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**MDR Gram-negatives - clinical observations**

# TIGECYCLINE ACTIVITY AGAINST ENTERIC PATHOGENS RESISTANT TO AMIKACIN AS DETERMINED FROM TEST PROGRAM ANALYSIS OVER TEN YEARS - TEST 2013

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**Objectives**: Aminoglycoside resistance is achieved through three basic mechanisms, namely ribosome alteration, decreased permeability, and inactivation of the drugs by aminoglycoside modifying enzymes. When resistance occurs with an aminoglycoside, therapeutic choices, especially monotherapy, are often quite limited. The Tigecycline Evaluation and Surveillance Trial (TEST) program has been monitoring the development of aminoglycoside resistance since 2004. This study evaluates the development of aminoglycoside resistance against Gram-negative enterics and the *in vitro* activity of tigecycline against these pathogens during the years 2004 – 2013. **Methods**: 2,163 aminoglycoside-resistant isolates were analyzed from a collection of >120,000 *Enterobacteriaceae* by 1,497 cumulative sites in 68 countries from 2007 through 2013. Aminoglycoside resistance was determined by amikacin susceptibility. MICs were determined by broth microdilution, and interpreted using current CLSI and FDA (tigecycline) guidelines. **Results**: Aminoglycoside resistance rate have steadily increased globally against Gram-negative enteric isolates from a low of 0.3% in 2004 to a high of 3.1% in 2008 ($p<0.0001$, Cochran-Armitage trend test) and now are decreasing ($p<0.0001$). The aminoglycoside resistant rate in 2013 is currently at 0.74%. Aminoglycoside resistance is highest among ESBL-positive isolates at 6.3%. Resistant rates ranging from 0.9% to 3.0% were seen against *E. coli* and *K. pneumoniae* over the 10 year period. The *in vitro* activity of tigecycline and 8 comparators are presented in the following table for all aminoglycoside-resistant isolates:

| | % Susceptible | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Organism** | **TGC** | **AMC** | **AMP** | **CRO** | **FEP** | **IPM** | **LVX** | **TZP** | **MEM** |
| *Enterobacteriaceae (2163)* | 92 | 7 | 1 | 5 | 28 | 89 | 30 | 34 | 65 |
| *ALL ESBL-positive Isolates (717)* | 96 | 8 | 0 | 0 | 20 | 91 | 26 | 33 | 75 |
| *Klebsiella pneumoniae (894)* | 94 | 8 | 0 | 4 | 20 | 90 | 25 | 27 | 60 |
| *Enterobacter cloacae (478)* | 87 | 1 | 0 | 3 | 34 | 91 | 27 | 27 | 71 |
| *Escherichia coli (320)* | 99 | 18 | 6 | 12 | 34 | 91 | 23 | 51 | 70 |
| *Serratia marcescens (273)* | 88 | 2 | 0 | 7 | 32 | 88 | 55 | 47 | 68 |
| *Enterobacter aerogenes (96)* | 84 | 2 | 0 | 5 | 34 | 90 | 29 | 31 | 58 |
| *Klebsiella oxytoca (54)* | 91 | 13 | 0 | 11 | 37 | 83 | 39 | 41 | 64 |

**TGC**, tigecycline; **AMC**, amoxicillin/clavulanic acid; **AMP**, ampicillin; **CRO**, ceftriaxone; **FEP**, cefepime; **IPM,** imipenem; **LVX**, levofloxacin; **TZP**, piperacillin tazobactam; **MEM**, meropenem; Species with n ≤10 not shown.

**Conclusions**: Aminoglycoside-resistance rates among Gram-negative enterics have varied from 0.3% to 3.1% over the past 10 years ($p<0.0001$). The resistance rate for tigecycline of 0.6% against all enterics has not varied significantly during this same time frame ($p=0.9888$). Only tigecycline inhibited >90% of all aminoglycoside-resistant enterics at its FDA susceptible breakpoint of 2 mg/L. However, susceptibility varied among individual species. Tigecycline demonstrated potent *in vitro* activity against all Gram-negative enterics without regard to the aminoglycoside-resistant phenotype in a global population.