# Efficacy of generic meropenem products in combination with colistin in carbapenemase-producing Klebsiella pneumoniae experimental osteomyelitis

P Tattevin, A Dinh, I Ghout, W Mouton, M.-C. Verdier, F Laurent, F Lemaître, L Gatin, A Saleh-Mghir, A.-C. Cremieux

## Highlights

- Carbapenemase-producing *Enterobacteriaceae* are emerging multidrug-resistant bacteria responsible for invasive infections, including osteomyelitis.
- Although optimal antibacterial regimen remains undefined, most experts recommend a combination of two active agents, including meropenem if MIC $\leq$ 8 mg/L
- We compared the efficacy of five meropenem products in combination with colistin, *in vitro*, and in a rabbit model of carbapenemase-producing *Enterobacteriaceae* osteomyelitis.
- We found no significant difference *in vitro* and *in vivo*, between the princeps and the four meropenem generics, in terms of bactericidal activity and selection of resistance

# Efficacy of generic meropenem products in combination with colistin in carbapenemase-producing *Klebsiella pneumoniae* experimental osteomyelitis

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**Running title**: Meropenem Generics for KPC Osteomyelitis

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**ABSTRACT**

Guidelines for the management of carbapenemase-producing Enterobacterales (CPE) infections recommend a combination of two active agents, including meropenem if MIC $\leq$ 8 mg/L. The therapeutic equivalence of meropenem generics has been challenged. We compared the bactericidal activity of meropenem princeps (AstraZeneca), and four different generic products (Actavis, Kabi, Mylan, Panpharma), *in vitro* and *in vivo*, in association with colistin. *In vitro* time-kill studies were performed at 4 x MICs. An experimental model of KPC-producing *Klebsiella pneumoniae* osteomyelitis was induced in rabbits by tibial injection of a sclerosing agent followed by 2 x $10^8$ CFU of KPC-99YC (meropenem MIC, 4 mg/L; colistin MIC, 1 mg/L). Treatment started 14 days after inoculation, for 7 days, in 7 groups of >10 rabbits: control group, colistin, and one group for each meropenem product (i.e., the princeps, and the 4 generics), in combination with colistin.

*In vitro*, meropenem + colistin were bactericidal with no viable bacteria after 6 h, and this effect was similar with all meropenem products. In the osteomyelitis model, there was no significant difference between meropenem generics and the princeps when combined with colistin. Colistin-resistant strains were detected after treatment with colistin + meropenem princeps (n=3), and generics (n=3). In conclusion, the efficacy of four generics of meropenem was not different from the princeps *in vitro*, and in an experimental model of KPC-producing *K. pneumoniae* osteomyelitis in rabbits, in terms of bactericidal activity, and emergence of resistance.

**Key words:** Meropenem; generics; princeps; colistin; carbapenemase; KPC; *Klebsiella pneumoniae*; osteomyelitis; experimental model

## 1. Introduction

The worldwide emergence of multidrug-resistant Gram-negative bacteria with decreased susceptibility to carbapenems is a major concern [1]. In Enterobacterales, resistance to carbapenems may be due to: i) a beta-lactamase with significant hydrolytic activity towards carbapenems (i.e., a carbapenemase), or ii) a combination of overexpression of beta-lactamases possessing a weak carbapenemase activity towards carbapenems (i.e., extended spectrum beta-lactamase and/or cephalosporinase), with a decreased outer-membrane permeability or efflux overexpression. The most clinically-relevant carbapenemases encountered in Enterobacterales belong to Ambler class A, mostly *Klebsiella pneumoniae* carbapenemase (KPC)-type [2], Ambler class B (metallo-beta-lactamases, such as IMP-, VIM- and NDM-types), and Ambler Class D (OXA-48-like enzymes) [1]. Based mostly on cohort studies, guidelines for the management of carbapenemase-producing Enterobacterales (CPE) infections recommend a combination of two active agents, including meropenem if MIC $\leq$ 8 mg/L [3-5]. Recent international consensus guidelines for the optimal use of the polymyxins recommend that for invasive infections due to CPE, polymyxin B or colistin be used in combination with one or more additional agent(s) active *in vitro* [6].

