Rabbit Models of Pseudomonas Pneumonia

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Disclosures

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Why rabbits?

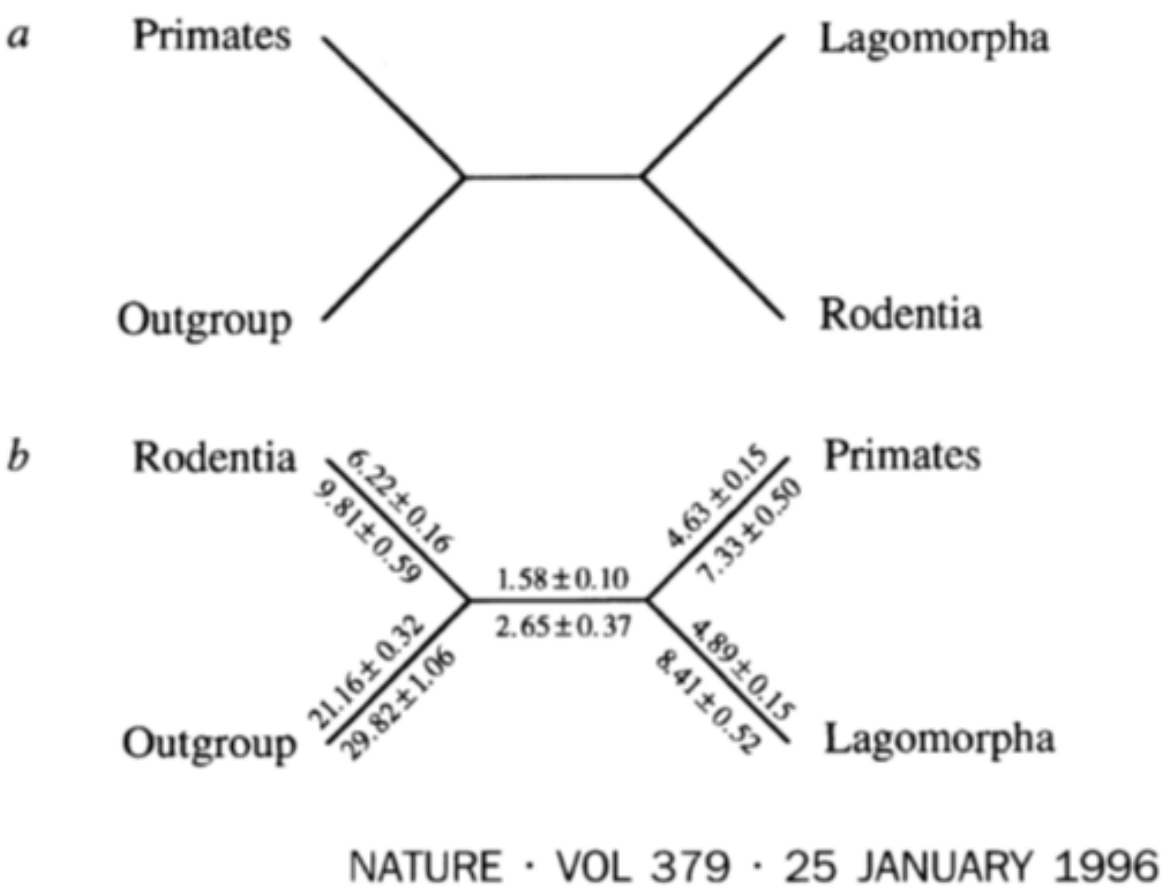

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Table 5 | Comparison of the LPS dose required to induce physiological changes across species, relative to the LPS dose required in humans.

	Threshold of physiological changes	Severe sepsis or lethal dose
Humans	1–5 ng/kg (i.v.)	
Chimpanzees	1–5 ng/kg (i.v.)	
Baboons and old world monkeys	0.1–6 mg/kg (i.v.)	
Rabbits	2–4 ng/kg (i.v.)	10 μg/kg (i.v.) (100% of animals)
Swine		10 μg/kg (i.v.) (30% of animals)
Mice	0.5 mg/kg (i.p.)	8 mg/kg (i.p.)
Rats		15 mg/kg (i.p.) to 40 mg/kg (i.v.)

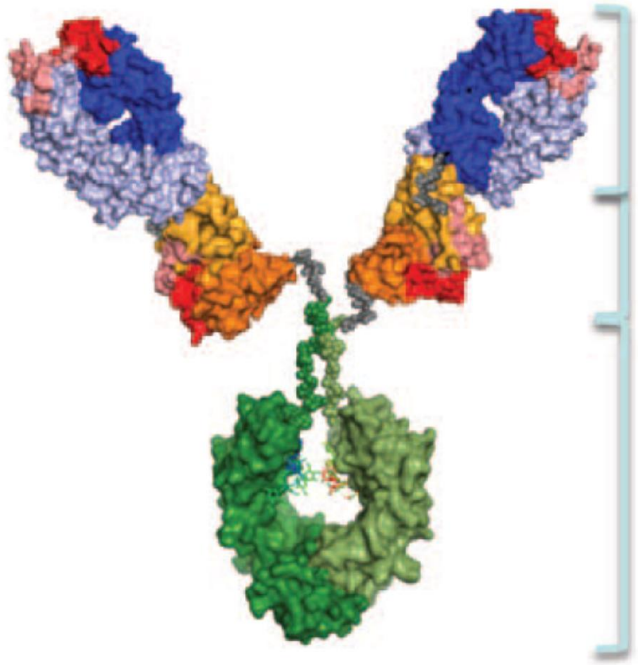
Mathison, JCI 1988;
Vaure, Liu, FII 2014

Preclinical Rabbit Models For Drug Development

- Initial Lead Candidate Selection/Validation in Higher-Throughput Models
  - Rabbit Model of Acute Pneumonia (PNAS 2010, STM 2016, AAC 2016/17)
  - Rabbit Model of Severe Sepsis (PLoS ONE 2008)
  - Rabbit Model of Acute Bacterial Skin and Skin Structure Infection (AAC 2016)

- Further Efficacy Testing/MOA Study in Lower-Throughput Surgical Models
  - Rabbit Model of Aortic Valve Endocarditis (AAC 2008, AAC 2010)
  - Rabbit Model of Prosthetic Joint Infection (ISSSI 2016)
  - Rabbit Model of Ventilator-Associated Pneumonia and Septic Shock

Evaluation of MEDI3902, a Multifunctional Bispecific Antibody, in Rabbit Models of Acute Pneumonia and Ventilator-Associated Pneumonia and Septic Shock



Fab = anti-PcrV

scFv = anti-Psl

Hinge-Fc

Rabbit Study Endpoints: Reduction in Mortality and/or
Prevention of Major Morbidity

