Ten Year Trend in Aminoglycoside Resistance from a Worldwide Collection of Gram-Negative Pathogens (1998-2007)

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ABSTRACT

Objectives: To assess resistance (R) trends to aminoglycosides (AGs) over ten years from a global sample of Gram-negative (GN) pathogens. This study determined the R rates of gentamicin (GEN), tobramycin (TOB) and amikacin (AMK) against nine common GN species groups from medical centers in North America (NA), Latin America (LA), Europe (EU) and the Asia-Pacific (APAC).

Methods: Non-duplicate isolates from bloodstream and respiratory tract infections were collected from 38 countries between 1998-2000 (27,491 strains) and 2005-2007 (30,430 strains) via the SENTRY Program. Organisms included *E. coli* (EC), *Klebsiella* spp. (KBS), *Enterobacter* spp. (EBS), *Citrobacter* spp. (CBS), *Serratia* spp. (SER), *P. mirabilis* (PM), Indole-positive Proteae (IPP), *P. aeruginosa* (PSA) and *Acinetobacter* spp. (ACB). Susceptibility (S) testing was performed by two central monitoring laboratories using CLSI methods (M7-A7, M100-S18) and concurrent quality control testing.

Results: With the exception of KBS in EU, R to GEN increased in all regions for the three most prevalent Enterobacteriaceae (listed first in Table 1). Nearly all pathogens in NA showed increased GEN-R rates (0.6-11.1%) during the last surveillance period (2005-2007), while significant variations were noted in other regions. The dramatic increase in GEN-R for nearly all species in APAC countries was due to strains sampled from countries not included in the earliest sample (e.g. India and Indonesia). Between 60-70% of the ACB were GEN-R in regions outside of NA, with the USA rate approaching 43% in the most recent years. R to all three AG agents for each of these pathogens was generally <1% among enteric pathogens from NA. However, much higher GEN/TOB/AMK-R rates were observed in other geographic areas for the most common Enterobacteriaceae, highest in LA 1.4-17.1% during both time periods. R to all three AGs ranged from 3.1% (NA) to 25.3% (LA) for the PSA isolates collected during 2005-2007.

Table 1. % GEN R[a] 1998-2000 (27,491 isolates)/ 2005-2007 (30,430 isolates)

Organism	NA	LA	EU	APAC
EC	3.2/9.3	10.4/15.4	6.4/7.8	15.5/43.1
KBS	3.9/7.9	30.5/38.4	20.9/12.3	12.0/37.6
EBS	5.8/8.7	21.2/29.9	9.7/10.1	12.8/30.4
CBS	3.2/3.8	26.5/12.5	14.1/5.0	5.4/28.4
SER	2.7/3.9	26.0/20.6	14.8/8.9	22.8/13.2
PM	6.4/6.3	36.1/28.1	20.2/11.0	6.2/21.5
IPP	11.5/12.4	20.5/43.9	15.9/12.0	21.5/24.3
PSA	14.7/12.6	38.6/36.7	30.0/22.6	15.7/33.6
ACB	31.6/42.7	65.6/67.9	69.2/63.0	35.3/60.0

a. Isolates were non-S to GEN.

Conclusions: Significant geographic variability in AG-S was observed in the analysis of this large sample of GN pathogens with highest R rates in LA and APAC. The AG-R-mechanisms associated with these isolates were assessed (companion abstract) and it appears that a new generation of AG compounds would be a valuable therapeutic alternative to GEN, TOB and AMK for GN infections.

INTRODUCTION

Aminoglycosides (AGs) are bactericidal compounds that bind the 30S ribosome and have a broad spectrum of antimicrobial activity. In the United States (USA), the most commonly prescribed AG agents include gentamicin, tobramycin and amikacin. These antimicrobial agents have been utilized for the treatment of numerous types of infections caused by both Gram-positive and –negative bacterial pathogens. The mechanisms of resistance to these and other AGs include ribosomal alteration, decreased permeability, and inactivation of the drugs by aminoglycoside modifying enzymes (AMEs). AMEs have significant clinical importance as the genes encoding these resistances can be disseminated by plasmids or transposons. The enzymes that act as AMEs include acetyltransferases, adenylyltransferases and phosphotransferases and many examples of each type have been characterized.

