1595

In Vitro Activity of Ertapenem and Comparators Against Aerobic Gram-negative Intra-Abdominal Infection (IAI) Pathogens in the USA—SMART 2012

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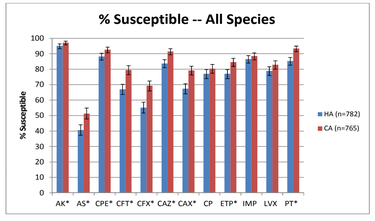
Revised Abstract

Background: The IDSA and the SIS updated guidelines for IAI therapy in 2010. The Study for Monitoring Antimicrobial Resistance Trends (SMART) is a longitudinal surveillance study that has tracked the *in vitro* activity of drugs commonly used to treat IAI since 2002. This report summarizes *in vitro* activity of amikacin (AK), ampicillin-sulbactam (AS), cefepime (CPE), cefotaxime (CFT), cefoxitin (CFX), ceftazidime (CAZ), ceftriaxone (CAX), ciprofloxacin (CP), ertapenem (ETP), imipenem (IMP), levofloxacin (LVX), and piperacillin-tazobactam (PT), against aerobic Gram-negative bacilli (GNB) isolated in 2012 from IAI in the USA. **Methods:** 18 laboratories in the USA each collected up to 100 consecutive isolates of GNB from IAI in 2012 for a total of 1,547 isolates. Isolates were sent to a central laboratory for confirmation of identification; ESBL status and broth microdilution susceptibility were determined using CLSI broth microdilution. IAI was defined as hospital-associated (HA) or community-associated (CA) if cultured ≥48 hours or <48 hours post admission, respectively. Statistical significance was determined using Fisher's exact test. **Results:** The two most prevalent species, *E. coli* and *K. pneumoniae*, accounted for 56% of all isolates, and had ESBL rates in HA/CA of 7%/5% and 13%/5%, respectively. 97% of 1,284 *Enterobacteriaceae* were ETP susceptible. Susceptibility (with 95% confidence limits) of all isolates combined, using breakpoints appropriate for each species (0% susceptible assumed for species with no breakpoints for any given drug) is summarized by HA and CA, below; asterisks by drug names indicate a significant difference (p<0.05) between HA and CA values.



AK=amikacin, AS=ampicillin-sulbactam, CPE=cefepime, CFT=cefotaxime, CFX=cefoxitin, CAZ=ceftazidime, CAX=ceftriaxone, CP=ciprofloxacin, ETP=ertapenem, IMP=imipenem, LVX=levofloxacin, PT=piperacillin-tazobactam, HA=hospital-associated, CA=community-associated.

Conclusions: ESBL rates in IAI in the USA are relatively unchanged from earlier SMART reports, and remain much lower than reported in most countries, leading to higher levels of susceptibility to cephalosporins and fluoroquinolones than typically seen internationally. All study drugs except CP, LVX, and IMP had significantly lower %S in HA than in CA infections. AK (98.4%) and ETP (97.2%) were the most active vs. *Enterobacteriaceae*, while AK (84.4%) and CAZ (77.2%) were the most active vs. non-*Enterobacteriaceae*. SMART data can be useful to help guide evolving IAI treatment guidelines to reflect resistance trends.

Introduction

The Infectious Diseases Society of America (IDSA) and the Surgical Infection Society (SIS) published updated guidelines for treatment of intra-abdominal infections (IAI) in 2010 [1]. Therapy of these infections, especially empiric treatment, has been complicated by extended-spectrum β-lactamases (ESBLs), which have been spreading among *Enterobacteriaceae*, with increasing rates reported from multiple countries and regions [2-5]. Antibiotic options in the treatment of ESBL-producing organisms are very limited with carbapenems often remaining the treatment of choice.

The Study for Monitoring Antimicrobial Resistance Trends (SMART) has tracked and reported on the susceptibility trends of aerobic gram-negative pathogens of intra-abdominal infections (IAI) since 2002. This report summarizes the *in vitro* activity of amikacin (AK), ampicillin-sulbactam (AS), cefepime (CPE), cefotaxime (CFT), cefoxitin (CFX), ceftazidime (CAZ), ceftriaxone (CAX), ciprofloxacin (CP), ertapenem (ETP), imipenem (IMP), levofloxacin (LVX), and piperacillin-tazobactam (PT) against the aerobic Gram-negative bacilli isolated in 2012 in the USA.

