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Measures to Prevent and Control Transmission of Multidrug-Resistant Gram-Negative Bacilli (Excluding Carbapenemase-Producing Enterobacteriaceae) in Acute Care Settings in Québec

COMITÉ SUR LES INFECTIONS NOSOCOMIALES DU QUÉBEC

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Gram-negative bacilli (GNB) are bacteria frequently encountered in clinical settings, both as normal flora and as pathogens in a variety of infections.

The use of antibiotics has led to the emergence of various resistance mechanisms and some of these bacteria are now resistant to several classes of antibiotics.

This document was created to help healthcare-associated infection prevention and control (IPC) teams identify major multidrug-resistant Gram-negative bacilli (MDR-GNB) and implement IPC measures to prevent them from being transmitted to acute care settings in Québec. This document replaces the document published in 2015 and discusses all GNB excluding carbapenemase-producing Enterobacteriaceae (CPE). Since the latter are important, a separate document has been created containing the information that pertains to them (CINQ 2017).

This document is primarily intended to be used as a basic reference for centres that are not dealing with an outbreak. While the measures to be implemented in the case of an outbreak are often mentioned in the literature, few articles discuss the measures to be taken to avoid transmission of MDR-GNB (excluding CPEs) outside such a context. The following recommendations are therefore based in large part on the opinion of the working group, the collaborators and the members of the Comité sur les infections nosocomiales du Québec (CINQ) [Québec healthcare-associated infections committee]. The recommendations take the current data into account and should be revised to reflect changes in the epidemiology and knowledge on the reservoirs and on transmission (Wilson, 2016; Otter, 2015; Chinese XDR Consensus Working Group, 2016; Tacconelli, 2014; Ontario Agency for Health Protection and Promotion, 2013; PHAC, 2010; Drees, 2014; Cohen, 2008; Harris, 2006; Siegel, 2006; Friedman, 2017; Mandell, 2015; Benett, 2015).

In addition to the specific measures, routine IPC practices, in particular hand hygiene, play an important role in preventing transmission of multidrug-resistant bacteria. The best practices of the Programme québécois des soins sécuritaires [Québec safe care program] are an important tool for controlling infections caused by these bacteria (INSPQ, 2018). Antibiotic stewardship also plays an important role, by limiting exposure of bacteria to antibiotics and by avoiding the selection of resistant bacteria, since antibiotic use is the main risk factor for bacteria acquiring resistance.

Québec

Resistance mechanisms

Antibiotic resistance of GNB can occur via four major mechanisms: enzymatic inactivation, target site modification, decreased permeability and efflux pumps. The following table briefly describes these mechanisms and mentions a few more characteristic examples.

Enzymatic inactivation
GNB can produce several enzymes that alter or destroy antibiotics before they have had time to act. The best-known category of these enzymes is the ß-lactamases. These enzymes can irreversibly hydrolyze (break down) the ß-lactam ring of ß-lactam antibiotics, which makes them ineffective. The ß-lactam class of antibiotics is generally divided into four families, namely the penicillins (e.g., ampicillin, piperacillin), the cephalosporins (e.g., ceftriaxone, ceftazidime, cefepime), monobactam (aztreonam) and the carbapenems (e.g., ertapenem, imipenem, meropenem). These agents are among the most widely prescribed antibiotics in human and veterinary medicine. There are hundreds of different ß-lactamases (e.g., ESBL, ampC, OXA, NDM, KPC). Each enzyme has its own unique hydrolytic profile, which means that each type of ß-lactamase is able to destroy a combination of different antibiotics. The carbapenemases are ß-lactamases that inhibit carbapenems. The Enterobacteriaceae that produce these ß-lactamases are called carbapenemase-producing Enterobacteriaceae (CPE). ß-lactamases are not the only enzymes that can confer antibiotic resistance on GNB. For example, there is also a group of enzymes called aminoglycoside-modifying enzymes (AMEs, or EMA in French). As the name of the group implies, these enzymes can modify aminoglycosides such as gentamicin, tobramycin and amikacin, preventing them from binding to their target sites, making them ineffective. There are a few dozen of these enzymes and they are not all able to alter the same antibiotics within the aminoglycoside class. The example frequently encountered is a strain of GNB that is resistant to gentamicin and to tobramycin, but that remains sensitive to amikacin.
Target site modification
The second way in which GNB can resist antibiotics is by changing the target site, that is, the antibiotic attack site. These changes are generally caused by mutations in the target site gene. The most significant example in GNB remains the mutations in the gyrase gene (gyrA) and in the topoisomerase gene (parC) that are the target sites for fluoroquinolones such as ciprofloxacin, levofloxacin and moxifloxacin. These mutations can accumulate, resulting in an increasingly higher level of resistance.
Decreased permeability
The cell wall of GNB is fairly impermeable to several agents, including some antibiotics. As the target sites of these antibiotics are often within the cell, the antibiotics must pass through proteins from the wall, often called porins, which are literally tunnels that pass through the cell wall allowing some substances to penetrate the bacteria. In some circumstances, including in the presence of antibiotics, some GNB can decrease the quantity of porins produced or modify the type of porins. This decrease in the membrane's permeability to antibiotics results in a weaker concentration of the antibiotic within the bacterium and makes the antibiotic less effective or ineffective. The best-known example of this phenomenon in GNB is the loss of the porin OprD in *Pseudomonas aeruginosa* making it resistant to imipenem. This phenomenon can occur in approximately 25% of cases of *P. aeruginosa* infection treated with this antibiotic. There are several types of porins. Some modifications of porins can prevent a single antibiotic from penetrating the cell, while others block the entrance of several antibiotics from several different classes.

