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Population pharmacokinetics of antibiotics to prevent group B streptococcal disease: from mother to neonate

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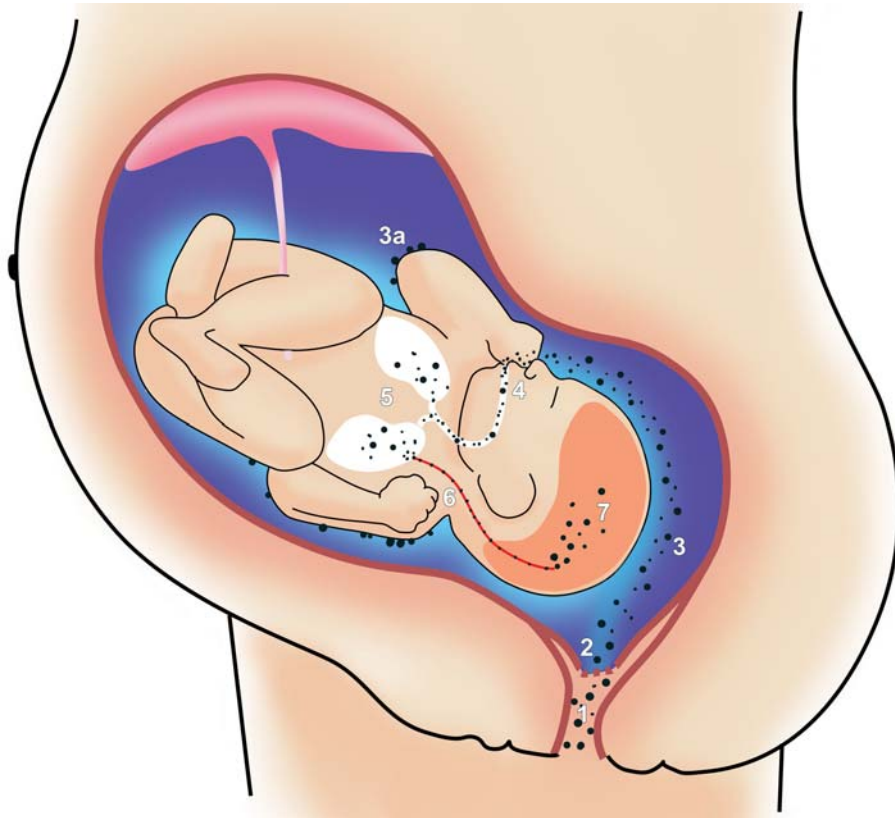
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A photograph of a beach scene. The foreground is dominated by sand with intricate, wavy ripples. A shallow, clear stream flows through the middle ground, reflecting the sky. In the background, a wide sandy beach meets the ocean under a clear blue sky. The text "Color figures" is centered in the middle of the image.

