ANTIMICROBIAL RESISTANCE AMONG GRAM-NEGATIVE BACILLI FROM BACTERAEMIA, 2007

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SUMMARY

The initial antimicrobial treatment of bacteraemia is almost always empirical, and therefore relies on knowledge of the most likely pathogens and their usual antimicrobial susceptibility profile. This national survey was the first ESR has undertaken of antimicrobial susceptibility among bacteraemic Gram-negative bacilli.

Twenty-two laboratories referred non-repeat isolates of all *Enterobacteriaceae*, *Pseudomonas aeruginosa* and *Acinetobacter* cultured from blood during a 3-month period in 2007. Patient demographic data was also collected. Susceptibility to amikacin, cefazolin, cefepime, ceftazidime, ceftriaxone, cefuroxime, ciprofloxacin, co-amoxiclav, colistin, co-trimoxazole, gentamicin, imipenem, meropenem, piperacillin/tazobactam, ticarcillin/clavulanic acid and tobramycin was determined by agar dilution. Cefoxitin susceptibility was determined by disc diffusion. Isolates meeting screening criteria were also tested for extended-spectrum β-lactamases (ESBLs), and for *imp* and *vim* metallo-β-lactamase genes.

A total of 669 isolates from 642 episodes of bacteraemia were included in the survey. The most common organisms were *Escherichia coli* (407 isolates, 60.8%), *Klebsiella* (82, 12.3%), *P. aeruginosa* (45, 6.7%) and *Enterobacter* (37, 5.5%). The majority (76.4%) of the bacteraemias were reported to be community-acquired. Community-acquired infections were generally more prevalent for most species, with the exceptions of *Acinetobacter* and *Serratia*, although the number of isolates of both these organisms was small.

Among the *E. coli* isolates, 2.9% produced an ESBL, 8.9% were ciprofloxacin resistant and 5.9% were gentamicin resistant. Resistance was more prevalent among *Klebsiella*, with 14.6% producing an ESBL, 11.0% ciprofloxacin resistant and 19.5% gentamicin resistant. While the ESBL-producing *E. coli* were isolated throughout New Zealand, the majority (75.0%) of the ESBL-producing *Klebsiella* were isolated from patients in Auckland hospitals. Among the *P. aeruginosa* isolates, 4.4% were ceftazidime resistant, 4.4% were piperacillin/tazobactam resistant, 6.7% were ciprofloxacin resistant and 2.2% were gentamicin resistant. Carbapenem resistance was only identified in *P. aeruginosa*, with 8.9% resistance to imipenem, but no resistance to meropenem. No *imp* or *vim* metallo-β-lactamases genes were detected.

With the exception of *Klebsiella*, rates of multidrug resistance (resistance to ≥3 antibiotic classes) were relatively low: 6.4% among *E. coli*, 15.9% among *Klebsiella*, 4.4% among *P. aeruginosa* and no multiresistance among the small number of *Acinetobacter* isolates included in the survey.

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E. coli from hospital-acquired bacteraemia were significantly ($P \leq 0.05$) more resistant to ciprofloxacin, gentamicin and tobramycin, less likely to be fully susceptible, and more likely to be multidrug resistant. While there were no significant differences in susceptibility among *Klebsiella* and *P. aeruginosa* from hospital-acquired bacteraemia compared with those from community-acquired infections, generally resistance was higher among the isolates from hospital-acquired infections.

International comparisons with the United Kingdom (UK) and Europe indicate that resistance among bacteraemic *E. coli* in New Zealand is lower than in the UK and similar to rates in Northern European (including Scandinavian) countries, which generally have the lowest rates of resistance in Europe. However, resistance among our bacteraemic *Klebsiella* isolates is similar or higher than in the UK, and similar to rates in many Central European countries.

RECOMMENDATIONS

1 Given the general trend of increasing resistance occurring elsewhere in the world, this survey should be repeated at regular intervals.

2 For any future surveys, the feasibility of using standard definitions for the patient demographic data, including whether the bacteraemia was community- or hospital-acquired, should be considered.

1. INTRODUCTION

Bloodstream infections are one of the most severe forms of bacterial infection. Despite advancements in diagnosis and antimicrobial therapy, bacteraemia still accounts for significant morbidity and mortality. The microbial epidemiology of bacteraemia seems to constantly evolve. In the 1980s, there was a shift from Gram-negative bacteria to Gram-positives being the most frequent cause of bacteraemia. However, there is evidence that this trend may have recently reversed, at least in some parts of the world.[1,2] In addition, antibiotic resistance among Gram-negatives is increasing.

