Cross-Canada survey of resistance of 2747 aerobic blood culture isolates to piperacillin/tazobactam and other antibiotics

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KR Forward, PA Franks, DE Low, R Rennie, AE Simor, and the Canadian Piperacillin/Tazobactam Study Group. Cross-Canada survey of resistance of 2747 aerobic blood culture isolates to piperacillin/tazobactam and other antibiotics. *Can J Infect Dis* 1998;9(1):33-44.

OBJECTIVE: To compare the activity of piperacillin/tazobactam with that of other broad parenteral antibiotics against aerobic and facultative anaerobic blood culture isolates in a Canada-wide survey.

DESIGN: Fifty-eight laboratories in nine provinces each contributed up to 50 consecutive clinically significant aerobic and facultative anaerobic isolates for susceptibility testing.

SETTING: Participating hospitals included both tertiary care and community hospitals.

MATERIALS AND METHODS: Testing was performed in five regional centres by using the same microbroth dilution method, and results were interpreted according to National Committee for Clinical Laboratory Standards M7-A3 and M100-S5 guidelines.

RESULTS: Piperacillin/tazobactam and imipenem were both active against more than 99% of the 1616 strains of *Enterobacteriaceae* species tested. The minimum inhibitory concentration of 90% of isolates (MIC₉₀) of all *Enterobacteriaceae* species was 2 mg/L for piperacillin/tazobactam compared with 64 mg/L for piperacillin alone. Seventeen per cent of strains of *Enterobacteriaceae* species were susceptible to piperacillin/tazobactam but resistant to piperacillin. Piperacillin/tazobactam was highly active against *Pseudomonas aeruginosa*, inhibiting 99.1% of strains. MIC₉₀ was 8 mg/L. Nine per cent of *P aeruginosa* strains were not susceptible to imipenem. Most of these strains had a MIC of 8 mg/L, which falls in the intermediate category. Ninety-seven per cent of *P aeruginosa* were susceptible to ciprofloxacin and 97.3% to tobramycin. Ninety-six per cent of strains of *Actinobacter* species were susceptible to piperacillin/tazobactam, whereas only 76% of strains were susceptible to piperacillin alone. Overall, piperacillin/tazobactam was the most active agent tested; 98% of all strains were susceptible, followed closely by imipenem, to which 97.8% of strains were susceptible.

CONCLUSIONS: Aerobic blood culture isolates from Canadian centres continue to be highly susceptible to a variety of antibiotics. The broad spectrum of activity of piperacillin/tazobactam suggests that this combination should be considered for empirical treatment of sepsis while awaiting results of cultures and susceptibility testing.

Key Words: Antibiotic resistance, Piperacillin, Tazobactam, Susceptibility survey

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Accepted for publication January 28, 1997. Accepted April 1, 1997

Enquête pancanadienne sur la résistance de 2 747 isolats d'hémocultures aérobies à l'endroit du pipéracilline/tazobactam et d'autres antibiotiques

OBJECTIF : Comparer l'activité du pipéracilline/tazobactam à celle d'autres antibiotiques parentéraux à large spectre contre des isolats d'hémocultures aérobies et anaérobies facultatifs dans le cadre d'une enquête pancanadienne.

MODÈLE : Cinquante-huit laboratoires de neuf provinces ont chacun fourni jusqu'à 50 isolats aérobies et anaérobies facultatifs cliniquement significatifs aux fins d'épreuves de sensibilité.

CONTEXTE : Les hôpitaux participants étaient notamment des centres de soins tertiaires et communautaires.

MATÉRIEL ET MÉTHODES : Les épreuves ont été effectuées dans cinq centres régionaux au moyen, des mêmes méthodes de microdilution et les résultats ont été interprétés conformément aux directives M7-A3 et M100-S5 du NCCLS (*National Committee for Clinical Laboratory Standards*).

RÉSULTATS : Le pipéracilline/tazobactam et l'imipénem ont tous deux été efficaces contre plus de 99 % des 1 616 souches d'*Enterobacteriaceae* testés. Les concentrations inhibitrices minimum de 90 % des isolats (CMI₉₀) de tous les *Enterobacteriaceae* ont été de 2 mg/L pour le pipéracilline/tazobactam contre 64 mg/L pour la pipéracilline seule. Seize pour cent des souches d'*Enterobacteriaceae* se sont révélées sensibles au pipéracilline/tazobactam, mais résistantes à la pipéracilline. Le pipéracilline/tazobactam a été très efficace contre *Pseudomonas aeruginosa*, inhibant 99,1 % des souches. La CMI₉₀ a été de 8 mg/L; 9 % des souches de *P. aeruginosa* se sont révélées insensibles à l'imipénem. La plupart de ces souches avaient des CMI de 8 mg/L, ce qui les classe dans la catégorie de résistance intermédiaire. Quatre-vingt-dix-sept pour cent des isolats de *P. aeruginosa* ont été sensibles à la ciprofloxacine, 97,3 % à la tobramycine. Quatre-vingt-seize pour cent des souches d'*Actinobacter* ont été sensibles au pipéracilline/tazobactam, alors que 76 % seulement des souches étaient sensibles à la pipéracilline seule. Globalement, le pipéracilline/tazobactam a été l'agent le plus actif testé. Quatre-vingt-dix-huit pour cent de toutes les souches ont été sensibles, suivi de près par l'imipénem auquel 97,8 % des souches ont été sensibles.

