INESSS
LE SAVOIR PREND FORME

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ANTIBIOTIC TREATMENT GUIDE

INTRA-ABDOMINAL INFECTIONS IN ADULTS

THIS OPTIMAL USAGE GUIDE IS PROVIDED FOR INFORMATION PURPOSES ONLY AND SHOULD NOT REPLACE THE JUDGMENT OF A PROFESSIONAL.
The scientific content of this guide was developed in collaboration with the Association des pharmaciens des établissements de santé du Québec (A.P.E.S.).

CONTEXT

The present guide is based on the *Canadian Practice Guidelines* developed by the Association of Medical Microbiology and Infectious Disease Canada (AMMI) and the Canadian Association of General Surgeons (CAGS), as well as on the Infectious Disease Society of America (IDSA) guidelines on the treatment of intra-abdominal infections, which were adapted to Québec's reality by a panel of experts. These guidelines rely heavily on expert opinions due to limited scientific data, especially concerning the choice of antibiotic treatment for severe infections.

Like the AMMI/CAGS and IDSA guidelines, this guide recommends initial empirical therapy that depends on the severity of the clinical presentation. Although APACHE II scores are rarely used in routine practice, AMMI/CAGS strongly recommends their use to stratify patients according to the severity of their illness. The IDSA considers that clinical judgement is as accurate as a score to assess illness severity. The latter approach was adopted in this guide.

We chose not to present a classification of infections as complicated or uncomplicated because the two guidelines consulted did not use the classification in the same manner, and because it has no impact on the choice of antibiotic treatment.

The treatments suggested here are initial empirical therapies that must be re-examined in light of the patient's clinical state and the results of microbiological analyses. **They are not intended for the treatment of gynaecological infections.**

GENERAL POINTS

- The **severity of the clinical presentation** is determined using clinical predictors of a more complex infection:
  - Severely affected general state, degree of peritoneal involvement or diffuse peritonitis, APACHE II score >15, comorbidity and degree of organic dysfunction, hypoalbuminemia, poor nutritional status, cancer, clinically significant immunosuppression, advanced age, inability to achieve adequate debridement or control of drainage, delay in the initial intervention (>24 hrs).
- Intra-abdominal infections in adults are caused by a **polymicrobial flora**.
- The **origin of the infection** informs the clinician on the suspected etiology.
  - **Community-acquired infections**
    - Usually caused by the endogenous flora.
    - Etiology: often includes enterobacteria (e.g., *E. coli, Klebsiella* spp., *Proteus* spp., *Enterobacter* spp.), anaerobic bacteria (e.g., *Bacteroides fragilis*, *Bacteroides* spp., *Clostridium* spp.) and *streptococcaceae.*
  - **Health care-associated infections**
    - The infection is often associated with a complication from emergency or non-emergency surgery.
    - Nosocomial microorganisms vary depending on the surgical intervention, the hospital and the care unit.
    - Postoperative infections are caused by more highly resistant bacteria.
    - Etiology: often includes the following microorganisms: *Pseudomonas aeruginosa*, *Enterobacter* spp., *Proteus* spp., methicillin-resistant *Staphylococcus aureus* (MRSA), *Enterococcus* spp. and *Candida* spp.

Québec

PRINCIPLES OF TREATMENT

CLASSIFY THE INFECTION DEPENDING ON:

- **The severity of the clinical presentation**
- **The origin of the infection**

INFECTIONS WITH LOW TO MODERATE SEVERITY

- **Community-acquired infection with mild to moderately severe clinical presentation**

SEVERE INFECTION

- **Health care-associated infection**
- **Community-acquired infection with severe clinical presentation**

- In the presence of an abscess, the treatment of intra-abdominal infections very often requires drainage, either surgically or with radiological assistance, a step that is essential for the treatment's success.
- Empirical antimicrobial treatment, generally administered intravenously, should be initiated without waiting for a specific infectious diagnosis. Empirical treatment reduces mortality, particularly in the presence of associated septicaemia, and should be effective against a polymicrobial flora that includes enteric Gram-negative bacilli, *streptococcaceae* and anaerobes.
- The choice of the various agents to be used in monotherapy or in combination depends on the severity of the clinical presentation and the infection's original acquisition (health care-associated or community-acquired). Other factors to be considered are allergies, recent use (three months) of a broad-spectrum antibiotic, microorganism local resistance, adverse effects and cost.
- Antibiotic therapy should be continued until the signs and symptoms disappear (e.g., absence of fever, normal leukocyte count, return of bowel function). Following optimal drainage, a 4 to 7 day treatment is usually sufficient. In certain more complex situations, several experts suggest to continue treatment up to 14 days. The experts committee recommends identifying the day of the intervention (drainage, surgery, etc.) as Day 1, even if the antibiotics regimen was started before.
- When treating health care-associated infections, it is essential to consider the local nosocomial resistance patterns. Empirical treatment must be modified according to the results of the microbiological workup.