The initial antimicrobial treatment of bacteraemia is almost always empirical, and therefore relies on knowledge of the most likely pathogens and their usual antimicrobial susceptibility profile. Several studies have demonstrated that inadequate empirical antibiotic treatment of bacteraemia is associated with poor outcome.[3,4] Increasing antibiotic resistance and, in particular, multidrug resistance, is likely to result in more episodes of inadequate empirical therapy. Accordingly, bacteraemia due to multidrug-resistant organisms has been shown to have a worse prognosis due, at least in part, to a lower likelihood of adequate empirical therapy.[3,5] Therefore, the availability of accurate and current data on the susceptibility of the major bacteraemic pathogens is important.

There are several national and regional surveillance systems that monitor resistance among bacteraemic isolates, for example, the British Society of Antimicrobial Chemotherapy's (BSAC) Bacteraemia Surveillance Programme, which covers the United Kingdom (UK) and Ireland; the Health Protection Agency's (HPA) LabBase/CoSurv system, which covers England, Wales and Northern Ireland; and the European Antimicrobial Resistance Surveillance System (EARSS). The most recent reports from these systems indicate a trend of increasing resistance among bacteraemic Gram-negative bacilli.

Data from the BSAC and HPA surveillance systems has recently been published for both *Enterobacteriaceae* and Gram-negative non-fermenters from bacteraemia for the 2001-2006 period.[6,7] *Escherichia coli* was reported to be the commonest agent of bacteraemia and the one showing the most striking changes in resistance, especially to cephalosporins, fluoroquinolones and gentamicin.

EARSS monitors resistance among bacteraemic isolates of various species, including *E. coli*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*, from most European countries. The 2007 EARSS report noted alarming Europe-wide increases in resistance among bacteraemic *E. coli*.[8] Notably, resistance to third-generation cephalosporins, fluoroquinolones and aminoglycosides increased significantly in almost every participating country over the 2001-2007 period. Possibly the most alarming trend is the speed with which fluoroquinolone resistance is accumulating in *E. coli* all over Europe, with the highest rate of 53% recorded in Turkey. Longer-term trend data is not available for *K. pneumoniae* and *P. aeruginosa* as these organisms have only been included in the system since 2005.

This is the first survey that ESR has undertaken of antimicrobial susceptibility among bacteraemic Gram-negative bacilli. It was undertaken at the recommendation of the Surveillance

Subcommittee of the Ministry of Health's Antibiotic Resistance Advisory Group. The purpose of the survey was to obtain information on resistance among isolates of Gram-negative bacilli causing significant disease. The survey was confined to the *Enterobacteriaceae*, *P. aeruginosa* and *Acinetobacter*.

2. METHODS

2.1. Bacterial isolates and patient information

All tertiary- and secondary-care hospital microbiology laboratories, or laboratories providing services for these hospitals, were sent a preliminary questionnaire (Appendix 1) to ascertain:

1 whether the laboratory could participate in the survey;

2 the approximate number of *Enterobacteriaceae, P. aeruginosa* and *Acinetobacter* isolated from blood cultures per month;

3 whether the laboratory preferred to refer isolates already stored or preferred to refer isolates prospectively; and

4 whether the laboratory could provide key information about the patient and infection.

Based on the responses to the questionnaire, the survey collection period was set at 3 months. Participating laboratories that chose to send isolates prospectively were asked to refer all *Enterobacteriaceae, P. aeruginosa* and *Acinetobacter* isolated from blood cultures in May, June and July 2007. Laboratories that chose to send stored isolates, referred isolates cultured from blood during the 3-month period of February, March and April 2007 or the 3-month period of March, April and May 2007. Laboratories were asked to exclude repeat isolations of the same organism from the same patient.

Laboratories were asked to supply the following information, if known, with each isolate:

1 patient age and sex;

2 whether the patient was a haematology or oncology patient;

3 whether the patient had a central venous line;

4 the focus of infection: abdominal, urinary, line, neutropenic sepsis, other or unknown site; and

5 whether the bacteraemia was community-acquired or hospital-acquired. For this categorisation, laboratories were asked to use their institution's usual definition of hospital- and community-acquired bacteraemia.

2.2. Antimicrobial susceptibility testing

The susceptibility of the referred isolates to amikacin, cefazolin, cefepime, ceftazidime, ceftriaxone, cefuroxime, ciprofloxacin, co-amoxiclav, colistin, co-trimoxazole, gentamicin, imipenem, meropenem, piperacillin/tazobactam, ticarcillin/clavulanic acid and tobramycin was determined by agar dilution according to CLSI methodology and interpretive standards.[9,10] Cefoxitin susceptibility was determined by disc diffusion testing according to CLSI methodology and interpretive standards.[11]