Efflux pumps
The last resistance mechanism seen in GNB is the efflux pump. These pumps are cell wall proteins that can take substances that have entered the bacterium and expel them outside the bacterial cells. The molecular structure of these pumps is often complex and several families of various proteins act as an efflux pump. Efflux pumps are generally produced or activated in specific circumstances, including in the presence of some antibiotics. These pumps have the distinctive feature of being active simultaneously against several different classes of antibiotics, compared with the first three resistance mechanisms that are active against only a single antibiotic or a few from the same class. For example, the MexXY-OprM efflux pump in *P. aeruginosa* decreases its susceptibility to meropenem, aminoglycosides, fluoroquinolones, as well as penicillins and cephalosporins, significantly contributing to a multidrug-resistance phenotype.
Acquisition and transmission of multidrug resistance
The various resistance mechanisms can be inherently present in a bacterial species. For example, *Stenotrophomonas maltophilia* bacteria have a ß-lactamase in their chromosome called L1 that can hydrolyze carbapenems, while *Pseudomonas aeruginosae* normally do not have any ß-lactamases that can hydrolyze these antibiotics. GNB can also acquire new resistance mechanisms by point mutations, as mentioned above. A second way is by acquiring mobile genetic elements containing new resistance genes. These mobile genetic elements are called transposons, integrons, and plasmids and they allow bacteria of the same species, the same genus or even bacteria of different genera to exchange genetic material. For example, *Pseudomonas aeruginosa* can acquire a plasmid containing a carbapenemase and thus become resistant to antibiotics in this class. With the exception of efflux pumps and a few porins, most resistance mechanisms do not attack several different classes of antibiotics. A single element of resistance alone rarely makes a GNB multidrug-resistant. Most of the time, it is the result of a combination of mechanisms. For example, several *Enterobacter* spp. resistant to carbapenems encountered in hospital settings are considered multidrug-resistant owing to the combination of a very high production of their AmpC-type ß-lactamase and a loss of porin. The mobile genetic elements mentioned above are also responsible for a significant amount of multidrug resistance. In fact, they allow several different resistance genes to accumulate in the same plasmid that can then be spread from bacterium to bacterium.

Major Gram-negative bacilli

Enterobacteriaceae	
Infectious agent and reservoir	▪ Enterobacteriaceae are part of the normal flora, in particular in the gut flora, and are often found in specimens from all sources. ▪ The species most often associated with multi-resistance are *Klebsiella pneumoniae* and *Escherichia coli*.
Antibiotic resistance	▪ Enterobacteriaceae can acquire various types of resistance mechanisms, depending on the bacterium in question and on the antibiotic pressure exerted. These bacteria often accumulate several mechanisms to become resistant to several classes of antibiotics, such as the β-lactams, the quinolones and the aminoglycosides. ▪ The production of β-lactamases is the primary resistance mechanism of Enterobacteriaceae. ▪ Extended-spectrum β-lactamases (ESBLs, or BLSE in French) are especially prevalent in *E. coli* and *Klebsiella* spp., but are also found in *Enterobacter* spp., *Serratia* spp., *Citrobacter* spp. and *Proteus* spp. This resistance mechanism provides resistance to most cephalosporins. This type of resistance mechanism is becoming increasingly common in the community (particularly *E. coli*) and screening for them is no longer recommended (CLSI, 2017). ▪ AmpC-type β-lactamases predominantly occur in the chromosomes of *Enterobacter* spp., *Citrobacter* spp., *Serratia* spp., *Providencia* spp. and *Morganella* spp. They can also be found in the plasmid of *E. coli*, *Klebsiella* spp. and *Proteus* spp. in particular. In the chromosomes, these β-lactamases are often inducible, that is, they become active during an antibiotic treatment, making the bacterium resistant. ▪ Several mechanisms allow Enterobacteriaceae to become carbapenem-resistant, among others, the production of carbapenemases such as KPC (*Klebsiella pneumoniae* carbapenemase) or NDM-1 (New Delhi metallo-β-lactamase). The CINQ made specific recommendations regarding CPE (CINQ, 2018) and province-wide surveillance of these resistant strains started in April 2014 (SPIN-BGNPC) [provincial surveillance of healthcare-associated MDR-GNB]. This surveillance has been mandatory since April 1, 2017, for all health and social service facilities in Québec. Furthermore, the Laboratoire de santé publique du Québec (LSPQ) [Québec's public health laboratory] has been carrying out surveillance of strains since August 2010. ▪ Resistance by efflux pump and by porin modification also occurs frequently in Enterobacteriaceae.
Method of transmission	▪ Direct and indirect contact. ▪ *E. coli* is mainly transmitted from person to person in a community setting and is less prevalent in a hospital setting, while *Klebsiella pneumoniae* tends to be transmitted in hospitals with a potential to cause outbreaks. Other Enterobacteriaceae such as *Enterobacter* spp. and *Serratia* spp. are easily transmitted by direct and indirect contact, via the hands of healthcare staff, but also via the environment and contaminated objects. ▪ Enterobacteriaceae can survive from a few hours to weeks on dry surfaces (Wilson, 2016).
Duration of colonization	▪ Resistant Enterobacteriaceae are generally found in stools. The duration of colonization is unknown. However, studies, particularly on CPEs, seem to demonstrate that they can survive from several months to over a year (Wilson, 2016). ▪ A risk of transmission persists for as long as the patient remains a carrier.
Infections	▪ Enterobacteriaceae can cause many different infections, including urinary tract infections, intra-abdominal infections, pneumonias, wound infections and bacteremias.

