of days (usually seven days). Thus, there is a crucial need to determine rigorously the optimal duration of antimicrobial therapy for patients with community-acquired intra-abdominal infections. This information could assist in delineating the role of oral antimicrobials in the treatment of these lower-risk patients as well.

Overall, the challenges in management of low risk patients with community-acquired intra-abdominal infections are primarily those of defining and developing strategies limiting unnecessary over-treatment of the patients, whether it be overly aggressive surgical intervention or inappropriate antimicrobial therapy. However, it is important to remain vigilant to the possibility of compromising patient outcomes through utilization of more conservative treatment strategies. Changes to standard management approaches should be undertaken in light of carefully performed clinical studies documenting efficacy of less-aggressive approaches.

MANAGEMENT OF HIGHER-RISK PATIENTS

Although a primary challenge in the management of lower-risk patients with commu-

nity-acquired intra-abdominal infections is to decrease the potential morbidity of the interventions utilized to treat these patients, the primary challenge faced in the treatment of higher-risk patients is to improve clinical outcome, particularly mortality. Depending on the specific criteria used to define these patients, mortality rates are in the range of 17–32% [4]. There are many areas of controversy related to the management of these patients, both with regard to the surgical and non-surgical treatments utilized, and the optimal therapeutic strategies have not been standardized.

As discussed previously, there is no uniform definition of what constitutes a higher-risk patient with an intra-abdominal infection. However, for the purposes of this discussion, emphasis will be placed on the patient at higher risk because of: 1) compromised function of critical organs engendered by the acute physiological response to the infection and the patient's pre-existing medical conditions; 2) the extent of the peritoneal infection and the difficulty in achieving primary source control; and 3) infection due to resistant pathogens acquired nosocomially. Obviously, the distinction between these different sets of risk factors is somewhat artificial, but this separation does allow the therapeutic approaches to be divided into three general areas. For the first set of risk factors, overall management strategies for the patient with sepsis will be emphasized, for the second set, approaches to source control will be discussed, and for the third, the utilization of appropriate antimicrobial therapy will be stressed. However, these management strategies clearly overlap, and no one approach can be employed in isolation from the others. These aims correspond broadly to the treatment goals outlined by Marshall [2] for these patients, as discussed next.

In discussing management strategies for higher-risk patients with intra-abdominal infections, an immediate challenge is the lack of good clinical evidence for many of the therapies utilized. There is an increasing body of evidence regarding treatment of the patient with sepsis, but very little of the data focus specifically on patients with intra-abdominal infections as a cause of sepsis. There are virtually no prospective, randomized, controlled trials with respect to source control procedures for higher-risk patients with these infections. Finally, as indicated previously, antimicrobial registration trials have enrolled primarily lower-risk patients with community-acquired infections, and extrapolating the results of such studies to the treatment of higher-risk patients is problematic. Thus, most of the treatment approaches used in higher-risk patients with intra-abdominal infections have never been tested rigorously, and it is therefore difficult to develop firm recommendations with regard to both the general and specific therapies used. One of the challenges for the future, then, is to perform studies in carefully defined, higher-risk patient subsets, so that treatment strategies can be evaluated rigorously.

Management of sepsis in patients with intra-abdominal infections

In outlining management principles for patients with intra-abdominal infections, Marshall emphasizes "timely hemodynamic resuscitation and support of vital organ function" in addition to source control and appropriate antimicrobial therapy [2]. Although this was not stressed in the description of treatment of lower-risk patients with community-acquired infections, it is of clear importance in the management of higher-risk patients. Many of these patients have signs of severe sepsis with compromised vital organ function, and some have septic shock. The essence of these therapeutic interventions is the timely provision of critical care appropriate for the patient with intra-abdominal sepsis.