Enterobacteriaceae isolates with a ceftriaxone or ceftazidime minimum inhibitory concentration (MIC) of ≥1 mg/L were tested for extended-spectrum β-lactamase (ESBL) production using the CLSI disc confirmatory test.[10] As the CLSI confirmatory test is only recommended for *E. coli, K. pneumoniae, K. oxytoca* and *Proteus mirabilis,* other species were also tested for ESBL production by a modification of the double-disc synergy test. Cefotaxime (30 μg), ceftazidime (30 μg), cefpodoxime (10 μg) and cefepime (30 μg) discs were placed 20 mm (centre-to-centre) from a co-amoxiclav disc (ie, a source of clavulanate).[12]

Isolates with a ceftazidime MIC ≥8 mg/L and an imipenem or meropenem MIC ≥1 mg/L were tested for the presence of the *imp* and *vim* metallo-β-lactamase genes by PCR.[13,14]

The MIC_{50} and MIC_{90} values were defined as the MICs at which at least 50% and 90%, respectively, of isolates were inhibited.

For *Citrobacter koseri, Enterobacter agglomerans, E. coli, Klebsiella, Klyuvera, Pantoea, P. mirabilis, Salmonella, Shigella* and *Yersinia*, multiresistance was defined as resistance to three or more of the following antibiotic classes: any cephalosporin or cefoxitin, co-amoxiclav, piperacillin/tazobactam, carbapenems, aminoglycosides (gentamicin, tobramycin and/or amikacin), ciprofloxacin, or co-trimoxazole. For *C. braakii*, *C. freundii*, *E. aerogenes*, *E. cloacae*, *M. morganii* and *Serratia* (ie, *Enterobacteriaceae* that normally have an intrinsic, inducible, chromosomal AmpC β-lactamase), multiresistance was defined as resistance to three or more of the following antibiotic classes: ceftriaxone, piperacillin/tazobactam, carbapenems, aminoglycosides, ciprofloxacin or co-trimoxazole. ESBL producers were considered cephalosporin resistant irrespective of their cephalosporin MICs.

For *P. aeruginosa*, multiresistance was defined as resistance to three or more of the following antibiotic classes: ceftazidime, ticarcillin/clavulanic acid, piperacillin/tazobactam, carbapenems, aminoglycosides, ciprofloxacin or colistin.

For *Acinetobacter*, multiresistance was defined as resistance to three or more of the following antibiotic classes: ceftazidime, ticarcillin/clavulanic acid, piperacillin/tazobactam, carbapenems, aminoglycosides, ciprofloxacin, colistin or co-trimoxazole.

2.3. Data analysis

For the patient demographic analyses, any patient with more than one bacterial species or different strains of the same species, isolated from the same episode of bacteraemia, was only counted once.

For the susceptibility analyses, repeat isolates of the same strain from the same patient were excluded.

Statistical analyses were performed with SAS software v.9.1 (SAS Institute Inc, Cary, NC, USA).[15] The chi-square test or Fisher's exact test, as appropriate, were used to determine the

significance of any observed differences. An associated P value ≤0.05 was used to indicate that a difference was significant.

3. RESULTS

3.1. Participating laboratories

Twenty-two laboratories referred isolates for the survey. These laboratories, and the number of isolates they each referred, are listed in Appendix 2.

3.2. Isolates

A total of 642 patients and 669 non-duplicate isolates were included in the survey. Twenty-five patients had two different species or strains isolated during the same bacteraemic episode and one patient had three different species.

The identity of the isolates is shown in Table 1 and presented in greater detail in Appendix 3. The proportion of each species that were reported to be from community-acquired versus hospital-acquired bacteraemias is presented in Appendix 4.

Table 1. Identity of the bacteraemic Gram-negative bacilli included in the survey[1]

	Number	Percent
Acinetobacter species	13	1.9
Enterobacteriaceae	611	91.3
Citrobacter species	15	2.2
Enterobacter species	37	5.5
Escherichia coli	407	60.8
Klebsiella species	82	12.3
Klyuvera species	1	0.2
Morganella morganii	8	1.2
Pantoea species	3	0.5
Proteus mirabilis	20	3.0
Salmonella typhoidal	12	1.8
Salmonella non-typhoidal	4	0.6
Serratia species	20	3.0
Shigella flexneri	1	0.2
Yersinia pseudotuberculosis	1	0.2
Pseudomonas aeruginosa	45	6.7

1 Identity as reported by the referring laboratory.

3.3. Patient demographics

The age and sex distribution of the patients with bacteraemia due to Gram-negative bacilli, the number who were haematology or oncology patients, the number of patients who had a central venous line, the focus of infection, and the number of infections that were classified as community-acquired versus hospital-acquired, are shown in Table 2.

