Inhalation of antibiotics and its effectiveness in MDR Gram positives-caused VAP

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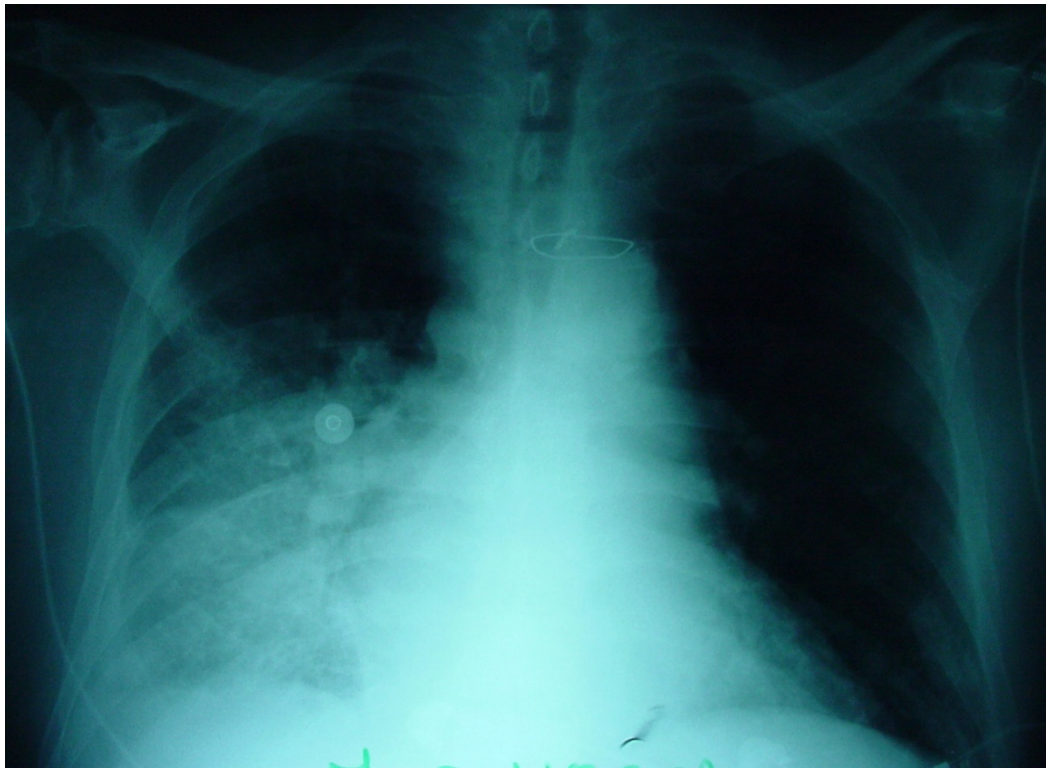

Inhalation of antibiotics and its effectiveness in MDR Gram positives-caused VAP

Jean Chastre,

Conflicts of interest:

- Advisory board: Aerogen Nektar
- Lecture fees: Pfizer, Brahms, Wyeth, Johnson-Johnson, Kimberly.