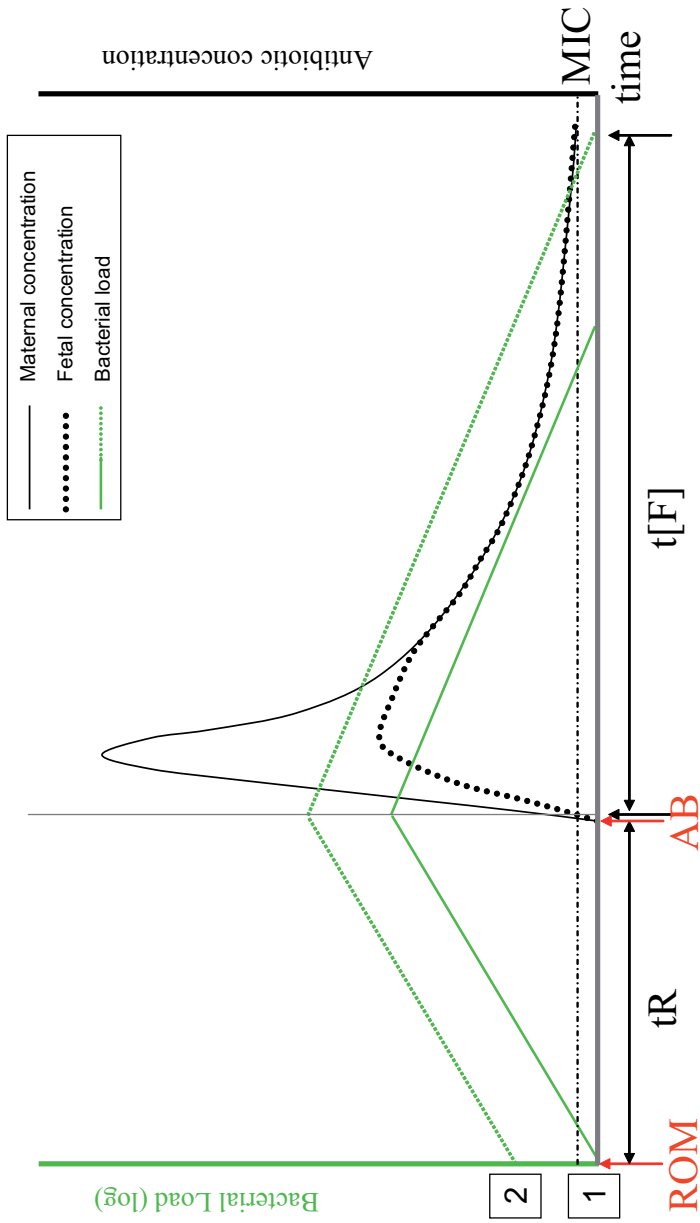
Color figures



Designed by Vincent Khouw (VMK designs)

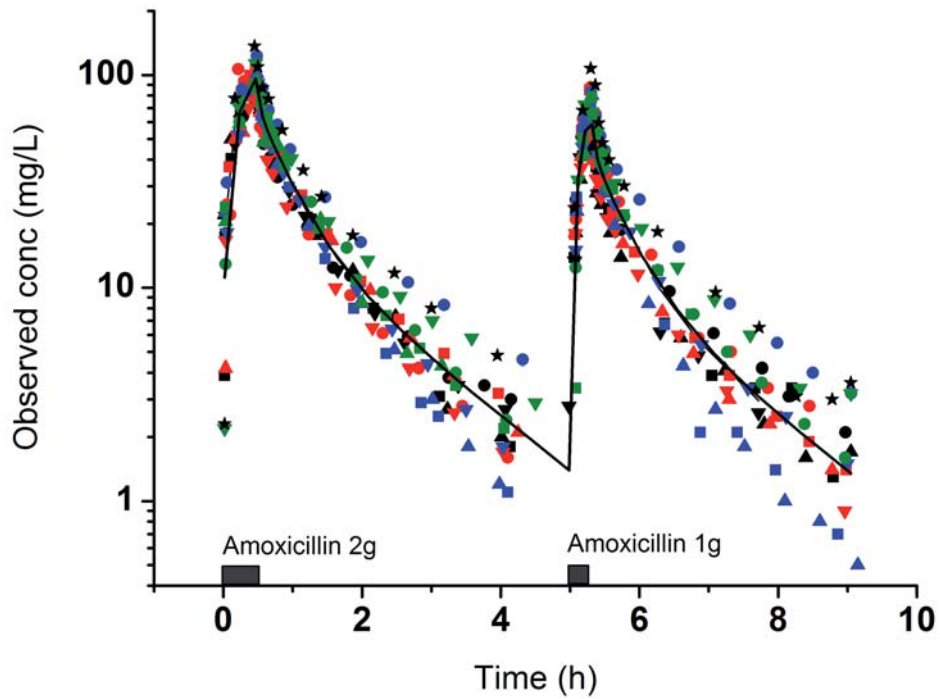
Chapter 2, Figure 1: Hypothesized pathogenesis of GBS-EOD.

1 Colonization in the rectovaginal compartment; 2 Rupture of the membranes; 3 GBS enters the amniotic fluid; 3a GBS colonization of skin and mucocutaneous areas; 4 Aspiration of infected amniotic fluid; 5 Infected amniotic fluid causes pneumonia (if the bacterial load is high enough); 6 Entry of GBS in the bloodstream (sepsis or bacteremia); 7 Entry in cerebrospinal fluid after hematogenous spread (meningitis).



