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

QUEBEC'S NATIONAL MEDICAL PROTOCOL

N° 888022

Initiation of diagnostic measures in the presence of symptoms and signs suggestive of a urinary tract infection (cystitis and pyelonephritis) and first-line oral pharmacological treatment for cystitis in an individual 14 years of age and older

Developed in collaboration with an advisory committee consisting of Québec clinicians and experts.

CLINICAL SITUATION OR TARGET POPULATION

An individual 14 years of age or older who has at least two of the following symptoms or signs of recent onset suggestive of cystitis:

- Burning sensation and discomfort during urination or difficulty in urinating (dysuria)
- Urgent urination (urgency)
- Frequent urination (frequency)
- Suprapubic pain or tenderness
- Hematuria (blood in the urine)

OR

An individual 14 years of age or older who has two or more of the following symptoms or signs of recent onset, suggestive of pyelonephritis:

- Fever or feverish (e.g., chills, shivering, sweating)
- Costovertebral angle (back) or flank pain
- At least one of the above symptoms or signs suggestive of cystitis

CONTRAINDICATIONS TO THE APPLICATION OF THIS PROTOCOL

Medical History:

- Anatomical or functional abnormality of the urinary tract
- Contraindication to the use of all recommended antibiotics
- Hemodialysis or chronic renal disease (e.g., kidney stone) other than severe renal failure
- Indwelling urinary catheter
- Pregnancy
- Recurrence (early relapse within 2-4 weeks or reinfection occurring more than twice per 6 months or more than 3 times per year) of cystitis or of pyelonephritis (with or without complicating factors).
- Urinary tract surgery within the last 3 months[1]

Symptomatology consistent with:

- Epididymo-orchitis
- Urinary retention (inability to empty the bladder with a feeling of bladder fullness or abdominal pain) (see related PMN)
- Gynecologic pathology (e.g., pelvic inflammatory disease, ectopic pregnancy, ruptured ovarian cyst)
- Hemodynamic instability (e.g., hypotension, tachycardia)
- Prostatitis

[1] Uncomplicated bladder catheterization and cystoscopy are not considered as urinary tract surgery.

- Suspicion of sepsis (e.g., significant tachypnea, altered state of consciousness) or significant impairment of general condition

INSTRUCTIONS

1. HEALTH STATUS ASSESSMENT

1.1 Symptoms

Check for the presence of at least two of the following new-onset symptoms suggestive of cystitis:

- Burning and discomfort with urination or difficulty in urinating (dysuria)
- Urgent urination (urgency)
- Frequent urination (frequency)
- Suprapubic tenderness
- Hematuria (blood in the urine)

In an elderly person, nonspecific (e.g., decreased general condition, recent onset or worsening of confusion) or atypical (e.g., urinary incontinence, urinary retention) manifestations may occur in the presence of urinary tract infection (UTI). Before concluding that a urinary tract infection is present based solely on these manifestations, it is important to look for the onset or persistence of symptoms and signs suggestive of a UTI and to consider another health condition (e.g., dehydration).

OR

Check for the presence of at least two of the following new-onset symptoms suggestive of pyelonephritis:

- Feverish (e.g., chills, shivering, sweating)
- Costovertebral angle (back) or flank discomfort
- At least one of the symptoms suggestive of cystitis

1.2 Health History

Check for the following that may be associated with **a contraindication to the protocol:**

- Anatomical or functional abnormality of the urinary tract
- Gynecologic pathology (e.g., pelvic inflammatory disease, ectopic pregnancy, ovarian cyst rupture)
- Hemodialysis or chronic renal disease other than severe renal failure (e.g., kidney stones)
- Hemodynamic instability (e.g., hypotension, tachycardia)
- History of urinary tract infection (treatment failure in the last 4 weeks or reinfection in the last 12 months)
- Inability to empty the bladder with a feeling of bladder fullness or abdominal discomfort (suspected urinary retention)
- Inability to take oral medication
- Pain or discomfort in the genitals, perineum, lower abdomen or lower back (consistent with prostatitis)
- Pregnancy
- Suspected sepsis (e.g., significant tachypnea, altered state of consciousness) or significant general condition impairment
- Testicular pain (suspected epididymo-orchitis)

- Urinary tract surgery in the last 3 months[2]
- Usage of a urinary catheter (indwelling catheter)

Check for the following that **may change the management OR influence treatment course OR be associated with a risk of failure to the first-line treatment**:

- Breastfeeding
- Clinical manifestations of sexually transmitted infection (STI) (see appendix 1)
- History of renal disease or comorbidity that may induce renal failure (e.g., diabetes, hypertension):
  - check for previous creatinine values
- Risk factor(s) for an STI. Consult the tool: : *ITSS à rechercher selon les facteurs de risque décelés.*
- Risk of antibiotic resistance (e.g., hospitalization within the past 3 months, long-term care accommodation, urological procedure within the past month, antibiotic use within the past 3 months, high local resistance prevalence, previously documented colonization with multidrug-resistant bacteria within the past 6 months, travel to a geographic area at high risk for antibiotic resistance[3] within the past 6 months)[4]
- Unusual vaginal discharge (e.g., vulvovaginal candidiasis, bacterial vaginosis) (see related PMN)

Check for the following associated with a **risk factor for UTI complication**:

- Immunosuppression[5] due to an underlying condition or disease, OR treatment thereof
- Male
- Non-surgical urologic procedure (e.g., uncomplicated bladder catheterization, cystoscopy) within 2-4 weeks
- Poorly controlled diabetes: HbA1c ≥ 8.5% or repeated hyperglycemia (fasting blood glucose > 10 mmol/L; postprandial blood glucose > 14 mmol/L) (based on recent laboratory tests)[6]
- Severe renal impairment: estimated glomerular filtration rate (eGFR)[7] <30 mL/min/1.73 m^2 (based on laboratory tests less than 6 months old)

1.3 Medication History

Check for:

- Contraindications to use of all recommended antibiotics:
  - if history of a beta-lactam allergy, check for reaction severity
- Recent use of an antibiotic (within the last 3 months)
- Use of medications considered immunosuppressive

[2] Uncomplicated bladder catheterization and cystoscopy are not considered urinary tract surgery.

[3] Examples of geographic areas at high risk for antibiotic resistance: Middle East, Far East, Indian subcontinent, Sub-Saharan Africa.

[4] Time periods are based primarily on experiential data. They are provided for information purposes and do not replace clinical judgment.

[5] https://msss.gouv.qc.ca/professionnels/vaccination/piq-vaccinologie-pratique/immunodepression.

[6] Laboratory tests less than 3 months old when capillary or interstitial blood glucose and HbA1c targets are not yet achieved or less than 6 months old when capillary or interstitial blood glucose and HbA1c targets are achieved.

[7] The glomerular filtration rate value measured by the laboratory can also be used.