A complete review of the treatment modalities used to treat patients with sepsis is beyond the scope of this paper. However, many of these management principles have been outlined in the Surviving Sepsis Campaign, a series of recommendations developed by representatives from eleven international organizations, including the SIS [41]. Treatment recommendations relate to initial, goal-directed resuscitation of the patient; the use of various agents for hemodynamic support; strategies of mechanical ventilation, fluid and blood product administration; control of hyperglycemia; the use of intravenous corticosteroids; and the

use of activated protein C (drotrecogen alfa (activated)), among others. Although these general interventions will not be discussed in detail, they should be considered of equal importance to the specific source control procedures and antimicrobial regimens utilized for treatment of patients with sepsis causes by an intra-abdominal infection.

Some of the general interventions used for treating patients with sepsis may need to be modified when applied to the higher-risk patient with an intra-abdominal infection. Because of the risk of bleeding, for instance, it is recommended that an infusion of activated protein C be deferred (or postponed, if begun already) for approximately 12 h after a major invasive procedure, such as a laparotomy needed for source control in a patient with a complicated intra-abdominal infection. A further concern with the use of this agent in surgical patients has also been the subject of a recent FDA warning against using the drug in postoperative patients with an APACHE II score < 25 and evidence of only single-organ failure. Although the original data demonstrated improved survival in patients with sepsis and failure of two or more organs who received activated protein C, including those who had undergone recent surgery [42], a review of more recent data in less severely ill surgical patients with failure of only a single organ showed that mortality was paradoxically higher. It is not known how many of these surgical patients underwent an operation because of an intra-abdominal infection. Nonetheless, it points to the need of careful studies of specific interventions utilized in higher-risk patients with intra-abdominal infections.

Source control for higher-risk patients with intra-abdominal infections

The general principles of source control for intra-abdominal infections, as outlined by Marshall [2] and described above, apply equally to lower-risk and higher-risk patients. As with lower-risk patients, it would be impossible to discuss exhaustively the options for surgical treatment of higher-risk patients with these infections. However, there are a few general trends in the use of source control procedures for higher-risk patients that are worthy of note.

One aspect of surgical therapy that is particularly pertinent to higher-risk patients is the utilization of a temporizing procedure versus a definitive one, as discussed by Fry [43]. With higher-risk patients, a prolonged surgical procedure may compromise further an already compromised host. In contrast, the use of temporizing measures may allow the critically ill patient to be stabilized, so that a definitive procedure may be performed under more favorable physiological conditions. Appropriate temporizing procedures range from percutaneous drainage of the gallbladder for acute cholecystitis, to performing a rapid bowel resection without re-establishment of gastrointestinal continuity (deferred anastomosis) in a patient with an intestinal perforation. The use of these temporizing procedures is analogous to the performance of "damage control" laparotomy for patients with severe abdominal trauma and the "lethal triad" of hypothermia, coagulopathy, and acidosis.

The use of temporizing measures may be especially pertinent to patients at higher risk because of limited physiological reserves or compromise of vital organs. However, as indicated previously, patients are also at higher risk because of the extent of the intra-abdominal infection. As already discussed, the inability to achieve adequate source control, which may itself be a consequence of the extent of the intra-abdominal infection, is a risk factor for an adverse clinical outcome. The management of infections developing in association with pancreatitis and the surgical treatment of patients with severe, generalized peritonitis will be discussed as an exemplar. A description of the treatment of pancreatic infections must begin with the acknowledgment that this infection occurs late in the course of this acute inflammatory process. Thus, some aspects of operative and nonoperative management of patients with necrotizing pancreatitis may pertain to the treatment of the patient before an intra-abdominal infection is actually present. However, it seems reasonable to include these aspects of treatment in the discussion, because they may have a direct impact on the development of an infec-

tion and the subsequent need for specific procedures to control the infection.

