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Best Practice in General Surgery
Guideline #4:
Management of Intra-Abdominal Infections

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A Quality Initiative of the Best Practice in General Surgery and the Toronto Antimicrobial Stewardship Corridor

Section 1. General Information about this Guideline

Aim

The aim of this guideline is to make recommendations on the management of complicated intra-abdominal infections with regards to source control and antibiotic choice and duration and management of biliary tract infections.

Outcomes of Interest

Eradication of intra-abdominal infection.

Target Population

Patients with complicated intra-abdominal infections.

Intended Users

General surgeons, infectious disease specialists, intensivists, and interventional radiologists

Overview of Process

This guideline conforms to recent recommendations published jointly by the Surgical Infection Society and the Infectious Diseases Society of America[1], but is tailored for practice in the University of Toronto's Division of General Surgery as part of the Best Practice in General Surgery initiative in conjunction with the Toronto Antimicrobial Stewardship Corridor.

Rationale for Guideline on the Appropriate Management of Intra-Abdominal Infections

Complicated Intra-Abdominal Infections (cIAIs) are infections that have spread beyond the source organ to contaminate the peritoneal cavity and thus are synonymous with secondary or tertiary peritonitis, or are due to a ruptured viscus. cIAIs are frequently encountered in general surgical practice and are a source of considerable morbidity and mortality. Appropriate management requires timely and appropriate antimicrobial therapy as well as control of the source of infection.

It is important to distinguish the antimicrobial treatment required for patients with cIAIs from those with uncomplicated IAI. As established infection is not part of the disease process in patients with uncomplicated IAI, these patients require only an ultra short course of antibiotics. Thus, patients with non-perforated appendix or simple cholecystitis require a dose of antimicrobials prior to operation and no post-operative antibiotic treatment. Similarly, patients with upper GI (stomach and duodenum) perforations that undergo operation within 24 hours and patients with traumatic (blunt, penetrating, or iatrogenic) bowel perforations operated on within 12 hours require antibiotics for 24 hours or less[1]. Patients with evidence of a previous perforated fistula (eg: from Crohn's Disease or diverticulitis with no evidence of infection should receive an ultra short course of antibiotics. This should be considered perioperative prophylactic antibiotics rather than treatment of established intra-abdominal infection.

The purpose of this document is to provide evidence-based recommendations for antimicrobial therapy as well as source control for patients with cIAIs.

Definitions of Key Terms (from the Canadian Practice Guideline for Surgical IAIs)

Uncomplicated IAIs: the process is characterized only by contamination or inflammation that does not extend beyond the source and the disease is completely excised at the time of operation. e.g. early traumatic perforation, simple appendicitis or cholecystitis..

Complicated IAIs (cIAI): 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. A cIAI is characterized either by pus or an exudate at the time of source control.

Community Acquired IAIs: include conditions such as gastroduodenal perforations, ascending cholangitis, cholecystitis, appendicitis, diverticulitis with or without perforation, bowel perforation and pancreatitis in patients without previous surgical intervention or hospitalization.

Heath Care-Associated IAIs: include infectious processes that are absent at the time of hospital admission, but becomes evident 5 or more days after admission, and include anastomotic leaks and perforations as well as abscesses that develop as a complication of surgery. They also

include infections acquired during the course of receiving treatment for other conditions in a health care setting, including nursing homes, dialysis units or surgical day care units, within the previous 12 months.

Mild-to-Moderate Severity: Not meeting criteria for high severity. These patients are typically cared for outside of the ICU.

High Severity: Infections characterized by the presence of organ dysfunction (e.g. acute lung injury, hypotension, renal dysfunction) or those infections occurring in a compromised patient: elderly, extensive comorbidity, immunosuppressed. These patients will typically require ICU care.

Section 2. Summary of Recommendations

Type of IAI	Examples	Selection of Antibiotics			
		Spectrum of Antimicrobial Activity	Recommended Antibiotics	PCN Allergic Patients	Duration
Community Acquired IAI: Uncomplicated					
Uncomplicated IAI	Non-perforated appendicitis	Enteric gram-negative bacilli & anaerobes	cefazolin & metronidazole	gentamicin & metronidazole	Preoperatively only
Perforation Without Established Infection	Perforations of stomach & duodenum & traumatic bowel perforations who are taken to the O.R. within 12 to 24 hrs	Gram-positive cocci & aerobic/ facultative anaerobes +/- anaerobes	cefazolin & metronidazole	gentamicin & metronidazole	"Ultrashort" 24 hours only
Community Acquired IAI: Complicated					
Mild-to-Moderate Severity	Perforated appendicitis; perforated diverticulitis	Enteric gram-negative bacilli & anaerobes	cefazolin (iv) or cephalexin (po) & metronidazole	gentamicin & metronidazole	3-7 days (until clinical signs of resolution)
High Severity	Shock; new organ failure; ICU patient	Enteric gram-negative bacilli & anaerobes; possibly enterococcus	ceftriaxone & metronidazole, (may consider piperacillin-tazobactam)	gentamicin & metronidazole	3-7 days (until clinical signs of resolution)
Other risk factors for treatment failure	Age >70; immunosuppression; poor nutrition; delayed/inadequate source control	Enteric gram-negative bacilli & anaerobes; possibly enterococcus in immunosuppressed	ceftriaxone & metronidazole (may consider piperacillin-tazobactam)	gentamicin & metronidazole	3-7 days (until clinical signs of resolution)
Health Care Associated cIAI					
Mild-to-Moderate	Hospitalized ≥ 5 days; anastomotic leak; postoperative abscess	Enterococcus, drug-resistant gram-negative bacilli	piperacillin-tazobactam* (may consider ceftriaxone & metronidazole)	vancomycin, gentamicin & metronidazole OR carbapenem** (meropenem or imipenem) & vancomycin	3-7 days (until clinical signs of resolution)
High Severity	Hospitalized ≥ 5 days; anastomotic leak; shock; ICU	Enterococcus, drug-resistant gram-negative bacilli	piperacillin-tazobactam*	vancomycin, gentamicin & metronidazole OR carbapenem** (meropenem or imipenem) & vancomycin	3-7 days (until clinical signs of resolution)

