

Development of Rabbit Models of Acute Pneumonia (Non-Ventilated) and Ventilator-Associated Pneumonia

Binh Diep, PhD
Associate Professor
University of California, San Francisco

William J Weiss
Director, PreClinical Services
UNT System College of Pharmacy
University of North Texas Health Science Center

Disclosures

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Our goals for the development of Acute Pneumonia and VAP rabbit models

1. Use outbred rabbits with normal immune system (not neutropenic)

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4. Use “humanized” meropenem regimen for rabbit model validation
5. Use survival as primary endpoint (not 2-log_{10} reduction in CFU) in efficacy studies
6. Determine whether meropenem treatment with or without ICU supportive care (fluid challenge and norepinephrine) could halt VAP progression using clinically relevant biomarkers as secondary endpoints

Distinct pathophysiology of

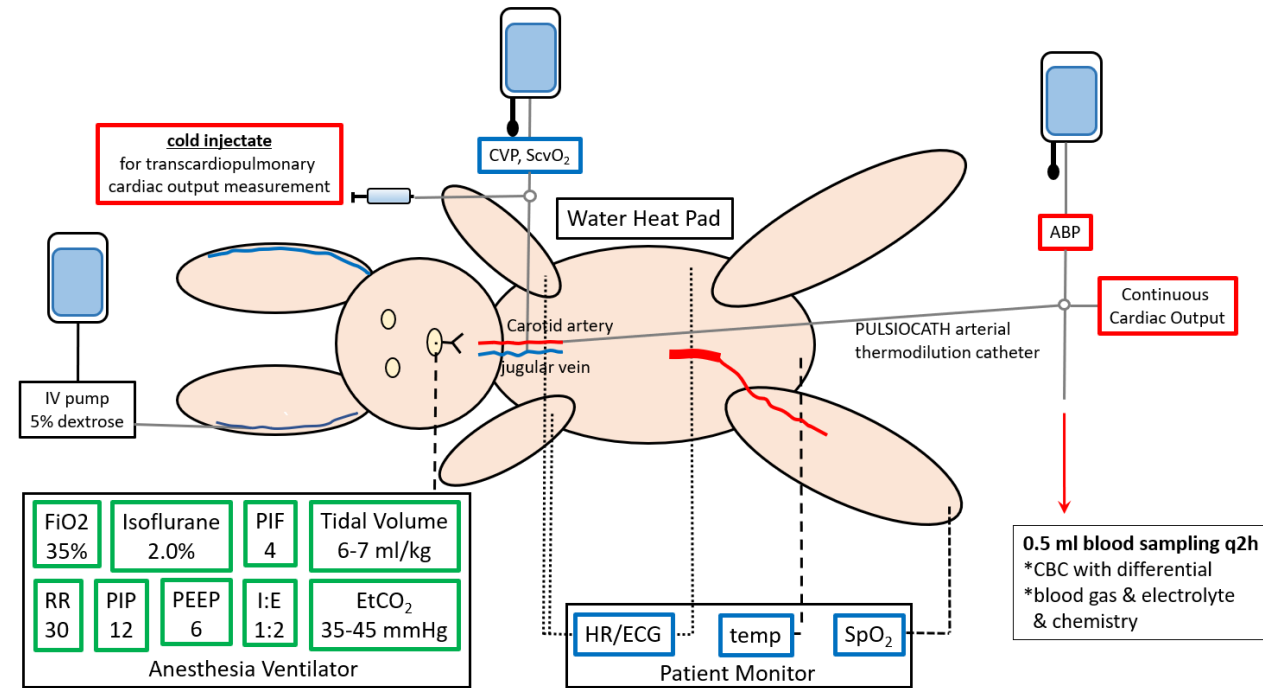
Rabbit Acute Pneumonia Model

Awake non-ventilated rabbits → nvHABP



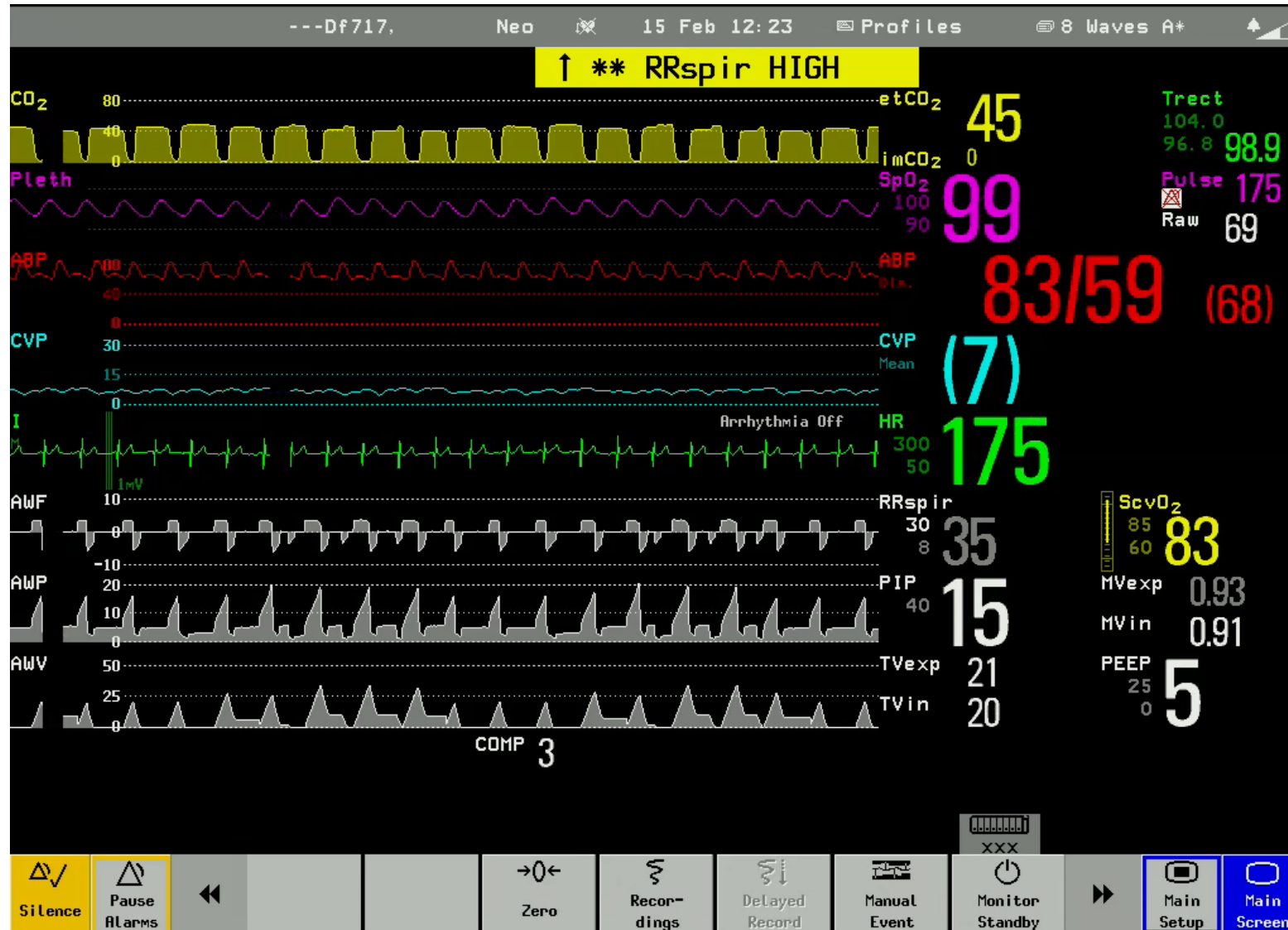
Rabbit VAP Model

Anesthetized ventilated rabbits → vHABP/VABP



Rabbit VAP Model: Comprehensive Physiologic Monitoring

Mainstream CO₂
Pulse oximetry
Arterial blood pressure
Central venous pressure
Electrocardiogram ECG
Airway Flow,
Pressure and
Volume

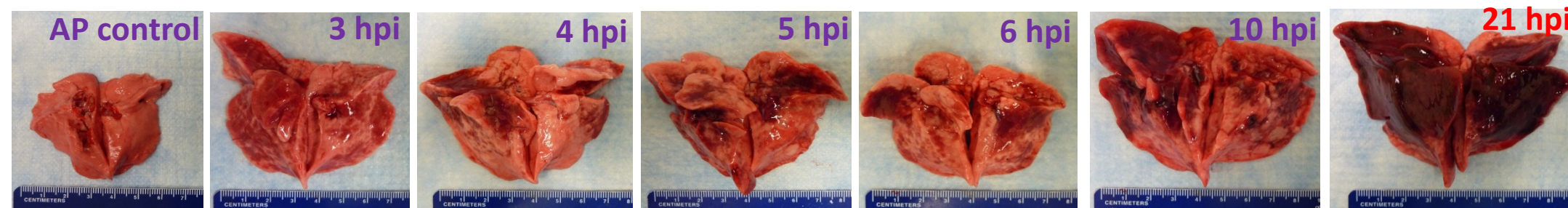
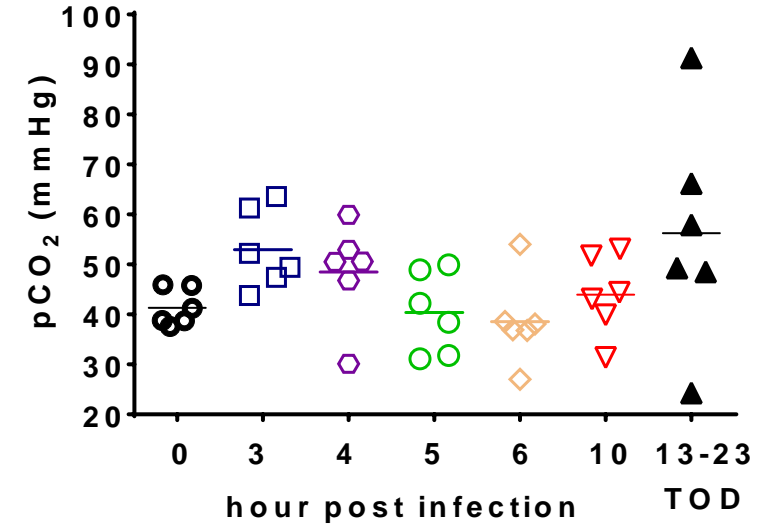
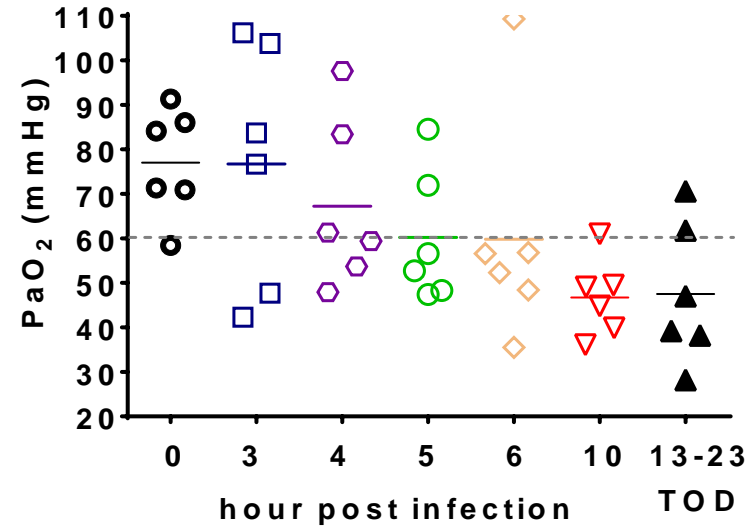
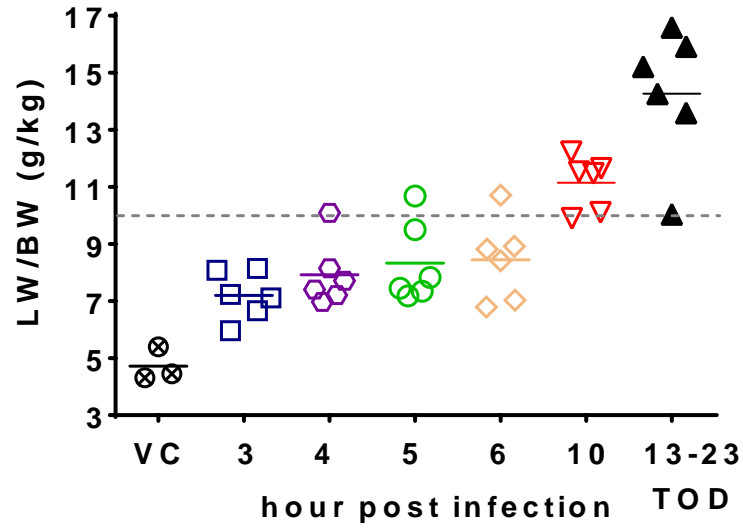


Rectal temperature

Intravascular Oxygen Saturation ScvO₂

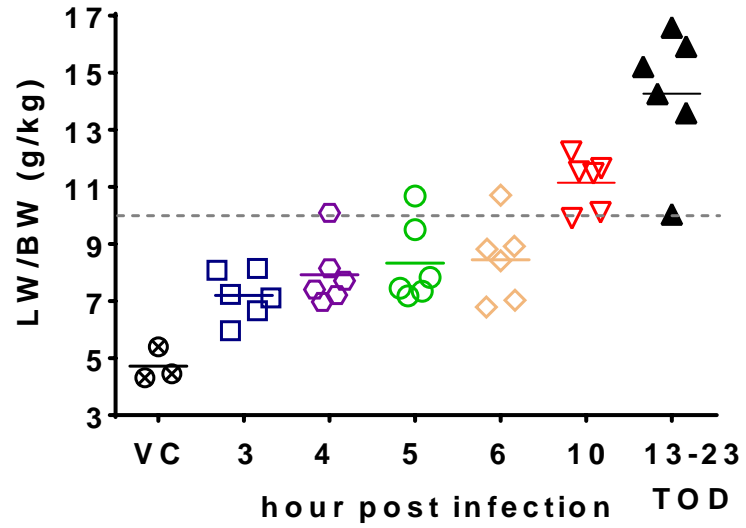
Distinct pathophysiology of Acute Pneumonia Model = respiratory failure