1.4 Physical Examination

Vital signs could be measured if deemed relevant to the clinical picture (e.g., feeling feverish, confusion, general condition impairment):

- Temperature
- Blood pressure
- Heart and respiratory rate

Based on health history and vital signs, an abdominal examination[8] could be performed to look for the following signs:

- Suprapubic pain on palpation (suggestive of a urinary tract infection)
- Costovertebral angle tenderness on percussion test ("positive renal punch") (suggestive of pyelonephritis)

If there is a suspected contraindication to the protocol (e.g., epididymo-orchitis, prostatitis) or another health condition (e.g., STI) and depending on the clinical picture:

- An abdominal-pelvic examination[8] could be performed to look for the following signs:
  - bladder globe (suspected urinary retention)
  - discomfort on palpation of the lower abdomen (suspected urinary retention)
  - gynecologic pathology (e.g., pelvic inflammatory disease, ectopic pregnancy, ruptured ovarian cyst)
  - signs consistent with an STI[9]
  - unusual vaginal discharge (e.g., vulvovaginal candidiasis, bacterial vaginosis)
- If fever is present, a testicular and prostate examination[8] should be performed to look for:
  - significant pain on palpation of the prostate (suspected prostatitis)
  - unilateral progressive testicular pain, epididymal or testicular tenderness on palpation, palpable epididymal swelling, scrotal erythema or edema on the affected side (suspected epididymo-orchitis)

Physical examination is particularly important in elderly or geriatric patients, as they may have difficulty expressing their symptoms and some symptoms may be masked or absent (e.g., fever).

[8] A health professional who is not authorized to carry out this physical examination must refer the person to an authorized professional (nurses, nurse practitioner specialists or physicians).

[9] Symptoms and signs consistent with STIs are listed in appendix 1 of this protocol.

2. BIO-MEDICAL TESTS

2.1 General Information

Bio-medical tests (urinalysis[10] or urine culture[11]) may, depending on the results obtained, reduce or increase the diagnostic suspicion of a UTI. The results must be interpreted in conjunction with the clinical symptoms and signs.

Use of the urine dipstick outside the laboratory depends on the clinical judgment and skill of the individual in reading and interpreting the results. The manufacturer's recommendations for the use of urine dipsticks or the instructions provided by the testing laboratory serving the health care facility should be followed to ensure validity of the results.

- Advantages: 1) can reduce or increase suspicion of diagnosis in the presence of symptoms and signs suggestive of cystitis, 2) aids in decision-making, 3) provides a rapid result.
- Limitations: risk of false-negative (limited sensitivity) or false-positive results (e.g., in the presence of a vaginal infection or STI).

The use of a laboratory urinalysis should be preferred over a urine dipstick test when access to a medical laboratory is easy (e.g., hospitals).

When requesting a urine culture, it is advisable to request a laboratory urinalysis at the same time, even if a urine dipstick has been used previously. If a laboratory urinalysis is not available, the results of the urine dipstick should be documented in the individual's record for traceability of results and follow-up.

2.2 Urinalysis and Urine Culture

2.2.1 If acute uncomplicated cystitis[12] (WITHOUT risk factors for complications) is suspected:

- Refer to the decision algorithm in appendix 3.
- In the ABSENCE of a high risk of antibiotic resistance or a concern related to the individual's health condition (e.g., geriatric profile[13], incomplete history, unconvincing symptoms):
  - bio-medical tests are optional if there is a high pretest probability of acute uncomplicated cystitis;
  - non-laboratory urine dipstick testing (if available in the health care setting) may be used to strengthen diagnostic suspicion.
- IN THE PRESENCE of high risk of antibiotic resistance or a concern related to the individual's health condition (as described above), proceed with obtaining a urine sample to:
  - use a urinalysis (urine dipstick if available in the health care setting or laboratory urinalysis) AND
  - perform a urine culture.
- When performing a urine dipstick test in a symptomatic individual:
  - detection of leukocytes, nitrites, or both, greatly increases the likelihood of cystitis;
  - an absence of leukocytes and nitrites decreases the likelihood of cystitis. Re-evaluation or further investigation should be considered if two or more symptoms or signs suggestive of a urinary tract infection are present;
  - if blood or protein is detected with the urine dipstick, a laboratory urinalysis should be requested to further clarify the abnormality.

[10] The term "urinalysis" is used here to refer to urine dipstick, urine macroscopic examination, urine physicochemical examination, or urinalysis summary examination.

[11] Synonymous with "culture and susceptibility test".

[12] See appendix 2 for terminology.

[13] Defined as an individual who has functional decline associated with loss of independence or major neurocognitive impairment.

- If deemed appropriate based on the clinical picture (e.g., advanced age, history of renal disease, comorbidity that may induce renal failure):
    - take a blood sample and use serum creatinine measurement to assess renal function (calculation of estimated glomerular filtration rate [eGFR]) if the one in the medical record is more than a year old.

2.2.2 If complicated acute cystitis or cystitis of becoming at risk[14] (WITH risk factor(s) for complication):

- Refer to the decision algorithm in appendix 4.
- Obtain a urine sample to:
    - use a urine dipstick test (if available in the health care setting) AND
    - use a urinalysis in a laboratory AND
    - perform urine culture.
- In cases of severe renal impairment (eGFR[15] < 30 ml/min/1.73 m^2), known renal disease or in the presence of a comorbidity that may induce renal failure (e.g., diabetes or poorly controlled hypertension):
    - take a blood sample and obtain a serum creatinine measurement to assess renal function (calculation of eGFR) if the one in the medical record is more than 6 months old.

2.2.3 If pyelonephritis is suspected (with or without risk factor(s) for complications):

- Refer to the decision algorithm in appendix 5.
- Obtain a urine sample to:
    - use a urine dipstick test (if available in the health care setting) AND
    - use a urinalysis in a laboratory AND
    - perform urine culture.
- If there is severe renal impairment (eGFR[15] < 30 ml/min/1.73 m^2), known renal disease or if there is a comorbidity that may induce renal failure (e.g., diabetes or poorly controlled hypertension), take a blood sample and use a serum creatinine measurement to assess renal function (calculation of eGFR) if that which is on the medical record is more than 6 months old.
    - A complete blood count and C-reactive protein assay could be considered on the same request, based on clinical judgment (e.g., if hospital referral).
- If fever with impairment of general condition is present, and based on clinical judgment, draw blood and perform two blood cultures (if available in the care setting) AND a complete blood count AND a serum creatinine test on the same request.
    - A C-reactive protein test could be considered on the same request, based on clinical judgment.
- The protocol should be discontinued after the medical tests are performed and the investigation should be continued.

[14] See appendix 2 for terminology.
[15] The glomerular filtration rate value measured by the laboratory can also be used.

2.3 Particularities Associated with Specimens

- For all types of samples, it is important to refer to the procedures established by the laboratory responsible for the test, in order to be aware of the particularities of locally used tests (e.g., conditions to be met for collection, storage and transport).
    - In the absence of guidelines provided by the laboratory responsible for the urinalysis, refer to the Guide to urine collection, transport, storage and analysis[16].
- The urine sample should be collected before antibiotic therapy, if possible.
- Transport together the different samples to be analyzed to the laboratory (urine, blood or other) according to the established service corridor.

3. THERAPEUTIC MANAGEMENT OF FIRST-LINE TREATMENT OF CYSTITIS

3.1 Treatment Objectives

- To relieve the individual of symptoms suggestive of cystitis, to avoid complications associated with cystitis and to prevent recurrence.
- Promote appropriate antibiotic prescribing to limit complications, damage to the microbiome and the development of antibiotic resistance.