DiGiandomenico et al. Sci Trans Med 2014

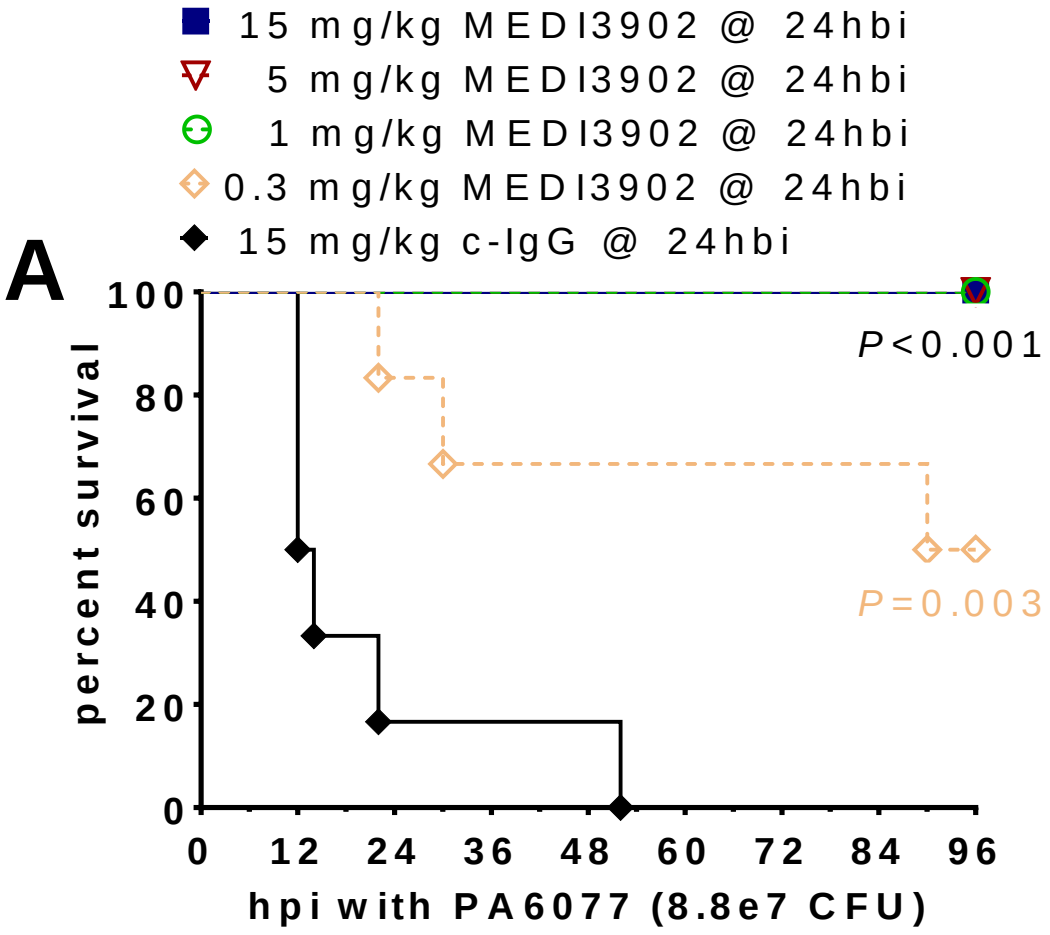
Rabbit Model of Acute Pneumonia

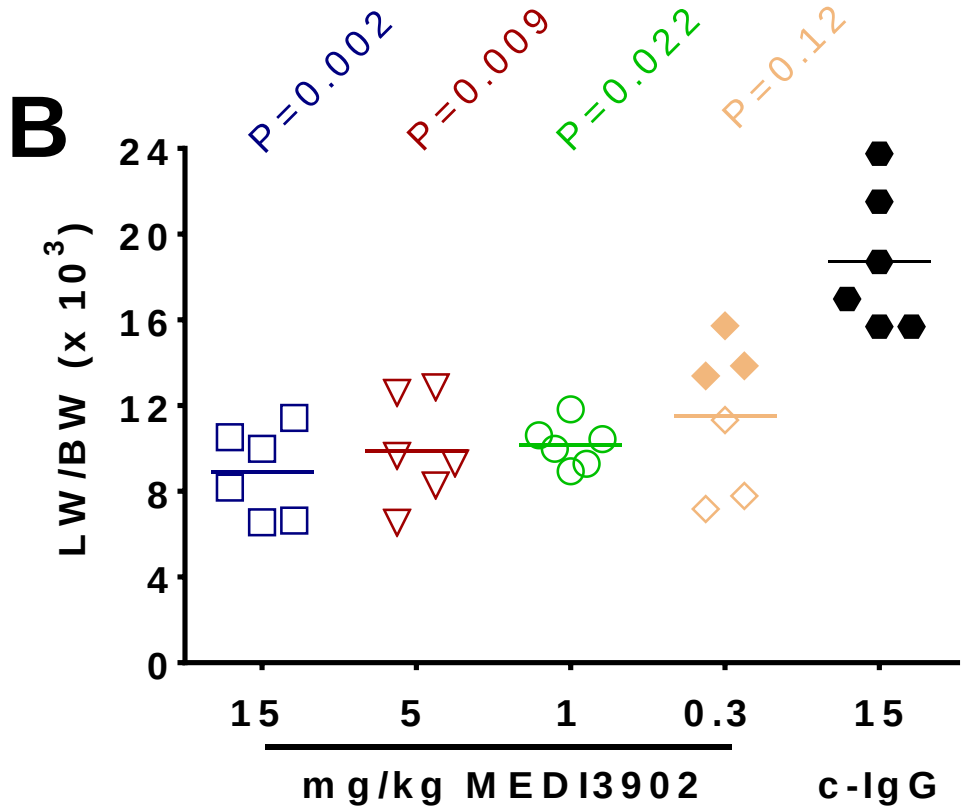
- Rabbits were randomized for prophylaxis (24hbi) or treatment (1hpi) with
  - 15, 5, 1, 0.3 mpk MEDI3902
  - 15 mpk c-IgG

- Rabbits were challenged with 9e7 CFU Pa6077 endobronchially

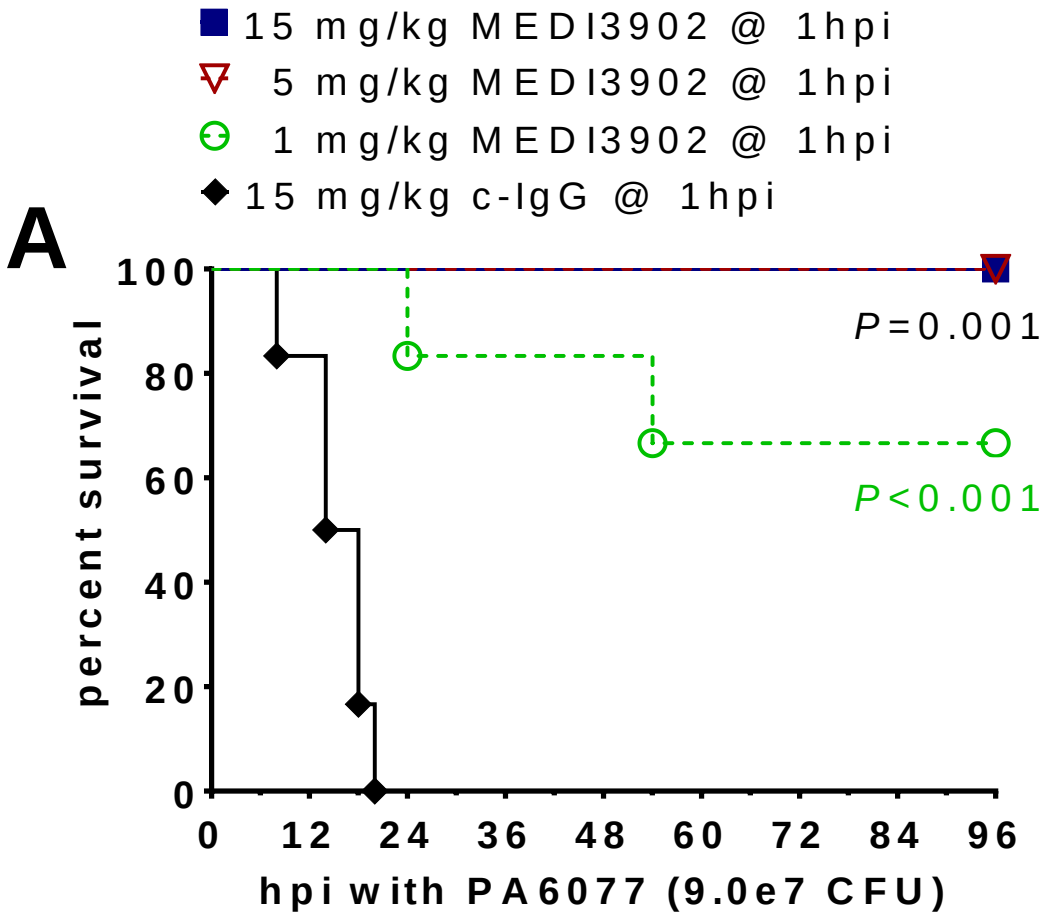
- Rabbits were monitored q2h for first 36 hpi, and then 3x daily thereafter
  - Humane criteria for euthanasia: respiratory rate > 90, cyanosis, and cough

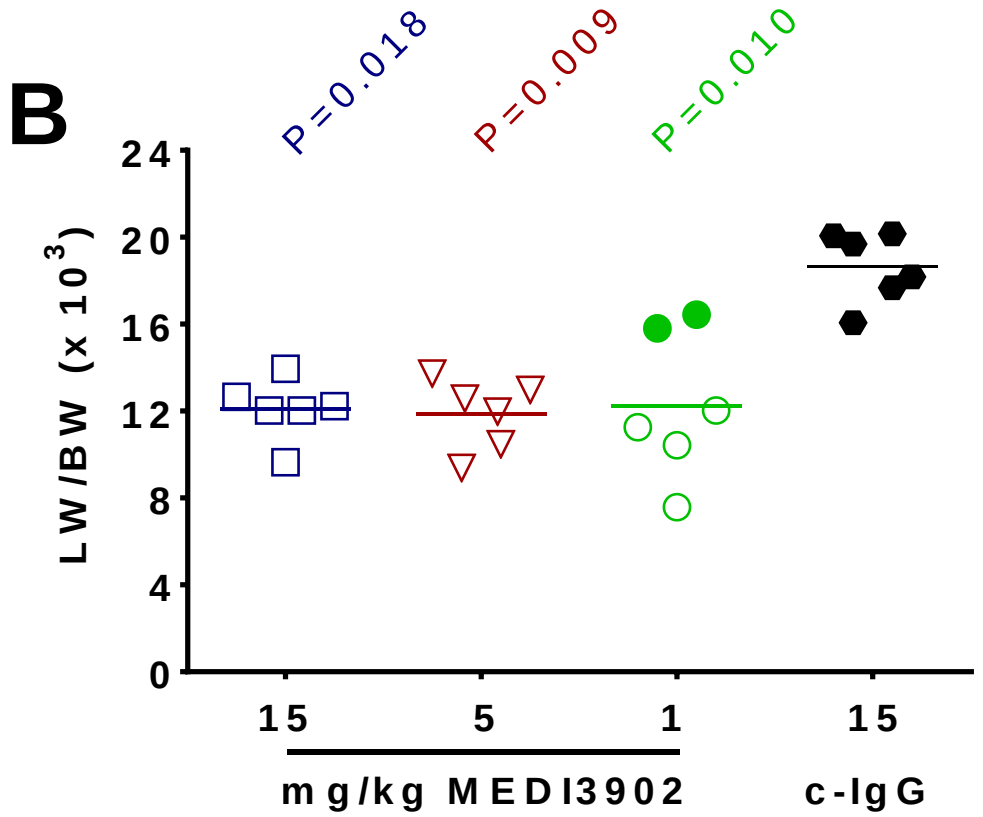
Rabbit Acute Pneumonia Model: MEDI3902 vs. c-IgG prophylaxis