Table 2. Demographics of patients with bacteraemia due to Gram-negative bacilli

	Number	Percent[1]	Age-specific rate (per 100 000)
Sex (n=641)[2]			
female	327	50.9	
male	314	48.9	
Age (years) (n=642)[2]			
<1	17	2.7	27.6
1-14	19	3.0	2.3
15-49	115	17.9	5.5
50-59	64	10.0	12.5
60-69	99	15.4	27.4
70-79	156	24.3	68.8
≥80	172	26.8	125.9
Haematology or oncology patient (n=577)[2]			
yes	85	14.7	
no	492	85.3	
Central venous line (n=541)[2]			
yes	79	14.6	
no	462	85.4	
Focus of infection (n=476)[2]			
urinary	220	46.2	
abdominal	72	15.1	
line	29	6.1	
wound	16	3.4	
neutropenic sepsis	13	2.7	
other	27	5.7	
unknown	99	20.8	
Community- or hospital-acquired infection (n=475)[2]			
community-acquired	363	76.4	
hospital-acquired	112	23.6	

1 Percent of patients for whom information reported.
2 Number of patients for whom information reported.

3.4. Antimicrobial susceptibility

The MIC_{50}, MIC_{90} and susceptibility of all *Enterobacteriaceae* are shown in Table 3. The β-

lactam susceptibility of members of the *Enterobacteriaceae* varies considerably due to several species having an intrinsic, inducible, chromosomal AmpC β-lactamase that usually confers resistance to first and second-generation cephalosporins, co-amoxiclav and cefoxitin. Therefore, Table 3 also presents the MIC_{50}, MIC_{90} and susceptibility to β-lactams for the *Enterobacteriaceae* species that do not have an intrinsic, inducible, chromosomal AmpC β-lactamase (ie, *C. koseri, E. agglomerans, E. coli, Klebsiella, Klyuvera, Pantoea, P. mirabilis, Salmonella, Shigella* and *Yersinia*).

Resistance among the two most common members of the *Enterobacteriaceae*, *E. coli* and *Klebsiella*, is presented later in Section 3.5, Tables 6 and 7, respectively.

Table 3. MIC_{50}, MIC_{90} and susceptibility of the bacteraemic *Enterobacteriaceae*[1]

	MIC_{50} (mg/L)	MIC_{90} (mg/L)	Susceptibility (%)[2]		
			S	I	R
cefazolin	2	≥128	78.2	3.6	18.2
	2[3]	16	88.9	3.9	7.3
cefuroxime	4	64	84.6	2.8	12.6
	4	8	90.9	2.8	6.3
ceftriaxone	≤0.03	0.25	94.4	1.3	4.3
	≤0.03	0.12	95.7	0.4	3.9
cefepime	0.03	0.12	98.0	1.2	0.8
	0.03	0.12	97.8	1.3	0.9
cefoxitin	na[4]	na[4]	86.3	3.6	10.2
	na	na	95.6	1.9	2.6
amoxicillin/clavulanic acid	8	128	60.6	14.4	25.0
	8	32	68.6	16.4	15.1
ticarcillin/clavulanic acid	8	≥256	62.9	18.0	19.2
	8	≥256	60.8	19.7	19.5
piperacillin/tazobactam	2	4	97.2	1.6	1.2
	2	4	98.3	0.9	0.7
imipenem	0.25	1	99.4	0.7	0
meropenem	≤0.12	≤0.12	100	0	0
gentamicin	0.5	2	93.0	0.3	6.7
tobramycin	1	2	93.0	3.0	4.1
amikacin	2	4	99.8	0.2	0
ciprofloxacin	0.016	0.5	91.5	0.8	7.7
co-trimoxazole	0.12	≥16	78.7	-	21.3

1 611 isolates tested.
2 S, susceptible; I, intermediate; R, resistant.
3 Shaded rows give data only for the *Enterobacteriaceae* species that do not have an intrinsic, inducible, chromosomal AmpC β-lactamase, that is, data for *C. koseri, E. agglomerans, E. coli, Klebsiella, Klyuvera, Pantoea, P. mirabilis, Salmonella, Shigella* and *Yersinia* only (n=538).
4 Cefoxitin susceptibility determined by disc testing only, so MIC_{50} and MIC_{90} data not available (na).

4.1% of Enterobacteriaceae produced an ESBL: 2.9% (12/407) of *E. coli,* 14.6% (12/82) of *Klebsiella* and 2.7% (1/37) of *Enterobacter*. While the ESBL-producing *E. coli* were isolated throughout New Zealand, the majority (75.0%) of the ESBL-producing *Klebsiella* were isolated

from patients in Auckland hospitals.

Among the isolates of *C. koseri, E. agglomerans, E. coli, Klebsiella, Klyuvera, Pantoea, P. mirabilis, Salmonella, Shigella* and *Yersinia*, 64.9% (349/538) were fully susceptible, 19.3% (104/538) were resistant to one class of antibiotics, 8.6% (46/538) were resistant to two classes, and 7.2% (39/538) were multiresistant to ≥3 antibiotic classes. Among the multiresistant isolates, no resistance pattern was dominant.

