Intra-abdominal Infections Educational Module
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with contributions from the CAHO ASP Project Team

Antimicrobial Stewardship Program (ASP) in Intensive Care Units (ICU) ARTIC Project
“Getting patients the right antibiotics, when they need them”

**SCENARIO**

CM, a 70-year-old male was recently diagnosed with colon cancer and underwent resection surgery. He received 2 doses each of cefazolin and metronidazole as perioperative antibiotic prophylaxis and was transferred to the surgical ward. On post-op day 5, CM deteriorated clinically (see Table 1) and required increased analgesia. Based on clinical assessment and abdominal CT, anastomotic leak was suspected and he returned to the OR for further resection and re-creation of an end-to-end anastomosis. Stool contamination in the peritoneum was noted during the procedure. He is to be admitted to the ICU post-op on vasopressors. Total parenteral nutrition is due to start the next day. At present, the ICU team is conferring with the surgical team on the most appropriate antibiotic regimen. CM has no known drug allergies and admission screening for methicillin-resistant S. aureus (MRSA) and vancomycin-resistant enterococci (VRE) were negative.

| Table 1: Lab Values and Vital Signs on Post-Op Day 5 (before returning to the OR) |
|---------------------------------|--------------------------|
| BP (mmHg)                      | 110/60 on vasopressors   |
| Temp (C)                       | 38.5                     |
| HR (BPM)                       | 80                       |
| WBC (counts/L)                 | 12.5x10^9/L              |
| SCr (micromole/L)              | 170                      |
| Lactic acid (millimol/L)       | 2.0                      |

Microbiology (resulted on Day 2 of ICU Admission):
Peritoneal fluid: mixed, heavy growth
KEY MESSAGES

+ Source control is an important determinant of outcome in IAI.
+ Choice of empiric antibiotic therapy depends on they type of IAI, while taking into account the patient’s prior antibiotic exposure and risk of acquiring resistant organisms.
+ For healthcare-associated IAI, patient’s institutional length-of-stay and local (institutional) susceptibility data should be considered in determining empiric antibiotic therapy.
+ Duration of therapy is influenced by achievement of source control. It should be no longer than 3-7 days if source control is achieved and patient is improving clinically.
+ Lack of clinical improvement should prompt further investigation for source of infection, rather than prolonged antimicrobial therapy.

BACKGROUND

Peritonitis is a bacterial infection within the peritoneum of the abdominal cavity. Primary peritonitis (e.g. spontaneous bacterial peritonitis) is an infection that arises in the absence of a gastrointestinal (GI) breach\(^1\). The more common secondary peritonitis (focus of this module) usually follows a perforation of the GI tract, which leads to contamination by gut flora into the sterile cavity\(^1\). Intra-abdominal infections (IAI) encompass a wide variety of pathological conditions, and are often subcategorized. Below is a list of key definitions.\(^2,3\)

*Uncomplicated IAI:* contamination or inflammation does not extend beyond the source and the disease is completely excised at the time of operation. Examples are early traumatic perforation, simple appendicitis and cholecystitis.

*Complicated IAI:* infectious process proceeds beyond the organ that is the source of the infection, and causes localized peritonitis (also referred to as intra-abdominal abscesses) or diffuse peritonitis, depending on the host’s ability to contain the process within a part of the abdominal cavity.

*Community-acquired:* examples include gastroduodenal perforations, ascending cholangitis, cholecystitis, appendicitis, diverticulitis with or without perforations, bowel perforations and pancreatitis in patients without previous surgical intervention or hospitalization.
Healthcare-associated: by definition, are infectious processes that are absent at the time of hospital admission, but become evident 5 or more days after admission. Examples are anastomotic leaks and perforations, and abscesses that develop as a complication of surgery. They may include infections acquired while receiving treatment in other healthcare setting, such as long-term care facilities, dialysis units or surgical day care units, within the previous 12 months. Most importantly, from the perspectives of empiric treatment and antimicrobial stewardship, the choice of empiric antibiotics and their modification should reflect the possibilities of drug-resistant pathogens and acquisition of nosomial organisms.

Severity: by definition, IAI that requires ICU admission constitute high-severity disease. Organ dysfunction (e.g. acute lung injury, renal dysfunction), and signs and symptoms of shock may be present. Patients may be elderly, with extensive comorbidities or immunocompromised state. Acute Physiologic and Chronic Health Evaluation II (APACHE II) score can be used for stratification of patients: low-to-moderate severity (score lower than 15); high severity (score 15 or greater).