3.2 Treatment Indication

3.2.1 For treatment of acute cystitis in women (with or without risk factor(s) for complications)

- In the ABSENCE of complication risk factors, consider delaying initiation of antibiotic therapy (deferred therapy) based on:
    - presence of mild to moderate symptoms;
    - general health status;
    - ability to follow up promptly after receipt of laboratory results (if relevant);
    - the individual's agreement after a discussion of the risk-benefit ratio.
- Prescribe pharmacological treatment:
    - consult treatment options described in section 3.3 or in section 3.4 based on the absence or presence of complication risk factors;
    - if appropriate, treatment can be adjusted based on renal function (based on laboratory tests less than 6 months old);
    - additional information on proposed pharmacological treatments is presented in appendix 6 (e.g., contraindications when breastfeeding) and alternative methods of administration for dysphagia are indicated in appendix 7.

[16] Published by the Ordre professionnel des technologistes médicaux du Québec (OPTMQ) and the Ordre des chimistes du Québec (OCQ).

3.2.2 For treatment of acute cystitis in a male

- Prescribe pharmacological treatment according to the treatment options described in section 3.5.
  - if relevant, treatment can be adjusted based on renal function (based on laboratory tests less than 6 months old);
  - additional information on the proposed pharmacological treatments is presented in appendix 6 and alternative methods of administration for dysphagia are provided in appendix 7.

3.2.3 For all treatment options

- The treatments listed below are suggested as first-line empirical treatment choices in the absence of urine culture results. With the exception of beta-lactams which are listed in alphabetical order, they are listed according to their efficacy, risk of adverse effects and increasing order of cost.
- According to the principles of antibiotic governance, a minimum duration of treatment is preferred. However, depending on clinical judgment, a longer duration may be considered.
- The choice of antibiotic should ideally be based on local antimicrobial resistance (consult regional data, if available) and on the previous urine culture results (if relevant).
- If treated with a fluoroquinolone within the last 3 to 6 months (regardless of the reason for treatment), consider a different class of antibiotic if possible.
  - The use of fluoroquinolone is associated with a risk of significant adverse events (e.g., aortic aneurysm and dissection, tendinopathy, *Clostridioides difficile* diarrhea or colitis) and increased bacterial resistance.

3.3 Choice of Pharmacological Treatment for Acute Uncomplicated Cystitis in Women (without risk factor(s) for complications)

ORAL TREATMENT OF UNCOMPLICATED CYSTITIS IN WOMEN					
Antibiotics[1]	**Dosage**	**Adjustment for renal function**[2,3]		**Preferred duration** *(possible window based on clinical judgment)*	**Breastfeeding**[4]
		Creatinine clearance (ml/min) **or eGFR** (ml/min/1.73m²)	**Adjustment**		
1st Line Treatment					
Nitrofurantoin monohydrate/ macrocrystals	100 mg PO BID	≤ 40	Contraindicated[5]	**5 days**	Compatible unless contraindicated[6]
Nitrofurantoin macrocrystals alone	50 mg PO QID				
Trimethoprim-sulfamethoxazole	160/800 mg PO BID	< 30	See section 3.4[7]	**3 days**	Compatible unless contraindicated[6]
Fosfomycin (tromethamine)	3 g PO	N.A.	N.A.	**A single dose**	Compatible
Alternative treatment if contraindication to all 1st line antibiotics or according to local bacterial resistance or adjustment of antibiotic therapy after obtaining the antibiogram (when relevant)					
Beta-Lactams[8,9]					
Amoxicillin-clavulanate	875/125 mg PO BID[10]	< 30	See section 3.4[7]	**5 days** *(5 to 7 days)*	Compatible
Cefadroxil	500 mg PO BID	N.A.	N.A.		
Cefixime	400 mg PO DIE	30-40	300 mg PO DIE		
Alternative treatment if contraindication to all 1st line antibiotics and if history of severe allergic reaction to beta-lactams					
Fluoroquinolones					
Ciprofloxacin	250 mg PO BID	< 30	See section 3.4[7]	**3 days**	Compatible[11]
Ciprofloxacin XL	500 mg PO DIE				
Levofloxacin	250 mg PO DIE				

Abbreviations : BID: twice daily; DIE: once daily; N.A.: not applicable; PO: *per os*; QID : four times a day; XL : Extended release

1. Alternative methods of administration should be offered for people with dysphagia (appendix 7).
2. Benchmarks for adjustment in renal failure are not a substitute for clinical judgment. If necessary, consult a pharmacist.
3. Creatinine clearance according to the Cockroft-Gault formula and eGFR according to CKD-EPI equation adjusted according to the body surface area. Body surface area can be calculated using several formulas available on the web (e.g., Boyd, Mosteller or Dubois formula).
4. Benchmarks for breastfeeding are not a substitute for clinical judgment. If necessary, consult appendix 6, other reference works or a pharmacist.
5. Nitrofurantoin use is contraindicated in renal failure with a creatinine clearance (CrCl) ≤ 40 ml/min.
6. Contraindicated if breastfeeding an infant with G6PD deficiency (risk of hemolytic anemia).
7. Severe renal impairment is a risk factor for complications, the duration of treatment with this antibiotic should be adjusted according to the recommendations for the treatment of complicated cystitis or cystitis at risk.
8. Beta-lactams are listed in alphabetical order.
9. Although evidence is limited, cefuroxime axetil may be considered for patients with a history of allergic reaction to penicillin, depending on the severity of the reaction. In this case, the dosage is 500 mg PO BID for a duration similar to that of other beta-lactams. For more information, consult other reference works or a pharmacist.
10. The 7:1 (875/125 mg) PO BID formulation of amoxicillin-clavulanate is preferred because of its better digestive tolerance.
11. Ciprofloxacin should be preferred to levofloxacin as it has shown lower excretion in milk.

3.4 Choice of Pharmacological Treatment for Complicated Acute Cystitis or at Risk of Becoming so in Women (with risk factor(s) for complications)

ORAL TREATMENT OF COMPLICATED CYSTITIS OR AT RISK OF BECOME COMPLICATED IN WOMEN					
Antibiotics[1]	**Dosage**	**Adjustment for renal function**[2,3]		**Preferred duration** *(possible window based on clinical judgment)*	**Breastfeeding**[4]
		Creatinine clearance (ml/min) **or eGFR** (ml/min/1.73m²)	**Adjustment**		
1st Line Treatment					
Nitrofurantoin monohydrate/ macrocrystals	100 mg PO BID	≤ 40	Contraindicated[5]	**7 days** *(7 to 10 days)*	Compatible unless contraindicated[6]
Nitrofurantoin macrocrystals alone	50 mg PO QID				
Trimethoprim-sulfamethoxazole	160/800 mg PO BID	15-30	160/800 mg PO DIE or 80/400 mg PO BID	**7 days** *(7 to 10 days)*	Compatible unless contraindicated[6]
		< 15	Contraindicated[7]		
Fosfomycin (tromethamine)	3 g PO	N.A.	N.A.	**3 doses 48 hours apart**	Compatible
Alternative treatment if contraindication to all 1st line antibiotics or according to local bacterial resistance or adjustment of antibiotic therapy after obtaining the antibiogram (when relevant)					
Beta-Lactams[8,9]					
Amoxicillin-clavulanate	875/125 mg PO BID[10]	10-30	500/125 mg PO BID	**7 days** *(7 to 10 days)*	Compatible
		< 10	500/125 mg PO DIE		
Cefadroxil	500 mg PO BID	10-25	500 mg PO DIE		
		< 10	500 mg PO every 36 h[11]		
Cefixime	400 mg PO DIE	20-40	300 mg PO DIE		
		< 20	200 mg PO DIE		
Alternative treatment if contraindication to all 1st line antibiotics and if history of severe allergic reaction to beta-lactams					
Fluoroquinolones					
Ciprofloxacin	250 mg PO BID	< 30	250 mg PO DIE	**5 days** *(5 to7 days)*	Compatible[12]
Ciprofloxacin XL	500 mg PO DIE	< 30	250 mg PO DIE		
Levofloxacin	250 mg PO DIE	< 20	250 mg PO every 48 h		