Enterobacteriaceae	

Laboratory detection[a]	▪ Phenotypic detection:
	  ▪ Antimicrobial susceptibility testing (resistance to classes of antibiotics);
	  ▪ Confirmation tests (CPE, ESBL, ampC);
	  ▪ Chromogenic agars (CPE, ESBL).
	▪ Genotypic detection:
	  ▪ Detection of antibiotic resistance genes (performed at the LSPQ for CPE).

Epidemiology	▪ The evolution of -lactamases in recent decades is the result of, among other things, the selective pressure exerted by the use of antimicrobial agents. Following the introduction of third-generation cephalosporins in Europe in the 1970s, the first ESBL emerged in Germany in 1983, and then, it wasn't until 1988 that the first ESBL was reported in the United States (Savard, 2013). Then, the emergence of ESBLs in Europe and in America necessitated a greater use of carbapenems that produced the same selective pressure, leading to the emergence of the first carbapenemases in Enterobacteriaceae. ▪ According to 2015 Canadian data, the national prevalence of ESBLs among the *Klebsiella* pneumoniae and *Escherichia coli* strains reached 4.6% and 12.3% respectively (CARA, 2017). A 2013 Centers for Disease Control and Prevention (CDC) report indicated 140,000 healthcare-associated infections due to Enterobacteriaceae, 19% of which (i.e. 26,000 infections) were due to ESBL-positive strains, causing 1,700 deaths and additional costs of $40,000 per infection (CDC, 2013). The main ESBL found in *E. coli* worldwide is CTX-M and its global spread (especially in community settings) was propelled by the easier transmission of an *E. coli* clone (ST 131). ▪ In Québec, the provincial surveillance data for healthcare-associated bacterial infections (SPIN-BACTOT) for 2016–2017 reveals that Enterobacteriaceae account for 40% of the isolated pathogens. Among these, 1.5% of *Klebsiella* spp., 4.0% of *E. coli* and 3.2% of *Enterobacter* spp. are resistant to three or more classes of antibiotics among the third-generation cephalosporins, the fluoroquinolones, the aminoglycosides, the carbapenems and piperacillin with or without tazobactam (SPIN-BACTOT, 2017). ▪ For Europe, the data available in EARS-Net for the year 2015 reveals a prevalence of resistance to three classes of antibiotics (third-generation cephalosporins, quinolones and aminoglycosides) of 5.3% for *E. coli* and 18.6% for *Klebsiella pneumoniae* (EARS-Net, 2017). ▪ Enterobacterial resistance to carbapenems by production of carbapenemase is emerging in Québec and throughout the world. Refer to the document on measures to prevent and control CPEs for more information on the epidemiology of CPEs (CINQ, 2018).

[a] Phenotypic detection refers to the expression of genes present in the bacterium (example: susceptibility to an antibiotic, growth on a selective culture medium) and is generally performed in clinical microbiology laboratories. Genotypic detection refers to the detection of genes.

Pseudomonas aeruginosa	
Infectious agent and reservoir	▪ *Pseudomonas aeruginosa* is ubiquitous in the environment and is especially prevalent in humid environments. This bacterium is most often involved in outbreaks associated with water-related contamination, for example, from faucets or other everyday liquid products such as hand soaps. It is also found in the gut flora and often colonizes the respiratory tracts of patients with chronic pulmonary disease or cystic fibrosis. ▪ It has been reported that *Pseudomonas* can remain on surfaces for up to 16 months (Wilson, 2016).
Antibiotic resistance	▪ *P. aeruginosa* is a bacterium that is inherently resistant to several antibiotics. It can also develop resistance to all of the antibiotics used in clinical settings, via several different resistance mechanisms, often by chromosome mutation when under antibiotic pressure. ▪ Efflux pumps, target site modification and porin modification are the resistance mechanisms most often encountered. Furthermore, in vivo biofilm formation increases its resistance to the antibiotic used (Wilson, 2016).
Method of transmission	▪ *P. aeruginosa* is transmitted by direct and indirect contact, via the hands of healthcare staff or from healthcare equipment that has come in contact with contaminated water or solutions.
Duration of colonization	▪ The duration of colonization is unknown and can vary from one patient to the other. Patients suffering from chronic pulmonary disease or cystic fibrosis tend to remain colonized over the long term, even after adequate antibiotic treatment.
Infections	▪ *P. aeruginosa* is found in a variety of infections, especially in pneumonias, bacteremias, healthcare-associated urinary tract infections, as well as skin and soft tissue infections, in particular in operative sites and in patients with serious burns.

Laboratory detection	▪ Phenotypic detection:
	  ▪ Antimicrobial susceptibility testing (resistance to classes of antibiotics).
	▪ Genotypic detection:
	  ▪ Detection of antibiotic resistance genes (reference laboratory, as necessary).