CONCLUSIONS : Les isolats d'hémocultures aérobies provenant de centres canadiens continuent d'être très sensibles à divers antibiotiques. Le vaste spectre d'activité du pipéracilline/tazobactam donne à penser que cette association médicamenteuse est à envisager en traitement empirique de la septicémie en attendant les résultats des cultures et des antibiogrammes.

Piperacillin/tazobactam is the most recent of a number of beta-lactam/beta-lactamase inhibitor combinations to become available to Canadian physicians. The combination offers a number of advantages over previously marketed compounds. Piperacillin has a broader spectrum of activity than either the amino or carboxy penicillins, and tazobactam is a potent inhibitor of both chromosomally mediated and plasmid-mediated beta-lactamases (1,2,3).

Numerous clinical trials have demonstrated the efficacy of piperacillin/tazobactam in the treatment of a variety of infections, including intra-abdominal infections, skin and skin structure infections, pelvic infections in women, pneumonia and fever in neutropenic patients undergoing chemotherapy for both solid and hematological malignancies (4-13). Non-comparative trials have also evaluated the efficacy of piperacillin/tazobactam with or without an aminoglycoside for the treatment of bacteremia (14,15).

We conducted a prospective study of susceptibilities of blood culture isolates collected in 1995 from 58 sites across Canada to determine the prevalence of resistance to commonly used broad spectrum antibiotics, including piperacillin/tazobactam. Such data may help to establish the degree of confidence with which single agents may be used to treat serious bacteremic infections.

MATERIALS AND METHODS

Strains: Fifty-eight teaching and community hospitals from nine Canadian provinces participated in the evaluation. In most cases, 50 consecutive aerobic cultures were collected, beginning in February 1995. A few smaller centres fell short of this goal. Methicillin-resistant *Staphylococcus* species and anaerobes were not included. Potential contaminants, such as coagulase-negative *Staphylococcus* species and viridans

streptococci, were submitted only if recovered on three different occasions from the same patient within one week. Only one strain from each species was submitted per patient.

Methods: Broth microdilution susceptibility studies were performed with 96-well microtitre plates containing serial twofold dilutions of study antibiotics. Panels were prepared by Sensititre (AccuMed International Inc, Ohio) and distributed to each of five regional testing centres. Organisms were speciated in their originating laboratory by using standard methods. Non-fastidious organisms were tested in accordance with National Committee for Clinical Laboratory Standards (NCCLS) guidelines (NCCLS M7-A3 and M100-S5) (16,17). Inocula were prepared by directly inoculating four to five colonies of an overnight culture of the organism incubated at 35 to 37°C into demineralized water to produce a suspension corresponding to a 0.5 McFarland standard. Ten microlitres of inoculum was suspended in 10 mL of cation-supplemented Mueller Hinton broth. Fifty microlitres of the resulting suspension was transferred to each well of the microtitre plates, which were then incubated aerobically at 34 to 36°C for 18 h.

For susceptibility testing of *Streptococcus pneumoniae*, the inoculum was prepared in Mueller Hinton broth from overnight growth on 5% sheep blood agar. After mixing, 100 µL of inoculum was added to 10 mL of cation-supplemented Mueller Hinton broth with added 2% to 5% lysed horse blood (PML Microbiological, Oregon). One hundred microlitres was inoculated to each well of the microtitre panel with an autoinoculator. Plates were incubated aerobically at 35°C for 20 to 24 h.

Susceptibility testing for streptococci other than *S pneumoniae* was performed as for *S pneumoniae* except that only 10 µL was added to 10 mL of Mueller Hinton broth and 50 µL was added to each well.

For *Haemophilus influenzae*, the inoculum was prepared in

TABLE 1

Overall proportion of strains susceptible to antibiotics tested against all isolates in rank order

	% susceptible
Piperacillin-tazobactam	98.0
Piperacillin	87.5
Imipenem	97.8
Ceftazidime	91.8
Ciprofloxacin	92.8
Ticarcillin-clavulanate	90.8
Ceftriaxone	91.5

Mueller Hinton broth from isolated colonies on chocolate agar. Fifty microlitres of inoculum was transferred to 10 mL of *Haemophilus* species test medium broth (HTM) (BBL, Becton Dickinson and Company, Maryland). One hundred microlitres of HTM was added to each well. Plates were incubated at 35°C in carbon dioxide for 20 to 24 h.

All testing was performed using the same lot number of panels, *Haemophilus* species test medium and cation-supplemented Mueller Hinton broth. American type culture collection (ATCC) organisms were tested as appropriate, with each batch of organisms run against both Gram-positive and Gram-negative microtitre panels – *Staphylococcus aureus* ATCC 29213, *Enterococcus faecalis* ATCC 29212 *Escherichia coli* ATCC 25922, *E coli* ATCC 35218 and *Pseudomonas aeruginosa* ATCC 27853.