Abbreviations : BID: twice daily; DIE: once daily; N.A.: not applicable; PO: *per os*; QID : four times a day; XL : Extended release

1. Alternative methods of administration should be offered for people with dysphagia (appendix 7).
2. Benchmarks for adjustment in renal failure are not a substitute for clinical judgment. If necessary, consult a pharmacist.
3. Creatinine clearance according to the Cockroft-Gault formula and eGFR according to CKD-EPI equation adjusted according to the body surface area. Body surface area can be calculated using several formulas available on the web (e.g., Boyd, Mosteller or Dubois formula).
4. Benchmarks for breastfeeding are not a substitute for clinical judgment. If necessary, consult appendix 6, other reference works or a pharmacist.
5. Nitrofurantoin use is contraindicated in renal failure with a creatinine clearance (CrCl) ≤ 40 ml/min.
6. Contraindicated if breastfeeding an infant with G6PD deficientcy (risk of hemolytic anemia).
7. The use of trimethoprim-sulfamethoxazole is contraindicated in patients with renal insufficiency with a creatinine clearance (CrCl) < 15 ml/min, in cases where renal function cannot be monitored during treatment.
8. Beta-lactams are listed in alphabetical order.
9. Although evidence is limited, cefuroxime axetil may be considered for patients with a history of allergic reaction to penicillin, depending on the severity of the reaction. In this case, the dosage is 500 mg PO BID for a duration similar to that of other beta-lactams. For more information, consult other reference works or a pharmacist.
10. The 7:1 (875/125 mg) PO BID formulation of amoxicillin-clavulanate is preferred because of its better digestive tolerance.
11. The administration of cefadroxil every 24 hours is acceptable although the recommendations recommend rather an administration every 36 hours.
12. Ciprofloxacin should be preferred to levofloxacin as it has shown lower excretion in milk.

3.5 Choice of Pharmacological Treatment for Acute Cystitis in Men (with or without other complication risk factors)

ORAL TREATMENT OF CYSTITIS IN MEN (WITH OR WITHOUT OTHER COMPLICATION RISK FACTORS)				
Antibiotics[1]	**Dosage**	**Adjustment for renal function**[2,3]		**Preferred duration** *(possible window based on clinical judgment)*
		Creatinine clearance (ml/min) **or eGFR** (ml/min/1.73m²)	**Adjustment**	
1st Line Treatment				
Trimethoprim–sulfamethoxazole	160/800 mg PO BID	15-30	160/800 mg PO DIE or 80/400 mg PO BID	**7 days** *(7 to 10 days)*
		< 15	Contraindicated[4]	
Fluoroquinolones				
Ciprofloxacin	500 mg PO BID	< 30	500 mg PO DIE or 250 mg PO BID	**7 days** *(7 to 10 days)*
Ciprofloxacin XL	1,000 mg PO DIE	< 30	500 mg PO DIE	
Levofloxacin	500 mg PO DIE	20-50	500 mg PO x 1 dose then 250 mg PO DIE	
		< 20	500 mg PO x 1 dose then 250 mg PO every 48 h	
Alternative treatment if contraindication to all 1st line antibiotics or according to local bacterial resistance or adjustment of antibiotic therapy after obtaining the antibiogram (when relevant)				
Nitrofurantoin monohydrate/ macrocrystals	100 mg PO BID	≤ 40	Contraindicated[5]	**7 days** *(7 to 10 days)*
Fosfomycin (tromethamine)	3 g PO	N.A	N.A	**3 doses spaced 48 hours to 72 hours apart**[6]
Beta-Lactams[7,8,9]				
Amoxicillin-clavulanate	875/125 mg PO BID[10]	10-30	500/125 mg PO BID	**7 days** *(7 to 10 days)*
		< 10	500/125 mg PO DIE	
Cefadroxil	500 mg PO BID	10-25	500 mg PO DIE	
		< 10	500 mg PO every 36 h[11]	
Cefixime	400 mg PO DIE	20-40	300 mg PO DIE	
		< 20	200 mg PO DIE	

Abbreviations : BID: twice daily; DIE: once daily; PO: *per os*; N.A.: not applicable; XL : Extended release

1. Alternative methods of administration should be offered for people with dysphagia (appendix 7).
2. Benchmarks for adjustment in renal failure are not a substitute for clinical judgment. If necessary, consult a pharmacist.
3. Creatinine clearance according to the Cockroft-Gault formula and eGFR according to CKD-EPI equation adjusted according to the body surface area. Body surface area can be calculated using several formulas available on the web (e.g., Boyd, Mosteller or Dubois formula).
4. The use of trimethoprim-sulfamethoxazole is contraindicated in patients with renal insufficiency with a creatinine clearance (CrCl) < 15 ml/min, in cases where renal function cannot be monitored during treatment.
5. Nitrofurantoin use is contraindicated in renal failure with a creatinine clearance (CrCl) ≤ 40 ml/min.
6. As evidence is very limited, the use of fosfomycin for the treatment of cystitis in men is based on expert opinion.
7. Beta-lactams are listed in alphabetical order.
8. If a history of an allergic reaction to penicillin antibiotics consult the decision support tool for penicillin–related allergies.
9. Although evidence is limited, cefuroxime axetil may be considered for patients with a history of allergic reaction to penicillin, depending on the severity of the reaction. In this case, the dosage is 500 mg PO BID for a duration similar to that of other beta-lactams. For more information, consult other reference works or a pharmacist.
10. The 7:1 (875/125 mg) PO BID formulation of amoxicillin-clavulanate is preferred because of its better digestive tolerance.
11. The administration of cefadroxil every 24 hours is acceptable although the recommendations recommend rather an administration every 36 hours.

4. INFORMATION TO BE PROVIDED IN THE CASE OF CYSTITIS WITH OR WITHOUT RISK FACTORS FOR COMPLICATIONS

Discuss the following with the individual:

- For pain relief, consider acetaminophen or ibuprofen unless contraindicated.

  Ibuprofen should be avoided, especially in the elderly, because of the increased risk of adverse effects (e.g., gastrointestinal bleeding, renal failure) and the risk of interactions with several drugs commonly used in geriatrics (e.g., angiotensin-converting enzyme inhibitors), as well as individuals with hypertension.

