#P1026

# Vancomycin pharmacokinetics and activity in a novel *in vivo* model of biofilm-related infection of tissue cages in guinea pigs: comparison with *in vitro* data

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## Introduction

Orthopaedic device-related infections represent a devastating complication, causing high rates of morbidity and mortality. Among these, **periprosthetic joint infections (PJI)**, are a complication of joint replacement surgery and one of the leading causes of failure following hip and knee replacement (1). Their management is complicated by the presence of bacteria forming **biofilms** that are recalcitrant to antibiotherapy (2). ***Methicillin-Resistant S. aureus* (MRSA)** represent nearly 50% of isolated species in these infections and **are a significant risk factor for treatment failure** (3). ***In vivo* models** of biofilms growing on implanted material are needed to evaluate therapeutic strategies.

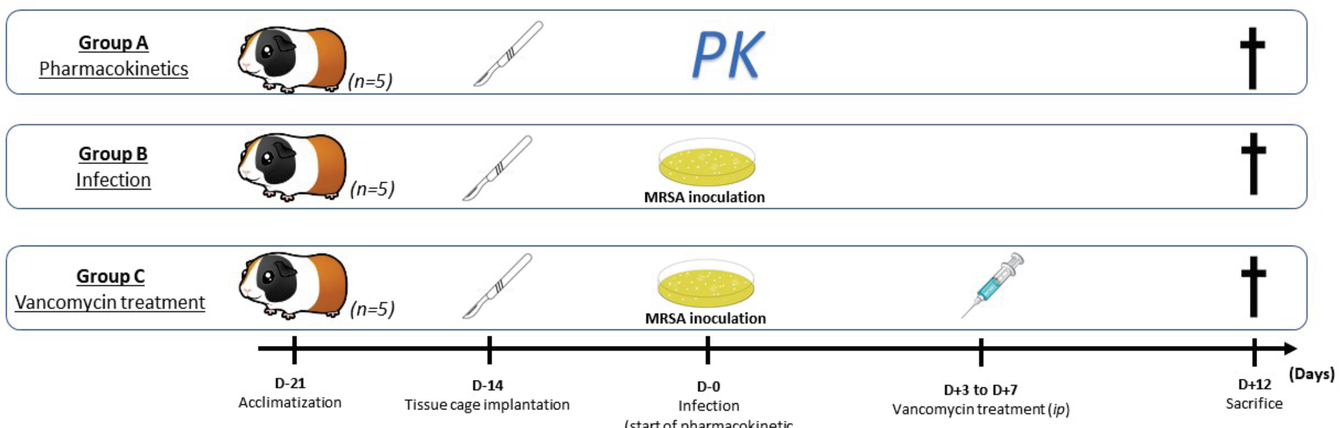
## Objectives

(A) To develop a preclinical relevant model of foreign-body infection in guinea pigs, using vancomycin as an exemplative antibiotic
(B) To determine the pharmacokinetic profile of vancomycin in the serum and at the site of infection
(C) To compare vancomycin activity in this in-vivo model with that measured in an in-vitro model of biofilm growing on titanium coupons

## Study design and methods

***In vivo* model.** This model is adapted from (PMID: 7119479) (4). Sterile multiperforated tissue cages (*figure 1*) containing titanium beads were implanted in the back of guinea pigs. Animals were assigned to three groups: vancomycin pharmacokinetics (A), infected/non-treated (B) and infected/treated (C). (A): single intraperitoneal (*ip*) dose of vancomycin (15 mg/kg) then follow-up of pharmacokinetic profile over 12h in serum and tissue cage fluid. (B-C): cages infected by MRSA ATCC33591 (10*7 CFU/mL). (C): 15 mg/kg q12h vancomycin ip over 4 days, with tissue cages fluid samples collected regularly in all animals and implanted material collected from euthanized animals at preset times. Tissue cage fluid and cages/beads processed for bacterial counts.

***In vitro* model**. ATCC33591 biofilms were grown on titanium coupons, exposed 24h to vancomycin at increasing concentrations and processed for bacterial counts.



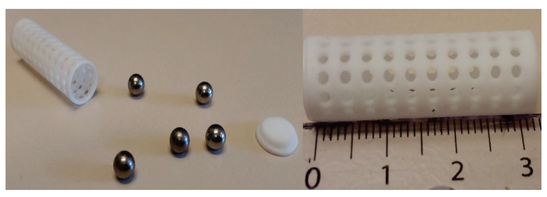
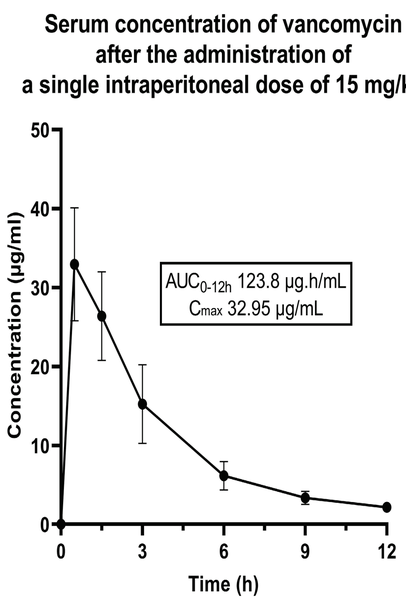



