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INESSS
LE SAVOIR PREND FORME

CORTICOSTEROID AND ANTIBIOTICS

ACUTE EXACERBATION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

This optimal use guide is intended primarily for front-line clinicians. It is provided for information purposes only and should not replace the clinical judgment of the person who performs activities reserved under a statute or regulation. The recommendations were developed using a systematic process and are supported by the scientific literature and by the knowledge and experience of Québec clinicians from different specialties and areas of expertise. This tool complements Québec's national medical protocol No. 62800. For further details, go to inesss.qc.ca.

GENERAL INFORMATION

- An **acute exacerbation of chronic obstructive pulmonary disease** (AECOPD) is defined as follows:
  - An increase in respiratory and inflammatory symptoms, e.g., dyspnea and sputum, which worsen beyond the daily variations associated with the underlying chronic obstructive pulmonary disease (COPD);
  - And do so persistently (for 48 hours or longer but less than 14 days), requiring an adjustment to the inhaled treatment and possibly the addition of other treatments, depending on their severity.

ETIOLOGY

- An AECOPD can be of infectious (50-70%), environmental (10%) or undetermined (30%) origin.

Bacterial		Viral	Environmental
Main bacteria involved in AECOPD • *Haemophilus influenzae* • *Streptococcus pneumoniae* • *Moraxella catarrhalis*	If frequent exacerbations, recent hospitalization, bronchiectasis or poor pulmonary function, other bacteria may be involved • *Pseudomonas aeruginosa* • Other Gram-negative bacteria • *Staphylococcus aureus*	Main viruses involved in AECOPD • Adenoviruses • Coronaviruses (e.g., SARS-CoV-2) • Influenza viruses • Parainfluenza viruses • Rhinoviruses • Syncytial respiratory virus (RSV)	• Particles in suspension measuring ≤ 2.5 µm and ≤ 10 µm in diameter • Sulfur dioxide • Nitrogen dioxide

DIAGNOSTIC APPROACH

- The clinical diagnosis of AECOPD is based on:
  - Assessing the respiratory signs and symptoms suggestive of an AECOPD with daily variations beyond those generally associated with the underlying COPD:
    - Worsening dyspnea
    - Increased respiratory rate
    - New or worsening cough
    - Change in sputum (colour, consistency or quantity)
  - Checking adherence to the maintenance therapies and if the patient is using their inhalation devices properly
  - Assessing all the factors that might be associated with an acute exacerbation, e.g., exposure to aggravating factors, allergens or respiratory viruses

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DIAGNOSTIC APPROACH (CONT'D)

- Ruling out other medical conditions and determining the etiology of the AECOPD
  - If another disease is suspected, e.g., pneumonia, COVID-19, influenza, pneumothorax, pleural effusion, pulmonary embolism, pulmonary edema, cardiac arrhythmia or heart failure, consider a chest X-ray and other tests and exams (e.g., angiogram or echocardiogram), as per the facility's current recommendations.
  - Identifying the infectious agent may prove useful in certain situations and contexts, particularly in the case of hospitalization or repeated respiratory infections.
- The documented AECOPD episodes in the past year and any hospitalizations
  - Frequent AECOPD lead to a more rapid deterioration in lung function and a poor prognosis.
  - A review of the number of exacerbations in the past year is used to determine the exacerbation risk, which, in turn, is used to adjust the pharmacological treatment of the COPD and to determine the risk of therapeutic failure or of complications, in the case of a presumed bacterial AECOPD.
- Determining the severity of the AECOPD

BENCHMARKS WHEN AN INFECTIOUS ETIOLOGY IS SUSPECTED

An AECOPD **is presumed to be bacterial** if there is a change in the sputum (purulence)
AND at least one of the following two criteria applies:

- Increased dyspnea OR
- Increased quantity of sputum

(!) There is **generally no fever during a bacterial AECOPD**. A fever indicates the possibility of another condition, such as a viral AECOPD or pneumonia.