A recent international consensus conference developed some management guidelines for the treatment of critically ill patients with severe acute pancreatitis [44]. These recommendations will be taken as a starting point for this discussion. As with most questions relating to the appropriate therapy for higher-risk patients with intra-abdominal infections, most of these recommendations could not be based on large, prospective, randomized, controlled studies. Where such studies did exist, they actually provided somewhat conflicting data. One issue concerns the indications and timing of surgical procedures for the treatment of patients with necrotizing pancreatitis. Although the evidence was not definitive, the conference guidelines called for pancreatic debridement/drainage only in patients for whom the presence of an infection had been established by either a positive culture of the area of pancreatic necrosis obtained by fine needle aspiration, or by radiographic criteria such as the presence of gas in the area of pancreatic necrosis. The guidelines also suggested that such procedures are optimally delayed until two or three weeks after the development of severe acute pancreatitis, in order to allow for better demarcation of areas of necrosis. Routine debridement of pancreatic necrosis that is not infected was not recommended. Thus, these guidelines move away from routine operative interventions for management of severe pancreatitis, and suggest that aggressive source control procedures be reserved for patients with a complicating pancreatic infection.

The use of prophylactic, broad-spectrum antibiotics for patients with pancreatic necrosis is an issue that generates substantial controversy. Although this question does not relate directly to the use of specific source control procedures, it could have a substantial indirect impact on the need for such procedures. The use of broad-spectrum antimicrobial prophylaxis could be beneficial if it prevented the development of a pancreatic infection and thereby eliminated the need for operative debridement. However, if this approach failed to prevent an infection, it could lead to the selection of resistant pathogens and make the infection even more difficult to treat, from both surgical and medical perspectives [44].

Unfortunately, this is an issue for which prospective trials have reached conflicting conclusions. Some earlier studies supported the use of prophylactic, broad-spectrum, antimicrobial therapy in these patients, based on decreases in pancreatic infections, the need for operative debridement, or mortality. However, the most recent prospective trial, which was double-blind, found no such improvement in outcome among patients randomized to receive prophylactic ciprofloxacin and metronidazole compared to those randomized to receive a placebo [45]. Examining the data in aggregate, the consensus recommendation was that broad-spectrum, prophylactic antimicrobial therapy should not be administered routinely to patients with pancreatic necrosis [44]. Additional data are needed.

Another issue that generates much controversy is the optimal surgical treatment of patients with severe, generalized, intra-abdominal infections, including those with persistent or tertiary peritonitis. There has been some enthusiasm for routine re-exploration and abdominal irrigation for patients with severe, diffuse peritonitis. Wittmann et al. [46] suggested that certain, very high-risk patients with severe secondary peritonitis be treated with a program of multiple planned re-laparotomies, with the decision to re-operate being based on the operative findings at the time of the initial procedure. Schein [47] suggests that the best indication for the use of planned re-laparotomy is an inability to achieve source control at the time of the initial intervention. Additional indications may be for patients with poorly localized infections requiring multiple debridements, and for patients with an overwhelming amount of peritoneal contamination/infection.

There are no large prospective trials available to judge the results of routine, planned relaparotomy for patients with severe intra-abdominal infections. Most of the studies that have been reported are retrospective and either uncontrolled or poorly controlled. Several have found no improvement in clinical outcome using planned re-laparotomy [8,48,49], whereas others have suggested a benefit to routine re-exploration [50,51]. Obviously, this is another

area where there is an unmet need for well-designed prospective trials to evaluate this approach to these higher-risk patients.

Antimicrobial therapy for higher-risk patients with intra-abdominal infections

For lower-risk patients with community-acquired intra-abdominal infections, the specific antimicrobial regimen selected does not appear to have a major impact on outcome, as long as appropriate agents are utilized. In contrast, antimicrobial selection may play a much more important role in the treatment of higher-risk patients. For instance, as already described, isolation of microorganisms resistant to the initial empiric antimicrobial regimen was identified as a risk factor for mortality among patients with postoperative intra-abdominal infections [17]. Resistant microorganisms are increasingly isolated from patients with intra-abdominal infections as their length of hospitalization, and particularly their exposure to prior antimicrobial therapy, increases. In patients with persistent or tertiary peritonitis, the predominant pathogens are nosocomial microorganisms, such as *Pseudomonas* sp., enterococci, staphylococci, and *Candida* sp. [52,53], rather than the gram-negative *Enterobacteriaceae* and anaerobic organisms typical of secondary peritonitis.