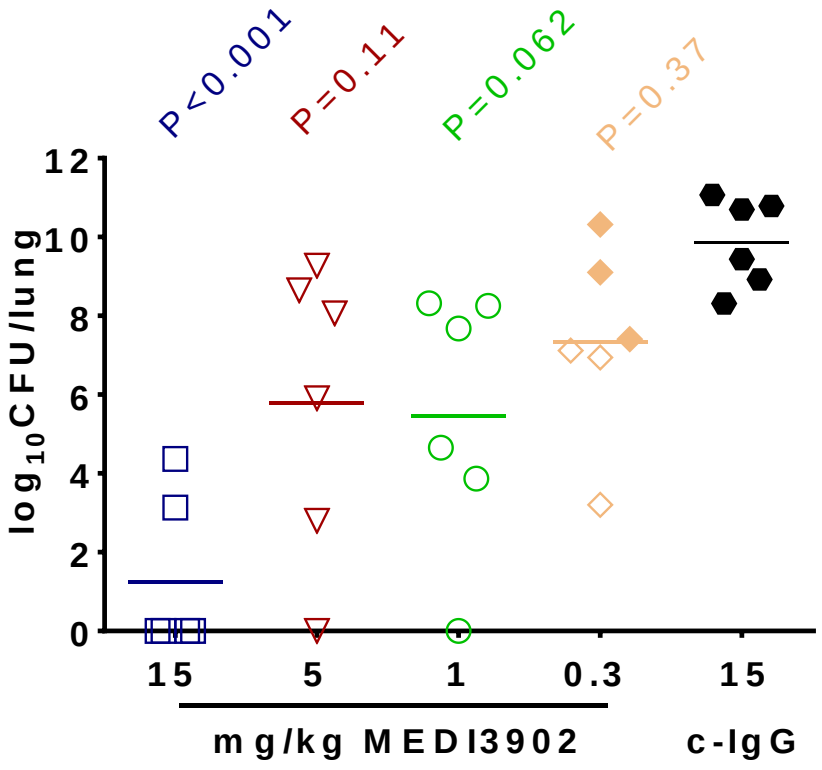


Rabbit Acute Pneumonia Model: MEDI3902 vs. c-IgG treatment

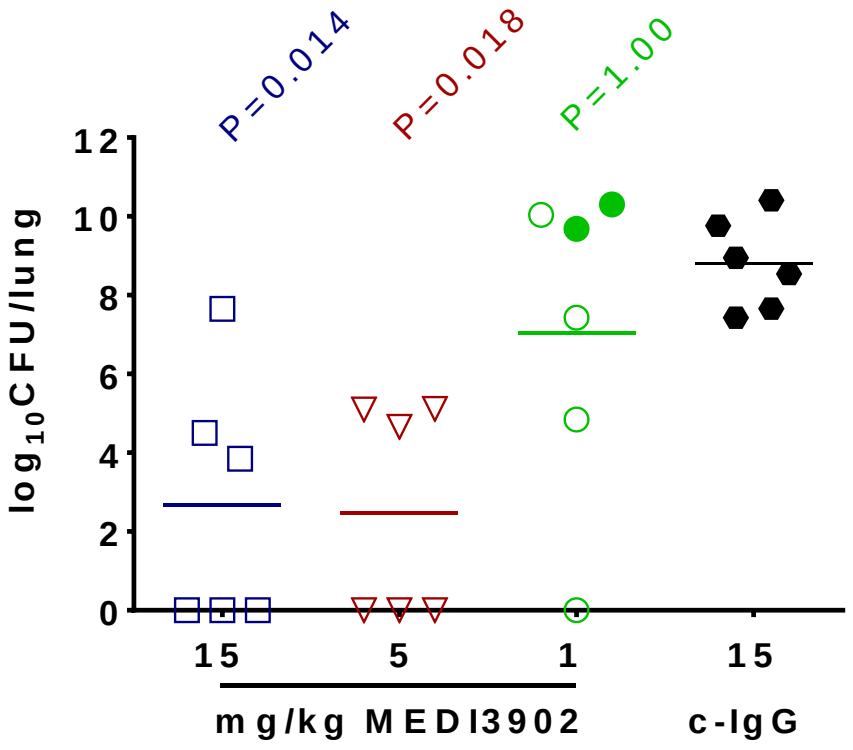




Rabbit Acute Pneumonia Model: MEDI3902 vs. c-IgG



prophylaxis

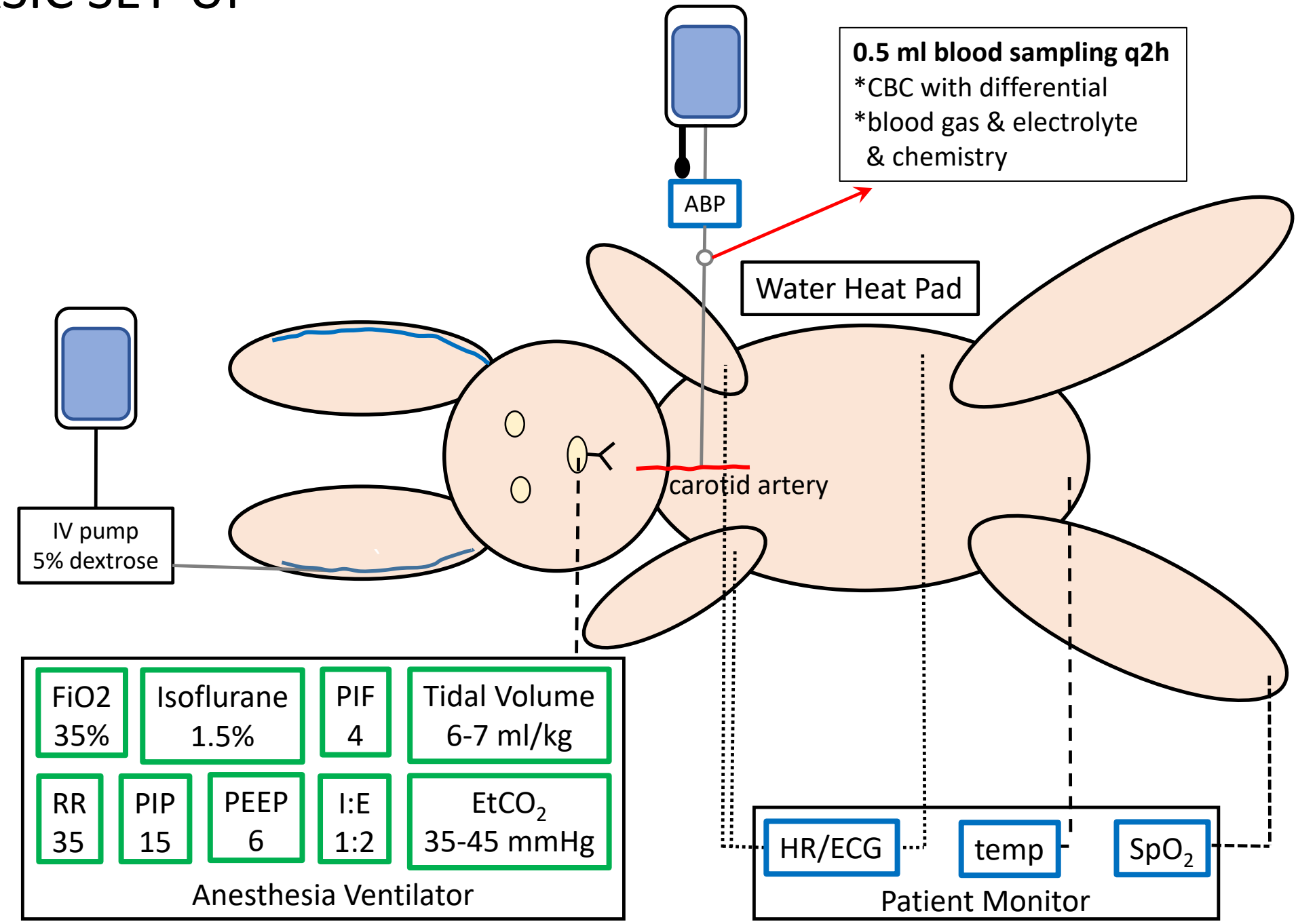


treatment

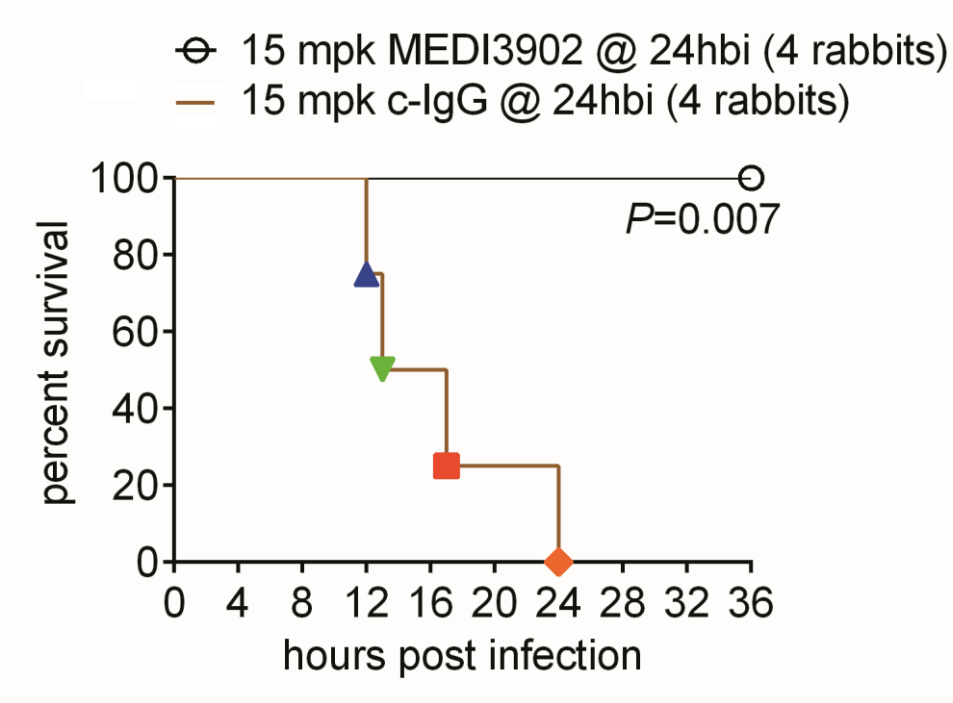
Rabbit Model of Ventilator-Associated Pneumonia and Septic Shock

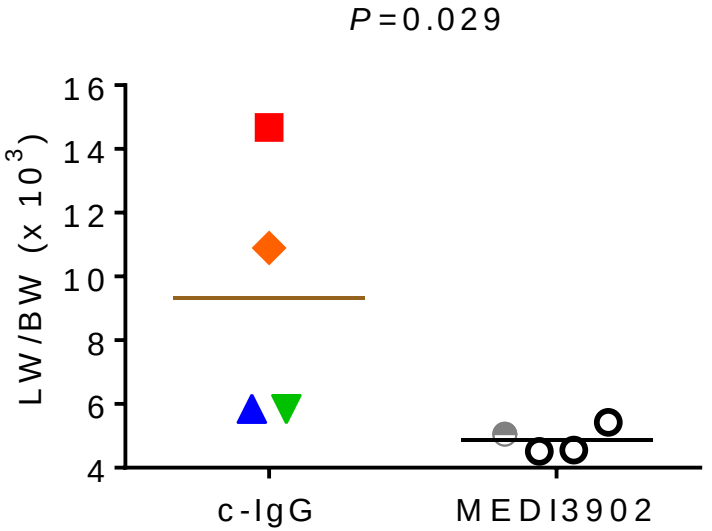
- Rabbits were randomized for prophylaxis at 24 h before challenge
  - 15 mpk R347 (4 rabbits)
  - 15 mpk MEDI3902 (4 rabbits)
- Rabbits were mechanically ventilated with lung-protective low-tidal volume (6-7 ml/kg) for 2 h, then challenged with 2.5e7 CFU Pa6077
