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Activity of Solithromycin Against Clinical Isolates of *S. pneumoniae* with Variable Susceptibilities to Conventional Antibiotics

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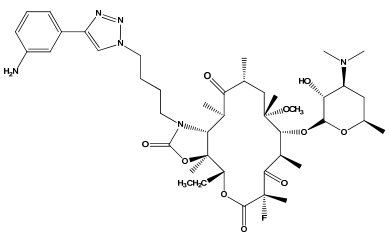
Background and Aims

Conventional macrolide antibiotics (e.g., clarithromycin) have a long history of efficacy in respiratory tract infections and of safety in adults and children, but are now losing pace in face of the increasing resistance of *S. pneumoniae*. The discovery and development of ketolides (macrolides devoid of a cladinose moiety) was first considered as a promising new avenue to tackle the resistance problem [1]. However, the clinical use of telithromycin, the first clinically developed ketolide, has been quickly marred by observation of major life-threatening and organ-dysfunction side effects [2,3].

Solithromycin (CEM-101) [4] is a new generation fluoroketolide that is safer than telithromycin and is currently entering Phase III trials in North America and Europe [5].



Solithromycin (CEM-101)

The aim of our study was to assess the activity of solithromycin against clinical isolates of *S. pneumonie* starting from two large collections assembled in Belgium and Germany that contain a significant proportion of strains with decreased susceptibility or full resistance to commonly recommended as well as to "second line" antibiotics (i.e. "*when other antibiotics can no longer be used*") for the treatment of respiratory tract infections [6].

Materials and Methods

Isolates

Non-duplicate *S. pneumoniae* isolates (n=175) were selected from patients with respiratory tract infections (mainly bacterial exacerbations of chronic bronchitis and community acquired pneumonia) and with suspicion of MICs for macrolides, β-lactams, and/or fluoroquinolones close to or above the EUCAST breakpoints [7].

MICs

MICs were determined in cation-adjusted Mueller-Hinton broth supplemented with horse blood, using the *S. pneumoniae* strain ATCC 49619 as control and re-identification of each isolate by the optochin test.

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 fitting, bivariate normal ellipse analysis (0.9 overlap), and quantile density contour coincidence (0.1 to 0.9).

References

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3. Liu & Somps. Toxicol Lett. 2010;194:66-9. PMID: 20153815.
4. Liang *et al.* Patent WO 2004080391 Sep 23, 2004.
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6. Woodhead *et al.* Clin Microbiol Infect 2011;17(Suppl. 6): E1–E59. PMID 21951385.
7. EUCAST clinical breakpoints 2013: http://www.eucast.org/clinical_breakpoints/

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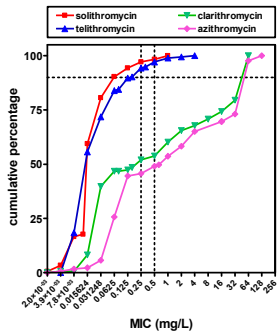
Results

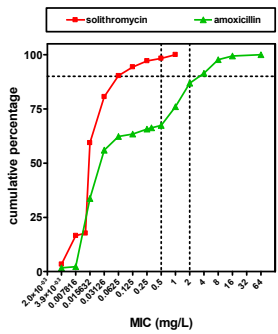
1. Cumulative MIC distributions

(vertical dotted lines correspond to EUCAST "S" and "R" breakpoints [see blue boxes])



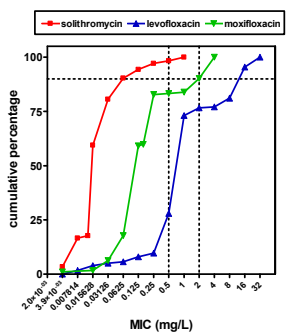
EUCAST breakpoints
- clarithromycin: S ≤ 0.25 - R > 0.5
- azithromycin: S ≤ 0.25 - R > 0.5

- Solithromycin and telithromycin show quite similar distributions (with 1 log_2 dilution difference in favor of solithromycin for isolates with MICs > 0.016 mg/L) and covers most isolates at concentrations ≤ 0.25 mg/L
- In contrast, clarithromycin and azithromycin cover only ~ 50 % of these isolates



EUCAST breakpoint
- amoxicillin: S ≤ 0.5 - R > 2

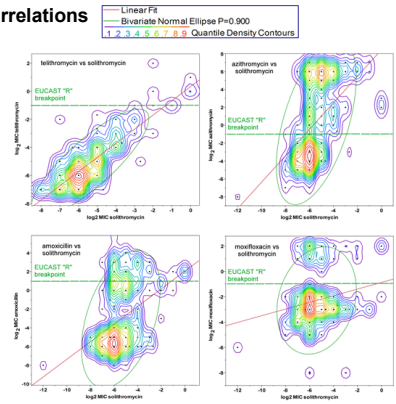
- At a concentration of 0.5 mg/L, solithromycin covers almost all isolates.
- In contrast, about 20% of isolates are intermediate (between "S" and "R" breakpoints) and 10% are fully resistant (> the "R" breakpoint) to amoxicillin



EUCAST breakpoints
- moxifloxacin: S ≤ 0.5 - R > 0.5
- levofloxacin: S ≤ 2 - R > 2

- At a concentration of 0.5 mg/L, solithromycin covers almost all isolates
- In contrast, about 20% of isolates are above the "R" breakpoints of moxifloxacin and 25% above the "R" breakpoint of levofloxacin.

2. Correlations



- The MICs of telithromycin and solithromycin correlate well with most isolates within the telithromycin-susceptible zone.
- In contrast, solithromycin shows similar activity towards isolates susceptible or resistant to the other antibiotics, which are clearly separated in two "hot spots" below and above the EUCAST "R" breakpoints
  (data with clarithromycin and levofloxacin are similar to those of azithromycin and moxifloxacin, respectively)

Conclusions

Solithromycin shows unimpaired activity against *S. pneumoniae* isolates resistant to antibiotics commonly recommended (1st or 2nd line) for respiratory tract infections, suggesting that it may represent a useful alternative in environments where resistance is problematic.

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