

Canadian practice guidelines for surgical intra-abdominal infections

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EXECUTIVE SUMMARY

Complicated intra-abdominal infections (IAIs) remain a major challenge in clinical practice. In addition to significant morbidity and mortality for patients, they consume substantial hospital resources. This is compounded by the potential misuse of antimicrobial agents that may result in suboptimal treatment, as well as encourage the selection and spread of antibiotic-resistant microorganisms in the health care setting. The present guideline was developed jointly by the Canadian Surgical Society (CSS) and the Association of Medical Microbiology and Infectious Disease (AMMI) Canada. The primary goal was to provide updated recommendations for the medical and surgical management of complicated IAIs since publication of the 2003 antimicrobial treatment guideline by the Infectious Diseases Society of America (IDSA) (1). Particular focus is directed at risk stratification for poor outcome based on epidemiological studies, current status of antimicrobial susceptibility and resistance profiles among enteric pathogens, therapeutic efficacy of antimicrobial regimens based on randomized clinical trials, operative versus percutaneous approaches for source control, the role of intra-abdominal hypertension (IAH) and abdominal compartment syndrome (ACS) in IAI, and infection control and preventive measures for postoperative IAIs and surgical site infections. An additional objective is to categorize the recommendations according to the strength and quality of the available evidence using a standardized grading system. Importantly, the current guideline provides recommendations for initial empirical antimicrobial management of complicated IAIs based on clinical settings and issues unique to the Canadian health care system.

Summarized below are the key evidence-based recommendations grouped according to the main sections discussed in more detail in the guideline. Each recommendation is rated by the strength of support (category A to C) and quality of evidence (grade 1 to 3) as assessed by the working group of the guideline.

Key recommendations for risk assessment and stratification

Recommendation 1. Categorize the severity of illness by using the Acute Physiology and Chronic Health Evaluation II (APACHE II) score: low-moderate (lower than 15) or high (15 or greater) (A-2

evidence). Although the APACHE II scoring is infrequently used clinically outside of the critical care setting at present, it is recommended that physicians and surgeons consider introducing it into clinical use in patients with IAIs. A user-friendly APACHE II calculator can be found on the following Web site <www.globalrph.com/apacheii.htm>.

Recommendation 2. Identify high-risk patients for poor outcome by stratification according to community-acquired versus health care-associated IAIs, previous antibiotic exposure, and underlying comorbid conditions such as diabetes, severe cardiopulmonary disease or immunosuppression (A-2 evidence)

Recommendation 3. Use the severity of illness score (APACHE II) and other risk factors outlined above to plan appropriate medical or surgical therapy, and for evaluating the efficacy of different antimicrobial regimens for complicated IAIs (A-2 evidence)

Key recommendations for microbiology and antimicrobial susceptibility testing

Recommendation 4. Due to the predominance of certain virulent pathogens in IAIs, the concept of 'core' pathogens is recommended for planning initial empirical antimicrobial therapy (A-2 evidence).

Recommendation 5. The microbiology of community-acquired IAIs in the absence of previous antimicrobial exposure generally consists of 'core' pathogens that are readily predictable (A-2 evidence). In such patients and particularly those with mild to moderate severity of illness, routine bacteriological cultures of abdominal fluid or pus and antibiotic susceptibility testing of intra-abdominal isolates are optional and not routinely required to guide empirical antimicrobial therapy. However, such cultures may be useful for ongoing surveillance studies and generating local epidemiological data regarding antimicrobial susceptibility profiles and emerging resistance (A-2 evidence).

Recommendation 6. Patients with health care-associated IAIs who have prolonged previous hospitalization (five days or more), are severely ill (APACHE II score of 15 or greater) or have received previous antimicrobial therapy (more than two days) are at a greater risk for antimicrobial-resistant pathogens. In

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such patients, blood and intraoperative cultures as well as antimicrobial susceptibility testing of all bacterial isolates should be performed routinely (A-2 evidence).

Recommendation 7. For specimen collection, abdominal fluid or pus should be collected in a capped airless syringe or be directly inoculated into appropriate aerobic and anaerobic transport media. Cultures should be sent for Gram stain and susceptibility testing. Swab specimens are not recommended (B-2 evidence).

Recommendation 8. In patients who develop treatment failures, their intra-abdominal cultures at reoperation are more likely to contain antibiotic-resistant isolates including non-fermenters and *Candida* species (A-2 evidence). Routine cultures and antimicrobial susceptibility testing of all isolates should be performed to guide subsequent antimicrobial therapy (A-2 evidence).

Key recommendations for initial empirical antimicrobial therapy

Recommendation 9. For patients with community-acquired IAIs with mild to moderate severity (APACHE II score lower than 15) who have not undergone prolonged previous hospitalization (five days or more) or received previous antimicrobial therapy (more than two days), initial empirical antimicrobial therapy should be directed against 'core pathogens' only, including enteric Gram-positive cocci as well as facultative and anaerobic Gram-negative bacilli, particularly *Escherichia coli* and *Bacteroides fragilis* (A-1 evidence). For adult patients, monotherapy with ceftazidime, ticarcillin-clavulanate, ertapenem, moxifloxacin or tigecycline is appropriate; alternatively, combinations of cefuroxime, cefotaxime, ceftriaxone or ciprofloxacin, each with metronidazole, are preferable to broader-spectrum regimens (A-1 evidence).

Recommendation 10. Ampicillin-sulbactam (not available in Canada), cefotetan and clindamycin are no longer recommended for routine empirical therapy of complicated IAIs because of the high rate of resistance among community-acquired *E coli* against ampicillin-sulbactam, and among *B fragilis* against cefotetan and clindamycin (B-2 evidence).

Recommendation 11. In light of the availability of less toxic regimens and unfavourable clinical response rates in randomized clinical trials, aminoglycosides are not recommended for routine empirical treatment of complicated IAIs (A-1 evidence).

Recommendation 12. For health care-associated surgical IAIs and seriously ill patients with community-acquired infections (APACHE II score of 15 or greater, previous hospitalization of five days or more, or previous antimicrobial therapy of two days or more), antimicrobial agents with broader spectrum of activity against facultative and anaerobic Gram-negative bacilli are recommended (B-2 evidence). For adult patients, monotherapy with piperacillin-tazobactam, imipenem-cilastatin, meropenem, or combinations of ceftazidime, cefepime or ciprofloxacin with metronidazole, or tigecycline in combination with ciprofloxacin are appropriate (B-2 evidence).

Recommendation 13. Intravenous (IV) to oral (PO) sequential treatment with a fluoroquinolone (such as monotherapy with moxifloxacin or combination therapy with ciprofloxacin plus metronidazole) may be a cost-effective alternative

(B-2 evidence). Continued surveillance for emerging resistance, particularly against facultative Gram-negative bacilli, should be implemented and periodic review of their efficacy and safety should be considered when choosing monotherapy or combination therapy with a fluoroquinolone (A-1 evidence).

Recommendation 14. In light of the emerging concern of extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae species due to selection pressure by increased use of oxyimino-cephalosporins (ceftazidime, ceftriaxone and cefotaxime), as well as *ampC*-producing nosocomial pathogens (resistant to all cephalosporins), the prolonged use of all cephalosporins in the health care setting is actively discouraged in favour of beta-lactam-beta-lactamase inhibitors or carbapenems (A-2 evidence).

Recommendation 15. Routine coverage for enterococci is not recommended in patients with community-acquired IAIs of mild to moderate severity (A-1 evidence). However, empirical antienterococcal therapy should be considered for immunosuppressed patients with health care-associated, postoperative or recurrent IAIs, those with antimicrobial exposure to cephalosporins and other broad-spectrum regimens selecting for enterococci, and those with valvular heart disease or intravascular prosthetic devices (B-3 evidence).

Recommendation 16. Coverage for *Pseudomonas aeruginosa* should be considered if it is the only pathogen recovered, if it is isolated from blood cultures, or if the patient has not responded to antimicrobial treatment that does not cover *P aeruginosa* in the setting of health care-associated IAIs (B-2 evidence).

Recommendation 17. Anti-methicillin-resistant *Staphylococcus aureus* (MRSA) therapy should be administered for health care-associated IAIs in patients who are known to be colonized with the organism or have a history of MRSA infection. Vancomycin remains the agent of choice, although linezolid, daptomycin, tigecycline and quinupristin-dalfopristin may also be used. Vancomycin may also be considered for surgical prophylaxis in patients who are known to be MRSA carriers or if they come from facilities with a high prevalence of MRSA infection (B-2 evidence).

Recommendation 18. Targeted antifungal therapy is recommended for patients with severe community-acquired or nosocomial IAIs only if *Candida* species is isolated from intra-abdominal or blood cultures. Fluconazole is the agent of choice if *Candida albicans* is isolated. For non-*albicans Candida* species, either an echinocandin (such as caspofungin, micafungin or anidulafungin) or a triazole (such as voriconazole) to which the organism is susceptible may be considered (B-2 evidence).

Recommendation 19. Amphotericin B is not recommended as initial therapy because of its toxicity (B-2 evidence).

Recommendation 20. Pre-emptive antifungal therapy with fluconazole or an echinocandin may be considered for seriously ill patients with a high risk for invasive candidiasis (eg, immunosuppression, postoperative or recurrent peritonitis, *Candida* colonization at multiple sites, etc); however, such a strategy has not been shown to impact mortality (C-2 evidence).

Recommendation 21. The duration of antimicrobial therapy should be guided by intraoperative findings and clinical response as assessed by resolution of fever and leukocytosis,

abdominal examination and gastrointestinal function, and should be no more than five to seven days, unless it is difficult to achieve adequate source control (B-3 evidence).

Recommendation 22. Patients who continue to exhibit clinical evidence of infection at the end of seven days of antimicrobial therapy should be evaluated for residual infection, resistant microorganisms and other possible causes of treatment failure, rather than simply prolonging or broadening antimicrobial therapy (C-3 evidence).

Recommendation 23. In patients with postoperative or other health care-associated infections and those with clinical treatment failure, the acquisition or selection of resistant microorganisms should be strongly suspected, and further antimicrobial therapy should be guided by intraoperative cultures and susceptibility testing obtained directly from abscess fluid or the peritoneal cavity (B-2 evidence).

Recommendation 24. Development of clinical pathways (ie, a protocol approach) for the management of complicated IAIs based on local epidemiology of antimicrobial utilization and antibiotic resistance profiles is highly recommended. Such locally developed clinical pathways should standardize the approach to diagnosis, microbiological and radiological investigations, empirical antimicrobial therapy as well as policies regarding discharge and outpatient management. Such local guidelines should be established by a multidisciplinary team including surgeons, infectious disease and medical microbiology specialists, emergency physicians and other health care providers, and should reflect local resources and local standards of care (B-3 evidence).

Recommendation 25. Each institution should develop its own suite of performance measures to provide ongoing evaluation of the effectiveness and appropriateness of the local clinical pathways for complicated IAIs, ultimately leading to improved quality of care (B-3 evidence).

Key recommendations for source control

Recommendation 26. Adequate source control is the primary means of managing IAIs and should not be subjugated to antimicrobial therapy (A-2 evidence).

Recommendation 27. Operative approaches to source control should be used when it is necessary to resect a gangrenous or perforated viscus, patch a perforated viscus, divert the enteric stream or when percutaneous approaches to abscess drainage are not possible or have not been effective (A-3 evidence).

Recommendation 28. Small abscesses (less than 3 cm) might be amenable to antimicrobial therapy without drainage (B-2 evidence).

Recommendation 29. In select patients, source control of perforated diverticulitis may be achieved by laparoscopic lavage and drainage (C-2 evidence).

Recommendation 30. In select patients, source control of infected pancreatic necrosis may be achieved using percutaneous approaches (B-2 evidence).

Key recommendations for IAH in IAIs

Recommendation 31. The presence of risk factors that may predispose to the development of IAH or ACS should be assessed in all acutely ill patients (APACHE II score greater than 15) with complicated IAIs (B-2 evidence).

Recommendation 32. Baseline intra-abdominal pressure (IAP) measurements should be determined in all critically ill patients

with complicated IAIs if two or more risk factors for IAH or ACS are present (B-2 evidence). If IAH (IAP greater than 12 mmHg) or ACP (IAP greater than 20 mmHg) is present, serial IAP measurements should be performed throughout the patient's critical illness (A-3 evidence).

Recommendation 33. Surgical decompression should be considered for patients with refractory IAH or evidence of ACS. In addition, medical approaches to reduce IAP and associated end-organ dysfunction should be implemented, consistent with local practices in the care of critically ill patients (B-2 evidence).

Key recommendations for infection control and prevention

Recommendation 34. General measures important for reducing the risk of surgical site infections, such as avoiding hyperglycemia perioperatively, cessation of tobacco use at least 30 days before elective surgery, instructing the patient to shower with an antiseptic agent the night before the surgical procedure, etc, should be instituted in all patients undergoing intra-abdominal surgery (B-2 evidence). Hair removal is indicated only in cases in which the hair may hamper the surgical procedure itself. If hair has to be removed, it should be performed immediately before the surgery using electric clippers (A-1 evidence).

Recommendation 35. Surgical team members should adopt a recommended scrubbing procedure for at least 2 min, including hands, arms and elbows (A-2 evidence).

Recommendation 36. A two-filter system installed in series should be in place in the operating room to ensure a clean environment, and air should enter the operating room through the ceiling and exhaust near the floor (B-2 evidence). Regular check-up of all physical parameters of the operating room and a complete maintenance program should be instituted at the local level (B-3 evidence).

Recommendation 37. Antibiotics for surgical prophylaxis should be used only if evidence from clinical trials is available, and in situations for which a surgical site infection may have major consequences (A-1 evidence). If surgical prophylaxis is to be administered, both the timing and dosing of the antibiotic infusion should be adjusted to attain peak tissue concentrations at the moment of incision and throughout surgery (A-1 evidence). In cases of prolonged surgical procedures, prophylactic antibiotics may need to be readministered intraoperatively (B-2 evidence).

Recommendation 38. The duration of antimicrobial therapy for the purpose of surgical prophylaxis in the absence of established infection should be limited to 24 h or less in patients with penetrating bowel trauma repaired within 12 h, intraoperative contamination by enteric contents or nonperforating appendicitis in the absence of abscess or local peritonitis (A-1 evidence).