The antimicrobial regimens recommended in the SIS and IDSA guidelines for higher-risk patients with intra-abdominal infections are listed in Table 3. These regimens include agents with a broader spectrum of activity against gram-negative and anaerobic organisms than those utilized in lower-risk patients with community-acquired infections. In general, these regimens will provide adequate activity against most of the common organisms isolated in higher-risk patients, even those with intra-abdominal infections acquired nosocomially [54]. Nonetheless, additional antimicrobial therapy should be considered for higher-risk patients who are believed likely to be harboring resistant microorganisms. A major challenge is identifying such patients so that empiric antimicrobial regimens are designed to have activity against an expected set of pathogens. Some of the general principles of antimicrobial therapy for resistant gram-negative, gram-positive, and fungal microorganisms will now be outlined.

With respect to gram-negative organisms acquired nosocomially, one problem faced increasingly is the growing resistance of these organisms to many antibiotics that are available currently. This was studied in isolates of *Enterobacteriaceae* and of the non-fermentative, gram-negative bacilli, *Pseudomonas aeruginosa* and *Acinetobacter baumannii,* obtained over a period of several years in the United States [55,56]. Increasing resistance to fluoroquinolones, such as ciprofloxacin, was common among all gram-negative pathogens, and there was also increasing resistance of *P. aeruginosa* to gentamicin, but not to amikacin. Another recent development is the identification of strains of *P. aeruginosa* that are resistant to virtually all anti-pseudomonal antibiotics. It has been necessary to resort to treatment with colistin to salvage patients infected with these highly-resistant strains [57].

Table 3. Recommended Antimicrobial Agents for Patients at Higher Risk Due to Intra-Abdominal Infection

SIS Guidelines [3] (Higher-risk patients)	*IDSA Guidelines [5] (high-severity, community-acquired infections)*
Imipenem/cilastatin	Imipenem/cilastatin
Meropenem	Meropenem
Piperacillin/tazobactam	Piperacillin/tazobactam
An aminoglycoside plus an anti-anaerobe	Aztreonam plus metronidazole
Aztreonam plus clindamycin	Ciprofloxacin plus metronidazole
Ciprofloxacin plus metronidazole	A third/fourth-generation cephalosporin plus metronidazole
A third/fourth-generation cephalosporin plus an anti-anaerobe	

For patients with serious nosocomial infections due to *P. aeruginosa*, there is an ongoing debate regarding the utility of treating the organism with a combination of an aminoglycoside and a cell wall-active agent, such as an anti-pseudomonal penicillin, cephalosporin, or carbapenem. Combination therapy was tested in two clinical trials of severely ill patients with intra-abdominal infections, but did not prove beneficial in either [58,59]. Thus, the SIS guidelines recommend against the use of combination therapy for higher-risk patients with serious intra-abdominal infections.

The problem of resistance among gram-negative organisms producing nosocomial intra-abdominal infections is likely to remain a challenge into the foreseeable future. Unfortunately, there does not appear to be many new antimicrobial agents on the horizon that are intrinsically active against resistant, gram-negative organisms, particularly *P. aeruginosa*. Thus, measures to decrease the transmission of highly-resistant pathogens, such as adherence to standard infection control practices, are of great importance. If organisms such as the pan-resistant strains of *P. aeruginosa* become widespread, it will greatly complicate management of patients with nosocomial intra-abdominal infections.

The gram-positive organisms involved in nosocomial, intra-abdominal infections are enterococci and staphylococci. Although *Enterococcus* spp. are isolated occasionally as part of the polymicrobial flora found with community-acquired intra-abdominal infections, enterococci appear to play a much greater role in infections acquired nosocomially. Routine treatment of *Enterococcus* spp. is not recommended for most patients with community-acquired intra-abdominal infections, with the possible exception of patients with serious valvular heart disease or prosthetic valves, who might be at risk for endocarditis in the event of enterococcal bacteremia [60].

