#E-204

Evaluation of EUCAST and CLSI Cephalosporin Breakpoints vs. ESBL+ and ESBL- *E. coli, K. pneumoniae*, and *K. oxytoca* in the SMART Study

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Revised Abstract

Background: CLSI guidelines state that confirmed ESBL+ isolates of *E. coli, K. pneumoniae,* and *K. oxytoca* are to be reported as resistant to all cephalosporins, penicillins, and aztreonam. In 2010 CLSI breakpoints for many of these agents will be lowered to better ensure that such isolates are correctly called non-susceptible, perhaps obviating the need for ESBL confirmatory testing. EUCAST breakpoints are already lower than CLSI, and will remain lower for cefepime (CPE) and ceftazidime (CAZ) even upon introduction of the CLSI 2010 breakpoints. This analysis of data from the Study for Monitoring Antimicrobial Resistance Trends (SMART) evaluates the ability of EUCAST, current CLSI, and forthcoming CLSI cephalosporin breakpoints to separate ESBL+/- populations.

Methods: ESBL status of 19,707 *E. coli*, 5,484 *K. pneumoniae*, and 1,278 *K. oxytoca* from intra-abdominal infections in 2002-2008 from the Americas, Asia/Pacific, Europe, and Africa was confirmed by CLSI methods. Percent susceptibility of these isolates to CPE, cefotaxime (CFT), CAZ, ceftriaxone (CAX), ertapenem (ETP), imipenem (IMP), and pip-tazo (PT) was determined by CLSI microdilution, and interpreted by EUCAST as well as current and future CLSI guidelines.

Results: ETP and IMP %S were ≥90 for all groups, ex. ETP vs. ESBL+ *K. pneumoniae* (82%). For ESBL- isolates of all 3 species, the %S of the 4 cephalosporins were always within 4 points of each other regardless of breakpoints used, and always >92%. For ESBL+ isolates, however, %S for the cephalosporins ranged from 13-61% with current CLSI breakpoints, 6-61% with new CLSI breakpoints, and 6-39% with EUCAST. ESBL+ *K. oxytoca* accounted for the highest rate of "false susceptible" errors, especially with CAZ and CPE.

Conclusions: Although the lower EUCAST cephalosporin breakpoints and those forthcoming from CLSI are better able to separate ESBL+/- populations of *E. coli*, *K. pneumoniae*, and *K. oxytoca*, many ESBL+ isolates remain below the breakpoints. Confirmation testing of ESBL status thus may still be necessary to ensure proper recognition of these isolates.

Introduction

Extended-spectrum beta-lactamase (ESBL) producing *Enterobacteriaceae*, particularly *Escherichia coli*, *Klebsiella pneumoniae*, and *K. oxytoca*, have been the intense focus of discussion among microbiologists and clinicians for many years, and despite all the research, how best to detect them and manage the infections they cause remains the subject of continuing debate. The Clinical and Laboratory Standards Institute (CLSI, formerly NCCLS) recently concluded several years of often contentious discussion by approving lower susceptibility breakpoints for most of the third-generation cephalosporins in an effort originally undertaken to differentiate ESBL+ from ESBL- isolates, and largely eliminate the need for laboratories to do ESBL screening and confirmation testing. Over the past few years, the focus of that debate shifted somewhat as pharmacokinetic/pharmacodynamic (PK/PD), animal model, and retrospective study data were presented suggesting that (a) currently approved dosage regimens of third-generation cephalosporins were unlikely to achieve target blood levels necessary to inhibit ESBL+ **or** ESBL- isolates with minimal inhibitory concentrations (MICs) greater than 1 mcg/ml (i.e., be above the MIC for at least 50% of the dosing interval); and (b) the outcome of treatment of ESBL+ and ESBL- isolates with cephalosporins was virtually the same, as long as the PK/PD susceptible breakpoint of 1 mcg/ml was used [1, 2].