RESULTS

Of the 2747 blood culture isolates tested, piperacillin/tazobactam was most active, inhibiting 98% of strains, followed closely by imipenem, which inhibited 97.8% of strains (Table 1). Ceftazidime, ceftriaxone, ciprofloxacin and ticarcillin-clavulanate each inhibited over 90% of strains. Overall, the proportion of strains susceptible to third-generation cephalosporins and ciprofloxacin was lower than this percentage, primarily because of their intrinsic inactivity against enterococci, which comprised 160 of 2747 isolates. Against the 1611 strains of *Enterobacteriaceae* species tested, piperacillin/tazobactam was second only to imipenem in terms of the percentage of strains susceptible; only 0.2% of strains were resistant (Table 2). The minimum inhibitory concentration of 90% of isolates (MIC₉₀) of *Enterobacteriaceae* species was 2 mg/L compared with 64 mg/L for piperacillin alone. Seventeen per cent of *Enterobacteriaceae* species were susceptible to piperacillin/tazobactam but resistant to piperacillin. *Enterobacteriaceae* species remained highly susceptible to all agents tested, with the exception of piperacillin and cefoxitin, which inhibited 82% and 81% of strains, respectively. Figure 1 compares piperacillin/tazobactam with piperacillin MICs against strains of *Enterobacteriaceae* species, *E coli*, *Enterobacter cloacae* and *Acinetobacter* species. The majority of strains had lower piperacillin MICs in the presence of tazobactam than with piperacillin alone.

Figure 1) Comparison of the minimal inhibitory concentration (MIC) of piperacillin alone with that of piperacillin/tazobactam (8:1 ratio)

Piperacillin/tazobactam was the most active agent against *P aeruginosa*, inhibiting 99.1% of strains; MIC₉₀ was 8 mg/L. Ninety-one per cent of strains were susceptible to imipenem and 8% had a MIC of 8 mg/L, which fell into the intermediate category. Of the 111 strains of *P aeruginosa* tested, 97.3% of

TABLE 2
Comparative activity of piperacillin/tazobactam and other antibiotics against 2747 aerobic blood culture isolates

Organism (number of strains)	Antibiotic	Range (mg/L)	MIC ₅₀ (mg/L)	MIC ₉₀ (mg/L)	% S	% I	% R
<i>Escherichia coli</i> (805)	Piperacillin/tazobactam	0.25 - 256	0.5	1	99.9	0	0.1
	Piperacillin	0.25 - 256	1	128	77.8	8.9	13.3
	Imipenem	0.12 - 8	0.12	0.12	99.9	0.1	0
	Ceftazidime	0.12 - 64	0.25	0.5	97.1	0.6	2.2
	Ciprofloxacin	0.12 - 8	0.12	0.12	98.1	0.4	1.5
	Tobramycin	0.12 - 32	0.25	1	98.3	1	0.7
	Gentamicin	0.12 - 32	0.25	0.5	97.4	1.1	1.5
	Ticarcillin-clavulanate	0.25 - 128	1	8	98.4	1.5	0.1
	Ceftriaxone	0.25 - 128	0.25	0.5	97.4	0.9	1.7
	Cefotaxime	0.25 - 128	0.25	0.5	97.5	0.9	1.6
	Cefoxitin	0.25 - 64	2	16	88.6	3.7	7.7
<i>Klebsiella pneumoniae</i> (152)	Piperacillin/tazobactam	0.25 - 16	1	4	100	0	0
	Piperacillin	0.5 - 64	4	8	94.7	5.3	0
	Imipenem	0.12 - 8	0.12	0.25	99.3	0.7	0
	Ceftazidime	0.25 - 64	0.25	1	96.7	1.3	2
	Ciprofloxacin	0.12 - 4	0.12	0.12	98.7	0.7	0.7
	Tobramycin	0.12 - 16	0.25	0.5	98	0.7	1.3
	Gentamicin	0.12 - 32	0.25	0.5	97.4	0.7	2
	Ticarcillin-clavulanate	0.25 - 128	1	4	97.4	1.3	1.3
	Ceftriaxone	0.25 - 128	0.25	1	98	1.3	0.7
	Cefotaxime	0.25 - 64	0.25	0.5	97.4	2	0.7
	Cefoxitin	0.5 - 64	2	16	86.8	3.9	9.2
<i>Klebsiella oxytoca</i> (48)	Piperacillin/tazobactam	0.25 - 16	0.5	2	100	0	0
	Piperacillin	1 - 256	4	8	95.8	2.1	2.1
	Imipenem	0.12 - 0.5	0.12	0.25	100	0	0
	Ceftazidime	0.25 - 16	0.25	4	97.9	2.1	0
	Ciprofloxacin	0.12 - 1	0.12	0.12	100	0	0
	Tobramycin	0.12 - 2	0.25	0.5	100	0	0
	Gentamicin	0.12 - 4	0.25	0.5	100	0	0
	Ticarcillin-clavulanate	0.25 - 64	1	8	97.9	2.1	0
	Ceftriaxone	0.25 - 64	0.25	2	95.8	2.1	2.1
	Cefotaxime	0.25 - 64	0.25	1	97.9	0	2.1
	Cefoxitin	0.5 - 64	1	16	89.6	2.1	8.3
<i>Citrobacter freundii</i> (9)	Piperacillin/tazobactam	0.5 - 8	2	8	100	0	0
	Piperacillin	0.5 - 64	2	64	77.8	22.2	0
	Imipenem	0.12 - 0.5	0.12	0.5	100	0	0
	Ceftazidime	0.25 - 32	0.25	32	88.9	0	11.1
	Ciprofloxacin	0.12 - 1	0.12	1	100	0	0
	Tobramycin	0.12 - 0.5	0.25	0.5	100	0	0
	Gentamicin	0.12 - 1	0.25	1	100	0	0
	Ticarcillin-clavulanate	0.5 - 64	2	64	77.8	22.2	0

