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Measures to Prevent and Control Transmission of Multidrug-Resistant Gram-Negative Bacilli in Acute Care Settings in Québec

COMITÉ SUR LES INFECTIONS NOSOCOMIALES DU QUÉBEC

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 has been prepared to help healthcare-associated infection prevention and control (IPC) teams recognize the major multidrug-resistant Gram-negative bacilli (MDR-GNB) and to implement IPC measures to avoid their transmission in acute care settings in Québec.

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, very few articles discuss the measures to be taken to avoid transmission 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 (Tacconelli, 2014; Ontario Agency for Health Protection and Promotion, 2013; PHAC, 2010; Drees, 2014; Cohen, 2008; Harris, 2006; CDC, 2013; Siegel, 2006).

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 *Campagne québécoise des soins sécuritaires* [Québec safe care campaign] are an important tool for controlling infections caused by these bacteria (INSPQ, 2014). Antibiotic stewardship also plays an important role, by limiting exposure of bacteria to antibiotics and by avoiding the selection of resistant bacteria.

Québec

Resistance mechanisms

Antibiotic resistance of GNB can occur via 4 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 degradation
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 bacteria 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, and are frequently found in clinical specimens from all sources (Mandell, 2015).
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 (Bennett, 2007). ▪ 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 several laboratories no longer screen for ESBLs.
	▪ 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 in October 2010 (CINQ, 2010) and province-wide surveillance of these resistant strains started in April 2014 (SPIN-BGNPC) [provincial surveillance of healthcare-associated MDR-GNB]. The Laboratoire de santé publique du Québec (LSPQ) [Québec's public health laboratory] has been carrying out surveillance of strains since August 2010.
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	
Duration of colonization	▪ Resistant Enterobacteriaceae are generally found in stools. The duration of colonization is unknown. ▪ The risk of transmission continues as long as the patient carries the bacteria.
Infections	▪ Enterobacteriaceae can cause many different infections, including urinary tract infections, intra-abdominal infections, pneumonias and bacteremias.

Laboratory detection[1]	▪ 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).

ESBL epidemiology	▪ The evolution of β-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. ▪ ESBLs: According to 2012 Canadian data, the national prevalence of ESBLs among the *Klebsiella pneumoniae* and *Escherichia coli* strains reached 3.6% and 7.6% respectively (source: CARA). In the United States, data compiled in 2010 in a major hospital in the Northeastern United States showed a prevalence of 5.7% in *E. coli* strains and 11.6% for the *K. pneumoniae* isolates. 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). For Europe, the data available in EARS-Net for 2012 shows a prevalence of resistance to third-generation cephalosporins (primarily secondary to the production of ESBL) of 4.9% to 16.2% for *E. coli*, while it ranges from 3.2% to 70.9% for *Klebsiella pneumoniae* depending on the country. 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 proportion of the *Klebsiella* spp., *Escherichia coli* and *Proteus* spp. strains resistant to third-generation cephalosporins represented 9.8% of the Enterobacteriaceae reported in blood cultures in 2013 (SPIN-BACTOT).

[1] 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.