Other risk factors for Health-Care Associated Infection	Nursing home; rehab facility; dialysis patient; recent antibiotics	Enterococcus, drug resistant gram negative bacilli	piperacillin-tazobactam* (may consider ceftriaxone & metronidazole)	vancomycin, gentamicin & metronidazole OR carbapenem** (meropenem or imipenem) & vancomycin	3-7 days (until clinical signs of resolution)
Biliary Tract					
Mild-to-Moderate	Ascending cholangitis; acute calculous cholecystitis	Enteric gram-negative bacilli	cefazolin	gentamicin	3-7 days (until clinical signs of resolution)
High Severity		Enteric gram-negative bacilli	ceftriaxone & ampicillin	gentamicin & vancomycin	3-7 days (until clinical signs of resolution)

* Add fluconazole if yeast identified in peritoneal samples

** Risk of cross-reactivity between penicillin and carbapenems is considered to be ≤1%

Part 1: Complicated Intra-Abdominal Infections

1. Selection of Empiric Antimicrobial Agents

1.1 Patients with mild-to-moderate community-acquired IAI require empiric coverage for enteric gram-negative bacilli and anaerobes. Cefazolin and metronidazole are recommended. In patients with IgE-mediated allergy or other severe reaction to beta-lactams, Gentamicin and metronidazole are recommended.

1.2 Most patients with mild-to-moderate community-acquired IAI do not require coverage of Enterococcus spp. unless other risk factors are present.

1.3 Patients with high severity community-acquired IAI may benefit from broader coverage against gram-negative bacilli. Ceftriaxone and metronidazole are recommended or gentamicin and metronidazole for IgE-mediated allergy or other severe reaction to beta-lactams. Piperacillin-tazobactam could also be considered.

1.4 Most patients with health care-associated IAI should receive broad spectrum empiric antimicrobial therapy, including coverage for drug-resistant gram-negative bacilli and Enterococcus spp. Piperacillin-tazobactam is recommended for those with high severity disease. Some patients with mild-moderate severity health care-associated IAI may not require as broad of coverage and thus, ceftriaxone and metronidazole may be appropriate. In patients with IgE-mediated penicillin allergy or other severe reaction, vancomycin, gentamicin and metronidazole OR vancomycin plus a carbapenem are recommended.

1.5 Patients with health care-associated IAI should receive antifungal therapy if yeast are identified in peritoneal samples. Fluconazole should be the empiric agent of choice in the majority of patients. Patients with community-acquired IAI likely do not require antifungal therapy.

2. Timing and Duration of Antimicrobial Therapy

2.1 Antimicrobial therapy should be initiated once cIAI is diagnosed or considered likely.

2.2 Most patients with cIAI require antimicrobial therapy for 3-7 days after source control.

2.3 After source control is complete, antimicrobial therapy should be discontinued when clinical signs of infection have improved, usually 3-7 days after source control. Oral step-down therapy is rarely required, with the exception of patients with perforated appendicitis or perforated diverticulitis, in whom a very short length of stay precludes a thorough assessment of clinical response. In these patients, a total of a 5-day course (with a transition to oral ceflexin) is reasonable. A prolonged course of antimicrobials (> 7 days) should be avoided unless source control is incomplete.

2.4 Patients with evidence of ongoing infection at 4-7 days should be re-evaluated for source control rather than continuing with a prolonged course of antimicrobials.

3. Use of Culture and Sensitivity Specimens to Guide Antimicrobial Therapy

3.1 Blood cultures should only be obtained if the diagnosis of IAI is unclear or if there is a high suspicion of bacteremia.

3.2 Peritoneal samples should not be routinely obtained in mild-to-moderate community-acquired IAI.

3.3 Peritoneal samples should be obtained in all patients with health care-associated IAI and high severity community-acquired IAI.

3.4 Peritoneal fluid should be sent to the lab in aerobic and anaerobic blood culture bottles.

4. Source Control

4.1 All patients with IAI should undergo evaluation for a potentially controllable source of infection.

4.2 Percutaneous drainage is the preferred source control technique for localized abscesses.

4.3 Operative source control should be undertaken for most patients with cIAI not amenable to percutaneous drainage. The principles of the operation should be to drain infected fluid, debride non-viable tissue and control continued contamination by resection of the source organ or by gastrointestinal tract diversion.

4.4 An on-demand re-laparotomy strategy is preferred over planned re-laparotomy or laparostomy (open abdomen) strategies in most cases of cIAI.

4.5 Laparostomy should only be employed for specific indications: intra-abdominal hypertension, mesenteric ischemia, necrotizing abdominal wall infection, or damage-control surgery (with intestinal discontinuity or incomplete source control).

4.6 There is currently insufficient evidence to make a recommendation about primary colonic anastomosis versus stoma in the setting of peritonitis. Patients with less severe sepsis might be safely managed with primary anastomosis.

Part 2: Biliary Tract Infections

5. Biliary Tract Infections

5.1 All patients with ascending cholangitis should receive antimicrobial therapy. Patients with acute calculous cholecystitis should receive antimicrobial therapy if there is an increased likelihood of bactibilia (fever, leukocytosis, advanced age, immunosuppression or diabetes) or a suspicion of superimposed infection (adjacent abscess, air in the gallbladder wall or lumen, or suspicion of perforation).

5.2 All patients with acute cholecystitis taken to the operating room should receive antibiotic prophylaxis prior to skin incision. If the cholecystitis is uncomplicated then no further antibiotics are required after cholecystectomy . In cases of complicated cholecystitis characterized by either perforation, gangrene, or empyema, the antimicrobial duration should conform to the duration of antimicrobial therapy for cIAI detailed in Section 2, Timing and Duration of Antimicrobial Therapy.

