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Characterization of *Acinetobacter baumannii* and meropenem-resistant *Pseudomonas aeruginosa* in Canada: results of the CANWARD 2007–2009 study

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Abstract

A total of 66 (0.35% of overall isolates) *Acinetobacter baumannii* and 102 (0.55%) meropenem-resistant *Pseudomonas aeruginosa* were identified among 18 538 isolates collected from medical centers across Canada during the 2007–2009 period. *A. baumannii* was most frequently recovered from patients in intensive care units (ICUs; 42.4%) and was isolated mostly from blood cultures (53.0%) and respiratory tract specimens (33.3%). Colistin, meropenem, and amikacin were the most active agents against *A. baumannii* strains (≥92.4% coverage). Gentamicin, levofloxacin, and tigecycline were also active against this bacterial species (MIC_{50} 1, 0.12, and 0.5 μg/mL, respectively). Multidrug resistance (MDR; resistance to ≥3 antimicrobial classes) was noted in only 4 strains (6.1%), and molecular typing revealed 6 clusters of 2 isolates per cluster that displayed >85% similarity on the dendrogram. Meropenem-resistant *P. aeruginosa* isolates were primarily obtained from patients in ICUs (40.2%) and the most prevalent specimen types were those collected from the respiratory tract (63.7%), followed by blood cultures (18.6%). Most of the meropenem-resistant *P. aeruginosa* were resistant to all antimicrobial agents tested, and low susceptibility rates were observed for levofloxacin (8.8%) and gentamicin (28.4%). Amikacin and colistin were active against 67.7% and 88.2% of the isolates, respectively. A total of 68.6% (n = 70) of meropenem-resistant *P. aeruginosa* were MDR. Pulsed-field gel electrophoresis analysis revealed 94 unique isolates and 2 small clusters (6 and 4 isolates, 1 hospital each). In summary, MDR *A. baumannii* are rare in Canada and, conversely, meropenem-resistant *P. aeruginosa* were mostly MDR; however, there was minimal clonal spread among these nonfermentative bacilli.

Keywords: *Acinetobacter baumannii*; *Pseudomonas aeruginosa*; Resistance

1. Introduction

Acinetobacter baumannii have emerged over the years as an important opportunistic pathogen (Bergogne-Berezin and Towner, 1996). A recent study ranked this bacterial species as the 20th most common organism isolated from intensive care units (ICUs) in Canada (Zhanel et al., 2008a, 2008b), and it is often the cause of nosocomial pneumonia particularly in patients in ICUs and burn units (Chaster, 2003).

Antimicrobial resistance in *A. baumannii* has been reported more frequently over the years often leaving limited treatment options (Pournaras et al., 2006). These organisms are a cause of outbreaks in hospitals (Morgan et al., 2009; Pournaras et al., 2006), and the multidrug resistance (MDR) patterns observed among *A. baumannii* isolates often leave carbapenems as the only effective treatment for severe infections (Pournaras et al., 2006). However, carbapenem-resistant *A. baumannii* are an emerging issue worldwide and have been observed in several countries (Livermore et al., 2010; Morgan et al., 2009; Peleg et al., 2008; Pournaras et al., 2006; Tankovic et al., 1994; Ying et al., 2006).

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Table 1
Patient demographics of *A. baumannii* and meropenem-resistant *P. aeruginosa* from CANWARD 2007–2009