Recommendation 39. A hospital-wide surgical site infection surveillance program with continuous collaboration and feedback with the surgical team should be implemented to reduce surgical site infections (A-1 evidence).

Recommendation 40. To effectively control the spread of antibiotic-resistant organisms, an effective infection control program coupled with a rigorous antibiotic stewardship program should be implemented locally (A-1 evidence).

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1. INTRODUCTION

IAIs remain a major challenge in clinical practice. They are the main cause of postoperative morbidity following abdominal surgery and the most frequent cause for admission to a surgical intensive care unit (2,3). IAIs differ from infections encountered elsewhere in several respects. First, the clinical spectrum of IAI is extremely wide, ranging from uncomplicated acute appendicitis with a relatively benign course to diffuse peritonitis from perforated viscus or ischemic bowel with high morbidity and mortality. While both scenarios comprise of IAIs, they require different approaches to diagnosis and treatment. Additionally, the role of surgery in the management of patients with IAIs is pivotal and generally considered to be a decisive factor in the outcome. The clinical and microbiological diagnosis is also often problematic: IAIs are typically polymicrobial, and not every microorganism involved can be identified in the clinical microbiology laboratory by routine cultures; the pathogenicity of certain microorganisms cultured from IAIs is not considered to be the same for every patient and often relates more directly to the severity of underlying disease or comorbid conditions of the host; and the clinical signs and symptoms do not often match the severity of disease and may lead to substantial delays in appropriate diagnosis and management (3-8). Additionally, antibiotic resistance among enteric pathogens has evolved globally and at an alarming rate, while very few newer agents have emerged to replace older therapeutic regimens.

The current clinical practice guideline was jointly developed by the CSS and AMMI Canada. The primary goal was to develop updated recommendations for the medical and surgical management of complicated IAIs since publication of the 2003 antimicrobial treatment guideline by the IDSA (1). Particular focus is directed at risk stratification for poor outcomes based on epidemiological studies, current status of antimicrobial susceptibility and resistance profiles among enteric pathogens, therapeutic efficacy of antimicrobial regimens based on randomized clinical trials, operative versus percutaneous approaches for source control, the role of IAH and ACS in IAIs, and infection control and preventive measures for postoperative IAIs and surgical site infections. An additional objective is to categorize the recommendations according to the strength and quality of the available evidence using a standardized grading system. Importantly, the current guideline provides recommendations for initial empirical antimicrobial management of complicated IAIs based on clinical settings and issues unique to the Canadian health care system (eg, publicly funded health care system and regionalization of health care delivery).

2. METHODOLOGY

These guidelines were prepared by a working group comprised of individuals with expertise in the disciplines of infectious disease, medical microbiology, general surgery, intensive care and pharmacy. Members were chosen based on their expertise and recommendations by the co-chairs of the Guidelines Committee who represent the professional societies of AMMI Canada and the CSS. Each member of the working group was responsible for specific sections of the guideline in accordance with their clinical knowledge, practice and expertise. The final document was derived from these individual contributions and edited by the co-chairs for organization, flow and consistency in style. The Medline database was searched for articles published

in the English language between 1980 and May 2008. The general search strategy included 26 primary search terms including the following: “abdominal”, “abscess”, “acute pancreatitis”, “anaerobes”, “appendicitis”, “cholecystitis”, “intra-abdominal”, “infection”, “necrotizing pancreatitis”, “pancreatitis”, “sepsis”, “surgery”, “abdominal compartment syndrome”, “intra-abdominal hypertension” and “risk factors”. Additional search terms such as “cephalosporins” or “tertiary” were further paired with words and phrases indicating an IAI (such as “tertiary peritonitis”, “intra-abdominal infection” or “intra-abdominal sepsis”). Review was limited to randomized clinical trials in adults. Inclusion of antimicrobial agents was limited to agents currently approved by Health Canada or the Federal Food and Drug Administration of the United States. Reports from meta-analyses, practice guidelines, clinical conferences and major reviews were also examined. In addition, the Cochrane database on antibiotic regimens for secondary peritonitis of gastrointestinal origin in adults, published in 2006 (9), was searched to ensure that all prospective trials were included. Citations were imported into Reference Manager Software (Professional Edition, version 10, ISI ResearchSoft Inc, USA) for sorting, retrieval and in-depth analysis. Studies that were nonrandomized, had fewer than 25 evaluable patients in either study arm or represented duplicate publications were excluded. Outcome measures assessed were clinical success rates from evaluable patients and mortality from infection, unless otherwise specified. These studies form the basis of therapeutic and management recommendations, which were further categorized based on study design and quality according to the IDSA Public Health Service grading system for rating recommendations in clinical guidelines (10) (Table 1). Consensus was achieved using a Delphi process (11).

Contributions and approval process

Generation of the idea to develop the guideline was a group effort, facilitated by GAE in his role as Chairman of the AMMI Canada Clinical Guidelines Committee. Writing of the first draft was undertaken by AWC and GH, with input by all members of the panel. Review was undertaken by the whole group, with consensus achieved using a Delphi process. The final draft underwent extensive review, both internally by members of the AMMI Canada Clinical Guidelines Committee and the CSS, and externally by experts in the field. The final version was approved by the AMMI Canada Clinical Practice Guidelines Committee and endorsed by the Canadian Association of General Surgeons Committee on Acute Care Surgery and Critical Care.

Disclosures

All members of the Working Group complied with the AMMI Canada and CSS policy on conflicts of interest, which requires disclosure of any financial or other interests that might be construed as constituting an actual, potential or apparent conflict. Members of the Working Group were provided a conflict of interest disclosure statement and were asked to identify any affiliations or financial interests with pharmaceutical companies that might potentially be affected by the guideline. Information was requested regarding ownership of stock or stock options, employment or paid consultancy within the past two years, honoraria,

TABLE 1
Infectious Diseases Society of America Public Health Service grading system for rating recommendations in clinical guidelines (10)

Rating	Definition
category (strength of recommendation)	
A	Strong support of a recommendation for or against use
B	Moderate support of a recommendation for or against use
C	Weak support of a recommendation for or against use
Grade (quality of evidence)	
1	Evidence from at least 1 properly randomized controlled trial
2	Evidence from at least 1 well-designed clinical trial without randomization, from cohort or case-controlled studies, or from dramatic results from uncontrolled experiments
3	Evidence from opinions of respected authorities, descriptive studies or reports of expert committees

speaker fees, educational grants and travel assistance to attend meetings. No potential conflicts were identified.

3. EPIDEMIOLOGY

3.1 Definitions and classification of IAIs

From a clinical viewpoint, two major types of IAI can be distinguished: uncomplicated and complicated. In uncomplicated IAIs, the infectious process only involves a single organ and no anatomical disruption is present. Generally, patients with such infections can be managed with surgical resection alone and no antimicrobial therapy besides perioperative prophylaxis is necessary. In complicated IAIs, the infectious process proceeds beyond the organ that is the source of the infection, and causes either localized peritonitis (often referred to as abdominal abscess) or diffuse peritonitis, depending on the ability of the host to contain the process within a part of the abdominal cavity (1,4,5,12,13). Complicated IAIs usually require an invasive surgical procedure for source control (hence, also known as ‘surgical IAI’).

IAIs can be further classified as ‘community acquired’ or ‘health care associated’. Community-acquired IAIs involve conditions such as gastroduodenal perforation, ascending cholangitis, cholecystitis, appendicitis or diverticulitis with or without perforation, and pancreatitis without previous surgical intervention or hospitalization (14,15). Health care-associated IAI is defined as an infectious process that is absent at the time of hospital admission, but becomes evident at 48 h or more after admission, and includes anastomotic leaks and perforations as well as abscesses that develop as a complication of surgery (3,4,16,17). Health care-associated IAI also includes infections acquired during the course of receiving treatment for other conditions in a health care setting, including the nursing home, dialysis unit or surgical day care, within the previous 12 months (18).

Peritonitis associated with IAI can be classified as primary, secondary or tertiary depending on the clinical presentation. Primary bacterial peritonitis is typically defined as a group of diseases with different causes, having in common only an infection in the peritoneal cavity without an obvious source of peritoneal contamination, such as in patients with chronic liver disease and ascites and those undergoing peritoneal dialysis (8,19,20). Secondary peritonitis refers to infections that arise from microbes in the alimentary tract due to perforation of a hollow viscus causing contamination of the otherwise sterile peritoneal cavity.

Tertiary peritonitis has been an evolving term, but is generally regarded as an infection in those patients who require more than one surgical intervention for source control and can often be classified as recurrent or persistent infections of the peritoneal cavity (3,6,17). Such patients commonly present with frequent septic episodes due to an exaggerated host inflammatory response (21).

3.2 Incidence and mortality

Several studies have attempted to clarify the incidence and mortality rates of IAIs within specific patient populations, including the anatomical site and nature of the surgical setting such as trauma versus nontrauma or duration of surgery. These rates vary greatly. For example, the overall prevalence of acute pancreatitis has been reported to vary from as low as 1% to as high as 80% of IAIs (22-26). Rates of postoperative IAIs are reported to vary by anatomical site, with the highest occurring after small bowel surgery (5.3% to 10.6%), followed by colon surgery (4.3% to 10.5%), gastric surgery (2.8% to 12.3%), liver/pancreas surgery (2.8% to 10.2%), exploratory laparotomy (1.9% to 6.9%) and appendectomy (1.3% to 3.1%) (27).

Despite the introduction of new surgical techniques, broad-spectrum antimicrobials, as well as improved supportive care within surgical intensive care units, the overall mortality rates in complicated IAIs have remained high, approaching 25% in secondary peritonitis (28-30). Patients who develop tertiary peritonitis have an even higher mortality rate (3,6,31). Depending on the cause and severity of illness, mortality rates of tertiary peritonitis are approximately twice as high as those with secondary peritonitis, ranging from 30% to 64% (3,8). Dellinger et al (32) and others (33) showed that mortality in IAIs was more closely related to the severity of illness and associated organ failure than the origin or site of infection. Importantly, multiple studies (34-36) have demonstrated the adverse effect of inappropriate antimicrobial therapy on overall mortality of complicated IAIs.

3.3 Risk stratification for poor outcomes

Regardless of antimicrobial therapy, patients can be stratified into different risk groups for mortality based on predictable clinical parameters and comorbid conditions: 'low' (less than 5% mortality), 'moderate' (5% to 15% mortality) and 'high' (15% to 30% mortality) (37). The APACHE II scoring system has been extensively validated for assessing severity of illness and predicting mortality in patients with complicated IAIs (38,39). Patients can be stratified into those with mild to moderate severity (APACHE II score lower than 15) and high-severity (APACHE II score of 15 or greater) illness. These indexes may be particularly useful in planning appropriate medical or surgical therapy, and for evaluating the therapeutic efficacy of different antimicrobial regimens for complicated IAIs. Apart from the severity of illness, other prognostic factors include older age, hypoalbuminemia, prolonged hospitalization and previous antibiotic exposure (37). Such patients have a more variable clinical course, and are more likely to harbour health care-associated multiresistant pathogens (15). Conversely, patients with low or moderate APACHE II scores (10 or lower) have a more predictable microflora and favourable clinical course (40,41).

Risk factors that predict treatment failure in IAI are more variable. Traditionally, local factors, such as the degree of peritoneal contamination and surgical technique, have been regarded as important predictors for surgical site infection and postoperative wound dehiscence (42,43). More recent studies (44,45) have focused on systemic factors and those known to affect tissue healing such as old age, smoking, malnutrition, diabetes, cardiovascular or lung disease, male sex, degree of blood loss and the operation itself as well as the inability to obtain source control as playing a significant role in the outcome of IAI. Multivariate analyses have identified a number of risk factors that largely relate to the patients' underlying physiological status, including a low serum albumin concentration, pre-existing medical disorders such as significant cardiovascular disease, and severity of illness as determined by high APACHE II scores (12,20,32,37,46-49). Taken collectively, these studies have revealed that the overall severity of illness (as determined by a high APACHE II score), receipt of inactive antimicrobial therapy, and the inability to achieve adequate source control with the initial operative procedure are the strongest prognosticators for mortality and poor outcome in complicated IAIs (12,46,48,50,51). Additionally, certain underlying diseases and comorbid conditions such as diabetes, obesity, smoking and malnutrition, have been shown to play an important role in increasing the risk of surgical site infections. The role of corticosteroids on surgical site infections remains controversial. Some authors have reported an increased risk of surgical site infections in patients receiving immunosuppressive therapy, but others did not find any significant relationship. The influence of microbiological findings on prognosis is seldom mentioned. However, Christou et al (52) demonstrated that IAI treatment failure was significantly correlated with the presence of resistant microorganisms at the time of reoperation and that resistant Gram-negative organisms, such as *P aeruginosa*, are more commonly encountered in high-risk patients.

3.4 Key recommendations for risk assessment and stratification

Recommendation 1. Categorize the severity of illness by using the APACHE II score according to low-moderate (lower than 15) or high (15 or greater) (A-2 evidence). Although the APACHE II scoring is infrequently used clinically outside of the critical care setting at present, it is recommended that physicians and surgeons consider introducing it into clinical use in patients with IAIs. A user-friendly APACHE II calculator can be found on the Web site <<http://www.globalrph.com/apacheii.htm>>.

Recommendation 2. Identify high-risk patients for poor outcome by stratification according to community-acquired versus health care-associated IAIs, previous antibiotic exposure, and underlying comorbid conditions such as diabetes, severe cardiopulmonary disease or immunosuppression (A-2 evidence).

Recommendation 3. Use the severity of illness score (APACHE II) and other risk factors outlined above to plan appropriate medical or surgical therapy, and for evaluating the efficacy of different antimicrobial regimens for complicated IAIs (A-2 evidence).

