Amoxicillin-clavulanic acid susceptibility testing: fixed ratio versus fixed concentration of clavulanic acid and clinical outcome implications in bacteraemia caused by Enterobacteriaceae

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Introduction

Clinical breakpoints for susceptibility are settled with the aim of helping physicians in their decisions about antibiotic therapy. There is scarce clinical information to support the establishment of clinical breakpoints. During last years, both the Clinical Laboratory Standards Institute (CLSI) and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) introduced some important changes in their recommendations about breakpoints for Enterobacteriaceae which have raised some controversy. Currently, EUCAST and CLSI differ in their recommendations about the microdilution methodology and susceptibility breakpoints for amoxicillin-clavulanate (AMC).

The aim of this analysis is compare susceptibility testing results when using EUCAST and CLSI recommendation, and the implications of discrepancies in clinical outcome.

Material and Methods

- A multicenter prospective cohort of patients with bloodstream infections (BSI) due to Enterobacteriaceae who received initial monotherapy with AMC was performed; 13 Spanish hospitals belonging to the Spanish Network for Research in Infectious Diseases (REIPI) participated.
- Susceptibility testing was performed by microdilution, following EUCAST (2mg/L fixed clavulanate concentration) and CLSI (amoxicillin:clavulanate 2:1 ratio) recommendations.
- Essential agreement was calculated, considering EUCAST as the reference method. Kappa index was calculated for evaluate the concordance. For categorical agreement, clinical categories according to EUCAST and CLSI interpretative criteria were used, and very major errors, major errors, and minor error were calculated.
- Outcome variables were clinical response defined as follows:
  - At the end of treatment (EOT) with AMC (EOT-A) and at the end of treatment with all antibiotics used for the episode (EOT-B):
    - "Cure" was defined as the infection was completely resolved plus further antibiotic treatment is not required.
    - "Clinical improvement": the infection was resolved but antibiotic therapy is required to continue with a different agent because of sequential therapy (oral), de-escalation or intolerance to previous drug.
    - "Clinical failure" if any of the following: the infection was not resolved, antibiotic regimen was changed because of perceived clinical and/or microbiological failure, or death.
  - 30-day mortality.
- Patients were followed from the diagnosis of bacteremia until day 30 or death.
- Clinical analysis of errors was evaluated according to outcome variables.

Results

- 264 episodes (202 caused by *E. coli*).
- 15 (5.7%) isolates were ESBL-producers and 5 (1.9%) OXA-1 producers.
- Median age was 75 (range, 64-82)
- Acquisition was community in 155 (58.7%), healthcare-associated in 55 (20.8%), and nosocomial in 54 (20.5%) cases.
- Source was the urinary tract in 171 (64.7%); 49 (18.6%) presented with severe sepsis or shock.
- The MIC distribution shown in Figure 1. Essential agreement was 73.1%, and categorical agreement was 34.5%; the kappa index was 0.24.
- 45 (17.0%) very major errors, 1 (0.4%) major error, and 45 (17.0%) minor errors were detected. Table 2.
- The outcome data are shown in the table 3.

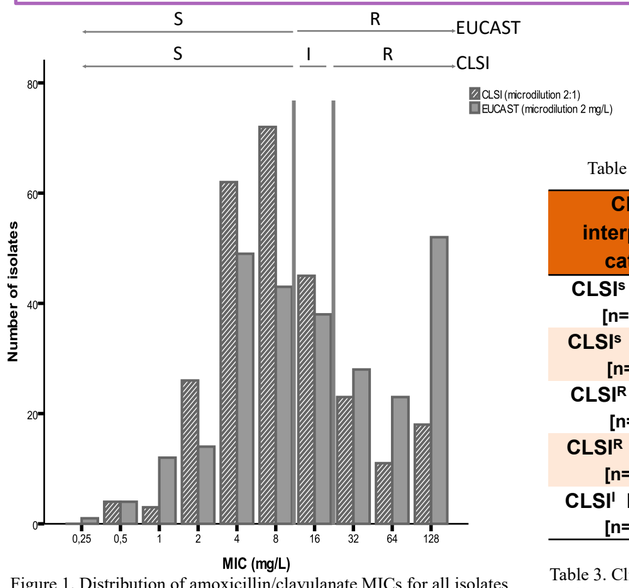

Figure 1. Distribution of amoxicillin/clavulanate MICs for all isolates according to the method used.

Clinical interpretation	EUCAST (%)	CLSI (%)
Susceptible	46.6	63.3
Intermediate	-	17.0
Resistant	53.4	19.7

Table 2. Concordance between susceptibility interpretation according EUCAST and CLSI criteria.

Clinical interpretative category	Failure at the EOT-A	Failure at the EOT-B	Mortality
CLSI^{S} EUCAST^{S} [n=122 (%)]	6/122 (13.1)	4/122 (3.3)	8/122 (6.6)
CLSI^{S} EUCAST^{R} [n=45 (%)]	6/45 (13.3)	3/45 (6.7)	4/45 (8.9)
CLSI^{R} EUCAST^{S} [n=1 (%)]	0/1 (0)	0/1 (0)	0/1 (0)
CLSI^{R} EUCAST^{R} [n=51 (%)]	12/51 (23.5)	5/51 (9.8)	4/51 (7.8)
CLSI^{I} EUCAST^{SR} [n=45 (%)]	10/45 (22.2)	3/45 (6.7)	3/45 (6.7)

Table 3. Clinical outcome of patient with bacteraemia treated with amoxicillin/clavulanate according to discordance between CLSI and EUCAST in clinical interpretative category.

Conclusions

Important discrepancies in MIC values and clinical categorization between both committees were detected. Resistance levels obtained with EUCAST methods were higher than those obtained with CLSI. No outcome implications were found regarding theses discrepancies in this study.