An Extended Aminoglycoside Resistance Profile in Isolates of Enterobacteriaceae from the SENTRY Surveillance Program in the Asia-Pacific region, 2007

J.M. Bell,[1] J.D. Turnidge,[1] and R.N. Jones[2]

[1]Women's and Children's Hospital, Adelaide, Australia; [2]JMI Laboratories, North Liberty, Iowa, USA

jbell@wcharl.net

C2-3914

48th ICAAC, 2008, Washington

INTRODUCTION

Despite the development of new ß-lactams and fluoroquinolones, aminoglycosides are still a very important class of antibacterials for the treatment of severe illness caused by Gram-negative bacteria, particularly if the pathogen has developed resistance to third-generation cephalosporins.

Three mechanisms of resistance have been recognized, namely ribosome alteration, decreased permeability, and inactivation of the drugs by aminoglycoside modifying enzymes. The latter mechanism is of most clinical importance since the genes encoding aminoglycoside modifying enzymes can be disseminated by plasmids or transposons.[1]

Methylation of 16S ribosomal RNA (rRNA) has recently emerged as a new mechanism of resistance against aminoglycosides among gram-negative pathogens. This event is mediated by a newly recognized group of 16S rRNA methylases. Their presence confers a high level of resistance to all parenterally administered aminoglycosides that are currently in clinical use. The responsible genes are mostly located on transposons within transferable plasmids, which provides them with the potential to spread horizontally.

Recent studies have demonstrated that enteric Gram-negative bacteria can acquire resistant to the three main therapeutic aminoglycosides: gentamicin, tobramycin, and amikacin. This extended aminoglycoside resistant profile (EARP) can be due to the acquisition of multiple genes encoding aminoglycoside–modifying enzymes or to the newly described mechanism of 16S rRNA methylation.

Resistance to multiple agents is very common in some countries of the Asia-Pacific region. As part of the SENTRY surveillance program in the Asia-Pacific region, we analysed rates of EARP in clinical isolates Enterobacteriaceae.

METHODS

Isolates

Enterobacteriaceae (excluding Proteae and *Serratia* spp.) from infected hospitalized patients in 10 countries (39 medical centres) collected during 2007. Isolates came from patients with bacteraemia, pneumonia, complicated skin and skin structure infections, and other infections. All strains were referred to the Women's and Children's Hospital, Adelaide, Australia for testing.

Susceptibility testing

Isolates were tested using custom made dry-form broth microdilution (BMD) panels (TREK Diagnostic Systems) against a wide range of antimicrobials including gentamicin (GEN) , tobramycin (TOB) and amikacin (AMK) according to CLSI standards.[2] Breakpoints for resistance were those recommended by the CLSI.[3]

Quality control strains utilized included *Escherichia coli* ATCC 25922 and 35218, *P. aeruginosa* ATCC 27853; all MIC results were within CLSI specified ranges.

Aminoglycoside Resistant Profile

Isolates with extended aminoglycoside resistant profiles were resistant to GEN, TOB and AMK.

Figure 1. Source of Isolates

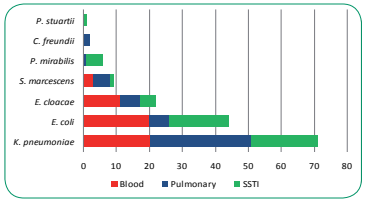

Table 1. Aminoglycoside Resistant Profiles amoung 2567 Enterobacteriaceae isolated in the Asia-Pacific Region, 2007

Profile	N	Australia	Hong Kong	India	Indonesia	Korea	China	Philippines	Singapore	Taiwan	Thailand
	1503	166	55	216	266	107	450	107	17	69	50
Tob	118	2	4	59	7	6	28		2	7	3
TobAmk	1			1							
Gen	185	8	7	21	13	2	112	5		8	9
GenTob	605	2	5	303	90	17	154	9	2	12	11
GenTobAmk	155		2	76		14	55			8	
	6.0%	0.0%	2.7%	11.2%	0.0%	9.6%	6.9%	0.0%	0.0%	7.7%	0.0%