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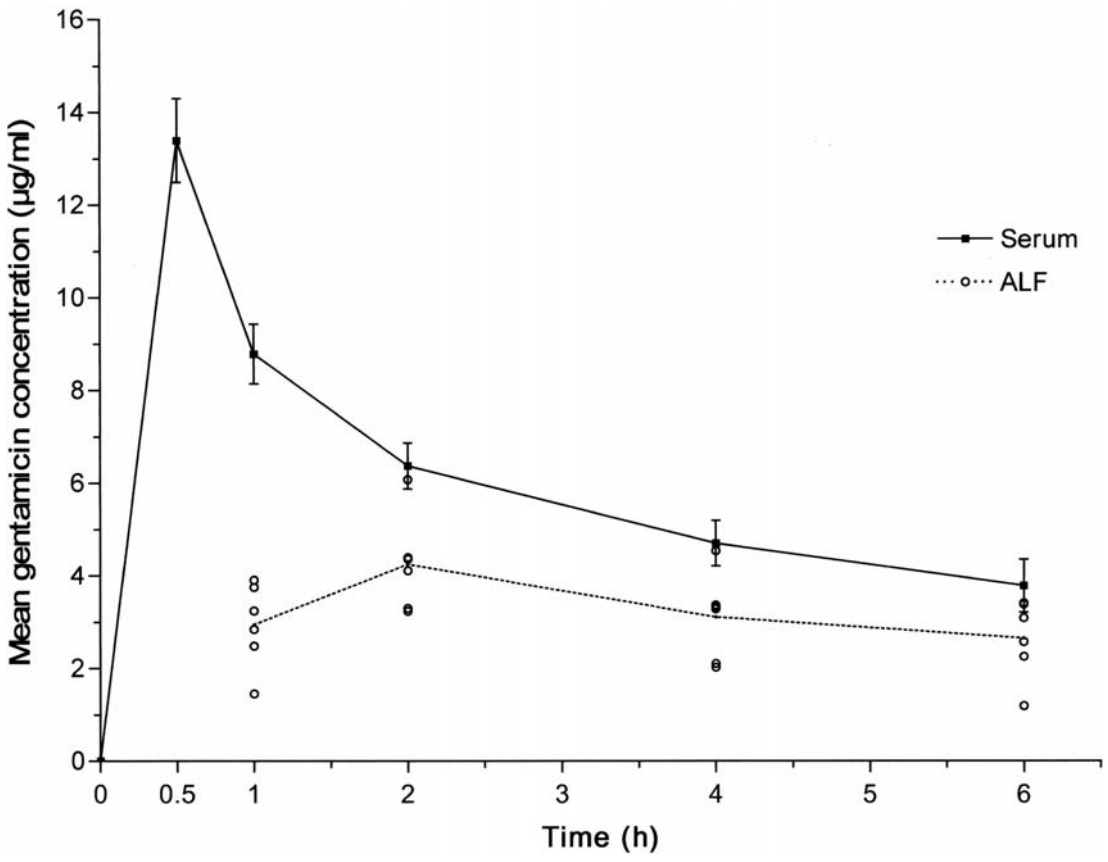
Penetrating the Lung Tissue: *Rationale*

- Lung deposition of antibiotics administered by the IV route is often limited and can lead to treatment failure, as frequently observed in case of infection caused by difficult-to-treat pathogens, such as MRSA and other MDR Gram positives.

Penetration of Gentamicin into the Alveolar Lining Fluid of Patients with VAP

Panidis et al. Chest 2005

- 24 patients with VAP who received a once-daily, 240-mg dose of gentamicin
- Bronchoscopy with BAL to determine gentamicin concentration in ALF at 1, 2, 4, and 6 h after the start of antibiotic infusion
- Average peak antibiotic concentration in ALF was only 4.24 ug/ml, giving a penetration ratio of 0.32