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TABLE 2 continued

Comparative activity of piperacillin/tazobactam and other antibiotics against 2747 aerobic blood culture isolates

Organism (number of strains)	Antibiotic	Range (mg/L)	MIC ₅₀ (mg/L)	MIC ₉₀ (mg/L)	% S	% I	% R
<i>C. freundii</i>	Ceftriaxone	0.25 - 32	0.25	32	88.9	11.1	0
	Cefotaxime	0.25 - 16	0.25	16	88.9	11.1	0
	Cefoxitin	2 - 64	32	64	22.2	11.1	66.7
<i>Proteus mirabilis</i> (41)	Piperacillin/tazobactam	0.25 - 1	0.25	0.5	100	0	0
	Piperacillin	0.25 - 8	0.25	1	100	0	0
	Imipenem	0.12 - 4	0.5	1	100	0	0
	Ceftazidime	0.25 - 1	0.25	0.25	100	0	0
	Ciprofloxacin	0.12 - 0.25	0.12	0.12	100	0	0
	Tobramycin	0.12 - 16	0.5	1	90.2	4.9	4.9
	Gentamicin	0.12 - 16	0.5	1	90.2	2.4	7.3
	Ticarcillin-clavulanate	0.25 - 8	0.25	1	100	0	0
	Ceftriaxone	0.25 - 2	0.25	0.25	100	0	0
	Cefotaxime	0.25 - 1	0.25	0.25	100	0	0
	Cefoxitin	1 - 16	2	2	97.6	2.4	0
<i>Enterobacter cloacae</i> (77)	Piperacillin/tazobactam	0.25 - 256	1	32	89.6	9.1	1.3
	Piperacillin	0.5 - 256	2	128	76.6	10.4	13
	Imipenem	0.12 - 4	0.12	0.25	100	0	0
	Ceftazidime	0.25 - 64	0.25	64	75.3	2.6	22.1
	Ciprofloxacin	0.12 - 8	0.12	0.25	96.1	1.3	2.6
	Tobramycin	0.12 - 16	0.25	0.5	97.4	0	2.6
	Gentamicin	0.12 - 8	0.12	0.5	97.4	2.6	0
	Ticarcillin-clavulanate	0.25 - 256	2	128	74	11.7	14.3
	Ceftriaxone	0.25 - 128	0.25	128	74	6.5	19.5
	Cefotaxime	0.25 - 128	0.25	128	74	7.8	18.2
	Cefoxitin	2 - 64	64	64	6.5	3.9	89.6
<i>Enterobacter aerogenes</i> (16)	Piperacillin/tazobactam	0.25 - 32	2	32	87.5	12.5	0
	Piperacillin	0.25 - 64	4	64	75	25	0
	Imipenem	0.12 - 0.5	0.12	0.5	100	0	0
	Ceftazidime	0.25 - 64	0.25	32	62.5	12.5	25
	Ciprofloxacin	0.12 - 2	0.12	0.5	93.8	6.3	0
	Tobramycin	0.12 - 8	0.25	2	93.8	6.3	0
	Gentamicin	0.12 - 8	0.25	2	93.8	6.3	0
	Ticarcillin-clavulanate	0.5 - 64	8	64	68.8	31.3	0
	Ceftriaxone	0.25 - 128	0.25	16	75	18.8	6.3
	Cefotaxime	0.25 - 128	0.25	8	93.8	0	6.3
	Cefoxitin	1 - 64	64	64	6.3	12.5	81.3
<i>Serratia marcescens</i> (22)	Piperacillin/tazobactam	0.25 - 16	1	2	100	0	0
	Piperacillin	0.25 - 16	2	16	100	0	0
	Imipenem	0.12 - 32	0.25	0.5	95.5	0	4.5
	Ceftazidime	0.25 - 1	0.25	0.5	100	0	0
	Ciprofloxacin	0.12 - 2	0.12	0.12	95.5	4.5	0

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TABLE 2 continued

Comparative activity of piperacillin/tazobactam and other antibiotics against 2747 aerobic blood culture isolates