- Rabbits were monitored continuously for 36 hpi
- Blood samples were obtained at 0, 2, 4,…, 24, 28, 32, 36 hpi for comprehensive blood analysis
  - Veterinary Hematology Analyzer (Heska HT5)
    - 5-part WBC differential, RBC, and PLT
  - Blood Gas & Electrolyte Analyzer (Heska EPOC)
    - Blood gas: pO_2 and pCO_2
    - Acid-base: pH, bicarbonate, TCO_2, base excess, anion gap
    - Electrolytes: sodium, potassium, chloride
    - creatinine, lactate, glucose
  - Blood Chemistry Analyzer (Abaxis VetScan VS2)
    - Renal: ALB, BUN, Ca, CRE, GLU
    - Liver: ALB, ALP, ALT, BUN, TBIL

THE BASIC SET-UP



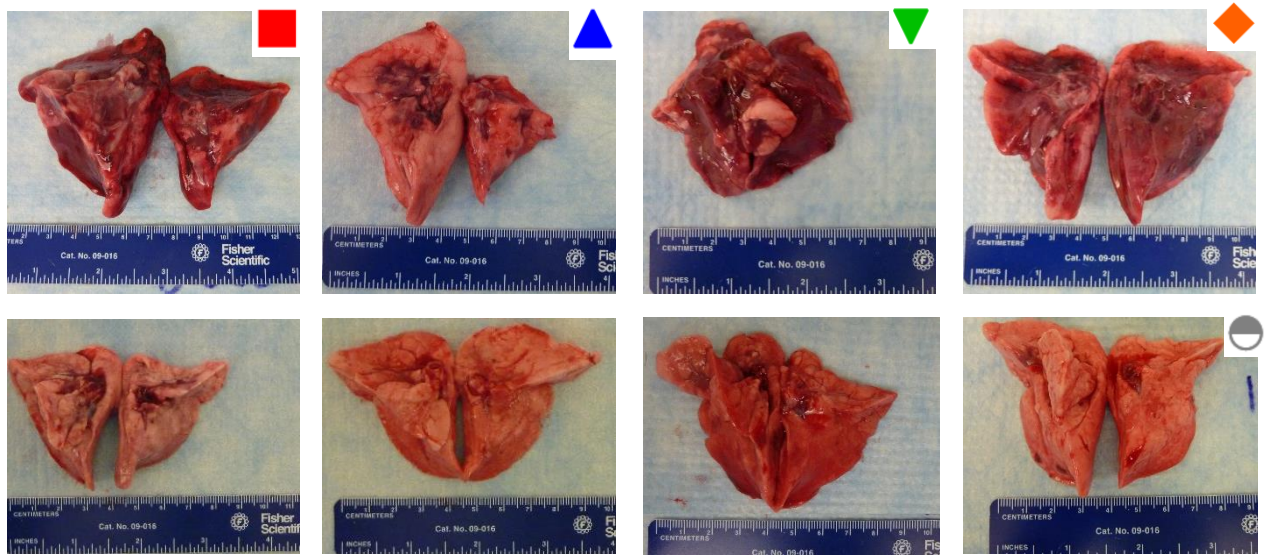
Rabbit VAP/SS Model: MEDI3902 vs. c-IgG prophylaxis



