Study of the comparative activity of piperacillin/tazobactam with currently available antibiotics against 8206 aerobic isolates

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OBJECTIVES: To compare the activity of piperacillin-tazobactam with piperacillin and other parenterally administered antibiotics against aerobic Gram-negative bacilli and Gram-positive cocci isolated from across Canada, and to determine the prevalence of resistance mediated by extended-spectrum cephalosporinases.
METHODS: Sixty-one laboratories participated. Disk diffusion testing was performed in accordance with methods outlined by the National Committee for Clinical Laboratory Standards. Susceptibilities were performed on 8206 strains. *Escherichia coli* and *Klebsiella pneumoniae* with reduced susceptibilities to third-generation cephalosporins were screened for extended-spectrum beta-lactamases (ESBLs).
RESULTS: Piperacillin-tazobactam was active against 92% of the strains, piperacillin against 81% and ticarcillin-clavulanic acid against 88%. Few differences were observed in the relative susceptibility of strains from teaching or community hospitals, from different anatomic sites or from different regions of the country. Aerobic Gram-negative bacilli tested tended to be more susceptible to all the agents than was recently reported in a similar American study. Only 43% of *Enterococcus faecium* were susceptible to ampicillin and 42% to piperacillin piperacillin with and without tazobactam. Only two enterococcal strains were resistant to vancomycin, and 19 had intermediate zone sizes. Of the 10 strains of *E coli* and eight strains of *K pneumoniae* with reduced susceptibility to extended spectrum cephalosporins, only one demonstrated typical ESBL activity.
CONCLUSIONS: Canadian aerobic Gram-positive cocci and Gram-negative bacilli remain highly susceptible to many currently available antibiotics. The findings confirm a broad spectrum of activity of piperacillin-tazobactam and indicate that the pattern of susceptibility is quite uniform from different body sites, in both teaching and community hospitals, and across the country.

Key Words: *Canadian, Piperacillin-tazobactam, Resistance, Susceptibility*

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Étude de l'activité comparative de la pipéracilline/tazobactam et des antibiotiques actuellement utilisés contre 8 206 isolats aérobies

OBJECTIFS : Comparer l'activité de la pipéracilline/tazobactam et de la pipéracilline et d'autres antibiotiques administrés par voie parentérale contre des bacilles gram-négatifs aérobies et des cocci gram-positifs isolés, provenant de plusieurs centres canadiens et déterminer la prévalence de la résistance associée aux céphalosporinases à spectre élargi.

MÉTHODES : Soixante-et-un laboratoires ont participé à l'étude. Des techniques de diffusion ont été utilisées, conformément aux normes du *National Committee for Clinical Laboratory Standards.* Des antibiogrammes ont été effectués sur 8 206 isolats. On a procédé à un dépistage d'*Escherichia coli* et de *Klebsiella pneumoniæ* présentant une sensibilité moindre aux céphalosporines de troisième génération pour y déceler la présence de bêtalactamases à spectre élargi (BLSE).

RÉSULTATS : La pipéracilline/tazobactam a été efficace contre 92 % des souches, la pipéracilline, contre 81 % et la ticarcilline-acide clavulanique, contre 88 %. Peu de différences ont été observées quant à la sensibilité relative des souches provenant des hôpitaux communautaires ou universitaires, provenant de différents sites anatomiques ou de différentes régions du pays. Les bacilles gram-négatifs aérobies testés tendaient à être plus sensibles à tous les agents, comparativement à un récent rapport d'une étude américaine similaire. Quarante-trois pour cent seulement des *Enterococcus fæcium* ont été sensibles à l'ampicilline et 42 % à la pipéracilline avec et sans tazobactam. Seules deux souches entérococciques ont été résistantes à la vancomycine et 19 présentaient des zones de taille intermédiaire. Parmi les dix souches de *E. coli* et les huit souches de *K. pneumoniæ* présentant une sensibilité réduite aux céphalosporines à large spectre, une seule a présenté une activité BLSE typique.