The quality of meropenem generics approved for use in humans have been recently challenged [7-10]. The fact that two products of parenteral use are therapeutically equivalent if they are pharmaceutically equivalent, as considered by the

World Health Organization (WHO) and drug regulatory agencies [11], has been questioned. This controversy may have important consequences, as i) it suggests that patients may be currently treated with sub-optimal anti-infective treatment, depending on the meropenem generics available; ii) changes would be required in the process that lead to antibacterial generics approval. Indeed, additional studies on efficacy would be required, which would translate into increased costs. However, a systematic review found that data currently available on the quality of antibacterial generic products are limited and heterogeneous, and that more evidence is necessary to advocate for a revision of the marketing authorization process for antibacterial generic products [12]. We aimed to compare the bactericidal activity of the meropenem princeps (AstraZeneca), and four different generic products (Actavis, Kabi, Mylan, Panpharma), *in vitro* and *in vivo*, in association with colistin, in an experimental model of KPC-producing *K. pneumoniae* osteomyelitis.

## 2. Methods

### *2.1 Bacterial strain*

KPC-99YC is a clinical strain of carbapenemase-producing *K. pneumoniae*, intermediate to meropenem (MIC, 4 mg/L), and susceptible to colistin (MIC, 1 mg/L) [13,14]. This strain belongs to the epidemic clone ST-258. Virulence of the strain was verified by intra-peritoneal injection in mice. Meropenem MICs were determined with the E-test method (BioMerieux, La Balme-les-Grottes, France), as recommended by the manufacturer. Colistin MICs were determined by liquid broth dilution methods based on the UMIC colistin reagents (Biocentric, Bandol, France), as previously described [13,14].

*2.2 Antibacterial agents*

Meropenem products manufactured by AstraZeneca (princeps), and Actavis, Kabi, Mylan, and Panpharma (generics), and colistin (colistimethate sodium, Sanofi) were bought from local drug purchases companies and prepared following label instructions for clinical use in humans.

*2.3 Time-kill curve studies*

The *in vitro* bactericidal activity of meropenem princeps and generics in association with colistin was determined in triplicate. Overnight cultures of KPC-99YC were adjusted to a 0.5 MacFarland standard, and diluted in 10 mL of fresh Mueller–Hinton broth to yield an inoculum of $10^5$ CFU/mL. The antibiotic concentrations used were equivalent to 4 x MICs (i.e. 4 mg/L colistin, 16 mg/L meropenem). After 0, 3, 6, 9, and 24 h of incubation at 37°C, serial dilutions of 0.1 mL samples were subcultured onto tryptic soy agar plates (bioMérieux, La Balme-les-Grottes, France), and incubated at 37°C for 24 h before CFU were counted. Bactericidal effect was defined as a $\geq 3$ $\log_{10}$ decrease of the initial inoculum at 24 h. Synergy was defined as a decrease of $\geq 2$ $\log_{10}$ CFU/mL for the combination, as compared to its most active constituent.

*2.4 Selection of meropenem and colistin doses in rabbits*

Plasma antibiotic concentrations were measured in uninfected rabbits, to select doses that lead to plasma concentrations equivalent to those obtained in humans. Initial doses were selected based on previous experimental studies in rabbits, and we verified

that they achieved pharmacokinetic (PK) and pharmacodynamic (PD) targets for the KPC-99YC strain. Each antibiotic was tested on groups of 4 rabbits. Samples were obtained after 24 h of treatment to better estimate steady-state concentrations. Blood was drawn 15 min and 1, 2, 4, 6, 8, and 12 h after the injection, centrifuged, and plasma was frozen until assayed. Concentrations were measured by high-performance liquid chromatography (HPLC) tandem-mass spectrometry, using an electrospray ionization method.

For colistin, samples were purified by solid-phase extraction on OASIS HLB Cartridges (Waters, Milford, USA). PK parameters were calculated by using Monolix version 4.3.3 (Lixoft SAS, Antony, France). After extraction, eluates were analyzed using triple stage quadrupole spectrometer Acquity H Class-Quattro Premier XE from Waters. Reversed-phase chromatography was performed on a C18 XBridge Tmcolumn (3.5 µm, 2.1x100 mm; Waters). The mobile phase consisted in 0.1% formic acid in acetonitrile/water. The mass spectrometer was operated in the positive-ion mode. Ions were analyzed by multiple-reaction monitoring (MRM) by employing the transition of the [M + 3H]3+ precursor to the product ions for the analytes and internal standard (polymyxin B). The transition ions were m/z 390.82>100.73 for colistin A, m/z 386.18>100.73 for colistin B, and m/z 402.16>100.85 for the polymyxin B. The concentration range was 0.0625 to 8 mg/L for colistin A + B.