5.3 Patients with biliary infection should receive antibiotics to cover enteric gram-negative organisms. Cefazolin is recommended in mild-to-moderate cases and ceftriaxone and ampicillin in patients meeting criteria for a high severity infection. Only patients with biliary-enteric anastomoses require anaerobic coverage, such as

metronidazole. For IgE-mediated or other severe reaction to beta-lactams, gentamicin or gentamicin and vancomycin should be used.

5.4 Patients with ascending cholangitis should receive prompt decompression of the common bile duct. Endoscopic or percutaneous approaches are preferred to open common bile duct exploration whenever feasible.

5.5 Patients with acute calculous cholecystitis should be considered for early laparoscopic cholecystectomy (within 72-96 hours of symptom onset).

5.6 Prophylactic antibiotics should NOT be administered to patients with necrotizing pancreatitis.

Section 3. Recommendations and Key Evidence

1. Selection of Empiric Antimicrobial Agents

1.1 Patients with mild-to-moderate community-acquired IAI require empiric coverage for enteric gram-negative bacilli and anaerobes. Cefazolin and metronidazole are recommended. In patients with IgE-mediated allergy or other severe reaction to beta-lactams, Gentamicin and metronidazole are recommended.

1.2 Most patients with mild-to-moderate community-acquired IAI do not require coverage of Enterococcus spp. unless other risk factors are present.

1.3 Patients with high severity community-acquired IAI may benefit from broader coverage against gram-negative bacilli. Ceftriaxone and metronidazole are recommended or gentamicin and metronidazole for IgE-mediated allergy or other severe reaction to beta-lactams. Piperacillin-tazobactam could also be considered.

1.4 Most patients with health care-associated IAI should receive broad spectrum empiric antimicrobial therapy, including coverage for drug-resistant gram-negative bacilli and Enterococcus spp. Piperacillin-tazobactam is recommended for those with high severity disease. Some patients with mild-moderate severity health care-associated IAI may not require as broad of coverage and thus, ceftriaxone and metronidazole may be appropriate. In patients with IgE-mediated penicillin allergy or other severe reaction, vancomycin, gentamicin and metronidazole OR vancomycin plus a carbapenem are recommended.

1.5 Patients with health care-associated IAI should receive antifungal therapy if yeast are identified in peritoneal samples. Fluconazole should be the empiric agent of choice in the majority of patients. Patients with community-acquired IAI likely do not require antifungal therapy.

Summary of Evidence

When selecting antimicrobial therapy for cIAIs, a clear distinction must be made between patients with community-acquired IAI and those with health care-associated cIAI. Patients who have been hospitalized for 5 or more days[2], who have received previous antibiotic therapy with activity against enteric organisms, or who are post-operative[3] undergo a notable shift in their bacterial flora, resulting in a greater number of significant infections from Enterococcus spp., Staphylococcu aureus, drug-resistant gram-negative bacilli such as Pseudomonas spp., and yeast[4]. Patients from nursing homes and rehabilitation facilities and on chronic dialysis should also be considered at risk of harbouring resistant organisms. Although there are no data from these populations specific for cIAI, shifts in nursing home patients' bacterial flora has been well-documented in other infections such as bacterial pneumonia.

In general, patients with IAI require therapy that covers enteric gram-negative bacilli and anaerobes. Patients with proximal gastrointestinal perforations, including stomach, duodenum and proximal jejunum, require coverage only for gram-positive cocci and aerobic/facultatively anaerobic gram- negative bacteria, provided there is no obstruction, malignancy or acid-

suppressing therapy. Patients with biliary infections usually require coverage only for enteric gram-negative bacilli (see Biliary Infections, Section 5).

Patients with community-acquired IAIs should be assessed for the severity of the infection. Those patients with new organ failure or are in shock and require care in an Intensive Care Unit (ICU) should be classified as high severity. Some patients at high risk of treatment failure on the basis of advanced age (>70 years old), immunosuppression, poor nutritional status, or delayed or inadequate source control), may also be considered to have high severity infections. Patients with mild-to-moderate community-acquired IAI's require antimicrobial coverage directed against enteric gram-negative and anaerobic bacteria, such as cefazolin and metronidazole. There is increasing worldwide and local resistance to fluoroquinolones among gram-negative bacteria. Recent antibiogram data from three University of Toronto teaching hospitals indicate that 31% of non-ICU E. coli isolates are resistant to ciprofloxacin whereas only 15% are resistant to gentamicin. Once daily dosing of aminoglycosides (5-7 mg/kg) has been in use for approximately 15 years with the rationale of decreased nephrotoxicity and ototoxicity as it takes advantage of the concentration dependent killing effects of aminoglycosides and therefore allows for a period of time where the kidney and ear are free from drug exposure. As well, nephrotoxicity with aminoglycosides is not an acute event and is associated with duration longer than 7 days. Therefore, because of the high resistance rates to fluoroquinolones and low risk of nephrotoxicity with appropriate dosing and short courses of aminoglycosides,.patients with IgE-mediated or other severe reactions to beta-lactam antibiotics should be treated with gentamicin and metronidazole. Patients with high severity community-acquired IAI's are presumably at greater risk of adverse events in the event of treatment failure and thus should likely receive broader gram-negative coverage, such as ceftriaxone and metronidazole, although there are no trial data to support this recommendation.

Most patients with community-acquired IAI's do not require empiric coverage against Enterococcus spp[1]. Antibiotics which cover enterococci include ampicillin, vancomycin and piperacillin-tazobactam, but not cephalosporins or fluoroquinolones. Antimicrobial regimens covering enterococci have not been shown to improve outcomes in this patient population[5]. The exceptions to this recommendation are patients with high severity infections, particularly those requiring ICU care or who are immunosuppressed[6] .