Control of the source of infection is an important determinant of outcome, and can be achieved either by surgical (e.g. resection) or non-surgical means (e.g. CT-guided percutaneous drainage of abscesses).

Antimicrobial therapy plays an integral role in IAI management, especially in critically ill patients, as inappropriate empiric therapy is strongly associated with unfavourable outcomes. [See Pharmacotherapy]

**CLINICAL PRESENTATION**

- Abdominal pain, which may be aggravated by motion or respiration
  - Decreased intensity and extent of pain with time may suggest localization of the inflammatory process
- Epigastric pain may be associated with peptic ulcer rupture
- Constitutional symptoms (e.g. anorexia, fever, chills, rigors, night sweats)
- Nausea, vomiting, diarrhea/constipation
- Muscle rigidity (“guarding”) of abdominal wall due to peritonitis
- Decreased or absent bowel sounds
- Signs and symptoms of sepsis and septic shock due to progression of IAI (refer to “Sepsis” Module)
 Imaging studies:
  - X-ray—may reveal bowel distension, obstruction, free air (esp. CXR showing free air under the diaphragm)
  - Ultrasound—frequently the initial step in evaluating IAI; can also guide drainage of fluid collections/abscesses
  - Computerized tomography (CT)—apart from detecting intra-abdominal processes; can also guide fluid collections/abscesses

 Cultures
  - Peritoneal fluid sampling is more likely to give modifying information in healthcare-associated IAI or severely ill patients. In early community-acquired IAI, they are often not available.
  - Blood cultures are not clinically relevant in community-acquired IAI, but may add diagnostic information to healthcare-associated infections. Obtained only if the diagnosis of IAI is unclear or if there is a high suspicion of bacteremia.

 ETIOLOGY

Secondary peritonitis tends to be polymicrobial. In community-acquired IAI, especially during the early stage, the pathogens are closely related to the normal microflora of the GI tract. In the stomach, there are few organisms that cause peritonitis (although pH-altering therapy can modify this). Both volume and variety of bacterial species increase progressively from the duodenum to the ileum, dominated by streptococci, lactobacilli and Enterobacteriaceae (enteric gram negative bacilli). In the colon, bacteria load is very high \(10^9\) to \(10^{11}\) colony forming unit (cfu)/g, dominated by obligate anaerobes (Bacterioides spp.; Clostridium spp.; non-spore forming gram-positive bacilli) and Enterobacteriaceae. Therefore in community-acquired IAI without previous exposure to antibiotics, the microbial causes of the infection are relatively predictable.

Core pathogens:\(^\text{3}\)

  - *Streptococcus* spp.
  - Enterobacteriaceae (enteric gram negative bacilli) (e.g. *E coli*, *Klebsiella* spp., *Proteus* spp., *Serratia marcescens*)
  - Anaerobes (e.g. *B. fragilis*, non-*fragilis* Bacteroides, Clostridium spp., Fusobacterium spp., Lactobacillus spp., Peptostreptococcus spp., Veillonella spp.)
*top three most frequently isolated
In health-care associated IAI, the etiology is influenced by the patient’s prior antibiotic exposure (selection pressure) and colonization risks (e.g. institutional length of stay). Therefore, in addition to core pathogens, coverage against drug-resistant and nosocomial organisms should be considered:

- More difficult to treat gram-negative bacilli (e.g. *Pseudomonas aeruginosa*)
- Drug-resistant gram-negative bacilli (e.g. extended-spectrum beta-lactamase-producing (ESBL) *E. coli* or *K pneumoniae*; ampC-producing gram-negative bacilli)
- *Enterococcus* spp.
- Methicillin-resistant *S. aureus* (MRSA) in colonized patients
- *Candida* spp. (yeast) [see Empiric Antifungal Therapy]

**PHARMACOTHERAPY**

**EMPIRIC**

Empiric therapy should be directed against core pathogens in community-acquired IAI. Additional coverage against resistant organisms or non-core pathogens as described above should be considered in healthcare-associated infections and in patients with high severity IAI, taking into account local antibiogram in the selection of treatment options. Broadening of coverage is recommended due to the high risk of mortality and morbidity in severely ill patients and those with healthcare-associated infections, leaving little margin for error in this patient population.