Bacterial etiology- sputum culture	In a hospital setting, a sputum culture is generally useful in the following situations: • Recurrent acute exacerbations • A suspected antibiotic-resistant bacterium • The need for hospitalization
Viral vs. bacterial etiology	During the flu, RSV and SARS-CoV-2 seasons, **tests for respiratory viruses** may be useful in a hospital setting for distinguishing a viral etiology from a bacterial one. The judicious use recommendations in this context or those for special populations should be followed. In certain settings or in certain clinical cases, even if the patient tests positive for a virus, the clinician cannot rule out a bacterial infection. An increase in certain acute-phase biomarkers, such as procalcitonin (PCT), can help determine whether an infection is bacterial or viral in origin, even if the level of scientific evidence in the context of AECOPD is still low. Thus, in a hospital setting, particularly in the emergency department, the decision to use PCT should be made jointly with a medical specialist and be based on its clinical appropriateness, the availability of the test, the local recommendations, and the pros and cons of not offering an antibiotic or of stopping one, if applicable, depending on the clinical picture. *PCT cutoff values should not be considered when deciding to start or stop an antibiotic in the case of a severe AECOPD requiring intensive care.*

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SEVERITY OF THE AECOPD	
SEVERITY	**Clinical signs and symptoms** (the cutoff values shown here are not a substitute for clinical judgment)
MILD	• Dyspnea slightly worse than usual • Increased respiratory rate (< 24 breaths/minute) • Increased heart rate (< 95 bpm) • Oxygen saturation ≥ 92% AND variation ≤ 3% (when known)
MODERATE	• Dyspnea moderately to significantly worse than usual • Accelerated respiratory rate (≥ 24 breaths/minute) • Accelerated heart rate (≥ 95 bpm) • Oxygen saturation < 92% AND/OR variation > 3% (when known)
SEVERE	• Increased dyspnea, respiratory rate and heart rate, and decreased oxygen saturation, as defined for a moderate exacerbation, AND - Hypercapnia ($PaCO_2$ > 45 mm Hg) with acidosis (pH < 7.35) OR - Condition requires hospitalization

BACK TO DIAGNOSTIC APPROACH

TREATMENT PRINCIPLES

- The therapeutic objectives are:
  - To maintain a preventive approach by ensuring that the COPD maintenance therapy is optimized to prevent subsequent or recurrent AECOPD.
  - To relieve symptoms and prevent complications, e.g., respiratory failure or hospitalization, etc.
  - To promote appropriate antibiotic prescribing, based on the principles of antibiotic stewardship, if a presumed bacterial AECOPD is suspected, e.g., administering the right antibiotic at the right dose and opting for the shortest duration in order to limit complications, damage to the microbiome, and the development of antibiotic resistance.
- The following are part of the basic treatment of any AECOPD:
  - Optimization of the dose or frequency of use of the short-acting β2-agonist (SABA) bronchodilator, regardless of the severity or etiology of the AECOPD.
  - Maintaining or optimizing the long-acting inhalers and the inhaled corticosteroid according to the COPD treatment recommendations.
- Unless contraindicated, prednisone is administered during a moderate or severe exacerbation, regardless of its etiology.
- Antibiotic therapy is used only when a moderate or severe AECOPD is presumed to be bacterial:
  - Ideally, the choice of antibiotic should be based on local antimicrobial resistance data, if available, and on recent previous results obtained in the patient.

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DRUG	ACTION	
Bronchodilator (short-acting β_2 agonists with or without an anticholinergic)	▸ Increase the dose or the frequency of use	
Methylxanthines	▸ Use not recommended	
Systemic corticosteroid (prednisone)	▸ Initiate when the patient is referred to a hospital or during a moderate or severe exacerbation *Its use can improve pulmonary function and oxygenation and reduce the duration of the exacerbation and hospital stay.*	
Antimicrobials	**Antivirals**	▸ In the case of a presumed viral AECOPD (e.g., influenza or SARS-CoV-2), consider, in accordance with the optimal use recommendations, early treatment of these infections to limit complications, based on the patient's vaccination status, the multiple risk factors, and the severity of the exacerbation
	Antibiotics	▸ Initiate if moderate or severe presumed bacterial AECOPD

CONDITIONS OF USE

PREDNISONE		
Population	**Posology**	**Duration**
No special circumstances	50 mg PO QD	5 days
In one of the following special situations: • Frail or underweight person • Polypharmacy (e.g., ≥ 5 medications) • History of delirium (e.g., caused by corticosteroid use or polypharmacy) • Concurrent psychiatric illness • Poorly controlled diabetes	25 mg PO QD	5 days

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IN CASES OF A HISTORY OF ALLERGIC REACTION (IMMEDIATE OR DELAYED) TO A *PENICILLIN*:

- Verify whether the allergy has been confirmed by an allergist; if not, assess the following:
  - the risk of a true allergy to the concerned *penicillin* (rare), the type of reaction, its severity, and the time since the reaction; and
  - the risk of a reaction of similar or more important severity upon re-exposure, or exposure to another beta-lactam.