Enterobacteriaceae	
CPE Epidemiology	▪ The emergence of CPE was identified by both the Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO) as being a serious threat to public health owing to their resistance profile and their rapid spread in the populations affected (CDC, 2009). Global spread of CPE, initially fairly well defined for each of them, became accelerated because of, among other things, population movements and the easier transmission of some clones well adapted to the Enterobacteriaceae, resulting in sporadic cases being reported in the literature around the world for KPC enzymes as well as NDM or VIM enzymes (Verona Integron-encoded Metallo-β lactamase). ▪ KPC: The first KPC-1 enzyme-producing *K. pneumoniae* strain was isolated in North Carolina, United States in 1996. It then spread mainly in major hospitals in New York State that reported outbreaks starting in the early 2000s. KPC enzymes remain the most prevalent type of carbapenemase today in the United States and among the 50 American States, 48 reported at least one case of a patient colonized or infected with a KPC-producing Enterobacteriaceae. (CDC, 2015). This same strain of KPC-positive *K. pneumoniae* (molecular typing ST258) was introduced to Israel via the United States in 2005, where it rapidly became endemic with an almost exclusively healthcare-associated acquisition (Schwaber, 2014). According to the data published in Israel, the proportion of KPC-positive *K. pneumoniae* reached 22% of *Klebsiella* spp. strains isolated from blood cultures in 2007. KPCs are also endemic in Greece where nearly 22% of *Klebsiella* spp. strains carry them. Other countries such as China and some South American countries (Columbia, Brazil) recently reported KPC endemic regions. Lastly, France, Italy, the United Kingdom, Norway and Canada have reported sporadic cases in the past. ▪ NDM-1: The first reports of cases of NDM-type CPE were published at the end of 2009 by Yong and colleagues after having been isolated in a Swedish traveller returning from India (Yong, 2009). From that time on, epidemiological prevalence studies conducted on carbapenem-resistant Enterobacteriaceae in India, Pakistan and the United Kingdom have shown a high prevalence of this new resistance mechanism in these first two countries, with importation of cases in the last (Kumarasamy, 2010). Nonetheless, bacterial strains recorded in the SENTRY databases show the presence of NDM-1 in strains isolated in hospitalized patients in India from 2006 onwards (Castanheira, 2011). Other epidemiological studies published by Walsh and colleagues established that CPE were found in runoff waters and in drinking water in some districts of New Delhi, and also established the presence of the NDM-1 gene in several genera and species of Enterobacteriaceae and various other bacterial species (Walsh, 2011). NDM-type enzymes rapidly spread throughout the world as a result of, among other things, accelerated population movements, medical tourism reported by some authors, as well as easier transmission of plasmids carrying the gene from one bacterium to the other (Savard, 2012). To date, sporadic cases of colonized or infected patients have been reported in various European countries (the United Kingdom, France, Austria, Belgium, Greece, Denmark, Finland, Italy, Switzerland, Norway, Sweden, Germany, the Netherlands), in America (Canada, United States, Brazil), in Asia (China, South Korea, Japan, Taiwan, Singapore), in Africa (Morocco, South Africa, Egypt, Kenya) and in Oceania (Australia), among others. A recent review of the nine first strains of NDM-1 reported in the United States was recently published; most of the patients in whom such a strain was isolated in the United States had a history of recent hospitalization in India or in Pakistan (Rasheed, 2013). ▪ The other metallo-β-lactamases: VIM and IMP: VIM-type enzymes, initially described in *Pseudomonas* spp. strains have been transferred to Enterobacteriaceae and have mainly been reported in the Mediterranean region (Italy and Greece) where they are frequently encountered in patients hospitalized in intensive care units. Isolated cases were then reported in France, Ireland, Scandinavia, South Korea, Taiwan, Mexico and Columbia. A first case was reported in the United States in 2010, but no sustained transmission has been reported in North America to date. The IMP-producing strains (“active on imipenem”) were initially described in Asia and remain mainly prevalent in this region of the world, in particular in China, Taiwan and Japan. Rare cases have been reported to date in Australia and the United States. ▪ In Québec, surveillance of carbapenemase-producing Enterobacteriaceae is part of the SPIN-BGNPC program that started in April 2014. The number of acquisitions remains limited, but they are present in some centres.

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 patients with cystic fibrosis.
Antibiotic resistance	▪ *P. aeruginosa* is a bacterium that is inherently resistant to several antibiotics. This bacterium 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.
Method of transmission	▪ *P. aeruginosa* is transmitted by direct and indirect contact, via the hands of healthcare staff or from health care 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.

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

Epidemiology	▪ Multidrug-resistance of *P. aeruginosa* strains has been traced to an accumulation of various mechanisms within the strain. 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. According to the European CDC 2013 annual report, the situation of multidrug-resistant *P. aeruginosa* strains in Europe seems to have remained stable since 2008 accounting for 15% of isolates. Canadian and Québec data are not available.
Acinetobacter baumannii	
Infectious agent and reservoir	▪ *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. It can sometimes be found on the skin of patients and staff.
Antibiotic resistance	▪ *A. baumannii* easily develops resistance via several different resistance mechanisms, such as the production of β-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. ▪ The lungs and the gastrointestinal tract are *A. baumannii*'s preferred sites of infection.
Infections	▪ *A. baumannii* is most often responsible for pulmonary infections and bacteremias, in particular in intensive care patients. It can also be involved in wound infections or urinary tract infections.

