

THIS OPTIMAL USAGE GUIDE IS PROVIDED FOR INFORMATION PURPOSES ONLY AND SHOULD NOT REPLACE THE JUDGMENT OF A PROFESSIONAL.

This information sheet is intended for health professionals involved in primary care services. It was developed as a guide for antibiotics prescription in ambulatory and long-term care settings, where treatment is usually empirically based. The information presented here refers to the clinical guides on antibiotic treatment (inesss.qc.ca), which take bacterial resistance into account.

CONTEXT

Some bacteria have developed means to resist the effects of antibiotics, through mechanisms such as the production of enzymes that inactivate antibiotics or the modification of their cell wall structure, making the pathogen “impervious” to the antibiotic.

The increase in antibiotics resistance witnessed over the last decades is worrisome. The widespread and non-optimal use of antibiotics has promoted the emergence of bacterial resistance and has contributed to the global increase of infection-related mortality. Administering antibiotics to animals (veterinary medicine or agriculture) further contributes to the problem. The link between antibiotics use and the emergence of bacterial resistance has been clearly established. Furthermore, several factors contribute to resistance propagation, including inadequate hygiene practices, the proximity of hospitalized patients, international travel, etc.

Since individual antibiotics prescriptions can have a direct collective impact, it is important that health care professionals consider this aspect of public health when writing a prescription. It is a concrete way to help in the fight against bacterial resistance.

DEFINITIONS AND CLINICAL IMPLICATIONS

Bacteria develop resistance through either genetic mutation or the acquisition of genetic material. The use of antibiotics promotes the emergence of resistance by eliminating sensitive bacteria and contributing to the selection of resistant bacteria. This phenomenon is called “selective pressure.”

MAIN RESISTANCE MECHANISMS

Enzyme inhibition (e.g., *Staphylococcus aureus*)
Production of an enzyme that inactivates or destroys the antibiotic

Examples:

β-lactams (●)

β-lactamases can break down penicillins and cephalosporins, inactivating them.

Aminoglycosides

Three enzymes have the capacity to inhibit these antibiotics.

Alteration of the antibiotic target site (e.g., *Staphylococcus aureus* and *Streptococcus pneumoniae*)

Modification of the site of action on the cellular membrane or in the cytosol, leading to decreased affinity for the antibiotic (●).

Examples:

Penicillin

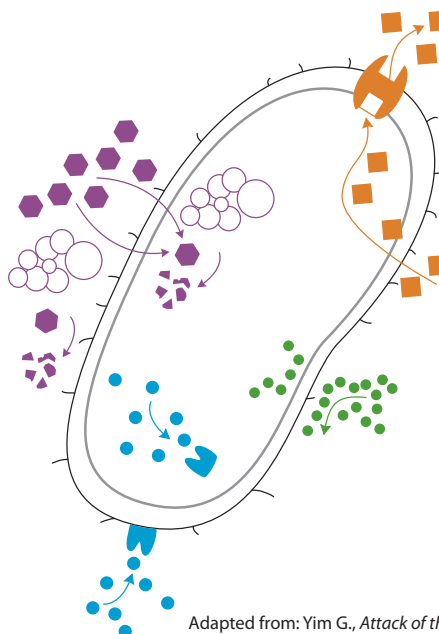
The alteration of penicillin-binding proteins (PBP) decreases the affinity for the antibiotic.

Fluoroquinolones

The spontaneous mutation of only one DNA gyrase or topoisomerase IV amino acid leads to fluoroquinolone resistance.

Macrolides

Intracellular modifications of the ribosomal target site inside the bacterium may decrease the effect of macrolides.



Efflux pumps

(e.g., *Staphylococcus aureus* and *Streptococcus pneumoniae*)

Presence of membrane transporters that carry the antibiotic (■) out of the cell and keep it from reaching adequate concentrations. These pumps are specific to one or several antibiotics classes.

Examples:

Tetracycline

Tetracycline, doxycycline

Macrolides

Azithromycin, clarithromycin

Fluoroquinolones

Ciprofloxacin, levofloxacin

Decreased permeability of the cellular membrane (e.g., *Escherichia coli*)

Closing of the membrane pores used by the antibiotic (●) to enter the cell.

Examples:

Fluoroquinolones

Ciprofloxacin, levofloxacin

Adapted from: Yim G., *Attack of the Superbugs: Antibiotic Resistance*, www.scq.ubc.ca.

In practice, there are two main definitions for bacterial resistance.

Microbiological resistance (*in vitro*) occurs when a bacterial strain is able to grow despite the presence of an antibiotic. This resistance depends on a few parameters, among which the serum concentration reached by a given antibiotic plays a significant role. In cases of life-threatening infections (bacteraemia, meningitis), the concept of *in vitro* resistance becomes extremely important.