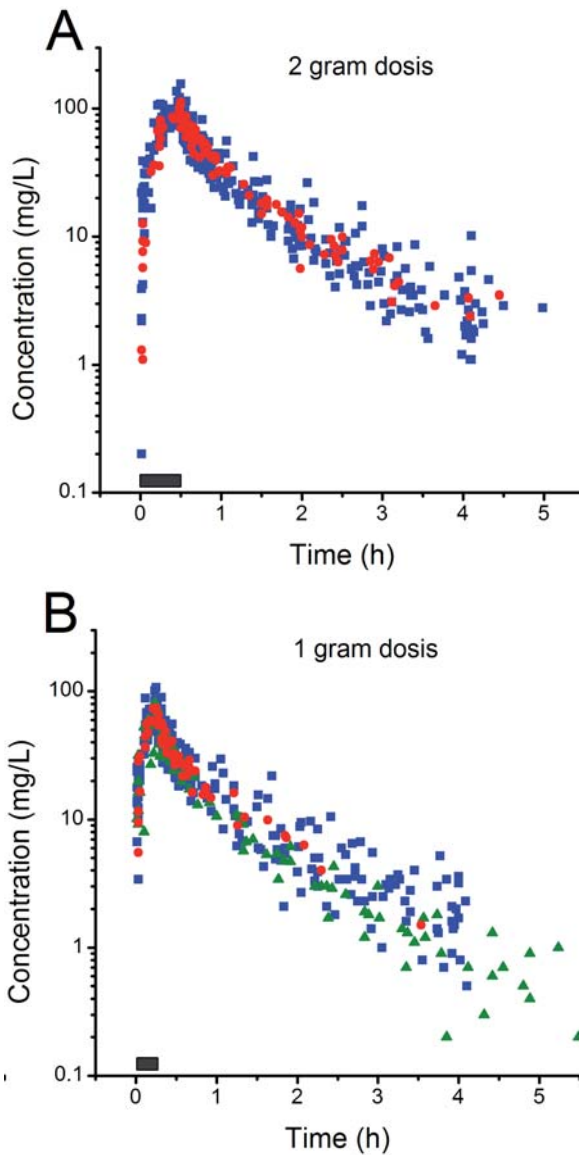
Chapter 2, Figure 2: The effect of antibiotic prophylaxis on the bacterial load of GBS.

ROM= Rupture of membranes, t_R = time between ROM and start of antibiotics, t_{AB} =start of administration of antibiotic, MIC=minimum inhibitory concentration, $t_{[F]}$ = time the fetal concentration exceeds the MIC; 1 changes in bacterial load. 2 enhanced bacterial load in maternal fever or prolonged ROM

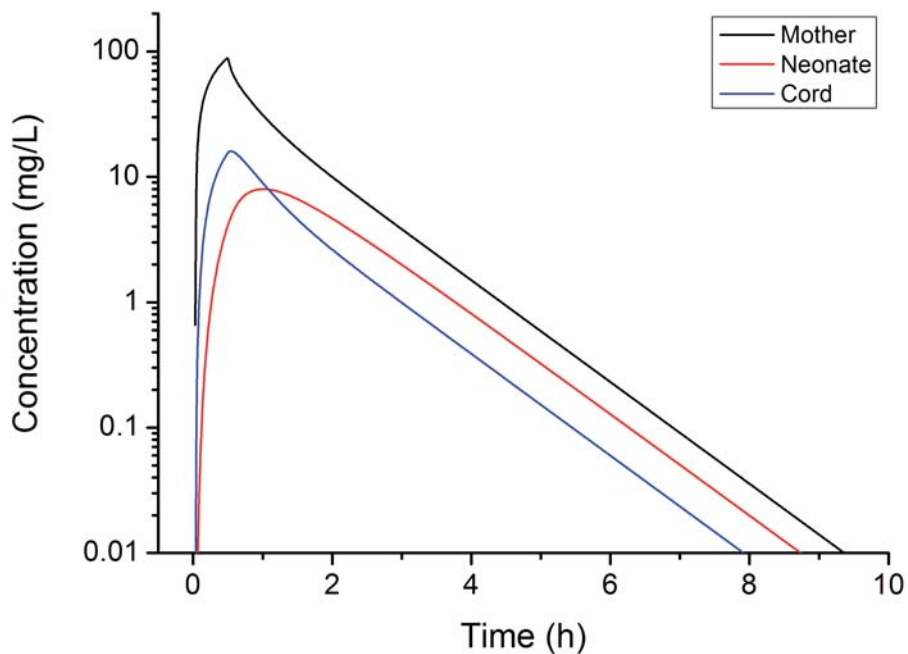


Chapter 4, Figure 1: Observed concentration-time profiles in patients with PPROM.

The superimposed bold line shows the predicted profile obtained with the final model. The blocks indicate the time at which the infusions of the amoxicillin was started and stopped. Because there was variation in the start-time of the second infusion due to the clinical situation, in this graph the data were adapted assuming that the second infusions started at $t=5.05h$ for all patients.