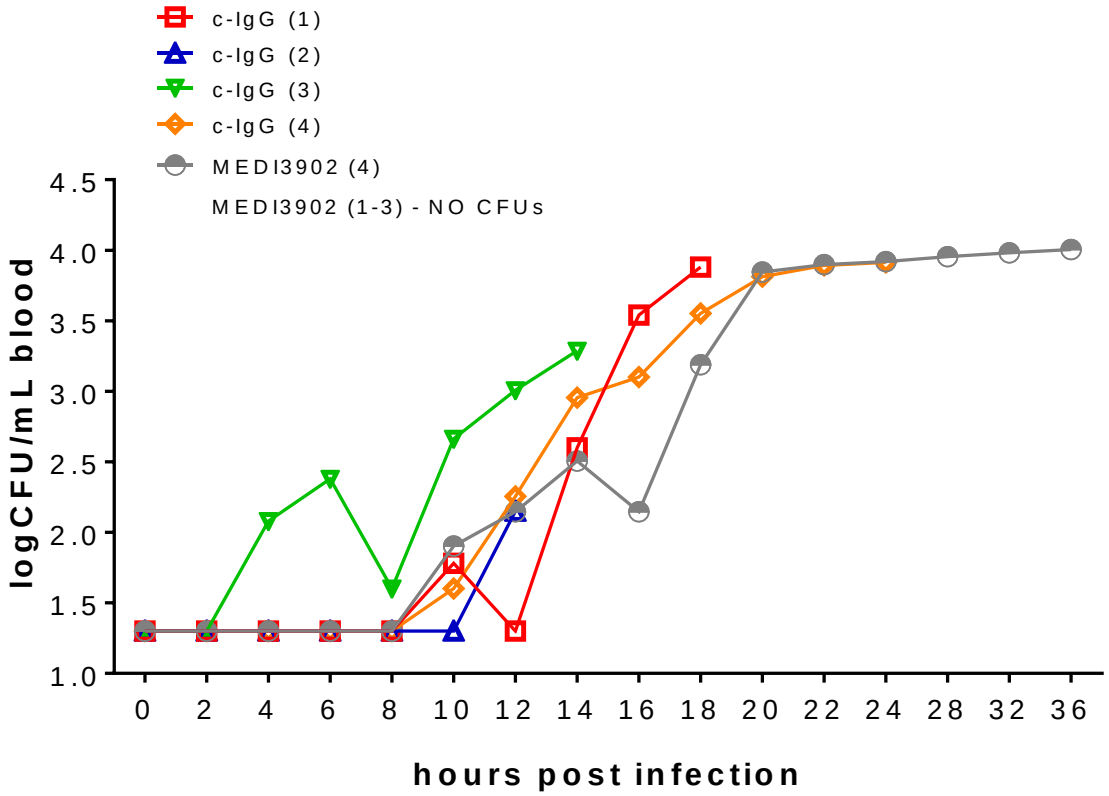


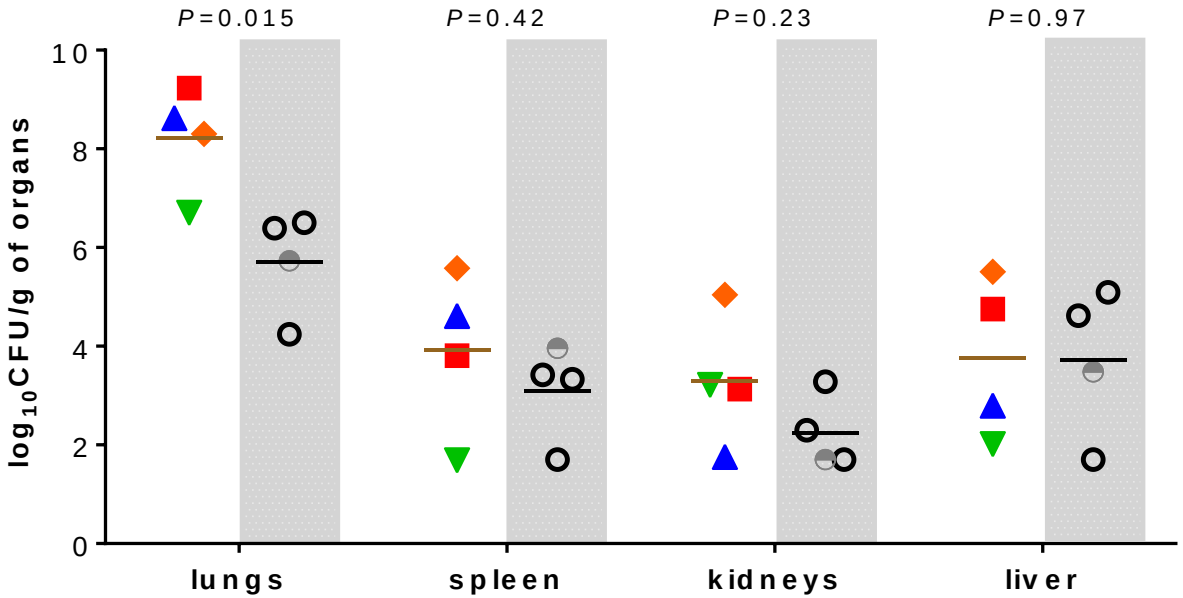
c-IgG

MEDI3909



Rabbit VAP/SS Model: MEDI3902 vs. c-IgG prophylaxis – BACTERIAL COUNTS

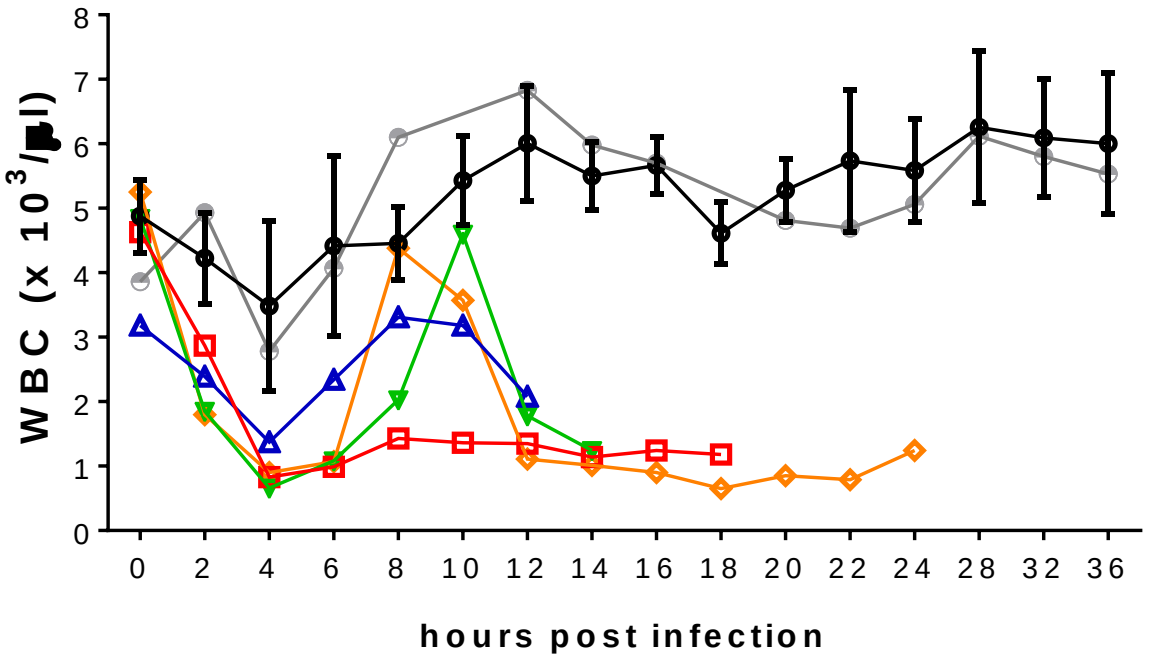


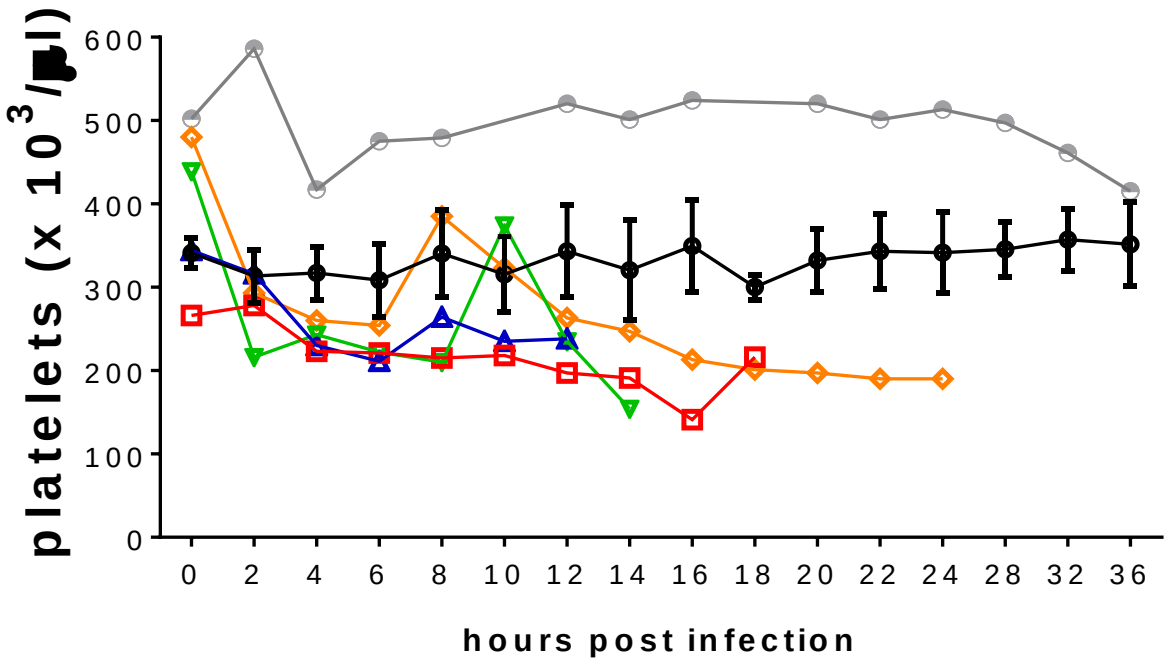


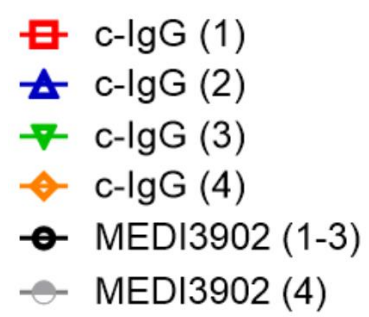
What causes death in the c-IgG (1-4) rabbits?

Although MEDI3902 (4) rabbit survived, what are the effects of persistent bacteremia on the host?