**Figure 1**. Cages and titanium beads.

## Results



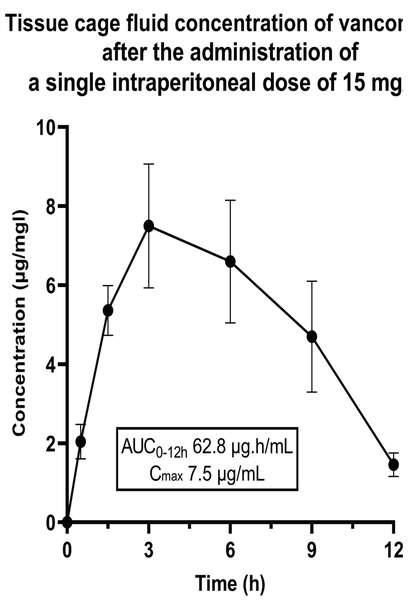
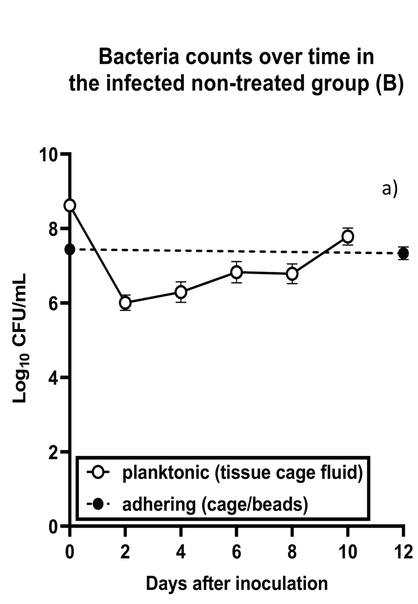




**Figure 2. Systemic and local pharmacokinetic profiles of vancomycin.** Values are means +/- SEMs (n= 5). Peak and AUC were 4.4 and 2-fold lower in tissue cage fluid than in serum.



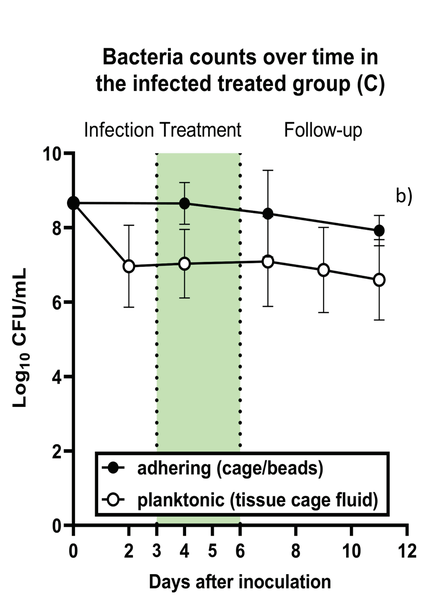
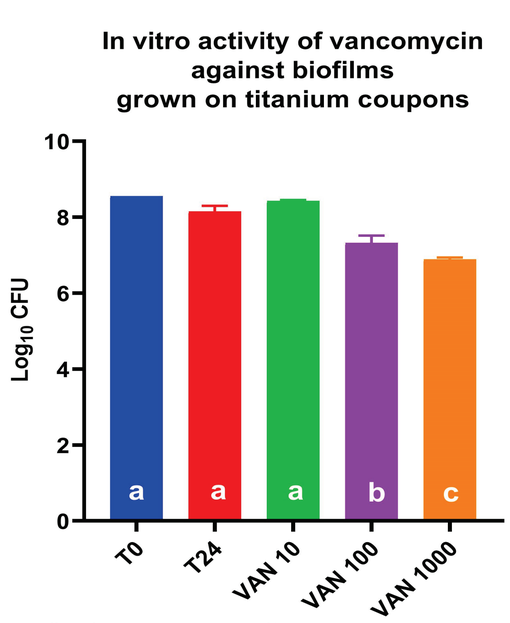




**Figure 3. Evolution of bacterial counts (planktonic [tissue cage fluid] and adhering [cage and beads]) in non-treated (left) and treated (right) animals.** Results are means +/-SD. (nB = 5 and nC = 5). 2a) No spontaneous recovery was observed 10 days after the infection. 2b) Vancomycin was ineffective against both planktonic and adherent bacteria.




.**Figure 4. Effect of vancomycin on MRSA biofilm in vitro.** CFU counts expressed in Log10 CFU per coupon. CFUs were counted at the time of drug addition (T0), after 24h incubation with Tris buffer (T24) or with increasing concentrations of vancomycin at the indicated concentrations (10-100-1000 µg/mL [10-100-1,000 x MIC]). Results are means +/- SD (n=3). Statistical analysis: one-way ANOVA with Tukey post hoc-test: $p < 0.05$ between column with different letters. Significant reduction in bacterial counts was observed for coupons exposed to ≥ 0.1 mg/mL during 24h, corresponding to an AUC0-24h 10-times higher than that reached in serum and 20-times higher than that reached in the cages.

## Conclusion

A reproducible guinea pig model has been successfully developed, allowing to follow drug local and systemic pharmacokinetics and activity. The fact that vancomycin was ineffective could be attributed to its insufficient concentration at the infection site to act against planktonic bacteria and biofilms. This model could be used to evaluate other strategies targeting biofilms.

## References

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