CONCLUSIONS : Les cocci gram-positifs aérobies et les bacilles gram-négatifs restent très sensibles aux nombreux antibiotiques actuellement sur le marché. Ces résultats confirment l'activité à large spectre de la pipéracilline/tazobactam et indiquent que le mode de sensibilité est assez uniforme, peu importe le site de l'infection, tant dans les hôpitaux universitaires que communautaires et d'un bout à l'autre du pays.

The recent approval of a new antimicrobial such as piperacillin-tazobactam (PT) provides an opportunity to examine the susceptibility profiles of this and other available antibiotics and to study the emergence of antibiotic resistance in different settings and among different genera in a cross-Canada survey.

Tazobactam is a beta-lactamase inhibiting penicillanic acid sulphone derivative which, when combined with piperacillin, expands its spectrum of activity to include most strains of *Staphlococcus aureus* and a number of Gram-negative bacilli producing beta-lactamases of Bush group two (1,2). The spectrum of activity of PT is the broadest of drugs in their class and typically approaches that of imipenem (2,3). We undertook to compare the activity of PT with other commonly used antibiotics against aerobic Gram-negative bacilli and Gram-positive cocci from across Canada and from a variety of clinical sources. We also screened *Escherichia coli* and *Klebsiella pneumoniae* for susceptibility patterns typical of strains producing extended-spectrum beta-lactamases (ESBLs). Because a large number of commonly occurring species were tested, we were able to compare the activity of piperacillin, PT and ticarcillin-clavulanate (TC) at different body sites, in university and community hospitals and in different regions of the country.

MATERIALS AND METHODS

Study design: Sixty-one laboratories in 10 Canadian provinces each tested up to 150 clinical strains from hospitalized patients. To ensure representative surveillance patterns, only one strain of each species per patient was included in the study, and strains were collected consecutively. Strains were tested only if they met the criteria for clinical significance established in individual laboratories. Included in the analysis were isolates from blood, lower respiratory tract, skin and soft tissue, intra-abdominal and female pelvic sites. Urinary, fecal, upper respiratory and vaginal isolates were not included. Also excluded from analysis were methicillin-resistant *S aureus*, anaerobes, Gram-positive bacilli, Gram-negative cocci and fastidious aerobic Gram-negative bacilli. Coagulase-negative staphylococci were included for analysis only if they were recovered from multiple specimens collected from known sterile sites at different times.

Susceptibility testing: Disk susceptibility testing was performed in accordance with National Committee for Clinical Laboratory Standards (NCCLS) documents M2-A5 and MS1 00-S5 (4,5). To ensure optimal standardization of test results, centres were obliged to use disks (Becton Dickinson Laboratories, Maryland) of the same batch number provided by the study co-ordinator. Organisms were included as controls as appropriate for the organisms and agents tested. These included *S aureus* ATCC 25923, *E coli* ATCC 25922, *E coli* ATCC 35218, *Enterococcus faecalis* ATCC 29212 and *Pseudomonas aeruginosa* ATCC 27853. Strains of *Klebsiella* species and *E coli* that exhibited decreased susceptibility to third-generation cephalosporins were referred centrally and screened by one of the researchers for ESBLs using both the double disk diffusion method and E test ESBL strips (AB Biodisk, Solona, Sweden) (6). Inhibition of ESBL by clavulanic acid reduces the minimum inhibitory concentration (MIC) of ceftazidime when the two are tested together. A ratio of the ceftazidime MIC without and with clavulanic acid of 16 or more was interpreted as indicating ESBL production.