Patients with health care-associated IAI's require broader coverage than those with community-acquired disease[7]. As noted above, Enterococcus spp.[8] and drug-resistant gram-negative bacilli are more likely to cause significant IAI in this setting. This is particularly true in post-operative patients, many of whom have been exposed to antibiotics, such as cephalosporins and fluoroquinolones, which lack significant activity against these more resistant organisms. When possible, patients who have received previous antibiotics should have broader coverage initiated. Ideally, a different class of antibiotics should be selected in these patients. Patients with health care-associated IAI's should have intra-operative peritoneal cultures sent as these may allow identification of potentially important pathogens such as multi-drug-resistant (MDR) gram-negative bacilli and yeast. Some patients with health

care-associated IAI who are clinically well and have had minimal exposure to broad-spectrum antibiotics (i.e. a single perioperative dose) may be considered for treatment with agents such as ceftriaxone and metronidazole that lack activity against MDR pathogens. Patients who are critically ill should have broader coverage initiated, such as piperacillin-tazobactam.

Patients with health care-associated IAI who have yeast identified on gram stain or culture should have antifungal therapy initiated[9]. Fluconazole should be the empiric antifungal agent of choice in most patients. Patients known to be colonized with non-albicans Candida species, such as C. glabrata or C. krusei, or critically ill patients in the ICU with risk factors for non-albicans fungal infection should receive broader empiric coverage, at least until the sensitivities are known[10]. An Infectious Diseases consult is recommended in these circumstances to aid with appropriate antifungal selection. Patients with health care-associated IAI may benefit from empiric antifungal therapy if they have been on prolonged broad-spectrum antibiotics and have incomplete source control.

Patients with health-care associated IAI and severe IgE-mediated beta-lactam allergy are difficult to treat. Options include vancomycin, gentamicin and metronidazole, accepting an increased risk of acute kidney injury, or vancomycin plus a carbapenem (such as imipenem or meropenem). Carbapenems have <1% risk of cross-reactivity to other beta-lactam agents.

2. Timing and Duration of Antimicrobial Therapy

- **2.1 Antimicrobial therapy should be initiated once cIAI is diagnosed or considered likely.**
- **2.2 Most patients with cIAI require antimicrobial therapy for 3-7 days after source control.**
- **2.3 After source control is complete, antimicrobial therapy should be discontinued when clinical signs of infection have improved, usually 3-7 days after source control. Oral step-down therapy is rarely required, with the exception of patients with perforated appendicitis or perforated diverticulitis, in whom a very short length of stay precludes a thorough assessment of clinical response. In these patients, a total of a 5-day course (with a transition to oral ceflexin) is reasonable. A prolonged course of antimicrobials (> 7 days) should be avoided unless source control is incomplete.**
- **2.4 Patients with evidence of ongoing infection at 4-7 days should be re-evaluated for source control rather than continuing with a prolonged course of antimicrobials.**

<u>Summary of Evidence</u>

Antimicrobial therapy should be initiated once a diagnosis of cIAI is made or considered likely[1]. For patients with severe sepsis (associated with hypotension or new organ failure) there is some evidence to suggest that delay in initiating antimicrobial therapy increases mortality[11]. There is little evidence to make recommendations with respect to antimicrobial duration in IAI. Antimicrobial therapy lasting greater than 7 days should be considered a prolonged course.

Antimicrobials should only be given for a prolonged course in circumstances where source control has been deemed inadequate. There are retrospective data to suggest that patients who receive shorter courses of antibiotics have no increase in infective or other complications versus those who receive longer courses of antibiotics when stratified by degree of contamination[12]. A small, prospective trial of patients with mild-to-moderate community-acquired IAI demonstrated that patients treated with 3 days of ertapenem had no increase in treatment failure or infectious complications compared to a standard (≥ 5 day) course[13]. Further trials of antimicrobial duration in IAI are currently underway at the time of this guideline's publication. Most patients with IAI only require antimicrobial therapy until clinical evidence of improving infection occurs[14], as characterised by normalization of the white blood cell (WBC) count, absence of fever and return of bowel function. Patients who do not demonstrate improvement of clinical signs of IAI at 4-7 days should be re-imaged for evidence of ongoing IAI amenable to further source control rather than continuing on prolonged courses of antimicrobial therapy.

There are little data to inform the rational use of antimicrobials in the context of a localized abscess undergoing percutaneous drainage. Periprocedural antimicrobial coverage should be provided in all cases. In cases where clinical signs of infection are minimal or resolve rapidly, antimicrobial therapy may be rapidly discontinued. One prospective series demonstrated that patients with localized peritonitis or abscesses treated with 48 hours of antibiotics after source control had a low rate of infectious complications[15]. Percutaneous drainage and operative source control should be considered equivalent when determining an appropriate duration of antimicrobials.

Patients with bacteremia arising from IAI can in most circumstances be treated for the same duration as a non-bacteremeic patient, guided by the improvement of their clinical status. One definite exception is *Staphylococcus aureus* bacteremia which should be treated for a minimum of 2 weeks. An Infectious Disease consult should be obtained on patients with enterococcal or *Staphylococcus aureus* bacteremia as there is a potential for metastatic infection. These patients typically require longer courses of antimicrobial therapy.

In most cases of cIAI, step-down to oral antimicrobials is unnecessary. A patient who has received source control and a course of effective antimicrobial therapy and who demonstrates improvement or resolution in clinical symptoms should have antimicrobial therapy discontinued rather than changed to oral agents. In rare circumstances, patients with incomplete source control or incomplete resolution of clinical symptoms may be discharged home with oral antimicrobials. Acceptable regimens would include cephalexin and metronidazole, amoxicillin-clavulanic acid, co-trimoxazole and metronidazole, or a fluoroquinolone plus metronidazole. The increasing resistance of enteric gram negative bacilli to fluoroquinolones should again be emphasized, which is likely driven to some degree by excessive outpatient prescribing of prolonged oral courses of fluoroquinolones.