- Drink enough water (at least 1.5 L per day, unless contraindicated) to pass urine frequently.
- Consult again if symptoms and signs persist, worsen or if the individual's general condition deteriorates within 48 hours of starting antibiotics.
- For cystitis in women:
  - explain what symptoms are consistent with a urinary tract infection;
  - provide advice on behaviours and personal hygiene that may help reduce the risk of urinary tract infection (e.g., copious hydration, wiping from front to back after defecation, post-coital voiding, regular bowel movements, complete emptying of the bladder during urination);
  - remember that a pharmacy consultation is possible in case of future suspicion of cystitis[17].

These aspects should also be discussed with the caregiver or the care team for people with a decline in functional autonomy that may be accompanied by a major cognitive disorder.

5. FOLLOW-UP OF CYSTITIS WITH OR WITHOUT RISK FACTORS FOR COMPLICATION

After receipt of urine culture results:

- When empiric therapy has been initiated, verify that the bacterial strain is susceptible to the antibiotic:
  - based on clinical judgment and after a reassessment of symptoms, consider changing the antibiotic to a narrower spectrum or to promote first-line therapy.
- Document the results of medical biology tests in the file (if not automated).

Monitor for adverse effects of drug therapy:

- For individuals residing in a health care facility
- If the infrastructure of the care setting permits

Consideration for individuals on anticoagulation therapy: for individuals treated with a vitamin K antagonist (e.g., warfarin), close monitoring of the International Normalized Ratio (INR), by the professional in charge of monitoring, is recommended after the start of pharmacological treatment.

[17] In Quebec, pharmacists are authorized to prescribe an antibiotic for the treatment of cystitis in women for a 5-year period, if it has been prescribed in the past. There can be a maximum of 1 treatment per 6-month period and 2 treatments in the last 12 months.

6. SITUATIONS REQUIRING SPECIAL ATTENTION, A REASSESSMENT OR FURTHER INVESTIGATION

When assessing the health condition:

- If the scope of practice does not allow for a physical examination required to assess health condition
- Suspected pyelonephritis for therapeutic management
- Suspected STI (e.g., cervicitis or urethritis caused by *Chlamydia trachomatis* or *Neisseria gonorrhoeae*)
- Unusual vaginal discharge (e.g., vulvovaginal candidiasis, bacterial vaginosis)

After obtaining the results of the medical biology analyzes :

- Bacterial resistance to the prescribed antibiotic
- Negative urinalysis result despite the presence of recent symptoms and signs suggestive of a urinary tract infection
- Negative urine culture result when cystitis is suspected

During or after treatment:

- Intolerance to the medication
- Persistence, worsening of symptoms and signs, or deterioration in the person's general condition following the start of antibiotics
- Problem with adherence to treatment (e.g., refusal to take treatment, vomiting making oral treatment impossible)
- Rapid recurrence of symptoms (2 to 4 weeks)
- Recurrence caused by a pathogen other than *Escherichia coli*, *Klebsiella pneumoniae*, *Staphylococcus saprophyticus* or *Enterococcus* (e.g., *Pseudomonas aeruginosa*, *Proteus mirabilis*)
- Serious adverse events or drug interactions:
    - document the type of injury, severity of reaction and time to onset of symptoms (see Drug allergies: definitions and clinical manifestations)
    - if drug allergy, complete the New allergy drug reaction reporting form

REFERENCES

This protocol is based on the latest scientific data and best practice recommendations, which were enhanced with contextual information and experiential knowledge provided by Québec clinicians, experts and patients. For further details on the process used to develop this medical protocol and to consult the references, see the detailed report in support of this protocol.

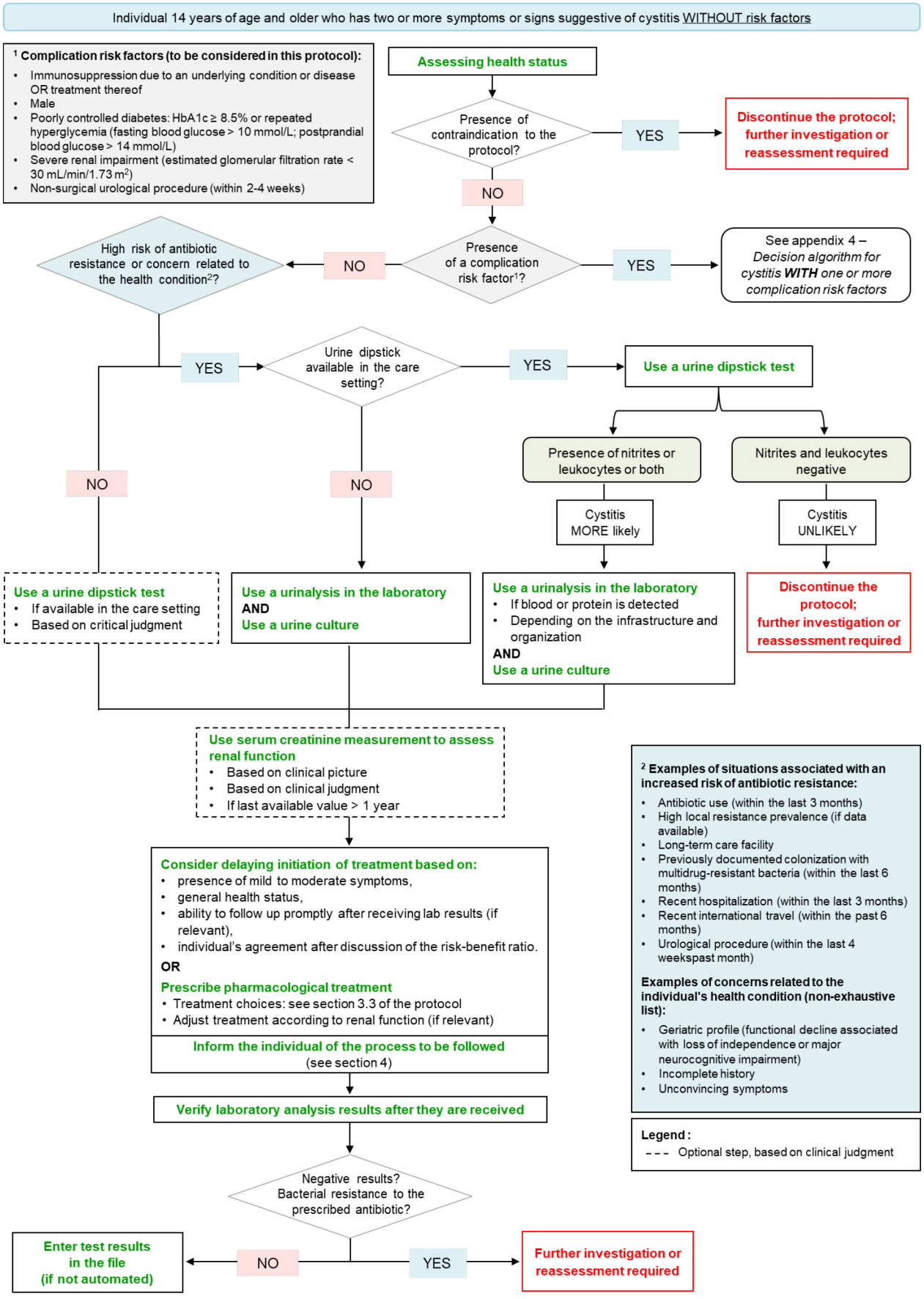
APPENDIX 1 - CLINICAL MANIFESTATIONS SUGGESTIVE OF STI(S)