Nevertheless, other investigators continue to present data suggesting that it is still important to know the ESBL status of an isolate to ensure proper therapy, or at least to know local ESBL prevalence data so that empiric therapy can be as targeted as possible [3]. Given the fact that ESBL+ isolates are often, if not usually, also resistant to non-beta-lactam classes of drugs (fluoroquinolones, aminoglycosides, etc.), empiric therapy selections are much more limited in areas with widespread ESBL problems, especially Asia, Latin America, and increasingly in Europe.

The Study for Monitoring Antimicrobial Resistance Trends (SMART) is a longitudinal surveillance study which has tracked susceptibility and epidemiologic trends of pathogens causing intra-abdominal infections worldwide since 2002. All isolates of *E. coli, K. pneumoniae,* and *K. oxytoca* collected during this period had their ESBL status confirmed using CLSI guidelines [4]. This report compares the susceptibility rates of these isolates, using current (2009) and future (2010) CLSI guidelines as well as those of the European Committee on Antimicrobial Susceptibility Testing (EUCAST) [5].

Materials and Methods

- All isolates were non-repeat isolates derived from IAIs. Only one isolate per species per patient was accepted into the study. Participating laboratories in 33 countries in Europe, North America, South America, Asia/Pacific, Middle East, and Africa each collected up to 100 consecutive non-selected gram-negative pathogens in 2002-2008. Isolates were identified to the species level and tested for susceptibility at each site each year, until 2008, when isolates were sent to a central laboratory (Laboratories International for Microbiology Studies, a subsidiary of International Health Management Associates, Inc., Schaumburg, IL,USA) for susceptibility testing and confirmation of identification.
- Minimum inhibitory concentrations (MICs) were determined using MicroScan dehydrated broth microdilution panels manufactured by Siemens Medical Solutions Diagnostics (West Sacramento, California, USA), following CLSI guidelines [6]. All antimicrobial agents were supplied by the panel manufacturer.
- Cefotaxime was not added to the panels until the third year of the study; hence the n values for this drug are lower than the other cephalosporins.
- MIC results for ertapenem, imipenem, piperacillin-tazobactam, cefotaxime, ceftriaxone, ceftazidime, and cefepime were interpreted following three sets of guidelines: those currently published by the Clinical and Laboratory Standards Institute (CLSI) [4] and by the European Committee on Antimicrobial Susceptibility Testing (EUCAST), www.eucast.org [5], as well as the new previously approved CLSI guidelines due to be published early in 2010.

Table 1. Susceptible breakpoints for ceftriaxone, ceftazidime, and cefotaxime specified in the 2009 CLSI, 2010 CLSI, and 2008 EUCAST guidelines.

	2009 CLSI	2010 CLSI	2008 EUCAST
Ceftriaxone	≤ 8	≤ 1	≤ 1
Ceftazidime	≤ 8	≤ 4	≤ 1
Cefotaxime	≤ 8	≤ 1	≤ 1

- Quality control testing (QC) was done by each testing site on each day of testing using the CLSI-recommended QC strains: *E. coli* ATCC 25922 and *P. aeruginosa* ATCC 27853 [4].

References

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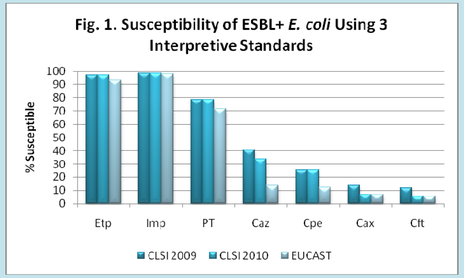
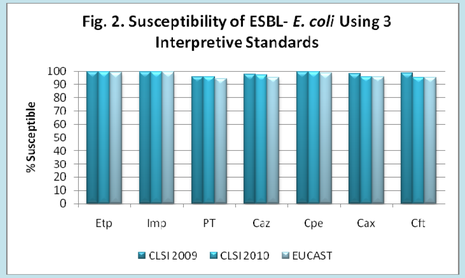
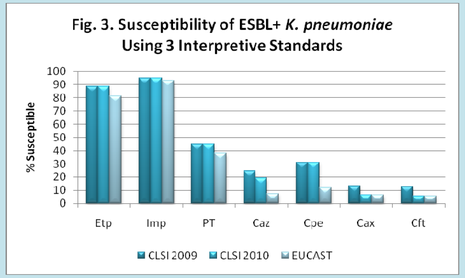
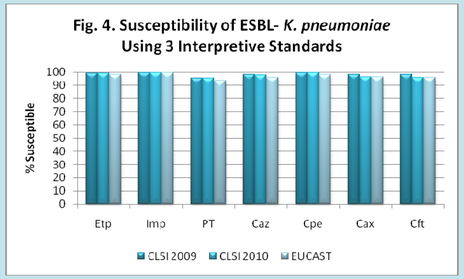
Results