Data analysis: Organisms were coded by species, hospital type (community or teaching) and geographic region (Atlantic, Quebec, Ontario, Western). The clinical site of infection was recorded. Results were collected on a standardized data collection form. Results were interpreted using NCCLS interpre-

TABLE 1
Comparative activity of piperacillin-tazobactam and other parenterally administered antibiotics against 5132 aerobic Gram-negative bacilli isolated at 61 Canadian hospitals

		Percentage of strains susceptible to							
Organism	# tested	Piperacillin-tazobactam	Piperacillin	Ticarcillin-clavulanate	Gentamicin	Ceftazidime	Ceftriaxone	Cefotaxime	Cefazolin
Escherichia coli	1069	98	74	92	97	100	100	99	95
Klebsiella pneumoniae	552	96	82	95	98	100	99	100	98
Klebsiella oxytoca	235	96	84	97	99	100	99	99	71
Enterobacter cloacae	531	88	85	80	99	86	84	82	5
Enterobacter aerogenes	100	84	81	80	86	85	82	82	19
Proteus mirabilis	234	100	97	98	94	100	100	97	90
Morganella morganii	101	98	91	94	94	93	96	88	1
Serratia marcescens	228	97	97	93	93	100	98	95	1
Citrobacter freundii	117	83	76	77	77	81	79	78	13
Pseudomonas aeruginosa	1240	96	95	88	88	95	21	9	1
Stenotrophomonas maltophilia	244	27	12	69	69	54	75	72	39
Acinetobacter species	201	90	54	94	94	88	20	16	3
All aerobic Gram-negative bacteria	5132	92	81	88	92	93	69	66	41
Rank order*		2	4	3	2	1	5	6	7

Rank order based upon the percentage of all aerobic Gram-negative bacilli inhibited

tive criteria and, where none were available, criteria for related species were applied. P values from Fishers exact test were calculated with m–1 degrees of freedom for the comparison of m proportions. Multiple comparisons were performed for the overall statistically significant results ($P \leq 0.05$). Because there were six pairwise comparisons among four proportions in Tables 3 and 5, using a 5% level of significance implies that some of comparisons were likely to be significant by chance alone. To maintain the overall $P \leq 0.05$ a fixed significance level, the Bonferroni method was applied as follows: P was divided by the number of pairwise comparisons and its result was then used as a cut-off point of significance level. For this case, dividing $P=0.05$ by 6 yields 0.083, which was used as a cut-off point of significance level for multiple comparisons in supplementary Tables 3 and 5.

RESULTS

The 61 participating laboratories submitted susceptibility results on 8026 strains, including 1240 *P aeruginosa*, 1069 *E coli*, 974 *S aureus,* and *649 Enterococcus* species. Table 1 lists the results of testing of aerobic Gram-negative bacilli, the number of strains of each group and the proportion of strains tested and susceptible to each antibiotic tested. Of 5132 aerobic Gram-negative rods tested, 93% were susceptible to ceftazidime, 92% to PT, 92% to gentamicin, 88% to TC and 81% to piperacillin. Against *E coli*, PT was active against 98% of strains compared with 74% for piperacillin alone, 92% for TC, 97% for gentamicin and 99% for each of the third-generation cephalosporins tested.

Of *K pneumoniae*, 96% were susceptible to PT compared with 95% for TC and 82% for piperacillin alone. The third-generation cephalosporins were each active against more than 99% of strains. PT was the most active of the agents tested against *P aeruginosa*. Ninety-six per cent of strains were susceptible to PT, while 95% of strains were susceptible to ceftazidime, piperacillin and gentamicin. *Acinetobacter* species were considerably more susceptible to both PT and TC than to piperacillin alone. Only 54% of strains were susceptible to piperacillin, whereas more than 90% of strains were susceptible to the beta lactam-inhibitor combinations. Overall, only *Stenotrophomonas maltophilia* was usually resistant to PT.

Table 2 shows results of testing of aerobic Gram-positive cocci. Of the *E faecalis* strains that were speciated, 99.8% were susceptible to PT and piperacillin compared with 42% and 43% of *E faecium* strains, respectively. Only two vancomycin-resistant enterococci were identified. Of *S aureus*, 99% were susceptible to PT, whereas 72% were susceptible to piperacillin and 87% were susceptible to erythromycin.