TABLE 2
Microbial flora in the gastrointestinal tract

Anatomical site	Inoculum (cfu/mL or g)	Organisms
Stomach	0 – few	<i>Lactobacillus</i> species
Duodenum, jejunum	0–≥10 ⁶	<i>Streptococcus</i> species, <i>Lactobacillus</i> species, Enterobacteriaceae
Ileum	10 ⁶ –10 ⁷	<i>Streptococcus</i> species, <i>Lactobacillus</i> species, Enterobacteriaceae, <i>Bacteroides</i> species
Colon	Dominant flora 10 ⁹ –10 ¹¹	<i>Bacteroides</i> species, <i>Prevotella</i> species, <i>Eubacterium</i> species, <i>Bifidobacterium</i> species, <i>Clostridium</i> species, <i>Streptococcus</i> species, <i>Porphyromonas</i> species
	Subdominant flora 10 ⁶ –10 ⁸	Enterobacteriaceae (mostly <i>Escherichia coli</i>), <i>Streptococcus</i> species, <i>Enterococcus</i> species, <i>Lactobacillus</i> species
	Sparse flora <10 ⁶	Enterobacteriaceae (non- <i>E coli</i>), <i>Klebsiella</i> species, <i>Citrobacter</i> species, <i>Proteus</i> species, <i>Enterobacter</i> species
	Transient flora <10 ⁶	<i>Pseudomonas</i> species, <i>Candida</i> species

cfu Colony-forming units. Adapted from references 4, 78 and 79

4. MICROBIOLOGY AND ANTIMICROBIAL RESISTANCE

4.1 Normal flora of the gastrointestinal tract

The endogenous microbial flora of the human gastrointestinal tract is complex, consisting of hundreds of different facultative and anaerobic bacterial species. The density and composition of the normal flora depends on the anatomical location in the gastrointestinal tract (Table 2) (53-55). In the stomach, there are only a few organisms, but the numbers and variety of bacterial species progressively increase from the duodenum to the ileum. In the colon, the bacterial load is very high (10⁹ colony-forming units [cfu]/g to 10¹¹ cfu/g) with the dominant flora being obligate anaerobes, especially *Bacteroides* species, *Clostridium* species and nonspore-forming Gram-positive bacilli. The subdominant colonic flora represents a lower bacterial load (10⁶ cfu/g to 10⁸ cfu/g), with *E coli* being the predominant organism, followed by other *Enterobacteriaceae* species present in lower numbers. Exogenous flora, such as *Pseudomonas* species and *Candida* species, may appear transiently, especially after exposure to antimicrobials.

The endogenous microbial flora of the human gastrointestinal tract remains quite constant over time and is similar among different individuals. However, this flora is readily influenced by a variety of host and environmental factors, including diet, underlying disease, hospitalization, previous antimicrobial therapy and recent surgery (Table 3) (56-59). Thus, knowledge of the anatomical location of the primary source of infection, underlying comorbid conditions, and whether the infection is community or health care associated, are the critical factors in predicting the most likely pathogens and their antibiotic susceptibility profiles. This information is pivotal in the selection of initial empirical antimicrobial therapy.

4.2 Microbial causes of IAIs

In contrast to primary peritonitis associated with chronic liver disease or peritoneal dialysis that is usually caused by a single

TABLE 3
Effect of host factors on the composition of the intestinal microflora

Site	Host factor	Effect on intestinal flora
Proximal small bowel	Achlorhydria	↑ <i>Escherichia coli</i> , <i>Bacteroides fragilis</i>
	Vagotomy and pyloroplasty	↑ <i>B fragilis</i> , <i>Bifidobacterium</i>
Mid and distal small bowel	Regional enteritis, blind loop, diverticulitis, irradiation, obstruction	'Colonic flora'
Colon	Colonic resection with ileostomy	↓ Anaerobes and some aerobes

pathogen, secondary or tertiary peritonitis are generally polymicrobial in etiology. Up to 15 different bacterial species may be cultured intraoperatively from the infected peritoneal cavity (average of 2.7 aerobic and 7.4 anaerobic species isolated per specimen) (Table 4) (60). Anaerobic species generally predominate over facultative isolates (15,30,61-74). The pathogenesis of polymicrobial infections associated with secondary or tertiary peritonitis is complex (62,75,76) and presents unique challenges to the clinician. First, it is not always clear which constituent(s) of the complex microflora are the key pathogens following peritoneal contamination and which are simply symbionts or commensals. The numerical predominance of an organism within its natural ecological niche of the gastrointestinal tract does not necessarily imply greater pathogenicity or clinical significance. Thus, whereas *E coli* and encapsulated *B fragilis* constitute less than 5% of the total colonic microflora, nevertheless, they are recognized as the key pathogens in intra-abdominal sepsis and abscess formation (60,75). Conversely, a highly virulent organism may be missed or overgrown in mixed culture due to its low density within the inoculum.

Due to the predominance of certain virulent pathogens and the polymicrobial nature of IAIs, the concept of 'core' pathogens was developed (Table 5). In community-acquired IAIs in which no previous antimicrobial exposure has occurred, the microbial causes of infection are relatively predictable and consist of the 'core' pathogens outlined in Table 5. These include anaerobes particularly *B fragilis*, non-*fragilis Bacteroides* species, *Clostridium* species, *Fusobacterium* species, *Peptostreptococcus* species, *Lactobacillus* species and *Veillonella* species. Facultative isolates include *Streptococcus* species, and Enterobacteriaceae species such as *E coli*, *Klebsiella* species, *Enterobacter* species, *Proteus* species and *Serratia* species. Although methicillin-sensitive *S aureus* is commonly recovered from patients with IAIs, it is not a common pathogen in community-acquired IAIs (4,77-79).

4.3 Proper specimen collection and handling

The issue of whether routine intraperitoneal culture and antimicrobial susceptibility testing for obligate anaerobes should be performed for all patients with mild to moderately severe community-acquired surgical IAIs is controversial. As noted previously, the enteric microflora in patients with gangrenous or perforated appendicitis is complex. Routine cultures for these specimens are both time-consuming and costly (80). A number of studies (81-83) reported that routine performance of such cultures in mild to moderately severe community-acquired

TABLE 4
Common microbial causes of intra-abdominal infections

Microbiological diagnosis	Frequency of isolation (% of patients)
Gram-negative bacilli	
<i>Escherichia coli</i>	50–100
<i>Klebsiella</i> species	
<i>Enterobacter</i> species	
<i>Proteus</i> species	
<i>Serratia marcescens</i>	
Gram-positive cocci	
<i>Streptococcus</i> species	10–44
Anaerobes	
<i>Bacteroides fragilis</i>	48–92
Non- <i>fragilis</i> <i>Bacteroides</i> species	
<i>Clostridium</i> species	
<i>Fusobacterium</i> species	
<i>Peptostreptococcus</i> species	
<i>Lactobacillus</i> species	
<i>Veillonella</i> species	

IAIs has failed to demonstrate any beneficial impact on clinical outcome. Accordingly, routine culture of enteric contents from the peritoneal cavity in such patients may not be necessary (B-2 evidence). On the other hand, in patients with postoperative or other health care-associated infections and those with clinical treatment failure, the acquisition or selection of resistant microorganisms is more likely. In such patients, intraoperative cultures obtained directly from abscess fluid or the peritoneal cavity may be important for guiding therapeutic decisions and are strongly recommended (60,84) (B-2 evidence).

4.4 Antimicrobial activity against IAI pathogens

The in vitro activity of commonly used antimicrobials against IAI pathogens including facultative Gram-positive cocci and Gram-negative bacilli and anaerobes are listed in Appendixes 1 to 3. These tables demonstrate that second-generation cephalosporins (eg, cefoxitin), third-generation cephalosporins (eg, cefotaxime, ceftriaxone, ceftazidime and cefepime), broad-spectrum penicillins (eg, piperacillin/tazobactam and ticarcillin/clavulanate), fluoroquinolones (eg, ciprofloxacin, levofloxacin and moxifloxacin), aminoglycosides (eg, gentamicin, netilmicin, tobramycin and amikacin), carbapenems (eg, imipenem, meropenem and ertapenem) and tigecycline have broad-spectrum activity against both Gram-positive cocci and Gram-negative bacilli commonly isolated in IAIs. Aminoglycosides such as gentamicin have very good activity against Gram-negative bacilli, but limited activity against Gram-positive cocci. Other agents, such as clindamycin, linezolid and vancomycin, have excellent activity against facultative Gram-positive cocci, but minimal activity against Gram-negative bacilli. The most active antimicrobials against anaerobes include metronidazole, carbapenems and broad-spectrum penicillins. Clindamycin has retained activity against most anaerobes, but resistance among *B fragilis* and *B fragilis* group is escalating (85). Cefoxitin also exhibits decreased activity, particularly against the *B fragilis* group organisms (86,87). Tigecycline has excellent anaerobic activity including *Peptostreptococcus* species, *B fragilis* and *B fragilis* group organisms. Moxifloxacin is the most active fluoroquinolone against *B fragilis*.

TABLE 5
'Core' pathogen concept in intra-abdominal infections

Infection	Classification	Diagnostic	
		features	Likely pathogens
Community acquired	Group 1	No previous antimicrobial use*	'Core' pathogens [†]
Community acquired	Group 2	Previous antimicrobial use*	'Core' pathogens [†] plus resistant Gram-negative bacilli, <i>Enterococcus</i> species, <i>Pseudomonas aeruginosa</i> and MRSA
Health care associated	Group 3	With/without previous antimicrobial use*	'Core' pathogens [†] plus resistant Gram-negative bacilli, <i>Enterococcus</i> species, <i>P aeruginosa</i> and MRSA

*Risk factors for antimicrobial-resistant pathogens include nosocomial infection and/or previous antimicrobial therapy in the past 90 days; [†]Core pathogens include *Streptococcus* species, *Enterobacteriaceae* (eg, *Escherichia coli*, *Klebsiella* species, *Proteus* species, *Serratia marcescens*) and anaerobes (eg, *Bacteroides fragilis*, non-*fragilis* *Bacteroides* species, *Clostridium* species, *Fusobacterium* species, *Lactobacillus* species, *Peptostreptococcus* species and *Veillonella* species). MRSA Methicillin-resistant *Staphylococcus aureus*

4.5 Increasing antimicrobial resistance among intra-abdominal isolates

Extensive surveillance studies (88-90) have demonstrated increasing antibiotic resistance globally among intra-abdominal isolates including *B fragilis*, *B fragilis* group species and *Enterobacteriaceae* species. For example, national surveys in the United States revealed that resistance to clindamycin among *B fragilis* and *B fragilis* group species has climbed steadily since 1997, reaching 19% and 26%, respectively, in 2004 (85). Similarly, resistance to cefotetan among *B fragilis* group species has exceeded 40% (91,92). Accordingly, clindamycin and cefotetan are no longer recommended as empirical therapy for surgical IAIs. In addition, ampicillin-sulbactam (not marketed in Canada) is no longer recommended as routine empirical therapy for surgical IAIs due to widespread resistance of *E coli* to this agent (88).

Patients with health care-associated infection or tertiary peritonitis are more likely to harbour resistant enteric Gram-negative bacilli (such as *Klebsiella* species, *Enterobacter* species, *Serratia* species, *Acinetobacter* species and *Pseudomonas* species, as well as other nonlactose-fermenting Gram-negative bacilli), facultative Gram-positive cocci (such as *Enterococcus* species and MRSA) and yeasts (particularly *Candida albicans* and *Candida glabrata*) (15,90). Patients with postoperative IAIs and those with prolonged previous hospitalization (five days or more) or those who received previous antimicrobial therapy (more than two days) are particularly at risk for the acquisition or selection of resistant enteric pathogens (90). ESBL-producing *Enterobacteriaceae* species (10% to 20% of isolates) (89) and fluoroquinolone-resistant *E coli* (2% to 7%) (93,94) are of particular concern in such patients.

4.6 Microbiology of treatment failures

The microbiology associated with treatment failures has been documented in several randomized clinical trials (52,95-105). Cultures obtained from treatment failures are frequently polymicrobial and more likely to isolate *E coli*, *Enterococcus* species, *P aeruginosa* and other nonfermenters. Furthermore, organisms

isolated at reoperation for treatment failures are more likely to be resistant to the original treatment regimens (52).

4.7 Key recommendations for microbiology and antimicrobial susceptibility testing

Recommendation 4. Due to the predominance of certain virulent pathogens in IAIs, the concept of 'core' pathogens is recommended for planning initial empirical antimicrobial therapy (A-2 evidence).

Recommendation 5. The microbiology of community-acquired IAIs in the absence of previous antimicrobial exposure generally consists of 'core' pathogens that are readily predictable (A-2 evidence). In such patients and, particularly those with mild to moderate severity of illness, routine bacteriological cultures of abdominal fluid or pus and antibiotic susceptibility testing of intra-abdominal isolates are optional and not routinely required to guide empirical antimicrobial therapy. However, such cultures may be useful for ongoing surveillance studies and generating local epidemiological data regarding antimicrobial susceptibility profiles and emerging resistance (A-2 evidence).

Recommendation 6. Patients with health care-associated IAIs who have prolonged previous hospitalization (five days or more), are severely ill (APACHE II score of 15 or greater) or have received previous antimicrobial therapy (more than two days) are at greater risk for antimicrobial-resistant pathogens. In such patients, blood and intraoperative cultures as well as antimicrobial susceptibility testing of all bacterial isolates should be performed routinely (A-2 evidence).

Recommendation 7. For specimen collection, abdominal fluid or pus should be collected in a capped airless syringe or be directly inoculated into appropriate aerobic and anaerobic transport media. Cultures should be sent for Gram stain and susceptibility testing. Swab specimens are not recommended (B-2 evidence).

Recommendation 8. In patients who develop treatment failures, their intra-abdominal cultures at reoperation are more likely to contain antibiotic-resistant isolates including non-fermenters and *Candida* species (A-2 evidence). Routine cultures and antimicrobial susceptibility testing of all isolates should be performed to guide subsequent antimicrobial therapy (A-2 evidence).

5. ANTIMICROBIAL THERAPY

The selection of initial anti-infective agents for complicated IAI was previously reviewed in 2003 by the IDSA (1). However, a number of newer antimicrobial regimens have been prospectively evaluated for the treatment of IAI since then, particularly ciprofloxacin plus metronidazole as sequential therapy, and monotherapy with moxifloxacin or tigecycline. The current practice guideline aims to update the contemporary status of antimicrobial agents for the empirical treatment of surgical IAIs. A strategy of risk stratification based on severity of illness, hospital versus community acquisition, previous antimicrobial therapy and likelihood of resistant pathogens is proposed.