		A. baumannii				*P. aeruginosa*			
		CANWARD 2007 total = 26 (%)	CANWARD 2008 total = 16 (%)	CANWARD 2009 total = 24 (%)	CANWARD 2007–2009 total = 66 (%)	CANWARD 2007 total = 50 (%)	CANWARD 2008 total = 20 (%)	CANWARD 2009 total = 32 (%)	CANWARD 2007–2009 total = 102 (%)
Gender	Male	18 (69)	9 (56.0)	17 (71.0)	44 (66.7)	25 (50.0)	16 (80.0)	18 (56.3)	59 (57.8)
	Female	8 (31)	7 (44.0)	7 (29.0)	22 (33.3)	25 (50.0)	4 (20.0)	14 (43.7)	43 (42.2)
Hospital Wards	Clinics	8 (31.0)	0 (0.0)	1 (4.2)	9 (13.6)	13 (26.0)	1 (5.0)	6 (18.7)	20 (19.6)
	ER	5 (19.2)	5 (31.3)	3 (12.5)	13 (19.7)	2 (4.0)	2 (10.0)	0 (0.0)	4 (3.9)
	ICU	8 (31.0)	5 (31.3)	15 (62.5)	28 (42.4)	20 (40.0)	6 (30.0)	15 (46.9)	41 (40.2)
	Medical	4 (15.4)	4 (25.0)	4 (16.7)	12 (18.2)	12 (24.0)	6 (30.0)	9 (28.1)	27 (26.5)
	Surgical	1 (3.8)	2 (12.5)	1 (4.2)	4 (6.1)	3 (6.0)	5 (25.0)	2 (6.3)	10 (9.8)
Type of specimen	Urine	3 (11.5)	0 (0.0)	1 (4.2)	4 (6.1)	4 (8.0)	2 (10.0)	0 (0.0)	6 (5.9)
	Blood	18 (69.2)	8 (50.0)	9 (37.5)	35 (53.0)	8 (16.0)	7 (35.0)	4 (12.5)	19 (18.6)
	Wound	2 (7.7)	1 (6.3)	2 (8.3)	5 (7.6)	7 (14.0)	2 (10.0)	3 (9.4)	12 (11.8)
	Respiratory	3 (11.5)	7 (43.8)	12 (50.0)	22 (33.3)	31 (62.0)	9 (45.0)	25 (78.1)	65 (63.7)
Age	≤17	0 (0.0)	2 (12.5)	2 (8.3)	4 (6.1)	3 (6.0)	2 (10.0)	2 (6.2)	7 (6.9)
	18-65	20 (76.9)	10 (62.5)	18 (75.0)	48 (72.7)	36 (72.0)	10 (50.0)	19 (59.4)	65 (63.7)
	≥66	6 (23.1)	4 (25.0)	4 (16.7)	14 (21.2)	11 (22.0)	8 (40.0)	11 (34.4)	30 (29.4)

Infections caused by these isolates have limited therapeutic options, often forcing clinicians to turn to an older class of antimicrobials known as the polymyxins. The use of these antimicrobial agents, however, has its consequences as the polymyxins can be neurotoxic and nephrotoxic (Falagas and Kasiakou, 2005a; Falagas et al., 2005b).

Pseudomonas aeruginosa is also a common Gram-negative nosocomial pathogen. This organism is an important cause of hospital-acquired pneumonia, urinary tract, wound, and bloodstream infections (Walkty et al., 2008). *P. aeruginosa* has been ranked as the most prevalent nosocomial pathogen reported from ICUs in the United States and the third more common species in Canadian ICUs (Obritsch et al., 2004; Richards et al., 1999; Zhanel et al., 2008a; b). Infections caused by this organism are often difficult to treat because of the multidrug-resistant nature of this bacterial species and *P. aeruginosa* strains are often carbapenem-resistant, which can severely limit therapeutic options (Scheffer et al., 2010). Over the years, carbapenem-resistant *P. aeruginosa* have been observed more frequently in North America (Gales et al., 2001b), including Canadian hospitals (Walkty et al., 2008).

In this report, we describe the patient demographics, antimicrobial susceptibilities, and genetic relatedness of *A. baumannii* and meropenem-resistant *P. aeruginosa* identified as part of the Canadian Ward Surveillance Study (CANWARD) national surveillance study in Canada during the 2007 to 2009 period.

2. Materials and methods

2.1. Bacterial isolates

A total of 18 538 isolates were obtained during the years 2007 (7881 isolates), 2008 (5282), and 2009 (5375) as part of the annual, ongoing CANWARD surveillance study, as previously described in this symposium (Zhanel et al., 2011). Participant medical centers were located in 8 of the 10 Canadian provinces.