Acute Pneumonia Model

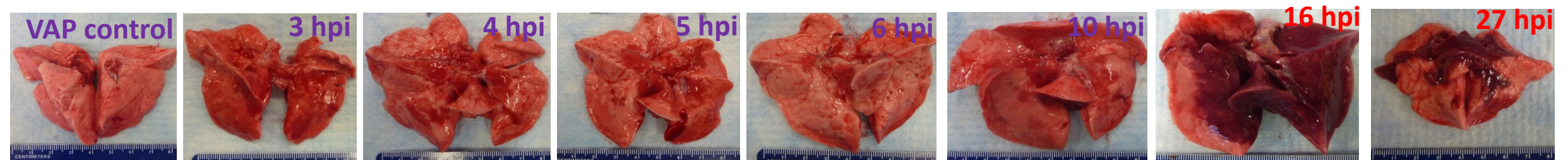
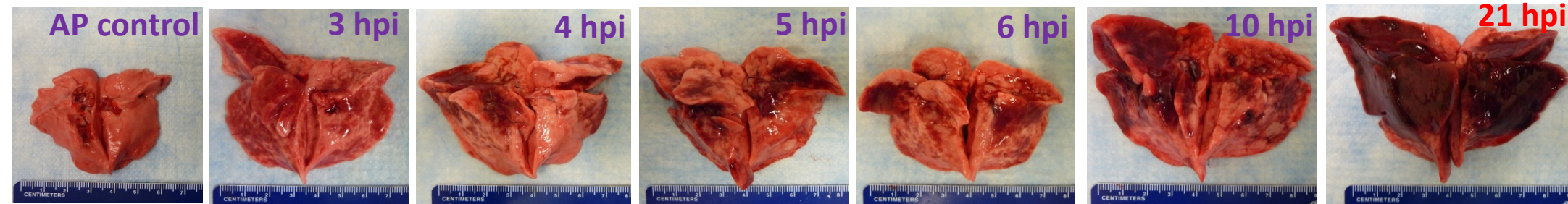
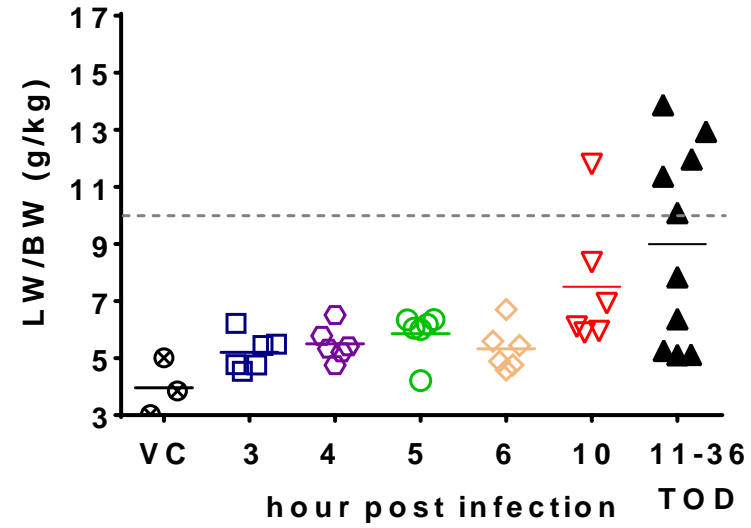


Distinct pathophysiology of

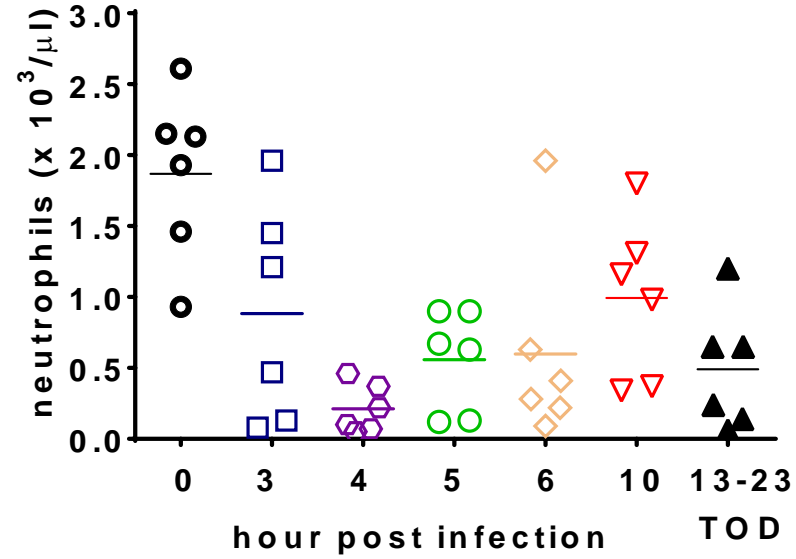
Acute Pneumonia Model



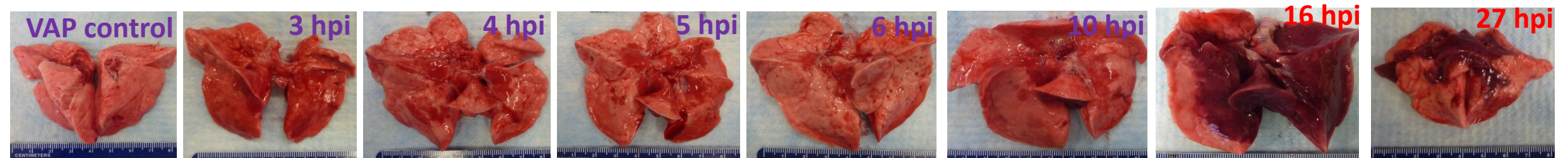
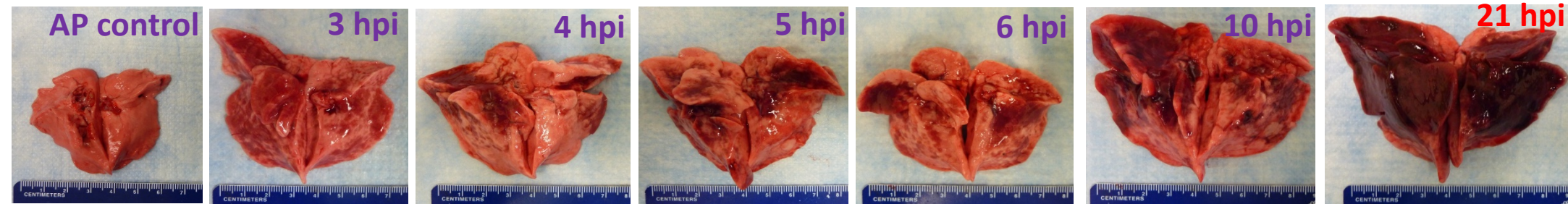
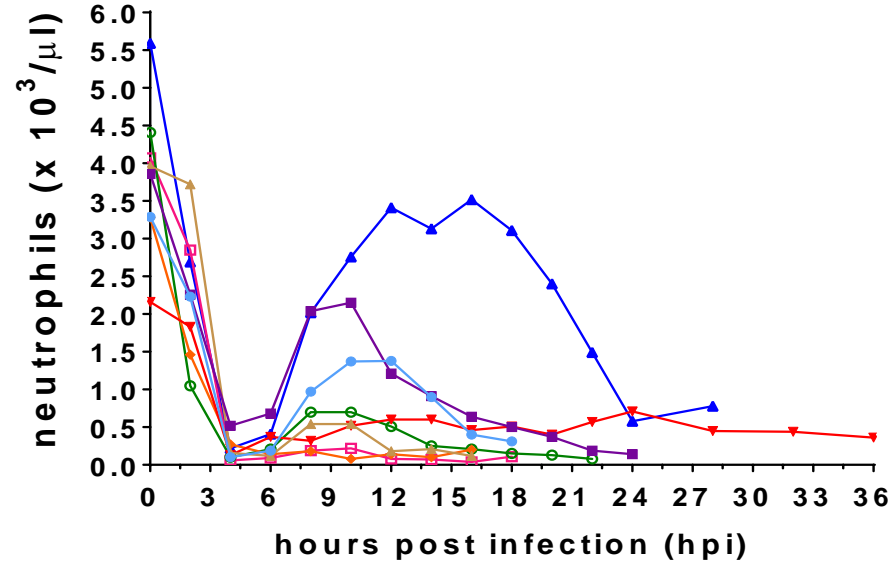
VAP Model



Distinct pathophysiology of Acute Pneumonia Model

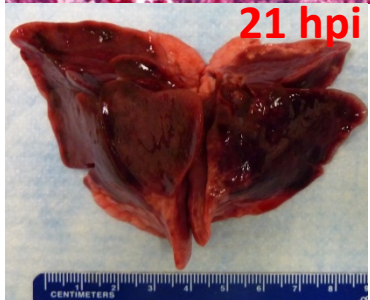
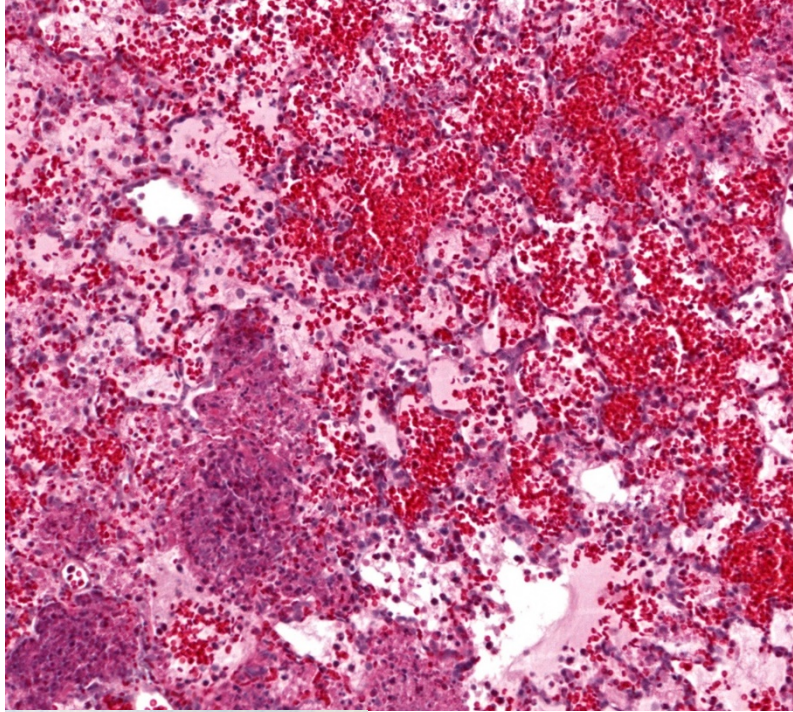


VAP Model



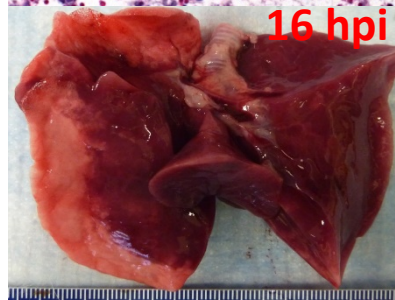
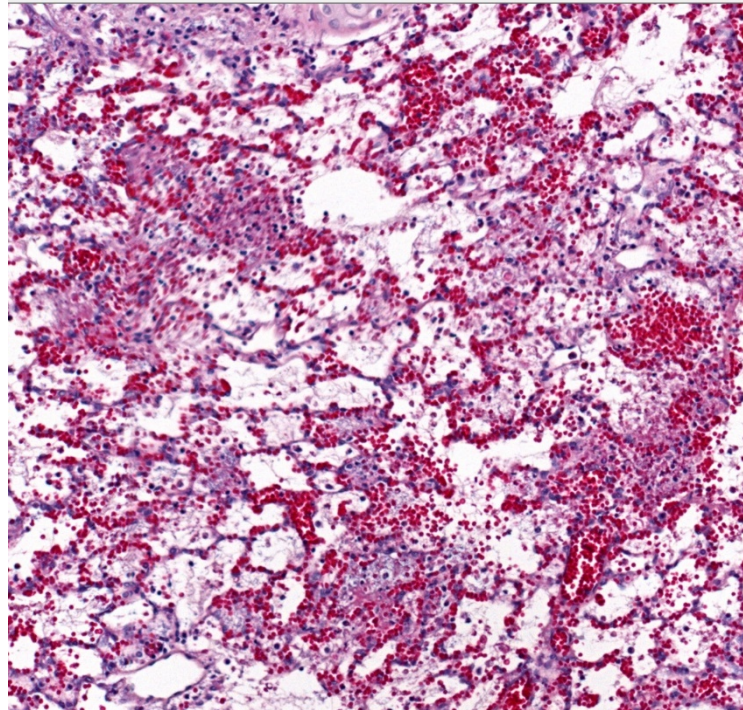
Distinct pathophysiology of