ⓘ Refer to the algorithm (Appendix A) or the comprehensive tool on Presumed *penicillin* allergies as a benchmark for choosing the optimal therapeutic course of action.

⚠ If a drug provocation test is being considered, ensure that the necessary logistical arrangements (e.g., scheduling, access to injectable epinephrine) are in place so the test can be completed before prescribing.

FIRST-LINE ANTIBIOTIC THERAPY FOR A MODERATE OR SEVERE PRESUMED BACTERIAL AECOPD

⚠ It is important to switch to another class of antibiotics[1] between episodes of presumed bacterial AECOPD.

Risk of therapeutic failure or of complications	Antibiotic[2] and dosage	Preferred duration (possible window, depending on judgment)
LOW • < 2 episodes a year and none requiring hospitalization **AND** • FEV_1 >50% **AND** • Comorbidity with limited risk **AND** • Patient in ambulatory setting	**Amoxicillin**[3] ⇢ 1000 mg PO TID[8] **OR** **Azithromycin**[4] ⇢ 500 mg PO QD on 1st day, then 250 mg PO QD on days 2 to 5 **OR** **Clarithromycin** ⇢ 500 mg PO BID[5] **OR** **Clarithromycin XL** ⇢ 1000 mg PO QD[5] **OR** **Doxycycline** ⇢ 100 mg BID **OR** **Trimethoprim-sulfamethoxazole** ⇢ 160/800 mg PO BID[5]	**5 days** (5 to 7 days)
	Other options ⚠ The 2nd-generation cephalosporines carry a higher risk of *Clostridioides difficile* diarrhea/colitis	
	Cefuroxime axetil[3] ⇢ 500 mg PO BID[5] OR **Cefprozil**[3,6] ⇢ 500 mg PO BID[5]	
HIGH • ≥ 2 episodes a year, including one in the past 6 months (≥ 4 episodes a year = greater likelihood of P. aeruginosa) or ≥ 1 episode that required hospitalization **OR** • Established major comorbidity • FEV1 < 50% **OR** • Hypoxemia or hypercapnia **OR** • Antibiotic resistance to 1st-line treatment **OR** • Patient hospitalized or desaturated	**Amoxicillin-clavulanate**[3,7] ⇢ 875/125 mg PO BID[5] **OR** If *P. aeruginosa* is suspected: **Levofloxacin**[8,9] ⇢ 750 mg PO QD[5] ⚠ These antibiotics carry a higher risk of *Clostridioides difficile* diarrhea/colitis	**5 days** (5 to 7 days)

1. The classes concerned are the cephalosporines, macrolides, penicillins, quinolones, sulfonamides and tetracyclines (AHFS classification).
2. The antibiotics are listed alphabetically by generic name.
3. If the patient has a history of allergic reaction to *penicillins* and no other 1st-line antibiotic can be prescribed, refer to the decision algorithm.
4. Vanderkooi et al. found a significantly lower risk of macrolide resistance emergence with the use of clarithromycin than with the use of azithromycin.
5. Requires an adjustment in the presence of renal impairment. For further information, consult Québec's national medical protocol No. 628007, other reference works or a pharmacist.
6. Cefprozil is not approved by Health Canada for the treatment of AECOPD. It is, however, commonly prescribed for this purpose and is considered by the experts to be a valid treatment option. Also, it has this indication in the United States.
7. The 7:1 formulation of amoxicillin-clavulanate (875/125 mg) PO BID is preferred because of its better gastrointestinal tolerance.
8. If the bacterium *P. aeruginosa* is found, use ciprofloxacin (750 mg PO BID; 7-10 days) to treat a high-risk AECOPD.
9. Moxifloxacin could also be used to treat a high-risk AECOPD, but it has broader anaerobic coverage than the other fluoroquinolones in the same class.

SECOND-LINE ANTIBIOTIC THERAPY FOR A MODERATE OR SEVERE PRESUMED BACTERIAL AECOPD

(!) It is important to switch to another class of antibiotics[1] between episodes of presumed bacterial AECOPD.