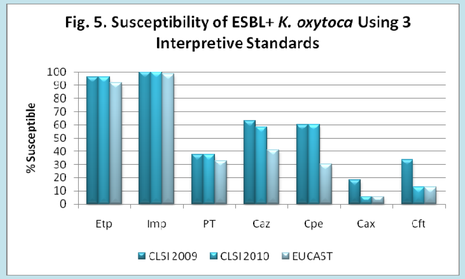
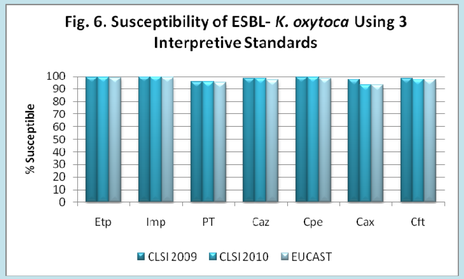
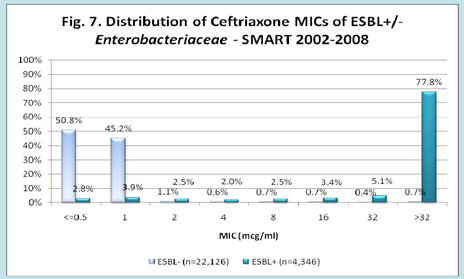
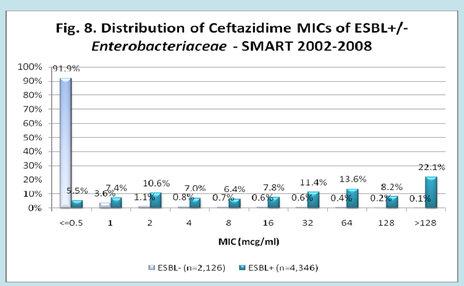


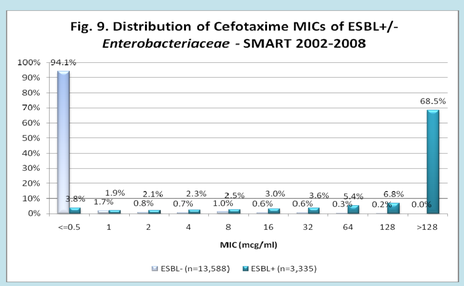
Table 2. Percent of ESBL+ isolates called susceptible using 2009 CLSI, 2010 CLSI, and EUCAST breakpoints for ceftriaxone, ceftazidime, and cefotaxime.

	2009 CLSI	2010 CLSI	EUCAST
Ceftriaxone	14%	7%	7%
Ceftazidime	37%	31%	13%
Cefotaxime	13%	6%	6%









Conclusions

❖ Although the lower cephalosporin breakpoints of EUCAST and those that will be published by CLSI in 2010 designated a larger number of ESBL+ isolates resistant than do the current CLSI guidelines, they still fail to identify many ESBL+ isolates. This was especially so with *K. oxytoca* vs. ceftazidime and cefepime, where nearly 60% of ESBL+ isolates were still called susceptible using EUCAST and the new CLSI guidelines.

❖ Confirmation testing of ESBL status thus may still be necessary to ensure proper recognition of these strains and enable optimal therapy to be initiated. Even if one considers ESBL+ isolates with MICs of ≤1 (cefotaxime, ceftriaxone), ≤4 (ceftazidime), or ≤8 mcg/ml (cefepime) to be treatable with one of these drugs, institutions in areas experiencing high ESBL+ incidence rates may need to continue ESBL testing to help maximize the probability of successful therapy.