Among the isolates of other *Enterobacteriaceae* (ie, species that normally have an inducible, chromosomal AmpC β-lactamase - *C. braakii*, *C. freundii*, *E. aerogenes*, *E. cloacae*, *M. morganii* and *Serratia*), 86.3% (63/73) were fully susceptible, 5.5% (4/73) were resistant to one class of antibiotics, 5.5% (4/73) were resistant to two classes, and 2.7% (2/73) were multiresistant to ≥3 antibiotic classes.

The MIC_{50}, MIC_{90} and susceptibility of the *P. aeruginosa* isolates are shown in Table 4. Among these isolates, 80.0% (36/45) were fully susceptible, 13.3% (6/45) were resistant to one class of antibiotics, 2.2% (1/45) were resistant to two classes, and 4.4% (2/45) were multiresistant to ≥3 antibiotic classes.

Table 4. MIC_{50}, MIC_{90} and susceptibility of the bacteraemic *Pseudomonas aeruginosa*[1]

	MIC_{50} (mg/L)	MIC_{90} (mg/L)	Susceptibility (%)[2]		
			S	I	R
ceftazidime	2	4	93.3	2.2	4.4
cefepime	2	8	95.6	2.2	2.2
ticarcillin/clavulanic acid	32	64	91.1	-	8.9
piperacillin/tazobactam	4	16	95.6	-	4.4
imipenem	4	8	84.4	6.7	8.9
meropenem	0.5	2	91.1	8.9	0
gentamicin	2	4	95.6	2.2	2.2
tobramycin	0.5	1	100	0	0
amikacin	2	8	100	0	0
ciprofloxacin	0.12	1	93.3	0	6.7
colistin	2	2	91.1	8.9	0

1 45 isolates tested.
2 S, susceptible; I, intermediate; R, resistant.

The MIC_{50}, MIC_{90} and susceptibility of the *Acinetobacter* isolates are shown in Table 5. Among these isolates , 76.9% (10/13) were fully susceptible, 15.4% (2/13) were resistant to one class of antibiotics, and 7.7% (1/13) were resistant to two classes. No *Acinetobacter* were multiresistant to ≥3 antibiotic classes.

Table 5. MIC_{50}, MIC_{90} and susceptibility of the bacteraemic *Acinetobacter*[1]

	MIC_{50} (mg/L)	MIC_{90} (mg/L)	Susceptibility (%)[2]		
			S	I	R
ceftazidime	4	16	76.9	15.4	7.7
cefepime	4	8	100	0	0
ticarcillin/clavulanic acid	8	32	76.9	23.1	0
piperacillin/tazobactam	1	8	100	0	0
imipenem	0.5	1	100	0	0
meropenem	0.5	0.5	100	0	0
gentamicin	0.5	2	92.3	0	7.7
tobramycin	1	1	100	0	0
amikacin	2	4	100	0	0
ciprofloxacin	0.12	0.25	100	0	0
colistin	0.5	2	100	-	0
co-trimoxazole	0.12	8	84.6	-	15.4

1 13 isolates tested.
2 S, susceptible; I, intermediate; R, resistant.

No *imp* and *vim* metallo-β-lactamases genes were detected in any isolates tested for these genes, that is, isolates of any species with a ceftazidime MIC ≥8 mg/L and an imipenem or meropenem MIC ≥1 mg/L.

3.5. Comparison of resistance among isolates from community-acquired bacteraemia versus hospital-acquired bacteraemia

This comparison was undertaken for the three most common organisms: *E. coli*, *Klebsiella* and *P. aeruginosa*.

Two hundred and fifty-seven of the *E. coli* were reported to be from community-acquired bacteraemias and 53 from hospital-acquired infections. This information was not reported for the remaining 97 *E. coli* bacteraemias. *E. coli* from hospital-acquired bacteraemia were significantly ($P \leq 0.05$) more resistant to ciprofloxacin (17.0 versus 7.0%), gentamicin (11.3 vs 3.1%) and tobramycin (5.7 vs 0.8%); less likely to be fully susceptible to all antibiotics (49.1 vs 67.7%) and more likely to be multidrug-resistant (13.2 vs 4.7%) (Table 6).