Organism (number of strains)	Antibiotic	Range (mg/L)	MIC ₅₀ (mg/L)	MIC ₉₀ (mg/L)	% S	% I	% R
<i>S marcescens</i>	Tobramycin	0.12 - 8	0.5	4	95.5	4.5	0
	Gentamicin	0.12 - 8	0.25	1	95.5	4.5	0
	Ticarcillin-clavulanate	1 - 128	4	32	86.4	4.5	9.1
	Ceftriaxone	0.25 - 8	0.25	2	100	0	0
	Cefotaxime	0.25 - 16	0.25	8	90.9	9.1	0
	Cefoxitin	4 - 64	16	64	45.5	22.7	31.8
Other <i>Enterobacteriaceae</i> (39)	Piperacillin/tazobactam	0.25 - 16	1	4	100	0	0
	Piperacillin	0.5 - 256	1	64	89.2	2.7	8.1
	Imipenem	0.12 - 0.25	0.12	0.12	100	0	0
	Ceftazidime	0.25 - 64	0.25	0.5	94.6	0	5.4
	Ciprofloxacin	0.12 - 0.25	0.12	0.12	100	0	0
	Tobramycin	0.12 - 1	0.25	0.5	100	0	0
	Gentamicin	0.12 - 0.5	0.12	0.5	100	0	0
	Ticarcillin-clavulanate	0.25 - 32	1	8	94.6	5.4	0
	Ceftriaxone	0.25 - 128	0.25	8	94.6	0	5.4
	Cefotaxime	0.25 - 128	0.25	2	94.6	2.7	2.7
	Cefoxitin	0.25 - 64	1	4	91.9	0	8.1
<i>Morganella morganii</i> (7)	Piperacillin/tazobactam	0.25 - 4	0.25	4	100	0	0
	Piperacillin	0.25 - 4	1	4	100	0	0
	Imipenem	0.12 - 2	1	2	100	0	0
	Ceftazidime	0.25 - 64	0.25	64	85.7	0	14.3
	Ciprofloxacin	0.12 - 8	0.12	8	85.7	0	14.3
	Tobramycin	0.25 - 16	0.5	16	85.7	0	14.3
	Gentamicin	0.25 - 2	0.5	2	100	0	0
	Ticarcillin-clavulanate	0.25 - 4	2	4	100	0	0
	Ceftriaxone	0.25 - 64	0.25	64	85.7	0	14.3
	Cefotaxime	0.25 - 16	0.25	16	85.7	14.3	0
	Cefoxitin	4 - 64	4	64	85.7	0	14.3
<i>Pseudomonas aeruginosa</i> (111)	Piperacillin/tazobactam	0.5 - 256	2	8	99.1	0	0.9
	Piperacillin	0.5 - 256	4	16	96.4	0	3.6
	Imipenem	0.12 - 16	1	4	91	8.1	0.9
	Ceftazidime	0.25 - 64	1	16	89.2	6.3	4.5
	Ciprofloxacin	0.12 - 8	0.12	0.25	97.3	0	2.7
	Tobramycin	0.12 - 32	0.25	1	97.3	0.9	1.8
	Gentamicin	0.12 - 32	0.5	4	95.5	1.8	2.7
	Ticarcillin-clavulanate	0.5 - 256	16	64	93.6	0	6.4
<i>Pseudomonas</i> species (5)	Piperacillin/tazobactam	1 - 4	2	4	100	0	0
	Piperacillin	4 - 256	4	256	80	0	20
	Imipenem	0.25 - 1	0.5	1	100	0	0
	Ceftazidime	1 - 64	16	64	20	60	20
	Ciprofloxacin	0.12 - 4	0.12	4	80	0	20

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TABLE 2 continued

Comparative activity of piperacillin/tazobactam and other antibiotics against 2747 aerobic blood culture isolates

Organism (number of strains)	Antibiotic	Range (mg/L)	MIC ₅₀ (mg/L)	MIC ₉₀ (mg/L)	% S	% I	% R
<i>Pseudomonas</i> species	Tobramycin	0.25 - 1	0.5	1	100	0	0
	Gentamicin	0.12 - 2	0.5	2	100	0	0
	Ticarcillin-clavulanate	0.25 - 256	64	256	20	40	40
	Ceftriaxone	2 - 128	8	128	60	0	40
	Cefotaxime	4 - 128	8	128	60	20	20
	Cefoxitin	8 - 64	64	64	20	0	80
<i>Acinetobacter</i> species (25)	Piperacillin/tazobactam	0.25 - 32	0.5	8	96	4	0
	Piperacillin	0.5 - 256	8	256	76	12	12
	Imipenem	0.12 - 32	0.12	0.5	96	0	4
	Ceftazidime	0.25 - 64	2	8	92	0	8
	Ciprofloxacin	0.12 - 8	0.12	8	88	0	12
	Tobramycin	0.12 - 32	0.25	16	76	4	20
	Gentamicin	0.12 - 32	0.5	32	76	4	20
	Ticarcillin-clavulanate	0.25 - 128	4	64	84	12	4
	Ceftriaxone	0.25 - 128	8	64	68	20	12
	Cefotaxime	0.25 - 64	4	64	70.8	16.7	12.5
	Cefoxitin	1 - 64	64	64	28	4	68
<i>Stenotrophomonas maltophilia</i> (13)	Piperacillin/tazobactam	8 - 256	8	256	61.5	0	38.5
	Piperacillin	8 - 256	32	256	38.5	23.1	38.5
	Imipenem	32	32	32	0	0	100
	Ceftazidime	0.5 - 64	2	64	84.6	0	15.4
	Ciprofloxacin	0.12 - 8	1	8	53.8	7.7	38.5
	Tobramycin	4 - 32	32	32	30.8	15.4	53.8
	Gentamicin	2 - 32	32	32	15.4	23.1	61.5
	Ticarcillin-clavulanate	4 - 128	8	64	76.9	15.4	7.7
	Ceftriaxone	16 - 128	128	128	0	30.8	69.2
	Cefotaxime	2 - 128	32	128	15.4	46.2	38.5
	Cefoxitin	64	64	64	0	0	100
<i>Haemophilus influenzae</i> (27)	Piperacillin/tazobactam	0.25 - 0.25	0.25	0.25	100	0	0
	Piperacillin	0.25 - 64	0.25	2	88.9	0	11.1
	Imipenem	0.12 - 0.25	0.12	0.25	100	0	0
	Ceftazidime	0.25 - 0.25	0.25	0.25	100	0	0
	Ciprofloxacin	0.12 - 0.12	0.12	0.12	100	0	0
	Ticarcillin-clavulanate	0.25 - 0.5	0.25	0.25	100	0	0
	Ceftriaxone	0.25 - 0.25	0.25	0.25	100	0	0
	Cefotaxime	0.25 - 0.25	0.25	0.25	100	0	0
	Cefoxitin	0.25 - 2	1	2	100	0	0
Other Gram-negative rods (7)	Piperacillin/tazobactam	0.25 - 16	0.5	16	100	0	0
	Piperacillin	0.25 - 64	1	64	71.4	28.6	0
	Imipenem	0.12 - 0.5	0.12	0.5	100	0	0
	Ceftazidime	0.25 - 16	0.5	16	85.7	14.3	0