Quantification of meropenem in rabbit plasma has been performed using tandem mass spectrometry (LC-MS/MS) after protein precipitation with acetonitrile and liquid/liquid extraction by dichloromethane. The HPLC system was interfaced with a

triple stage quadrupole spectrometer Finnigan TSQ Quantum Discovery Max from ThermoFisher. Reversed-phase chromatography was performed on Atlantis® T3 dC18 column (3 µm, 2.1 x 100 mm, Waters). The mobile phase consisted in 0.1% formic acid and methanol. The mass spectrometer was operated in the positive-ion mode. Ions were analyzed by single-reaction monitoring (SRM) by employing the transition of the [M+H]+ precursor to the product ions for the analytes and internal standard (faropenem). The transition ions were m/z 384.0>141.0 for meropenem and m/z 286.0>182.0 for the faropenem. The concentration range was 1 to 120 mg/L. The limit of quantification was 0.25 mg/L.

*2.5 Rabbit osteomyelitis model*

Norden's method [15], was used to induce osteomyelitis in female New Zealand white rabbits, each weighing 2 to 3 kg, as previously described [13]. A 2 x $10^8$ CFU inoculum was selected because preliminary experiments (data not shown) revealed that it induced persistent osteomyelitis in 90% of animals, with low sepsis-related early mortality (<10%).

*2.6 Treatment and its evaluation*

Fourteen days post-infection, rabbits were assigned to one of the seven following groups: Group 1, no treatment (control); group 2, colistin 150 000 IU/kg t.i.d im

(equivalent to 3 M IU t.i.d in humans), groups 3-7, colistin + meropenem princeps (group 3) or generics (groups 4-7) 80 mg/kg sc t.i.d, (250 mg t.i.d in humans). Rabbits not infected, and those who died before the start of treatment were not included (Table S1). Each regimen was administered for 7 days. Animals were euthanized by intravenous (iv) injection of pentobarbital, 3 days after the end of therapy (day 24 post-infection), to allow for bacterial regrowth after treatment discontinuation, while avoiding the persistence of residual antibiotic in the bone. Control rabbits were also euthanized on day 24. The right hind limb was dissected, and the tibia and femur were separated from the surrounding soft tissues. Bacterial counts were evaluated as previously described [13]. Results are expressed as median [IQR] $\log_{10}$ CFU/g of bone, and as the percentage of animals with sterile bones. Bone was considered sterile when the culture showed no growth after incubation for 48 h at 37°C, and the number of CFU was recorded as the lowest detectable bacterial count (1.10 to 1.30 CFU/g of bone, depending on the weight of the sample).

*2.7 In vivo selection of mutants*

Each undiluted bone homogenate (50 µL) was plated onto Mueller-Hinton II agar and onto Mueller-Hinton II agar supplemented with colistin (0.125, 0.25, 0.5, 1, 2, 4 or 8 mg/L) to detect resistant mutants after 24 h of incubation at 37°C. When bacterial growth was observed, *K. pneumoniae* identification was confirmed using matrix-assisted laser-desorption ionization time of flight (MALDI-TOF) mass spectrometry (Vitek MS, bioMérieux, La Balme-les-Grottes, France). Colistin MICs were determined as

previously described. Mutants were defined by a MIC >2 mg/L (i.e. two folds compared to the initial strain).

*2.8 Data analysis*

The data were analyzed with R software (R Development Core Team, 2012) [16], as previously described [13]. Due to the small sample size and asymmetric distributions of the variables, exact nonparametric test implemented in the coin package were used [17]. The effect size of antibiotics and their 95% confidence intervals (CI) on $\log_{10}$ CFU criteria were calculated by the Hodges-Lehmann estimator and the Bauer algorithm, respectively. The effect size of the antibiotics on the sterility criteria was estimated by the difference of proportion of sterile bones, and 95%CI. A *P* value < 0.05 was considered statistically significant.