Acute Pneumonia Model



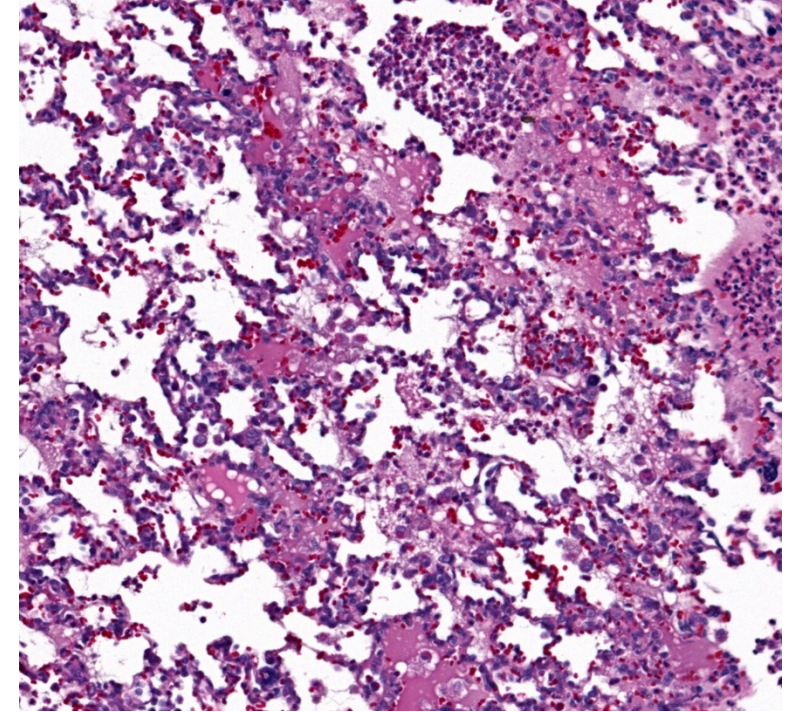
21 hpi

VAP Model



16 hpi

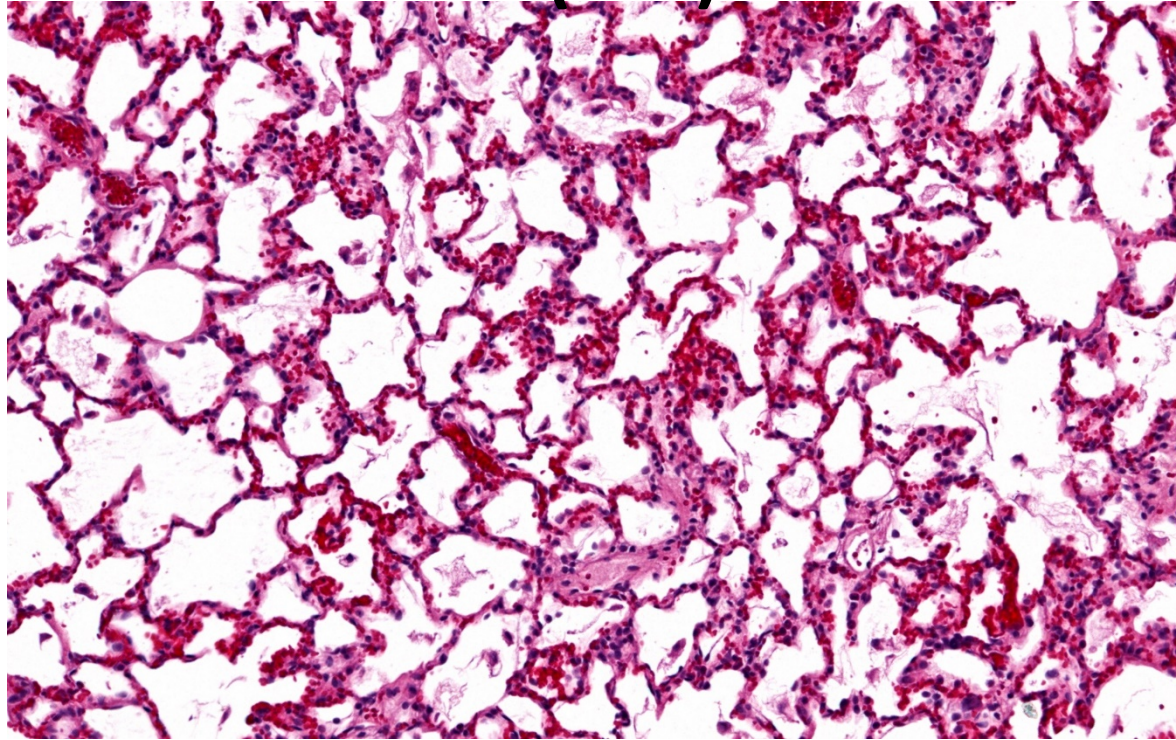
VAP Model



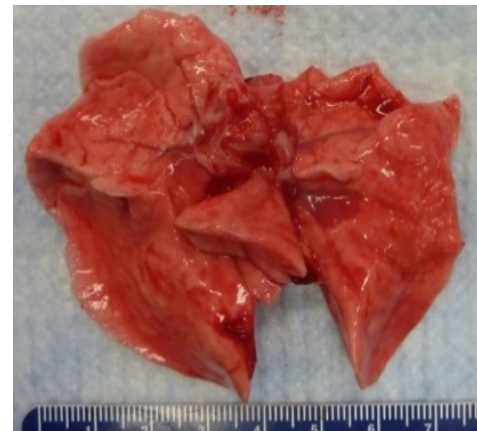
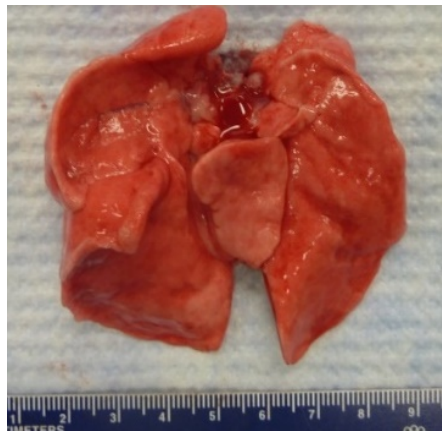
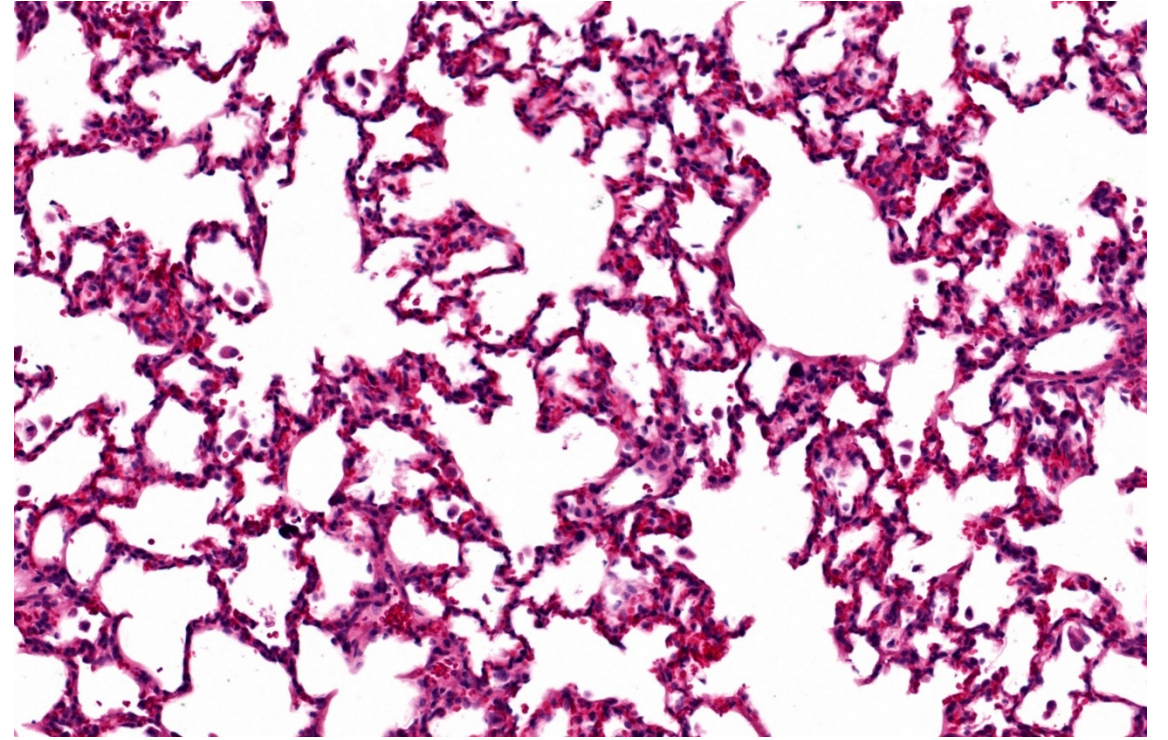
27 hpi

VAP model: minimal lung injury from instillation with

vehicle control (LRS)

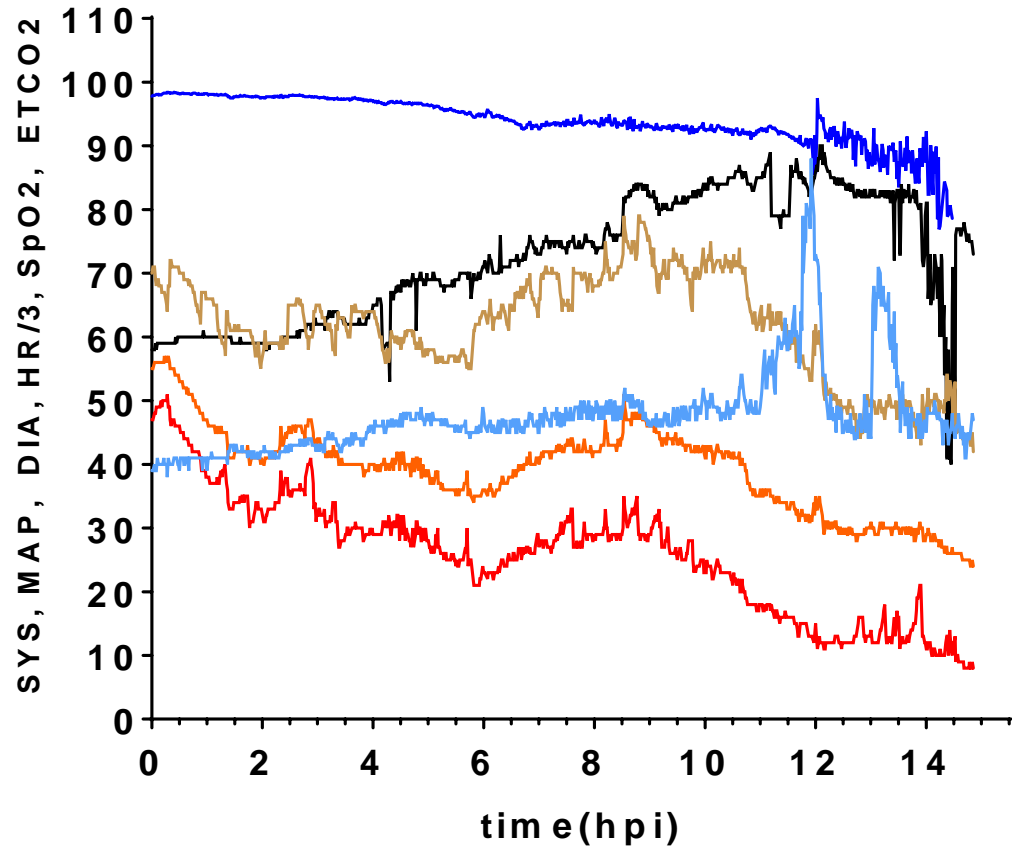


UV-killed *Pa6206*

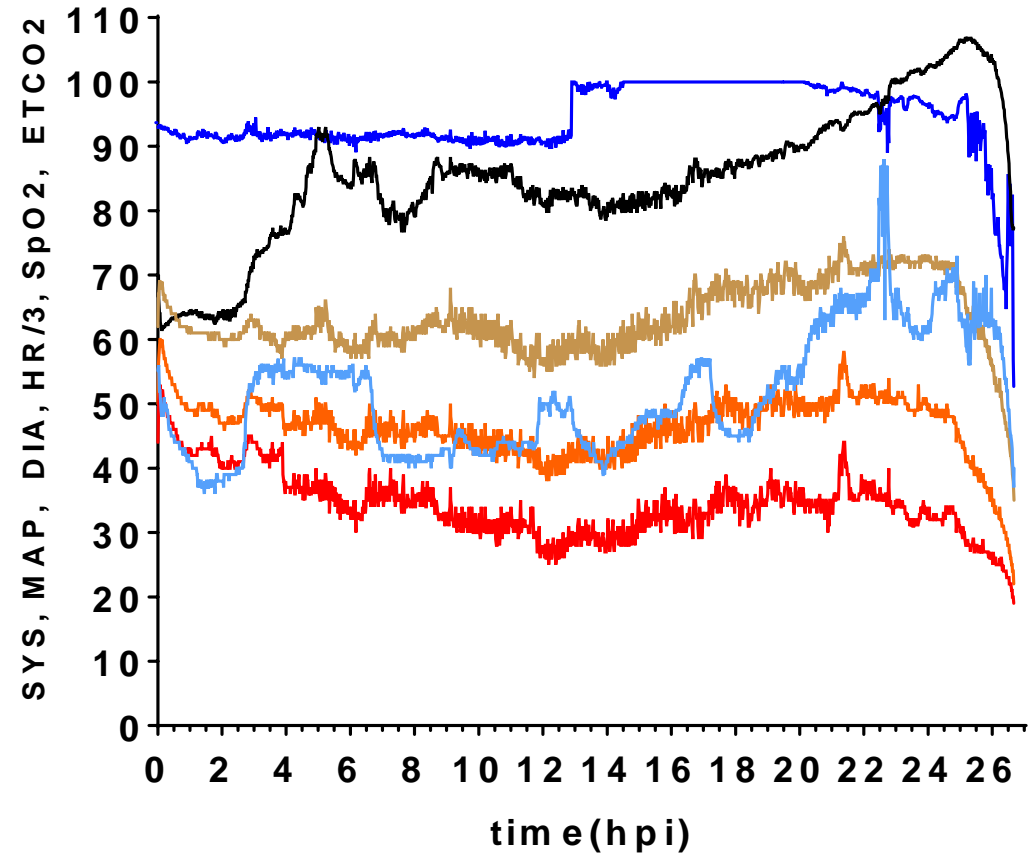


Distinct pathophysiology of VAP model → septic shock

— SYS (m m Hg) — SpO2 (%)
— MAP (m m Hg) — EtCO2 (m m Hg)
— DIA (m m Hg)
— HR/3 (beats/m in)