Epidemiology	▪ Amongst the 51,000 *P. aeruginosa* infections reported in 2013 in the United States, 6,700 (13%) were caused by multidrug-resistant strains and 440 resulted in death. ▪ The data available in EARS-Net for 2015 shows a percentage of resistance of *Pseudomonas* to three classes of antibiotics of 13.7% and of 5.5% to five classes of antibiotics (piperacillin-tazobactam, fluoroquinolones, ceftazidime, carbapenems and aminoglycosides). ▪ In Québec, *Pseudomonas* accounts for 4% of pathogens isolated in healthcare-associated bacteremias in 2016–2017. It is resistant to imipenem or to meropenems in 11.2% of cases, to fluoroquinolones in 7.6% of cases and to three or more classes in 6.2% of cases (cefepime or ceftazidime, carbapenems, fluoroquinolones, aminoglycosides, or piperacillin with or without tazobactam) (SPIN-BACTOT, 2017).

Acinetobacter baumannii	
Infectious agent	▪ *Acinetobacter baumannii* is found in the environment and can also be found in drinking water. It can survive for long periods on inanimate dry surfaces. The environment can therefore be a reservoir during, among others, natural disasters and when members of the military return from war zones. ▪ *A. baumannii's* preferred site is the respiratory tract. It is sometimes found on the skin of patients and staff. It is an opportunistic agent and is associated with healthcare. However, it is usually not found in normal flora.
Antibiotic resistance	▪ *A. baumannii* easily develops different resistance mechanisms such as the production of -lactamases, loss of wall permeability and efflux pumps. This enables it to become resistant to most antibiotics.
Method of transmission	▪ Direct and indirect contact. ▪ *A. baumannii* is mainly transmitted via the hands of healthcare staff but can also be transmitted by a contaminated environment or materials.
Duration of colonization	▪ There is little information on the duration of colonization. However, it is apparently from a few days to weeks (Wilson, 2016).
Infections	▪ *A. baumannii* is most often responsible for pulmonary infections and bacteremias, in particular in mechanically ventilated patients and intensive care patients. It can also be involved in wound infections, abdominal infections or urinary tract infections.

Laboratory detection	▪ Phenotypic detection:
	  ▪ Antimicrobial susceptibility testing (resistance to classes of antibiotics).
	▪ Genotypic detection:
	  ▪ Detection of antibiotic resistance genes (reference laboratory, as necessary).

Epidemiology	▪ Multidrug resistance of *A. baumannii* strains is mainly endemic in the United States. According to the CDC 2013 annual report, 12,000 healthcare-associated infections can be traced to *A. baumannii* yearly and 7,300 of these (63%) are caused by a multidrug-resistant strain, leading to nearly 500 deaths. ▪ In Canada in 2012, 100% of strains tested were susceptible to amikacin, ciprofloxacin, meropenem, gentamicin and TMP-SMX, while 91.9% were susceptible to the piperacillin-tazobactam combination. ▪ A few cases of multidrug-resistant *A. baumannii* were reported in Québec and came from patients repatriated from overseas hospitals. Between 2007 and 2009, members of the military who had been injured during a mission in Afghanistan were admitted to a Québec hospital. Out of 31 repatriated military members, 15 (48%) screened positive for multidrug-resistant *A. baumanii*, being mainly in the wounds and in the groin region. An outbreak involving four cases of healthcare-associated transmission occurred and was linked to the hospitalization of one of these members of the military (verbal communication, infection prevention and control team of the CHU de Québec). ▪ An outbreak of a multidrug-resistant *Acinetobacter* clone was described in a tertiary care hospital in Montréal between March 2012 and January 2014. Nine patients were colonized or infected by this strain and five of these patients died of a bacteremia involving this bacterium. The outbreak was controlled by implementing various strategies, including cohorting the cases, thorough environmental decontamination, staff training, a dedicated team, daily baths with 2% chlorhexidine and audits of hand hygiene and environmental decontamination (Gray, 2016). ▪ During province-wide surveillance of healthcare-associated bacteremias in 2016–2017, 8.3% of *Acinetobacter* strains tested were resistant to imipenem or meropenem, but none were resistant to three or more classes of antibiotics (SPIN-BACTOT, 2017).

Stenotrophomonas maltophilia	
Infectious agent and reservoir	▪ *Stenotrophomonas maltophilia* is ubiquitous in the environment, in particular in water. In hospitals, it can be found in a variety of aqueous reservoirs, including drinking water, chlorhexidine diluted with contaminated deionized water, faucet aerators and in parts of mechanical ventilators. It ranks second in importance, after *P. aeruginosa*, for being responsible for outbreaks associated with water contamination. ▪ In humans, it is mainly found in the respiratory tract.
Antibiotic resistance	▪ *S. maltophilia* carry multiple drug resistances through various resistance mechanisms, among others, efflux pumps, selective membranous porins and -lactamases. ▪ The best antibiotic for treatment remains trimethoprim-sulfamethoxazole (TMP-SMX), but we are seeing the emergence of resistance against this antibiotic. ▪ *S. maltophilia* is inherently resistant to ß-lactamases, including carbapenems, except for ticarcillin/clavulanic acid and ceftadizime. In fact, few antibiotics are effective against *S. maltophilia* (levofloxacin, minocycline and colistin), which greatly limits our choice as soon a TMP-SMX resistance emerges.
Method of transmission	▪ Direct and indirect contact. ▪ Particular attention should be paid to the risk of indirect transmission by contamination of healthcare equipment and of the environment.
Duration of colonization	▪ The duration of colonization is unknown.
Infections	▪ *S. maltophilia* is a bacterium that can be involved in various infections, in particular pneumonias and bacteremias in immunocompromised patients and patients admitted to intensive care units.