SYMPTOMS AND SIGNS COMPATIBLE WITH CHLAMYDIA *TRACHOMATIS* OR *NEISSERIA GONORRHOEAE* INFECTION	
Cervicitis	▶ Mucopurulent or purulent endocervical exudate ▶ Unusual vaginal discharge ▶ Intermenstrual or postcoital vaginal bleeding
Urethritis	▶ Urinary burning ▶ Urethral discharge ▶ Urethral discomfort
Epididymitis / Epididymo-orchitis	▶ Progressive testicular pain usually unilateral ▶ Urethral discharge ▶ Erythema or edema of the scrotum on the affected side ▶ Fever ▶ Hydrocele ▶ Tenderness of the epididymis or testis on palpation ▶ Palpable swelling of the epididymis
Pelvic Inflammatory Disease	The following manifestations, whether or not associated with cervicitis, suggest pelvic inflammatory disease: ▶ Deep dyspareunia ▶ Fever ▶ Lower abdominal tenderness to one or both adnexa or to mobilization of the cervix
OTHER CAUSES OF ABNORMAL VAGINAL DISCHARGE	
Vulvovaginal Candidiasis	▶ Erythema ▶ Excoriations ▶ Cracks ▶ Edema ▶ Unusual vaginal discharge ▶ Associated symptoms (pain, superficial dyspareunia, external dysuria)
Trichomoniasis	▶ Superficial dyspareunia ▶ Dysuria ▶ Unusual vaginal discharge ▶ Hemorrhagic spots on the genital epithelium (red vascular stained cervix)
Bacterial Vaginosis	▶ Unusual vaginal discharge ▶ Malodorous vaginal discharge ▶ Absent or mild pruritus

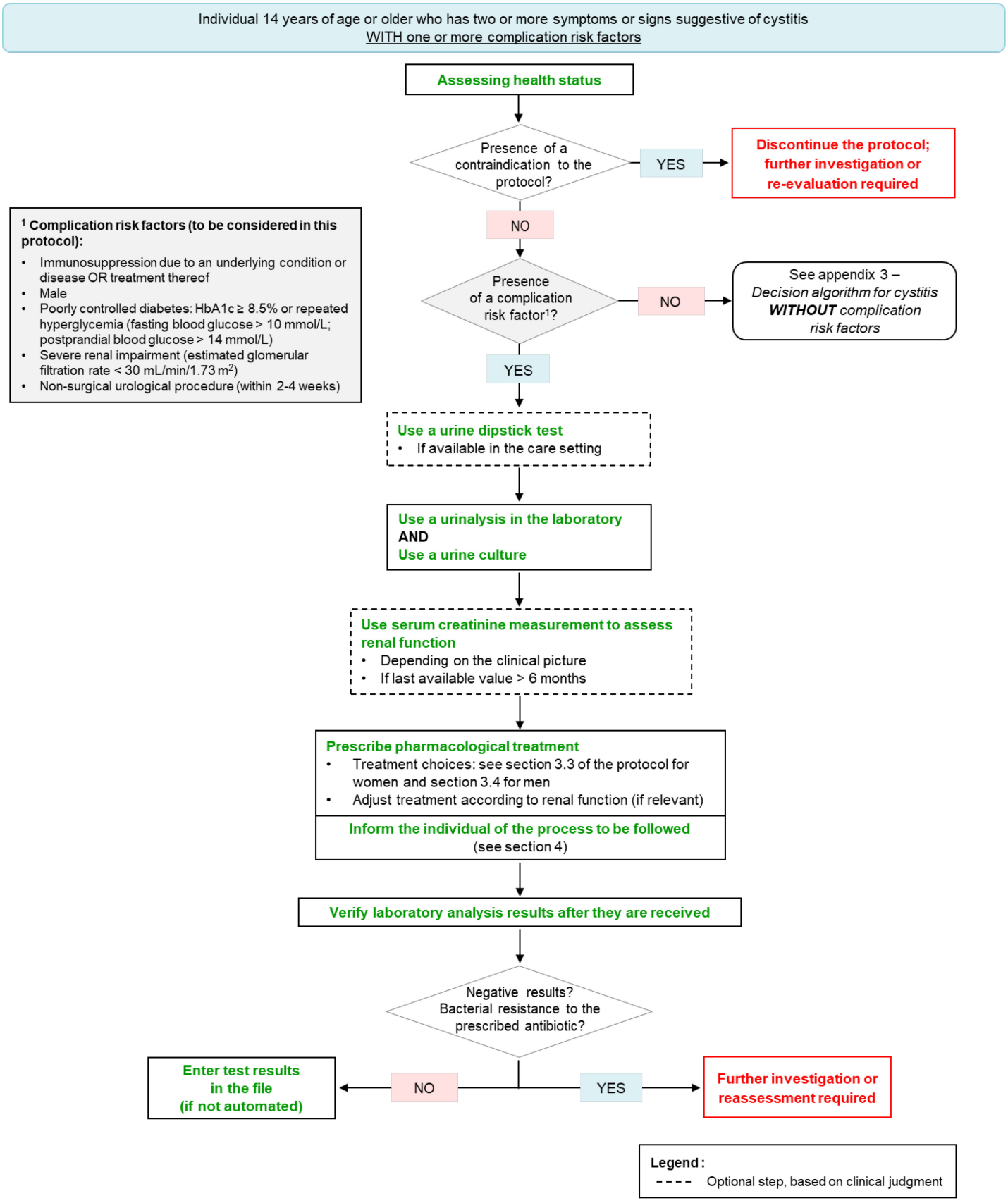
APPENDIX 2 - TERMINOLOGY

Uncomplicated urinary tract infection	Acute or recurrent urinary tract infection (cystitis or pyelonephritis) that occurs in women (or females assigned at birth) without risk factors for complications, regardless of age.
Complicated urinary tract infection or at risk of becoming so	Acute or recurrent urinary tract infection (cystitis or pyelonephritis) in a person with at least one of the following complication risk factors: ▪ anatomical or functional abnormality of the urinary tract (including a history of reconstructive surgery of the urinary system) ▪ poorly controlled diabetes ▪ male (or male gender assigned at birth) ▪ pregnancy ▪ immunosuppression ▪ urological manipulation within 2-4 weeks (e.g., uncomplicated bladder catheterization, cystoscopy) ▪ chronic renal pathology (e.g., severe or end-stage renal failure) ▪ urinary catheter use (indwelling urinary catheter) ▪ urinary tract obstruction (e.g., kidney stone)
Recurrent urinary tract infection	Urinary tract infection with episodes occurring more than twice in 6 months or more than 3 times per year. In most cases, it is a new infection of the urinary tract (reinfection). When it occurs 2 to 4 weeks after initial treatment, it may also be a persistent infection (early relapse) due to bacterial resistance, inadequate treatment, anatomical or functional abnormality of the urinary tract.