Vancomycin Pulmonary Penetration

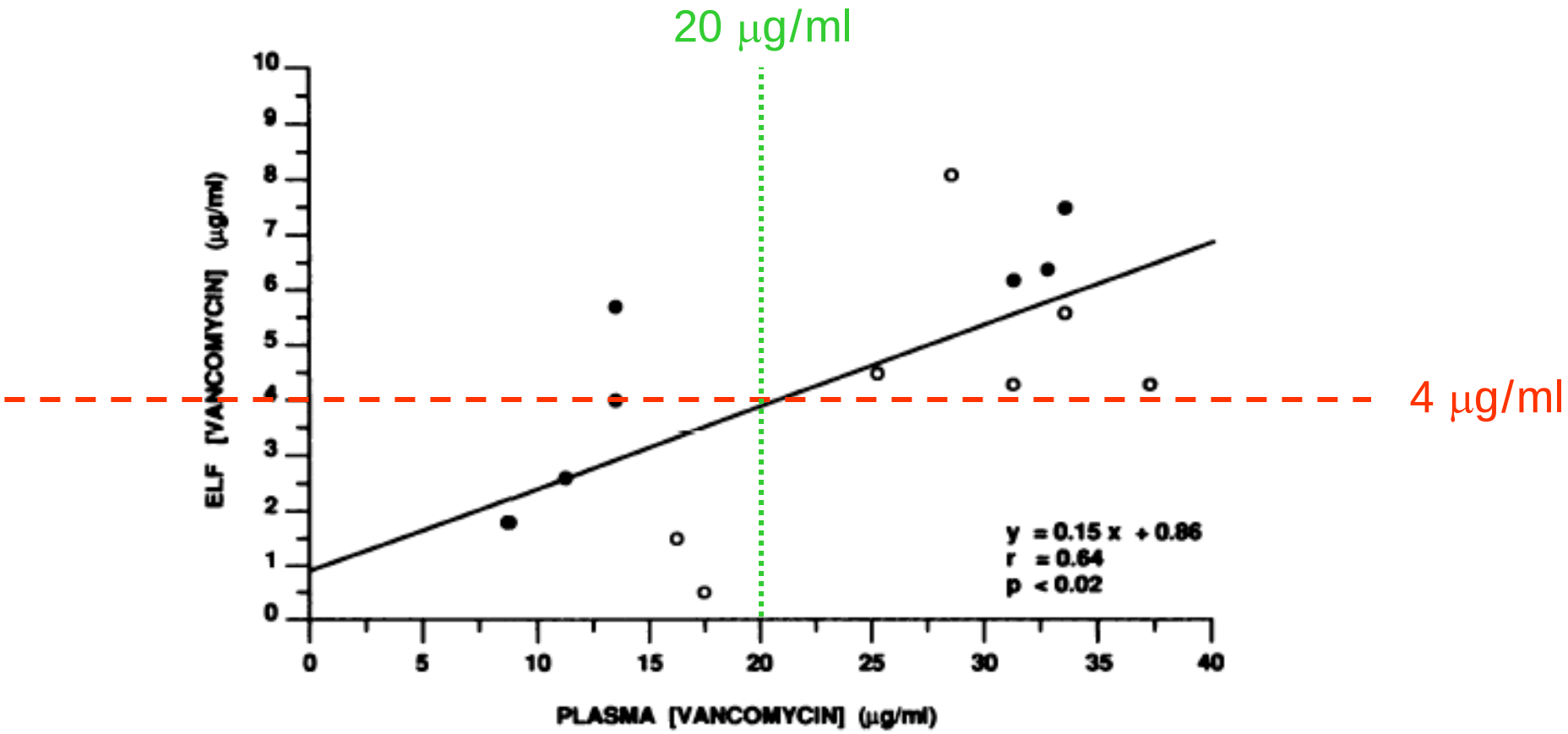