START ORAL STEP-DOWN THERAPY after consideration of the following factors:

- Infection identified and well-controlled
- Absence of fever for at least 24 hours
- Hemodynamically stable patient
- Patient able to feed
- No clinical, radiological or surgical sign of intra-abdominal collection from non-optimal drainage

TREATMENT

ORAL STEP-DOWN ANTIBIOTIC THERAPY[1]

MONOTHERAPY

TYPE OF THERAPY	ANTIBIOTIC[2]
Penicillin	**Amoxicillin/clavulanate potassium** (Clavulin™)[3] 500 mg/125 mg PO every 8 hours
Fluoroquinolone	**Moxifloxacine** (Avelox™) 400 mg PO every 24 hours

COMBINATION REGIMEN

TYPE OF THERAPY	ANTIBIOTIC[2, 3]
Fluoroquinolone	**Ciprofloxacin** (Cipro™) 500 mg PO every 12 hours **OR** **Levofloxacin** (Levaquin™)[4] 750 mg PO every 24 hours
AND **Metronidazole**	**AND** **Metronidazole** (Flagyl™) 500 mg PO every 8 hours

1. All suggested treatments are considered equivalent; none has been proven superior.
2. Only one trademark listed, although several manufacturers can offer the drugs under different brand names. Various generic versions are also available.
3. Few published clinical studies have demonstrated the efficacy of amoxicillin/clavulanate potassium in monotherapy; however, the association with metronidazole has been documented.
4. This recommendation is based on expert consensus (IDSA), although this agent is not approved by Health Canada for the treatment of intra-abdominal infections.

INFECTIONS WITH LOW TO MODERATE SEVERITY[1]

MONOTHERAPY

TYPE OF THERAPY	ANTIBIOTIC[2]
Penicillin	**Ticarcillin/clavulanate potassium** (Timentin™) 3 g/0,1 g IV every 4 or 6 hours
Cephalosporin	**Cefoxitin** (generic for Mefoxin™) 2 g IV every 6 hours
	Addition of metronidazole may be considered to ensure an optimal coverage of the anaerobic bacteria[3].
Carbapenem	**Ertapenem** (Invanz™) 1 g IV every 24 hours
Fluoroquinolone	**Moxifloxacin** (Avelox™) 400 mg IV every 24 hours
	Addition of metronidazole may be considered to ensure an optimal coverage of the anaerobic bacteria[3].

COMBINATION REGIMEN

TYPE OF THERAPY	ANTIBIOTIC[2]
Cephalosporin **AND** **Metronidazole**	**Cefuroxime** (generic for Zinacef™) 1,5 g IV every 8 hours **OR** **Ceftriaxone** (Rocephin™) 1-2 g IV every 24 hours **OR** **Cefotaxime** (Claforan™) 1-2 g IV every 8 hours **AND** **Metronidazole** (Flagyl™) 500 mg IV every 8 hours
Fluoroquinolone **AND** **Metronidazole**	**Ciprofloxacin** (Cipro™) 400 mg IV every 12 hours **OR** **Levofloxacin** (Levaquin™)[4] 750 mg IV every 24 hours **AND** **Metronidazole** (Flagyl™) 500 mg IV every 8 hours

SEVERE OR HEALTH CARE-ASSOCIATED INFECTION[1]

MONOTHERAPY

TYPE OF THERAPY	ANTIBIOTIC[2]
Penicillin	**Pipercilline/tazobactam** (Tazocin™)[6] 4 g/0,5 g IV every 6 or 8 hours 3 g/0,375 g IV every 4 or 6 hours
Carbapenem	**Meropenem** (Merrem™) 1 g IV every 8 hours **Imipenem/cilastatin** (Primaxin™) 500 mg IV every 6 hours **Doripenem** (Doribax™) 500 mg IV every 8 hours

COMBINATION REGIMEN

TYPE OF THERAPY	ANTIBIOTIC[2, 5]
Cephalosporin **AND** **Metronidazole**	**Ceftazidime** (Fortaz™) 2 g IV every 8 hours **OR** **Cefepime** (Maxipim™) 2 g IV every 8 hours **AND** **Metronidazole** (Flagyl™) 500 mg IV every 8 hours
Fluoroquinolone **AND** **Metronidazole**	**Ciprofloxacin** (Cipro™)[7] 400 mg IV every 8 or 12 hours **AND** **Metronidazole** (Flagyl™) 500 mg IV every 8 hours
Glycylcycline **AND** **Fluoroquinolone**	**Tigecycline** (Tigacyl™)[8] 100 mg IV x 1 dose, then 50 mg IV every 12 hours **AND** **Ciprofloxacin** (Cipro™)[7] 400 mg IV every 8 or 12 hours **OR** **Levofloxacin** (Levaquin™)[4] 750 mg IV every 24 hours