For higher-risk patients with nosocomial intra-abdominal infections, treatment of *Enterococcus* spp. is likely of greater importance. Isolation of *Enterococcus* spp. is more common in patients with nosocomial intra-abdominal infections [17], and their isolation is a risk factor for treatment failure and death [61–63]. Inadequate empiric antimicrobial therapy is also a risk factor for treatment failure and death in patients with intra-abdominal infections [6,17,36] and is a strong predictor of mortality in critically ill patients with nosocomial pneumonia [64]. Thus, it would seem reasonable to cover *Enterococcus* spp. empirically in higher-risk patients who are likely to harbor nosocomial pathogens. Such patients may include those with prior exposure to antimicrobials and those with complex infections of small- or large-bowel origin. Enterococcal coverage could be provided through the selection of agents that have intrinsic enterococcal coverage, such as some penicillins and carbapenems, or by the addition of an anti-enterococcal penicillin or vancomycin to regimens that lack enterococcal coverage. Specific anti-enterococcal therapy should not be continued in patients whose intra-abdominal cultures are negative for this organism, however.

The development of vancomycin-resistant strains of *Enterococcus*, particularly *E. faecium*, presents a new dilemma. Fortunately, intra-abdominal infections due to this microorganism are relatively uncommon. Several newer antimicrobial agents, including linezolid and daptomycin, are effective against vancomycin-resistant enterococci (VRE). Tigecycline also has *in vitro* activity against VRE [37]. Empiric therapy directed against VRE has not been tested, and cannot be recommended at the present time. The use of agents active against VRE should be reserved for patients who have culture-proven evidence of an infection due to this organism.

Staphylococci are rarely isolated from patients with community-acquired intra-abdominal infections, but are isolated with increased frequency from patients with postoperative infections [17], pancreatic infections [65], or tertiary peritonitis [52,53]. Both coagulase-negative and coagulase-positive staphylococci have been recovered from patients with nosocomial intra-abdominal infections, although the pathogenic role of the former has been questioned [66]. There has been little published with respect to antimicrobial therapy for patients with intra-abdominal infections due to staphylococci. Many of the antimicrobials recommended for treatment of intra-abdominal infections in

higher-risk patients, such as piperacillin/tazobactam, carbapenems, and several third-/fourth-generation cephalosporins have some activity against methicillin-sensitive *Staphylococcus aureus*. However, these agents are not generally considered first-line therapy for this pathogen. The use of an anti-staphylococcal penicillin would seem reasonable for patients with serious intra-abdominal infections due to this organism, especially if the patient had an associated bacteremia. For patients with a non-anaphylactoid penicillin allergy, a first-generation cephalosporin may be used because the incidence of cross-reactivity is only approximately 5%. Alternatively, vancomycin may be used.

For patients with methicillin-resistant *Staphylococcus aureus* (MRSA), the choices are more limited. Vancomycin is still probably the first line agent for this organism. However, there is some evidence that linezolid is more effective than vancomycin against this organism in critically ill patients with nosocomial pneumonia, and in other patients with skin and soft tissue infections [67,68]. It is unknown if this also applies to patients with intra-abdominal infections due to this organism. Quinupristin/dalfopristin and daptomycin are alternative agents with activity against MRSA [69,70], but experience in the treatment of intra-abdominal infections with these antimicrobials is quite limited as well. Tigecycline also has *in vitro* activity against MRSA, and has been studied in both skin and soft tissue infections and lower-risk intra-abdominal infections.

Vancomycin is the mainstay of therapy for patients with intra-abdominal infections due to coagulase-negative staphylococci, if that organism is to be treated. Most isolates of coagulase-negative *Staphylococcus* are resistant to anti-staphylococcal penicillins and cephalosporins. Although linezolid, daptomycin, and quinupristin/dalfopristin have activity against these gram-positive organisms *in vitro* [71,72], there is little clinical data available to make therapeutic recommendations regarding use of these agents for patients with intra-abdominal infections. Tigecycline also has *in vitro* activity against coagulase-negative staphylococci.