Table 2. Number (%) of Isolates Resistant to Gentamicin, Tobramycin and Amikacin

Organism	India	China	Korea	Taiwan	Hong Kong
Klebsiella pneumoniae (n=71)	37 (15.7)	16 (8.1)	10 (21.7)	7 (18.4)	1 (4.2)
Escherichia coli (n=44)	24 (8.5)	16 (5.2)	3 (5.1)		1 (2.9)
Enterobacter cloacae (n=22)	9 (14.1)	13 (11.9)			
Serratia marcescens (n=9)	2	6	1		
Proteus mirabilis (n=6)	3	2		1	
Citrobacter freundii (n=2)		2			
Providencia stuartii (n=1)	1				
Total (n=155)	76	55	14	8	2

Percentage of EARP Isolates Resistant to[a]:

ESBL[b]	CTR	CPM	CFT	CIP	PTZ	IMP	TGC
95.8	83.1	63.4	62.0	81.7	57.7	5.6	0.0
95.5	90.9	77.3	75.0	100.0	40.9	4.5	0.0
	100.0	77.3	100.0	68.2	59.1	0.0	0.0
	77.8	55.6	55.6	33.3	0.0	0.0	0.0
83.3	50.0	50.0	0.0	83.3	0.0	0.0	0.0
	50.0	50.0	100.0	0.0	0.0	0.0	0.0
	100.0	100.0	0.0	100.0	0.0	0.0	0.0
	85.8	68.4	68.4	81.3	46.5	3.9	0.0

[a] CTR, ceftriaxone; CPM, cefepime; CFT, cefoxitin; CIP, ciprofloxacin; PTZ, piperacillin-tazobactam; IMP, imipenem; TGC, tigecycline

[b] ESBL phenotype (ceftriaxone MIC > 1 mg/L, ceftazidime MIC > 1 mg/L, or aztreonam MIC > 1 mg/L)

RESULTS

- A total of 2,567 Enterobacteriaceae were collected from the APAC region during 2007. One third of all isolates were isolated from patients with bacteraemia (Figure 1).
- 155 (6.0%) were resistant to gentamicin, tobramycin and amikacin (Table 1). These isolates were found in India (49.0%); China (35.3%), Korea (9.0%); Taiwan (5.2%) and Hong Kong (1.3%) (Table 2).
- No isolates with extended aminoglycoside resistant profiles were detected from Australia, Indonesia, Philippines, Singapore or Thailand.
- The number of isolates and % of key species from each country in which EARP was detected is shown in Table 2. There was a very strong relationship between EARP and mutli-resistance to other drug classes.
- Over 95% of *E. coli* and *K. pneumoniae* isolates produced an extended-spectrum ß-lactamase.
- Three (30%) EARP *K. pneumoniae* from Korea were also metallo-ß-lactamase producers. A further nine isolates (5 *K. pneumoniae*; 4 *E. coli*) from India also produced a metallo-ß-lactamase.
- One *K. pneumoniae* isiolate from China contained KPC-2
- All isolates with EARP were susceptible to tigecycline (MIC ≤ 2 mg/L)
- The mechanisms responsible for this resistance EARP is undergoing further investigation.

References

1. Shaw, K.J., P.N. Rather, R.S. Hare, and G.H. Miller. 1993. Molecular genetics of aminoglycoside resistance genes and familial relationships of the aminoglycoside-modifying enzymes. Microbiol. Rev. 57:138-163.
2. CLSI. 2006. Methods for Dilution Antimicrobial Susceptibility Testing for Bacteria That Grow Aerobically. M7-A7, Wayne, PA.
3. CLSI. 2008. Performance standards for Antimicrobial Susceptibility Testing; 18th Informational Supplement. M100-S18. Wayne, PA.

Conclusions

- Extended resistance to aminoglycosides is a major problem in Enterobacteriaceae in Asian countries with high rates of multi-resistance to other drug classes.
- Coproduction of extended-spectrum-ß-lactamases is very common; and metallo-ß-lactamases were also coproduced in isolates from India and Korea.
- 16S rRNA methylases are likely to be responsible for at least some the EARPs in the Asia-Pacific region.