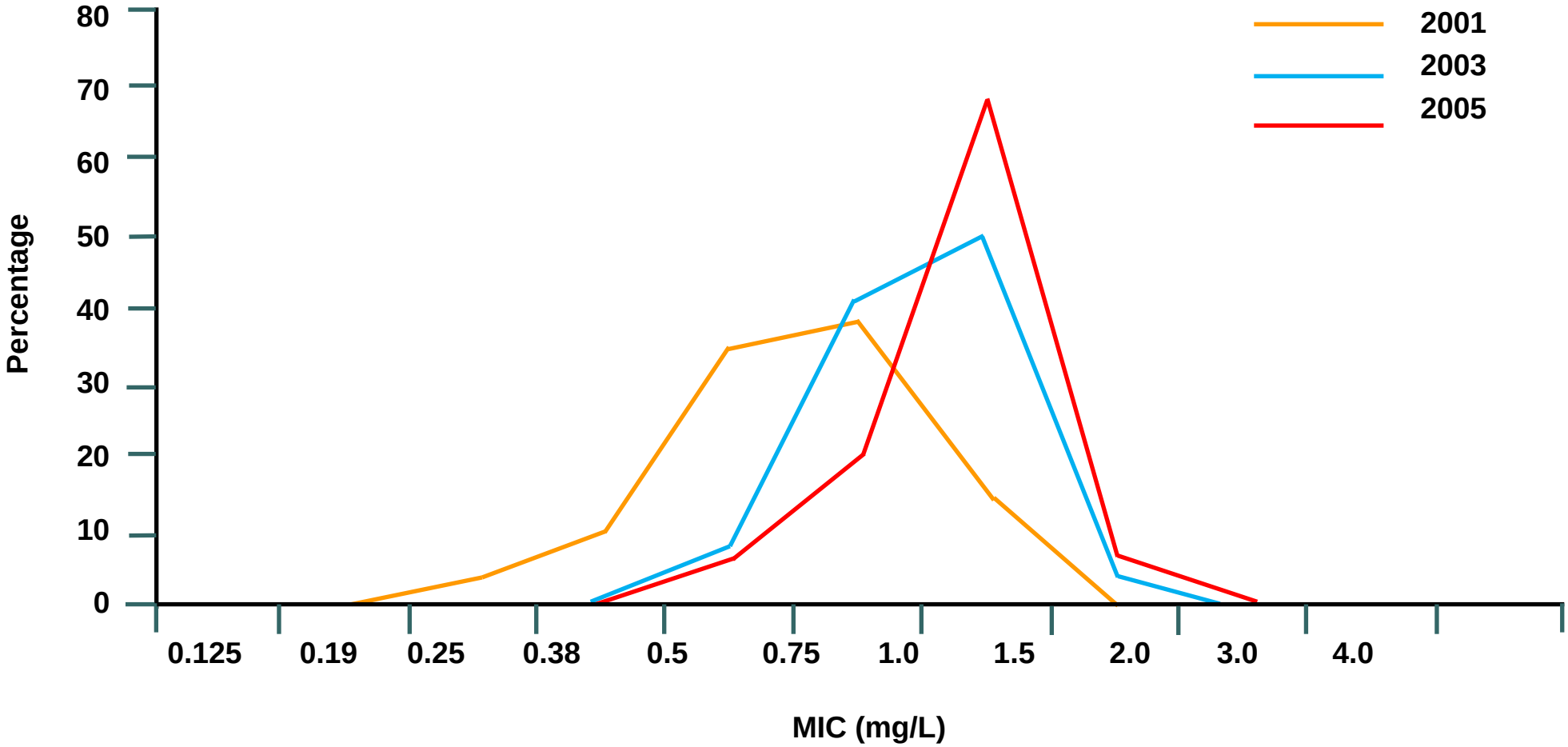