Laboratory detection	▪ Phenotypic detection:
	  ▪ Antimicrobial susceptibility testing (resistance to TMP-SMX).
	▪ Genotypic detection:
	  ▪ Detection of antibiotic resistance genes (reference laboratory, as necessary).

Epidemiology	▪ *S. maltophilia* is one of the 10 main healthcare-associated pathogens reported in Europe and accounts for 3.9% of isolates found in hospital-acquired infection specimens. In Canada, 68.7% of strains reported in 2015 were resistant to ceftazidime, while 16.4% were resistant to trimethoprim sulfamethoxazole (CARA, 2017).

Antibiotic Classes for Determining Multidrug Resistance

In the presence of a GNB carrying multiple drug resistances, it is important to determine whether we are dealing with a multidrug-resistant bacterium for which prevention and control measures must be implemented to prevent transmission. The literature contains several different definitions of multidrug resistance, the resistance to three or more classes of antibiotics being the most used definition (Wilson, 2016; Otter, 2015; Chinese XDR Consensus Working Group, 2016; Magiorakos, 2012; Mattner, 2012). In order to make it easier to determine the measures to be taken depending on the number of antibiotic classes to which the bacterium is resistant, the working group and the members of CINQ agreed to use the antibiotic classes most often tested in microbiology laboratories. In practice, the laboratories should test at least one antibiotic from each class and a process for notifying the IPC team should be set up so that quick action can be taken when a Gram-negative bacillus is resistant to three or more classes of antibiotics. The following table shows the antibiotics from each class selected for the purpose of determining whether or not the bacterium is resistant to this class of antibiotics. A bacterium that is resistant (R) or intermediate (I) to one antibiotic from the class indicated in the table means that the bacterium is resistant to this class. The measures to put in place will be determined depending on the number of classes to which the bacterium is resistant.

Enterobacteriaceae (e.g., *E. coli, Klebsiella* spp., *Proteus* spp., *Enterobacter* spp., *Citrobacter* spp., *Serratia* spp.)				
Penicillin + β-lactamase inhibitor R to the class: R or I to 1 of the following agents:	**3rd- or 4th-generation cephalosporins** R to the class: R or I to 1 of the following agents:	**Carbapenems** R to the class: R or I to 1 of the following agents:	**Aminoglycosides** R to the class: R or I to 1 of the following agents:	**Fluoroquinolones** R to the class: R or I to 1 of the following agents:
Piperacillin/tazobactam Ticarcillin/clavulanic acid	Cefotaxime Ceftriaxone Ceftazidime Cefepime	Imipenem[a] Meropenem	Amikacin Gentamicin Tobramycin	Ciprofloxacin Levofloxacin Moxifloxacin
***Pseudomonas* spp., *Acinetobacter* spp. and other Gram-negative bacilli excluding Enterobacteriaceae (e.g., *Burkholderia* spp., *Alcaligenes* spp.)**				
Penicillin +/- β-lactamase inhibitor R to the class: R or I to 1 of the following agents:	**3rd- or 4th-generation cephalosporins** R to the class: R or I to 1 of the following agents:	**Carbapenems** R to the class: R or I to 1 of the following agents:	**Aminoglycosides** R to the class: R or I to 1 of the following agents:	**Fluoroquinolones** R to the class: R or I to 1 of the following agents:
Piperacillin Piperacillin/tazobactam Ticarcillin/clavulanic acid	Cefepime Ceftazidime	Imipenem Meropenem	Amikacin Gentamicin Tobramycin	Ciprofloxacin Lévofloxacin
Stenotrophomonas maltophilia				
Resistance to TMP-SMX				

[a] *Proteus* spp., *Morganella* spp. and *Providencia* spp. are characterized by an inherent reduced susceptibility or resistance to imipenem. This antibiotic should therefore not be used for the purpose of determining whether or not these bacteria are resistant to the carbapenem class of antibiotics.

Measures to Prevent and Control Transmission of MDR-GNB

To facilitate the implementation of measures to prevent and control infections, we have separated the GNB into two groups. In general, group 1 multiresistant GNB, i.e. *Acinetobacter* resistant to 5 classes or more, are those requiring active screening and measures to prevent their transmission. Group 2 MDR-GNBs are multiresistant bacteria with a potential for transmission involving a clinical impact that is lesser or less well-known and that does not require active screening. However, finding them in a clinical specimen often indicates a larger inoculum and an increased risk of transmission.

The measures described in this section are recommendations to guide IPC teams. They may be adjusted in accordance with the local epidemiology, the at-risk clientele, the frequency of outbreaks or the results of local surveillance. The IPC teams may implement measures that differ from those mentioned below.