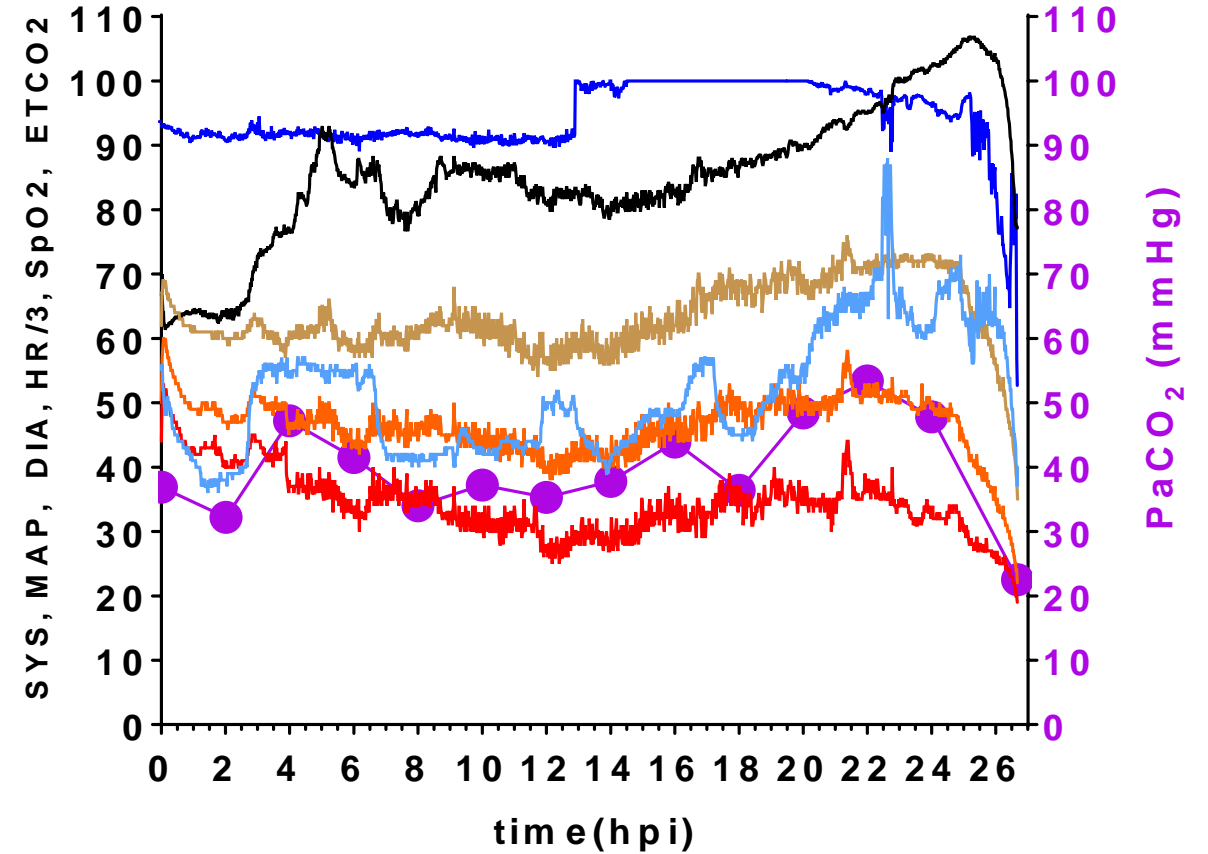
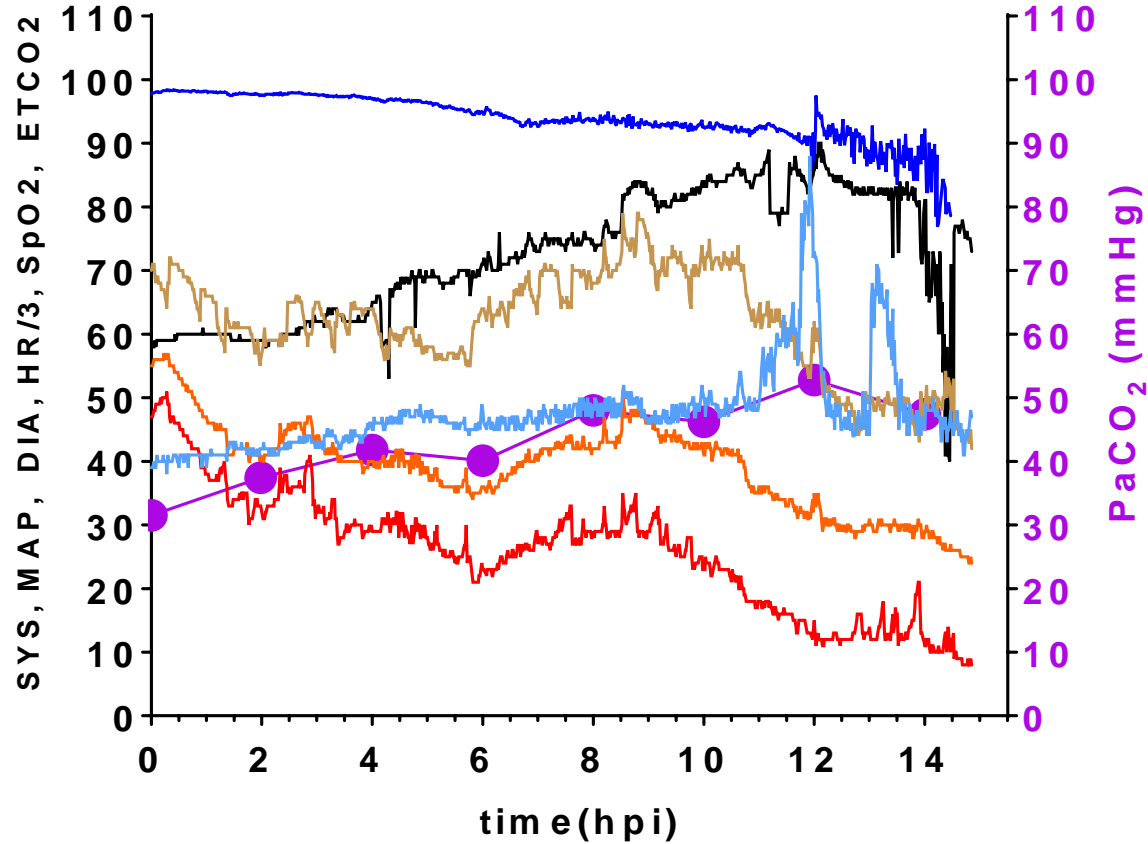
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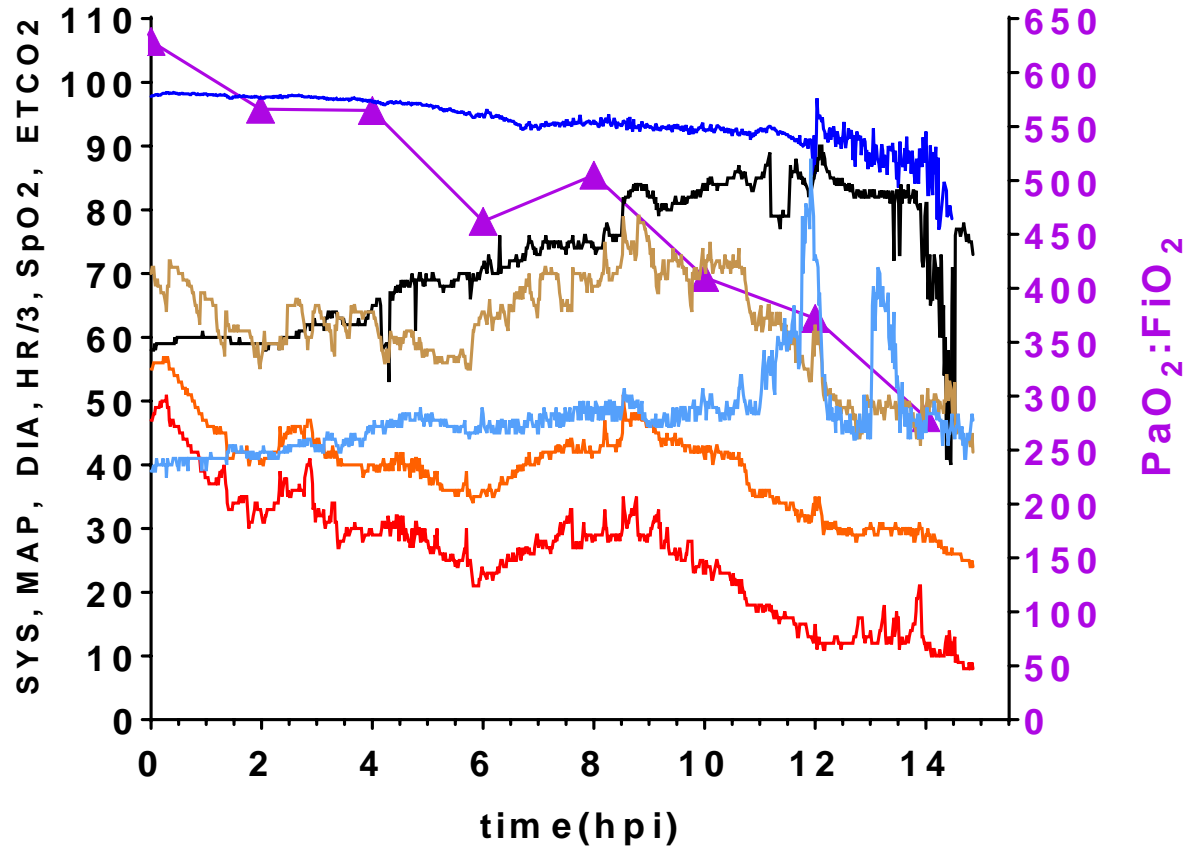
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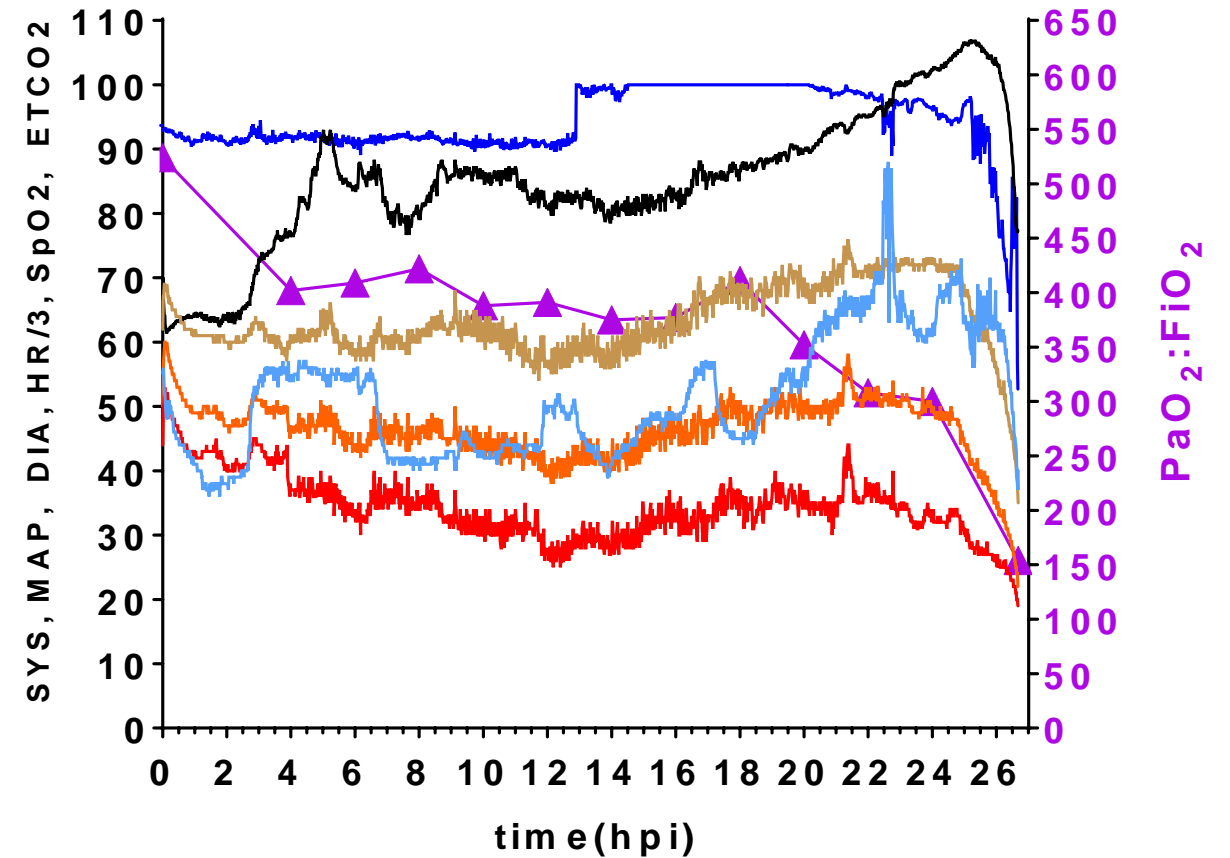


Distinct pathophysiology of VAP model → septic shock

— SYS (mmHg) — SpO₂ (%)
— MAP (mmHg) — EtCO₂ (mmHg)
— DIA (mmHg) ▲ PaO₂/FiO₂
— HR/3 (beats/min)