Table 6. Comparison of resistance among community-acquired and hospital-acquired bacteraemic *Escherichia coli*

	Percent resistant			
	Community-acquired n=257	**Hospital-acquired n=53**	**All n=407[1]**	**P value[2]**
cefazolin	6.2	9.4	6.4	0.3750
cefuroxime	4.3	5.7	4.7	0.7145
ceftriaxone	2.3	3.8	2.5	0.6287
cefepime	0.4	0	0.5	1.0000
cefoxitin	1.6	5.7	2.7	0.0996
amoxicillin/clavulanic acid	14.0	17.0	16.2	0.5758
ticarcillin/clavulanic acid	20.6	17.0	21.6	0.5462
piperacillin/tazobactam	0.4	0	0.25	1.0000
imipenem	0	0	0	-
meropenem	0	0	0	-
gentamicin	3.1	11.3	5.9	0.0189
tobramycin	0.8	5.7	2.5	0.0367
amikacin	0	0	0	-
ciprofloxacin	7.0	17.0	8.9	0.0296
co-trimoxazole	21.8	32.1	25.6	0.1081
	Percent			
ESBL-positive	2.3	3.8	2.9	0.6287
fully susceptible	67.7	49.1	61.4	0.0098
multidrug resistant	4.7	13.2	6.4	0.0275

1 All *E. coli* isolates, including 97 for which information on whether the infection was community- or hospital-acquired was not reported.

2 Resistance among community-acquired infections compared with that among hospital-acquired infections by the Chi-square test or Fishers Exact test, as appropriate.

Forty-one of the *Klebsiella* were reported to be from community-acquired bacteraemias, 20 from hospital-acquired infections and this information was not reported for the remaining 21 *Klebsiella* bacteraemia. There were no significant differences in susceptibility between *Klebsiella* from hospital-acquired bacteraemia and those from community-acquired infections (Table 7). However, with the exception of cefuroxime and co-trimoxazole, resistance was higher among the isolates from hospital-acquired infections. These differences probably failed to reach

statistical significance due to the relatively small numbers of isolates.

Table 7. Comparison of resistance among community-acquired and hospital-acquired bacteraemic *Klebsiella*

	Percent resistant			
	Community-acquired n=41	**Hospital-acquired n=20**	**All n=82[1]**	**P value[2]**
cefazolin	9.8	20.0	14.6	0.4198
cefuroxime	17.1	15.0	17.1	1.0000
ceftriaxone	9.8	15.0	13.4	0.6736
cefepime	0	5.0	3.7	0.3279
cefoxitin	0	0	1.2	-
amoxicillin/clavulanic acid	9.8	25.0	15.9	0.1385
ticarcillin/clavulanic acid	12.2	25.0	19.5	0.2729
piperacillin/tazobactam	0	0	3.7	-
imipenem	0	0	0	-
meropenem	0	0	0	-
gentamicin	12.2	25.0	19.5	0.2729
tobramycin	9.8	25.0	15.9	0.1385
amikacin	0	0	0	-
ciprofloxacin	7.3	15.0	11.0	0.3835
co-trimoxazole	22.0	20.0	23.2	1.0000
	Percent			
ESBL-positive	9.8	20.0	14.6	0.4198
fully susceptible	65.9	75.0	68.3	0.4690
multidrug resistant	9.8	25.0	15.9	0.1385

1 All *Klebsiella* isolates, including 21 for which information on whether the infection was community- or hospital-acquired was not reported.

2 Resistance among community-acquired infections compared with that among hospital-acquired infections by the Chi-square test or Fishers Exact test, as appropriate.

Twenty-two of the *P. aeruginosa* were reported to be from community-acquired bacteraemias, 15 from hospital-acquired infections and this information was not reported for the remaining 8 *P. aeruginosa* bacteraemia. There were no statistically significant differences in resistance

among *P. aeruginosa* from community-acquired bacteraemia compared with those from hospital-acquired infections (Table 8).

Table 8. Comparison of resistance among community-acquired and hospital-acquired bacteraemic *Pseudomonas aeruginosa*

	Percent resistant			
	Community-acquired n=22	**Hospital-acquired n=15**	**All n=45[1]**	**P value[2]**
ceftazidime	4.6	6.7	4.4	1.0000
cefepime	4.6	0	2.2	1.0000
ticarcillin/clavulanic acid	9.1	13.3	8.9	1.0000
piperacillin/tazobactam	4.6	6.7	4.4	1.0000
imipenem	9.1	13.3	8.9	1.0000
meropenem	0	0	0	-
gentamicin	0	6.7	2.2	0.4054
tobramycin	0	0	0	-
amikacin	0	0	0	-
ciprofloxacin	13.6	0	6.7	0.2568
colistin	0	0	0	-
	Percent			
fully susceptible	77.3	73.3	80.0	1.0000
multidrug resistant	4.6	6.7	4.4	1.0000

1 All *P. aeruginosa* isolates, including eight for which information on whether the infection was community- or hospital-acquired was not reported.

2 Resistance among community-acquired infections compared with that among hospital-acquired infections by the Chi-square test or Fishers Exact test, as appropriate.