In this study, a very large global collection of nearly 100,000 Gram-negative bacterial isolates from nine species groups were tested for susceptibility to three AG agents over a ten-year period (SENTRY Antimicrobial Surveillance Program; 1998-2007). Numerous countries contributed isolates to investigate the trends in resistance to gentamicin, tobramycin and amikacin over the last decade.

MATERIALS AND METHODS

Bacterial isolates. During a ten year period (SENTRY Program; 1998-2007), investigators in four geographic regions contributed isolates for this study. These regions included North America (NA; 51 USA sites and 5 sites in Canada), Latin America (LA; 16 sites, six countries), Europe (EU; 46 sites, 18 countries) and the Asia-Pacific (APAC; 57 sites, 12 countries). These medical centers referred 97,184 isolates from nine species/species groups including *E. coli* (34,301 strains), *Klebsiella* spp. (17,993), *Enterobacter* spp. (9,711), *Citrobacter* spp. (1,697), *Serratia* spp. (4,121), *P. mirabilis* (3,065), indole-positive Proteae (1,549), *P. aeruginosa* (18,047) and *Acinetobacter* spp. (6,700). A near equivalent number of strains were collected in NA and EU (32,994 and 34,616). The isolate numbers collected in LA and APAC were also very similar from centers in these two regions (14,666 and 14,908).

Susceptibility testing. Susceptibility testing was performed at referral laboratories (JMI Laboratories, North Liberty, Iowa, USA and The Women's and Children's Hospital, North Adelaide, Australia). The AGs tested each year included gentamicin, tobramycin and amikacin. All isolates were processed using reference broth microdilution methods recommended by the Clinical Laboratory Standards Institute (CLSI; M7-A7, 2006). Isolates were tested in cation-adjusted Mueller-Hinton broth using validated broth microdilution panels manufactured by TREK Diagnostics (Cleveland, Ohio, USA). CLSI approved susceptible breakpoint criteria were used to categorize susceptibility (M100-S18, 2008). American Type Culture Collection (ATCC) quality control organisms were tested to confirm the validity of test results and included *E. coli* ATCC 25922 and *P. aeruginosa* ATCC 27853.

RESULTS

- Resistance to gentamicin increased between 1998-2000 and 2005-2007 in NA, LA and APAC for the majority of the Gram-negative pathogens reported in this study (Table 1). In contrast, EU isolates showed an overall decline in gentamicin resistance for seven of nine species reported during these two surveillance periods.

- The overall highest rate of AG resistance was observed in LA for the majority of the species groups (Table 2). Enterobacteriaceae and *P. aeruginosa* isolates from NA remain quite susceptible to AGs, however, gentamicin susceptibility decreased during 2005 – 2007 for nearly all species (Table 1).

- Amikacin was the most active AG tested against Enterobacteriaceae (84.9 - 100% susceptible) and *P. aeruginosa* (72.1 – 95.9%) in all regions (Table 2). Gentamicin was more active than tobramycin against most species with the exception of *P. mirabilis*, indole-positive Proteae and *P. aeruginosa*.

- Less than half of *Acinetobacter* spp. collected during 2005-2007 in LA, EU and APAC were susceptible to gentamicin (Table 2). Tobramycin was the most active AG against *Acinetobacter* spp. in geographic areas outside of NA.

- In NA, gentamicin resistance rates among Gram-negative species were higher in the USA (6.5 - 40.3%) compared to Canada (3.8 - 13.3%; Table 3).

Table 2. Aminoglycoside susceptibility rates in four geographic regions monitored over a ten year period (1998-2007)[a].