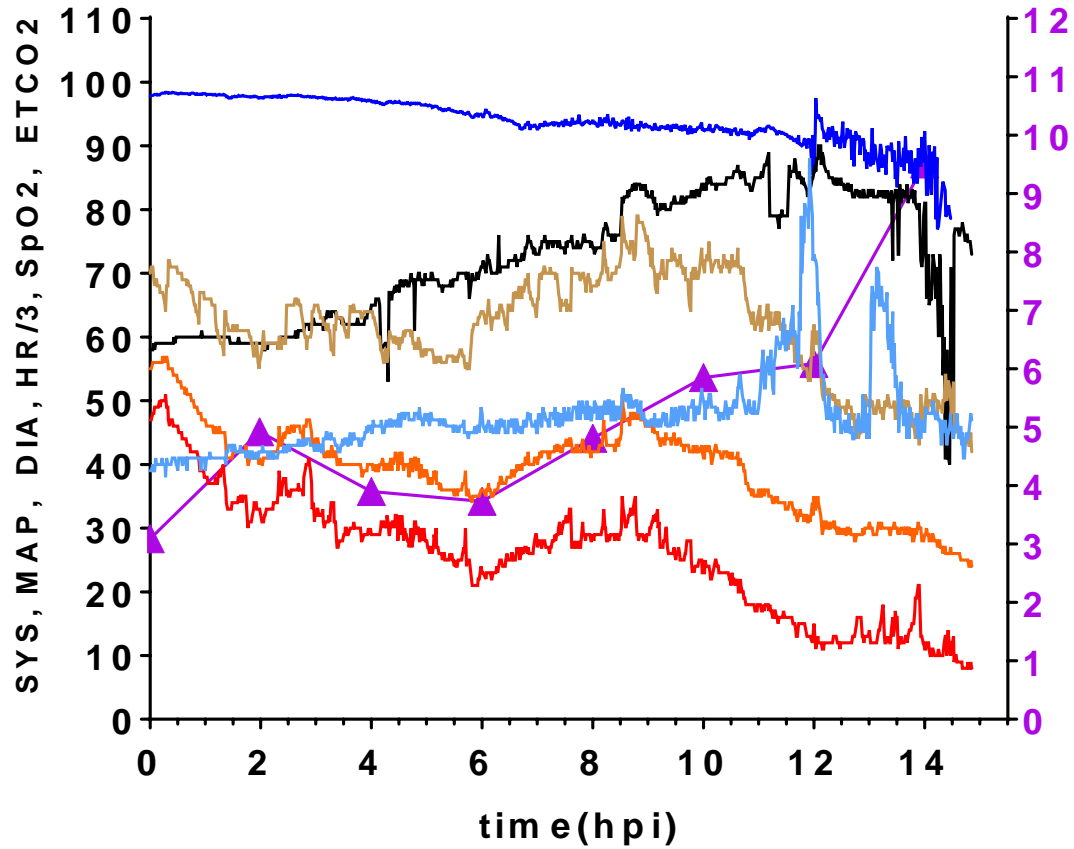


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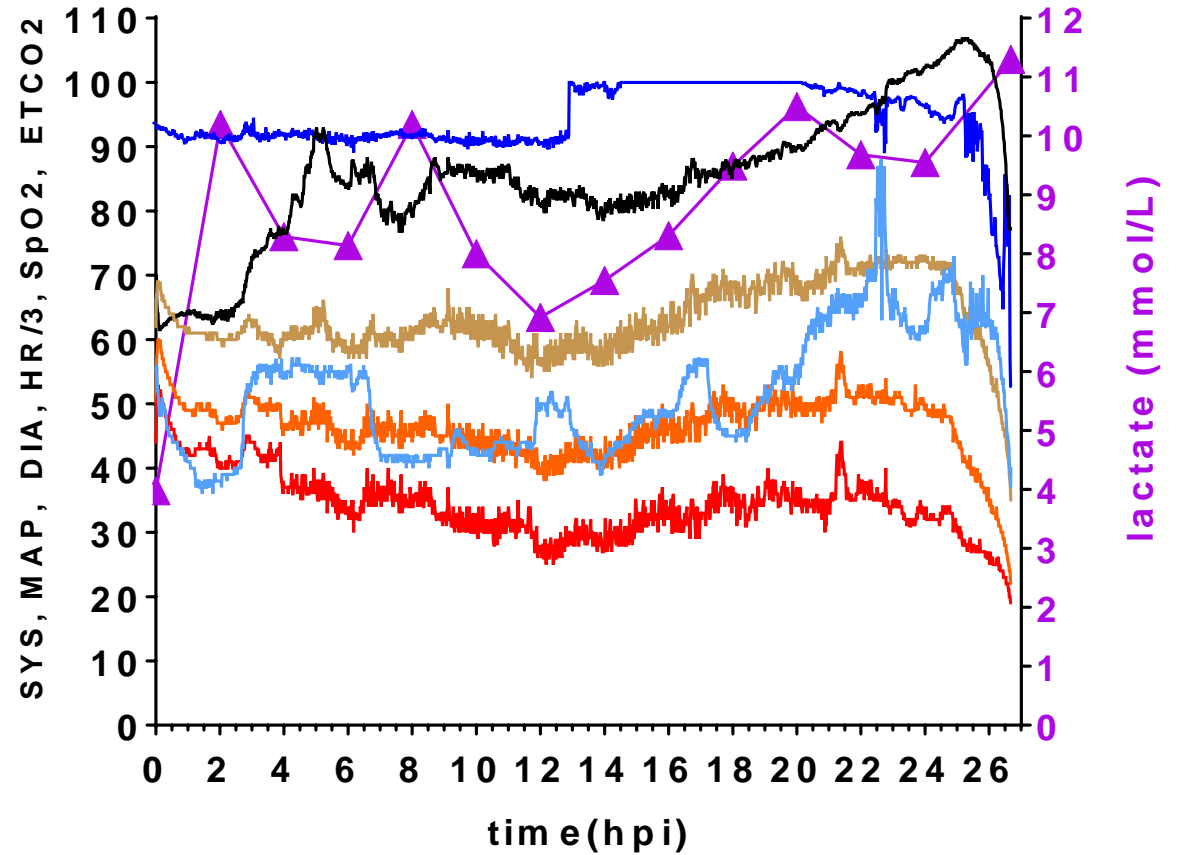


Distinct pathophysiology of VAP model → septic shock

— SYS (mmHg) — SpO₂ (%)
— MAP (mmHg) — EtCO₂ (mmHg)
— DIA (mmHg) ▲ lactate (mmol/L)
— HR/3 (beats/min)

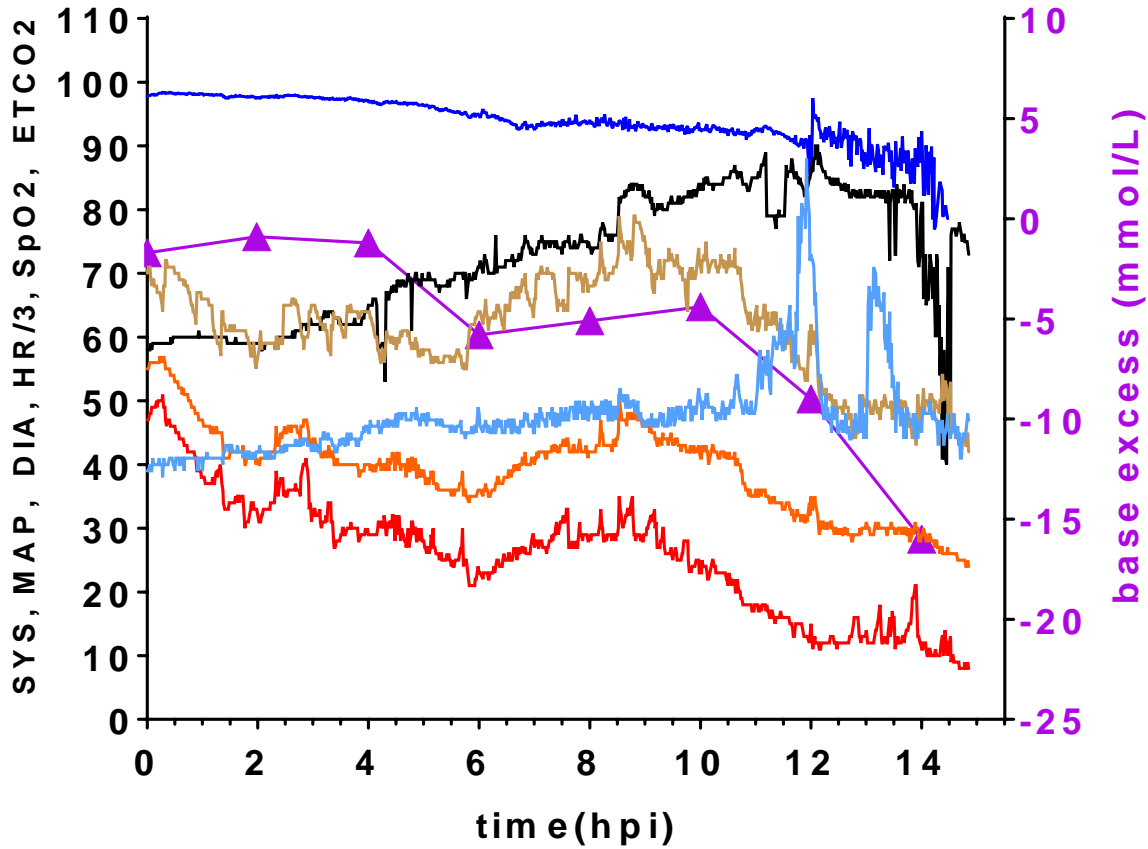


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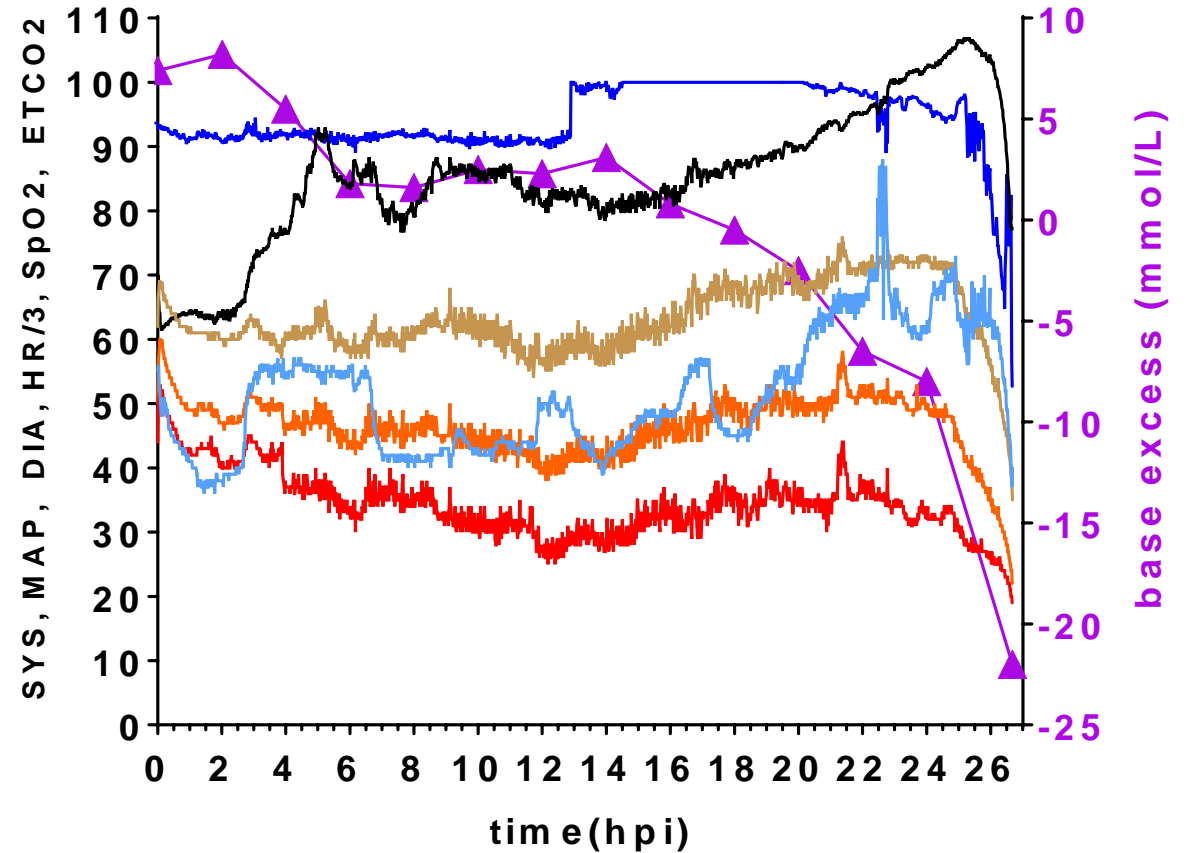


Distinct pathophysiology of VAP model → septic shock

— SYS (mmHg) — SpO₂ (%)
— MAP (mmHg) — EtCO₂ (mmHg)
— DIA (mmHg) ▲ base excess (mmol/L)
— HR/3 (beats/min)

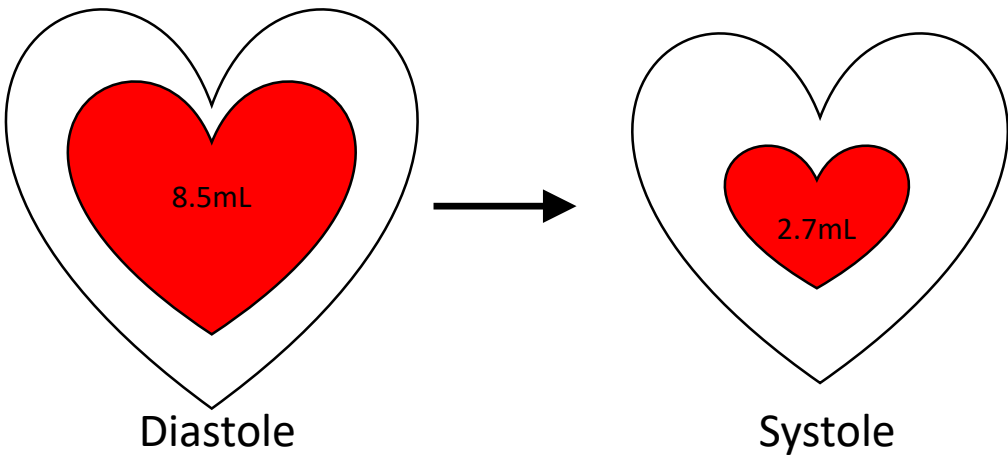
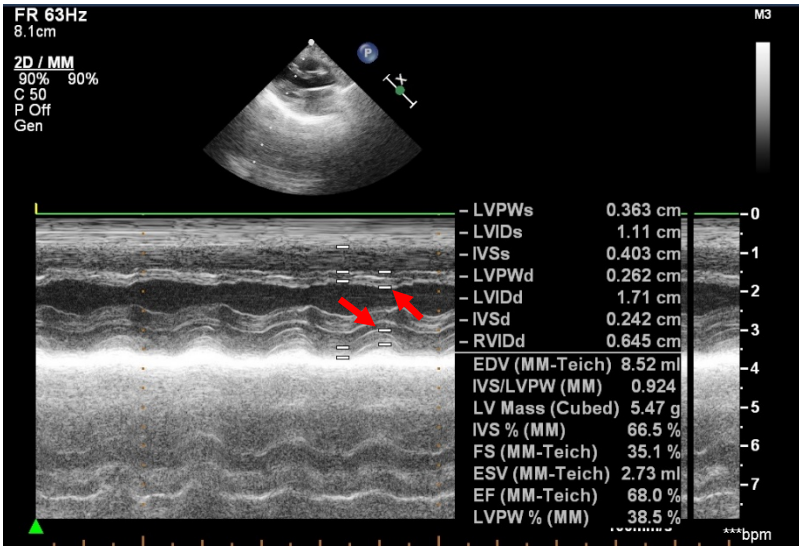