Acinetobacter baumannii	

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,* with the positive sites being in the wounds and in the groin region. An outbreak involving four cases of healthcare-associated transmission was linked with the hospitalization of one of these military members (verbal communication, infection prevention and control team of the CHU de Québec [the Québec university hospital centre]).
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.
Antibiotic resistance	▪ *S. maltophilia* carry multiple drug resistances through various resistance mechanisms, among others, efflux pumps, selective membranous porins and β-lactamases. The best antibiotic for treatment remains trimethoprim-sulfamethoxazole (TMP-SMX), but we are seeing the emergence of resistance against this antibiotic. ▪ Controlling the use of antibiotics seems to have little effect in decreasing *S. maltophilia* infections.
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. *S. maltophilia* is inherently resistant to β-lactams with the exception of ticarcillin/clavulanic acid and ceftazidime. In Canada, however, 83.7% of strains reported in 2012 were resistant to ceftazidime, while 31% were resistant to trimethoprim-sulfamethoxazole. Moreover, there are few antibiotics that are effective against *S. maltophilia* (levofloxacin, minocycline and colistin) which significantly limits our arsenal as soon as resistance to TMP-SMX emerges.

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 applied 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 (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 bacteria 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 (two in the case of aminoglycosides) 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 more than three classes of antibiotics. The following table shows the antibiotics from each class retained for the purpose of determining whether or not the bacterium is resistant to this class of antibiotic. A bacterium that is resistant (R) or intermediate (I) to one antibiotic from the class (two antibiotics in the case of aminoglycosides) 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 agent of the class)	**3rd- or 4th-generation cephalosporins** (R to the class: R or I to 1 agent of the class)	**Carbapenems** (R to the class: R or I to 1 agent of the class)	**Aminoglycosides** (R to the class: R or I to **2 agents** of the class)	**Fluoroquinolones** (R to the class: R or I to 1 agent of the class)
Piperacillin/tazobactam Ticarcillin/clavulanic acid	Cefotaxime Ceftriaxone Ceftazidime Cefepime	Imipenem[2] Meropenem	Amikacin Gentamicin Tobramycin	Ciprofloxacin Levofloxacin Moxifloxacin
***Pseudomonas* spp., *Acinetobacter* spp. and other Gram-negative bacilli besides Enterobacteriaceae (e.g., *Burkholderia* spp., *Alcaligenes* spp.)**				
Penicillin +/- β-lactamase inhibitor (R to the class: R or I to 1 agent of the class)	**3rd- or 4th-generation cephalosporins** (R to the class: R or I to 1 agent of the class)	**Carbapenems** (R to the class: R or I to 1 agent of the class)	**Aminoglycosides** (R to the class: R or I to **2 agents** of the class)	**Fluoroquinolones** (R to the class: R or I to 1 agent of the class)
Piperacillin Piperacillin/tazobactam Ticarcillin/clavulanic acid	Cefepime Ceftazidime	Imipenem Meropenem	Amikacin Gentamicin Tobramycin	Ciprofloxacin Levofloxacin
Stenotrophomonas maltophilia				
Resistance to TMP-SMX				

[2] *Proteus* spp., *Morganella* spp. and *Providencia* spp. are characterized by an inherent intermediate 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

The measures described in this section are minimum recommendations, which can be adjusted taking into account the local epidemiology. Depending on the at-risk population, the frequency of outbreaks and the results of local surveillance, the healthcare-associated infection prevention and control teams can implement measures different 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 a bacterium resistant to the other classes, meaning to four classes of antibiotics.
- A centre with a clientele in which ESBL-carrying *E. coli* resistant to two other classes of antibiotics are frequently found could choose to not take these into account and take measures for bacteria other than *E. coli.*
- 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.
- Some centres could take more significant measures for high-risk units, such as transplant units or intensive care units.

In general, group 1 multidrug-resistant bacteria (table, pages 10 and 11) are those necessitating active screening and measures to avoid transmission. The bacteria from group 2 (table, page 12) are multidrug-resistant bacteria with a lesser transmission potential or clinical impact and do not require active screening. However, finding them in a clinical specimen often indicates a larger inoculum and an increased risk of transmission.