Risk of therapeutic failure or of complications	Antibiotic[2] and dosage	Preferred duration (possible window, depending on judgment)
LOW • < 2 episodes a year and none requiring hospitalization **AND** • FEV1 >50% **AND** • Comorbidity with limited risk **AND** • Patient in ambulatory setting	**Amoxicillin-clavulanate**[3,7] ⇢ 875/125 mg PO BID[4] **OR** IF *P. aeruginosa* is suspected: **Levofloxacin**[5,6] ⇢ 750 mg PO QD[4] (!) These antibiotics carry a higher risk of *Clostridioides difficile* diarrhea/colitis	**5 days** (5 to 7 days)t
HIGH • ≥ 2 episodes a year, including one in the past 6 months (≥ 4 episodes a year = greater likelihood of *P. aeruginosa*) or • ≥ 1 episode that required hospitalization **OR** • Comorbidity with potential risk • FEV1 < 50% **OR** • Hypoxemia or hypercapnia **OR** • Antibiotic resistance to 1st-line treatment **OR** • Patient hospitalized or desaturated	Do a medical reassessment, look for the pathogenic agent[5,6] and consult a specialist, if necessary.	

1. The classes concerned are the cephalosporines, macrolides, *penicillins*, quinolones, sulfonamides and tetracyclines (AHFS classification).
2. The antibiotics are listed alphabetically by generic name.
3. The 7:1 formulation of amoxicillin-clavulanate (875/125 mg) PO BID is preferred because of its better gastrointestinal tolerance.
4. Requires an adjustment in the presence of renal impairment. For further information, consult Québec's national medical protocol No. 628007, other reference works or a pharmacist.
5. If the bacterium *P. aeruginosa* is found, use ciprofloxacin (750 mg PO BID; 7-10 days) to treat a high-risk AECOPD.
6. Moxifloxacin could also be used to treat a high-risk AECOPD, but it has broader anaerobic coverage than the other fluoroquinolones in the same class.
7. If the person has a history of allergic reaction to *penicillins*, refer to the decision algorithm.

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FOLLOW-UP

- If the symptoms are worse 48 to 72 hours after the start of treatment, consider a medical reassessment.
  - The decision to refer a patient to a hospital is based on a number of factors, such as their overall health, oxygen satu-ration, dyspnea, autonomy, and help available at home.
- Remind the patient to continue with their COPD maintenance therapy and usual medical follow-up.
- Check the patient's inhalation technique and assess their tolerance of and satisfaction with the COPD treatment during stable periods.
- Remind the patient that the symptoms of an exacerbation can last for 7 to 10 days and sometimes longer, but that a deterioration is not normal.
- A diagnostic process concerning COPD should be initiated after an acute-exacerbation episode if there is no such diagnosis in the chart, despite adequate treatment. In such case, the patient should be advised to consult a health professional who can make a diagnosis, this during a stable period.
- If an allergic reaction occurs following the administration of an antibiotic, the standardized form for reporting a new drug allergy reaction (AH-707DT-9308) should be completed. If applicable, discontinue the antibiotic, initiate treatment for the reaction as needed, notify the person, update the medical record and assess the need for an allergology consultation.

PATIENT EDUCATION

With a view to self-management

- Encourage the person to:
  - Begin a smoking cessation process, if applicable, and provide resources
  - Avoid exposure to irritants whenever possible (e.g., smoke, biomass), extreme temperatures, and outdoor pollution (e.g., wildfire smoke);
  - Get vaccinated to prevent respiratory infections (influenza, pneumococcal disease, SARS-CoV-2 , respiratory syncytial virus)
  - Adopt healthy life habits (physical activity, diet, alcohol consumption)
  - Learn about the disease and seek answers to any questions related to COPD.
- Discuss vaccination with the person to prevent respiratory infections (e.g., pneumococcal disease, influenza, SARS-CoV-2, respiratory syncytial virus).
- Inform the person about pulmonary rehabilitation programs specifically designed for individuals with COPD.
- Educate the person and aim for changes in day-to-day behaviour so that they can:
  - Demonstrate correct use of inhalation devices and adherence to dosage
  - Improve the self-management of their symptoms – breathing and energy-conserving techniques, stress management strategies, and recognizing aggravating factors for acute exacerbations
  - Recognize a worsening of their health (acute exacerbation), have and understand their action plan and make the right decisions to reduce complications.
- Inform the person that returning empty or unused inhalation devices to the pharmacy, for recycling or responsible disposal, helps reduce their environmental impact.

CONSULTATION WITH SPECIALIST

- For a patient with an AECOPD, consider a consultation with a respirologist or an experienced colleague if:
  - The patient has had more than three AECOPD in the past year
  - It would be appropriate to initiate or reassess an antibiotic prophylaxis.
- If in doubt about the veracity or severity of an allergic reaction to a prescribed antibiotic, or a suspected allergy to beta-lactam antibiotics, obtain advice via the conseil numérique (in French). Allergy consultation criteria are available in the INESSS Presumed *penicillin* allergies tool.