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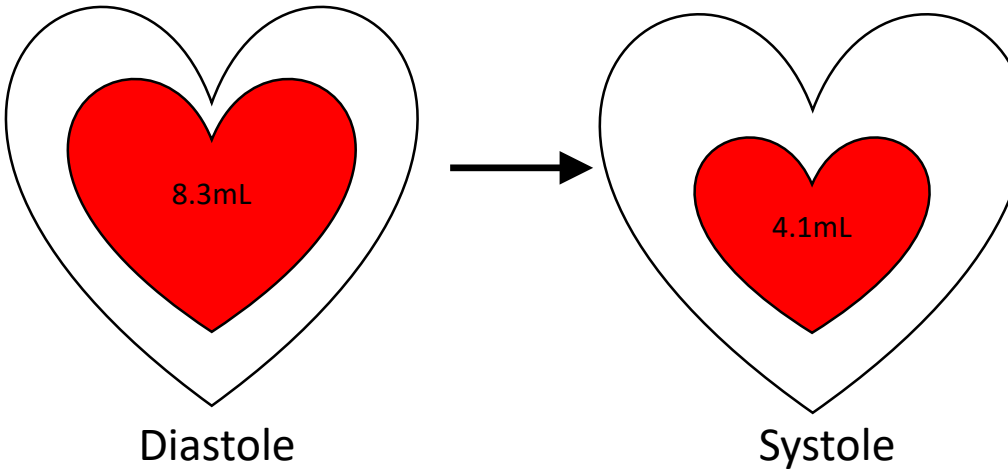
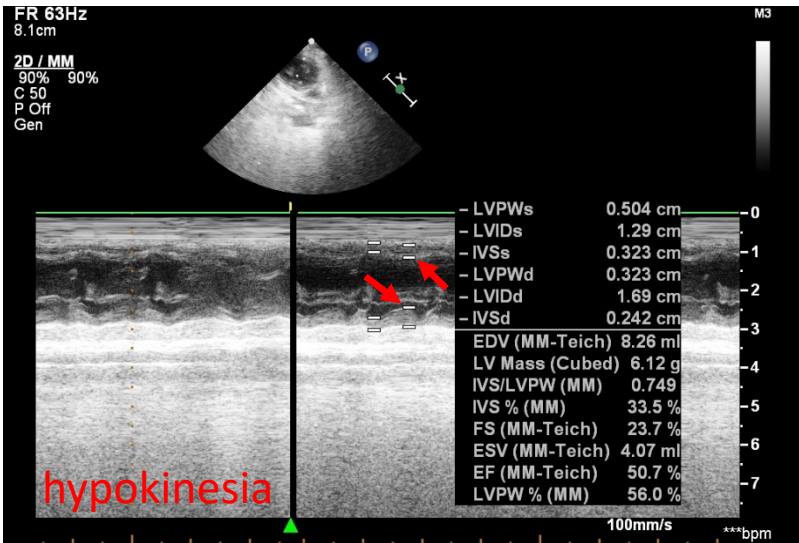


Distinct pathophysiology of VAP model → septic shock/**acute myocardial depression**

pre-infection baseline



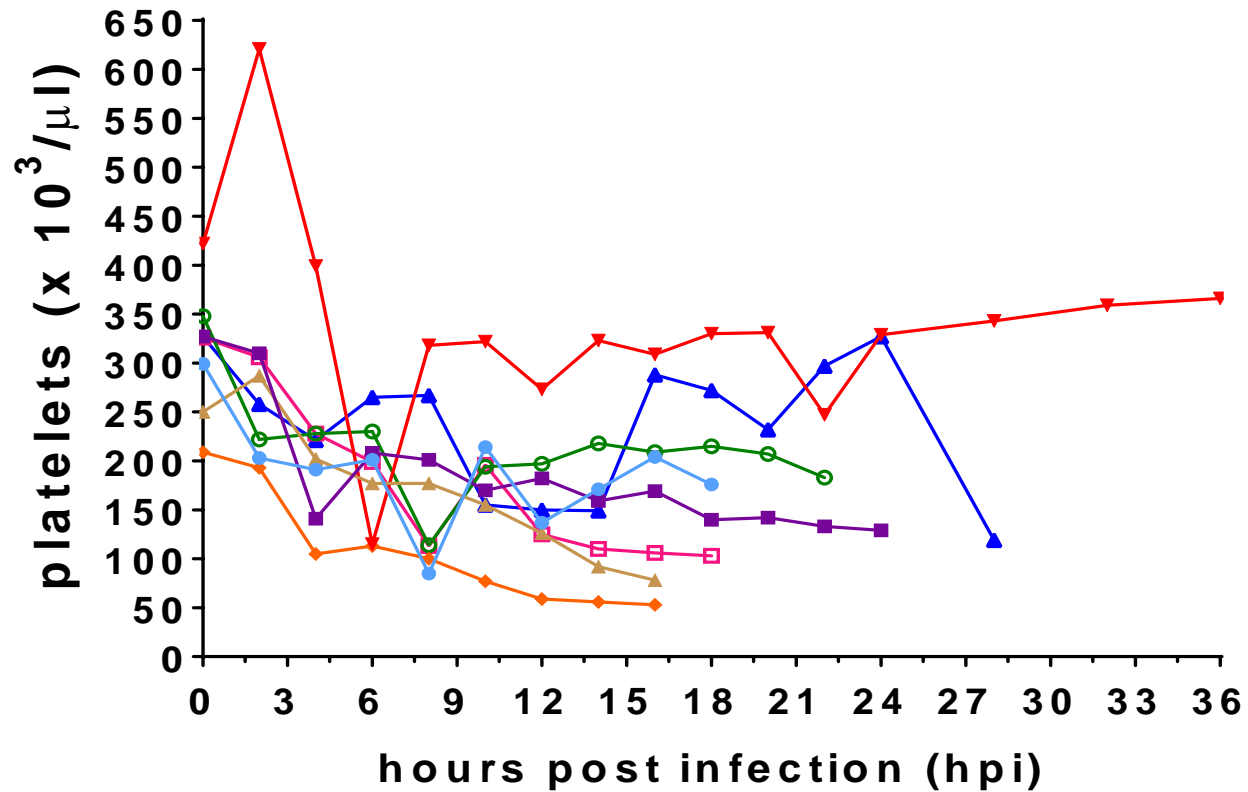
terminal phase showing global left ventricular hypokinesia



Distinct pathophysiology of VAP model → septic shock/**disseminated intravascular coagulation**

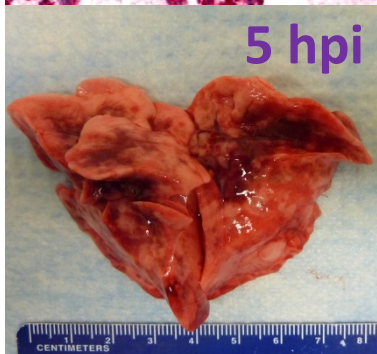
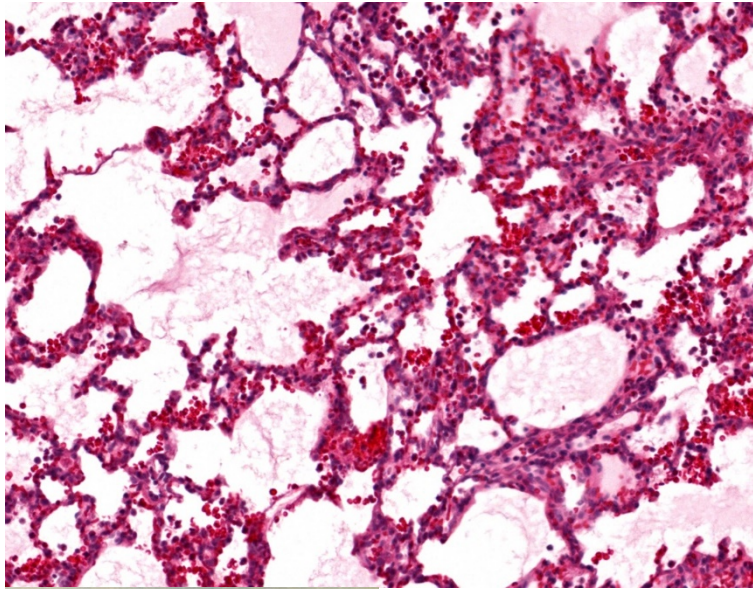
systemic bleeding and clotting in skin, GI tract and bladder

VAP Model

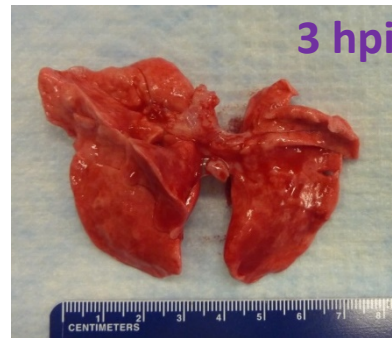
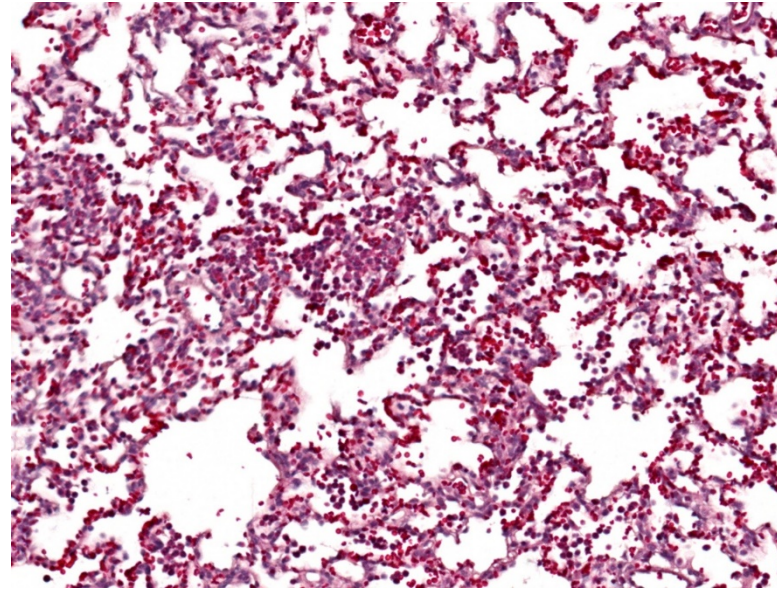


Evidence of pneumonia at **the trigger to treat (determined empirically)**

Acute Pneumonia Model at 5 h post infection



VAP Model at 3 h post infection



Rabbit VAP efficacy studies: *Experimental Details*

Procedures

mechanical ventilation	constant ($V_T=6-7\text{mL/kg}$; $FiO_2=35\%$; $PEEP=5\text{cmH}_2\text{O}$; $PIP=15\text{ cmH}_2\text{O}$; flow=4 L/min; 30 breadths/min)			
induction of anesthesia	X	X		
sedation	continuous (2% isoflurane)			
intubation & catheterization	1.5h per rabbit			
fluid maintenance	continuous (Normosol-R D5 2.5 mL/kg/h)			
bacterial infection		X		
norepinephrine	0.05-0.6	0.05-0.6	based on algorithm (0.1 - 10.0 $\mu\text{g/kg/min}$)	
fluid challenge	algorithm		based on algorithm (0.9% NaCl 15 mL/kg over 15 min infusion; additional doses permitted to 180 mL/kg)	
antibiotic exposure		X	X	X

Assessments

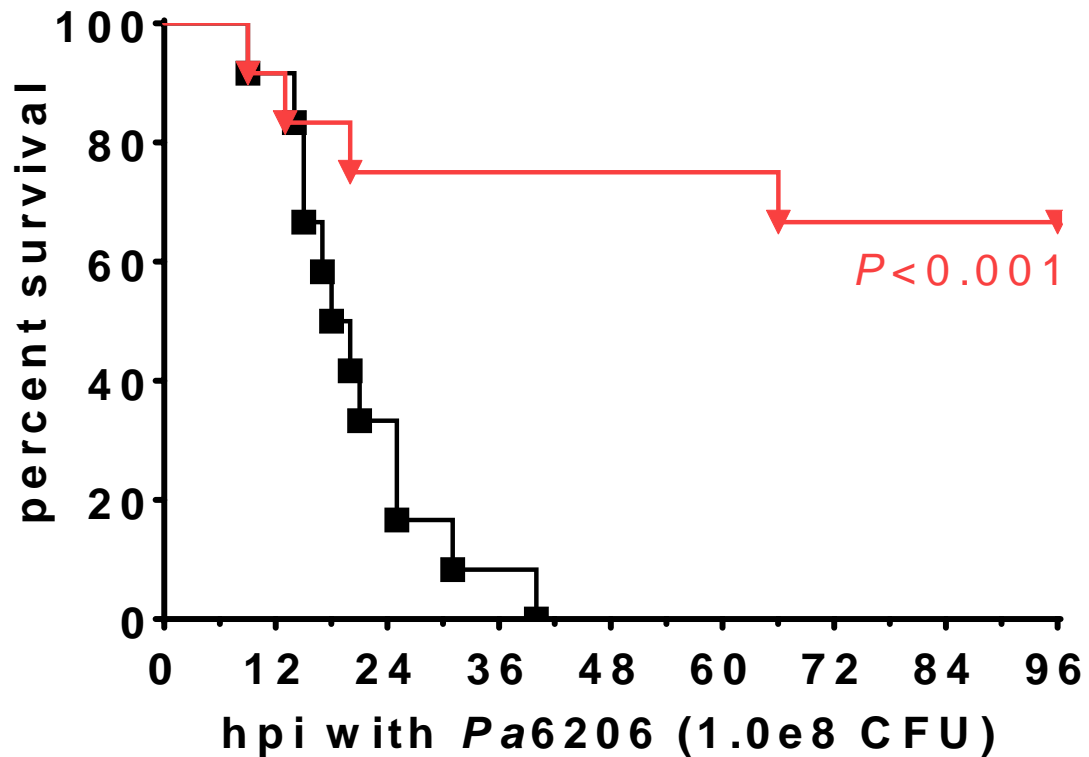
patient monitor	continuous (ABP, $ETCO_2$, SpO_2 , HR, ECG, T_{rectal})			
complete blood count		X	X	X
arterial blood gas		X	X	X
troponin I, CKMB, myoglobin		X	X	X
metabolic panel		X	X	X