1. All suggested treatments are considered equivalent; none has been proven superior.
2. Only one trademark listed, although several manufacturers can offer the drugs under different brand names. Various generic versions are also available.
3. Canadian data (study CANWARD) published recently indicate a high rate of resistance of the anaerobic bacteria of the group *B.fragilis* to cefoxitin (34,1% resistance) and to moxifloxacin (44,4% resistance).
4. This recommendation is based on expert consensus (IDSA), although this agent is not approved by Health Canada for the treatment of intra-abdominal infections.
5. In very severe clinical presentations, combination regimens including an aminoglycoside may be considered for initial treatment.
6. Preferably choose a dosage of 4 g/0.5 g IV every 6 hours or 3 g/0.375 g IV every 4 hours if *Pseudomonas aeruginosa* or other resistant microorganisms are suspected.
7. Preferably choose a dosage of 400 mg IV every 8 hours if *Pseudomonas aeruginosa* or other resistant microorganisms are suspected.
8. The committee's experts consider that combination regimens including tigecycline should be reserved for patients who are allergic to β-lactams, in whom MRSA infection is suspected or docu mented, or in patients in whom tigecycline-sensitive microorganisms that are resistant to other treatment options have been identified. This recommendation is based on the high cost of tigecycline and its very wide spectrum, on the fact that it is a bacteriostatic antibiotic, and on the manufacturer's warning concerning its use in monotherapy.

TREATMENT-SPECIFIC CONSIDERATIONS

- **Aminoglycosides:**
  - Relatively narrow therapeutic range, and associated with a higher risk of nephrotoxicity than other classes of antibiotics.
  - No longer recommended for routine treatment:
    - Should be reserved for patients who are allergic to β-lactams and fluoroquinolones.
    - In very severe clinical presentations, a combination regimen including an aminoglycoside may be considered.
- **Clindamycin** (Dalacin™)**:**
  - Should no longer be used regularly for empirical treatment due to increasing resistance rates in anaerobes.
- **Yeasts:**
  - Even if yeasts (mostly *Candida*) are isolated, antifungal therapy is rarely necessary. However, in the presence of health care-associated infections or in certain special circumstances (positive blood cultures or intra-abdominal cultures from usually sterile sites, recent chemotherapy for neoplasia, organ transplants, recurrent postoperative intra-abdominal infection), antifungal treatment should be initiated.
- **Enterococci:**
  - Enterococci coverage is not recommended for low or moderate severity community-acquired intra-abdominal infections. It should be reserved for health care-associated infections in which enterococci were found in cultures, or for certain patients in whom this pathogen is more frequently found (health care-associated postoperative infection, presence of severe immunosuppression, recurrent infection, patients who received long-term cephalosporin treatment).

PARTICULAR ANTIBIOTIC TREATMENTS

- **Antibiotic treatment for less than 24 hours** is adequate for the following conditions:
  - Traumatic bowel injuries (perforations) operated on within 12 hours
  - Contamination of the operative field by enteric contents
  - Stomach, duodenum or proximal jejunum perforations, in the absence of therapy reducing acidity or cancer
  - Acute appendicitis without evidence of perforation, abscess, or peritonitis: short-term treatment using agents active against anaerobic and aerobic bacteria is recommended
- **Acute cholecystitis:**
  - Enterobacteria coverage is recommended
  - Enterococci coverage is not necessary
  - Anaerobe coverage is recommended in the presence of anastomosis between the bile ducts and the digestive tract
- **Uncomplicated diverticulitis:**
  - Treated orally in most cases
- **Necrotizing pancreatitis:**
  - Flora similar to what is found in cases of perforation of the colon
  - TREAT ONLY IN THE PRESENCE OF A CONCOMITANT INFECTION

Complex cases must be referred to a specialist.

REFERENCES

Chow AW, Evans GA, Nathens AB, *et al.* Canadian practice guidelines for surgical intra-abdominal infections. Can J Infect Dis Med Microbiol 2010;21(1):11-37.

Solomkin JS, Mazuski JE, Bradley JS, *et al.* Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. Clin Infect Dis 2010;50(2):133-64.

This guide was developed in collaboration with professional corporations (CMQ, OPQ, ODQ), the federations (FMOQ, FMSQ) and Québec associations of pharmacists and physicians.

APES
Association des pharmaciens des établissements de santé du Québec

Institut national d'excellence en santé et en services sociaux
Québec