Clinical resistance (*in vivo*) is defined as the lack of sign and symptom improvement (fever, overall condition, etc.) after 72 hours of treatment. This type of resistance is more relevant to common medical practice, since it indicates treatment failure of the course of antibiotics.

In certain cases, microbiological resistance does not translate into clinical resistance. In that regard, the tissue concentration of the antibiotic has a major impact and must be considered along with the antibiogram. Here are some examples:

- ▶ Macrolides and some fluoroquinolones are significantly concentrated in the respiratory tract. Therefore, these molecules may remain clinically effective despite *in vitro* resistance.
- ▶ Except for moxifloxacin, fluoroquinolones reach high concentrations in the urinary tract because they are mostly eliminated unchanged by the kidney. Urine concentrations may exceed the bacterial resistance threshold.
- ▶ *Streptococcus pneumoniae* may acquire resistance to penicillin by altering the affinity of the antibiotic's binding site. This type of resistance is usually overcome by administering high-dose amoxicillin, for example in cases of acute otitis media.

FACTORS CONTRIBUTING TO EMERGENCE AND PROPAGATION

PRESCRIPTION-ASSOCIATED FACTORS	PATIENT-ASSOCIATED FACTORS	HOSPITAL ENVIRONMENT-ASSOCIATED FACTORS
<ul style="list-style-type: none"> ▪ Liberal use of antibiotics ▪ Use of broad-spectrum antibiotics ▪ Use of antibiotics with a long tissue half-life (e.g., azithromycin, long-lasting subtherapeutic residual concentration after treatment completion) ▪ Suboptimal use of antibiotics (duration of treatment too short or too long, subtherapeutic dose) 	<ul style="list-style-type: none"> ▪ Recent exposure to an antibiotic from any class (promotes the emergence of resistance, usually within the same class) ▪ Child under two years old ▪ Child attending a daycare centre ▪ Immunosuppression ▪ Lack of compliance with treatment due to adverse effects, excessively complex dosage, drug unavailability ▪ International travel 	<ul style="list-style-type: none"> ▪ Failure to follow the policies and measures recommended for infection control, including hand washing, hygiene practices and health measures ▪ Failure to follow policies and procedures related to intra- and inter-institution communication when transferring patients

QUESTIONS TO ASK BEFORE PRESCRIBING AN ANTIBIOTIC

PATHOGEN	<ul style="list-style-type: none"> ▪ What is the likelihood of a bacterial etiology? ▪ Which bacteria are the most likely cause for this type of infection? ▪ Is it recommended to confirm bacterial etiology before starting treatment? ▪ What is the usual sensitivity profile of the pathogens involved? ▪ Which antibiotics are the most likely to be effective against these bacteria?
PATIENT	<ul style="list-style-type: none"> ▪ Has the patient taken antibiotics within the last three months, and if yes, which ones? ▪ Does the patient attend a place with a higher risk of bacterial resistance, such as daycare centres? ▪ Has the patient travelled in an area with known bacterial resistance? ▪ Is the patient a known carrier of resistant bacteria? ▪ Does the patient present significant comorbidities or immunosuppression? ▪ Is the patient at risk of not taking the medication properly?
ANTIBIOTIC	<ul style="list-style-type: none"> ▪ What is the first-line antibiotic for this type of infection? ▪ What are the main pharmacokinetic parameters (tissue distribution, elimination route, etc.) of the antibiotic considered? ▪ Is there a risk of drug interaction that may modify its efficacy? ▪ What are the appropriate dose and duration for the treatment?