Group 1 Bacteria

▪ **Carbapenemase-producing Enterobacteriaceae (CPE)** ▪ **Enterobacteriaceae resistant to ≥ 5 classes of antibiotics** ▪ ***Acinetobacter* or other Gram-negative bacilli resistant to ≥ 5 classes of antibiotics, besides *Pseudomonas aeruginosa* and *Stenotrophomonas maltophilia***	
Indication for screening[3]	▪ Hospitalization ≥ 24 hrs. in the past year at a centre outside Québec (CPE and *Acinetobacter*). ▪ 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 MSSS [Québec's ministry of health and social services] (screening for the particular bacterium). ▪ Known patient (screening for the bacterium identified). ▪ Weekly screening of the wards where a patient who is a carrier is staying and for a minimum of three weeks following his or her discharge (screening of the bacterium present). ▪ Some experts recommend screening (CPE and *Acinetobacter*) when a patient has travelled to India or to South Asia, or in the case of an invasive procedure at a high-risk centre, even when the patient wasn't admitted to a hospital.
Frequency of screenings	▪ Screening on day 0 (admission) and day 7 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 month. ▪ Screening on day 0 (admission) and day 3[4] in cases where a patient has been hospitalized in a high-risk centre in the past year and more than one month previously. ▪ Screening on day 0 for a known patient, to be repeated every week if the result is negative. ▪ A single screening during weekly ward screening, without taking into account the specimen collections done on admission (e.g., screening of all patients on Monday, even those who were admitted and screened the previous day).

Clinical specimens for screening	▪ Stool or rectal swab.
	▪ In the case of *Acinetobacter*, besides stool or rectum, add:
	  ▪ Throat, or endotracheal secretions if intubated
	  ▪ Wounds
	  ▪ Ostomies, drain and catheter sites
	  ▪ Groin/axillary regions (a single swab can be used for these sites)
	  ▪ Urine in the presence of a catheter.

Additional precautions	▪ Contact precautions in a private room with a private toilet for a patient carrying the bacterium ▪ Preventive contact precautions for screened cases waiting for results[5], except in cases of weekly ward screening. ▪ Contact/droplet precautions if presence in a respiratory specimen[6]. ▪ Enhanced hand hygiene with an alcohol-based hand rub or water and soap. ▪ Cleaning of the environment, the healthcare materials and the medical equipment with the usual products to isolate contact, according to the protocol established by the facility.

[3] See section "Special Measures in Case of Outbreak" for contact screening when a non-isolated case is discovered.

[4] A second screening on day 3 is recommended to increase sensitivity and owing to intermittent excretion.

[5] Depending on the local epidemiology and depending on the sensitivity of the screening tests used in the laboratory, isolation could be ended after the first negative result.

[6] There is no literature demonstrating transmission by droplets; however, as a precautionary measure, it is suggested that a mask be worn as well when the resistant bacterium is found in a respiratory specimen.

Duration of additional precautions	▪ For the duration of the hospital stay, unless otherwise notified by the healthcare-associated infection prevention and control team. ▪ Before ending the isolation, remember that excretion can be intermittent and a screening can be positive after several negative results. As well, the screening can be falsely negative if the patient is on antibiotics, even if the strain is resistant to the administered antibiotic. ▪ When the isolation is ended, it is suggested that weekly screening be continued.
Carrier status alert in the chart	▪ Computerized alert, in the medical record and card given to the patient. ▪ It is up to the IPC team to remove the alert from the patient's medical record. However, since excretion can be intermittent and as we do not know the average duration of colonization, it is difficult to specify when the alert can be removed. ▪ Advise the receiving centre when a patient is being transferred to another centre. ▪ In the case of CPE, the type of carbapenemase, not the bacterium itself, must be taken into consideration. For example, a person carrying *Klebsiella* spp. with KPC who becomes a carrier of *Klebsiella* spp. with NDM1 has acquired a new CPE. They must have a new alert placed in their chart identifying them as an NDM1 carrier, besides the alert identifying them as a KPC carrier. If an *E. coli* is found with KPC for this patient, it is the same carbapenemase, and the patient has therefore not acquired another CPE.

Group 2 Bacteria

Group 2 bacteria are multidrug-resistant bacteria with a lesser clinical impact and transmission potential. The prevention measures will be applied 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).