3. Use of Culture and Sensitivity Specimens to Guide Antimicrobial Therapy

- **3.1 Blood cultures should only be obtained if the diagnosis of IAI is unclear or if there is a high suspicion of bacteremia.**
- **3.2 Peritoneal samples should not be routinely obtained in mild-to-moderate community-acquired IAI.**
- **3.3 Peritoneal samples should be obtained in all patients with health care-associated IAI and high severity community-acquired IAI.**
- **3.4 Peritoneal fluid should be sent to the lab in aerobic and anaerobic blood culture bottles.**

Summary of Evidence

Blood cultures are of little value in patients with IAI with yields reported from 0 to 5%. The yield of blood cultures may be higher in immunocompromised patients, such as solid organ transplant recipients. Peritoneal samples should be obtained from patients with high severity community-acquired IAI and, especially, health care-associated IAI. These patients have an increased incidence of drug-resistant organisms and will likely benefit from therapy tailored to peritoneal culture results. Patients with mild-to-moderate community-acquired IAI do not require routine peritoneal samples as these rarely alter management or affect outcome even if resistant organisms are identified[16]. For peritoneal sampling, culture swabs provide suboptimal yield. Ideally, 1-10 mL of representative fluid should be sent to the lab in both aerobic and anaerobic culture bottles. Additional fluid may be sent for gram stain and fungal cultures.

4. Source Control

- **4.1 All patients with IAI should undergo evaluation for a potentially controllable source of infection.**
- **4.2 Percutaneous drainage is the preferred source control technique for localized abscesses.**
- **4.3 Operative source control should be undertaken for most patients with cIAI not amenable to percutaneous drainage. The principles of the operation should be to drain infected fluid, debride non-viable tissue and control continued contamination by resection of the source organ or by gastrointestinal tract diversion.**
- **4.4 An on-demand re-laparotomy strategy is preferred over planned re-laparotomy or laparostomy (open abdomen) strategies in most cases of cIAI.**
- **4.5 Laparostomy should only be employed for specific indications: intra-abdominal hypertension, mesenteric ischemia, necrotizing abdominal wall infection, or damage-control surgery (with intestinal discontinuity or incomplete source control).**

4.6 There is currently insufficient evidence to make a recommendation about primary colonic anastomosis versus stoma in the setting of peritonitis. Patients with less severe sepsis might be safely managed with primary anastomosis.

Summary of Evidence

All patients with suspected IAI must be evaluated for a source of infection amenable to surgical or percutaneous source control. This may be accomplished by physical exam or plain X-rays, but more often requires Computed Tomography (CT) scanning. Ideally, patients with cIAI should undergo source control within 24 hours of presentation[1]. Those who present with severe sepsis or septic shock should undergo source control within 6 hours, as recommended in the Surviving Sepsis Guidelines[17]. Close attention must be paid to the resuscitation of such patients and they may benefit from dedicated resuscitation in an ICU prior to source control, provided the source control procedure is not unduly delayed.

If a localized abscess is identified as the source of infection by physical exam and imaging studies, percutaneous drainage via image-guided techniques is the preferred management, resulting in good cure rates with a low incidence of complications[18]. Percutaneous drainage is not indicated for patients with clinical evidence of generalized peritonitis or with diffuse free air or free fluid on imaging. The resolution of intra-abdominal abscesses should be confirmed by a follow-up CT scan as well as absent or minimal drainage (less than 10 mL/24 hrs) from the drain and a resolution of clinical signs of infection[19]. Absence of any of these conditions should prompt consideration of further source control. Some patients will require repeat drainage, catheter exchange or, rarely, subsequent operation[20]. Reimaging to guide further percutaneous drainage attempts may be undertaken as early as 48 hours post-procedure in patients who fail to improve. Multiple attempts at drainage may be required and should not be considered a failure of the technique.

Operative source control is required for most patients who are not suitable for percutaneous drainage. There are many acceptable surgical approaches, depending on the organ involved, degree of contamination and patient's clinical condition, the exact selection of which is beyond the scope of this document to review. The principles of surgical source control for IAI are to drain infected fluid and to debride or resect any non-viable tissue. However, extensive debridement of fibrinous debris has not been demonstrated to improve outcome in a randomized controlled trial of surgical source control for cIAI[21]. Control of ongoing contamination may require resection of the source organ, diversion of the gastrointestinal tract or placement of drains.

Patients with IAI are best managed with an on-demand re-laparotomy approach in the majority of cases. In a well-conducted, multicenter, randomized controlled trial, patients treated with on-demand re-laparotomy had similar morbidity and mortality, shorter ICU and hospital stays, and were spared unnecessary operations, compared to a planned re-laparotomy approach[22]. With the on-demand strategy, a high index of suspicion must be maintained for ongoing IAI, particularly in those patients who manifest new or persistent organ failure after their index operation[23].

An open abdomen strategy (also known as laparostomy) should rarely be employed for the management of IAI, and only for specific indications: known or suspected intra-abdominal hypertension, mesenteric ischemia requiring relook laparotomy, necrotizing abdominal wall infection, or profound hemodynamic instability requiring damage-control laparotomy techniques (such as intestinal discontinuity or incomplete source control)[24]. The disadvantages of the open abdomen include ongoing fluid and protein loss, retraction of the abdominal wall musculature resulting in loss of abdominal domain and post-operative hernia, a high incidence of enteric fistulae, and potentially a prolongation of the systemic inflammatory response.

There is ongoing controversy regarding the safety of primary colonic anastomosis in the setting of peritonitis. Most studies on this subject have been retrospective and subject to considerable selection bias[25]. Patients with less severe peritonitis are likely safely managed with primary anastomosis, although this has not been the subject of a randomized controlled trial. The use of a scoring system such as the Peritonitis Severity Score or the Mannheim Peritonitis Index may help to identify patients who can safely be managed with primary anastomosis[26].

5. Biliary Infections

5.1 All patients with ascending cholangitis should receive antimicrobial therapy. Patients with acute calculous cholecystitis should receive antimicrobial therapy if there is an increased likelihood of bactibilia (fever, leukocytosis, advanced age, immunosuppression or diabetes) or a suspicion of superimposed infection (adjacent abscess, air in the gallbladder wall or lumen, or suspicion of perforation).