Example:

- A centre with a large pediatric clientele, for whom quinolones are generally not recommended, could disregard this class of antibiotics and take measures in the case of *Acinobacte*r resistant to other classes, i.e. to four classes of antibiotics rather than five.
- ESBL-carrying *Klebsiella* spp. have the potential to be involved in healthcare-associated transmission, unlike *E. coli*, which is mainly found in the community. Therefore, some centres could carry out screening, particularly on at-risk wards, and take certain measures when a patient is found to be a carrier (Tissot, 2014).
- A centre where there is frequently ESBL-carrying *E. coli* resistant to two other classes of antibiotics could choose to not take these into account and take measures for bacteria other than *E. coli.*
- A centre where antimicrobial susceptibility testing with two aminoglycosides is performed could consider a bacterium resistant to this class where there is resistance to two agents rather than one.
- A centre with several patients suffering from pulmonary disease who are carrying TMP-SMX-resistant *Stenotrophomonas maltophilia* or multidrug-resistant *Pseudomonas* with no evidence of transmission could decide not to isolate the carriers.
- As *Stenotrophomonas maltophilia* is a bacteria that is resistant to several antibiotics, a centre could take measures if this bacterium is discovered in a clinical specimen, even if there is no TMP-SMX resistance, especially on certain at-risk wards.
- While controversial, the epidemiological situation could lead some centres to take more significant measures for at-risk wards, such as transplant wards, or the intensive care unit, carry out screening for ESBL for the patients admitted to the intensive care unit.
- Given the difficulties related to treating GNBs resistant to the five classes of antibiotics, some centres could take more significant screening measures when these bacteria are isolated in a clinical specimen, even if the bacterium found is not an *Acinetobacter* (e.g., screening of close contacts).

However, it is important to remember that CPEs have a greater transmission potential than the other MDR-GNB, and that as a result, efforts must prioritize screening and control of transmission of these bacteria. The document on measures to prevent and control transmission of CPEs contains detailed recommendations (CINQ, 2018).

Group 1 bacteria

***Acinetobacter* resistant to ≥ 5 classes of antibiotics**	
Indication for screening on admission	▪ Hospitalization ≥ 24 hrs in the past year at a centre outside Québec. ▪ Hospitalization ≥ 24 hrs in the past year at a centre with active or recent transmission, according to the Avis sur les BMR-Rapport cumulatif des signalements d'éclosion [Advisory on multidrug-resistant bacteria - A cumulative report on outbreak reporting] prepared by the Ministère de la Santé et des Services sociaux (MSSS) [Québec's ministry of health and social services]. ▪ Known carrier.
Indication for screening during a hospital stay	▪ Wards where a carrier is staying ▪ Close contacts (≥ 24 hrs in the same room) and more distant contacts (≥ 24 hrs on the same ward) of a non-isolated carrier.
Frequency of screenings	▪ Screening on day 0 (admission), day 7 and day 14 in cases where a patient has been directly transferred from a high-risk centre or has been hospitalized in a high-risk centre in the past three months. ▪ Screening on day 0 (admission) and day 7[a] in cases where a patient has been hospitalized in a high-risk centre in the past year and more than three months previously. ▪ Screening on day 0 for a known patient, to be repeated every week if the result is negative or as indicated by the infection prevention department. ▪ Weekly ward screening where a carrier has been hospitalized, for a minimum of four weeks after his or her departure. Plan a day for the weekly screening of all the unit's patients (e.g., Monday), irrespective of samples taken at admission. ▪ Screening on days 0, 7 and 14 of close and distant contacts.
Clinical specimens or collection sites for screening	▪ Stool or rectal swab. ▪ Throat or endotracheal secretions if intubated. ▪ Wounds. ▪ Ostomies, drain and catheter sites. ▪ Groin/axillary region (only one swab must be used for these two sites). ▪ Urine if a catheter is present. ▪ Sites that have previously been positive in known carriers.

[a] A second screening is recommended to increase sensitivity.

***Acinetobacter* resistant to ≥ 5 classes of antibiotics**	
Additional precautions	▪ Implement additional precautions to prevent contact transmission for colonized or infected patients. ▪ Implement additional precautions to prevent contact transmission on a preventive basis for patients who have been screened while waiting for the results,[a] except during weekly ward screenings. ▪ Implement additional precautions to prevent contact and droplet transmission if present in a respiratory specimen.[b] ▪ Step up implementation of hand hygiene with an alcohol-based hand rub or soap and water.
Duration of additional precautions	▪ For the duration of the hospitalization, unless otherwise indicated by the healthcare-associated infection prevention and control department. ▪ It is suggested that screening of the carrier continue following discontinuation of additional precaution measures.
Accommodation	▪ Accommodation in a single room with a dedicated toilet for the carrier. ▪ Cohorting with dedicated staff for the cohorted carriers may be considered.
Disinfection of the environment	▪ Clean the environment, healthcare materials and medical devices with the usual products when additional precautions are implemented to prevent contact transmission in compliance with the facility's established procedures.
Healthcare materials and medical devices	▪ Use disposable medical devices, or dedicate devices to a single patient. ▪ Limit the amount of healthcare materials that enter the room. ▪ Reusable multiple-patient medical devices that could not be dedicated must be disinfected prior to their being used for another patient. ▪ Daily assessment of the need for an invasive device, and removal as soon as no longer required, in order to prevent infection.
Waste management	▪ Perform waste management so that the risk of environmental contamination is limited.
Dishwashing	▪ Implement the facility's established procedures for washing dishes and utensils.
Laundry	▪ Implement the facility's established procedures.
Waste management	▪ Implement the facility's established procedures.
Movement outside their room	▪ Limit carriers' movement outside their room to essential functions (e.g., tests, treatments). ▪ Consultants must meet the patient in his or her room. ▪ Perform hand hygiene using an alcohol-based hand rub (ABHR) or soap and water, and make sure patients wear clean clothes and incontinence briefs, if needed, before leaving their room.
Consultation, appointments or transfer to another setting	▪ Inform the receiving facility when a patient is being transferred or has an appointment, in compliance with the facility's established procedures. ▪ Indicate the date of the last positive screening, if this information is available.