Continued on next page

TABLE 2 continued
Comparative activity of piperacillin/tazobactam and other antibiotics against 2747 aerobic blood culture isolates

Organism (number of strains)	Antibiotic	Range (mg/L)	MIC ₅₀ (mg/L)	MIC ₉₀ (mg/L)	% S	% I	% R
Other Gram-negative rods (7)	Ciprofloxacin	0.12 - 0.5	0.12	0.5	100	0	0
	Tobramycin	0.12 - 16	2	16	71.4	0	28.6
	Gentamicin	0.12 - 16	1	16	71.4	0	28.6
	Ticarcillin-clavulanate	0.25 - 32	0.25	32	85.7	14.3	0
	Ceftriaxone	0.25 - 8	0.25	8	100	0	0
	Cefotaxime	0.25 - 8	0.25	8	100	0	0
	Cefoxitin	0.25 - 64	8	64	57.1	0	42.9
<i>Enterococcus faecalis</i> (124)	Piperacillin/tazobactam	0.25 - 32	2	4	96.8	0	3.2
	Piperacillin	0.25 - 32	2	8	92.7	0	7.3
	Imipenem	0.25 - 32	1	2	96	0.8	3.2
	Ciprofloxacin	0.12 - 8	0.5	8	72.6	2.4	25
	Ticarcillin-clavulanate	0.5 - 64	16	32	27.4	0	72.6
	Vancomycin	0.25 - 64	1	1	97.6	0	2.4
<i>Enterococcus faecium</i> (29)	Piperacillin/tazobactam	0.25 - 32	32	32	34.5	0	65.5
	Piperacillin	0.25 - 32	32	32	37.9	0	62.1
	Imipenem	0.25 - 32	32	32	37.9	0	62.1
	Ciprofloxacin	0.12 - 8	8	8	31	6.9	62.1
	Ticarcillin-clavulanate	0.25 - 64	64	64	24.1	0	75.9
	Vancomycin	0.25 - 6	0.5	2	99.1	0	6.9
Other enterococci (7)	Piperacillin/tazobactam	1 - 8	1	8	100	0	0
	Piperacillin	1 - 8	4	8	100	0	0
	Imipenem	0.5 - 32	0.5	32	85.7	0	14.3
	Ciprofloxacin	0.12 - 4	0.5	4	85.7	0	14.3
	Ticarcillin-clavulanate	8 - 64	16	64	28.6	0	71.4
	Vancomycin	0.5 - 2	0.5	2	100	0	0
<i>Staphylococcus aureus</i> (492)	Piperacillin/tazobactam	0.25 - 32	0.5	1	99.2	0	0.8
	Piperacillin	0.25 - 32	2	16	88	0	12
	Imipenem	0.12 - 16	0.25	0.25	99.8	0	0.2
	Ceftazidime	0.25 - 64	4	8	92.1	2.6	5.3
	Ciprofloxacin	0.12 - 8	0.12	0.25	95.9	0.4	3.7
	Ticarcillin-clavulanate	0.25 - 128	1	4	94.3	0	5.7
	Ceftriaxone	0.25 - 128	2	4	96.7	2.4	0.8
	Oxacillin	0.12 - 8	0.12	0.5	97.6	0	2.4
	Vancomycin	0.25 - 64	0.5	0.5	99.8	0	0.2
	Clindamycin	0.12 - 16	0.25	0.5	90.4	1.4	8.1
	Cefuroxime	0.25 - 64	1	1	97	1	2
	Cefazolin	0.25 - 64	0.25	1	98.6	0.8	0.6
Coagulase-negative staphylococci (104)	Piperacillin/tazobactam	0.25 - 32	0.5	8	91.3	0	8.7
	Piperacillin	0.25 - 32	2	32	86.5	0	13.5
	Imipenem	0.25 - 32	0.25	2	93.3	0	6.7
	Ceftazidime	0.25 - 64	8	64	66.3	8.7	25

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TABLE 2 continued

Comparative activity of piperacillin/tazobactam and other antibiotics against 2747 aerobic blood culture isolates