2.2. Antimicrobial susceptibilities

In vitro activity of selected antimicrobial agents was determined by the broth microdilution reference method according to the Clinical and Laboratory Standards Institute (CLSI, 2010) guidelines. Antimicrobial minimum inhibitory

Table 2
Antimicrobial susceptibility patterns of 66 *A. baumannii collected* from Canadian hospitals in 2007–2009

Antimicrobial agent	CLSI breakpoint interpretation			MIC (μg/mL)			
	%S	%I	%R	MIC_{50}	MIC_{90}	Min range	Max range
Cefepime	83.3	4.5	12.1	4	32	≤0.5	>64
Ceftriaxone	42.4	44	13.6	16	64	≤1	>256
Meropenem	92.4	0	7.6	0.5	4	≤0.12	32
Piperacillin/ tazobactam	78.8	9.1	12.1	2	128	≤1	>512
Ciprofloxacin	87.9	1.5	10.6	0.25	4	≤0.06	>16
Levofloxacin	90.9	0	9.1	0.12	1	≤0.06	16
Amikacin	92.4	0	7.6	2	4	≤1	>64
Gentamicin	90.9	0	9.1	1	4	≤0.5	>32
Colistin (polymyxin E)	94	n/a	6.1	1	2	0.5	>16
Tigecycline	89.4	n/a	6.1	0.5	4	0.12	>16
Trimethoprim/ sulfamethoxazole	86.3	n/a	13.6	0.25	8	≤0.12	>8

%S = percent susceptible; %I = percent intermediate; %R = percent resistant; n/a = not applicable.