4. DISCUSSION

As expected, the most numerous Gram-negative bacilli isolated from bacteraemia cases were *E. coli* (60.8%), followed by *Klebsiella* (12.3%), *P. aeruginosa* (6.7%) and *Enterobacter* (5.5%). No other genera or species constituted more than 3% of the isolates. The majority (76.4%) of the bacteraemias, for which the information was reported, were community-acquired. Community-acquired infections were generally more prevalent for most species, with the exceptions of *Acinetobacter* and *Serratia*, although the number of isolates of both these organisms was small.

This is the first national survey of resistance among Gram-negative bacilli from blood that ESR has undertaken, so comparisons with earlier surveys and analysis of any change over time are not possible. However, data on resistance among bacteraemic *E. coli* and *Klebsiella* is collected annually from diagnostic laboratories and collated to produce national resistance estimates.[16] The resistance estimates for 2007 were quite similar to the resistance rates obtained in this survey for bacteraemic *E. coli*, but less so for *Klebsiella*. The prevalence of ESBL-producing *Klebsiella* was higher in this survey and consequently so was resistance to several β-lactams, fluoroquinolones and gentamicin. This discrepancy may well have been due to the collection period for this survey coinciding with an outbreak or outbreaks of ESBL-producing *Klebsiella*. The majority of the ESBL-producing *Klebsiella* were isolated from patients in Auckland hospitals.

Time trends in resistance among bacteraemic *E. coli* have been analysed using the data collected annually from diagnostic laboratories. The latest available trend analysis indicated that there were increases in resistance to second- and third-generation cephalosporins, fluoroquinolones and gentamicin among bacteraemic *E. coli* between 2001 and 2005. However, these increases were only significant for gentamicin at the 95% confidence level.[17] Data on trends in resistance among bacteraemic *Klebsiella* is not available, as data on this organism has only been collected since 2004.

Comparison of 2006 data from the UK BSAC/HPA surveillance with the results for the bacteraemic *E. coli* included in this survey, indicates that resistance is almost universally lower in this country. For example, resistance to cefuroxime, 19.4 in the UK vs 4.7% in New Zealand; cefotaxime/ceftriaxone, 11.6 vs 2.5%; ESBL production, 12.0 vs 2.9%; piperacillin/tazobactam, 10.3 vs 0.25%; ciprofloxacin, 25.2 vs 8.9%; and gentamicin, 9.1% vs 5.9%.[6]

However, this was not the situation when resistance in bacteraemic *Klebsiella* was compared, with resistance as high or higher in New Zealand. This was probably due to the high rate of ESBL producers, which are usually multiresistant, found among the *Klebsiella* included in this survey – 14.6 vs 13.1% in the UK in 2006.[6]

Comparing the results from this survey with the EARSS 2007 data shows that resistance (specifically third-generation cephalosporin, fluoroquinolone and aminoglycoside resistance) among bacteraemic *E. coli* and *P. aeruginosa* in New Zealand is similar to that in Northern European (including Scandinavian) countries, which generally have the lowest rates of resistance in Europe. However, resistance among our bacteraemic *Klebsiella* isolates was higher than in

Northern Europe and more similar to many Central European countries.[8]

As expected, resistance was usually more prevalent among isolates reported to be from hospital-acquired infections rather than community-acquired infections. For this survey, participating hospitals were requested to use their own definition of hospital-acquired and community-acquired bacteraemia. It would have been preferable to have all participants use standard definitions for this parameter and some of the other patient demographics collected, for example, the Australian Council on Healthcare Standards' clinical indicators. But past experience with ESR surveys has shown it is difficult to organise such standardisation for a short-term survey. However, perhaps the use of standard definitions should be considered for future surveys, or at least participants' ability and willingness to use such definitions should be investigated.

There were some reassuring results from this survey. First, with perhaps the exception of *Klebsiella*, rates of multidrug resistance were relatively low. Second, there was no carbapenem resistance among *Enterobacteriaceae* or *Acinetobacter*. Nine percent of *P. aeruginosa* were imipenem resistant, but none tested as meropenem resistant and no metallo-β-lactamases were detected in any isolates. Third, while *Acinetobacter* have a propensity to develop resistance to antibiotics,[18] we found relatively low rates of resistance, and no multiresistance, among the *Acinetobacter* included in this survey, albeit there were only a small number of isolates.

Given the general trend of increasing resistance occurring elsewhere in the world, and the emergence and alarming spread of certain specific resistances, for example, KPC carbapenemases reaching a level of 26% among invasive *K. pneumoniae* in New York,[19] it would seem prudent to repeat this survey at regular intervals. While data on resistance among bacteraemic *E. coli* and *Klebsiella* is collected each year from diagnostic laboratories, it has some limitations compared with the data able to be generated from surveys such as this. First, as it is currently collected, the diagnostic laboratory data does not enable multiresistance to be determined, but rather only resistance to the individual antibiotics. Second, data from some laboratories cannot be included in the national estimates of resistance as these laboratories provide data that includes the category of intermediate resistance with resistance. Third, data is not available on newer emerging resistance mechanisms, such as metallo-β-lactamases and KPC carbapenemases.