FIG. 1. Relationship between vancomycin concentrations in plasma and ELF. Symbols: ○, patients with albumin level in ELF of <3.4 mg/ml; ●, patients with albumin levels in ELF of ≥3.4 mg/ml.

Lamer C et al. *Antimicrob Agents Chemother.* 1993;37:281-86.

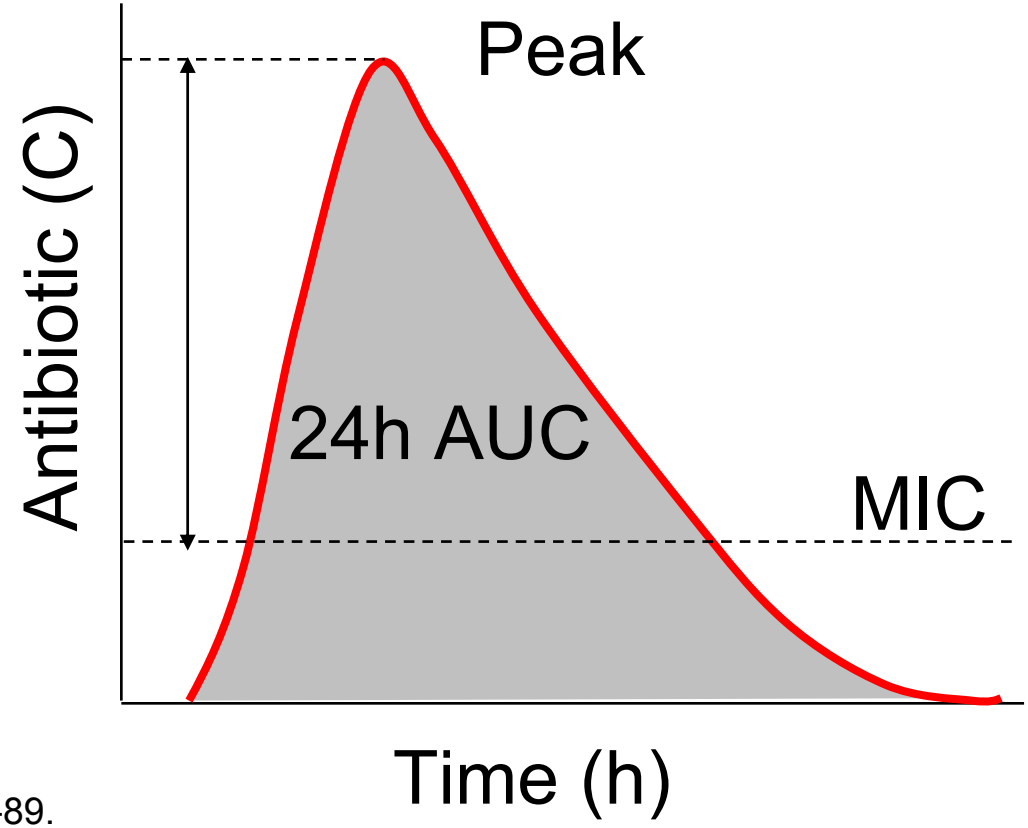
Vancomycin MIC creep



Steinkraus, et al. *J Antimicrob Chemother* 2007;60:788-794

PK-PD Parameters Required for Optimal Treatment of Patients with Severe MRSA Infection