TABLE 2
Comparative activity of piperacillin-tazobactam and other parenterally administered antibiotics against 2074 Gram-positive organisms isolated at 61 Canadian hospitals

		Percentage of strains susceptible to						
Organism	# Tested	Piperacillin-tazobactam	Piperacillin	Vancomycin	Erythromycin	Ticarcillin-clavulanate	Penicillin	Ampicillin
Enterococcus faecalis	479	100	100	96	–	96	97	100
Enterococcus faecium	66	42	43	98	–	26	32	43
Enterococcus (not speciated)	101	96	96	98	–	97	95	98
Staphylococcus aureus	974	99	72	100	87	100	–	–
Other staphylococci	290	97	89	100	58	100	–	–
Streptococcus pneumonias	453	100	100	100	96	100	88*	94
Streptococcus pyogenes	151	100	100	100	85	100	99	97
Streptococcus agalactiae	213	99	99	100	87	100	84	59
Other streptococci	167	99	99	99	84	100	93	86

**As determined by the oxacillin disk screening method*

TABLE 3
Comparative activity of piperacillin-tazobactam and other parenterally administered antibiotics against aerobic Gram-negative bacilli isolated from different body sites

	Percentage of strains susceptible to														
	Piperacillin-tazobactam					Piperacillin					Ticarcillin-clavulanate				
Organism	Blood	SST	IA	Resp	P	Blood	SST	IA	Resp	P	Blood	SST	IA	Resp	P
Escherichia coli	98	98	97	98	0.85	71	77	77	70	0.19	92	93	92	90	0.75
Klebsiella species	94	97	93	96	0.24	79	88	78	83	0.062	93	97	95	96	0.28
Enterobacter species	87	92	81	85	0.050	84	89	76	83	0.044	81	86	70	76	0.009
Proteus-Providentia group	98	100	97	100	0.26	91	96	91	98	0.17	97	97	97	98	1.00
Pseudomonas aeruginosa	99	98	97	94	0.018	98	96	97	93	0.15	90	89	87	88	0.86

IA Intra-abdominal; Resp Lower respiratory tract; SST Skin and soft tissue

Tables 3, 4 and 5 show the proportion of strains submitted from different body sites, hospital type and geographic regions. A total of 2215 strains were submitted from the four western provinces, 2876 from Ontario, 2196 from Quebec, and 739 from the four Atlantic provinces.

DISCUSSION

Piperacillin in combination with tazobactam has been shown to be effective in the treatment of a variety of infections in a variety of settings, including intra-abdominal sepsis infections associated with febrile neutropenia, skin and soft tissue infections, and nosocomial pneumonia (7-18). It is likely that this drug will be used widely for the treatment of polymicrobial infections caused by piperacillin-susceptible organisms and organisms producing one of the of beta-lactamase susceptible to tazobactam. Among these are beta-lactamases of the Bush-Jacoby-Medeiros group 2 that include both the conventional TEM and SHV enzymes and the emerging extended-spectrum beta-lactamases (TEM-3 to TEM-26 and SHV-2 to SHV-5). Also included among the beta-lactamases inhibited by tazobactam are those of *S aureus*, *Haemophilus influenzae*, *Moraxella catarrhalis* and *Bacteroides fragiles*. Beta-lactamases of the Bush-Jacoby-Medeiros group 1, including the inducible cephalosporinases of *Enterobacter* species, *Citrobacter* species, *Serratia marcescens* and *P aeruginosa,* are not inhibited by either tazobactam or other currently available lactamase inhibitors. Tazobactam is, however, a less potent inducer of group 1 lactamases than other beta-lactamases (19).

Several of the antibiotics tested, including PT, gentamicin and ceftazidime, were highly active against the 5132 strains of aerobic Gram-negative bacilli tested, each inhibiting more than 90% of isolates. The addition of tazobactam to piperacillin increased the proportion of *E coli* susceptible from 74% to 98%; of *K pneumoniae* from 82% to 96%; and of *Klebsiella oxytoca* from 84% to 96%, reflecting the prevalence of group 2 beta-lactamases in this group of organisms.