5.2 All patients with acute cholecystitis taken to the operating room should receive antibiotic prophylaxis prior to skin incision. If the cholecystitis is uncomplicated then no further antibiotics are required after cholecystectomy . In cases of complicated cholecystitis characterized by either perforation, gangrene, or empyema, the antimicrobial duration should conform to the duration of antimicrobial therapy for cIAI detailed in Section 2, Timing and Duration of Antimicrobial Therapy.

5.3 Patients with biliary infection should receive antibiotics to cover enteric gram-negative organisms. Cefazolin is recommended in mild-to-moderate cases and ceftriaxone and ampicillin in patients meeting criteria for a high severity infection. Only patients with biliary-enteric anastomoses require anaerobic coverage, such as metronidazole. For IgE-mediated or other severe reaction to beta-lactams, gentamicin or gentamicin and vancomycin should be used.

5.4 Patients with ascending cholangitis should receive prompt decompression of the common bile duct. Endoscopic or percutaneous approaches are preferred to open common bile duct exploration whenever feasible.

5.5 Patients with acute calculous cholecystitis should be considered for early laparoscopic cholecystectomy (within 72-96 hours of symptom onset).

5.6 Prophylactic antibiotics should NOT be administered to patients with necrotizing pancreatitis.

Summary of Evidence

Biliary infections discussed herein include acute cholecystitis and ascending cholangitis. Although acute calculous cholecystitis generally begins as a sterile inflammatory process, a significant fraction of patients (40-70% in most reports) will develop bactibilia, particularly if the time course of the disease progresses beyond 48 hours[27], although predictive models for patients with bactibilia in the setting of acute cholecystitis are imperfect. Patients with bactibilia are at increased risk for infectious complications, which may include gallbladder gangrene or perforation, intra-abdominal abscess or post-operative wound infection[28].

Antimicrobial therapy is indicated for all cases of known or suspected ascending cholangitis. Many cases of acute calculous cholecystitis should receive antimicrobial therapy, unless they are mild cases. Specifically, any patient with acute cholecystitis and a fever or elevated WBC count or with imaging evidence of infection (air in the gallbladder lumen or gallbladder wall, or intra-abdominal or hepatic abscess) should receive antimicrobial therapy. Patients who are elderly, immunosuppressed or who have diabetes also have a higher risk of infection and should receive antimicrobial therapy. Patients with evidence of intense gallbladder inflammation (such as a palpable gallbladder or right upper quadrant peritonitis) are also at higher risk of infection. All patients with acute cholecystitis who are undergoing cholecystectomy should have antibiotics administered prior to skin incision as prophylaxis for surgical site infections. In cases of simple cholecystitis (without rupture or peritoneal cavity contamination) antimicrobials should be discontinued after source control is complete. Patients with complicated acute cholecystitis should receive antimicrobial therapy until clinical signs of IAI have resolved, as detailed in Section 2, Timing and Duration of Antimicrobial Therapy.

The organisms most frequently involved in biliary infection are enteric gram-negative bacilli, with enterococci and anaerobes less frequently identified. As such, patients with biliary infection require coverage against gram-negative bacilli: cefazolin is recommended in most cases. Ceftriaxone is recommended in severe infections. Only patients with biliary-enteric anastomoses require anaerobic coverage for biliary infections. Consideration of enterococcal coverage for biliary infections should conform to the previously detailed indications for enterococcal coverage in Section 1 of this guideline. Of note, liver transplant recipients with ascending cholangitis are at high risk of enterococcal infection.

As with other IAI's, patients with biliary infection must undergo evaluation for source control as early as is feasible. For ascending cholangitis, decompression of the common bile duct should be undertaken in all except mild cases, which may resolve with antibiotic therapy alone[29]. This is preferably achieved with Endoscopic Retrograde Cholangiography (ERC) combined with sphincterotomy and/or stenting. Percutaneous Transhepatic Cholangiography (PTC) is another minimally-invasive modality that may be employed if ERC is not available or feasible. The

mortality of open common bile duct exploration in acutely ill patients with ascending cholangitis is high and thus should be avoided if ERC or PTC can achieve ductal decompression[30].

Patients with acute calculous cholecystitis should be considered for early laparoscopic cholecystectomy. A recent Cochrane review noted no increase in adverse events and a shorter hospital stay with early (within 7 days of symptom onset) versus delayed laparoscopic cholecystectomy. Of note, 17.5% of patients in the delayed group had to undergo emergency laparoscopic cholecystectomy due to persistent or recurrent symptoms, with a very high rate of conversion to open cholecystectomy (45%)[31]. However, it must be noted that rare but important adverse events such as bile duct injury may not be adequately captured by small- or moderately-sized randomized controlled trials, such as those included in the Cochrane review. Those patients with severe acute cholecystitis (associated with new organ failure or need for ICU admission) are likely better treated with percutaneous cholecystostomy rather than open or laparoscopic cholecystectomy[26].

Patients with acute pancreatitis should not receive antimicrobial therapy unless the pancreatitis is complicated by ascending cholangitis, or documented or strongly suspected infected pancreatic necrosis[32]. The presence of pancreatic necrosis alone is not an indication for prophylactic antimicrobial therapy, and such treatment risks the selection of resistant organisms. Recent randomized controlled trials demonstrate no benefit to prophylactic antibiotic administration in patients with necrotizing pancreatitis[33 34].