A final issue with regard to higher-risk patients with nosocomial intra-abdominal infections is the treatment of fungal pathogens, primarily *Candida albicans*. Although these organisms are isolated with some frequency from patients with community-acquired infections, antifungal therapy is not necessary in that setting. Isolation of *Candida* spp. is primarily a concern when isolated from higher-risk patients, particularly those with nosocomial intra-abdominal infections. Antifungal therapy is not recommended for lower-risk patients with community-acquired infections, even when abdominal cultures are positive for *Candida* [3,5]. However, for higher-risk patients, and particularly those with nosocomial intra-abdominal infections, antifungal therapy may be warranted when this organism is recovered. In one prospective, randomized, controlled trial [73], pre-emptive antifungal therapy with fluconazole was tested in patients at high risk for *Candida* infections. This study demonstrated a decreased incidence of *Candida* peritonitis in the patients given pre-emptive fluconazole therapy. However, this approach has yet to be adopted universally. Its utilization is probably most appropriate at centers where the incidence of intra-abdominal or other infections due to *Candida* is high.

For patients with invasive candidal infections, several antifungal agents are now available. These include amphotericin B and its lipid formulations, the azoles fluconazole and voriconazole, and the echinocandins caspofungin and micafungin. The newer agents have primarily been evaluated in patients with candidal blood stream infections, so their utility for patients with candidal intra-abdominal infections has to be inferred from the results obtained from fungemic patients. There has been some controversy regarding antifungal therapy for patients with confirmed intra-abdominal infections due to *Candida albicans*. Based on very limited data, it had been suggested that amphotericin B is more efficacious than fluconazole for treatment of these patients [74]. However, the toxicity of this agent, even in its lipid formulations, makes the use of other agents preferable [5,75]. It is unclear if the use of voriconazole or caspofungin will supplant the use of fluconazole for patients infected with this organism. Some non-*C. albicans* species, especially *C. glabrata* and *C. krusei,* are less sus-

ceptible to fluconazole. Although the use of higher doses of fluconazole has been proposed to treat these patients, the efficacy of this approach has not been proved [75]. These non-*albicans* species are susceptible to both voriconazole and caspofungin *in vitro* [76,77]. Thus, these newer agents will likely be useful in the treatment of intra-abdominal infections due to these resistant candidal species, although there is little published experience to date [5,75].

Clearly, a major challenge exists in selecting appropriate antimicrobial regimens for higher-risk patients with intra-abdominal infections, especially those with infections acquired nosocomially. These regimens should be based on the suspected pathogens in a given patient. A better understanding of how specific risk factors influence the likelihood of infection with specific nosocomial pathogens could thereby facilitate the selection of antimicrobial therapy. Ultimately, however, this knowledge will have to be combined with knowledge of local, institutional, and unit-specific trends in the types of nosocomial pathogens encountered and their resistance patterns, so that an appropriate empiric antimicrobial regimen can be tailored to a specific patient.

What, then, is the overall management strategy for the higher-risk patient with an intra-abdominal infection? It would seem reasonable to base therapy on the specific risk factors that categorize the patient as being at higher risk. For patients with severe sepsis or septic shock, interventions to maintain critical organ perfusion and compensate for disordered organ function would be of high priority. The guidelines outlined in the Surviving Sepsis Campaign guideline represent a reasonable initial approach to the treatment of these patients. For patients at higher-risk due to the extensive nature of the intra-abdominal infection, source control should be achieved in an expedient manner. The use of temporizing measures rather than definitive procedures may be quite important in patients with disordered physiology. The use of re-laparotomy, although controversial, could be considered, particularly when it is not possible to achieve adequate source control at the time of the initial procedure. For patients at higher risk due to the presence of resistant

Table 4. Summary of Challenges in the Management of Intra-Abdominal Infections

Identifying Patient Risk

1) What are the appropriate endpoints to use for risk factor analysis?
2) What acute physiological changes and chronic medical problems actually determine patient risk? Can a simplified system be devised that has the same predictive value as the APACHE II score?
3) Can a uniform system, such as the Mannheim Peritonitis Index, be used to characterize the extent of the intra-abdominal infection?
4) What characteristics can be used to identify patients harboring nosocomial pathogens?