**3. Results**

*3.1 In vitro bactericidal effect*

MICs were similar for meropenem princeps and generics (4-8 mg/L). In time-kill curves at 4 x MIC, colistin alone was rapidly bactericidal during the first 6 h, but regrowth occurred after 9 h of incubation. MICs of bacteria growing after 9 h were similar to the MICs of the initial strain. Meropenem alone was poorly bactericidal, with a decrease of the initial inoculum by only 2 $\log_{10}$ at 9 h. The combination of meropenem to colistin prevented the regrowth and was synergistic, with no viable bacteria found after 6

h. As meropenem alone was not bactericidal on KPC-99YC, the comparison of the bactericidal activity of princeps and generic products of meropenem by time-kill curves were performed only with combinations of meropenem and colistin at 4 x MICs, in triplicate. In these experiments, all generic products exerted bactericidal activity, as defined by at least 3 $\log_{10}$ decreases compared with controls. No significant differences were found between the 4 meropenem generics tested, and the princeps (figure 1).

*3.2 Serum concentrations of meropenem and colistin in rabbits*

For colistin, the PK/PD target was a plasma $AUC_{24}$/MIC ratio of 25-50. This target was achieved with the dosing regimen of 150 000 IU t.i.d. im, equivalent to 3 M IU t.i.d. in humans. Mean $AUC_{24}$/MIC ratio was 48$\pm$11, mean plasma Cmax was 2.64$\pm$0.33 mg/L and mean Cmin was 0.35$\pm$0.18 mg/L. For meropenem, the initial objective was to maintain plasma concentrations above the MIC during at least 50% of the time between two injections. This target was achieved with 250 mg/kg t.i.d., but the treatment was very poorly tolerated, with severe diarrhea in rabbits, and a letality >50%. Hence, a dosage of 80 mg/kg t.i.d. was finally selected. With this dosing schedule, the plasma concentrations were maintained above MIC during 20% of time between two injections, and no severe side effect was observed. The plasma meropenem concentrations measured in 12 infected rabbits after 24 h of treatment with 80 mg/kg t.i.d. (steady-state concentrations), were as follows: mean Cmax, 17.9 $\pm$ 12.4 mg/L, and mean Cmin, 0.35 $\pm$ 0.11 mg/L, which is comparable to plasma Cmax and Cmin observed with 250 mg t.i.d. in humans.

*3.3 Therapeutic studies*

All control rabbits, except one (9%), were infected at day 24. The median [IQR] of bacterial count was 6.0 [5.75, 6.44] $log_{10}$ CFU/g of bone. Rabbits treated with colistin alone were not different from controls, with a median bacterial count of 5.5 [4.29, 6.15] $log_{10}$ CFU/g of bone, and no sterile bone at day 24. All meropenem products associated with colistin significantly decreased bone bacterial concentrations as compared to controls (median $log_{10}$ CFU/g $\leq$ 5.45, $P < 0.05$), except for the colistin + meropenem (Aztrazeneca) group (median $log_{10}$ CFU/g 5.67, $P = 0.076$, figure 2). There was no significant difference between each meropenem generics and the princeps when combined with colistin, in terms of bacterial count, and proportion of sterile bones (figure 3). Colistin-resistant strains were detected in rabbits treated with colistin plus meropenem princeps AstraZeneca (n=3, MICs=32 mg/L), colistin plus meropenem generic Mylan (n=2; MIC=32, and MIC> 64 mg/L), and colistin plus meropenem generic Actavis (n=1, MIC=32 mg/L).