5.1 Determinants of antimicrobial therapy

5.1.1 Host factors: Complicated IAIs develop in the presence of impaired host defences either due to local trauma of

abdominal organs or systemic immune dysfunction from comorbid disease, or both. The peritoneum mounts three major host defence mechanisms in response to infectious agents: bacterial clearance via the diaphragmatic lymphatics; phagocytic killing by resident peritoneal macrophages and recruited neutrophils; and sequestration processes, which involve T cell activation (106,107), deposition of fibrin exudates (108) and walling off the infection. Should these local and systemic host defences fail to control the infection, diffuse peritonitis may ensue. Alternatively, if the acute inflammatory host response to infection is overwhelming, bacterial products and deleterious biological host response mediators (such as cytokines) lead to tissue hypoxia, irreversible shock, multiple organ system failure and, ultimately, death (21). Thus, host factors, particularly the balance between host defences and the systemic inflammatory response, are critical determinants of eventual outcome. Accordingly, effective antimicrobial therapy is only one component of the treatment goal. Timely hemodynamic resuscitation and support of vital organ function to prevent irreversible hypoperfusion and shock, and rapid anatomical diagnosis to institute adequate source control are just as important as appropriate antimicrobial therapy.

5.1.2 Microbial factors: IAIs that arise from the endogenous enteric flora are polymicrobial in nature (1,4,79,109). The polymicrobial etiology of IAIs presents several dilemmas in clinical practice. For example, microorganisms in mixed infections may respond to antimicrobial agents differently than those in monomicrobial infections, and it may not be necessary to eradicate every bacterial species in mixed infections to achieve a cure. A case in point is the isolation of enterococci from intraperitoneal cultures in patients with mild to moderately severe community-acquired surgical IAIs. Despite the routine isolation of enterococci, treatment regimens providing antienterococcal coverage were not superior to comparative regimens that did not provide such coverage in prospective, blinded and randomized clinical trials (1,110). However, in seriously ill or immunocompromised patients, and in patients with health care-associated infections, the isolation of enterococci is a risk factor for treatment failure and increased mortality; hence, empirical antienterococcal coverage in such patients appears warranted (111,112). Similarly, isolation of *P aeruginosa* in a polymicrobial infection does not necessarily require treatment because it may represent a transient flora. However, treatment should be considered when *P aeruginosa* is the only pathogen recovered, if the patient is bacteremic, or if the patient has not responded to initial antimicrobial treatment that does not cover *P aeruginosa* (1,4,8,13,16,37,53,79,109,113,114). Thus, initial empirical antimicrobial therapy should be directed at the 'core' pathogens discussed earlier. Modification of therapy will be required depending on host factors such as severity of illness, underlying disease, whether health care associated or community acquired, and previous antimicrobial exposure.

5.2 Antimicrobial regimens in randomized clinical trials for IAIs

A total of 102 antimicrobial regimens have been adequately studied in randomized clinical trials for IAIs in adults over the

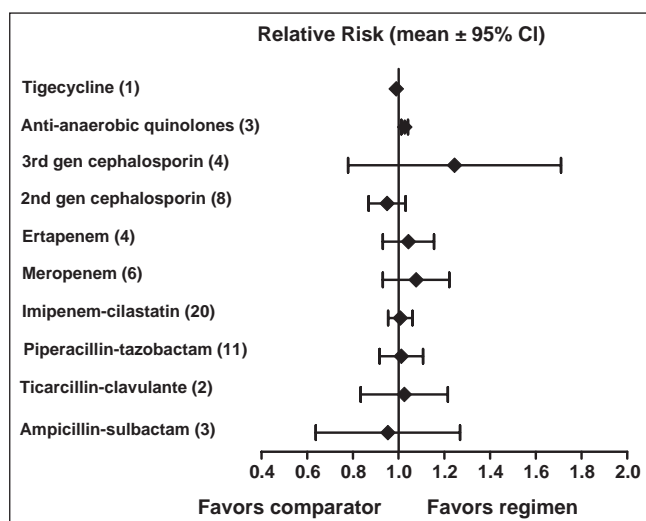


Figure 1 Ratio of clinical success rates over comparators in randomized controlled trials among 63 monotherapy regimens for complicated intra-abdominal infections. Data are expressed as mean \pm 95% CIs of study regimens over the comparator in each trial. Number of studies for the antimicrobial groups are shown in parentheses. Second-generation (gen) cephalosporins include cefoxitin, cefotetan, cefuroxime and cefamandole. Third-gen cephalosporins include cefoperazone with/without sulbactam. Antianaerobic fluoroquinolones include moxifloxacin, clinafloxacin and trovafloxacin. Data were compiled from published results of prospective randomized comparative trials (49,52,62,70,95,96,98,100-104,110,116-120,129,217-243)

past two decades (Figures 1 and 2). These regimens were administered to 9900 evaluable patients, with an average of 97 evaluable patients per study regimen (range 26 to 631; median 65). These study regimens can be grouped into 63 monotherapy regimens with single agents (beta-lactam antibiotics with/without beta-lactamase inhibitors, carbapenems, fluoroquinolones, or glycylicycline [tigecycline]) (Figure 1), and 39 combination regimens with two or more agents active against facultative Gram-negative bacilli (aminoglycosides, cephalosporins, monobactam or fluoroquinolones) and anaerobes (clindamycin or metronidazole) (Figure 2). Among monotherapy regimens, imipenem-cilastatin was most frequently studied (20 trials), followed by meropenem or ertapenem (10 trials), piperacillin with/without tazobactam (11 trials), second-generation cephalosporins (cefoxitin, cefotetan, cefuroxime, cefamandole; eight trials), ampicillin or ticarcillin plus beta-lactamase inhibitor (five trials), third-generation cephalosporins (cefoperazone with/without sulbactam; four trials), fluoroquinolones (trovafloxacin, clinafloxacin, moxifloxacin; three trials) and tigecycline (pooled analysis of two trials). Among the combination regimens, aminoglycoside plus clindamycin was most frequent (19 trials), followed by cephalosporin (cefuroxime, cefotaxime, ceftriaxone, cefoperazone or cefepime) plus metronidazole (11 trials) or clindamycin (one trial), fluoroquinolone plus metronidazole (five trials), aztreonam plus clindamycin (two trials) and piperacillin-tazobactam plus amikacin (one trial). Three randomized clinical trials evaluating two new monotherapy regimens were included. One of these evaluated the efficacy, safety and cost-savings of moxifloxacin as sequential therapy compared with piperacillin-tazobactam in both community- and health

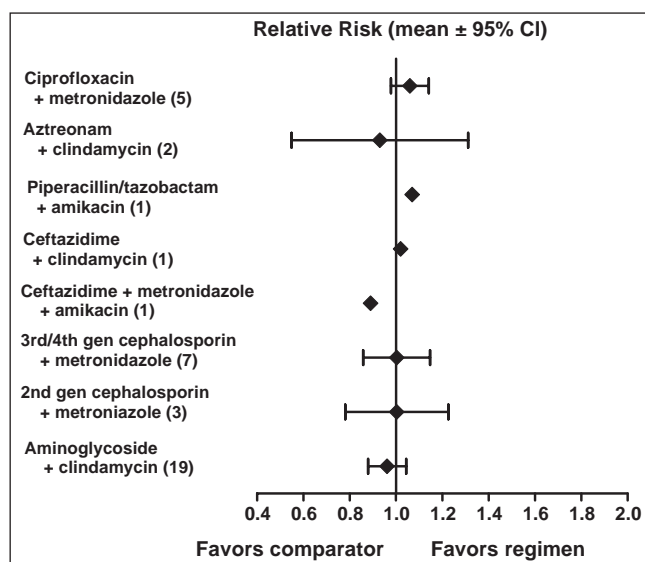


Figure 2 Ratio of clinical success rates over comparators in randomized controlled trials among 39 combination regimens for complicated intra-abdominal infections. Data are expressed as mean \pm 95% CIs of study regimens over the comparator in each trial. Number of studies for the antimicrobial groups are shown in parentheses. Second-generation (gen) cephalosporins include cefuroxime. Third- or fourth-gen cephalosporins include cefotaxime, ceftriaxone and cefepime. Data were compiled from published results of prospective, randomized comparative trials (49,62,70,95,100,103,104,110,117-120,127,218,219,223-226,229-232,237-247)

care-associated complicated IAIs (102). The other is a pooled analysis of two phase 3, double-blind, randomized trials evaluating the efficacy and safety of tigecycline compared with imipenem-cilastatin (98,115). Only one study (116) examined the duration of empirical antimicrobial therapy comparing the efficacy and safety of ertapenem 1 g/day for three days versus five days or more in a prospective, double-blind, multicentre trial. No statistically significant differences in outcome were identified.

Overall, the clinical outcome of all these regimens was favourable, with mean success rates ranging from 44% to 100% (mean 82%, median 83%), and infection-related mortality rates ranging from 0% to 17% (mean 3.7%, median 2.5%) in the different study groups. However, the disease severity score of enrolled patients was generally low, with 48% to 90% (mean 77%, median 82%) of patients having an APACHE II score of 10 or lower, and mean APACHE II scores ranging from 5.5 to 13.1 (mean 8.0, median 7.8) in the different treatment groups. Furthermore, more than 80% of study populations had community-acquired infections. Among these 102 therapeutic regimens, only eight studies demonstrated a statistically superior clinical success rate of the study arm over its comparator (49,62,96,110,117-120). Of interest, the aminoglycoside (gentamicin or tobramycin) plus clindamycin regimen was inferior to the comparator (cefoperazone-sulbactam and imipenem-cilastatin, respectively) in two separate prospective, randomized trials (49,118). Conversely, cefoperazone was superior to the comparator in two separate prospective trials (ceftazidime/metronidazole/amikacin and gentamicin/clindamycin, respectively) (62,118). However,

TABLE 6
Antimicrobial agents for empirical therapy of community-acquired surgical intra-abdominal infections with low to moderate severity (APACHE II score lower than 15)

Monotherapy
Cefoxitin 2 g IV q6h
Ticarcillin-clavulanate 3 g/0.1 g IV q4–6h →Amoxicillin-clavulanate 500 mg/125 mg PO q8h
Ertapenem 1 g IV once daily*
Moxifloxacin 400 mg IV→PO once daily*
Tigecycline 100 mg IV loading, then 50 mg IV q12h
Combination
Second- or third-generation cephalosporin (cefuroxime 1.5 g IV q8h, cefotaxime 1.5 g IV q8h or ceftriaxone 1–2 g IV once daily*) plus metronidazole 500 mg IV→PO q8h
Ciprofloxacin 200 mg IV q12h→500 mg PO q12h plus metronidazole 500 mg IV→PO q8h

*Suitable for home or outpatient intravenous (IV) therapy. Exact dosing may require modification based on renal and/or hepatic function. IV→PO IV to oral sequential therapy; q Every

no single regimen was consistently superior to another regimen in more than one study. This is demonstrated by the similar relative risk values of clinical success rates (expressed as the ratio of the study regimen over the comparator in each trial) among the 63 monotherapy regimens (mean 1.02; 95% CI 0.99 to 1.06) (Figure 1), and the 39 combination regimens (mean 0.99; 95% CI 0.94 to 1.03) (Figure 2).

It should be noted that these published studies primarily enrolled patients with mild to moderately severe, community-acquired IAIs. Furthermore, these studies do not address the changing trend and local epidemiology of antibiotic resistance patterns of intra-abdominal isolates. In addition, although prospective, randomized clinical trials have been the gold standard for formulating therapeutic recommendations, the study populations enrolled in such trials may be vastly different from those not enrolled in a clinical trial. Study patients generally have a more favourable outcome due to less severe illness, infrequent association with antibiotic resistance, or exclusion of complex underlying diseases (121). Thus, conclusions drawn from prospective, randomized clinical trials may not be generally applicable to all patients with IAI in the 'real world' setting of clinical practice.

5.3 Initial empirical antimicrobial therapy

Based on the above discussion of microbial and host factors that predict outcome, and published studies of randomized clinical trials, it is recommended that the selection of initial antimicrobial therapy for surgical IAI be stratified according to the following risk factors: community- versus health care-associated infection, severity of illness as assessed by APACHE II scores (15 or lower for mild to moderately severe and greater than 15 for highly severe), and prolonged previous hospital stay (five or more days) or antimicrobial therapy (two or more days). Patients with prolonged previous hospitalization or antimicrobial exposure are more likely to harbour resistant microorganisms and should be treated as for health care-associated infections (90) (A-1 evidence). Empirical antimicrobial therapy should be initiated as soon as the diagnosis of IAI is suspected (preferably within 8 h of presentation to a health care facility) (122,123).

TABLE 7
Antimicrobial agents for empirical therapy of health care-associated surgical intra-abdominal infections, or for severely ill patients (APACHE II score of 15 or greater) with community-acquired infection*

Monotherapy
Piperacillin-tazobactam 3.375 g IV q4–6h or 4.5 g IV q6–8h
Imipenem-cilastatin 0.5 g IV q6h or meropenem 0.5 g IV q6h to 1 g IV q8h
Combination
Third- or fourth-generation cephalosporin (ceftazidime 2 g IV or cefepime 2 g IV q8h) plus metronidazole 500 mg IV q8h
Ciprofloxacin 400 mg IV q12h (q8h if for <i>Pseudomonas aeruginosa</i>) → 500 mg PO bid, plus metronidazole 500 mg q8h IV→PO
Tigecycline 100 mg IV loading, then 50 mg IV q12h plus ciprofloxacin 400 mg IV q8h
Piperacillin-tazobactam 3.375 g IV q4–6h or 4.5 g IV q6–8h plus an aminoglycoside
Imipenem-cilastatin 0.5g IV q6h or meropenem 0.5 g IV q6h to 1 g IV q8h plus an aminoglycoside

*Includes patients with prolonged previous hospitalization (five days or more) or previous antimicrobial therapy (two days or more). Exact dosing may require modification based on renal and/or hepatic function. bid Twice a day; IV Intravenous; PO Oral; q Every

Antimicrobial therapy is directed at a polymicrobial infection caused by 'core' pathogens including facultative enteric Gram-negative bacilli and intestinal anaerobes, particularly *E coli* and *B fragilis*. For most mild to moderately severe community-acquired IAIs, the microbiology and antibiotic susceptibility profile of peritoneal isolates are predictable. Routine intra-abdominal cultures and antibiotic susceptibility testing in such patients are optional and may not be cost-effective. Monotherapy with single agents possessing a relatively narrow spectrum of activity may suffice (Table 6). As noted earlier, ampicillin-sulbactam, clindamycin and cefotetan are no longer recommended for routine empirical therapy of IAIs because of the high rate of resistance to ampicillin-sulbactam among *E coli*, and to cefotetan and clindamycin among *B fragilis*.