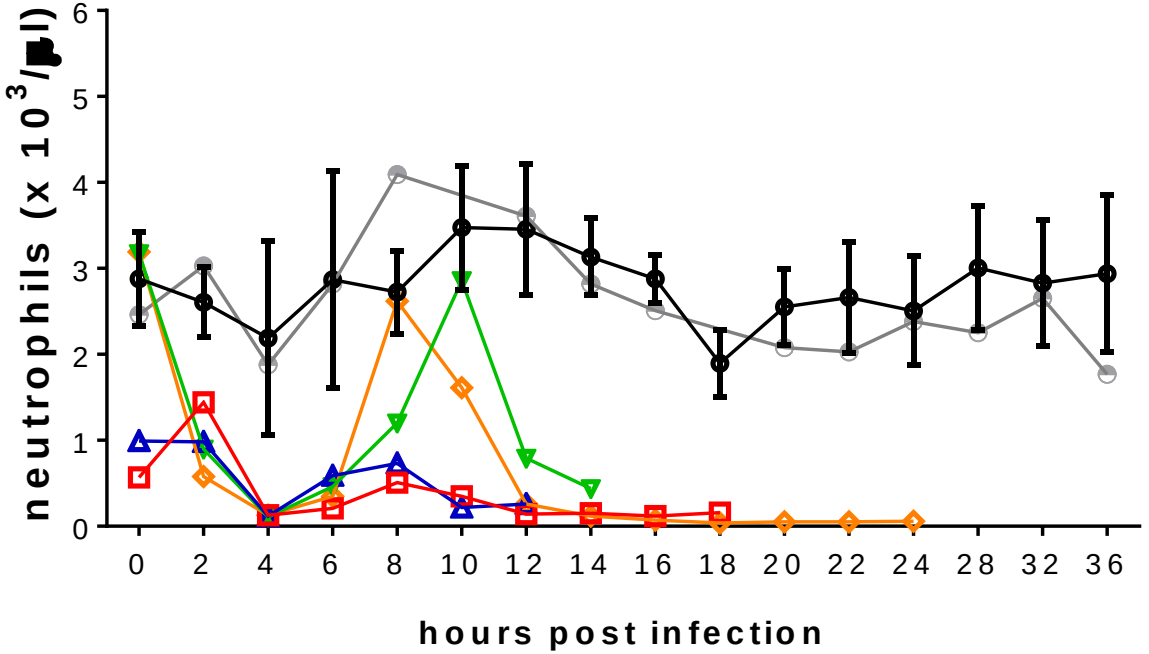
Rabbit VAP/SS Model: MEDI3902 vs. c-IgG prophylaxis – WBCs & platelets

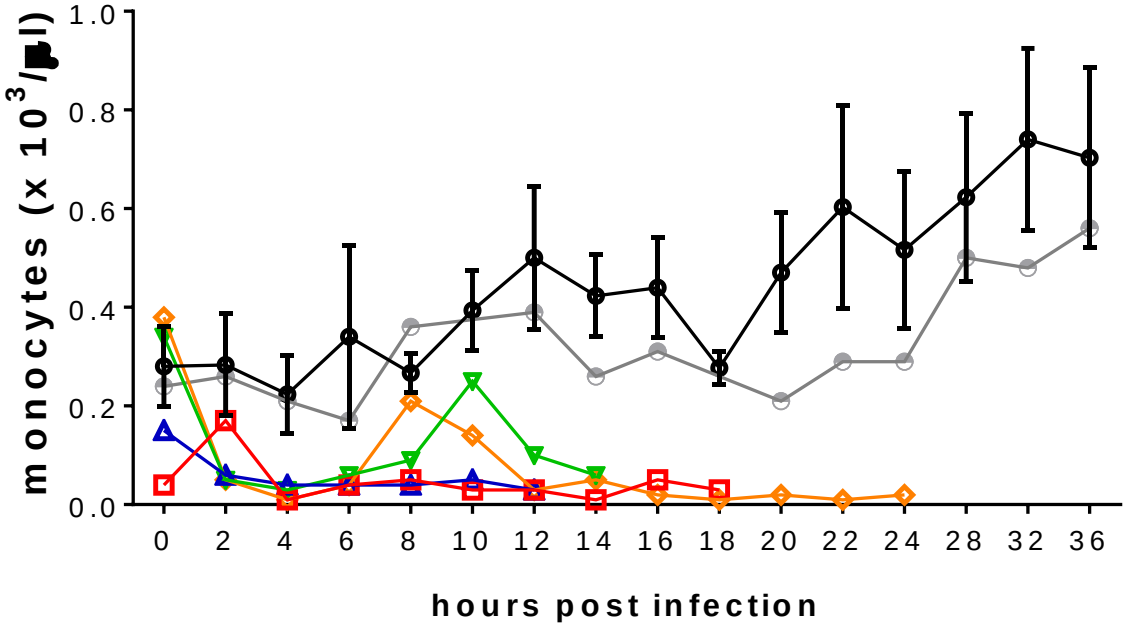


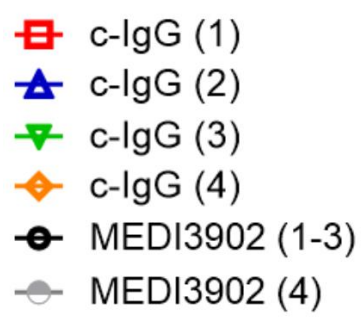




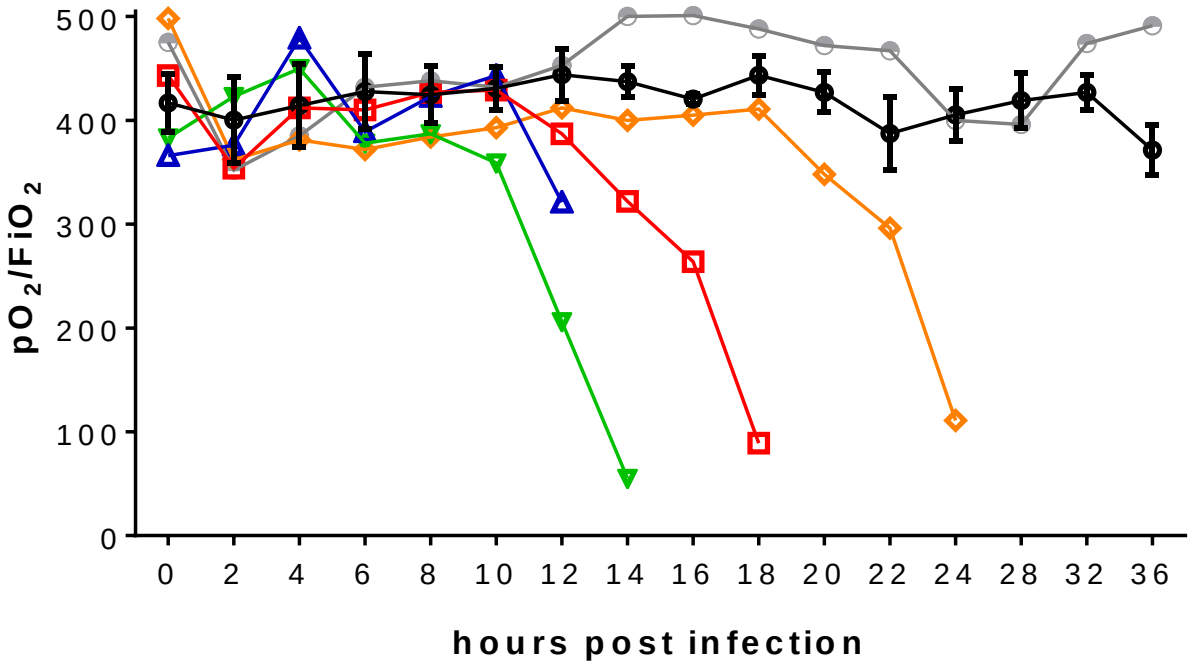
Rabbit VAP/SS Model: MEDI3902 vs. c-IgG prophylaxis – neutrophils & monocytes