Materials & Methods

- Participating sites each collected up to 100 consecutive non-selected aerobic Gram-negative pathogens from IAI each year of the study. Only one isolate per species per patient was accepted. For this report, 1,547 aerobic Gram-negative bacilli were collected from IAI by 18 labs in the USA in 2012. An IAI was defined as hospital-associated (HA) if the specimen was cultured ≥48 hours post admission to hospital, and community-associated (CA) if the specimen was cultured <48 hours post admission to hospital.
- Isolates were identified to the species level and sent to a central lab (International Health Management Associates, Inc., Schaumburg, IL, USA [IHMA]) for susceptibility testing and confirmation of identification.
- Organism collection, transport, confirmation of organism identification, susceptibility testing, and development and management of a centralized database were coordinated by IHMA.
- Minimum inhibitory concentrations (MICs) were determined by the Clinical and Laboratory Standards Institute (CLSI) broth microdilution testing method using custom MicroScan dehydrated panels (Siemens Medical Solutions Diagnostics, West Sacramento, CA) [6]. All antimicrobics were supplied by the panel manufacturer.
- MIC interpretive criteria followed CLSI guidelines [7]. Susceptibility was calculated for all *Enterobacteriaceae*, for all non-*Enterobacteriaceae,* and for all aerobic Gram-negative bacilli combined; 0% susceptibility was assumed for species with no breakpoints for any given drug.
- *Escherichia coli*, *Klebsiella pneumoniae, Proteus mirabilis*, and *Klebsiella oxytoca* isolates were classified as ESBL-producers if there was at least an eight-fold reduction of MIC values for ceftazidime or cefotaxime tested in combination with clavulanic acid versus their MICs when tested alone [7].
- Quality controls (QC) were performed on each day of testing using appropriate ATCC control strains, following CLSI and manufacturer guidelines. Results were included in the analysis only when corresponding QC results were within the acceptable ranges [7].
- The adjusted Wald method was used to calculate 95% confidence intervals. The Fisher exact test was used to assess differences in % ESBL-positive and in % susceptible between HA and CA isolates. A two-tailed p-value <0.05 was considered statistically significant.

References

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Acknowledgments

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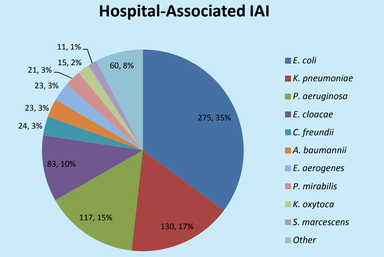
Results

Figure 1. Frequency distribution (n, %) of aerobic Gram-negative bacilli from IAI, USA 2012.



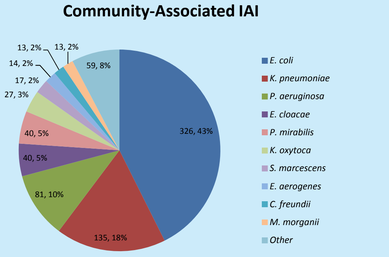
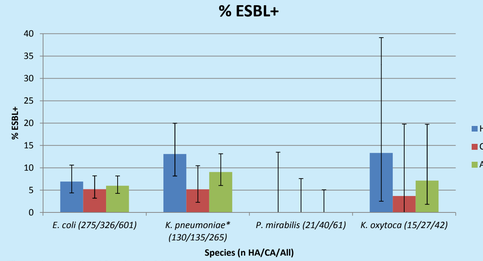


Figure 2. Percent ESBL-positive *Enterobacteriaceae* in IAI, USA 2012.



* Significant difference between HA and CA values (p<0.05).
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Figure 3. Percent susceptible for all *Enterobacteriaceae* combined in IAI, USA 2012.

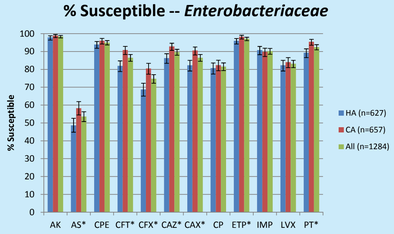

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Figure 4. Percent susceptible for all non-*Enterobacteriaceae* in IAI, USA 2012.

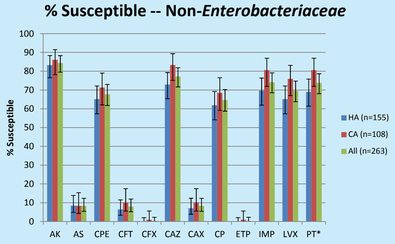

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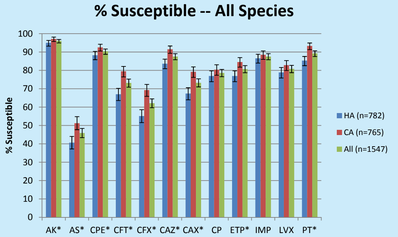
Figure 5. Percent susceptible for all aerobic Gram-negative bacilli combined in IAI, USA 2012.



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Conclusions

- Although the distribution pattern of species was similar in HA and CA infections, the proportions of *E. coli* and *K. pneumoniae* were lower in HA IAI while the proportions of *P. aeruginosa* and *A. baumannii* were higher.
- ESBL rates in IAI in the USA are relatively unchanged from earlier SMART reports on North America [5,8,9] and remain much lower than reported in most countries and regions [2,3,4], leading to higher levels of susceptibility to cephalosporins and fluoroquinolones than typically seen internationally.
- For all aerobic Gram-negative bacilli combined, all study drugs except ciprofloxacin, levofloxacin, and imipenem had significantly lower susceptibility in HA than in CA infections.
- Amikacin (98.4%) and ertapenem (97.2%) were the most active against *Enterobacteriaceae*, while amikacin (84.4%) and ceftazidime (77.2%) were the most active against non-*Enterobacteriaceae*.
- SMART data can be useful to help guide evolving IAI guidelines for empiric therapy to reflect resistance trends.