For high-risk patients (those with health care-associated infection, previous antimicrobial therapy, severe physiological impairment [APACHE II score of 15 or greater] and those who failed to respond to initial treatment), an antimicrobial regimen with a broader spectrum of activity against resistant facultative Gram-negative rods as well as anaerobes is recommended (Table 7). In such patients, availability of intraoperative cultures from the peritoneal cavity and in vitro susceptibility testing of recovered isolates are critical to guide further adjustments in antimicrobial therapy. The selection of specific antimicrobial regimens is discussed below.

5.3.1. Mild to moderately severe community-acquired IAI:

For patients with community-acquired infection of mild to moderate severity (APACHE II score lower than 15), an antibiotic regimen with a relatively narrow spectrum of activity, low toxicity profile and low cost is recommended. These include monotherapy with cefoxitin, a beta-lactam-beta-lactamase inhibitor (eg, ticarcillin-clavulanate), ertapenem, moxifloxacin or tigecycline, and combination regimens of a second- or third-generation cephalosporin or ciprofloxacin, each with metronidazole (Table 6) (A-1 evidence). Combination therapy with ciprofloxacin plus metronidazole offers the additional

benefit of IV to oral PO sequential therapy, enabling earlier discharge from hospital and potential cost savings to the health care system. Furthermore, the fluoroquinolones such as ciprofloxacin have enjoyed a long history of successful treatment for a variety of gastrointestinal and IAIs (124). Meta-analysis of several randomized trials in 1431 patients have demonstrated that the ciprofloxacin/metronidazole combination is at least as effective, if not superior, to beta-lactam-based regimens (110,125-127). In one study by Cohn et al (110), the clinical success rate among 134 patients receiving ciprofloxacin/metronidazole was significantly higher than that among 116 patients who received piperacillin-tazobactam (74% versus 63%; $P<0.05$). There was no difference in all-cause mortality or toxicity between ciprofloxacin/metronidazole and the comparison arms. However, the availability of ciprofloxacin/metronidazole as IV to PO sequential therapy offers considerable cost advantage because patients may be discharged from hospital several days earlier (128).

More recently, moxifloxacin once daily as sequential therapy has been shown to be equally effective as piperacillin-tazobactam IV four times daily followed by amoxicillin-clavulanate PO in community-acquired IAIs (clinical success rates, 80% versus 82%) (102). In contrast to trovafloxacin and clinafloxacin, which were also comparable to imipenem-cilastatin in efficacy (101,129), moxifloxacin did not exhibit severe adverse effects such as hepatotoxicity, hypoglycemia or phototoxicity. (Note: The European Medicines Agency [EMA] released a recommendation to restrict the use of oral formulations of moxifloxacin-containing medicines in July 2008 after completing a review of new data related to significant hepatotoxicity <http://www.ema.europa.eu/pdfs/human/referral/moxifloxacin_107/Q&A_Moxifloxacin_38045408en.pdf>.) It remains to be seen whether this fluoroquinolone will replace ciprofloxacin/metronidazole as a major therapeutic regimen in more seriously ill patients. In contrast to ciprofloxacin and moxifloxacin, there are no randomized clinical trials evaluating the use of levofloxacin or gatifloxacin in combination with metronidazole for complicated IAIs. One concern with the increased use of fluoroquinolones is the emergence of resistance among Enterobacteriaceae species, particularly ESBL-producing strains (89,93). The rates of fluoroquinolone resistance from 1993 to 2004 among 74,394 Gram-negative bacilli isolated from intensive care unit patients in a large number of American acute care hospitals were compared (130). The per cent of *E coli* isolates resistant to ciprofloxacin rose from 0.9% from 1993 to 1995, to 17.3% from 2002 to 2004, while that among *P aeruginosa* rose from 11.2% to 28.9%. The rate of fluoroquinolone resistance was directly linked to total fluoroquinolone usage. This relationship was also demonstrated by other studies (131,132). Thus, continued vigilance through surveillance, and innovative approaches to minimize or delay the emergence of resistance, are necessary if the clinical utility of these agents as initial empirical therapy is to be preserved.

Although aminoglycoside plus an antianaerobic agent has been the gold standard against which newer agents were compared for more than a decade, this combination is no longer considered to be standard therapy even for mild to moderately severe community-acquired infections (A-2 evidence). This is primarily due to unacceptable nephrotoxicity and ototoxicity of aminoglycosides in the presence of alternative safer agents

such as beta-lactam-beta-lactamase inhibitors, third- and fourth-generation cephalosporins and fluoroquinolones (133). More importantly, meta-analysis of clinical success rates comparing regimens using aminoglycoside plus an antianaerobic agent against all other regimens in the Cochrane database revealed significantly lower response rates of the former (OR 0.65, 95% CI 0.46 to 0.92; $P=0.02$) (9). In particular, the clinical success rates of imipenem-cilastatin and cefoperazone-sulbactam (no longer available in Canada) were both superior to aminoglycoside/clindamycin regimens in two prospective, randomized trials by Solomkin et al (49) and Jauregui et al (118), respectively. The outcome of microbiological success was also significantly different in favour of the comparator regimens (OR 0.49; 95% CI 0.31 to 0.76; $P=0.001$) (9).

In light of the emerging concern of ESBL-producing Enterobacteriaceae species due to selection pressure by increased use of oxyimino-cephalosporins (ceftazidime, ceftriaxone and cefotaxime), as well as *ampC*-producing nosocomial pathogens (resistant to all cephalosporins), the prolonged use of all cephalosporins in the health care setting is actively discouraged in favour of beta-lactam-beta-lactamase inhibitors or carbapenems (A-2 evidence).

5.3.2 Health care-associated or severe community-acquired IAIs:

There is paucity of data from randomized clinical trials to document the efficacy of various antimicrobial regimens for the treatment of health care-associated or severe community-acquired IAIs. Thus, recommendations for such patients are primarily based on the clinical experience of respected authorities, descriptive studies, or consensus reports from expert committees (Table 7) (B-3 evidence). In general, antimicrobial regimens with a broader spectrum of activity and relatively low rates of resistance are recommended. Monotherapy with piperacillin-tazobactam, imipenem-cilastatin or meropenem are recommended. Ciprofloxacin plus metronidazole can also be used. Combination regimens with third- or fourth-generation cephalosporins (eg, ceftazidime, ceftriaxone or cefepime) plus metronidazole are additional alternatives; however, due to the concern for selection of ESBL- and *ampC*-producing multiresistant Gram-negative bacilli as discussed above, prolonged and wide-spread use of cephalosporins are generally discouraged (A-2 evidence). For severely ill patients and those with prolonged previous hospitalization or antimicrobial exposure, infection with multiresistant Gram-negative bacilli is more common, and the addition of an aminoglycoside may be desirable to broaden the antimicrobial spectrum and delay the emergence of resistance despite their known toxicities (9) (B-3 evidence).

A subset of moderately ill patients with health care-associated IAIs were studied prospectively in a double-blind, randomized clinical trial involving sequential IV to PO monotherapy with moxifloxacin (102). Moxifloxacin was found to be superior to piperacillin-tazobactam IV → amoxicillin-clavulanate PO sequential therapy in this subset analysis (clinical success rates 82% versus 55%; $P<0.05$). The bacteriological eradication rates as well as safety profiles in the two study arms were comparable. Moxifloxacin has excellent pharmacokinetic and pharmacodynamic properties, and penetrates well into peritoneal exudates and abscess cavities (134,135). Other potential advantages include once daily dosing, IV to PO switch without dosage adjustment, and convenience as well as cost-savings due

to shortened hospitalization. If confirmed by additional studies in seriously ill patients, moxifloxacin may become a treatment option for patients with community- as well as health care-associated complicated IAI (B-2 evidence). However, these advantages must be balanced against the potential for fluoroquinolones to select for ESBL-producing pathogens, the emergence of resistance among *B fragilis*, and the reported association between fluoroquinolone use and superinfection by *Clostridium difficile* (89,93). Other newer fluoroquinolones with broad-spectrum activity against both Enterobacteriaceae and anaerobes are currently under investigation (71).

Tigecycline has excellent in vitro activity against intra-abdominal isolates, including aerobic and anaerobic Gram-positive and Gram-negative bacteria, ESBL-producing Enterobacteriaceae, MRSA and vancomycin-resistant enterococci (VRE). It is, however, relatively inactive against *P aeruginosa* (136). It also has favourable pharmacokinetic and pharmacodynamic properties that theoretically make it a good candidate for the treatment of health care-associated infections if used in combination with ciprofloxacin to cover for *P aeruginosa*. Unfortunately, in the two phase 3 trials reported, although noninferiority to imipenem-cilastatin was established, the study populations uniformly had only mild to moderate severity of infection (mean APACHE II scores were 6.3 for tigecycline and 6.0 for imipenem-cilastatin). It remains to be seen whether tigecycline is efficacious and safe for seriously ill patients with health care-associated infections.

5.3.3 Empirical anti-MRSA therapy: MRSA is isolated with increasing frequency in both community-acquired and health care-associated infections (137). Patients with prolonged hospitalization, an indwelling intravenous catheter, previous antimicrobial exposure in the preceding three months and a nursing home residence are particularly at risk for MRSA infections (138). However, the role of MRSA in IAIs other than surgical site infections is unclear (139,140). In health care-associated postoperative and surgical site infections, empirical anti-MRSA therapy should be considered for those who are known to be colonized with the organism or have a history of MRSA infection. Vancomycin remains the agent of choice, although quinupristin-dalfopristin, linezolid, daptomycin and tigecycline may also be used. Vancomycin may also be considered for surgical prophylaxis in patients who are known to be MRSA carriers or if they come from facilities with a high prevalence of MRSA infection (141) (B-2 evidence).

5.3.4 Empirical antienterococcal therapy: Enterococci are frequently isolated in intraperitoneal cultures in patients with community-acquired surgical IAIs. However, treatment regimens that provide antienterococcal coverage were not superior to comparative regimens that did not provide such coverage in prospective, blinded and randomized clinical trials (1,110,142). Thus, routine empirical coverage for enterococci for community-acquired, mild to moderately severe surgical IAIs is not required (A-1 evidence). However, enterococci are recovered more commonly in certain populations with complicated IAIs, particularly those with health care-associated, postoperative infections, severe immunosuppression, recurrent infections and those receiving prolonged antimicrobial therapy

with cephalosporins that select for enterococci (111). Such individuals are also at increased risk for treatment failure and poor outcome (143). Thus, empirical antienterococcal therapy is recommended for the following at-risk populations until definitive culture results become available: immunosuppressed patients with health care-associated postoperative IAIs; patients with severe sepsis of abdominal origin or recurrent peritonitis who have previously received cephalosporins and other broad-spectrum antimicrobial agents that select for enterococci, patients with biliary sepsis undergoing liver transplantation, and patients with peritonitis and valvular heart disease or prosthetic intravascular devices that place them at high risk for enterococcal endocarditis (C-3 evidence). Initial empirical antienterococcal therapy should be directed at *Enterococcus faecalis*, which can be treated with penicillin, ampicillin, piperacillin-tazobactam, imipenem-cilastatin, tigecycline or vancomycin (C-3 evidence). Empirical coverage directed against *Enterococcus faecium* should be considered in patients with prolonged previous antimicrobial exposure, particularly those with hepatobiliary sepsis undergoing liver transplantation, and vancomycin is the agent of choice. Tigecycline or daptomycin may be considered if the isolates are vancomycin resistant (C-3 evidence).

5.3.5 Pre-emptive antifungal therapy: *Candida* species are not common pathogens in community-acquired IAIs. However, invasive candidiasis is an important cause of mortality in immunosuppressed patients with health care-associated or postoperative IAIs (144,145). Severity of disease (APACHE II of 15 or greater), previous antimicrobial therapy, upper gastrointestinal source of infection, intraoperative cardiopulmonary failure and demonstration of yeast in Gram stain of peritoneal fluids are independent risk factors for culture-documented *Candida peritonitis* (146). Antifungal therapy should be initiated if *Candida* species is isolated from intra-abdominal cultures, and fluconazole is the antifungal agent of choice if *C albicans* is identified (B-2 evidence). For non-*albicans* *Candida* species resistant to fluconazole, an echinocandin (eg, caspofungin, micafungin or anidulafungin) or a triazole (eg, voriconazole) to which the organism is susceptible is appropriate (B-3 evidence). Amphotericin is not recommended for initial antifungal therapy due to its toxicity (B-2 evidence).

Pre-emptive antifungal therapy with either fluconazole or an echinocandin may be considered in immunosuppressed and seriously ill patients who present with recurrent or postoperative IAIs, and are known to be colonized with *C albicans* at multiple sites (144) (C-2 evidence). Such a strategy has been shown to prevent the development of invasive candidiasis or candidemia, but has no impact on overall mortality (147-149).