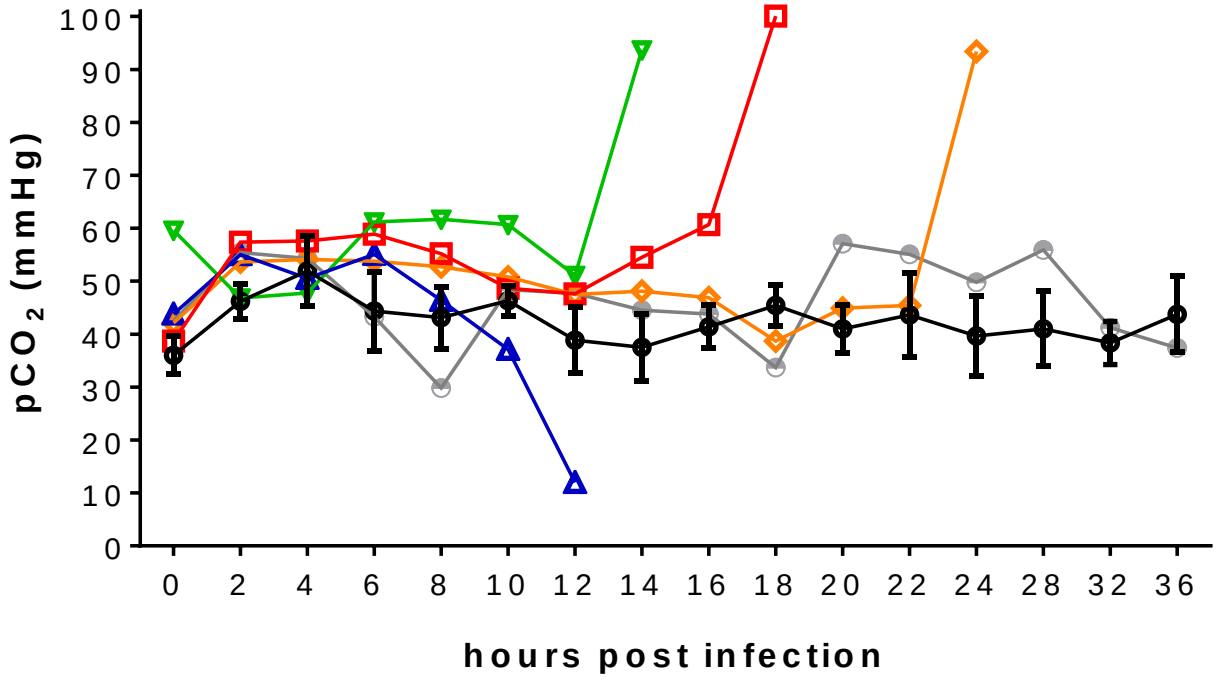


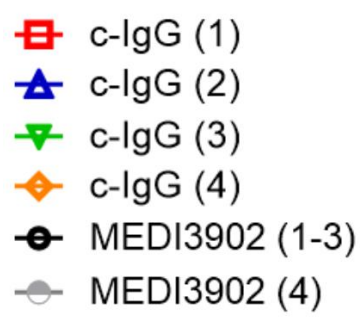




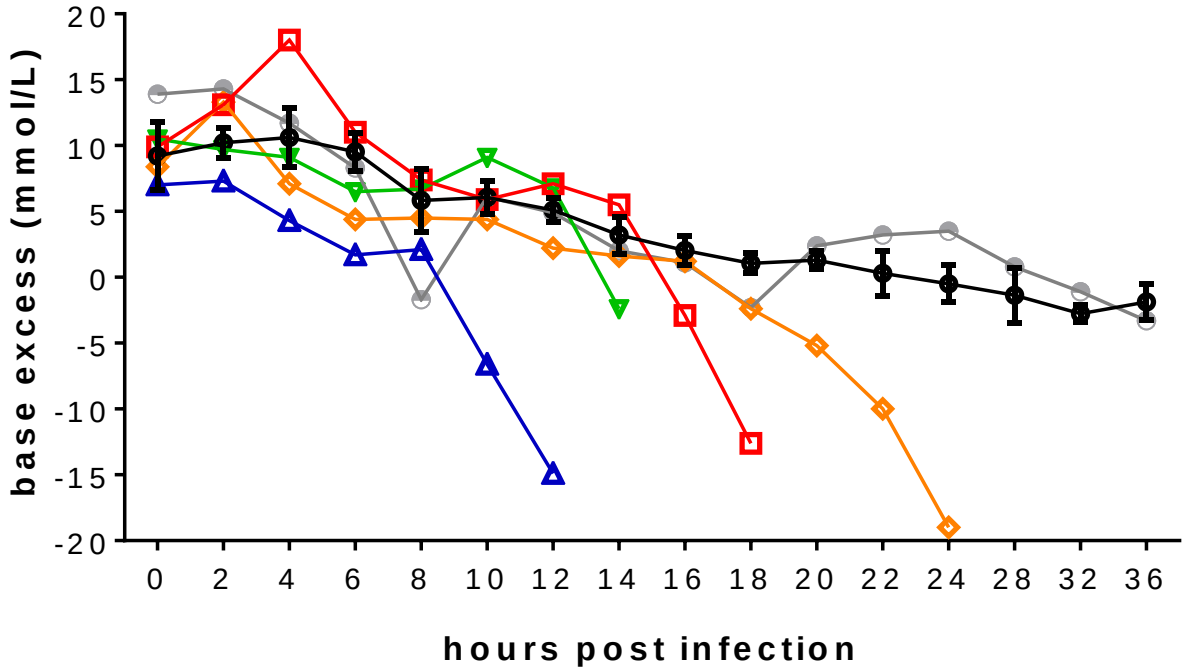
Rabbit VAP/SS Model: MEDI3902 vs. c-IgG prophylaxis – pO_2/FiO_2 and pCO_2

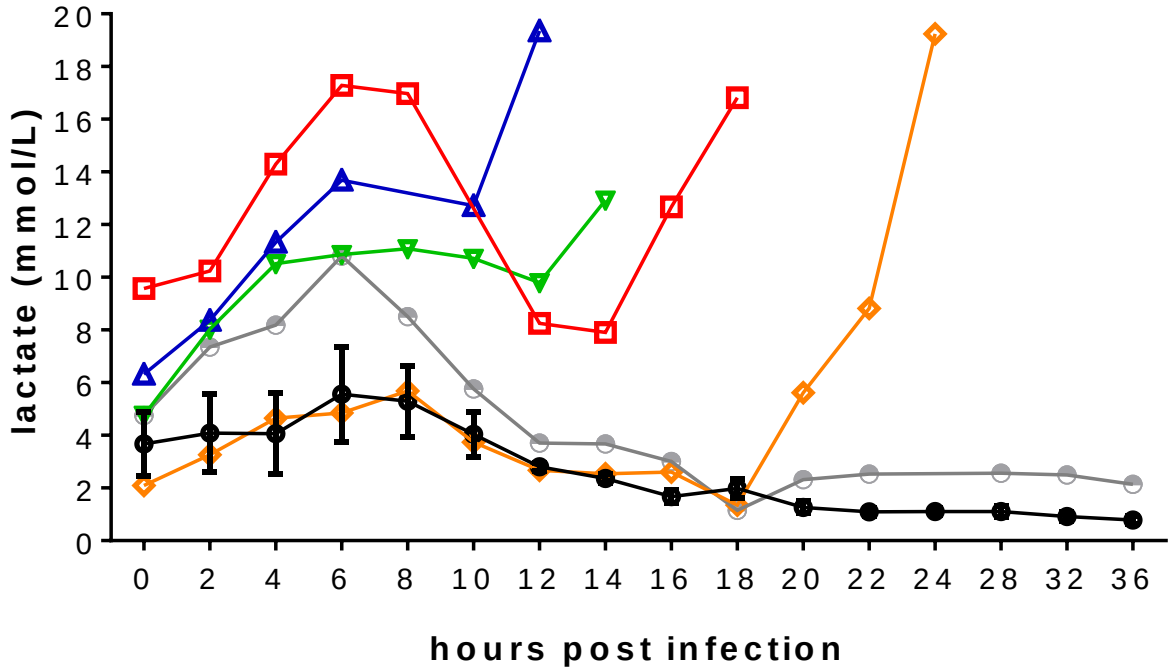


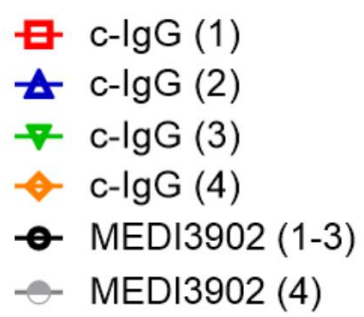




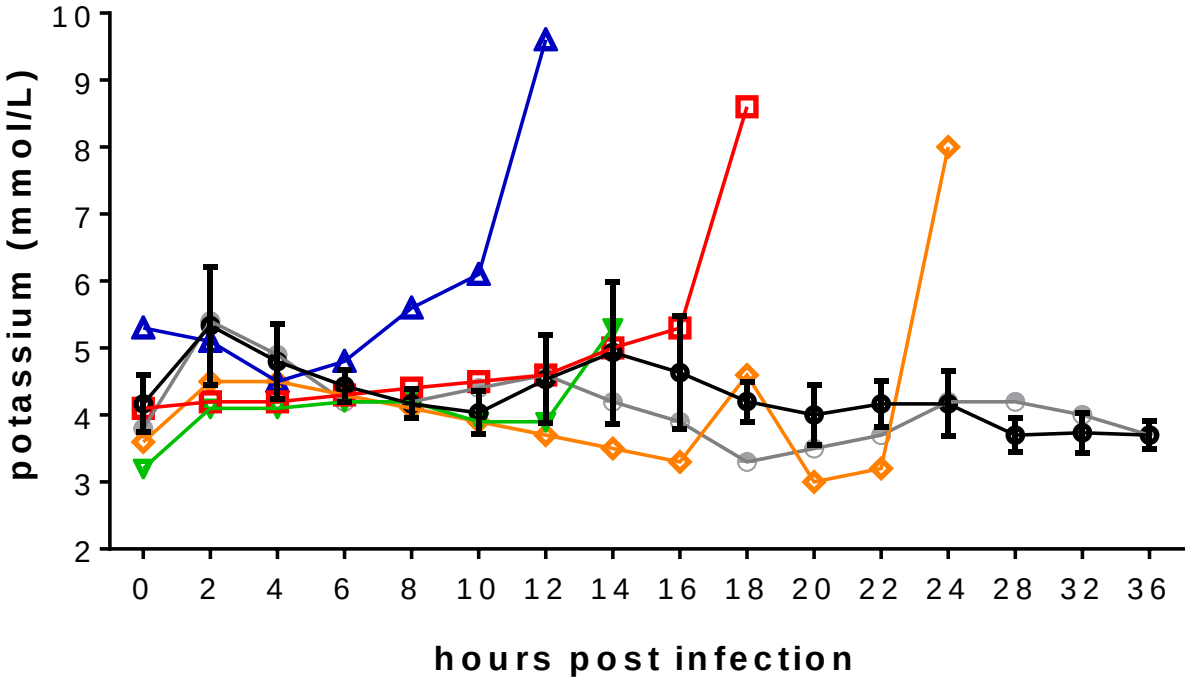
Rabbit VAP/SS Model: MEDI3902 vs. c-IgG prophylaxis – base excess and lactate

