Title: Mechanistic Model to Characterize and Predict Fecal Excretion of Ciprofloxacin Resistant Enterobacteria with Various Dosage Regimens

Authors: Thu Thuy Nguyen (1,2), Jeremie Guedj (1,2),Elisabeth Chachaty (3), Jean de Gunzburg (4),Antoine Andremont (1,5,6), France Mentré (1,2,6)
Institutions: (1)University Paris Diderot; (2) INSERM, UMR 738, Paris, France; (3) Institut Gustave-Roussy, Paris, France; (4) Da Volterra, Paris, France; (5) EA3964, "Emergence de la résistance bactérienne in vivo", Paris, France; (6) AP-HP, Hospital Bichat, Paris, France

Objectives: Dissemination in the environment of antibiotic-resistant enterobacteria via fecal excretion upon treatments with fluoroquinolones is a major public health burden [1]. However little has been done to gain a precise understanding of the *in vivo* kinetics of antibioticsensitiveand resistant enterobacteria (EB) during and after treatment. Here we aimed to characterizeby mathematical modeling the relationship between intestinal exposure to ciprofloxacin (CIP) and excretion of resistance for various dosage regimens.
Methods:29 piglets were randomlyassigned to oral treatment with placebo (n = 9), CIP 1.5 (n = 10) or 15 mg/kg/day (n = 10) during 5 days. Concentrations of CIP and counts of resistant and totalEB were obtained from fecal samples before, during and after treatment. A mechanistic mathematical model was developed to fit simultaneously CIP pharmacokineticsas well astotal and resistant EBkinetics in feces. The concentration of CIP wasdescribed using a one compartment model with first-order elimination and assuming a constant rate of CIP arriving in the intestine during 5 days.We assumed that resistant EB could be present in absence of treatment due to random mutation and/or through continuous arrival in the digestive tract by ingestion. Initiation of treatment resulted in a concentration-dependent killing rate of susceptible EB through an Emax model. The joint modeling of CIP concentrations, fecal counts of resistant and total EB (i.e. sum of resistant and sensitiveEB) from all piglets was performed by nonlinear mixed effect model, using SAEM algorithm[2] in the software MONOLIX 4.2.0. From the model and estimated parameters, we evaluated by simulation the effect of dosage regimens of 0.05 to 15 mg/kg/day administered for 3 to 10 days on thefecal excretion of resistance.
Results: Although resistant EB had a low replicative fitness of 14%, the rapid elimination of susceptible EB with a half-life of 37 minutes during treatment allowed with both dosage regimens the inverse expansion of resistance which remained in high counts up to 3 weeks after treatment end. By simulations we show that it would be necessary to reduce fecal antibiotic concentrations to those obtained with treatment doses of 0.6, 0.3 and 0.15 mg/kg/day for durations of 3, 5 and 10 days, respectively, in order to prevent the expansion of resistance.
Conclusions: To our knowledge, this is the first model developed on *in vivo* data to characterize the dynamics of resistance to fluoroquinolones in the colonic commensal flora and its correlation with drug fecal concentrations. This approach provides new insights into the mechanism of dissemination of resistance during treatments and can be used to design strategies aiming to reduce it [3].

References:

[1] Carlet J. (2012). The gut is the epicentre of antibiotic resistance. *Antimicrob. Resist. Infect. Control.* 1:39.
[2] Kuhn E, Lavielle M. (2005).Maximum likelihood estimation in nonlinear mixed effects model,*Comput. Stat. Data Anal.*, 49:1020-1038.
[3] Khoder M, Tsapis N, Domergue-Dupont V, Gueutin C, Fattal E. (2010). Removal of residual colonic ciprofloxacin in the rat by activated charcoal entrapped within zinc-pectinate beads. *Eur. Jour. Pharm. Sci*. 41:281–288.