REFERENCES

For references, see the report associated with this tool and Quebec's national medical protocol No. 628007, and the Allergie présumée aux *pénicillines* report.

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APPENDIX A – ALGORITHM IN CASE OF PRESUMED *PENICILLIN* ALLERGIES

INDIVIDUAL REPORTING AN ALLERGY TO A *PENICILLIN*[1]

Pregnancy[2] → management equivalent to that of the general population

EVALUATION[4]

Confirmed allergy by an allergologist?

YES → **FOLLOW THE ALLERGOLOGIST RECOMMENDATIONS**
- ✓ A reassessment may be necessary, especially if tested more than 5 years ago.

NO/UNCERTAIN[3]

Clinical picture non suggestive of an allergy?
- Reexposure to same antibiotic without reaction;
- Isolated gastrointestinal symptoms, headache, fatigue, chills, exacerbation of fever;
- Family history of allergy to a *penicillin*.

YES → **ABSENCE OF ALLERGY**
- ✓ Prescribe any beta-lactam WITHOUT special precaution.
- ✓ Remove the allergy label from the file.

NO/UNCERTAIN[3]

Type of allergic reaction
Did the presumed allergic reaction:
- appear **IN LESS THAN AN HOUR** following the administration of the **FIRST DOSE** of a *penicillin* treatment **AND**
- disappear **IN LESS THAN A DAY**?

YES → **IMMEDIATE-TYPE ALLERGIC REACTION**

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NO/UNCERTAIN[3]

POSSIBLE DELAYED-TYPE ALLERGIC REACTION
(including certain cases of urticaria or angioedema)[4]

Some clinical presentations may occur in a para-infectious context and be confused with a drug allergy[4].

Presence of severity criteria?

YES → **VERY SEVERE** cutaneous reaction

AGEP, DRESS, SJS/TEN

YES

NO/INCERTAIN → **NON SEVERE cutaneous reaction**
- Isolated
- With or without pruritus
- Without desquamation
- Appeared during or after end of treatment AND
- Disappeared in less than 7 days

e.g., maculopapular rash or serum sickness like reaction[6]

NO/INCERTAIN → **SEVERE cutaneous reaction lasting 7 days or more, AND:**
- affecting a significant portion of the body surface area;
- that may have caused desquamation, blisters, vesicles, or pustules (especially in adults);
- without systemic involvement (e.g., fever or organ involvement);
- not corresponding to urticaria or angioedema[4].

CONDITIONS FOR ADMINISTRATION

LOW RISK

Of recurrence of a **NON SEVERE** reaction to a ***penicillin***.
In this case, prescribe:

WITHOUT precaution
- Amoxicillin ± Clavulanate[7]

Consultation not necessary. Reexposure[8] to be favored.

MODERATE RISK

Of recurrence of a **SEVERE** reaction to a ***penicillin***.
In this case, prescribe:

ONLY IF NECESSARY[11]
- Amoxicillin ± Clavulanate[7]
  → Close monitoring for possible recurrence[12].

Consultation beneficial, but reexposure[8] **also acceptable.**

HIGH RISK

Of recurrence of a **VERY SEVERE** reaction to a ***penicillin***.
In this case, prescribe:

AVOID
- Amoxicillin ± Clavulanate
- Cefprozil

Consultation highly recommended.

WITH precautions[7]
- Cefuroxime axetil → Close monitoring for possible recurrence[8,12].

WITHOUT precaution: Cefuroxime axetil[9] or Cefprozil[9,10]

Alternative OPTIONS[13] – *If there is refusal or issues with close monitoring*
- Levoflaxacin[14,15]

Allergology consultation

AGEP: Acute Generalized Exanthematous Pustulosis
DRESS: Drug Reaction with Eosinophilia and Systemic Symptoms
SJS: Stevens-Johnson Syndrome
TEN: Toxic Epidermal Necrolysis

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⚠ Use only after determining the type of allergic reaction during the assessment (see previous page).

REPORTED IMMEDIATE-TYPE ALLERGIC REACTION
Pregnancy[2] → management equivalent to that of the general population

*Reaction appeared in **LESS THAN AN HOUR** following the administration of the **FIRST DOSE** of a penicillin treatment **AND** disappeared in **LESS THAN A DAY** (less than 24 h).*

EVALUATION[5]

Presence of severity criteria?

YES → Anaphylactic shock WITH intubation OR cardiac arrest?