<table>
<thead>
<tr>
<th>Type of IAI</th>
<th>Examples</th>
<th>Selection of Antibiotics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Community-acquired and uncomplicated:</td>
<td></td>
<td></td>
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<tr>
<td>No perforation</td>
<td>Non-perforated appendicitis, operated</td>
<td></td>
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<tr>
<td>Perforation without established infection</td>
<td>Perforations of stomach/duodenum, traumatic bowel perforations operated on within 12-24 hrs</td>
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<td></td>
<td></td>
<td>Spectrum of coverage</td>
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<tr>
<td></td>
<td></td>
<td>Recommended regimen</td>
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<td></td>
<td></td>
<td>Alternative for Penicillin-allergic patients</td>
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<tr>
<td></td>
<td></td>
<td>Cefazolin + metronidazole</td>
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<td></td>
<td></td>
<td>Gentamicin + metronidazole</td>
</tr>
<tr>
<td>Type of IAI</td>
<td>Examples</td>
<td>Spectrum of coverage</td>
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<td>------------</td>
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</tr>
<tr>
<td>Community-acquired, complicated</td>
<td>Perforated appendicitis, perforated diverticulitis</td>
<td>Enteric gram negative bacilli, anaerobes</td>
</tr>
<tr>
<td>High severity &amp; Other risk factors for treatment failure</td>
<td>Shock, new organ failure, ICU admission</td>
<td>Enteric gram-negative bacilli, anaerobes, may include enterococci</td>
</tr>
<tr>
<td>Health-care associated</td>
<td>Hospitalized ≥5d; anastomotic leak, post-op abscess</td>
<td>Resistant gram-negative bacilli including <em>P. aeruginosa</em>; anaerobes; enterococci</td>
</tr>
<tr>
<td>High severity</td>
<td>Hospitalized ≥5d; anastomotic leak; shock; ICU admission</td>
<td>Resistant gram-negative bacilli including <em>P. aeruginosa</em>, ESBL-gram-negative bacilli; anaerobes; enterococci</td>
</tr>
<tr>
<td>Other risk factors for healthcare-associated infection</td>
<td>Nursing home; rehab facility; dialysis patient; recent antibiotic exposure</td>
<td>Resistant gram-negative bacilli, enterococci</td>
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</tbody>
</table>

Biliary Tract

<table>
<thead>
<tr>
<th>Type of IAI</th>
<th>Examples</th>
<th>Spectrum of coverage</th>
<th>Selection of Antibiotics</th>
<th>Alternative for Penicillin-allergic patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild-to-moderate</td>
<td>Ascending cholangitis; acute calculous cholecystitis</td>
<td>Enteric gram negative bacilli</td>
<td>Cefazolin</td>
<td>Gentamicin</td>
</tr>
<tr>
<td>High severity</td>
<td>Enteric gram negative bacilli, enterococci</td>
<td>Ceftriaxone + ampicillin</td>
<td>Gentamicin + vancomycin</td>
<td></td>
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</tbody>
</table>

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

*Carbapenem: note ertapenem does not have activity against enterococci or *Pseudomonas* sp. but is active against ESBL-producing gram-negative bacilli.

*Risk of cross-reactivity between penicillin and carbapenem is considered to be ≤1%.*
Biliary tract infections:2,6

All patients with ascending cholangitis should receive antimicrobial therapy. Patients with acute calculus cholecystitis should receive antimicrobial therapy if there is an increased likelihood of bactibilia (fever, leukocytosis, advanced age, immunosuppression or diabetes) or suspicion of superimposed infection (adjacent abscess, air in gallbladder wall or lumen, or suspicion of perforation). All patients with acute cholecystitis taken to the operating room should receive antibiotic prophylaxis prior to skin incision. In uncomplicated cholecystitis, no further antibiotics are required after cholecystectomy. In complicated cholecystitis characterized by perforation, gangrene or empyema, duration of antimicrobial therapy may be assessed based on achievement of source control [see Duration of Therapy].

As for coverage, the empiric antibiotic regimen should be active against Enterobacteriaceae. Consideration for enterococcal coverage should be given in high-severity infections [see Modifications to Empiric Therapy]. In patients with mild-to-moderate infections, enterococcal activity is not required. Anaerobic activity is not indicated unless a biliary-enteric anastomosis is present. Of note, liver transplant recipients with ascending cholangitis are at high risk of enterococcal infection. Only patients with biliary–enteric anastomoses require anaerobic coverage, such as metronidazole.