APPENDIX 3 - DECISION ALGORITHM FOR CYSTITIS WITHOUT RISK FACTORS FOR COMPLICATIONS

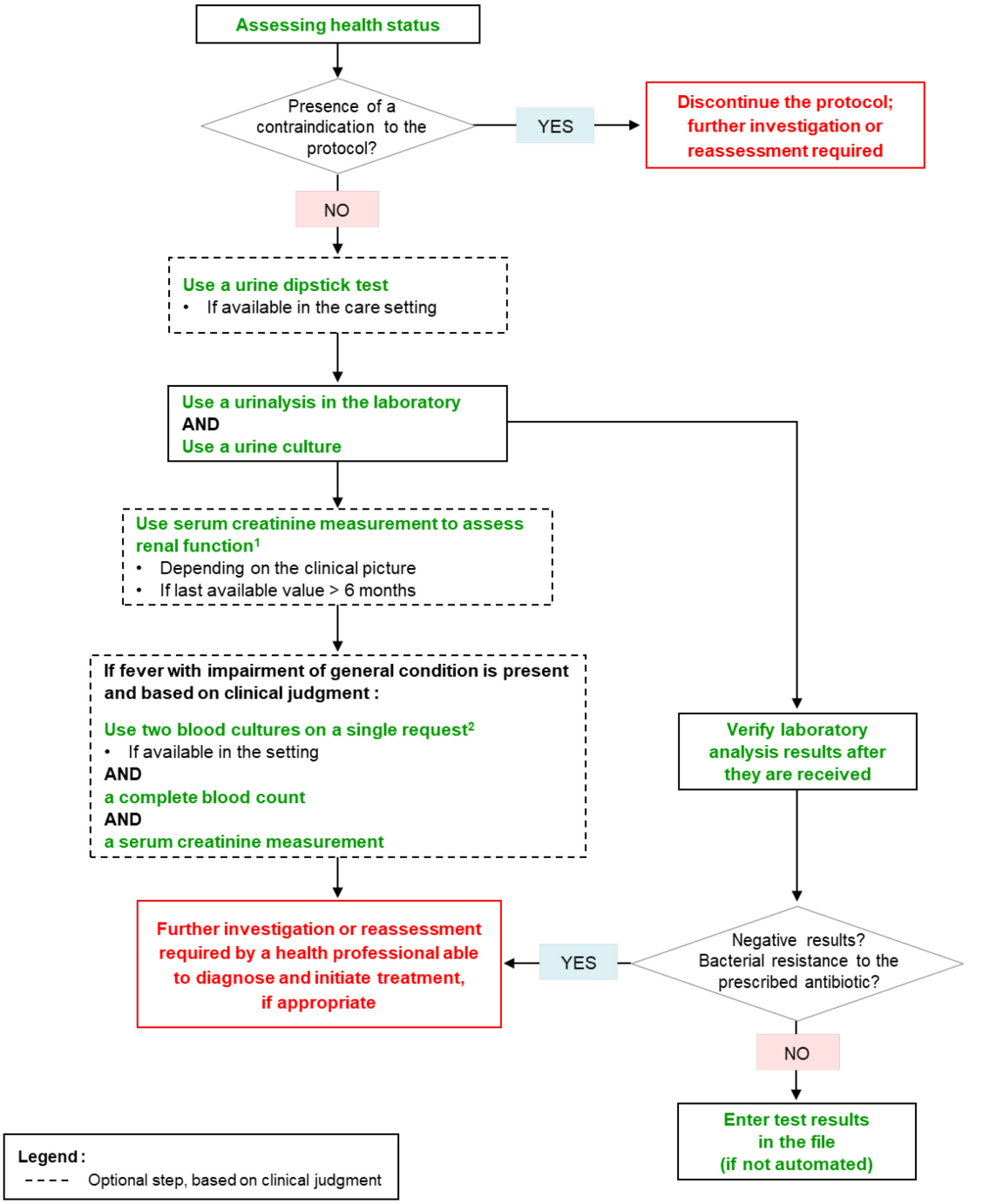


APPENDIX 4 - DECISION ALGORITHM FOR CYSTITIS WITH ONE OR MORE RISK FACTORS FOR COMPLICATION



APPENDIX 5 - DECISION ALGORITHM FOR PYELONEPHRITIS (WITH OR WITHOUT RISK FACTORS FOR COMPLICATIONS)

Individual 14 years of age or older with two or more symptoms or signs suggestive of pyelonephritis



[1] A complete blood count and C-reactive protein assay could be considered on the same request, based on clinical judgment (e.g., if hospital referral).

[2] A C-reactive protein test could be considered on the same request, based on clinical judgment.

APPENDIX 6 – ADDITIONAL INFORMATION ON PHARMACOLOGICAL TREATMENTS - CYSTITIS

The additional information on pharmacological treatments presented below is not exhaustive. These treatments contribute to modification of the microbiota and increase the risk of developing* Clostridioides difficile *infection, to varying degrees. Their overuse contributes to the expansion of antibiotic resistance.

Nitrofurantoin (monohydrate/macrocrystals or macrocrystals alone)

Contraindications:

- History of allergic reaction to Nitrofurantoin
- *Individual nursing an infant with G6PD deficiency (risk of hemolytic anemia)*
- Severe renal impairment (CIcr < 40 ml/min or clinically very high serum creatinine)
- Systemic infection

Precautions:

- Glucose-6-phosphate dehydrogenase (G6PD), erythrocyte enolase or glutathione peroxidase deficiency due to risk of hemolytic anemia.

Adverse drug reactions:

- Gastrointestinal effects: nausea, flatulence (*may be reduced if taken with food*)
- Headache
- Orange/brown coloration of urine
- Rare but serious situations, especially in the presence of renal failure:
    - Pulmonary reactions: acute or subacute pneumonitis, potentially irreversible interstitial pulmonary fibrosis
    - Peripheral neuropathy

Most significant drug interactions:

- Probenecid

Dysphagia:

- Nitrofurantoin (Macrocrystals Monohydrate): do not open capsules.
- Nitrofurantoin (macrocrystals alone): open capsule and mix its contents with food or juice for immediate administration. The tablets can be crushed.

Note: Compared to other protocols previously published by the INESSS, some information has been added in italics or deleted due to the target population of this protocol.

Fosfomycin (tromethamine)

Contraindications:

- History of allergic reaction to fosfomycin (tromethamine)

Precautions:

- Inherited disorders of fructose intolerance, glucose and galactose malabsorption or sucrase-isomaltase deficiency

Adverse drug reactions:

- Gastrointestinal: diarrhea, nausea, dyspepsia
- Headache
- Vaginitis

Most significant drug interactions:

- Domperidone, metoclopramide
- Probenecid

Note: Compared to other protocols previously published by the INESSS, some information has been added in italics or deleted due to the population targeted by this protocol.