NO/UNCERTAIN[3]

NON SEVERE cutaneous reaction
- Isolated
- With or without pruritus
- With redness
- Limited to a single part of the body **OR** generalized

e.g., urticaria

When did the presumed allergic reaction occur?[16]

- More than 5 years ago **OR** during childhood (12 years old or younger)
- 5 years ago or less **AND** after the age of 12

NO/UNCERTAIN[3] / YES

Skin rash with diffuse pruritic redness associated WITH at least one of the following symptoms:
- angioedema
- hypotension, loss of consciousness
- respiratory distress
- cardiovascular symptoms
- severe gastrointestinal symptoms[17]

e.g., anaphylaxis **WITHOUT** shock nor intubation

CONDITIONS FOR ADMINISTRATION

LOW RISK

Of recurrence of a **NON SEVERE** reaction to a ***penicillin***.
In this case, prescribe:

WITH precautions
- Amoxicillin ± Clavulanate[7] → provocation test[18] in **1 step** + observation period of 60 min[19].

Consultation not necessary. Reexposure to be favored.

WITHOUT precaution:
- Cefuroxime axetil[9] or Cefprozil[9,10]

MODERATE RISK

Of recurrence of a **NON SEVERE** reaction to a ***penicillin***.
In this case, prescribe:

WITH precautions
- Amoxicillin ± Clavulanate[7] → provocation test[18] in **2 steps** + observation period of 60 min.

Consultation beneficial, but reexposure also acceptable.

WITHOUT precaution:
- Cefuroxime axetil[9] or Cefprozil[9,10]

MODERATE RISK

Of recurrence of a **SEVERE** reaction to a ***penicillin***.
In this case, prescribe:

⚠ ONLY IF NECESSARY[11]
- Amoxicillin ± Clavulanate[7] → provocation test in **3 steps**[18,20] + observation period of 60 min or desensitization if complex health issues.

AVOID
- Cefprozil

Consultation generally recommended.

WITHOUT precaution:
- Cefuroxime axetil[9]

HIGH RISK

Of recurrence of a **VERY SEVERE** reaction to a ***penicillin***.
In this case, prescribe:

AVOID
- Amoxicillin ± Clavulanate or Cefprozil

Consultation highly recommended.

WITH precautions
- Cefuroxime axetil[9] → provocation test[18] in **2 steps** + observation period of 60 min.

Alternative OPTIONS[13] – *If there is refusal or issues with drug provocation test*
-Levoflaxacin[14,15]

1. Person without major neurocognitive disorder.
2. The drug provocation test can be performed at any time during pregnancy if indicated, ideally during the second trimester.
3. If the description is vague, the reaction was probably not severe.
4. Urticaria or angioedema lasting more than 24 hours are rarely allergic, but often para-infectious.
5. Vigilance: repeated reaction to same *penicillin* or history of SEVERE rash while taking amoxicillin in the context of mononucleosis: increase the probability of a true allergy.
6. Serum sickness like reaction: rather rare following *penicillin* treatment. Often of a para-infectious nature.
7. Amoxicillin-clavulanate is indicated if the patient with AECOPD is at high risk of therapeutic failure or complications.
8. Possible provocation test: 1/10 or full dose, with observation for 48 to 72 hours, in the clinic or at home.
9. Alternative options if the patient refuses or if a drug provocation test is not possible, and only if there is a LOW risk of therapeutic failure or complications.
10. Not approved by Health Canada for AECOPD, but commonly prescribed and considered valid by experts; approved for this indication in the United States.
11. To be used only when clinically justified or deemed essential, based on clinical judgment and the preferences of the individual concerned.
12. It is important that the person is aware of the risk of recurrence and that they can stop taking the antibiotic if symptoms appear.
13. According to the individual's characteristics and the specifics of the infection.
14. May be used if there is a high risk of therapeutic failure or complications.
15. Ciprofloxacin may be considered in high-risk AECOPD and if *P. aeruginosa* is present. Moxifloxacin is also an option, but it has broader anaerobic coverage.
16. Reactions occurring long ago are less likely to reflect persistent allergy or risk of recurrence.
17. Severe abdominal pain, repeated vomiting, sudden and profuse diarrhea: often expected adverse effects, rare and atypical in cases of *penicillin* anaphylaxis.
18. Provocation tests should be performed where epinephrine intramuscular (IM) injection is available.
19. Monitoring duration may differ according to institutional protocols and clinical judgment.
20. Drug provocation test ideally in 3 steps, may be adapt to 2 steps depending on the context, clinical judgment, and individual risk of the patient.

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