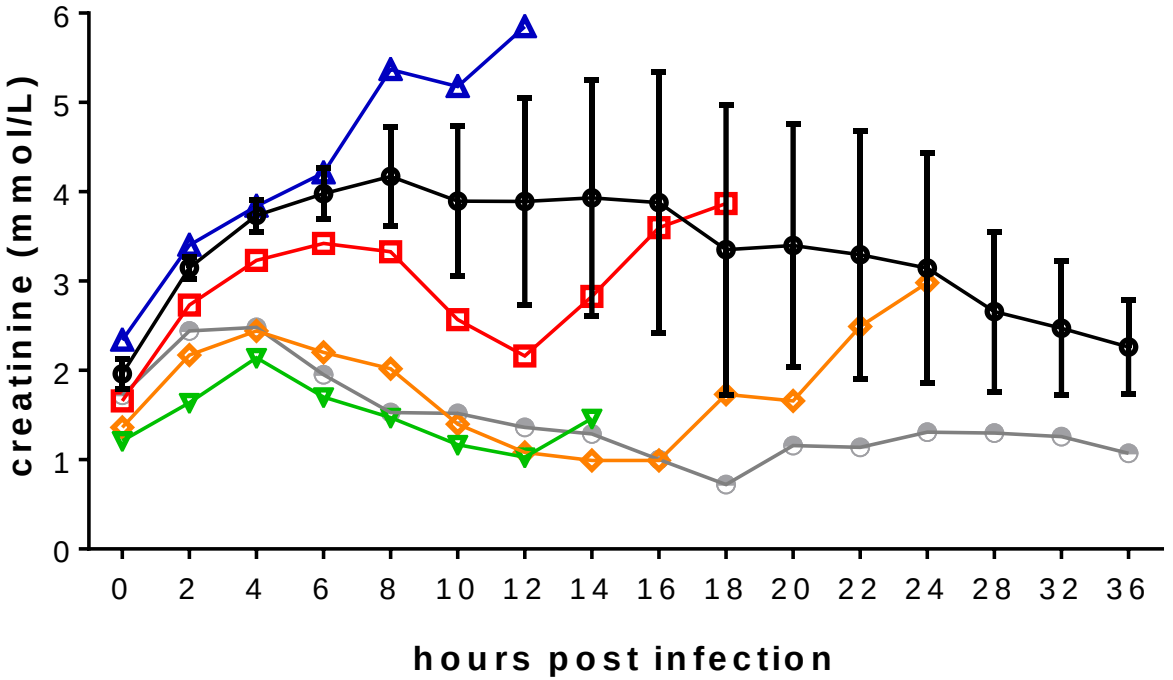


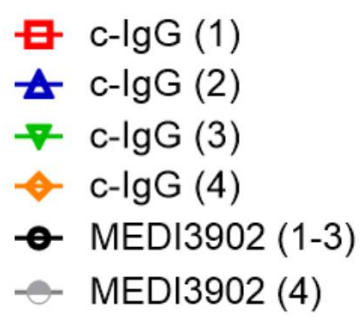




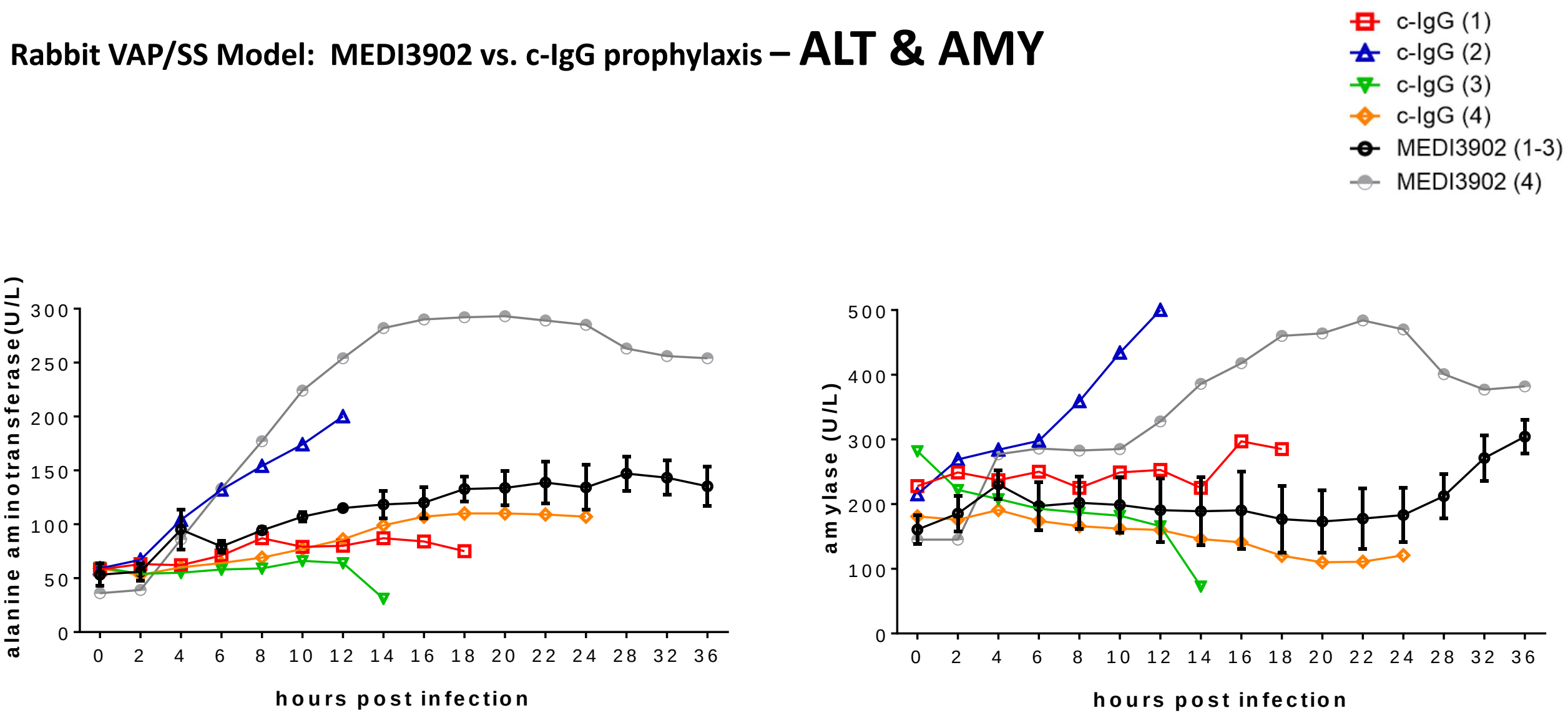
Rabbit VAP/SS Model: MEDI3902 vs. c-IgG prophylaxis – K+ and creatinine







Rabbit VAP/SS Model: MEDI3902 vs. c-IgG prophylaxis – ALT & AMY



SUMMARY

	c-IgG (1)	c-IgG (2)	c-IgG (3)	c-IgG (4)	MEDI3902(4)	MEDI3902(1-3)
blood counts	↓WBC ↓NEU	↓WBC ↓NEU	↓WBC ↓NEU	↓WBC ↓NEU	↑EOS ↑BAS	
pO_2/FiO_2	89	321	55	111	491	371
pCO_2	100	12	94	93	37	44
BE	-12.6	-14.9	-2.4	-19	-3.3	-1.9
lactate	16.8	19.4	12.9	19.2	2.1	0.8
K+	8.6	9.6	5.3	8.0	3.7	3.7
creatinine	3.9	5.9	1.5	3.0	1.1	2.3
ALT	--	↑ 3x	--	--	↑ 6x	--
AMY	--	↑ 2.5x	--	--	↑ 4x	--

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