5.4 Duration of antimicrobial therapy

The optimal timing and duration of antimicrobial therapy for complicated IAIs have not been determined. Whereas sub-optimal antibiotic therapy clearly results in enhanced failure rates and mortality, prolonged antibiotic administration leads to superinfections, selection for resistance, as well as adverse effects and added cost. In various clinical trials evaluating the efficacy and safety of antimicrobial regimens for surgical IAIs, a 'standard' duration of five to 14 days was chosen. However,

more recent studies have attempted to evaluate whether a shorter course of antimicrobial therapy in community-acquired IAIs might be more cost effective. Schein et al (150) prospectively evaluated the effect of limiting the duration of antimicrobial therapy based on intraoperative findings of the degree of contamination and extent of infection. Treatment for localized peritonitis (eg, perforated appendicitis, cholecystitis, diverticulitis, gastroduodenal or traumatic perforations, strangulated small bowel and colorectal surgery) was restricted to less than 48 h if adequate source control was achieved. Treatment for more extensive infection, including generalized peritonitis was limited to five days or less. This strategy yielded results comparable with historical controls. Another approach evaluated the effect of limiting the duration of antimicrobial therapy based on the clinical response as assessed by resolution of fever and leukocytosis, and improvement of abdominal examination and gastrointestinal function (151,152). These prospective studies confirmed that similar outcomes could be achieved with earlier cessation of antibiotic treatment based on a satisfactory clinical response. Finally, a prospective, double-blind, multicentre randomized trial was conducted to evaluate the efficacy and safety of administering ertapenem 1 g per day for three days compared with the 'standard' duration of therapy for five days or more (mean 5.7 days, range five to 10 days) in 111 adults with community-acquired IAIs (116). The clinical and bacteriological response rates in the two groups among 90 evaluable patients were similar (93% and 95%, respectively; versus 90% and 94%). It should be noted that disease severity was mild to moderate (mean APACHE II score of 6.2) in all patients, and intraoperative source control was considered adequate in all but one patient. This was the only prospective study that specifically examined the duration of antimicrobial therapy in complicated IAIs by a double-blind randomized study design.

Based on these findings, it is recommended that the duration of antimicrobial therapy for complicated IAIs should be no more than five to seven days, unless it is difficult to achieve adequate source control (B-3 evidence). Treatment duration should be guided by intraoperative findings and clinical response as assessed by resolution of fever and leukocytosis, abdominal examination and gastrointestinal function. Patients who continue to exhibit clinical evidence of infection at the end of seven days should be evaluated for residual infection, resistant microorganisms, noninfectious causes of inflammation and other possible reasons of treatment failure, rather than simply prolonging or broadening antimicrobial therapy (B-3 evidence).

It is further recommended that the duration of antimicrobial therapy for the purpose of surgical prophylaxis should be limited to 24 h or less in patients with penetrating bowel trauma repaired within 12 h, intraoperative contamination by enteric contents, or nonperforating appendicitis in the absence of abscess or local peritonitis (A-1 evidence).

5.5 Management of the nonresponsive patient

Patients with recurrent IAIs following initial surgical and antimicrobial therapy for secondary peritonitis are referred to as having 'tertiary' peritonitis (6,60). These patients are characterized by persistent or worsening organ dysfunction and an inability to localize their peritoneal infection due to poor host

defences. Their microbial flora also appears strikingly different, often dominated by *P. aeruginosa* and other nonfermentative Gram-negative bacilli, *Enterobacter* species, enterococci, *Candida* species, resistant *Bacteroides* species and low-virulence organisms such as coagulase-negative staphylococci. These organisms likely represent superinfections from the hospital flora or selection of resistant microbes from previous antimicrobial therapy (3,153). Treatment is difficult because the mortality remains high (exceeding 50%) despite prolonged systemic antibiotics and aggressive surgical management (63).

In the face of persistent or recurrent IAI, every effort should be made to ensure that adequate source control has been attained. Reimaging by computed tomography or magnetic resonance imaging is required to identify loculated foci of residual infection or anastomotic leak of the intestinal tract. Repeat laparotomy is recommended to achieve adequate source control and to facilitate pathogen-directed antimicrobial therapy by obtaining appropriate samples for microbiological evaluation. Repeat laparotomy may also be indicated for decompression in selected patients with IAH and the ACS (refer to section 7.2). Extra-abdominal sources of infection should be excluded. Every effort should be directed at treating underlying comorbid conditions, mitigating immunosuppression and bolstering innate mucosal immunity. It remains to be determined whether immunotherapy (either humoral or cellular) in conjunction with appropriate antimicrobial therapy will improve clinical outcome in such patients (106).

5.6 Key recommendations for initial empirical antimicrobial therapy

Recommendation 9. For patients with community-acquired surgical IAIs with mild to moderate severity (APACHE II score of lower than 15) who have not undergone prolonged previous hospitalization (five days or more) or received previous antimicrobial therapy (more than two days), initial empirical antimicrobial therapy should be directed against 'core pathogens' only, including enteric Gram-positive cocci as well as facultative and anaerobic Gram-negative bacilli, particularly *E coli* and *B fragilis* (A-1 evidence). For adult patients, monotherapy with cefoxitin, ticarcillin-clavulanate, ertapenem, moxifloxacin or tigecycline is appropriate; alternatively, combinations of cefuroxime, cefotaxime, ceftriaxone or ciprofloxacin, each with metronidazole, are preferable to broader-spectrum regimens (A-1 evidence).

Recommendation 10. Ampicillin-sulbactam (not available in Canada), cefotetan and clindamycin are no longer recommended for routine empirical therapy of complicated IAIs because of the high rate of resistance among community-acquired *E coli* against ampicillin-sulbactam, and among *B fragilis* against cefotetan and clindamycin (B-2 evidence).

Recommendation 11. In light of the availability of less toxic regimens and unfavourable clinical response rates in randomized clinical trials, aminoglycosides are not recommended for routine empirical treatment of complicated IAIs (A-1 evidence).

Recommendation 12. For health care-associated surgical IAIs and seriously ill patients with community-acquired infections (APACHE II score of 15 or greater, previous hospitalization of five days or more, or previous antimicrobial therapy of two days or more), antimicrobial agents with broader spectrum of

activity against facultative and anaerobic Gram-negative bacilli are recommended (B-2 evidence). For adult patients, monotherapy with piperacillin-tazobactam, imipenem-cilastatin, meropenem, or combinations of ceftazidime, ceftazidime or ciprofloxacin with metronidazole, or tigecycline in combination with ciprofloxacin are appropriate (B-2 evidence).

Recommendation 13. IV to PO sequential treatment with a fluoroquinolone (such as monotherapy with moxifloxacin or combination therapy with ciprofloxacin plus metronidazole) may be a cost-effective alternative (B-2 evidence). Continued surveillance for emerging resistance, particularly against facultative Gram-negative bacilli, should be implemented and periodic review of their efficacy and safety should be considered when choosing monotherapy or combination therapy with a fluoroquinolone (A-1 evidence).

Recommendation 14. In light of the emerging concern of ESBL-producing Enterobacteriaceae species due to selection pressure by increased use of oxymino-cephalosporins (ceftazidime, ceftriaxone and cefotaxime), as well as *ampC*-producing nosocomial pathogens (resistant to all cephalosporins), the prolonged use of all cephalosporins in the health care setting is actively discouraged in favour of beta-lactam-beta-lactamase inhibitors or carbapenems (154,155) (A-2 evidence).

Recommendation 15. Routine coverage for enterococci is not recommended in patients with community-acquired IAI of mild to moderate severity (A-1 evidence). However, empirical antienterococcal therapy should be considered for immunosuppressed patients with health care-associated, postoperative or recurrent IAIs, those with antimicrobial exposure to cephalosporins and other broad-spectrum regimens selecting for enterococci, and those with valvular heart disease or intravascular prosthetic devices (B-3 evidence).

Recommendation 16. Coverage for *P aeruginosa* should be considered if it is the only pathogen recovered, if it is isolated from blood cultures, or if the patient has not responded to antimicrobial treatment that does not cover *P aeruginosa* in the setting of health care-associated IAIs (B-2 evidence).

Recommendation 17. Anti-MRSA therapy should be administered for health care-associated IAIs in patients who are known to be colonized with the organism or have a history of MRSA infection. Vancomycin remains the agent of choice, although linezolid, daptomycin, tigecycline and quinupristin-dalfopristin may also be used. Vancomycin may also be considered for surgical prophylaxis in patients who are known to be MRSA carriers or if they come from facilities with a high prevalence of MRSA infection (B-2 evidence).

Recommendation 18. Targeted antifungal therapy is recommended for patients with severe community-acquired or nosocomial IAIs only if *Candida* species is isolated from intra-abdominal or blood cultures. Fluconazole is the agent of choice if *C albicans* is isolated. For non-*albicans Candida* species, either an echinocandin (such as caspofungin, micafungin or anidulafungin) or a triazole (such as voriconazole) to which the organism is susceptible may be considered (B-2 evidence).

Recommendation 19. Amphotericin B is not recommended as initial therapy because of its toxicity (B-2 evidence).

Recommendation 20. Pre-emptive antifungal therapy with fluconazole or an echinocandin may be considered for seriously ill patients with high risk for invasive candidiasis (eg, immunosuppression, postoperative or recurrent peritonitis, *Candida*

colonization at multiple sites, etc); however, such a strategy has not been shown to impact mortality (C-2 evidence).

Recommendation 21. The duration of antimicrobial therapy should be guided by intraoperative findings and clinical response as assessed by resolution of fever and leukocytosis, abdominal examination and gastrointestinal function, and should be no more than five to seven days unless it is difficult to achieve adequate source control (B-3 evidence).

Recommendation 22. Patients who continue to exhibit clinical evidence of infection at the end of seven days of antimicrobial therapy should be evaluated for residual infection, resistant microorganisms and other possible causes of treatment failure rather than simply prolonging or broadening antimicrobial therapy (C-3 evidence).

Recommendation 23. In patients with postoperative or other health care-associated infections and those with clinical treatment failure, the acquisition or selection of resistant microorganisms should be strongly suspected, and further antimicrobial therapy should be guided by intraoperative cultures and susceptibility testing obtained directly from abscess fluid or the peritoneal cavity (B-2 evidence).

Recommendation 24. Development of clinical pathways (ie, a protocol approach) for the management of complicated IAIs based on local epidemiology of antimicrobial utilization and antibiotic resistance profiles is highly recommended. Such locally developed clinical pathways should standardize the approach to diagnosis, microbiological and radiological investigations, empirical antimicrobial therapy as well as policies regarding discharge and outpatient management. Such local guidelines should be established by a multidisciplinary team including surgeons, infectious disease and medical microbiology specialists, emergency physicians and other health care providers, and should reflect local resources and local standards of care (B-3 evidence).

Recommendation 25. Each institution should develop its own suite of performance measures to provide ongoing evaluation of the effectiveness and appropriateness of the local clinical pathways for complicated IAIs, ultimately leading to improved quality of care (B-3 evidence).

6. SOURCE CONTROL

Complicated IAIs typically originate from a leak in the gastrointestinal tract and cannot be eradicated without first addressing the original source of bacterial contamination. The term 'source control' is derived from the environmental health literature and refers to efforts to reduce the amount of materials entering the waste stream from a particular source. Specifically, it refers to actions that prevent pollution at its origin (United States Environmental Protection Agency's *Handbook of Groundwater Protection and Cleanup Policies for RCRA Corrective Action* <www.epa.gov/correctiveaction>). Similarly, source control of IAIs in this context refers to any intervention directed toward the primary origin of the infectious process. There is little debate regarding the primacy of source control in the management of IAIs. Ideal antimicrobial therapy cannot mitigate the effects of poor or absent source control. In retrospective cohort studies, the strongest risk factor for recurrent infection (or failure) is poor source control, attesting to the critical importance of appropriate surgical interventions (A-2 evidence) (47,156).

6.1 Approaches to source control

Source control of complicated IAIs can be achieved using either operative or percutaneous approaches. The ideal approach depends on specific patient and local factors, including the source and extent of infection, and available resources. While there are some grey areas that are evolving (see below), in most cases, the approach to assure adequate source control is not controversial (157).

Operative source control is required when adequate source control cannot be achieved percutaneously. Typically, these circumstances are characterized by a need to resect a gangrenous or perforated viscus, defunction (divert the enteric stream) a more distal perforation of the gastrointestinal tract with an ileostomy or colostomy, or patch a perforated ulcer (A-3 evidence). Diffuse IAI or abscesses that cannot be accessed percutaneously also need to be drained using an operative approach (A-3 evidence). While conventional wisdom suggests that all abscesses need some form of drainage, there is increasing evidence suggesting that the relatively small (less than 3 cm) abscesses might not require drainage (B-2 evidence). These data are drawn primarily from studies of diverticular and renal abscesses, and might not necessarily be applicable to other clinical settings (158,159).

In the case of multiple intra-abdominal abscesses or very complex abscesses, either approach is acceptable. Complex abscesses are those with multiple loculations or those that have significant debris or whose contents are viscous (eg, pancreatic or fungal abscesses) and have a higher probability of failure using percutaneous approaches (160). However, if these can be approached percutaneously and the patient has sufficient physiological reserve to tolerate multiple drains and several attempts at source control, then this approach may be acceptable (B-3 evidence). In select cases, the use of thrombolytic agents administered through the drains might facilitate drainage and increase the probability of success (C-2 evidence) (161,162). If the patient is critically ill, has limited physiologic reserve or is suffering from overt ACS, it might be more expedient to simply address the source of infection using an operative approach (B-3 evidence).

There are two clinical settings in which accruing evidence is challenging the need for source control. Perforated diverticulitis is typically managed through resection of the sigmoid colon followed by either anastomosis or colostomy. In this context, definitive source control is achieved by resecting the colon with its perforation. However, there are several reports suggesting that laparoscopic irrigation of the peritoneal cavity and drainage of the perforation is sufficient and reduces the need for emergency resection with or without colostomy (163-166). Many of these reports have included patients with fecal peritonitis, with reasonable rates of success. Because none of these studies were randomized, the recommendation supporting this approach is relatively weak (C-2 evidence).

The approach to infected pancreatic necrosis is also evolving. Source control in this context traditionally mandates operative necrosectomy. However, data from multiple case series suggest that in select patients, percutaneous approaches might be acceptable (B-2 evidence) (167-171). Over time, infected necrosis typically undergoes liquefaction, ultimately forming a pancreatic abscess. In a critically ill and deteriorating patient with evidence of infected pancreatic necrosis that is

relatively early in its course, the limited degree of liquefaction mandates debridement as the operative intervention and such a patient might not be a suitable candidate for percutaneous drainage. By contrast, later in the course, liquefaction might have progressed sufficiently to allow for percutaneous management. Thus, the choice of technique depends on the anatomical position, the ratio of solid to fluid components within the collection and the degree of systemic organ dysfunction (169). If the patient has sufficient physiological reserve and can wait for further liquefaction to occur to allow for percutaneous drainage, then this might be the preferred approach.