Management of the Lower-Risk Patient

1) Which intra-abdominal infections can be treated safely without performing a primary source control procedure?
2) Can the morbidity of source control be reduced by performing less invasive or extensive procedures without sacrificing a good clinical outcome?
3) Are all the standard antimicrobial regimens still appropriate in the face of increasing resistance of community-acquired pathogens?
4) What is the optimal duration of antimicrobial therapy for patients with complicated intra-abdominal infections?
5) What is the appropriate role for oral antimicrobial agents?

Management of the Higher-Risk Patient

1) How can the general principles for the management of severe sepsis be applied to the patient with an intra-abdominal infection? Are there any components of the Surviving Sepsis Campaign guideline that need to be modified in treating patients with intra-abdominal infections?
2) When should temporizing procedures be utilized for source control?
3) What is the role of scheduled repeat laparotomy?
4) When should antimicrobial coverage be broadened to treat resistant, nosocomial pathogens?
5) What antifungal agents are appropriate to use in patients with intra-abdominal infections, and when?

nosocomial pathogens, the initial empiric regimen should be broad in spectrum, covering the likely resistant pathogens in a given patient, and then narrowed as soon as possible according to culture results. A regimen effective against gram-negative bacilli and anaerobic bacteria, with the specific agents selected according to the local patterns of gram-negative resistance, is the basis of that therapy. Coverage of *Enterococcus* spp. should be added for patients potentially infected with that organism, and pre-emptive antifungal therapy should also be considered in selected patients. The utility of this approach of directing management priorities based on the specific clinical risk factors of a given patient should be verified in prospective studies of higher-risk patients with intra-abdominal infections.

CONCLUSION

In this review, an attempt has been made to delineate some of the challenges faced in improving management of patients with intra-abdominal infections. This discussion has emphasized the concept that the needs of lower-risk patients with community-acquired infections are quite distinct from those of patients at higher risk due to their compromised physiological status, the extent of their intra-abdominal infection, or the presence of nosocomial pathogens. Within this context, the challenges have been grouped into three general categories: 1) facilitating the identification of higher-risk patients; 2) providing less morbid source control procedures and minimally toxic, short-duration, antimicrobial regimens for lower-risk patients; and 3) developing optimal treatment approaches to source control and antimicrobial therapy for higher-risk patients. Examples of some of the challenges in these different areas are listed in Table 4.

Most published articles conclude with a statement that further study is required, and it goes without saying that a similar statement could be made here. The challenges outlined in this review are not revelatory, having been identified previously by other authors. However, answers are still sought. The ultimate challenge faced in answering these research questions is the most difficult: How to ensure that the appropriate investigations needed to answer these research questions are actually performed. To date, much of the high quality data on the management of intra-abdominal infections has been generated directly or indirectly as a result of large clinical trials funded by pharmaceutical companies seeking approval of new antimicrobial agents. There is no question that these studies have expanded our knowledge base greatly and have led to the adoption of improved therapies for patients with intra-abdominal infections. Nonetheless, many of the challenges outlined here require studies of interventions that are likely to be of negligible commercial value. Unfortunately, such studies have received relatively little public research support, even though the solutions to these problems could lead to improvements benefiting not only individual patients, but health care as a whole. The challenge of promoting research into the effective management of patients with intra-abdominal infections is one that requires the cooperation of many individuals and organizations, and will not be solved by isolated investigators working alone. For such efforts, the role of scientific organizations such as the SIS is key. Hopefully, these organizations will increasingly serve not only as advocates of carefully done clinical research, but also as the coordinators of such investigations [78].

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