Section 4. External Review Process

Reviewer Comments and Responses

Reviewer Comment: For mild to moderate IAI – suggesting gentamicin for penicillin allergic patients, makes me nervous. We hardly use gentamicin at SB because of nephrotoxicity and having to monitor levels etc in patient who may already be dehydrated and have renal issues.
Authors Response: Recent antibiogram data from three University of Toronto teaching hospitals indicate that 31% of non-ICU E. coli isolates are resistant to ciprofloxacin whereas only 15% are resistant to gentamicin. Once daily dosing of aminoglycosides (5-7 mg/kg) has been in use for approximately 15 years with the rationale of decreased nephrotoxicity and ototoxicity as it takes advantage of the concentration dependent killing effects of aminoglycosides and therefore allows for a period of time where the kidney and ear are free from drug exposure. As well, nephrotoxicity with aminoglycosides is not an acute event and is associated with duration longer than 7 days. Therefore, because of the high resistance rates to fluoroquinolones and low risk of nephrotoxicity with appropriate dosing and short courses of aminoglycosides,patients with IgE-mediated or other severe reactions to beta-lactam antibiotics should be treated with gentamicin and metronidazole

Reviewer Comment: My only caution would be on the use of gentamicin as the alternative to Ancef in Pen-allergic people. I know it's a great antimicrobial but so many of us have essentially stopped using it because of toxicity reasons. Again, although it's rare if used properly, the fact is it gets blamed for any renal toxicity regardless of it being an innocent by-stander most of the time. I have done several medico-legal cases with General surgeons using Gentamicin and getting into trouble with renal toxicity. Something to consider. Even though you may only need to give one or two doses, these things have a way of being used for longer and changing practise will be a work in progress.
Authors Response: We will undertake education interventions to familiarize clinicians with the current evidence and hopefully ensure gentamicin is used appropriately and for the recommended duration.

Reviewer Comment: Selection of empiric antimicrobial agents-Last bullet—not sure fluconazole is always indicated, may consider changing the word should to should consider.
Authors Response: Agree with comment. Changes made: "Patients with health care-associated IAI should receive antifungal therapy if yeast are identified in peritoneal samples. Fluconazole should be considered as the empiric agent of choice in the majority of patients. Patients with community-acquired IAI likely do not require antifungal therapy."

Reviewer Comment: Is there any objective criteria to distinguish between those patients who should have coverage broadened with Ceftriaxone vs those that can be treated with cefazolin (with metronidazole for both)?
Authors Response: Agree with comment. Changes made. See Definitions Section

Reviewer Comment: When you suggest a carbapenem, also add ertapenem.
Authors Response: When we suggest a Carbapenum, we are suggesting it for hospital acquired infections. Ertapenem doesn't have the coverage required. Ertapenem is an option for community acquired but we have elected to keep the choices limited.

Reviewer Comment: When discussing the empiric coverage of enterococcus, dialysis pt could be an exception.
Authors Response: Agree with comment. Changes made. See Definitions Section

Reviewer Comment: There is no comment about source control for pancreatitis- this does not align with the other processes where source control is always mentioned. Might refer to the NEJM paper 2010, also Mier AJS paper.
Authors Response: Management of acute pancreatitis is outside the scope of this guideline.

Reviewer Comment: Recommendation #5 bullet 2: Clarify that source control for cholecystitis is cholecystectomy
Authors Response: Agree with comment. Changes made.

Reviewer Comment: In section 2 – define in recommendations point 2 what are you specifically looking for "when clinical signs of infection have improved" – no fever x 24 hrs? no fever x 48hrs? no WBC?
Authors Response: Agree with comment changes made.

Reviewer Comment: Are there data to support a 5-day course of IV transition to oral meds (supported by a reference)?
Authors Response: In these patients, a total of a 5-day course (with a transition to oral) is reasonable. A prolonged course of antimicrobials (> 7 days) should be avoided unless source control is incomplete. Evidence: J Gastrointest Surg. 2008 Mar;12(3):592-600. Epub 2007 Sep 11. A prospective, double-blind, multicenter, randomized trial comparing ertapenem 3 vs >or=5 days in community-acquired intraabdominal infection. Basoli A, Chirletti P, Cirino E, D'Ovidio NG, Doglietto GB, Giglio D, Giulini SM, Malizia A, Taffurelli M, Petrovic J, Ecari M; Italian Study Group and Pediatr Surg Int. 2004 Dec;20(11-12):838-45. Epub 2004 Oct 6. Minimum postoperative antibiotic duration in advanced appendicitis in children: a review. Snelling CM, Poenaru D, Drover JW.

Reviewer Comment: In terms of localized abscesses- most of us would use antibiotics for 14 days, even when a drain is placed.
Authors Response: The evidence does not support a prolonged course of antibiotics. Thus, this change has not been made.

Reviewer Comment: The recommendation to start antibiotics should probably put more emphasis on starting antibiotics rapidly. The Surviving Sepsis Campaign has reviewed this, and recommends that antibiotics be started within an hour of diagnosis for patients with severe sepsis or septic shock. Since obtaining cultures is not usually an issue in intra-abdominal infection, early initiation should be readily accomplished.
Authors Response: Agree with this suggestion in patients with severe sepsis. See "Summary of Evidence" under Recommendation #2. 'For patients with severe sepsis (associated with hypotension or new organ failure), there is some evidence to suggest that delay in initiating antimicrobial therapy increases mortality".

Reviewer Comment: The second paragraph talks about antibiotic use in specific types of IAI and calls it "prophylactic". I think that it is unwise to label these as prophylactic as there is IAI and they are clearly different from true elective antimicrobial. I think it might be a better idea to address this in the context of the duration of therapy indicating that there are specific circumstances where duration might be very short (ie like prophylaxis) due to the fact that the organ is removed, or the bacterial load is small etc**.**

Authors Response: Agree with comment. Instead of using “prophylaxis”, the term “ultrashort course” is used. See changes in preamble: “ It is important to distinguish the antimicrobial treatment required for complicated IAI’s from the ultra short course of antibiotic therapy required in uncomplicated IAI (such as non-perforated appendicitis or simple cholecystitis).”