6.2 Key recommendations for source control

Recommendation 26. Adequate source control is the primary means of managing IAI and should not be subjugated to antimicrobial therapy (A-2 evidence).

Recommendation 27. Operative approaches to source control should be used when it is necessary to resect a gangrenous or perforated viscus, patch a perforated viscus, divert the enteric stream, decompress overt ACS, or when percutaneous approaches to abscess drainage are not possible or have not been effective (A-3 evidence).

Recommendation 28. Small abscesses (less than 3 cm) might be amenable to antimicrobial therapy without drainage (B-2 evidence).

Recommendation 29. In select patients, source control of perforated diverticulitis can be achieved using laparoscopic lavage and drainage (C-2 evidence).

Recommendation 30. In select patients, source control of infected pancreatic necrosis can be achieved using percutaneous approaches (B-2 evidence).

7. IAH AND ACS

7.1 Definitions and pathophysiology

Pathologically raised IAP can be caused by a variety of conditions including complicated IAIs and the ACS. Sustained elevations in IAP have severe pathophysiological effects including impaired venous return and elevated cardiac afterload, increased difficulty in ventilation due to restricted lung volumes and atelectasis, impaired perfusion of the viscera including the kidneys, liver and the gastrointestinal tract, ultimately leading to multiple organ failure (172-176). Moderate increases in IAP have been shown to cause bacterial translocation from the gastrointestinal tract in animal models (177,178). ACS is a potentially lethal complication caused by any event that produces sustained IAH. Precipitating events include acute pancreatitis, ruptured abdominal aortic aneurysm, blunt abdominal trauma with intra-abdominal bleeding from splenic, hepatic and mesenteric injuries, and complicated IAI. Risk factors that predispose to either IAH or ACS are shown in Table 8. The World Society on the Abdominal Compartment Syndrome (WSACS) developed a consensus statement in 2006 that defined IAH as maximum or sustained IAP at or above 12 mmHg (179). ACS is defined as IAP above 20 mmHg with evidence of new organ dysfunction or failure. In addition to IAP, another potentially useful measurement is the abdominal perfusion pressure (APP) (179), which can be derived from the mean arterial pressure (MAP) using the formula: $APP = MAP - IAP$. This is an easily measured parameter and may be superior to IAP for monitoring critically ill patients. In a retrospective study of

144 critically ill surgical patients with intermittent IAP measurements, Cheatham et al (180) noted that an APP threshold of 50 mmHg proved superior to either MAP or IAP alone in predicting patient survival from IAH and ACS.

It should be recognized that IAH is neither infrequent, nor insignificant. Malbrain et al (181,182) reported a high occurrence of IAH (greater than 12 mmHg) including one-half of all patients in a multi-institutional point-prevalence study, as well as 32% of a second prospective evaluation of critically ill patients within 13 intensive care units in six countries. The presence of sustained IAH or ACS is associated with a significant increase in mortality (183). Bodnar et al (184) recently reported that 66% of general surgery patients developed IAH and 13% developed ACS. Mortality rates were 16% and 42% in those with IAH and ACS respectively, significantly higher than the mortality rate of 9% among those without IAH. A recent study from Canada also revealed a significant relationship between IAH and death before intensive care unit discharge, as well as organ dysfunction and requirement for renal replacement therapy (PB McBeth and AW Kirkpatrick, unpublished data). Despite their grave consequences, both IAH and ACS are poorly recognized in the routine practice of critical care in Canada.

7.2 IAH and complicated IAI

An association between IAH and increased rates of organ failure and death in cases of severe pancreatitis has been repeatedly demonstrated (185-187). Leppaniemi and Kempainen (188) suggested that many of the early deaths in cases of necrotizing pancreatitis, previously believed to be due to overwhelming systemic inflammatory response syndrome, were actually due to undiagnosed and untreated ACS. Plantefeve et al (189) reviewed the recent literature regarding any association of IAH or ACS with intra-abdominal sepsis and concluded that they were closely interrelated. Malbrain et al (182) also reported the presence of IAH in 80% of patients with abdominal infections in a prospective, multinational, point prevalence study in critically ill patients. Busani et al (190) evaluated the relationship between IAP and clinical outcome in 22 patients with urgent abdominal surgery for a variety of intra-abdominal processes including 12 with IAIs or other inflammatory conditions. Mortality among those with IAH was 28% versus 12% in patients without IAH. It should be noted that although the presence of IAH is clearly associated with increased morbidity and mortality in critically ill patients, a direct causal relationship between IAH and adverse outcome has not yet been established. To confirm a causal relationship, it would be critical to demonstrate that effective treatment of IAH or ACS leads to reduced mortality, but such data currently do not exist. Further research and controlled trials are urgently required, recognizing that patients with complicated IAIs have multiple predisposing risk factors for either IAH or ACS.

7.3 Management of IAH and ACS in complicated IAIs

Few prospective, randomized treatment data exist in the published literature for the management of patients with complicated IAIs and IAH. Although IAH in the setting of pancreatitis has been treated with a variety of modalities including open abdominal laparotomies (191-193), continuous renal replacement therapy (194) and a novel modified subcutaneous

TABLE 8
Risk factors associated with intra-abdominal hypertension or abdominal compartment syndrome

Diminished abdominal wall compliance
Acute respiratory failure, especially with elevated intrathoracic pressure
Abdominal surgery with primary fascial closure
Major trauma or burns
Prone positioning
Increased intraluminal contents
Gastroparesis
Ileus
Colonic pseudo-obstruction
Increased abdominal contents
Hemoperitoneum or pneumoperitoneum
Ascites or liver dysfunction
Capillary leak or fluid resuscitation
Acidosis (pH<7.2)
Hypotension
Hypothermia (core temperature <33°C)
Multiple transfusions (>10 units of blood over 24 h)
Coagulopathy (platelets <55,000/mm ³ , or activated partial thromboplastin time >2 times normal, or prothrombin time <50%, or international normalized ratio >1.5)
Massive fluid resuscitation (>5 L over 24 h)
Oliguria
Sepsis
Major trauma or burns
Damage control laparotomy
<i>Adapted from reference 176</i>

fasciotomy (195), there are no definitive data that any of these therapies improves patient outcomes. The WSACS recently published consensus guidelines regarding the management of IAH and ACS in the care of the critically ill (196,197). The following are recommended:

1. A baseline IAP measurement should be obtained in all critically ill patients if two or more risk factors for IAH or ACS are present (Table 8) (B-2 evidence);
2. If IAH (greater than 12 mmHg) is present, serial IAP measurements should be performed throughout the patient's critical illness (A-3 evidence); and
3. The management of IAH or ACS is based on four general principles: serial monitoring of IAP, optimization of systemic perfusion and organ function in the face of IAH, institution of specific medical procedures to reduce IAP and its effects on end-organ function, and prompt surgical decompression of refractory IAH (B-1 evidence).

Given the high mortality rate and grave consequences of IAH in complicated IAI, the WSACS recommendations to monitor IAP more regularly in critically ill patients seem reasonable, particularly because it is a relatively simple and low-cost procedure that typically requires only a bladder catheter connected to a pressure transducer monitor. In addition to the current standard of intermittent bladder pressure measurements, gastric tonometry has also been found to correlate well with more invasive direct pressure measurements from the peritoneal cavity (198). The specific measures to reduce IAP and improve multiorgan function in critically ill patients are beyond the scope of this guideline, but can be found on the WSACS Web site <www.wsacs.org>.

7.4 Key recommendations for IAH In IAIs

Recommendation 31. The presence of risk factors that may predispose to the development of IAH or ACS should be assessed in all acutely ill patients (APACHE II score greater than 15) with complicated IAI (B-2 evidence).

Recommendation 32. Baseline IAP measurements should be determined in all critically ill patients with complicated IAIs if two or more risk factors for IAH or ACS are present (B-2 evidence). If IAH (IAP greater than 12 mmHg) or ACP (IAP greater than 20 mmHg) is present, serial IAP measurements should be performed throughout the patient's critical illness (A-3 evidence).

Recommendation 33. Surgical decompression should be considered for patients with refractory IAH or evidence of ACS. In addition, medical approaches to reduce IAP and associated end-organ dysfunction should be implemented, consistent with local practices in the care of critically ill patients (B-2 evidence).

8. INFECTION CONTROL AND PREVENTION

Infection control issues in IAIs can be divided into three broad categories: a) patient-related risk factors for postoperative and surgical site infections; b) prevention of nosocomial infections by improving the operating room environment, use of topical antiseptics and antimicrobial prophylaxis for surgical site infections; and c) preventing the spread of antibiotic-resistant organisms (ARO) through surveillance and antibiotic stewardship. The incidence of surgical site infections increases dramatically in the presence of intestinal spillage and gross peritoneal contamination. Administration of preoperative systemic antibiotics, use of wound protective devices and lavage of surgical wounds at the end of operative procedures do not reliably prevent this complication. Meticulous postoperative care in wound dressing, intravenous catheter maintenance, skin antisepsis, and close attention to principles of infection control are the cornerstones to successful management (199). Preventing the spread of multiresistant pathogens in this patient population (especially ESBL-producing Enterobacteriaceae species, *C difficile*, MRSA and VRE) is a high priority.

It is important to recognize that the application of individual infection control measures is unlikely to have a major impact on outcome. Rather, it is the application of all the different intervention strategies that will decrease the risk of postoperative and surgical site infections following abdominal surgery. A hospital-wide surgical site infection surveillance program with continuous collaboration and feedback to surgeons has been proven to reduce the incidence of surgical site infections (200,201) (A-1 evidence). The National Nosocomial Infection Surveillance (NNIS) risk index with a score ranging from 0 to 3 is a valid tool for monitoring surgical site infections in a surveillance program (27,202).

8.1 Patient-related issues

Certain risk factors such as diabetes, obesity, smoking and malnutrition have been shown to play a role in increasing surgical site infections (203). Avoiding hyperglycemia perioperatively and encouraging tobacco cessation at least 30 days before elective surgery are well-recognized preventive measures (204,205). It is advisable to instruct the patient to shower with an antiseptic agent the night before the surgical procedure (B-2 evidence) (200). Products containing chlorhexidine gluconate have the

biggest impact on bacterial burden reduction. Hair removal is indicated only in cases in which hair may hamper the surgical procedure itself. If hair has to be removed, it should be performed immediately before surgery using electric clippers (A-1 evidence) (200). Hair removal more than 24 h before surgery is not advised (A-1 evidence).

Three types of topical antiseptic agents are currently used for skin preparation of the operative site and for preoperative scrubbing by the surgical team, including alcohol-based agents, iodophors (povidone-iodine) and chlorhexidine gluconate (Appendix 4). No data have ever shown superiority of one agent over another. Combination agents such as chlorhexidine and alcohol together have been shown to have better residual antimicrobial activity than single agents alone (200).

8.2 The operating room and related issues

The operating room environment should meet certain standards. A minimum of 15 air changes per hour with at least three air changes of outdoor fresh air is required. Physical parameters should meet the following criteria: a room temperature between 20°C to 23°C, and a relative humidity of 30% to 60%. The operating room must also be maintained at positive pressure with regard to the corridors and outside areas. A two-filter system installed in series should also be in place, and air should enter the room through the ceiling and exhaust near the floor (B-2 evidence) (206,207). A laminar airflow system is not warranted for abdominal surgeries. The use of this system has mainly been studied for orthopedic procedures, and no data supporting its use in abdominal surgery exist (200). An annual check of the physical parameters of the operating room and a complete maintenance program should be instituted at the local level (B-3 evidence).

The surgical team should adopt an approved scrubbing procedure for at least 2 min, which includes the hands, arms and elbows (A-2 evidence) (200). Numerous alcohol-chlorhexidine antiseptic solutions are commercially available and adequate as topical antiseptic agents (208). Artificial nails should not be worn; nail polish should not be scaled and jewellery should be disallowed. Masks are mainly used as a protective gear against splashing of potentially infectious body fluids. The occurrence of an unusually high number of postoperative infections involving *S aureus* or group A streptococcus should prompt an investigation for a common source reservoir among the operating room personnel. Routine screening for these pathogens is not indicated and should not be performed.

8.3 Antimicrobial prophylaxis for surgical site infections

Surgical antimicrobial prophylaxis plays a key role in abdominal surgery (209). The main objective is not to sterilize the surgical field, but to decrease the bacterial burden as much as possible at a critical time. Intravenous bactericidal antibiotics with an in vitro spectrum that covers the most likely intraoperative microorganisms should be administered in a timely fashion (199,210). In intra-abdominal surgical procedures, *S aureus*, Gram-negative bacilli and anaerobes from the distal part of the digestive tract are the main target pathogens. The vast majority of abdominal surgeries for which antimicrobial prophylaxis is required are classified as clean-contaminated. The abdominal procedures for which antimicrobial prophylaxis is indicated are listed in Table 9. Recommended prophylactic

antibiotic regimens are shown in Table 10. The following principles are the cornerstone of surgical antimicrobial prophylaxis:

1. Antibiotics should be used only if evidence of benefit is available from clinical trials, and in situations for which a postoperative surgical site infection would have major consequences (A-1 evidence) (200).
2. Timing of antibiotic infusion is critical so that the peak of tissue concentrations is obtained at the moment of incision, typically 30 min to 60 min before the time of incision (A-1 evidence) (210).
3. Therapeutic serum and tissue levels should be maintained throughout surgery and ideally a few hours after completion of the procedure. In cases of prolonged surgical procedures, prophylactic antibiotics may need to be readministered intraoperatively (B-2 evidence) (200).
4. The total duration of antimicrobial prophylaxis for abdominal surgery should not exceed 24 h.