▪ **Enterobacteriaceae resistant to 3 or 4 classes of antibiotics** ▪ **Enterobacteriaceae resistant to carbapenems[7] (CRE other than CPE; see comments)** ▪ ***Acinetobacter* spp. or other Gram-negative bacteria resistant to 3 or 4 classes of antibiotics** ▪ ***Pseudomonas aeruginosa* resistant to ≥ 5 classes of antibiotics** ▪ ***Stenotrophomonas maltophilia* resistant to TMP-SMX**	
Indication for screening[8]	▪ No systematic screening on admission or on the wards. ▪ No close or epidemiologically linked patients within the hospital screening when a non-isolated carrier is discovered.
Additional precautions	▪ Contact precautions if discovered in a clinical specimen. ▪ Contact/droplet precautions if presence in a respiratory specimen[9]. ▪ A cohort of patients carrying the same bacterium can be considered. ▪ Enhanced hand hygiene with an alcohol-based hand rub or water and soap. ▪ Cleaning of the environment, healthcare material and medical equipment with the usual products for contact isolation, according to the protocol established by the facility.
Duration of additional precautions	▪ For the duration of the hospital stay or as specified by the healthcare-associated infection prevention and control team. ▪ Some consider ending the precautions when three control specimens from the colonized or infected site performed at a one-week interval are negative.
Carrier status alert in the chart	▪ None. ▪ No screening or additional precautions if readmitted.
Comments	▪ The measures described in this section will be applied for any carbapenem-resistant enterobacteriaceae, while waiting for the confirmation from the LSPQ. If it is a CPE, the measures for CPE must then be implemented. If it is another resistance mechanism, the above measures will then be continued. This differs from the United States, where the CDC recommends measures as described for CPE in the case of a carbapenem-intermediate or resistant enterobacteriaceae that is also resistant to ceftriaxone, cefotaxime and ceftazidime (CDC, 2012). In Québec, surveillance of CPE carried out by the LSPQ allows us to adjust the measures based on the presence or absence of a carbapenemase gene (e.g., KPC, NDM, etc.). ▪ *Stenotrophomonas maltophilia* being a bacterium resistant to several antibiotics, the healthcare-associated infection prevention and control team of some facilities could take measures if it is discovered in a clinical specimen, even in the absence of resistance to TMP-SMX, in particular in some high-risk wards. ▪ In the presence of an ESBL-producing enterobacteriaceae, no special measures will be put in place, unless there is resistance to at least three classes of antibiotics. ▪ ESBL-carrying *Klebsiella* spp. can potentially be transmitted in healthcare settings, contrary to *E. coli* that is mainly found in the community. For this reason, some facilities could carry out screening, especially in high-risk wards, and implement some measures when a patient is found to be a carrier (Tissot, 2014).

[7] *Proteus* spp., *Morganella* spp. and *Providencia* spp. are characterized by an inherent intermediate 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.

[8] See section “Special Measures in Case of Outbreak” for contact screening when there is an outbreak.

[9] There is no literature demonstrating transmission by droplets; however, as a precautionary measure, it is suggested that a mask be worn as well when the resistant bacterium is found in a respiratory specimen.

Special measures in case of outbreak

The following measures are to be applied during an outbreak of MDR-GNB and are in addition to the measures described for group 1 or 2 bacteria, as well as the prevention and control measures required during any outbreak, such as: enhanced hand hygiene and routine practices, enhanced disinfection of the environment, healthcare material and medical equipment, staff training, determining a source of transmission, etc.

Definition of a MDR-GNB outbreak	▪ Occurrence of 2 new healthcare-associated cases (admitted more than 72 hours previously), colonized or infected, epidemiologically related. ▪ For group 1 MDR-GNB, the occurrence of one case, colonized or infected, in a non-isolated patient should raise suspicions of an outbreak. An alert status should be put in place and the outbreak measures described in this section should 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). ▪ Screening on day 0, day 7 and day 14 for epidemiologically linked patients within the hospital (patients who stayed on the same ward as a confirmed, non-isolated case). ▪ Screening on day 0, day 7 and day 14 of contacts who received care from the same staff, if a transmission via staff is suspected. ▪ Weekly screening of the affected ward up to a minimum of three weeks following the discharge of the last confirmed case. ▪ Staff screening is not recommended. ▪ Some facilities perform screening on admission and on discharge from a ward experiencing an outbreak.
Additional precautions	▪ Preventive contact precautions for close contacts while waiting for the screening results[10]. ▪ Preventive contact precautions for more distant contacts who were transferred to another ward while waiting for the screening results[10]. ▪ Cohort of patients who are carriers with dedicated staff.
Alert	▪ Put an alert in the medical record of close contacts and more distant contacts who were discharged so that they can be screened and put in preventive contact isolation while waiting for the screening results on readmission. ▪ Advise the receiving centre when a patient who is a carrier or a contact is transferred to another centre. ▪ Report the outbreak to the Direction de santé publique (DSP) [regional public health authority].
End of the outbreak	▪ When no new case has been discovered for a minimum of three consecutive weeks, following the identification of the last confirmed case. ▪ Advise the DSP of the end of the outbreak.

[10] Depending on the sensitivity of the screening tests performed in the microbiology laboratory and depending on the local epidemiology, contact precautions could be stopped if the result at day 7 is negative.

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