Amoxicillin-clavulanate

Contraindications:

- History of allergic reaction to penicillin or clavulanate[18]
- Infectious mononucleosis
- Liver failure associated with amoxicillin-clavulanate

Precautions:

- Hepatic dysfunction
- Phenylketonuria

Adverse drug reactions:

- Erythematous and maculopapular rash
- Gastrointestinal effects: diarrhea, nausea, vomiting
- Urticaria

Most significant drug interactions:

- Probenecid

Dysphagia:

- Crush tablet
- Use oral suspension

[18] Rare cases of allergic reactions have been observed in infants breastfed by mothers treated with beta-lactam antibiotics. The use of amoxicillin-clavulanate is compatible with breastfeeding, except for nursing infants with a history of severe allergic reaction to beta-lactam antibiotics.

Cephalosporins
Cefadroxil and Cefixime

Contraindications:

- Cephalosporins with penicillin-like properties (e.g., cefadroxil, cephalexin): history of immediate or delayed allergic reaction to penicillin[19]

Precautions:

- History of non-severe allergic reaction to penicillin

Adverse drug reactions:

- Gastrointestinal effects: diarrhea, nausea

Most significant drug interactions:

- No significant interaction

Dysphagia:

Cefadroxil	Cefixime
▪ Open capsule and mix contents with food	▪ Crush tablet ▪ Use oral suspension

Note: Compared to other protocols previously published by the INESSS (e.g., Chlamydia and Gonorrhoeae), information has been added in italics or deleted due to the population covered by this protocol.

[19] Rare cases of allergic reactions have been observed in infants breastfed by mothers treated with beta-lactam antibiotics. The use of amoxicillin-clavulanate is compatible with breastfeeding, except for nursing infants with a history of severe allergic reaction to beta-lactam antibiotics.

Fluoroquinolones
Ciprofloxacin, Ciprofloxacin XL and Levofloxacin

Contraindications:

- History of allergic reaction to a fluoroquinolone
- *History of serious adverse reaction to quinolones (e.g., tendinopathy, peripheral neuropathy, central nervous system disorder)*

Precautions:

- *Confirmed or suspected central nervous system disorder that predisposes to seizures or may lower the seizure threshold*
- Congenital or acquired QT interval prolongation (e.g., treatment with class IA or III antiarrhythmic drugs)
- History of *Clostridioide difficile*-related disease
- History of myasthenia gravis
- Presence or risk of aneurysm and aortic dissection (e.g., elderly, hypertension, known atherosclerosis): *anyone who experiences sudden severe abdominal, chest or back pain should seek medical attention as soon as possible.*
- *Risk of tendinopathy and tendon rupture (e.g., elderly > 60 years of age or taking corticosteroids, or rheumatoid arthritis)*
- *Severe hepatic impairment*
- *Severe renal impairment (for levofloxacin inhalation solution)*
- *Visual disturbances: Anyone reporting visual disturbances during or after treatment with fluoroquinolones should seek medical attention as soon as possible, as this complication is considered a medical emergency.*

Adverse drug reactions:

- *Arthralgia*
- *Central nervous system problems: headache, dizziness, vertigo, confusion, delirium, convulsion, psychosis, hallucinations*
- Gastrointestinal: diarrhea, nausea, vomiting
- *Myalgia*
- *Peripheral neuropathy*
- *Photosensitivity*
- *Tendinopathy and tendon rupture*

Most significant drug interactions:

Ciprofloxacin, Ciprofloxacin XL and Levofloxacin	Ciprofloxacin, Ciprofloxacin XL	Levofloxacin
▪ Vitamin K antagonists (e.g., acenocoumarol, warfarin) ▪ Antacids, calcium/iron/magnesium/zinc supplements, multivitamins with minerals ▪ Drugs that prolong the QT interval (e.g., antipsychotics, amiodarone, citalopram, domperidone, halopéridol, sotalol)	▪ Sildenafil ▪ Possible increase in the effect of these drugs (metabolism inhibited by ciprofloxacin): - Tizanidine - Clozapine - Olanzapine - Clomipramine - Duloxetine - Rasagiline - Ropinirole ▪ Sevelamer	▪ Probenecid

Dysphagia:

Ciprofloxacin, Ciprofloxacin XL	Levofloxacin
▪ Do not give ciprofloxacin XL (do not cut, chew or crush) ▪ Crush the regular tablet ▪ Use the oral suspension	▪ The tablet can be crushed, but it tastes bad (do not mix with food, but rather administer with water or juice).

Note: Compared to other previously published INESSS protocols (e.g., Chlamydia and Gonorrhoeae), some information has been added in italics or deleted due to the population covered by this protocol.

Trimethoprim-Sulfamethoxazole

Contraindications:

- *Breastfeeding a G6PD-deficient infant*
- History of allergic reaction to trimethoprim-sulfamethoxazole or trimethoprim alone or sulfonamides
- Megaloblastic anemia due to folate deficiency
- Porphyria
- Severe renal impairment (creatinine clearance < 15 mL/min), in cases where renal function cannot be monitored during treatment.

Precautions:

- *Difficulty with hydration*
- Glucose-6-Phosphate Dehydrogenase (G6PD) deficiency
- Hyperkalemia
- *Potential folate deficiency (e.g., anticonvulsant medication, undernutrition, chronic alcoholism)*
- Severe hepatic impairment (child-pugh score, category C)
- *Severe myelosuppression*

Adverse drug reactions:

- *Acute renal failure*
- *Crystalluria (drink plenty of water as prevention)*
- *Electrolyte disorders (hyperkalemia, hyponatremia)*
- Gastrointestinal effects: nausea, vomiting, anorexia
- Photosensitivity
- Skin rashes and urticaria

Most significant drug interactions:

- *Angiotensin Converting Enzyme (ACE) inhibitors*
- *Angiotensin Receptor Blockers (ARBs)*
- Antiarrhythmics (e.g., procainamide, amiodarone)
- *Digoxin*
- Drugs that may cause hyperkalemia (e.g., potassium supplements, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, potassium-sparing diuretics)
- *Memantine*
- Methotrexate, azathioprine, mercaptopurine
- Phenytoin
- Sulfonylurea-type oral hypoglycemic agents (e.g., glyburide) and repaglinide
- Vitamin K antagonist (e.g., acenocoumarol, warfarin)

Dysphagia:

- Crush the tablet or use the oral suspension

Note: Compared to other previously published INESSS protocols (e.g., EAMPOC), information has been added in italics or deleted (enzalutamide, rifabutin, recombinant tocilizumab, varenicline, memantine) due to the population covered by this protocol.

APPENDIX 7 - ALTERNATIVE METHODS OF ADMINISTRATION FOR DYSPHAGIA

Antibiotics[1]	Open the capsule and mix its contents with food	Crush tablet	Use the oral suspension
Nitrofurantoin (macrocrystals alone)[2]	✓	✓	
Trimethoprim-Sulfamethoxazole		✓	✓
Amoxicillin-Clavulanate		✓	✓
Cefadroxil	✓		
Cefixime		✓	✓
Ciprofloxacin[3]		✓	✓
Levofloxacin[4]		✓	

1. Since fosfomycin (tromethamine) is available as a sachet for dilution, no alternative option is proposed for dysphagic patients.
2. Unlike nitrofurantoin in macrocrystal monohydrate form, the macrocrystal-only capsule can be opened and mixed with juice.
3. Ciprofloxacin XL tablet cannot be cut, chewed or crushed.
4. The crushed tablet may have a bad taste. Do not mix with food, but rather administer it with water or juice.