Of interest, we did observe occasional differences in the susceptibilities of commonly occurring aerobic Gram-negative bacilli among the four regions of Canada. *Klebsiella* species were generally more resistant to piperacillin with or without tazobactam and to TC in the Atlantic provinces. Ontario strains

TABLE 4
Comparative activity of piperacillin-tazobactam and other parenterally administered antibiotics against aerobic Gram-negative bacilli isolated in community and teaching hospitals

	Percentage of strains susceptible to								
	Piperacillin-tazobactam			Piperacillin			Ticarcillin-clavulanate		
Organism	Community	Teaching	P*	Community	Teaching	P	Community	Teaching	P
Escherichia coli	99	97	0.071	77	72	0.13	95	90	0.0034
Klebsiella species	97	95	0.25	88	81	0.013	97	95	0.25
Enterobacter species	87	88	0.89	84	85	0.71	77	81	0.27
Proteus-Providentia group	100	99	0.56	91	97	0.020	100	96	0.020
Pseudomonas aeruginosa	98	95	0.0033	98	94	0.0023	91	86	0.0093

**Fishers Exact Test*

TABLE 5
Comparative activity of piperacillin-tazobactam and other parenterally administered antibiotics against aerobic Gram-negative bacilli isolated in four Canadian regions

	Percentage of strains susceptible to														
	Piperacillin-tazobactam					Piperacillin					Ticarcillin-clavulanate				
Organism	Atlan	Que	Ont	West	P	Atlan	Que	Ont	West	P	Atlan	Que	Ont	West	P
Escherichia coli	99	97	98	99	0.670	73	76	71	77	0.22	95	92	91	93	0.74
Klebsiella species	91	100	94	96	0.00055	75	88	78	88	0.0018	89	99	93	99	0.001
Enterobacter species	78	89	85	92	0.035	75	87	81	90	0.013	75	83	75	86	0.022
Proteus-Providentia group	100	99	99	99	1.00	93	93	97	95	0.39	96	96	98	98	0.71
Pseudomonas aeruginosa	98	94	97	95	0.082	97	94	96	94	0.24	85	90	88	89	0.58F

**Fishers exact test. Atlan Atlantic; Ont Ontario; Que Quebec; West Western provinces*

were less susceptible than Quebec and Western region strains. Not enough is known about patterns of antibiotic usage across the country to provide an explanation for this observation.

Generally, aerobic Gram-negative bacilli isolates from different body sites had similar levels of susceptibility to piperacillin with and without tazobactam and to TC. Intra-abdominal isolates of *Enterobacter* species were more likely to be resistant to TC than skin and soft tissue strains ($P<0.005$). Respiratory tract isolates of enterobacter were also significantly less susceptible to TC than skin and soft tissue isolates. Both intra-abdominal isolates and respiratory tract isolates of enterobacter were more resistant than blood culture isolates to TC. The reasons for these observations may relate to the difficulty eradicating organisms from these sites and the frequent need for prolonged antibiotic courses.

Few differences were seen between the susceptibilities of aerobic Gram-negative bacilli in community and teaching hospitals. *P aeruginosa* isolates recovered in teaching hospitals were more likely to be resistant to piperacillin with or without tazobactam or to TC. In many other pairwise comparisons, other aerobic Gram-negative bacilli from teaching hospitals were slightly less susceptible than community hospital strains; however, these differences were generally small in magnitude. It is not clear whether these differences relate to patient or hospital characteristics, but likely are a reflection of both.

We screened seven isolates of *K pneumoniae* and six strains of *E coli* with reduced susceptibility to third-generation cephalosporins for ESBLs using two methods. We identified one strain from a hospital in Toronto that demonstrated the typical susceptibility profile of ESBLs extended-spectrum beta-lactamases. This finding is consistent with other recently published surveys of Canadian strains (20). This is in sharp contrast to the experience in many other countries where both endemic and epidemic strains are frequently encountered (21-25).