Organism (number of strains)	Antibiotic	Range (mg/L)	MIC ₅₀ (mg/L)	MIC ₉₀ (mg/L)	% S	% I	% R
Coagulase-negative staphylococci	Ciprofloxacin	0.12 - 8	0.25	8	60.6	6.7	32.7
	Ticarcillin-clavulanate	0.25 - 128	0.5	32	80.8	0	19.2
	Ceftriaxone	0.25 - 128	4	64	81.7	6.7	11.5
	Oxacillin	0.12 - 8	2	8	54.8	0	45.2
	Vancomycin	0.25 - 2	0.5	1	100	0	0
	Clindamycin	0.25 - 16	16	16	42.3	3.8	53.8
	Cefuroxime	0.25 - 64	0.5	64	84.6	1.9	13.5
	Cefazolin	0.25 - 64	0.5	16	84.6	6.7	8.7
<i>Streptococcus pyogenes</i> (54)	Piperacillin/tazobactam	0.25 - 0.5	0.25	0.25	100	0	0
	Piperacillin	0.25 - 0.25	0.25	0.25	100	0	0
	Imipenem	0.25 - 0.5	0.25	0.25	100	0	0
	Ceftazidime	0.25 - 0.5	0.25	0.25	100	0	0
	Ciprofloxacin	0.12 - 1	0.25	0.5	100	0	0
	Ticarcillin-clavulanate	0.25 - 0.25	0.25	0.25	100	0	0
	Ceftriaxone	0.25 - 0.25	0.25	0.25	100	0	0
	Oxacillin	0.12 - 0.25	0.12	0.12	100	0	0
	Vancomycin	0.25 - 0.5	0.25	0.25	100	0	0
	Clindamycin	0.25 - 1	0.25	0.25	98.1	0	1.9
	Cefuroxime	0.25 - 0.5	0.25	0.25	100	0	0
	Cefazolin	0.25 - 0.25	0.25	0.25	100	0	0
	Ampicillin	0.06 - 0.25	0.06	0.06	100	0	0
<i>Streptococcus agalactiae</i> (81)	Piperacillin/tazobactam	0.25 - 0.25	0.25	0.25	100	0	0
	Piperacillin	0.25 - 16	0.25	0.25	98.8	0	1.2
	Imipenem	0.25 - 0.25	0.25	0.25	100	0	0
	Ceftazidime	0.25 - 2	0.25	0.5	95.1	2.5	2.5
	Ciprofloxacin	0.12 - 1	0.25	0.5	100	0	0
	Ticarcillin-clavulanate	0.25 - 4	0.25	0.25	100	0	0
	Ceftriaxone	0.25 - 1	0.25	0.25	98.8	1.2	0
	Oxacillin	0.12 - 1	0.12	0.12	100	0	0
	Vancomycin	0.25 - 1	0.25	0.5	100	0	0
	Clindamycin	0.25 - 2	0.25	0.25	92.5	5	2.5
	Cefuroxime	0.25 - 2	0.25	0.25	100	0	0
	Ampicillin	0.06 - 0.25	0.06	0.06	100	0	0
	Cefazolin	0.25 - 4	0.25	0.25	100	0	0
<i>Streptococcus pneumoniae</i> (361)	Piperacillin/tazobactam	0.12 - 2	0.12	0.12	100	0	0
	Piperacillin	0.12 - 8	0.12	0.12	100	0	0
	Imipenem	0.12 - 0.5	0.12	0.12	99.4	0.6	0
	Ceftazidime	0.12 - 16	0.12	0.5	90.5	2.2	6.9
	Ciprofloxacin	0.06 - 8	0.5	2	88.6	8.9	2.5
	Ticarcillin-clavulanate	0.12 - 16	0.12	0.25	96.7	0	3.3

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TABLE 2 continued
Comparative activity of piperacillin/tazobactam and other antibiotics against 2747 aerobic blood culture isolates

Organism (number of strains)	Antibiotic	Range (mg/L)	MIC ₅₀ (mg/L)	MIC ₉₀ (mg/L)	% S	% I	% R
<i>S pneumoniae</i>	Ceftriaxone	0.12 - 8	0.12	0.12	96.4	2.8	0.8
	Vancomycin	0.12 - 2	0.12	0.5	99.7	0	0.3*
	Clindamycin	0.12 - 16	0.12	0.12	98.6	0.3	1.1
	Cefuroxime	0.12 - 4	0.12	0.12	93.6	1.4	5
	Cefazolin	0.12 - 4	0.12	0.12	100	0	0
	Ampicillin	0.03 - 4	0.03	0.12	93.3	0	7.0
<i>Viridans streptococci</i> (40)	Piperacillin/tazobactam	0.25 - 4	0.25	1	100	0	0
	Piperacillin	0.25 - 8	0.25	1	100	0	0
	Imipenem	0.25 - 1	0.25	0.25	100	0	0
	Ceftazidime	0.25 - 32	0.5	4	55	15	30
	Ciprofloxacin	0.12 - 4	0.5	2	82.5	15	2.5
	Ticarcillin-clavulanate	0.25 - 32	0.25	8	90	0	10
	Ceftriaxone	0.25 - 2	0.25	1	87.5	10	2.5
	Vancomycin	0.25 - 0.5	0.25	0.5	100	0	0
	Clindamycin	0.25 - 0.25	0.25	0.25	100	0	0
	Cefuroxime	0.25 - 4	0.25	2	100	0	0
	Cefazolin	0.25 - 32	0.25	4	92.5	5	2.5
	Ampicillin	0.06 - 4	0.06	1	85	0	15
Other streptococci (31)	Piperacillin/tazobactam	0.25 - 2	0.25	0.25	100	0	0
	Piperacillin	0.25 - 2	0.25	0.5	100	0	0
	Imipenem	0.25 - 0.5	0.25	0.25	100	0	0
	Ceftazidime	0.25 - 64	0.25	2	87.1	0	12.9
	Ciprofloxacin	0.12 - 1	0.25	0.5	100	0	0
	Ticarcillin-clavulanate	0.25 - 64	0.25	0.25	96.8	0	3.2
	Ceftriaxone	0.25 - 32	0.25	0.25	90.3	3.2	6.5
	Vancomycin	0.25 - 1	0.25	0.5	100	0	0
	Clindamycin	0.25 - 16	0.25	0.25	90.3	3.2	6.5
	Cefuroxime	0.25 - 8	0.25	0.25	100	0	0
	Cefazolin	0.25 - 16	0.25	0.25	93.5	6.5	0
	Ampicillin	0.06 - 4	0.06	0.12	93.5	0	6.5

I Intermediate; MIC₅₀ Minimum inhibitory concentration required to inhibit 50% of isolates; MIC₉₀ Minimum inhibitory concentration required to inhibit 90% of isolates; R Resistant; S Susceptible

strains were susceptible to ciprofloxacin. Canadian strains remain highly susceptible to aminoglycosides, the MIC₉₀ for tobramycin being only 1 mg/L.