Organism/ region (no. tested)	Gentamicin			Tobramycin			Amikacin		
	% S	% I	% R	% S	% I	% R	% S	% I	% R
E. coli									
NA (11,797)	94.2	0.7	5.1	95.3	2.1	2.6	99.7	0.2	0.1
LA (4,171)	87.0	1.4	11.6	86.3	2.8	10.9	97.7	1.4	0.9
EU (13,537)	93.3	0.8	5.9	93.4	1.8	4.8	99.5	0.3	0.2
APAC (4,796)	77.7	0.9	21.4	77.7	7.1	15.2	98.4	0.5	1.1
Klebsiella spp.									
NA (6,840)	93.5	1.6	4.9	92.3	1.7	6.0	97.1	1.9	1.0
LA (2,913)	66.8	2.2	31.0	61.9	2.0	36.1	84.4	7.8	7.8
EU (4,962)	85.8	1.5	12.7	80.9	3.9	15.2	94.6	2.8	2.6
APAC (3,278)	77.8	0.8	21.4	74.3	2.8	22.9	94.5	1.4	4.1
Enterobacter spp.									
NA (3,753)	92.8	1.4	5.8	92.8	2.3	4.9	99.3	0.5	0.2
LA (1,505)	74.2	2.9	22.9	68.0	2.5	29.5	84.9	5.1	10.0
EU (3,050)	90.0	1.7	8.3	84.4	2.8	12.8	96.9	1.1	2.0
APAC (1,403)	81.5	1.1	17.4	80.3	2.0	17.7	95.2	1.3	3.5
Citrobacter spp.									
NA (705)	95.2	1.0	3.8	94.9	1.6	3.5	100.0	0.0	0.0
LA (179)	79.9	2.2	17.9	76.0	2.2	21.8	88.3	5.0	6.7
EU (587)	92.2	1.9	5.9	92.2	1.5	6.3	97.8	0.8	1.4
APAC (226)	84.5	1.3	14.2	84.1	3.1	12.8	95.6	0.9	3.5
Serratia spp.									
NA (1,889)	95.9	1.3	2.8	92.2	3.4	4.4	99.6	0.2	0.2
LA (580)	74.1	1.9	24	68.3	3.8	27.9	81.6	6.4	12
EU (1,111)	89.5	2.6	7.9	85.7	1.9	12.4	94.9	1.8	3.3
APAC (541)	81.3	4.5	14.2	74.1	5.2	20.7	93.0	1.5	5.5
P. mirabilis									
NA (1,227)	93.7	1.2	5.1	95.0	2.2	2.8	99.9	0.0	0.1
LA (331)	70.1	2.1	27.8	75.8	7.6	16.6	92.2	1.8	6.0
EU (1,160)	84.7	2.0	13.3	91.3	4.9	3.8	96.8	0.4	2.8
APAC (347)	87.3	2.3	10.4	88.8	4.0	7.2	96.6	1.7	1.7
Indole-positive Proteae									
NA (448)	86.8	5.4	7.8	90.6	4	5.4	98.4	0.7	0.9
LA (164)	66.5	2.4	31.1	70.7	8.6	20.7	98.8	0.0	1.2
EU (755)	88.2	1.9	9.9	92.3	3.6	4.1	99	0.5	0.5
APAC (182)	79.1	4.4	16.5	88.5	4.4	7.1	99.5	0.5	0.0
P. aeruginosa									
NA (6,419)	86.3	4.2	9.5	91.9	1.0	7.1	95.9	1.8	2.3
LA (3,171)	60.6	3.7	35.7	64.0	1.1	34.9	72.1	2.9	25
EU (5,903)	72.8	3.8	23.4	77.1	1.0	21.9	87.8	4.3	7.9
APAC (2,554)	78.7	3.4	17.9	82.8	0.4	16.8	89.5	2.6	7.9
Acinetobacter spp.									
NA (1,538)	61.6	4.1	34.3	74.5	3.8	21.7	81.2	5.7	13.1
LA (1,652)	35.2	8.0	56.8	50.3	3.7	46.0	33.9	4.9	61.2
EU (1,929)	37.0	4.7	58.3	54.8	6.3	38.9	48.2	3.1	48.7
APAC (1,581)	49.7	1.6	48.7	59.8	1.9	38.3	59.5	1.7	38.8

a. Breakpoints of the CLSI (2008).