## 4. Discussion

We found that the efficacy of four generics of meropenem, manufactured by Actavis, Kabi, Mylan, and Panpharma, was not different from the efficacy of the princeps in combination with colistin, on a clinical strain of carbapenemase-producing *K. pneumoniae*, in terms of bactericidal activity *in vitro*, in an experimental model of osteomyelitis in rabbits, and in terms of resistance selection. These data do not support recent results obtained by Agudelo et al. who found that, despite the concentration and potency of the active pharmaceutical ingredient, *in vitro* susceptibility testing, and mouse

PK were identical for three generics of meropenem and the princeps, two generics were significantly less active than the princeps in the neutropenic guinea pig and mouse models [7]. Although the generics evaluated in this latter study were different (i.e., manufactured by Vitalis, Procaps, and Farmioni, in Colombia), these discrepancies may be related to the selection of experimental models, which probably plays a major role in the evaluation of the efficacy of antibacterial treatment. Indeed, the neutropenic mouse models have mostly been developed to analyze the main PK/PD parameters predictive of success, as guides for establishing optimal dosing regimens in humans [18]. When it comes to the comparison of different antibacterial treatment, investigators usually select an animal model that closely reproduces the characteristics of the infectious disease(s) of interest in humans, and use dosing regimen that replicates as much as possible the PK in humans, so that the results may be extrapolated to clinical use. The rabbit model of osteomyelitis was selected for the following reasons: i) it closely reproduces a difficult-to-treat human infection [15, 19], with high inoculum, and diffusion issues [20,21]; ii) osteomyelitis due to KPC-producing *K. pneumoniae* or other CRE are emerging [22,26], and their optimal management remains largely unknown; iii) in contrast to acute models of murine septicemia or peritonitis, osteomyelitis may explore the *in vivo* selection of resistant strains in chronic infections, a good surrogate marker for sub-optimal treatment of multidrug-resistant bacteria.

Our study has limitations: Firstly, we used a low dose of meropenem, 80 mg/kg im t.i.d., equivalent to only 250 mg iv t.i.d. in humans, due to poor tolerability of higher doses in rabbits. We could not replicate current PK/PD targets for meropenem in humans, as initially planned. However, the use of sub-optimal concentrations in the rabbit model

of osteomyelitis, associated with high inoculum in difficult-to-reach sanctuaries (i.e., bone), could be considered as the perfect experimental setting to identify sub-optimal drugs in terms of sterilization rates, or the risk for selection of resistant subpopulations during treatment. Of note, the dose of colistin we used in the experimental model, 150 000 IU t.i.d., would translate into a daily dose of 150 000 IU/kg, similar to recommended doses in humans, which may be considered as a low dose, if we consider animal scaling (i.e. x3 for rabbits). In addition, we used the inactive prodrug of colistin, colistimethate sodium, for the in vivo efficacy study. However, we verified through serial measurement of colistin serum concentrations in a subgroup of four rabbits, that this regimen was able to reach the standard PK/PD target for colistin, a plasma $AUC_{24}$/MIC ratio of 25-50. Secondly, our study may have been underpowered to detect differences between generics due to limited sample size. However, $\geq$10 rabbits were evaluated for each group, in line with most experimental studies performed to compare in vivo efficacies of different antibiotics [27].

The debate on the equivalence of generic antibiotics have several major implications: i) it may apply to other therapeutic classes (e.g. anti-epileptic [28], cardiovascular [29]); ii) more than two-thirds of antibiotics currently in use worldwide are, indeed, generic drugs, and this is true in developed as well as in developing countries (source, IMS Health). The use of generic drugs has been promoted for economic reasons, and was instrumental to allow increased access to antiretroviral drugs in the countries most affected by the HIV pandemic. However, the need for increased access to essential drugs, such as antibiotics or antiretrovirals, should not translate into worldwide use of drugs with lower potency. In this regard, our study provides reassuring data.

## 5. Conclusions

In a stringent model of carbapenemase-producing *K. pneumoniae* experimental osteomyelitis in rabbits, we found no significant differences between four generic products of meropenem, and the princeps, in combination with colistin, the most active regimen in this model.

## Declarations

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**Competing Interests**: P. Tattevin has served as a scientific advisor for Astellas, AstraZeneca, Correvio, Gilead Sciences, MSD, Mylan, and Pfizer. A-C. Crémieux has received grants from Janssen–Cilag, Novartis, AstraZeneca, Aventis and Haeraus for consultancies, workshops and travel to meetings and accommodations.

**Ethical Approval:** The experimental protocol was in keeping with French legislation on animal experimentation and was approved by the Animal Use Committee of Maisons Alfort Veterinary School (Maisons-Alfort, France).