Twenty-five strains of *Acinetobacter* species were tested and 96% of these were susceptible to piperacillin/tazobactam compared with only 76% of strains susceptible to piperacillin. Only 76% of strains were susceptible to aminoglycosides, and only 68% were susceptible to ceftriaxone. Ceftazidime was somewhat more active than ceftriaxone (MIC₉₀ 8 mg/L versus 64 mg/L) against *Acinetobacter* species.

All 361 strains of *S pneumoniae* were susceptible to piperacillin/tazobactam, piperacillin and imipenem. The highest observed piperacillin/tazobactam MIC was 1 mg/L. The highest imipenem MIC was 0.25 mg/L. Only two ceftriaxone-resistant strains (MIC 2 mg/L or greater) were identified. The highest ceftriaxone MIC observed was 8 mg/L. Of the *S pneumoniae* strains tested, 11.3% had decreased susceptibility to ciprofloxacin (MIC 2 mg/L or greater).

Only three vancomycin-resistant *E faecalis* strains were identified, and only two of 29 *Enterococcus faecium* strains

were vancomycin resistant. While piperacillin/tazobactam was highly active against *E. faecalis*, only 34.5% of *E. faecium* strains were susceptible.

DISCUSSION

The antibiotic armamentarium offers a number of choices for the initial empirical treatment of severely ill patients with bacteremia. The choice of agents in this setting should take into account the observed susceptibility patterns of isolates most frequently encountered. In this study, we compared the activity of a number of broad spectrum antibiotics with Canadian strains collected from both tertiary centres, and community and regional hospitals. With the exception of anaerobes and methicillin-resistant staphylococci, the numbers and proportion of strains tested should be quite representative of the Canadian experience. We have previously made the observation that Canadian strains are often more susceptible to antibiotics than those in Europe and the United States, and, therefore, it is important to use Canadian susceptibility data when making therapeutic choices (18).

Of the agents tested, piperacillin/tazobactam and imipenem had the broadest spectrums of activity. We would also expect these agents to be active against the anaerobes that were recovered during the same period of time but were not tested (19). Of the strains tested, only *E. faecium* and *Stenotrophomonas maltophilia* were frequently resistant to these agents – *E. faecium*, by virtue of altered penicillin binding proteins and *S. maltophilia* because of its broad spectrum metalloenzyme and decreased permeability.

Piperacillin/tazobactam was much more active against *E. coli* than piperacillin (MIC₉₀ 1 mg/L versus 128 mg/L). Twenty-two per cent more strains were susceptible to piperacillin/tazobactam than to piperacillin alone. This presumably reflects the prevalence of TEM1 beta-lactamases in *E. coli* and their susceptibility to tazobactam (1). For all *Enterobacteriaceae* species tested, the MIC₉₀ was lower for piperacillin/tazobactam than for piperacillin. Possibly, this represents a small amount of intrinsic activity of tazobactam, as well as its activity against beta-lactamases from a number of classes. We also observed that *E. cloacae* strains usually had lower MICs to piperacillin/tazobactam than to piperacillin. This has been observed by others and is likely a reflection of the weak activity of tazobactam against class 1 beta-lactamases (20). When piperacillin/tazobactam was compared with ticarcillin-clavulanate, only *S. maltophilia* was more susceptible to ticarcillin-clavulanate (MIC₉₀ 64 mg/L versus 256 mg/L). This has been noted by others (21-24).

A number of agents showed reduced activity against *Acinetobacter* species. Only 76% of strains were susceptible to gentamicin and tobramycin, and only 71% were susceptible to cefotaxime. Imipenem remained highly active against *Acinetobacter* species, the MIC₉₀ being 0.5 mg/L. Ninety-six per cent of strains were susceptible to imipenem. Piperacillin/tazobactam was more active than piperacillin (MIC₉₀ 8 mg/L versus 256 mg/L), and 20% more strains were more susceptible to piperacillin/tazobactam. These findings likely reflect both the intrinsic

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activity of tazobactam against *Acinetobacter* species and the prevalence of beta-lactamases in *Acinetobacter* species (1,25).

CONCLUSIONS

Blood culture isolates from this Canada-wide study remain highly susceptible to a variety of commonly used antibiotics representing several different classes. Piperacillin and tazobactam together inhibited more than 98% of most organism groups tested, including *Enterobacteriaceae* species, *P. aeruginosa*, *H. influenzae* and streptococci. Piperacillin/tazobactam has a spectrum of activity that provides coverage for bloodstream infections in the vast majority of cases. Other factors, including the result of treatment trials, pharmacokinetics and pharmacoeconomics, will ultimately be required to define the place of piperacillin/tazobactam in the empirical treatment of suspected bacteremia.

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