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Concentration-dependent effect of amoxicillin against clinical strains of *Helicobacter pylori*

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Amoxicillin (AMX) is a beta-lactam antibiotic, and this class is generally considered to have "time-dependent" effects, i.e. its effect is correlated to the time during which its concentration exceeds a certain threshold (often 1 or 4 times the MIC)^{1,2}. This distinguishes them from so-called "concentration-dependent" antibiotics, such as aminoglycosides, whose effect is correlated to the maximum concentration level reached (C_{max}). This distinction has practical consequences: to optimize the effect of "time-dependent" antibiotics, continuous infusion regimens or close administration are recommended, whereas for "concentration-dependent" antibiotics, high doses are recommended³. Amoxicillin is one of the key antibiotics used to eradicate *Helicobacter pylori* (*H. pylori*) which colonizes half of the world population and is associated with peptic ulcer and gastric malignancy. In 2016, for the treatment of *H. pylori* infections, the Toronto consensus has recommended that amoxicillin, used in combination, should be administered at 1000 mg twice daily⁴. The concentration-dependent effect of amoxicillin against *H. pylori* was shown *in vitro* in an old study using a reference strain and a clinical isolate⁵. We present here complementary *in vitro* data that also suggest pharmacodynamic pattern.

The J99 reference strain and six clinical isolates (C1, C4, C8, C10, C22, C23) obtained from gastric biopsies (all susceptible to amoxicillin, MIC<0.125 mg/L) were at the inoculum of 10⁶ CFU/mL. A reference strain of *Streptococcus agalactiae* (*S. agalactiae*, ATCC 12386) was used as an example of the time-dependent pharmacodynamic profile of amoxicillin. Time kill curve (TKC) experiments were performed using liquid Brucella Broth (Condalab, Spain) media supplemented with 10 % of fetal calf serum (Eurobio, France). Amoxicillin (Merck, USA) was added at concentrations of 0, 0.125, 0.25, 0.5, 1, 2, 4, 8, 16, and 32-times MIC of each strain in broth medium. CFUs were counted at times 0, 4, 8, 24 and 30 h by sampling on Columbia agar plates (5% sheep blood) after incubation at 37°C and microaerophilic atmosphere. The limit of quantification (LOQ) of the CFU method was 50 CFU/mL for *H. pylori* and 800 CFU/mL for *S. agalactiae*. The number of colonies was determined and presented in the form of log₁₀ CFU/mL. The experiments were repeated at least two times for antibiotic concentrations ranging from 0 to 32 times the MIC (0- 2 x MIC; n=4 and 2-32 x MIC; n=2). The results were analyzed with R.

For the six clinical *H. pylori* isolates, the profile observed were similar over a wide range of concentrations, the higher the amoxicillin concentration, the greater the rate and extend of bactericidal activity. The bactericidal effect of amoxicillin was not saturable in the range of concentrations tested (0- 32 x MIC), for any of the *H. pylori* strains. Regarding *S. agalactiae*, the TKC results showed that the bactericidal effect of amoxicillin did not increase at concentrations above the MIC, amoxicillin seemed to have a time-dependent pharmacokinetic effect on *S. agalactiae*.