Modifications to Empiric Therapy Against Core Pathogens: Anti-enterococcal therapy:

Enterococci may be isolated from intra-operative specimens (incidence ~20%),7 but targeted therapy is generally not necessary in mild-to-moderate community-acquired IAI. Regimens with anti-enterococcal activity have not been shown to make a difference in outcomes compared to those that lack anti-enterococcal activity.3,6,8,9

In critically ill patients with severe community-acquired and healthcare-associated IAI, positive intra-abdominal cultures for enterococci are associated with worse outcomes. Risk factors associated with enterococcal IAI include:

- Recent exposure to cephalosporins
- Failed initial treatments that lack anti-enterococcal activity
- Post-operative peritonitis
- IAI following liver transplant
Severe immunosuppression

Patients with peritonitis and valvular heart disease or prosthetic intravascular device may be at risk of infective endocarditis caused by Enterococci spp.

Patients with these risk factors may therefore require empiric regimens with anti-enterococcal activity.

Anti-Pseudomonal Therapy and Coverage Against Resistant Gram-Negative Bacilli:

Routine anti-pseudomonal coverage and/or antibiotic against resistant gram-negative bacilli is not necessary in community-acquired, mild-to-moderate IAI.

Prior exposure to antibiotics has been shown to be an influencing factor on acquiring resistant pathogens in patients with IAI. Importantly, in critically ill, haemodynamically unstable patients with severe community-acquired IAI or healthcare-associated IAI, empiric coverage against multi-drug resistant pathogens, including against P. aeruginosa, is reasonable (see also “Etiology.”) As mentioned, it is also appropriate to provide anti-pseudomonal coverage empirically to those who failed initial therapy that lacked anti-pseudomonal activity, pending culture results (see section on “De-escalation”).

Empiric antifungal therapy:

In critically ill patients, invasive candidiasis is associated with significant mortality in healthcare-associated or post-op IAI, and in immunocompromised patients.

Risk factors:

- Yeast in peritoneal fluid
- Severe IAI (APACHE score 15 or greater)
- Female
- IAI of upper GI origin
- Intra-operative cardiopulmonary failure (e.g. shock)
- Recent prior exposure to antibiotics
- Multiple colonization sites
- Recurrent perforations
Antifungal treatment with fluconazole (IV or oral) should be initiated if yeast is isolated from intraoperative specimens. Echinocandins (anidulafungin, caspofungin, micafungin) are alternatives empirically if azole-resistant Candida spp. are common within the particular institution or if the patient was already on azole therapy prior to the development of peritonitis. Although early/pre-emptive antifungal therapy has been shown to reduce risk of candidemia or invasive candidiasis, it has not been shown to impact overall mortality, and therefore remains controversial. In addition, the risk of emergence of less susceptible yeast due to fluconazole overuse should be not be overlooked.

**TARGETED**

IAIs are often polymicrobial in their etiology, and while anaerobes are important pathogens, they are often difficult to culture in the microbiology laboratory, since they would require specialized environment and handling. It is not uncommon to see “mixed growth” reported from peritoneal specimens, which likely reflect the GI tract flora, especially in community-acquired IAI. Therefore therapy should target known pathogens if available, however, spectrum of activity should be maintained against core pathogens even if only one species is isolated (unless the Gram stain and culture results both reflect a pure monomicrobial infection).

**DE-ESCALATION**

Pseudomonas aeruginosa is not normal GI tract commensal flora. However, it may be an opportunistic pathogen when there is a disruption to normal flora, e.g. in patients who had recent exposure to antibiotics or underwent bowel surgery. If modifications were made to empiric therapy to include anti-pseudomonal activity in a critically ill patient, but P. aeruginosa was not identified in peritoneal (or blood) specimens, it is reasonable to discontinue antipseudomonal coverage.

**DURATION OF THERAPY**

From an antimicrobial stewardship perspective, emergence of drug-resistant pathogens in the patient and in an institution’s antibiogram, as well as C. difficile infections are collateral damage that may be attributed to overuse of antibiotics. Evidence is increasing that prolonged antibiotic therapy is unnecessary in IAI. Rather, duration of therapy is dependent on achievement of source control:

- Uncomplicated community IAI, such as non-perforated appendicitis, only requires antibiotics for surgical prophylaxis
Perforations that were operated on within 12-24 hrs may be treated with a 24-hr course of antibiotics.

In complicated IAI and healthcare-associated IAI, duration of therapy may be 3-7d after achievement of source control, provided that patient is clinically stable with signs of clinical resolution (e.g. normalization of white blood cell count; absence of fever; return of bowel function).

In patients who do not demonstrate improvement, re-assessment for the need for source control should be made at 4-7d for ongoing infection (e.g. diagnostic imaging), rather than prolonging the course of antibiotics.

(For established candidemia, refer to “Candidemia” module.)

REFERENCES