Reviewer Comment: If staph aureus is grown in blood, IV antibiotics are needed for at least 14 days.
Authors Response: Agree with comment. Changes made: “An Infectious Disease consult should be obtained on patients with enterococcal or staphylococcus aureus bacteremia as there is a potential for metastatic infection in. These patients typically require longer courses of antimicrobial therapy”.
Reviewer Comment: On page 6, third line from bottom, I would suggest removing "free air". There are circumstances where there can be free air but localized infection and PCD might be indicated. (appendicaeal or diverticular abscess). You might also indicate that PCD is not indicated in the very early postop period where there might be a dominant fluid collection seen on scan with a little elsewhere- example is cystic duct leak or inadvertant enterotomy.
Authors Response: Agree with comment. Changes made.

Reviewer Comment: Be careful when discussing anaerobic cultures- the lab can do these if sterile samples placed in blood culture bottles but are not able to do this from swabs.
Authors Response: Peritoneal fluid should be sent to the lab in aerobic and anaerobic blood culture bottles.

Reviewer Comment: Recommendation 3, page 5, “Peritoneal samples should be obtained in all patients with health care-associated IAI...” is a strong recommendation, and should be supported in the literature.
Authors Response: There is no evidence for this. Most would agree that this is necessary to tailor therapy post op. the bugs are much less predictable in these patients, hence the need for cultures.

Reviewer Comment: Recommendation #3 bullet 4: add blood cultures to aerobic and anaerobic bottles, i.e. aerobic and anaerobic blood culture bottles.
Authors Response: Agree with comment. Changes made.

Reviewer Comment: Recommendation 6, page 6, “Patients with less severe sepsis might be safely managed...”, could be re-stated to suggest that there is an option to manage these patients with primary anastomosis.
Authors Response: We believe that the statement as it is written addresses this issue. There is currently insufficient evidence to make a recommendation about primary colonic anastomosis versus stoma in the setting of peritonitis.

Reviewer Comment: Management of infected pancreatic necrosis has evolved substantially, and there are good RCT data supporting a staged approach, with percutaneous drainage (even if incomplete) followed by operative intervention if needed. It would be worth emphasizing that delayed intervention in suspected pancreatic infection is associated with a better outcome, or at least that infected pancreatic necrosis is an exception to the otherwise sound principle tat source control should be initiated early. An algorithm for the management of infected pancreatic necrosis is probably beyond the scope of the recommendations.
Authors Response: Management of pancreatitis is outside the scope of this guideline.

Reviewer Comment: Pyogenic liver abscess- may not be able to target cultured organism alone but widen to include enteric pathogens including anaerobes.
Authors Response: Pyogenic liver abscess is outside the scope of this guideline.

Reviewer Comment: Can you indicate in your guidelines the age limits upon which these guidelines are based? The question is applicability of these guidelines to pediatric or infant populations we see here at SickKids. Perforated NEC is the most common abdominal sepsis infant population we see with a need for clear antimicrobial guidelines (coverage and duration of therapy) and the perforated appendicitis population is the most common pediatric population we see in need of clear antimicrobial guidelines. While these guidelines may not apply to our infant population, we probably can adopt these for the "older" kids with "community-acquired" perf'd appy's and I would be thrilled if we have evidence to show that cefazolin+metronidazole or ceftriaxone+metronidazole is preferable to our current amp/gent/metrionidazole treatment.
Authors Response: Perforated NEC exceeds the extent of this guideline.

Reviewer Comment: Use plurals when "data" used.
Authors Response: Agree with comment. Changes made.

Reviewer Comment: Spell out Pip-taz, page 10.
Authors Response: Agree with comment. Changes made.

Reviewer Comment: Page 9 last paragraph, 3rd line: "coliform bacteria are the most common organisms if their source is the GI tract,".
Authors Response: Agree with comment. Changes made.

Reviewer Comment: p9- ref 26- should this be ref 27
Authors Response: Agree with comment. Changes made.

Reviewer Comment: It needs to be more "readable" in general. For most people, seeing a multi-page document like this may put them off reading it. Is there some way it could be formatted differently with almost an "Executive Summary", so to speak, right at the beginning giving the highlights of each category of recommendation.
Authors Response: Agree with comment. See changes to Preamble including "Summary of Recommendations". The "full" guideline will be available on the BPIGS website. In addition, a summary of the recommendations will be made available on cards and for download from the website.

Reviewer Comment: I would suggest that there be a brief summary with bulleted recommendations that can be easily downloaded onto a PDA.
Authors Response: Agree with comment. See Summary of Recommendations

Reviewer Comment: Recommendation #5 all bullet: reorganize bullets by biliary infection type so easier to read
Authors Response: Agree with comment. Changes made.

Reviewer Comment: Recommendation #2 bullet: move appendicitis comment currently in Recommendation #2 bullet 2 to bullet 3 so that duration of therapy comments all together.
Authors Response: Agree with comment. Changes made.

Reviewer Comment: Add definitions at beginning of document in an easy to find location, e.g. complicated IAI, mild-moderate IAI, high severity IAI.
Authors Response: Agree with comment. Changes made. See Definition Section.

Reviewer Comment: Is the definition of "mild-to-moderate" infection regarding IAI widely accepted?
Authors Response: Agree with comment. Changes made. See Definition Section.

Reviewer Comment: Recommendation #5 bullet 3: define mild-mod severity.
Authors Response: Agree with comment. Changes made. See Definition Section.

Reviewer Comment: The term "health care-associated" may need to be defined in more detail.
Authors Response: Agree with comment. Changes made. See Definition Section.

Reviewer Comment: I had difficulty with following the guideline in Section 1. I think early definitions and examples of 'Mild to moderate community acquired IAI' and 'High severity community acquired IAI'. A table might be a quick and easy way to describe this information for section 1 and for biliary sepsis.
Authors Response: Agree with comment. Changes made. See Definition Section.

Reviewer Comment: Use cIAI to refer to complicated IAI – Recommendations #1 bullet one refers to IAI without mention of complicated; Recommendation #2 bullet 1 refers to it as complicated IAI which suggests that these recommendations are not both referring to cIAI.
Authors Response: Agree with comment. Changes made.

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