REPORT

Carbapenem resistance in Canada

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For more than 2 decades, carbapenems have been considered the pharmacotherapy of last resort for managing multidrug-resistant infections caused by Enterobacteriaceae bacteria (e.g., *Escherichia coli* and *Salmonella*). Over the past decade, however, resistance to carbapenems has emerged and appears to be increasing among these pathogens, particularly *Klebsiella pneumoniae*. The mechanism of resistance is the bacterium's production of β-lactamase enzymes, which hydrolyze carbapenem antibiotics and render them inactive.[1,2] The *K. pneumoniae* carbapenemase (KPC) β-lactamases have a very broad spectrum of resistance and can inactivate virtually all other β-lactam antibiotics. In this article, we describe the epidemiologic features of infections with KPC-producing organisms, including their emergence in Canada, and the challenges in diagnosing and managing these infections.

Epidemiology

First described in *K. pneumoniae*, KPC enzymes have now been found in other Enterobacteriaceae bacteria.[1–3] The wide dissemination and transfer between bacterial species has occurred because KPC genes are carried on plasmids. Key features of organisms that produce KPC enzymes are summarized in Table 1.

Table 1: Key features of organisms that produce *Klebsiella pneumoniae* carbapenemase (KPC) enzymes

Feature	Details
Geographic spread	Canada, China, France, Greece, Israel, South America, United Kingdom, United States
Affected antibiotics	Direct: β–lactam antibiotics Indirect: fluoroquinolones, aminoglycosides, trimethoprim–sulfamethoxazole
Bacterial species	*K. pneumoniae*, *Escherichia coli*, and *Enterobacter*, *Citrobacter* and *Salmonella* species
Risk factors	Admission to intensive care unit; mechanical ventilation; previous use of antibiotics; poor general health; recent receipt of transplanted organ or stem cells; travel to an endemic area
Mechanism of resistance	Plasmid-encoded gene (bla_{KPC}) enables hydrolysis of β-lactam antibiotics
Methods of laboratory detection	Ertapenem to screen isolates; modified Hodge test to detect KPC activity; polymerase chain reaction assay to confirm presence of bla_{KPC}
Infection control	Isolation of infected patients; use of contact-related precautions; cleansing of environment
Alternative antibiotics	Tigecycline or colistin; choice of antibiotic should be guided by susceptibility testing

Large nosocomial and city-wide outbreaks of infections with KPC-producing organisms have been reported predominantly in the United States, especially in northeastern states such as New York.[4,5] Other outbreaks have occurred in Israel, the United Kingdom, Greece, France, China and South America.[2,6–9] As with other gram-negative pathogens, KPC-producing organisms have been readily transmitted nosocomially through clonal spread and are now endemic in some hospitals. Outbreaks have also been reported in long-term care facilities.[3]

Risk factors include admission to an intensive care unit, mechanical ventilation, previous use of antibiotics, poor general health and recent receipt of transplanted organs or stem cells.[7,10] Infection with KPC-producing organisms is associated with a high mortality (up to 40%–50%) and constitutes an independent risk factor of death.[5,7,10]

The prevalence of KPC-producing pathogens in Canada is currently unknown because laboratories may not be using the most sensitive methods for detection.

Diagnosis

The routine methods of detection and the automated systems commonly used by clinical laboratories may fail to consistently detect KPC-producing organisms. The pathogens may test as "susceptible" to carbapenems such as meropenem and imipenem using the usual interpretive criteria. In 2008, 10 isolates of *K. pneumoniae* were referred to the Ontario Public Health Laboratories for further testing.[11,12] The initial results of susceptibility testing of 1 of the 10 isolates using an automated method suggested that the organism was susceptible to meropenem. However, the initial results of testing using routine clinical laboratory methods showed general resistance to all lactams, with complete or intermediate resistance to meropenem, which raised the possibility of KPC production.

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This discrepancy could mislead a clinician into thinking that the carbapenem class of antibiotics is useful. When the 10 isolates were subsequently tested using phenotypic and molecular methods, all were confirmed to be producers of KPC.

Canadian laboratories should screen for KPC production, as recently recommended by the 2009 Clinical Laboratory Standards Institute.[13] KPC production should be suspected if in vitro testing shows resistance or reduced susceptibility to a carbapenem. Isolates of *K. pneumoniae* that are resistant to any of the extended-spectrum cephalosporins but that test "susceptible" to the carbapenems should also be evaluated for possible production of KPC. Screening with ertapenem is preferred, since this agent is more susceptible than other carbapenems to KPC hydrolysis.[13,14] Confirmation of carbapenemase activity can be performed phenotypically using the modified Hodge test.[15] Public health laboratories and other reference laboratories that can perform molecular testing should specifically confirm the presence of the bla_{KPC} gene using techniques such as the polymerase chain reaction.[14,15]

Management

Treatment of infections with KPC-producing organisms is problematic because of limited therapeutic options.[2,16] Fluoroquinolones, aminoglycosides or cotrimoxazole may be used if the organism is susceptible. More commonly, the pathogen will be resistant to these antibiotics, as shown by recent trends of resistance in Enterobacteriaceae.[17] Anecdotal reports suggest that tigecycline (a glycylcycline) or colistin (a polymyxin) may be effective.[18,19] However, tigecycline may not be suitable for septicemia, and colistin is associated with nephrotoxic and neurotoxic effects.

Despite the absence of definitive evidence, it would seem prudent to isolate infected patients and take contact-related precautions because of the potential for nosocomial transmission.[20] Resistance genes encoded by plasmids have a theoretical risk of rapid transmission from one species to the next, which implies that rigorous measures to limit the spread of infection will be crucial. The emergence of KPC-producing organisms in Canada reinforces the need for antimicrobial stewardship as a strategy to control the spread of these extremely drug-resistant organisms.[21]

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