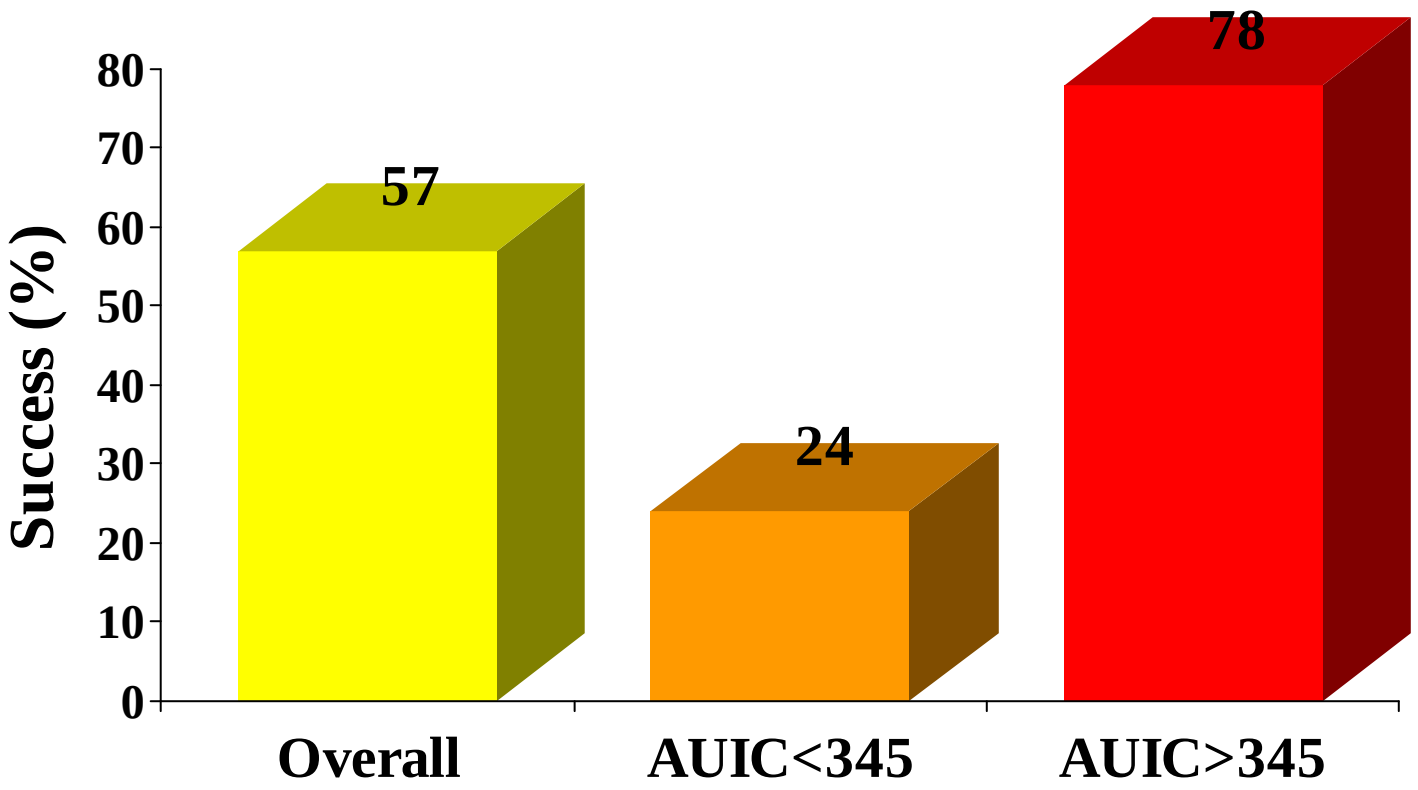
For vancomycin and linezolid:
the most important PK-PD parameter seems to be the 24h AUC, although both antibiotics demonstrate concentration independency.



Andes D et al. *Antimicrob Agents Chemother.* 2002;46:3484-89.
Moise PA et al. *Am J Health-Syst Pharm.* 2000;57:S4-S9.