This study has been presented at the 28th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID), Madrid, Spain, in 2018.

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**Figure 1.** *In vitro* time-kill curves for carbapenemase-producing *Klebsiella pneumoniae* (KPC-99YC), using princeps, and generics of meropenem, alone (FIG 1A), or in combinations with colistin (FIG 1B), at 4 x MICs (meropenem, 16 mg/L, and colistin, 4 mg/L)

Figure 1A

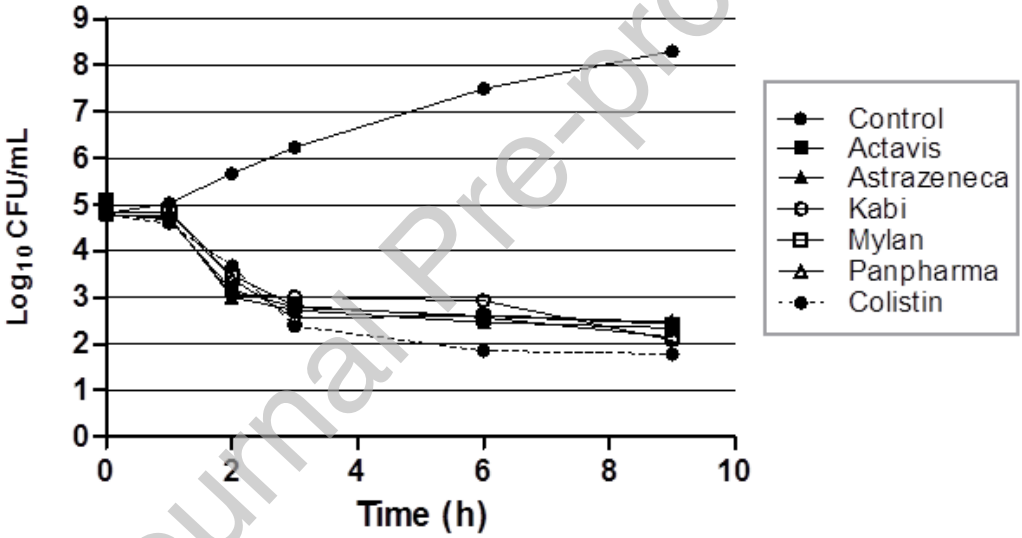



Figure 1B

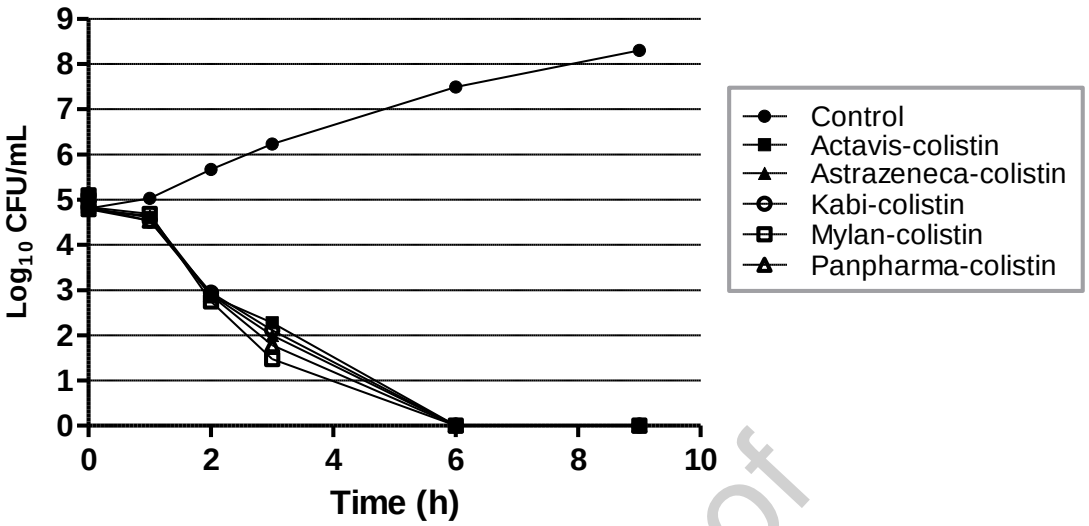
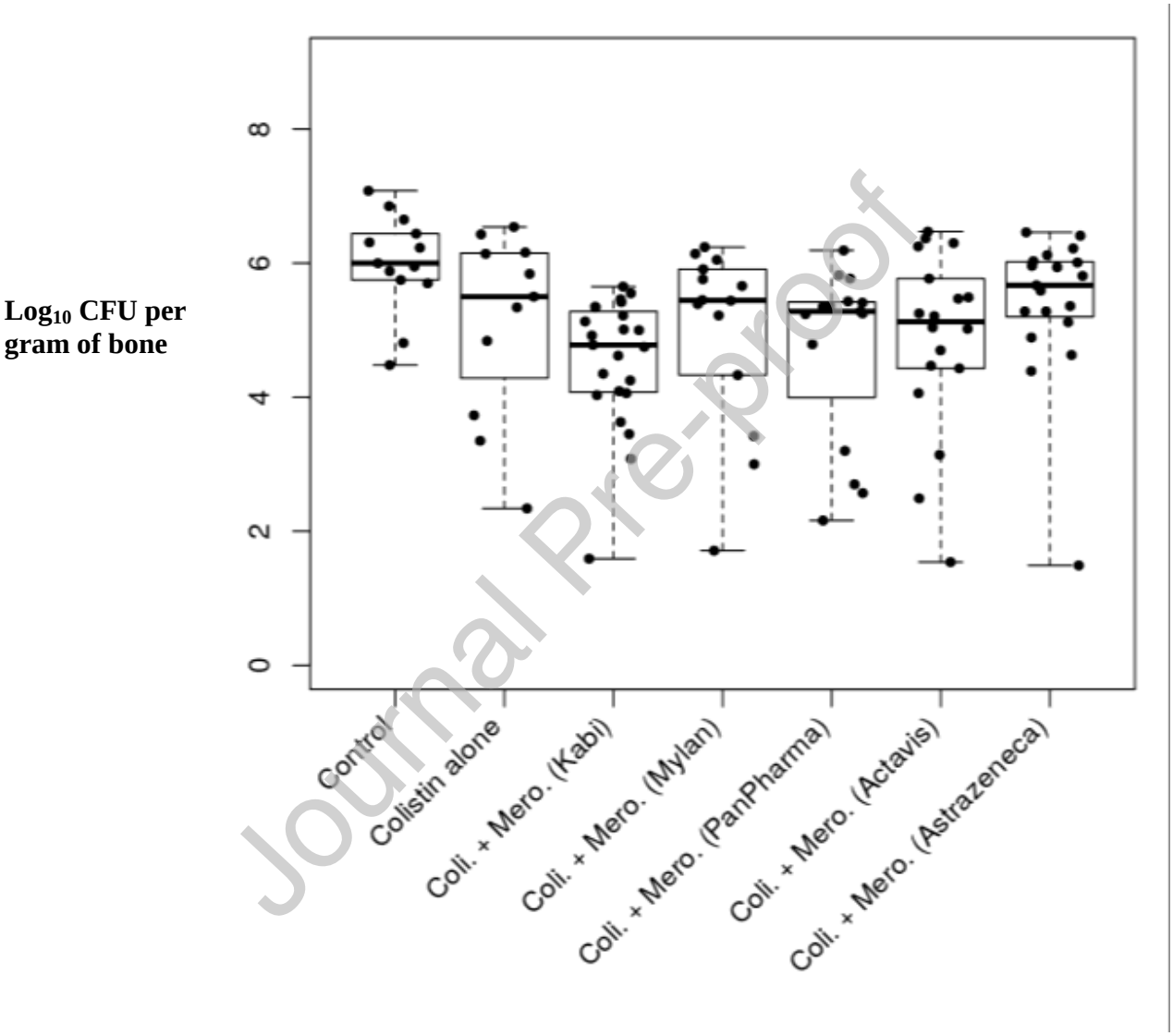


**Figure 2.** Organism titers ($log_{10}$ CFU/g of bones) in controls, and in rabbits treated with colistin alone, or in combination with meropenem princeps (AstraZeneca), or generics (Kabi, Mylan, Panpharma, and Actavis)




For each group, individual data for each rabbit are represented by a dot, and the median is represented by the horizontal bar.