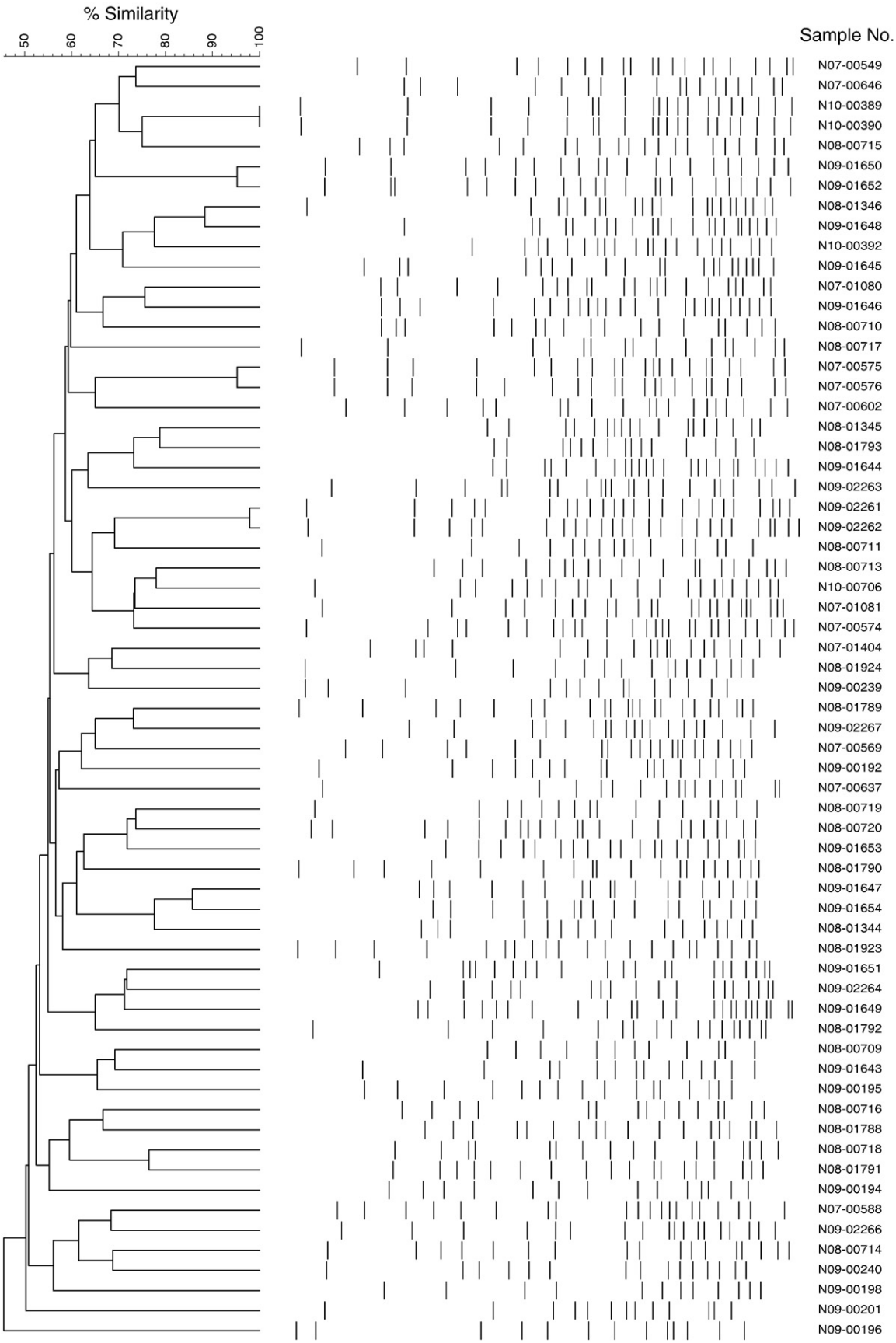

Fig. 1. Dendrogram depicting relatedness among *A. baumannii* described in this study.

concentration (MIC) interpretive criteria were defined according to CLSI breakpoints (CLSI, 2010).

In agreement with previous publications, the term *multidrug resistance* was used to describe resistance to 3 or more classes of antimicrobial agents (Falagas et al., 2005a; McCracken et al., 2009).

2.3. Molecular typing

Genetic relatedness was determined using pulsed-field gel electrophoresis (PFGE) for all *A. baumannii* and *P. aeruginosa* using *Apa*I and *Spe*I, respectively (Swaminathan et al., 2001). The fingerprints generated were analyzed using BioNumerics version 5.0 and compared with previously typed strains in our database. A 1.5% band tolerance was used for comparisons, and cluster analysis was performed using the unweighted pair-group method and DNA relatedness was calculated based on the Dice coefficient.

3. Results

3.1. A. baumannii

Among 18 538 isolates collected from patients across Canada from January 2007 to December 2009, 66 (0.35%) were identified as *A. baumannii*. Over the 3 study years, isolates were collected from patients hospitalized in institutions located in Ontario/Quebec (36.0%; n = 24), British Columbia/Alberta (24.2%, n = 16), Saskatchewan/Manitoba (19.7%; n = 13), and from the Maritime provinces (19.7%; n = 13). *A. baumannii* were mostly isolated from the ICU (42.4%; n = 28), followed by emergency rooms (19.7%; n = 13), medical wards (18.2%; n = 12), outpatient clinics (13.6%; n = 9), and surgery wards (6.1%; n = 4) (Table 1). Specimens were collected from blood cultures (53.0%; n = 35), respiratory tract (33.3%; n = 22), wounds (7.6%; n = 5), and urine (6.1%; n = 4). Patient age ranged from 1 to 86 years of age with a median of 52 years, and most (n = 40) were ≥50 years of age. Forty-four (66.0%) isolates came from male patients.

The majority of *A. baumannii* isolates were susceptible to most antimicrobials tested (Table 2). Four isolates (6.1%) were MDR. Two MDR strains were susceptible to colistin (2 μg/mL) and tigecycline (2 and 4 μg/mL) and the other 2 were only susceptible to colistin. Two other isolates were resistant to colistin (>16 μg/mL) but remained susceptible to all other antimicrobials tested.