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APPENDIX 1

Gram-negative bacilli from bacteraemia survey, 2007

Preliminary questionnaire

Will your laboratory participate in the survey? □ Yes □ No

Approximate number of gram-negative bacilli* isolated from blood cultures per month: [ ]

Do you store all your gram-negative bacilli isolated from blood? □ Yes □ No

If yes, would you prefer to send isolates you already have stored rather than refer isolates prospectively? □ Yes □ No

Will you be able to provide the following information about the patient and infection with at least the majority of isolates:

- Patient age and sex? □ Yes □ No
- Whether the patient was a haematology/oncology patient? □ Yes □ No
- Whether the patient had a central line? □ Yes □ No
- The focus of infection? □ Yes □ No
- Whether the bacteraemia was hospital-acquired or community-acquired? □ Yes □ No

Do you want us to supply agar slopes on which to store and send the isolates? □ Yes □ No

* all *Enterobacteriaceae, Pseudomonas aeruginosa* and *Acinetobacter*

Please return by 9 March 2007 to:

Helen Heffernan

Antibiotic Reference Laboratory, ESR

P O Box 50 348

PORIRUA 5420 [post-paid, addressed envelope enclosed]

APPENDIX 2

Participating laboratories

	Number of isolates referred
Canterbury Health Laboratories, Christchurch Hospital	78
Gisborne Hospital	3
Greymouth Hospital	5
Hawkes Bay Hospital	26
HealthLab Kew, Southland Hospital	9
Hutt Hospital	11
LabCare Pathology, Taranaki Base Hospital	21
LabPlus, Auckland City Hospital	117
Medlab Bay of Plenty, Tauranga Hospital	27
Medlab Central, Palmerston North Hospital	19
Medlab Timaru, Timaru Hospital	9
Middlemore Hospital	82
North Shore and Waitakere Hospitals	60
Rotorua Hospital	8
Southern Community Laboratories, Dunedin Hospital	36
Waikato Hospital	80
Wairarapa Hospital	5
Wairau Hospital	4
Wanganui Hospital	12
Wellington and Kenepuru Hospitals	37
Whakatane Hospital	14
Whangarei Hospital	6

APPENDIX 3

Identity of isolates included in the survey[1]

	Number	Percent
Acinetobacter baumannii	4	0.6
Acinetobacter calcoaceticus	2	0.3
Acinetobacter lwoffii	2	0.3
Acinetobacter species	5	0.8
Citrobacter braakii	1	0.2
Citrobacter freundii	7	1.1
Citrobacter koseri	6	0.9
Citrobacter species	1	0.2
Enterobacter aerogenes	6	0.9
Enterobacter agglomerans	1	0.2
Enterobacter asburiae	1	0.2
Enterobacter cloacae	26	3.9
Enterobacter species	3	0.5
Escherichia coli	407	60.8
Klebsiella oxytoca	24	3.6
Klebsiella pneumoniae	54	8.1
Klebsiella species	4	0.6
Klyuvera species	1	0.2
Morganella morganii	8	1.2
Pantoea agglomerans	2	0.3
Pantoea species	1	0.2
Proteus mirabilis	20	3.0
Pseudomonas aeruginosa	45	6.7
Salmonella Enteritidis	1	0.2
Salmonella Infantis	2	0.3
Salmonella Oranienburg	1	0.2
Salmonella Paratyphi A	2	0.3
Salmonella Typhi	10	1.5
Serratia marcescens	19	2.8
Serratia species	1	0.2
Shigella flexneri	1	0.2
Yersinia pseudotuberculosis	1	0.2

1 Identity as reported by the referring laboratory.

APPENDIX 4

Proportion of each species that were from community-acquired versus hospital-acquired infections

	Number[1]	Percent	
		Community-acquired	Hospital-acquired
Acinetobacter species	7	14.3	85.7
Enterobacteriaceae			
Citrobacter species	11	81.8	18.2
Enterobacter species	23	52.2	47.8
Escherichia coli	310	82.9	17.1
Klebsiella species	61	67.2	32.8
Klyuvera species	0	-	-
Morganella morganii	6	50.0	50.0
Pantoea species	2	100	0
Proteus mirabilis	16	87.5	12.5
Salmonella typhoidal	8	100	0
Salmonella non-typhoidal	3	100	0
Serratia species	10	30.0	70.0
Shigella flexneri	1	100	0
Yersinia pseudotuberculosis	0	-	-
Pseudomonas aeruginosa	37	59.5	40.5

1 Number of isolates for whom information reported.