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106

Comparing Susceptibility Profiles of Antibiotics by Contour Interval Analysis: Ceftaroline *vs.* Belgian *S. pneumoniae* (SP) and MRSA isolates

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Background and Aims

Most drugs are developed today on a world-wide basis following the requirements of the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA). While this has improved the quality of the clinical studies submitted for registration, it may make them poorly relevant to the situation prevailing in specific countries if epidemiology and/or comparators are different from those used in these global studies.

Ceftaroline (CPT; administered as its prodrug ceftaroline fosamil) has been approved by the US FDA for community acquired bacterial pneumonia (CABP) and acute bacterial skin and skin structure infections (ABSSSI), and by the EMA for community acquired pneumonia (CAP) and complicated skin and skin structure infections (cSSSI), based on non-inferiority data using ceftriaxone and vancomycin/aztreonam as comparators, respectively [1,2].

Amoxicillin, however, is the most often recommended antibiotic for the treatment of CAP in Europe [3] and vancomycin effectiveness against MRSA is variable amongst countries [4]. Moreover, patients from small countries such as Belgium (10^7 inhabitants) can only make a small proportion of patients included in international trials, which creates uncertainties due to potential local deviations in epidemiology of drug resistance.

Performing additional clinical studies in each target market is financially unrealistic and raises both scientific and ethical issues (the number of patients who can reasonably be enrolled in a given period of time will be too small to reach statistical significance; delaying the local introduction of a potentially useful drug can be detrimental to patients in need of the drug in that area).

This problem can, however, be addressed by measuring the susceptibility of the key local target pathogens towards the new antibiotic and comparing the results with those of the currently used antibiotics using EUCAST breakpoints since these separate organisms for likelihood of clinical success *vs* clinical failure on the basis of their MIC and taking into account both PK/PD and clinical data [5].

Our aim was to perform such a validation study for Belgium using a collection of recent local isolates.

Materials and Methods

Isolates

Non-duplicate *S. pneumoniae* (n=136) and methicillin-resistant *S. aureus* (MRSA; n=157) isolates were obtained from patients with confirmed CAP or skin and skin structures infections, respectively.

MICs

MICs were determined in cation-adjusted Mueller-Hinton broth (supplemented with horse blood for *S. pneumoniae* and with 2% NaCl for *S. aureus*), with re-identification of each isolate by optochin test or resistance to oxacillin.

Analyses

Data were first manually analyzed for basic statistics and susceptibility/resistance patterns (EUCAST interpretative criteria [7]), and thereafter with JMP software (version 10.0.2), for linear fit, bivariate normal ellipse analysis (0.9 overlap), and quantile density contour coincidence (0.1-0.9).

References

1. ZINFORO Summary of Product Characteristics: http://www.ema.europa.eu/
2. TEFLARO Prescribing Information: http://www.fda.gov
3. Woodhead et al. Clin Microbiol Infect 2011;17(Suppl. 6): E1–E59.
4. Canut et al. Eur J Clin Microbiol Infect Dis. 2012;31:2227-35.
5. EUCAST clinical breakpoints 2013 (v3.1) : http://www.eucast.org.

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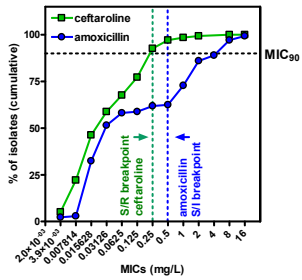
Results

1. Cumulative MIC Distributions

(vertical dotted lines correspond to EUCAST breakpoints [see [5] and blue boxes])

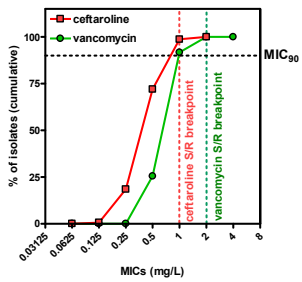
S. pneumoniae (n = 136)



EUCAST breakpoints
- amoxicillin: S ≤ 0.5 – R > 2
- ceftaroline: S ≤ 0.25 – R > 0.25

- Ceftaroline covers 92.6% of all isolates at its breakpoint of 0.25 mg/L (for a fixed dose of 2x 600 mg/day).
- For amoxicillin, 37.5% of isolates are > the "S" breakpoint. Amongst them, those with an MIC ≤ 2 mg/L may be covered if using a high dose (500 mg 3x/day), leaving about 1/3 in the "R" category and requiring still higher doses [9]

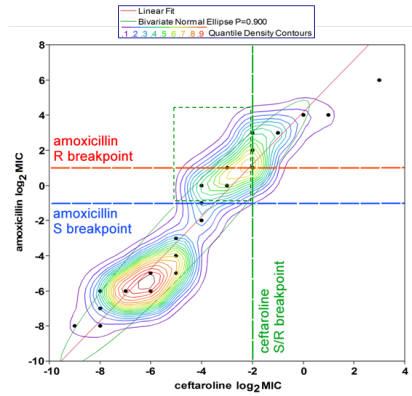
MRSA (N = 157)

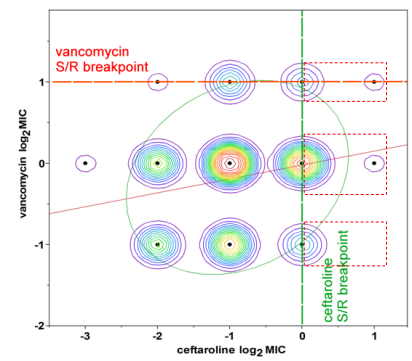


EUCAST breakpoints
- ceftaroline: S ≤ 1 – R > 1
- vancomycin: S ≤ 2 – R> 2

- Ceftraroline covers 98.7% of all isolates at its S/R breakpoint of 1 mg/L
- Vancomycin covers 100 % of all isolates at its S/R breakpoint of 2 mg/L

2. Correlations and Contour Interval Analysis





- Contour Interval Analysis shows that MICs amoxicillin and of ceftaroline correlate well but that a sizeable proportion of isolates categorized as intermediate or resistant to amoxicllin remain susceptible to cefatroline (see green box with thin dotted line).
- No correlation is seen between MICs of vancomycin and ceftaroline; only a small proportion of organisms are susceptible to vancomycin and resistant to ceftaroline (see red boxes with thin dotted lines).

Conclusions

Ceftaroline covers more *S. pneumoniae* isolates than amoxicllin and may, therefore, be useful in environments where insusceptibility to amoxicillin is problematic. For MRSA, vancomycin still remains fully usable but ceftaroline may be an alternative. Continuous surveillance is warranted.

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