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IN VIVO DEVELOPMENT OF FLUOROQUINOLONE AND MACROLIDE RESISTANCE IN STREPTOCOCCUS PNEUMONIAE

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Background

Increases in the prevalence of antimicrobial resistance have been related to antibiotic consumption. However, the in vivo development of resistance might depend on the characteristics of each antibiotic.

Objective

To analyse the in vivo development of fluoroquinolone (FQ) and macrolide resistance in patients with pneumococcal infection.

Methods

From January 1999-May 2013 the antimicrobial susceptibility of all *S. pneumoniae* clinical isolates collected at University Hospital Donostia (San Sebastián, north Spain) was determined by broth-microdilution and interpreted according to EUCAST criteria.

Pneumococcal isolates from patients having a first levofloxacin- and/or erythromycin- susceptible isolate and a subsequent isolate resistant to the same antibiotic were serotyped (Quellung, PCR and/or Pneumoarray) and genotyped (PFGE).

In isolates from the same patient showing the same PFGE pattern and developing FQ resistance, mutations at Ser-79 in *parC* and at Ser-81 in *gyrA* genes were studied by PCR-RFLP. In those developing macrolide resistance the presence of *mefA* and *ermB* genes was studied by PCR.

Results

A total of 10,197 episodes of pneumococcal disease were identified in 8,182 patients. Of them, 1,147 (14%) had two or more isolates: 918 adults (>14 years) and 229 children (≤ 14 years). Most frequent recurrences were in respiratory tract infections in adults (757/918; 82.5%) and in acute otitis media (158/229; 69%) followed by conjunctivitis (36/229; 15.7%) in children.

Globally 22 patients (18 were COPD) fulfilled the criteria of having isolates of the same serotype/genotype that had developed in vivo resistance:

· 19 patients to FQ. Serotypes: 1, 6B (n=2), 6C, 9V, 11 (n=2), 14 (n=3), 18C, 19F, 19A (n=3), 22F, 23 A (n=2) and 33F.

· 2 patients to macrolides. Serotypes: 11 and 23B.

· 1 patient to FQ and macrolides. Serotype: 3.

Mutations in *parC* (Ser-79) and *gyrA* (Ser-81) were detected in 16/20 and 17/20 levofloxacin-resistant isolates respectively. A mutation in *parC* and in *gyrA* without phenotypic expression of levofloxacin resistance was observed in 5/20 and 1/20 isolates, respectively. Most patients (15/20) had FQ antibiotic treatment before isolating the resistant isolate. In three, treatment data was not available.

Among erythromycin-resistant isolates, *ermB* or *mef* genes were not detected, so that resistance was attributed to other described mechanisms (ribosomal or ribosomal proteins mutations, under study). One patient received macrolide treatment before isolating the resistant strain; in the other two, treatment data was not available.

Conclusions

- The development of macrolide resistance during treatments was scarce and less frequent than that observed with FQ.

- Development of in vivo erythromycin resistance was mainly due to mechanisms different to acquisition of resistance determinants (*mef* or *erm*B genes).
- The in vivo development of fluoroquinolone resistance was not related to a concrete serotype and most of isolates showed the same gene point mutations (Ser-79 for *parC* and Ser-81for *gyrA*).