- Among the study sites in LA, a higher rate of gentamicin resistance was documented in Argentina for Enterobacteriaceae and *Acinetobacter* spp. (Table 3). The highest rate of gentamicin resistance among *P. aeruginosa* was detected in Brazil.

- Poland had the highest rate of gentamicin resistance in EU, although Greece had a slightly higher (53.7 vs. 52.7%) rate of resistance among *P. aeruginosa* (Table 3).

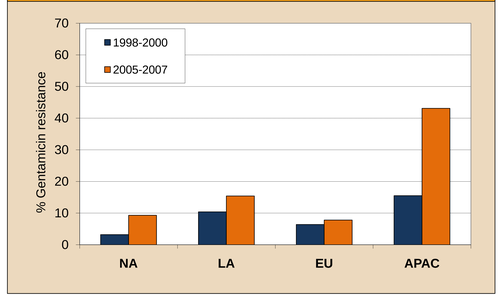
- The majority of Enterobacteriaceae and *P. aeruginosa* isolates from India were resistant to gentamicin (53.4 - 65.9%) and nearly 83% of *Acinetobacter* spp. isolated in Korea were also resistant.

Table 3. Gentamicin resistance rates among Enterobacteriaceae and non-enteric Gram-negative bacilli collected from 33 countries in four geographic regions (1998 -2007)[a].

Region/country[b]	Enterobacteriaceae	*P. aeruginosa*	*Acinetobacter* spp.
North America	6.2	13.7	38.4
Canada	3.8	13.3	7.9
USA	**6.5**[c]	**13.8**	**40.3**
Latin America	22.7	39.4	64.8
Argentina	**30.2**	39.4	**81.5**
Brazil	24.9	**45.5**	60.4
Chile	15.5	23.6	69.4
Columbia	12.9	23.3	46.9
Mexico	24.4	39.2	57.4
Venezuela	14.5	29.4	55.8
Europe	9.2	27.0	63.5
Belgium	4.5	21.7	16.7
France	5.4	29.6	30.9
Germany	6.8	19.5	17.2
Greece	12.3	**53.7**	75.7
Ireland	10.8	12.6	11.1
Italy	26.9	33.2	74.3
Israel	10.7	28.1	69.1
Poland	**28.9**	52.7	**86.1**
Spain	5.1	12.4	76.7
Sweden	1.3	2.5	4.2
Switzerland	3.3	7.9	11.1
Turkey	22.7	51.0	77.5
UK	8.1	8.6	38.2
Asia-Pacific	21.1	21.3	50.3
Australia	2.6	12.2	17.4
Hong Kong	24.5	12.3	24.3
India	**65.9**	**53.4**	73.9
Indonesia	20.2	22.4	12.0
Japan	5.3	10.2	17.9
Korea	23.3	33.3	**82.8**
P.R. China	40.8	34.7	59.0
Phillipines	18.7	14.3	7.3
Singapore	18.5	23.5	58.8
South Africa	10.3	32.1	74.4
Taiwan	24.3	16.4	57.9
Thailand	32.3	20.4	67.2

a. Isolates were non-susceptible to gentamicin (MIC, >4 mg/L).
b. Included only countries which contributed a significant number of isolates.
c. Bolded results indicated highest rates within the region.

Figure 1. Gentamicin resistance rates among four regions for *E. coli* isolates tested during two time periods.



CONCLUSIONS

- Resistance to AGs increased in all geographic regions among *E. coli*, the most common Gram-negative pathogen isolated in this global study (Figure 1).
- It is noteworthy that in regions outside of NA, <50% of *Acinetobacter* spp. and <80% of *P. aeruginosa* isolates collected during 1998-2007 were susceptible to gentamicin.
- Variability among AG susceptibility in different countries and geographic regions is likely due to the dissemination of plasmids harboring AG resistance determinants such as AME.
- This study documents a significant variability among AG resistance patterns between regions, countries and species groups which warrants continued surveillance efforts to monitor these antimicrobial agents, as new compounds in this class are studied.

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