***Acinetobacter* resistant to ≥ 5 classes of antibiotics**	
Visitors	▪ Make sure that information about prevention measures is communicated to and understood by visitors before they are authorized to enter the patient's room: ▪ Perform hand hygiene with an alcohol-based hand rub (ABHR) or soap and water before and after visiting. ▪ Do not use the patient's bathroom. ▪ A visitor who provides care must perform hand hygiene and wear a long-sleeved gown and gloves when they are in close physical contact (body-to-body) with the patient.
Carrier status alert in the medical record	▪ Place a carrier status alert in the patient's medical record and give them a carrier status card. ▪ It is up to the IPC department to remove the alert from the patient's medical record. However, since we do not know the average duration of colonization, it is difficult to specify when the alert can be removed. ▪ Notify the receiving centre when the patient is transferred to another centre.

[a] Depending on local epidemiology and the sensitivity of the screening tests performed in the laboratory, isolation may be discontinued after the first negative result.

[b] According to one reference (Otter, 2015), during an *Acinetobacter* outbreak, droplet precautions are recommended for the intensive care unit and during maneuvers that generate aerosols. However, these are not recommended in another reference (Wilson, 2016). As a precaution, it is recommended that a mask be worn when *Acinetobacter* is found in a respiratory specimen.

Group 2 bacteria are multidrug-resistant bacteria for which the clinical impact and transmission potential is lesser or less well-known. The prevention measures will be implemented only if the bacteria are found in a **clinical specimen**, given the larger inoculum resulting in a greater transmission potential. If the same bacterium is discovered in clinical specimens from more than one patient, a more easily transmissible strain or contamination of the environment should be suspected, and enhanced measures will then be necessary, with active screening of contacts (see "Special Measures in Case of Outbreak").

Group 2 bacteria

▪ **Enterobacteriaceae resistant to ≥ 3 classes of antibiotics** ▪ **Enterobacteriaceae resistant to carbapenems[a] (other than CPEs; see comments)** ▪ ***Acinetobacter* resistant to 3 or 4 classes of antibiotics** ▪ ***Pseudomonas aeruginosa* resistant to ≥ 5 classes of antibiotics** ▪ ***Stenotrophomonas maltophilia* resistant to TMP-SMX** ▪ **Other Gram-negative bacteria resistant to ≥ 3 classes of antibiotics**	
Indication for screening[b]	▪ No systematic screening on admission or on the wards. ▪ No screening of close or more distant contacts when a non-isolated carrier is discovered.
Additional precautions	▪ Implement additional precautions to prevent contact transmission if one of these bacteria is discovered in a clinical specimen. ▪ Implement additional precautions to prevent contact and droplet transmission if one of these bacteria is present in a respiratory specimen[c]. ▪ Step up implementation of hand hygiene with an alcohol-based hand rub or soap and water.
Duration of additional precautions	▪ Duration of hospitalization or as indicated by the infection prevention department. ▪ Some facilities consider discontinuing the additional precautions when three control specimens from the colonized or infected site performed one week apart are negative.
Accommodation	▪ Provide an individual room with a private bathroom, or apply additional precautions as required to the infected patient's bed. ▪ Grouping together all patients carrying the same bacteria can be considered.
Disinfection of the environment	▪ Clean the environment, healthcare materials and medical devices with the usual products when additional precautions are implemented to prevent contact transmission, in compliance with the facility's established procedures.
Healthcare materials and medical devices	▪ Use disposable medical devices, or dedicate devices to a single patient. ▪ Limit the amount of healthcare materials that enter the room. ▪ Reusable multiple-patient medical devices that could not be dedicated must be disinfected prior to their being used for another patient. ▪ Daily assessment of the need for an invasive device, and removal as soon as no longer required, in order to prevent infection.
Waste management	▪ Perform waste management so that the risk of environmental contamination is limited.
Dishwashing	▪ Implement the facility's established procedures for washing dishes and utensils.
Laundry	▪ Implement the facility's established procedures.
Waste management	▪ Implement the facility's established procedures.
Movement outside their room	▪ Limit carriers' movement outside their room to essential functions (e.g., tests, treatments). ▪ Consultants must meet the patient in his or her room. ▪ Perform hand hygiene using an alcohol-based hand rub (ABHR) or soap and water, and make sure patients wear clean clothes and incontinence briefs, if needed, before leaving their room.
Consultation, appointments or transfer to another setting	▪ Inform the receiving facility when a patient is being transferred or has an appointment, in compliance with the facility's established procedures. ▪ Indicate the date of the last positive screening, if this information is available.

Visitors	▪ Make sure that information about prevention measures is communicated to and understood by visitors before they are authorized to enter the patient's room:
	  ▪ Perform hand hygiene with an alcohol-based hand rub (ABHR) or soap and water before and after visiting.
	  ▪ Do not use the patient's bathroom.
	  ▪ A visitor who provides care must perform hand hygiene and wear a long-sleeved gown and gloves when they are in close physical contact (body-to-body) with the patient.