Of interest, each of the aerobic Gram-negative bacilli tested in sufficient numbers was more susceptible in Canada than those tested in the United States national survey of PT activity published by Baron and Jones (3). Table 6 is a compilation of American data from Baron and Jones (3) and Canadian data from this study. Both the current study and the American study used fresh clinical isolates; frozen stock cultures were not tested. Both studies used only one isolate of the same species from each patient to avoid the bias that might occur from multiple testing of the same strains. Neither study used urinary or fecal isolates, and the number of frequently occurring species was limited. In both cases, NCCLS methodology and interpretive criteria were applied. In almost all antibiotic-organism combinations compared in Table 6, a larger proportion of Canadian strains were susceptible. The exceptions were usually in those combinations where the species were intrinsically resistant, eg, ceftriaxone versus *P aeruginosa* and cefazolin versus *Enterobacter* species or for those combina-

TABLE 6
Comparative activity of aerobic Gram-negative bacilli in Canada (Can) and the United States (US)*

	Percentage of strains susceptible to																	
	PT			Piperacillin			Cefazolin			Gentamicin			Ceftazidime			Ceftriaxone		
Organism	US	Can	P†	US	Can	P	US	Can	P	US	Can	P	US	Can	P	US	Can	P
Escherichia coli	97	98	0.058	69	74	0.001	85	95	0.001	91	97	0.001	96	100	0.001	96	100	0.001
Klebsiella pneumoniae	89	96	0.001	62	83	0.001	86	98	0.001	86	98	0.001	91	100	0.001	91	99	0.001
Klebsiella oxytoca	91	96	0.0079	73	84	0.001	57	71	0.001	92	99	0.001	93	100	0.001	89	99	0.001
Enterobacter aerogenes	74	84	0.030	74	81	0.150	14	19	0.181	88	99	0.001	71	86	0.001	74	85	0.016
Enterobacter cloacae	77	88	0.001	71	85	0.001	5	5	0.912	92	99	0.001	73	86	0.001	69	84	0.001
Proteus mirabilis	99	100	0.164	91	97	0.001	91	90	0.637	85	94	0.001	96	100	0.001	94	100	0.001
Pseudomonas aeruginosa	91	96	0.001	86	95	0.001	0	1	0.001	74	90	0.001	87	95	0.001	20	21	0.438

**American data from reference 3 with permission; †Fishers exact test. PT Piperacillin-tazobactam*

tions where resistance was rare in either country, eg, *E coli* or *Proteus mirabilis* versus PT.

It is likely that the differences that we observed in the relative susceptibility of Canadian and American isolates to the antibiotics tested are real. The delay in the appearance in Canada of ESBL-producing organisms, vancomycin-resistant enterococci, methicillin-resistant *S aureus* and penicillin-resistant *S pneumoniae* have been noted by others (26-27). It has been suggested that more stringent controls on antimicrobial usage in hospitals and well developed infection control practices may contribute to these differences. It has also been suggested that Canada's widely scattered population may prevent transmission between geographic regions; however, this explanation seems improbable in our highly mobile society. Because the data by Baron and Jones were not analyzed by region or hospital type, we were not able to examine whether the American and Canadian differences might in some way be explained by differences in the proportion of isolates from each setting. Although we did not share isolates between the 61 Canadian and American laboratories, it is unlikely that there are enough systemic differences in the way that NCCLS methods are applied to account for the differences between countries. The relative roles played by each of these factors and whether other factors are responsible for the observed differences have yet to be studied in a systematic fashion.

CONCLUSIONS

PT is highly active against commonly occurring aerobic Gram-negative rods and Gram-positive cocci. Fairly uniform activity was seen between geographic regions within Canada between different body sites and between community and teaching hospitals. Canadian isolates were generally more susceptible to PT and to the other agents tested than were American strains tested using similar methods.

Differences between the susceptibility patterns in American and Canadian hospitals should be studied further to understand better the factors contributing to the lower levels of resistance in Canada.

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