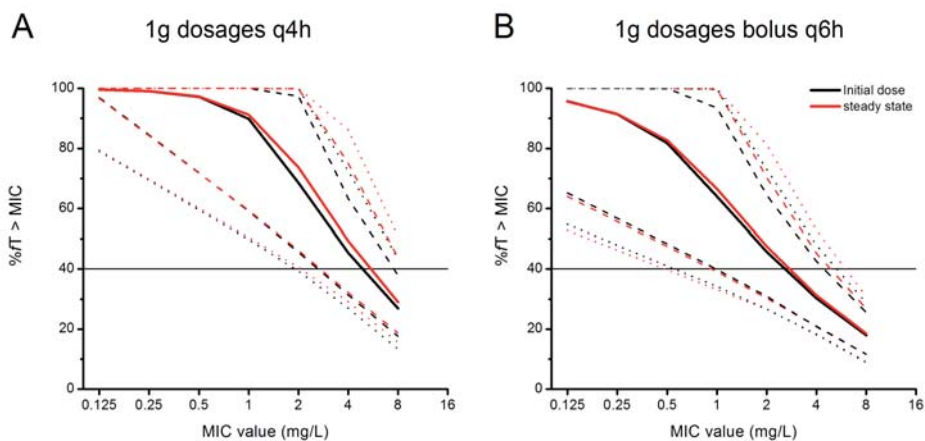


Chapter 5, Figure 3: Figure 3a shows the observed amoxicillin concentrations after a 2 gram dose and figure 3b after a 1 gram dose. Time of infusion is indicated by black bars. The blue squares represent all data points of the patients before the onset of labor; the red dots data points of patients during labor and data points of patients in the postpartum period are indicated by the green triangles. Because there was variation in the start-time of the second infusion, in figure 3b the data were adapted assuming that the 1 gram infusions started at $t=0$ for all patients.

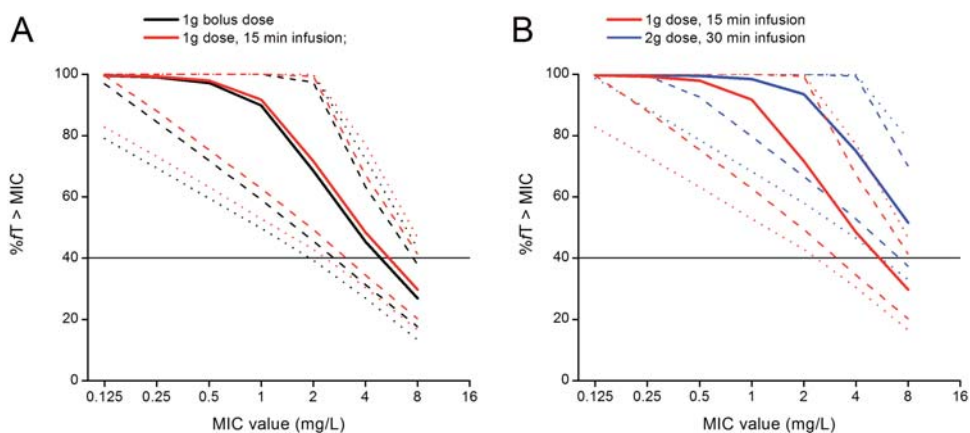


Chapter 7, Figure 4: Simulated concentration-time profiles for the mother, umbilical cord and neonate.

Concentration-time profile of amoxicillin in maternal, umbilical cord and neonatal serum simulated after a single dose of 2 gram amoxicillin infused over 30 minutes. The simulations were performed with PK parameter estimates based on the final 5-compartment model and carried out for 12 hours after a single antibiotic dose.



Chapter 8, Figure 2: Percent of time the unbound fraction of amoxicillin remained above the MIC ($\%fT > MIC$) as a function of the MIC for two dosing intervals, 4 hours (figure 2a) and 6 hours (figure 2b), in pregnant women with PPRM after the initial dose (black lines) and in steady state situation (red lines).



Chapter 8, Figure 3: Percent of time the unbound fraction of amoxicillin remained above the MIC ($\%fT > MIC$) as a function of the MIC for three different initial doses for a 4 hours dosing interval in pregnant women with PPRM. In figure 3A the $\%fT > MIC$ for a dose of 1 gram administered as bolus (black lines) and the 1 gram dose administered over 15 minutes (red lines) are shown. In figure 3B the $\%fT > MIC$ for the 1 gram dose administered over 15 minutes (red lines) and the 2 gram dose administered over 30 minutes (blue lines) are shown. The solid lines are the values for the average pregnant women; the interrupted lines represent the 95% confidence intervals and the dotted lines the 99% confidence intervals.