8.4 Prevention of the spread of antibiotic-resistant microorganisms

MRSA is a growing concern among Canadian institutions (211). Rates have been multiplied by a factor of 10 within the past decade. Compared with methicillin-sensitive *S aureus*, MRSA infections have been associated with increased mortality and morbidity. In addition, Canadian data have shown that the average increased cost per MRSA infection is more than \$14,000. Available antibiotics are either relatively ineffective for severe infections (vancomycin) or extremely costly (eg, linezolid and daptomycin). Increasing minimum inhibitory concentration of vancomycin (1 mg/L or greater) among MRSA strains is associated with an increased risk of treatment failure and is a serious concern (212).

Infections due to VRE remain rare in Canada and tend to occur in clusters. When found, they can involve the peritoneal cavity and, even more commonly, the biliary tract. Linezolid remains the best available agent against invasive infections caused by this microorganism.

To control the spread of AROs, an effective infection control program must be implemented in all institutions (A-1 evidence) (213). This should include a comprehensive hand hygiene program that has been proven to decrease the overall incidence of MRSA and VRE (214). Contact precautions, including gowns and gloves as well as patient and staff cohorting, have been advocated as methods of limiting the transmission of AROs.

8.5 Key recommendations for infection control and prevention

Recommendation 34. General measures important for reducing the risk of surgical site infections, such as avoiding hyperglycemia perioperatively, cessation of tobacco use at least 30 days before elective surgery, instructing the patient to shower with an antiseptic agent the night before the surgical procedure, etc, should be instituted in all patients undergoing intra-abdominal surgery (B-2 evidence). Hair removal is indicated only in cases where the hair may hamper the surgical procedure itself. If hair has to be removed, it should be performed immediately before the surgery using electric clippers (A-1 evidence).

TABLE 9
Clean-contaminated abdominal surgeries for which antibiotic prophylaxis is indicated

Colorectal surgery
Elective colon resection, low-anterior resection of the rectum and abdominal perineal resection of the rectum also require a specific colon preparation to empty the bowel contents and reduce the amount of microorganisms
Appendectomy
Perforated, gangrenous or necrotizing appendicitis
Esophageal surgery
If obstruction is present
Sclerotherapy of esophageal varices
Esophageal dilation
High-risk gastroduodenal surgery
Situations in which gastric acidity is decreased
Cancer, active bleeding
Decreased gastroduodenal motility (obstruction, obesity)
Small-intestine surgery
High-risk biliary tract surgery
Age >70 years, diabetes, obesity
Acute cholecystitis, cholelithiasis or obstructive jaundice
Nonfunctional gallbladder (excluding nonurgent laparoscopic cholecystectomy in low-risk patients)
Open biliary tract surgery

Recommendation 35. Surgical team members should adopt a recommended scrubbing procedure for at least 2 min, including hands, arms and elbows (A-2 evidence).

Recommendation 36. A two-filter system installed in series should be in place in the operating room to ensure a clean environment, and air should enter the operating room through the ceiling and exhaust near the floor (B-2 evidence). Regular check-up of all physical parameters of the operating room and a complete maintenance program should be instituted at the local level (B-3 evidence).

Recommendation 37. Antibiotics for surgical prophylaxis should be used only if evidence from clinical trials is available, and in situations for which a surgical site infection may have major consequences (A-1 evidence). If surgical prophylaxis is to be administered, both timing and dosing of the antibiotic infusion should be adjusted to attain peak tissue concentrations at the moment of incision and throughout surgery (A-1 evidence). In cases of prolonged surgical procedures, prophylactic antibiotics may need to be readministered intraoperatively (B-2 evidence).

Recommendation 38. The duration of antimicrobial therapy for the purpose of surgical prophylaxis in the absence of established infection should be limited to 24 h or less in patients with penetrating bowel trauma repaired within 12 h, intraoperative contamination by enteric contents, or nonperforating appendicitis in the absence of abscess or local peritonitis (A-1 evidence).

Recommendation 39. A hospital-wide surgical site infection surveillance program with continuous collaboration and feedback with the surgical team should be implemented to reduce surgical site infections (A-1 evidence).

Recommendation 40. To effectively control the spread of antibiotic-resistant organisms, an effective infection control program coupled with a rigorous antibiotic stewardship program should be implemented locally (A-1 evidence).

TABLE 10
Antimicrobial regimens for prophylaxis in abdominal surgery

Surgery	Likely microorganism	First choice	Second choice	Comments
Esophageal, gastroduodenal or biliary tract	GNB, GPC	Cefazolin 1–2 g IV	Clindamycin 900 mg + gentamicin (2 mg/kg IV)	Vancomycin if MRSA suspected
Colorectal	GNB, <i>Enterococcus</i> , anaerobes	Cefazolin 1–2 g IV + metronidazole 500 mg IV or cefoxitin 2 g IV	Clindamycin 900 mg + gentamicin (2 mg/kg IV)	Ciprofloxacin 400 mg + metronidazole may be an alternative in selected patients
Appendectomy	GNB	Cefazolin 1–2g IV + metronidazole 500 mg IV or cefoxitin 1–2 g IV	Clindamycin or metronidazole + gentamicin (2 mg/kg IV)	

GNB Gram-negative bacilli; GPC Gram-positive cocci; IV Intravenous; MRSA Methicillin-resistant *Staphylococcus aureus*

9. UNANSWERED QUESTIONS AND FUTURE DIRECTIONS

Many controversies in the management of complicated IAI remain. More prospective, randomized clinical trials are needed in patients at high risk for treatment failure or mortality. More accurate methods for risk assessment and stratification are needed to aid in the selection of initial antimicrobial therapy. The optimal timing and duration of antimicrobial therapy remains to be determined.

Several newer broad-spectrum antimicrobials are either investigational or recently marketed in North America, and further clinical studies are needed to determine their role in the treatment of complicated IAI. Ceftriboprole, which has recently been marketed in Canada, has broad-spectrum in vitro activity against Gram-positive cocci, including MRSA and methicillin-resistant *Staphylococcus epidermidis*, penicillin-resistant *Streptococcus pneumoniae*, *E faecalis*, facultative Gram-negative bacilli (including *ampC*-producing *E coli* and *P aeruginosa*, but not ESBL-producing strains) (215). Like other third- and fourth-generation cephalosporins, ceftibiprole demonstrates limited activity against *B fragilis* and non-*fragilis* *Bacteroides* species (215). Due to its lack of activity against the predominant colonic anaerobes, this agent would have to be used in combination with an antianaerobic agent such as metronidazole. Doripenem, an investigational carbapenem in Canada but already available in the United States, possesses broad-spectrum in vitro activity against many Gram-positive, Gram-negative and anaerobic bacteria. Like other carbapenems (eg, meropenem), doripenem lacks activity against *E faecium*, MRSA and *Stenotrophomonas maltophilia* (216). Doripenem has been studied in complicated IAIs and found to be noninferior in terms of bacteriological and clinical efficacy as well as safety (216). Further clinical trials are required to establish its exact role in the treatment of complicated IAIs.

Although the importance of surgical source control in complicated IAIs is well recognized, it is surprising that only one prospective study (101) has evaluated the adequacy of surgical interventions in addition to antimicrobial therapy. The role of enterococci, coagulase-negative staphylococci, MRSA and *Candida* species in complicated IAI must be assessed on an individual basis. The emerging resistance among Enterobacteriaceae species, *C difficile* and *B fragilis* will continue to be an issue even as new antimicrobial agents are developed to overcome them. Finally, the ability to treat or eliminate comorbid conditions, mitigate immunosuppression and bolster host defences will be the ultimate challenge.

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APPENDIX 1**In vitro antimicrobial activity against facultative Gram-positive cocci associated with intra-abdominal infections**

Bacteria	Ceftazidime/ cefepime	Ceftriaxone/ cefotaxime	Fluoro- quinolones*	Clindamycin	Amino- glycosides†	Ertapenem	Imipenem/ meropenem	Pip-tazo/ ticar-clav	Linezolid	Vancomycin	Tige- cycline
<i>Staphylococcus aureus</i> (MS)	+	++/+++	+++	++++	++	++++	++++	++++	++++	++++	++++
<i>S aureus</i> (MR)	-	-	-	+ / ++	+	-	++	- / +	++++	++++	++++
<i>Staphylococcus epidermidis</i> (MS)	+	++/+++	+++	+++	+	++	++++	++++	++++	++++	++++
<i>S epidermidis</i> (MR)	-	-	-	+	+	-	++	- / +	++++	++++	++++
<i>Enterococcus faecalis</i> (VS)	-	-	+	++	+	-	+++	++++	++++	++++	++++
<i>E faecalis</i> (VR)	-	-	-	- / +	+	-	+	+	++++	-	++++
<i>Enterococcus faecium</i> (VS)	-	-	+	- / +	+	-	+	+	++++	-	++++
<i>E faecium</i> (VR)	-	-	-	- / +	+	-	-	-	++++	-	-

*Includes ciprofloxacin, levofloxacin and moxifloxacin; †Includes gentamicin, netilmicin, tobramycin and amikacin. - Poor activity; + Limited activity and/or resistance $\geq 15\%$; ++ Moderate to good activity and/or resistance 10% to 14%; +++ Very good activity and/or resistance 5% to 9%; ++++ Excellent activity and/or resistance $< 5\%$; MR Methicillin resistant; MS Methicillin sensitive; Pip-tazo Piperacillin-tazobactam; Ticar-clav Ticarcillin-clavulanate; VR Vancomycin resistant; VS Vancomycin sensitive. Data adapted from references 216,248-255

APPENDIX 2**In vitro antimicrobial activity against facultative and aerobic Gram-negative bacilli associated with intra-abdominal infections**

Bacteria	Ceftazidime/ cefepime*	Ceftriaxone/ cefotaxime	Fluoro- quinolones†	Amino- glycosides‡	Erta- penem	Imipenem/ meropenem	Pip-tazo/ ticar-clav	Tige- cycline
<i>Acinetobacter</i> species	++	+ / ++	+++	+++	-	+++	+++	+++
<i>Citrobacter freundii</i>	++/+++	++/+++	++++	++++	++++	++++	+++ / ++++	NA
<i>Enterobacter aerogenes</i>	++/+++	++/+++	++++	++++	++++	++++	+++ / ++++	+++
<i>Enterobacter cloacae</i>	++/+++	++/+++	++++	++ / +++	++++	++++	++	+++
<i>Escherichia coli</i>	++++	++++	+++	++++	++++	++++	++++	++++
<i>E coli</i> (ESBL)	-	-	++	+++	++++	++++	- / +	+++
<i>Klebsiella pneumoniae</i>	++++	++++	++++	++++	++++	++++	++++	++++
<i>K pneumoniae</i> (ESBL)	-	-	+++	++++	++++	++++	- / +	+++
<i>K pneumoniae</i> (ampC)	++	++	++++	++++	+++	++++	- / +	++++
<i>Morganella morganii</i>	++/+++	++/+++	++++	+++ / ++++	++++	++++	++++	NA
<i>Proteus mirabilis</i>	++++	++++	+++ / ++++	++++	++++	++++	++++	+
<i>Proteus vulgaris</i>	++	++	++++	+++ / ++++	++++	++++	++++	NA
<i>Providencia rettgeri</i>	++/+++	+++	+++	+	+++	++++	++++	NA
<i>Providencia stuartii</i>	++/+++	+++	+++	++	+++	++++	++++	NA
<i>Pseudomonas aeruginosa</i>	+++	+	+++	+++	-	+++	+++	- / +
<i>Serratia marcescens</i>	+++	+++	+++	++	++++	++++	++++	+++

*Cefepime has activity against ampC-producing organisms; †Includes ciprofloxacin, levofloxacin, moxifloxacin (moxifloxacin has only moderate activity against *Pseudomonas aeruginosa*); ‡Includes gentamicin, netilmicin, tobramycin, amikacin. - Poor activity; + Limited activity and/or resistance $\geq 15\%$; ++ Moderate to good activity and/or resistance 10% to 14%; +++ Very good activity and/or resistance 5% to 9%; ++++ Excellent activity and/or resistance $< 5\%$; ESBL Extended-spectrum beta-lactamase; NA Not available; Pip-tazo Piperacillin-tazobactam; Ticar-clav Ticarcillin-clavulanate. Data adapted from references 216,248-255

APPENDIX 3**In vitro antimicrobial activity against anaerobes associated with intra-abdominal infections**

Bacteria	Clindamycin	Cefoxitin	Levofloxacin/ moxifloxacin	Imipenem/meropenem Ertapenem	Pip-tazo/ ticar-clav	Metronidazole	Tigecycline
<i>Bacteroides fragilis</i>	+ / ++	++	+ / +++*	++++	++++	++++	++++
<i>Bacteroides fragilis</i> group	+	++	+	++++	+++	++++	++++
<i>Fusobacterium</i> species	+++	++++	+ / ++	++++	++++	++++	++++
<i>Peptostreptococcus</i> species	++++	++++	+++	++++	++++	+	++++
<i>Clostridium perfringens</i>	+++	++++	+++	++++	++++	+++	+++
<i>Clostridium difficile</i>	- / +	- / +	++	+	++	+++	++++
<i>Lactobacillus</i> species	+	+	+ / ++	- / +	++	+	+
<i>Veillonella</i> species	++++	+	+	+++	++	+++	+

*Moxifloxacin has good activity against *Bacteroides fragilis*. - Poor activity; + Limited activity and/or resistance $\geq 15\%$; ++ Moderate to good activity and/or resistance 10% to 14%; +++ Very good activity and/or resistance 5% to 9%; ++++ Excellent activity and/or resistance $< 5\%$; Pip-tazo Piperacillin-tazobactam; Ticar-clav Ticarcillin-clavulanate. Data adapted from references 85,86,256-258

APPENDIX 4

Spectrum of activity of different antiseptic agents

Agent	Mechanism of action	Gram-positive	Gram-negative	Issues and toxicity	Indicated for surgical scrub
		bacteria	Bacteria		
Alcohol	Destroys proteins	E	E	Flammable Drying, no activity against spores	Yes
Iodophors/iodine	Oxidation by free iodine	E	G	Allergy, rashes, inactivation by blood and proteins	Yes
Chlorhexidine-based agents	Cell membrane disruption	E	G	Ototoxicity	Yes

E Excellent activity; G Good activity

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