Molecular typing by PFGE revealed 6 clusters of 2 isolates per cluster that displayed ≥85% similarity (Fig. 1). Two of these isolates were obtained from the same ward in the same hospital within 1 week. All other isolates were unique, displaying ≤85% similarity. Interestingly, *A. baumannii* strains from this initiative were not related to *A. baumannii* evaluated as part of other Canadian studies from our databases (data not shown; McCracken et al., 2009; Tien et al., 2007).

3.2. Meropenem-resistant P. aeruginosa

P. aeruginosa was identified among 1477 (8.0%) of the 18 538 isolates collected from patients across Canada in the study period. Among those, 102 (6.9%) were resistant to meropenem (MIC, ≥16 μg/mL). Meropenem-resistant *P. aeruginosa* strains were noted in all regions, and the prevalence varied as follows: 58.8% (n = 60) from Ontario/Quebec; 26.5% (n = 27) from British Columbia/Alberta; 11.8% (n = 12) from Saskatchewan/Manitoba; and 2.9% (n = 3) from the Maritime provinces. Most of these *P. aeruginosa* were isolated from the ICUs (40.2%; n = 41), followed by medical wards (26.5%; n = 27), outpatient clinics (19.6%; n = 20), surgery wards (9.8%; n = 10), and emergency rooms (3.9%; n = 4) (Table 1). Differently from *A. baumannii*, most of the meropenem-resistant *P. aeruginosa* were recovered from the respiratory tract (63.7%; n = 65), followed by blood cultures (18.6%; n = 19), wounds (11.8%; n = 12), and urine (5.9%; n = 6). Patient age ranged from 1 to 93 years with a median of 57 years, and 57.8% (n = 59) of the isolates were from male patients. Overall, antimicrobial agents demonstrated limited activity against meropenem-resistant *P. aeruginosa* strains (Table 3). Susceptibility rates for fluoroquinolones and aminoglycosides ranged from 8.8% for levofloxacin to 67.7% for amikacin; and MIC_{50} values for ciprofloxacin, levofloxacin, gentamicin, and amikacin were 4, 16, 16, and 16 μg/mL, respectively. Colistin (88.2% susceptible), amikacin (67.7%), and piperacillin/tazobactam (64.7%) displayed the higher susceptibility rates among the antimicrobial agents tested. Of the 102 meropenem-resistant isolates, 68.6% (n = 70) were MDR and only one meropenem-resistant isolate was also resistant to colistin (MIC, 8 μg/mL).

PFGE analysis revealed 94 unique fingerprints among 102 strains and 2 clusters (≥85% genetic similarity; Fig. 2). One cluster of 6 isolates was noted in a hospital in Eastern Canada, and all but one strain were from medical wards and ICUs. The other cluster of 4 isolates was observed in a

Table 3
Antimicrobial susceptibility patterns of 102 meropenem-resistant *P. aeruginosa* collected in Canadian hospitals during 2007–2009

Antimicrobial agent	CLSI breakpoint interpretation			MIC (μg/mL)			
	%S	%I	%R	MIC_{50}	MIC_{90}	Min range	Max range
Cefepime	20.6	35.3	44.1	16	64	2	128
Piperacillin/tazobactam	64.7	n/a	35.3	64	256	2	>256
Ciprofloxacin	18.6	12.8	68.6	4	16	0.12	16
Levofloxacin	8.8	19.6	71.6	16	32	0.25	32
Amikacin	67.7	13.7	18.6	16	64	1	64
Gentamicin	28.4	15.7	55.9	16	32	0.5	32
Colistin	88.2	10.8	1.0	2	4	0.06	8

%S = percent susceptible; %I = percent intermediate; %R = percent resistant; n/a = not applicable.