0 6 10 13 19 21 29 37 45

Pivotal efficacy studies in AP and VAP models: *Survival is the primary outcome*

Acute Pneumonia Model

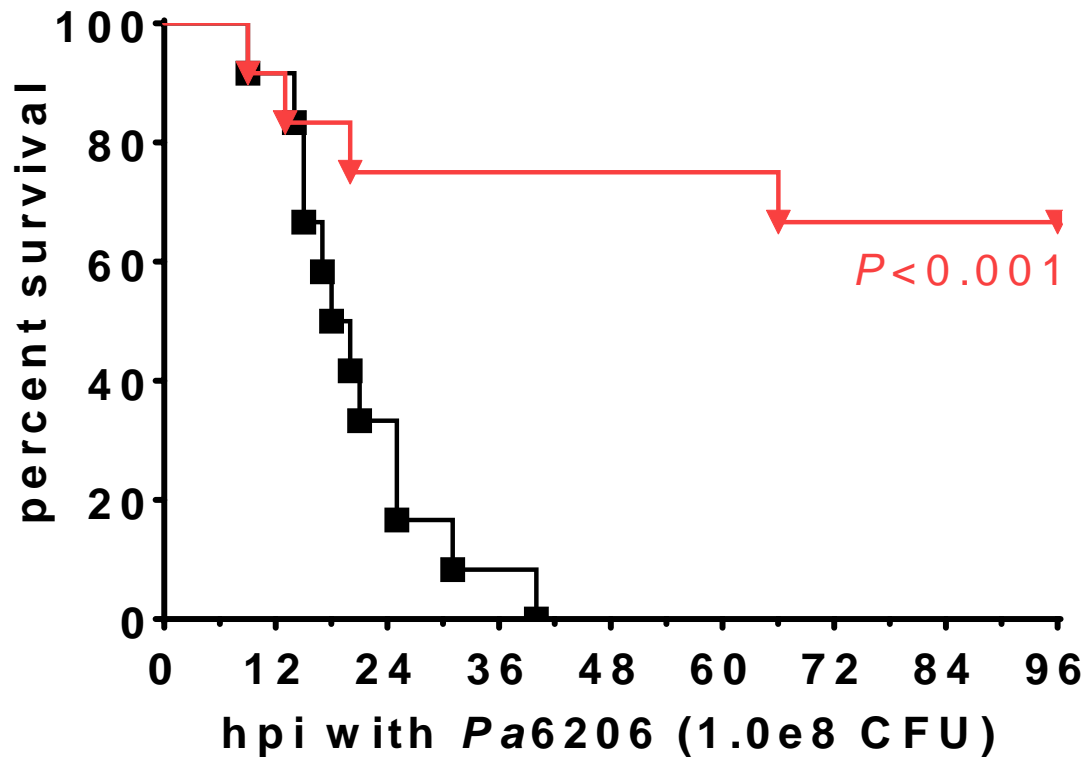
- ▼ 80 mpk meropenem IV q2h (12 doses)
- normal saline IV q2h (12 doses)



Pivotal efficacy studies in AP and VAP models: *Survival is the primary outcome*

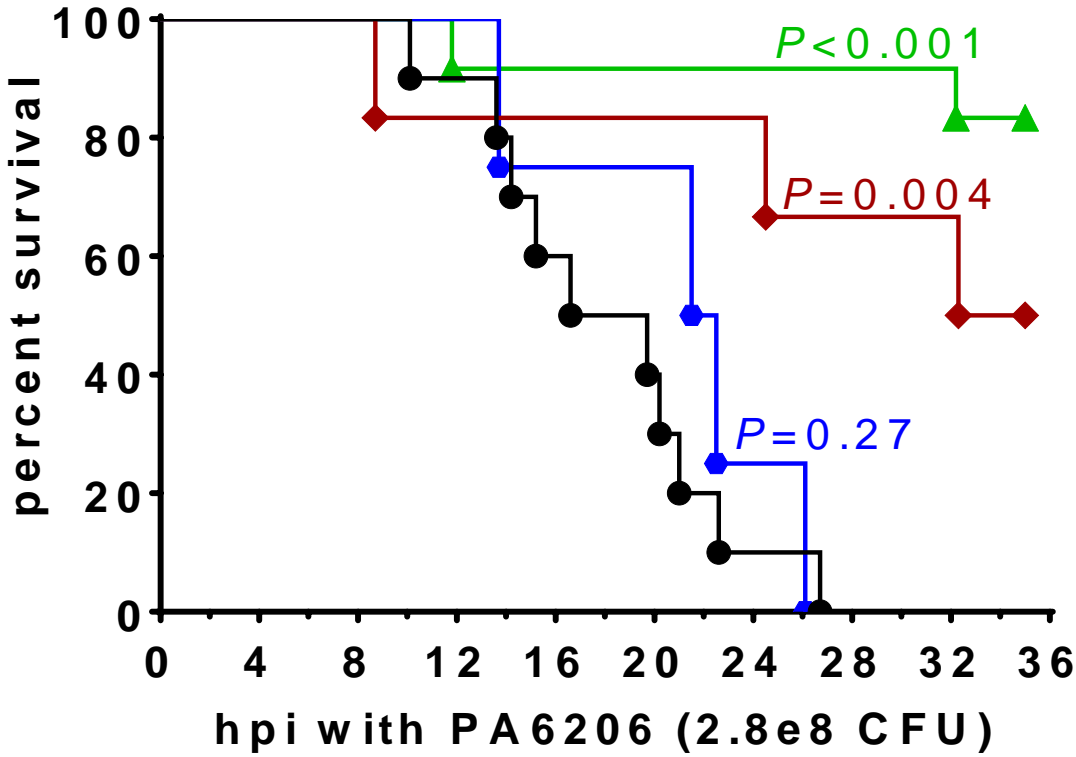
Acute Pneumonia Model

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VAP Model (preliminary data)

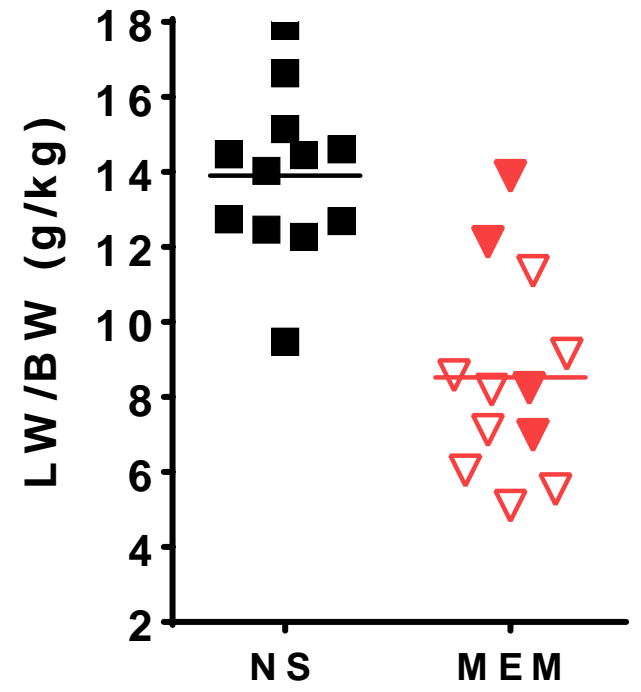
- ▲ meropenem and FC+NE
- ◆ meropenem 100mpk IV q8h (4 doses)
- fluid challenge (FC) + norepinephrine (NE)
- normal saline IV (equivolume as MEM)



Pivotal efficacy studies in AP and VAP models: Pulmonary edema (2° outcome)

Acute Pneumonia Model

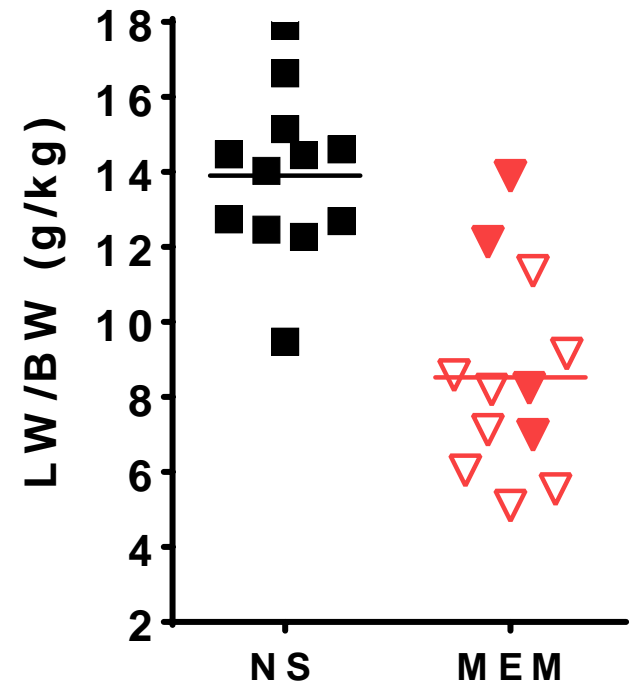
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Pivotal efficacy studies in AP and VAP models: Pulmonary edema (2° outcome)

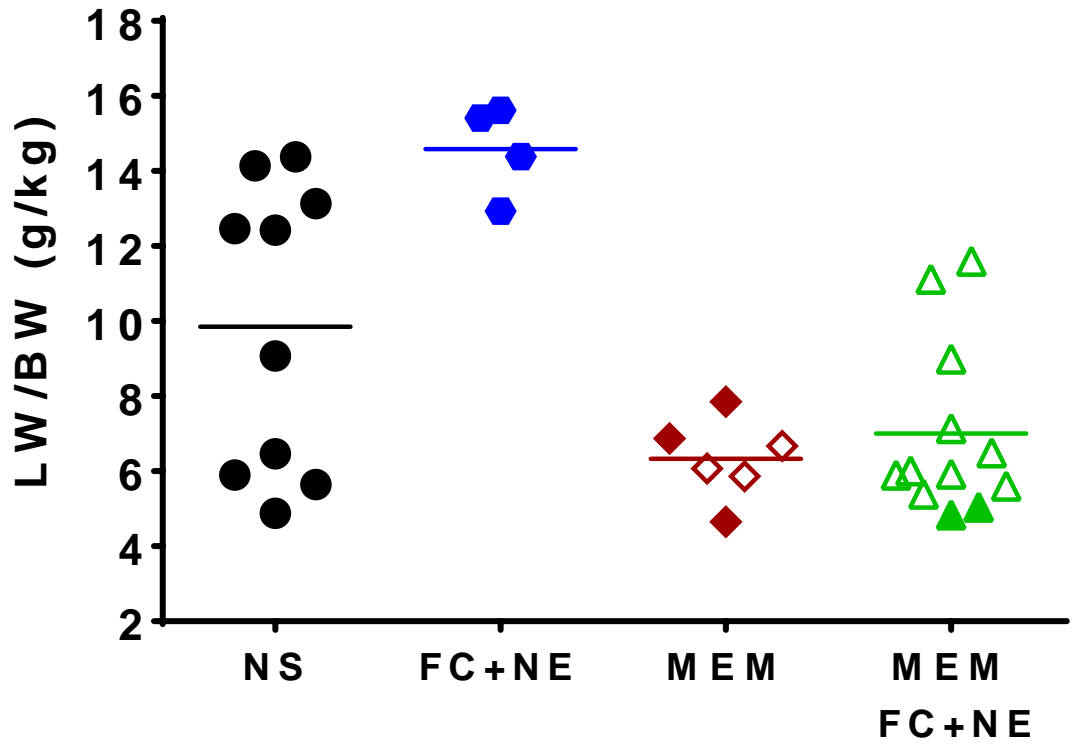
Acute Pneumonia Model

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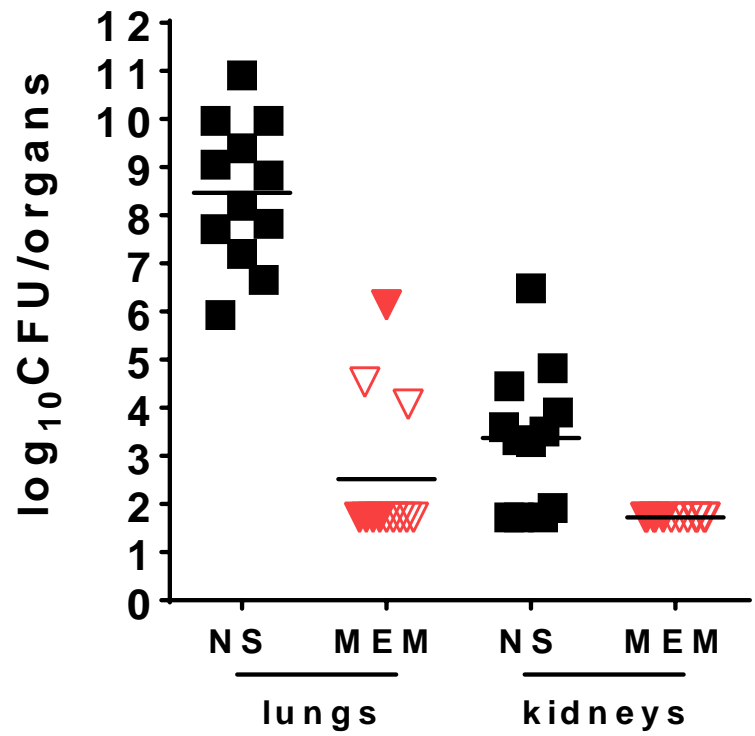
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Pivotal efficacy studies in AP and VAP models: **Bacterial burden (2° outcome)**