Alert in the carrier's medical record	▪ None. ▪ No screening is recommended, and no additional precautions are necessary if the patient is readmitted.
Comments	▪ The measures described in this section must be implemented in the presence of any carbapenemase-resistant Enterobacteriaceae, while waiting for the confirmation of carbapenemase production. If it is a CPE, the measures for CPE must be implemented, in accordance with the recommendations contained in the document "Entérobactéries productrices de carbapénémases : mesures de prévention et de contrôle dans les milieux de soins aigus du Québec" (CINQ, 2018). If other resistance mechanisms are involved, the above measures will be maintained. ▪ In the United States, the CDC use the term "CRE" (carbapenem-resistant Enterobacteriaceae) to refer to Enterobacteriaceae that are not sensitive to carbapenems, particularly CPEs. In 2012, the definition of a CRE was: an Enterobacteriaceae intermediate or resistant to carbapenems and resistant to ceftriaxone, cefotaxime and ceftazidime. This definition was modified in 2015 to include the production of a carbapenemase (CDC, 2015). However, the term still used is "CRE", and this term is often frequently used in the literature. In Québec, the term "CPE" is used when production of carbapenemase is present and the term "CRE" is used when there is resistance to carbapenems through any of the resistance mechanisms. ICP measures differ for Enterobacteriaceae that do not produce carbapenemase. In the United States, the term used for Enterobacteriaceae that are resistant to carbapenems through other mechanisms is "non-CP CRE" (absence of carbapenemase production). ▪ When the Enterobacteria in question is an ESBL producer, no special measures will be implemented, unless there is resistance to at least three classes of antibiotics.

[a] *Proteus* spp., *Morganella* spp. and *Providencia* spp. are characterized by an inherent reduced susceptibility or resistance to imipenem. This antibiotic should therefore not be used for the purpose of determining whether or not these bacteria are resistant to the carbapenem class of antibiotics.

[b] See section "Special Measures in Case of Outbreak" for contact screening when there is an outbreak.

[c] Droplet transmission was described for *Pseudomonas* in a patient with cystic fibrosis only, but as a precaution, it is recommended that a mask be worn when the resistant bacteria is found in a respiratory specimen.

Special measures in case of outbreak

These measures are recommended for group 1 bacteria, i.e. *Acinetobacter* that are resistant to ≥ 5 classes of antibiotics. For group 2 bacteria, the measures to be implemented depend on the pathogen in question, its degree of resistance, the screening techniques available at the laboratory, the care unit affected and the intensity of the outbreak.

These measures are to be implemented in association with the measures described previously, as well as with the prevention and control measures required during any outbreak such as: greater insistence on hand hygiene and addition precautions, enhanced disinfection of the environment, healthcare materials and medical devices, staff training, searching for the source of transmission, etc. The literature should be reviewed to gain a better understanding of the methods of transmission and the prevention and control measures of the pathogen involved in the outbreak.

Definition of a MDR-GNB outbreak	▪ Occurrence of two new healthcare-associated cases, colonized or infected, epidemiologically linked. ▪ For *Acinetobacter* resistant to ≥ 5 classes of antibiotics, the occurrence of one colonized or infected case in a non-isolated patient must raise suspicions of an outbreak. An alert status must be set up and the measures described for an outbreak must be implemented.

Contact screening	▪ Screening on day 0, day 7 and day 14:
	  ▪ of close contacts (patients who stayed more than 24 hours in the same room as a confirmed, non-isolated case);
	  ▪ of more distant contacts (patients who stayed on the same ward as a confirmed, non-isolated case);
	  ▪ of contacts who received care from the same staff, if a transmission via staff is suspected.
	▪ Weekly screening of the ward affected for at least four weeks after the last confirmed case has been discharged.
	▪ Staff screening is not recommended.[a]
	▪ Some care facilities perform screening on admission to and discharge from a ward where there is an outbreak.
	▪ Environmental screening should be considered if an outbreak persists despite implementation of prevention and control measures, in particular in cases of *Acinetobacter* and *Pseudomonas.*

Additional precautions	▪ Implement additional precautions to prevent contact transmission for close contacts while waiting for the results of screening tests.[b] ▪ Implement additional precautions to prevent contact transmission for more distant contacts who have been transferred to another ward while waiting for the screening results.[b] ▪ Cohorting with dedicated staff for the cohorted carriers.
Alert	▪ Place an alert in the medical record of close and more distant contacts who have been discharged so that they may be screened and implement additional precautions to prevent contact transmission on a preventive basis while waiting for the results when a patient is readmitted.[c] ▪ Notify the receiving centre when a carrier or contact is transferred to another centre.
Regional public health authority	▪ Report the outbreak to the Direction de santé publique (DSPu) [regional public health authority].

[a] On an exceptional basis, when the epidemiological study shows a strong suspicion of transmission via a staff member, screening of the suspected persons could be performed.

[b] Depending on the sensitivity of the screening tests performed at the microbiology laboratory and the local epidemiology, the contact precautions may be discontinued if the result at day 7 is negative.

[c] If there are a large number of contacts, it may be more advisable to perform systematic screening of all patients who were hospitalized during the outbreak.

End of outbreak

End of outbreak	▪ When no new case has been discovered for a minimum of four consecutive weeks, following the identification of the last confirmed case.
Regional public health authority	▪ Inform the DSPu of the end of the outbreak in accordance with regional procedures.

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Measures to Prevent and Control Transmission of Multidrug-Resistant Gram-Negative Bacilli (Excluding Carbapenemase-Producing Enterobacteriaceae) in Acute Care Settings in Québec

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