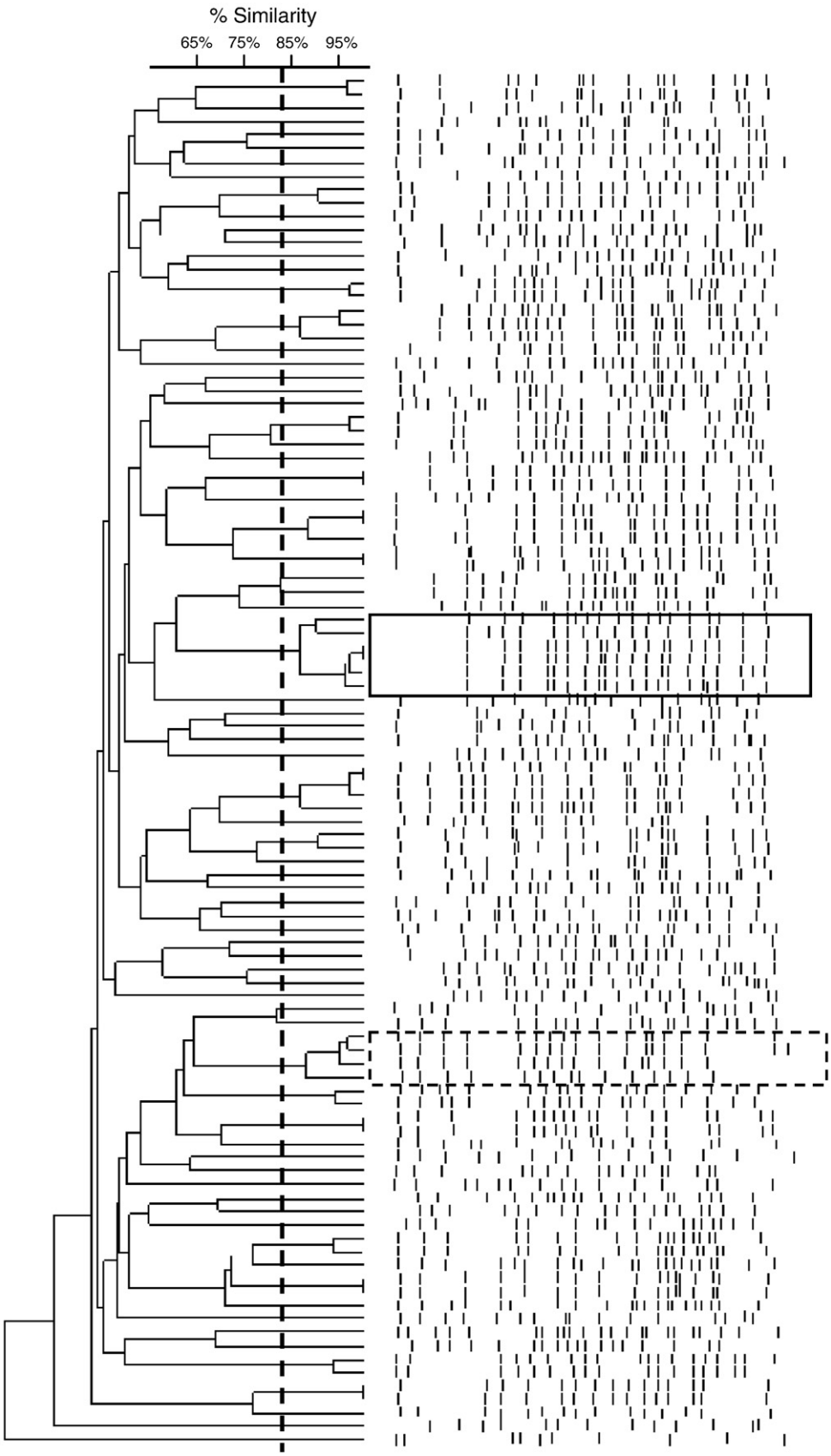

Fig. 2. Dendrogram depicting the genetic relationships among meropenem-resistant *P. aeruginosa* from 2007 to 2009. The vertical dashed line highlights 85% genetic similarity. The solid box highlights the related cluster from Eastern Canada. The hatched box highlights the related cluster from Western Canada.

hospital in Western Canada and the strains were isolated from either medical wards or outpatient clinics.