Acute Pneumonia Model

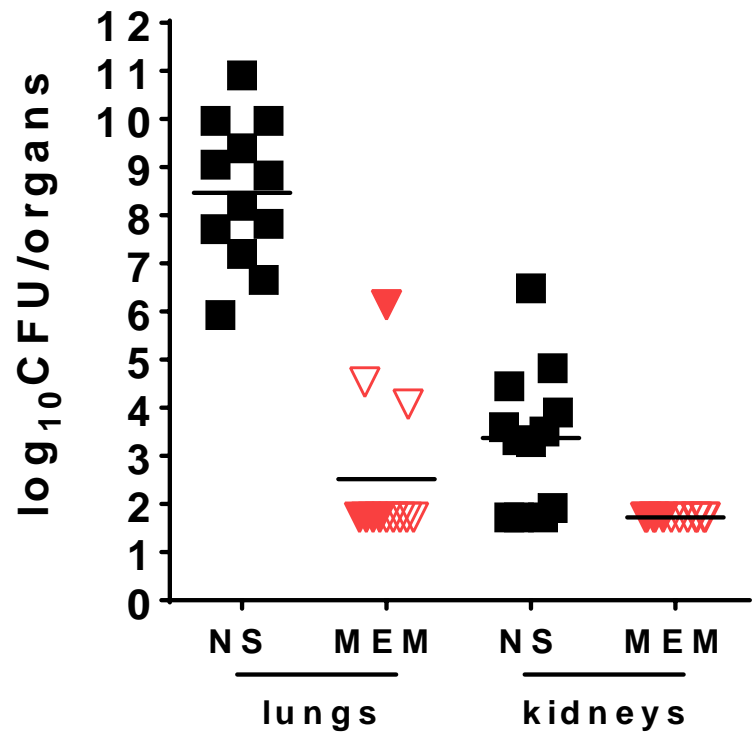
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Pivotal efficacy studies in AP and VAP models: **Bacterial burden (2° outcome)**

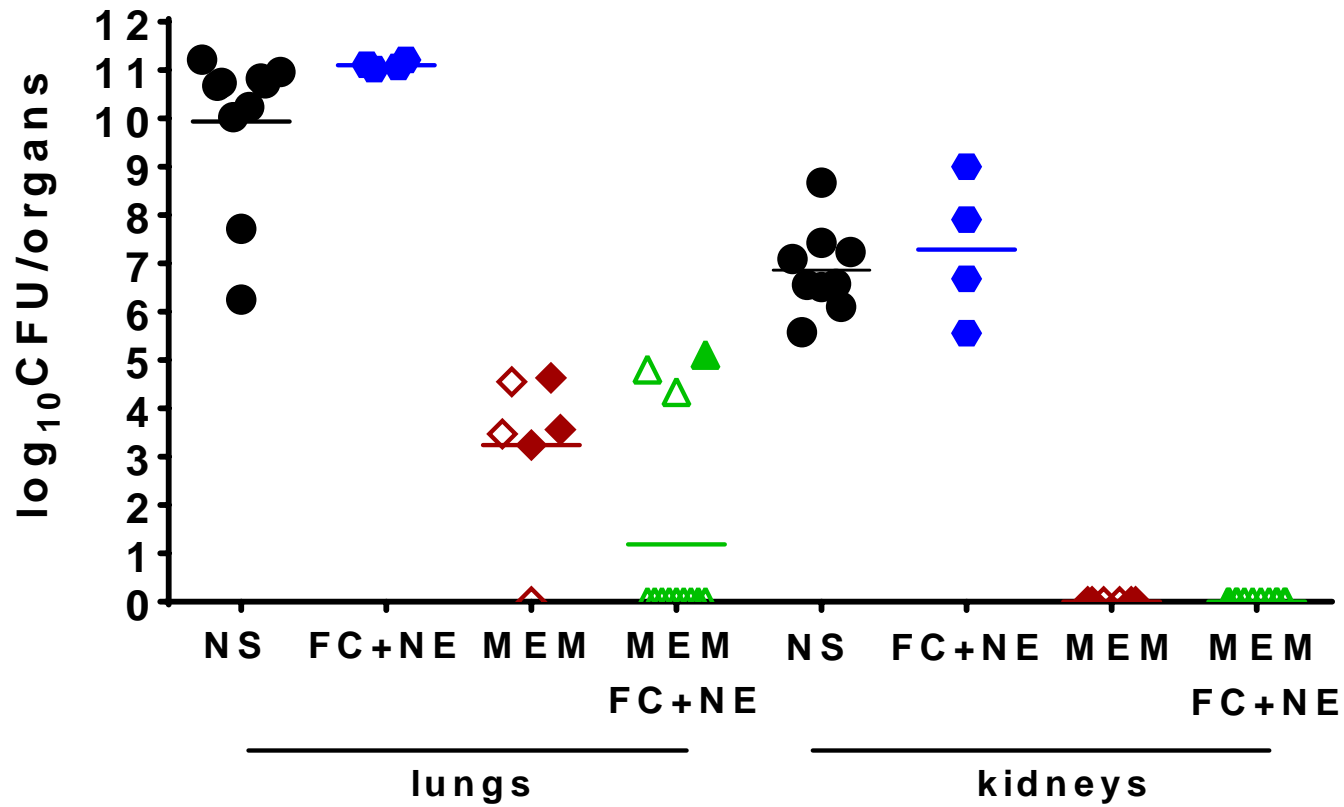
Acute Pneumonia Model

- normal saline IV q2h (12 doses)
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VAP Model (preliminary data)

- △ meropenem and FC+NE
- ◆ meropenem 100mpk IV q8h (4 doses)
- fluid challenge (FC)+norepinephrine (NS)
- normal saline IV (equivolume as MEM)



Pivotal efficacy studies in VAP model: **fluid challenge, norepinephrine (2° outcomes)**

	fluid challenge + norepi	meropenem fluid challenge + norepi
saline, mL/kg	115 ± 22	49 ± 42
norepinephrine, µg/kg/min	1.47 ± 0.48	0.91 ± 0.71

Pivotal efficacy studies in VAP model: **blood gas/acid-base (2° outcomes)**

		saline	fluid chal + norepi	meropenem	meropenem fluid chal + norepi
PaO₂/ FiO₂	0hpi	456	498	480	419
	3hpi	419	443	446	394
	9hpi	398	487	381	349
	TBE	187	134	269	262

Pivotal efficacy studies in VAP model: **blood gas/acid-base (2° outcomes)**

		saline	fluid chal + norepi	meropenem	meropenem fluid chal + norepi
PaO₂/ FiO₂	0hpi	456	498	480	419
	3hpi	419	443	446	394
	9hpi	398	487	381	349
	TBE	187	134	269	262
lactate (mmol/L)	0hpi	2.8	3.1	3.0	2.7
	3hpi	2.6	4.3	2.8	2.5
	9hpi	5.4	5.5	5.1	3.6
	TBE	12.8	11.0	8.0	4.2

Pivotal efficacy studies in VAP model: **blood gas/acid-base (2° outcomes)**

		saline	fluid chal + norepi	meropenem	meropenem fluid chal + norepi
PaO₂/ FiO₂	0hpi	456	498	480	419
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	3hpi	2.6	4.3	2.8	2.5
	9hpi	5.4	5.5	5.1	3.6
	TBE	12.8	11.0	8.0	4.2
base excess (mmol/L)	0hpi	3.6	3.3	3.5	2.0
	3hpi	0.9	1.4	0.2	-0.5
	9hpi	-5.1	-4.7	-3.7	-3.0
	TBE	-18.5	-24.2	-10.9	-6.4

Pivotal efficacy studies in VAP model: **blood gas/acid-base (2° outcomes)**

		saline	fluid chal + norepi	meropenem	meropenem fluid chal + norepi
WBC (x 10/ μ L)	0hpi	6.4	6.3	7.4	6.6
	3hpi	4.0	3.7	4.3	4.2
	9hpi	2.3	3.0	4.0	4.6
	TBE	1.7	1.8	6.1	8.0

Pivotal efficacy studies in VAP model: **blood gas/acid-base (2° outcomes)**

		saline	fluid chal + norepi	meropenem	meropenem fluid chal + norepi
WBC (x 10/ μ L)	0hpi	6.4	6.3	7.4	6.6
	3hpi	4.0	3.7	4.3	4.2
	9hpi	2.3	3.0	4.0	4.6
	TBE	1.7	1.8	6.1	8.0
NEU (x 10/ μ L)	0hpi	4.2	4.0	4.6	4.7
	3hpi	1.4	1.1	2.0	2.1
	9hpi	0.9	1.2	2.6	2.5
	TBE	0.2	0.1	4.1	4.2

Pivotal efficacy studies in VAP model: **blood gas/acid-base (2° outcomes)**

		saline	fluid chal + norepi	meropenem	meropenem fluid chal + norepi
WBC (x 10/ μ L)	0hpi	6.4	6.3	7.4	6.6
	3hpi	4.0	3.7	4.3	4.2
	9hpi	2.3	3.0	4.0	4.6
	TBE	1.7	1.8	6.1	8.0
NEU (x 10/ μ L)	0hpi	4.2	4.0	4.6	4.7
	3hpi	1.4	1.1	2.0	2.1
	9hpi	0.9	1.2	2.6	2.5
	TBE	0.2	0.1	4.1	4.2
platelets (x 10/ μ L)	0hpi	389	380	340	347
	3hpi	313	267	295	306
	9hpi	244	254	284	305
	TBE	184	121	280	301

SUMMARY

Rabbit Acute Pneumonia Model	Rabbit VAP Model
mimics human non-ventilated HABP	mimics human vHABP/VABP with ARDS
awake rabbits (non-ventilated)	anesthetized rabbits ventilated with low V_T
Pathophysiology: lung necrosis/pulmonary edema → profound respiratory failure	Pathophysiology: acute lung injury/inflammation, ARDS → septic shock (acute myocardial depression, systemic bleeding and clotting)
1° outcome: SURVIVAL	1° outcome: SURVIVAL
2° outcomes: CFU and LW/BW	2° outcome: CFU, LW/BW, physiologic monitoring, biomarkers
antibiotic dosing: bolus only	antibiotic dosing: programmable syringe pump to better mimic human PK
supportive care: none	supportive care: fluid challenge & vasopressor
feasibility: minimum set up	feasibility: experimental ICU set up

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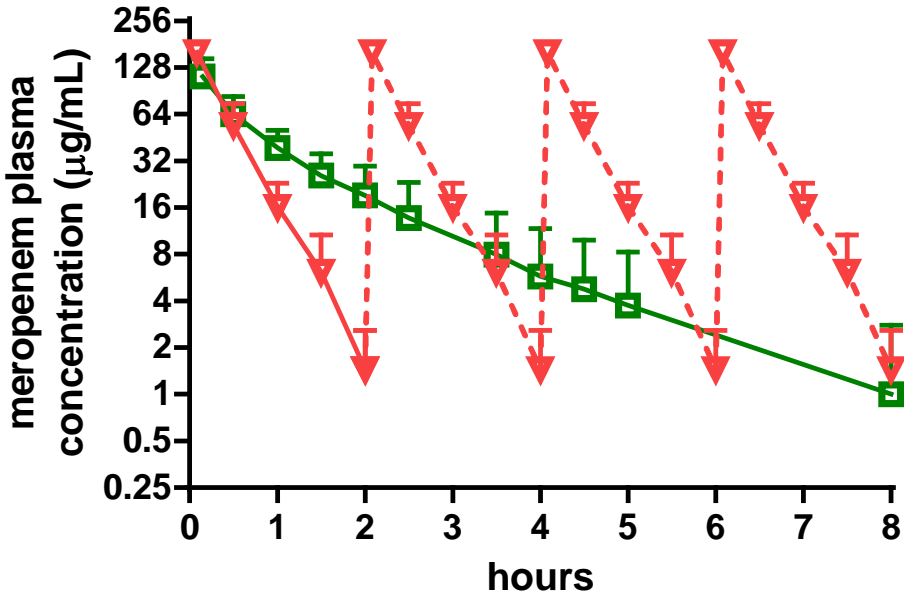
FDA contract no. HHSF223201710112C

Dosing strategies in rabbits to mimic human PK/PD for meropenem

Acute Pneumonia Model

■ VAP patients 1g q8h (10-min infusion) AAC 49:1337–1339
 $AUC_{0-8h}=124 \mu\text{g/mL}\cdot\text{h}$; %T>MIC=100%

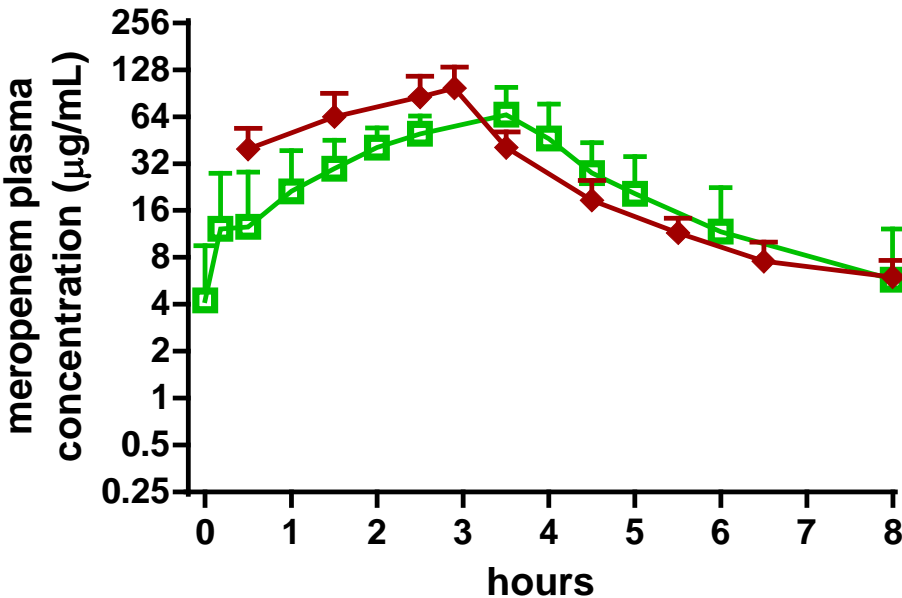
▼ AP model rabbits* 80 mg/kg q2h (2-min infusion)
 [actual data solid line; simulated data dashed line]
 $AUC_{0-8h}=264 \mu\text{g/mL}\cdot\text{h}$; %T>MIC=100%



VAP Model (preliminary data)

■ VAP patients 2g q8h (3h infusion) AAC 49:1337–1339
 $AUC_{0-8h}=232 \mu\text{g/mL}\cdot\text{h}$; %T>MIC=100%

◆ VAP model rabbits** 100 mg/kg q8h (staggered-continuous infusion)
 $AUC_{0-8h}=273 \mu\text{g/mL}\cdot\text{h}$; %T>MIC=100%



P. aeruginosa strain 6206 meropenem MIC 0.25 µg/mL; *infected AP rabbits; **uninfected VAP (PK in infected rabbits pending)
serum protein binding for meropenem: 10.5% to 21.7% in JW rabbits vs. 6.1% in humans (PMIDs 16433034 and 16493791)