**Figure 3.** Difference between each meropenem generics, and the princeps, when combined with colistin, in terms of bacterial count (Figure 3A), and in terms of proportion of sterile bones (Figure 3B)

Figure 3A

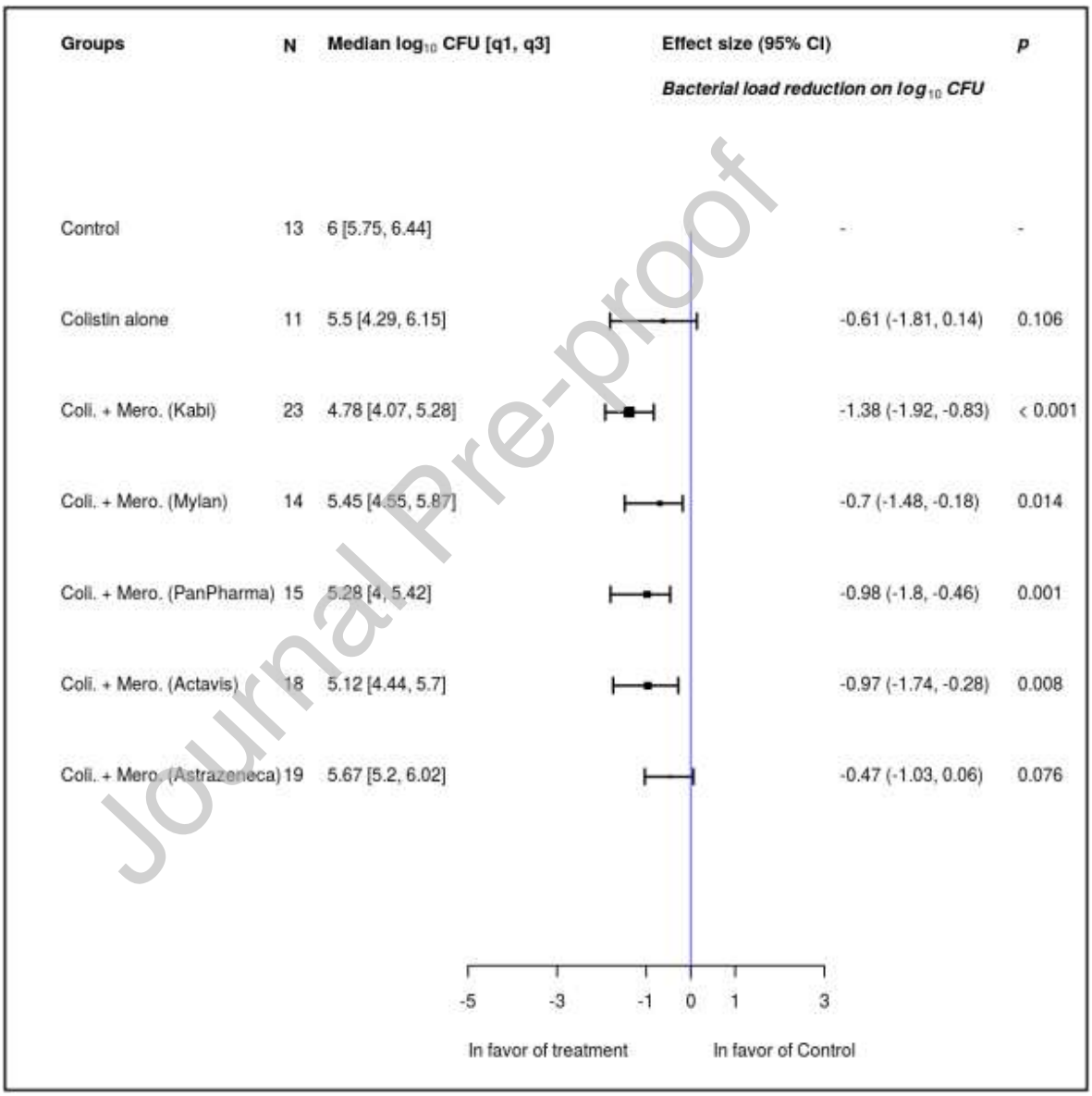


Figure 3B