4. Discussion

Despite the increased rates of *A. baumannii* infections reported worldwide and the findings of clonal expansion among these organisms throughout clinical settings, particularly ICUs (Chaster, 2003; Morgan et al., 2009; Pournaras et al., 2006), *A. baumannii* represented only 0.35% of all organisms isolated over a 3-year study period. Previous Canadian reports support this observation and corroborate the low MDR rates in this country (Zhanel et al., 2008b), which contrast the data from US studies that show that MDR rates among *A. baumannii* ranged from 24.2% to approximately 50% (Karlowsky et al., 2003; Keen et al., 2010).

The SENTRY surveillance study reported that *A. baumannii* were identified primarily from respiratory tract infections in the United States and Latin America, whereas in Canada, wounds were the most prominent infection site (Gales et al., 2001a). However, in our study, *A. baumannii* strains were mostly from blood cultures or respiratory tract infections. Interestingly, most of the *A. baumannii* in this study were isolated from patients in the ICU, which also differs from a previous study showing that *Acinetobacter* spp. was more frequent among internal medicine patients (Gales et al., 2001a). ICU isolates were ranked as second and third pathogens in Latin America and Canada/USA, respectively (Gales et al., 2001a). Our findings are of concern because of the high percentage of *A. baumannii* found in critically ill patients in the ICU.

Molecular typing identified 6 clusters of 2 isolates per cluster that displayed >85% similarity. Overall, no significant clusters of *A. baumannii* were observed suggesting sporadic infections were more frequent. Although clonal spread has been previously documented and can be extremely difficult to eradicate (Tien et al., 2007), it appears that clonal dissemination of *A. baumannii* or MDR *A. baumannii* is not common in Canadian hospitals. Furthermore, *A. baumannii* reported in this initiative showed no similarity with previously typed Canadian military isolates (Tien et al., 2007), although this was expected because many of the military strains were MDR and isolates from this study were mostly susceptible to several agents tested.

Meropenem resistance rates among *P. aeruginosa* detected in this study (6.9%) were slightly lower when compared to prior studies (Gales et al., 2001b; Walkty et al., 2008; Walsh et al., 2005; Zhanel et al., 2008a), likely due to the smaller sample size. Additionally, the limited activity of fluoroquinolones has also been previously observed among *P. aeruginosa* from Canadian institutions (Walkty et al., 2008; Zhanel et al., 2008a) and could be due to the overuse of these antimicrobial agents in the clinical setting. Colistin, amikacin, and piperacillin/tazobactam were the most active antipseudomonal antimicrobials evaluated, which is corroborated by previous Canadian studies (Walkty et al., 2008; Zhanel et al., 2008a). Because of the relatively high susceptibility, piperacillin/tazobactam has been reported as a viable alternative for treating infections among meropenem-resistant and/or MDR *P. aeruginosa* isolates (Lockhart et al., 2007; Turner, 2009; Zhanel et al., 2008a). Furthermore, colistin showed excellent activity as an antipseudomonal agent and could therefore be a useful alternative for treatment; however, this agent is considerably toxic (Falagas and Kasiakou, 2005a; Falagas et al., 2005b).

Clonal spread of *P. aeruginosa* strains is not unusual (Gales et al., 2001b) but was found only in 2 instances (6 and 4 strains) in this study. However, it should be noted that only meropenem-resistant isolates were examined using molecular fingerprinting.

In summary, MDR *A. baumannii* are rare in Canada. Isolates were relatively unique reflecting a low frequency of clonal spread within or between hospitals. Most of the meropenem-resistant *P. aeruginosa* demonstrated a multidrug-resistant phenotype with minimal clonal spread in Canada. Ongoing surveillance of these organisms is important to help direct antimicrobial therapy and to monitor the emergence of potentially drug-resistant clones in Canada.

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CANWARD data can also be found at www.can-r.ca, the official website of the Canadian Antimicrobial Resistance Alliance (CARA).

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