EXAMPLES OF CLINICAL SITUATIONS

TYPE OF INFECTION (pathogen)	SIGNS OF A RESISTANT PATHOGEN	ANTIBIOTICS INVOLVED	PREFERRED EMPIRICAL TREATMENT APPROACHES AND COMMENTS
ACUTE OTITIS MEDIA IN CHILDREN AND COMMUNITY-ACQUIRED PNEUMONIA IN CHILDREN <i>(Streptococcus pneumoniae)</i>	<ul style="list-style-type: none"> ▶ Children under two years old ▶ Daycare attendance ▶ Recent antibiotic treatment 	PENICILLINS	<ul style="list-style-type: none"> ▶ Pneumococcal resistance is stable in Québec. When treatment is indicated, resistance may easily be countered by increasing the dose of AMOXICILLIN (90 mg/kg/day): adequate concentrations in the middle ear and in the lung parenchyma for the treatment of <i>pneumococci</i> with intermediate resistance to penicillin and of most highly penicillin-resistant <i>pneumococci</i>.
COMMUNITY-ACQUIRED PNEUMONIA IN ADULTS <i>(Streptococcus pneumoniae)</i>	<ul style="list-style-type: none"> ▶ Macrolides taken within the previous 3 months 	MACROLIDES	<ul style="list-style-type: none"> ▶ Macrolides remain the first-line treatment for patients with a low risk for complications. Due to high macrolide concentrations in lung tissues, microbiological resistance does not always lead to clinical resistance. ▶ It is recommended to select an agent from another class when a macrolide has been used within the last three months. ▶ Another treatment option should be considered in cases where microbiological resistance has been confirmed through culture results. ▶ A higher risk of emergence of macrolide resistance has been shown when using azithromycin as opposed to using clarithromycin.
	<ul style="list-style-type: none"> ▶ Fluoroquinolone taken within the previous 3 months 	FLUORO-QUINOLONES	<ul style="list-style-type: none"> ▶ It is recommended to select an agent from another class when a fluoroquinolone has been used within the last three months. ▶ Fluoroquinolones should be reserved for higher-risk patients who are known or suspected carriers of first-line-agent resistant strains of <i>Streptococcus pneumoniae</i>. This class is also recommended for patients with a high risk of complications (comorbidities, immunosuppression, etc.). ▶ Fluoroquinolone resistance is rare in <i>Streptococcus pneumoniae</i>.
PHARYNGITIS-TONSILLITIS <i>(Streptococcus pyogenes or group A β-hemolytic streptococcus)</i>		MACROLIDES CLINDAMYCIN	<ul style="list-style-type: none"> ▶ <i>Streptococcus pyogenes</i>, or group A β-hemolytic streptococcus, responds to penicillin. ▶ Macrolides can be used as an alternative treatment in case of penicillin allergy. However, <i>Streptococcus pyogenes</i>, or group A β-hemolytic streptococcus, may be resistant to macrolides and clindamycin in some cases.
UNCOMPLICATED URINARY TRACT INFECTIONS <i>(Escherichia coli)</i>	<ul style="list-style-type: none"> ▶ Antibiotics taken within the previous months 	TMP-SMX	<ul style="list-style-type: none"> ▶ TMP-SMX should be the first-line treatment EXCEPT when the patient has recently been treated with TMP-SMX or has recently been hospitalized. ▶ In case of sulfonamide allergy, TMP alone is an alternative.
		FLUORO-QUINOLONES	<ul style="list-style-type: none"> ▶ The use of fluoroquinolones should be limited to: <ul style="list-style-type: none"> ▪ complicated urinary tract infections; ▪ recent antibiotic treatment with TMP-SMX; ▪ patients with recent hospitalizations. ▶ Recent treatment with an antibiotic from this class elevates the risk of encountering quinolone-resistant <i>Escherichia coli</i>.

For more information on the treatment of the infections discussed above, INESSS invites you to refer to the first series of clinical guides in antibiotic treatment on INESSS' website at: inesss.qc.ca, in the *Publications and Projects in Progress* section.

POSSIBLE CONSEQUENCES OF BACTERIAL RESISTANCE

- Treatment failure and risk of complications
- Use of potentially more toxic and costly antibiotics
- Increased number of invasive/surgical interventions
- Increased length of stay in a health facility
- Increased mortality rates
- Increased expenses

ASSESSMENT OF ANTIBIOTIC TREATMENT FAILURE – POSSIBLE CAUSES

- ▶ First-line interventions, such as abscess drainage, that were ineffective or not performed
- ▶ Wrong diagnosis, such as the diagnosis of a viral instead of bacterial infection, or non-infectious inflammatory response
- ▶ Pathogen not affected by the antibiotic
- ▶ Pathogen resistant to the antibiotic
- ▶ Loss of digestive tube integrity, leading to antibiotic malabsorption, for example
- ▶ Patient's lack of compliance with the treatment
- ▶ Drug interaction affecting the medication's pharmacokinetic parameters (e.g., decreased quinolone absorption when taken with calcium)
- ▶ Compromised vascularization of the infection site

RECOMMENDATIONS

- Limit the use of antibiotics to the appropriate indications.
- Choose the right antibiotic and the optimal dose and duration of treatment, according to acknowledged clinical guides.
- Promote clinical teaching by the prescriber and pharmacist to reinforce patient compliance with the treatment.
- Follow recommended policies and hygiene practices to control infections.
- Promote vaccination when indicated, following the recommendations of the *Protocole d'immunisation du Québec*.

RECOMMENDED LINKS FOR CONSULTATION

<http://www.fda.gov/AnimalVeterinary/SafetyHealth/AntimicrobialResistance/ucm134359.htm> (visual animation)
<http://www.niaid.nih.gov/topics/antimicrobialresistance/Pages/default.aspx>
<http://www.cdc.gov/drugresistance/index.html>
<http://www.can-r.com>
<http://www.inspq.qc.ca/domaines/index.asp?Dom=60&Axe=64>

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