In the present experiment, concentration-dependent effects could be observed up to 32 times the MIC for all *H. pylori* clinical isolates. Our results therefore suggest that amoxicillin behaves in a concentration-dependent manner towards *H. pylori in vitro*. This suggests that to eradicate *H. pylori* it would be preferable to use high doses of amoxicillin. It should be noted, however, that in our experimental model, exposure to amoxicillin was continuous for 30 h. Our results therefore provide no information on whether or not it is advisable to split the daily dose. Indeed, it has been shown in patients that dose fractioning (500 mg t.i.d vs. 750 mg b.i.d) results in better eradication of *H. pylori* ⁶.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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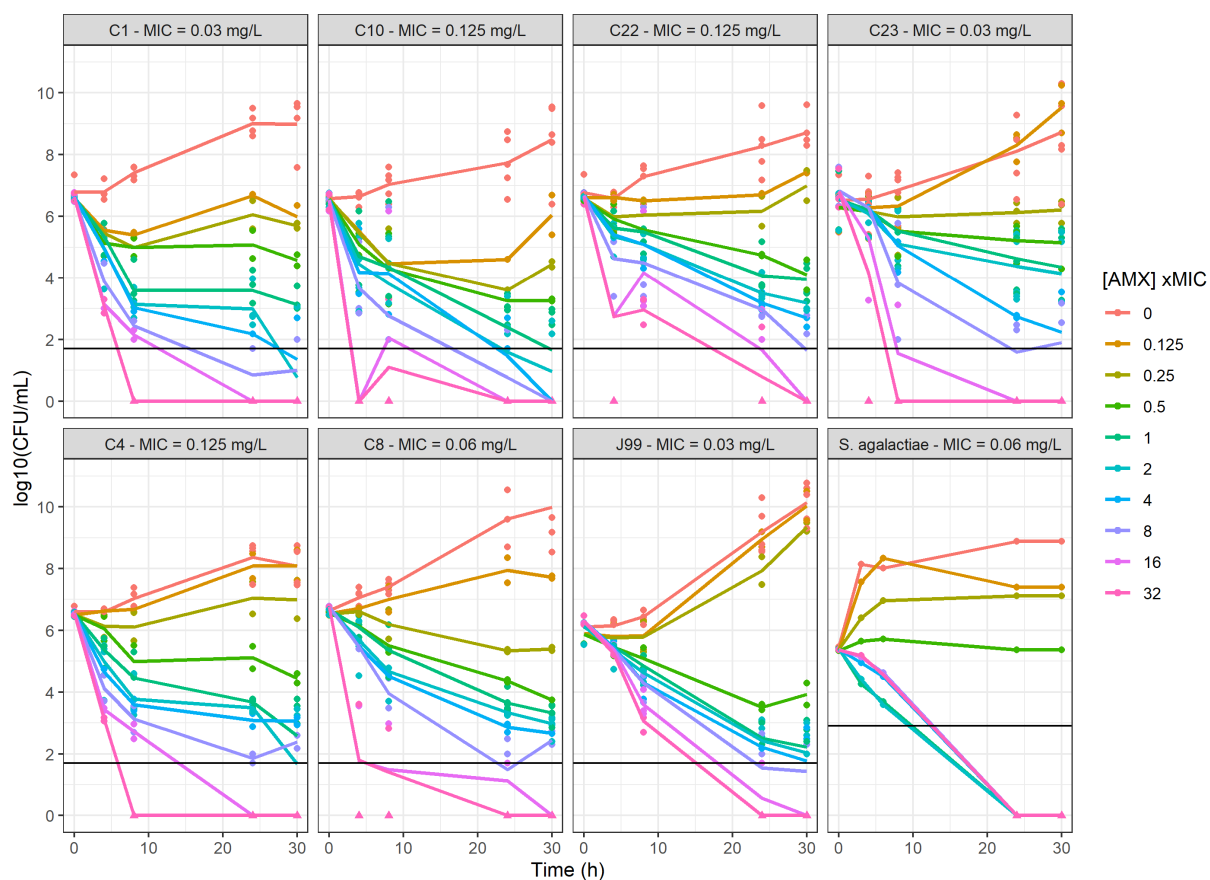


Figure 1. Time-kill curves of amoxicillin on 6 different clinical isolates of *H. pylori*, J99 and *S. agalactiae* at concentrations from 0.125 x MIC to 32 x MIC (+ control at 0 mg/L). Values below the limit of quantification (black lines, 50 CFU/mL for *H. pylori*; 800 CFU/mL for *S. agalactiae*) are represented by triangles instead of dots.