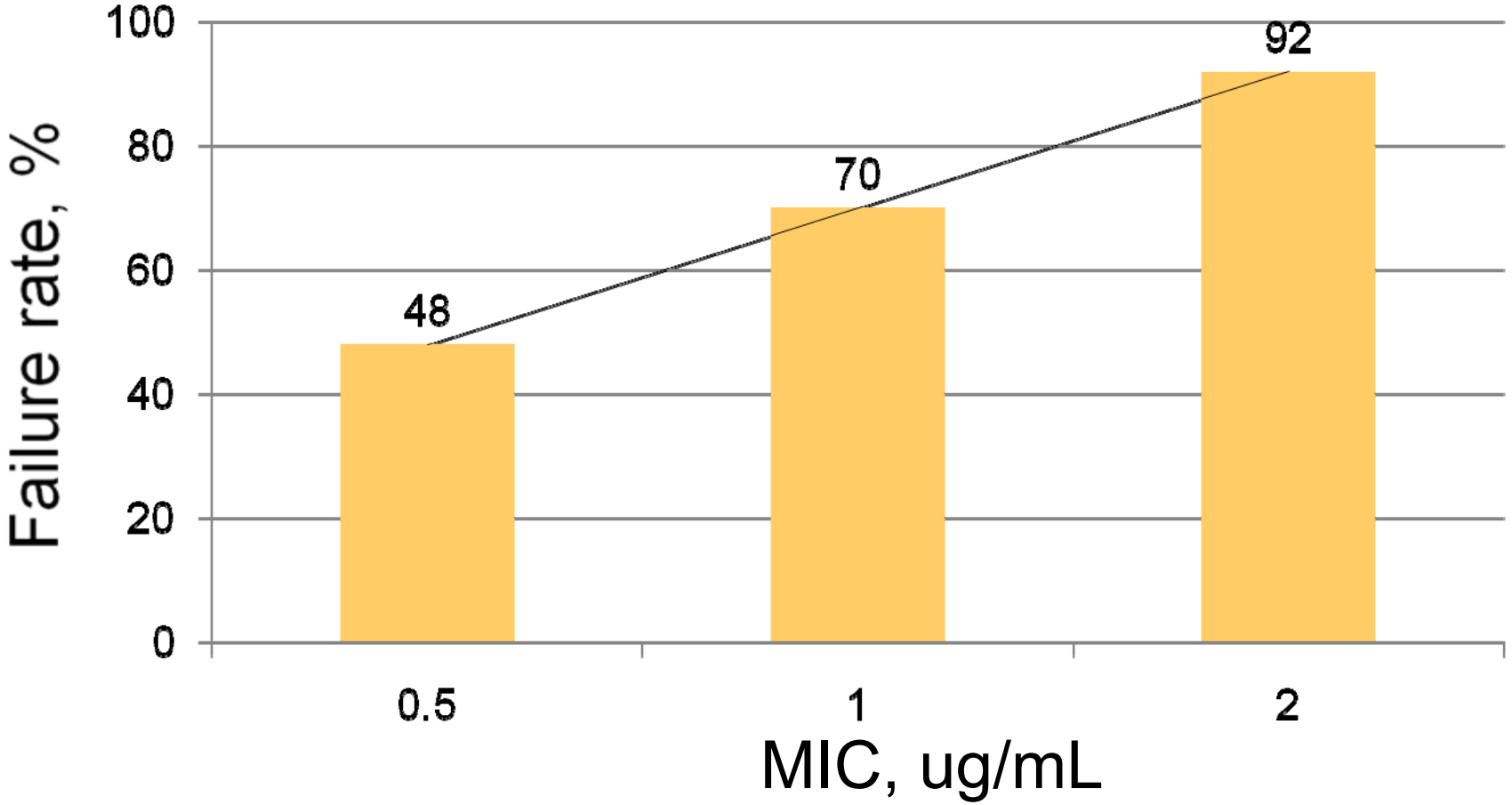
Vancomycin for MRSA Pneumonia

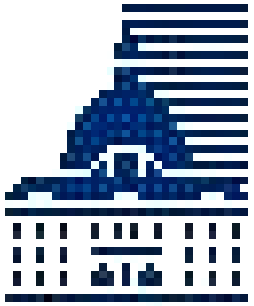
Moise PA et al. Am J Health-Syst Pharm. 2000;57:S4-S9.



Relation of the MIC to vancomycin treatment failure rates in 102 MRSA infections

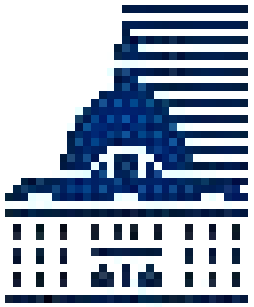
Moise-Broder PA et al. CID 2004;38:1700-5





Inhaled Antibiotics for Ventilator-Associated Pneumonia. *Rationale*

- Directly delivering the drug to the site of infection via nebulization may increase the pulmonary penetration of antibiotics used in this setting.
- Moreover, by limiting systemic exposure, it could also allow the administration of antibiotics characterized by a high systemic toxicity, such as aminoglycosides or polymixins.



Inhaled Antibiotics for Ventilator-Associated Pneumonia. *Questions*

- How much of the dose is delivered to the lung
- How is the delivered dose dispersed in the lung
- How much is absorbed into the blood
- How does the resulting serum PK-PD profile mimic an IV dose of the same drug
- How much is removed from the site by suctioning
- What are the safety and tolerability

Optimizing Aerosol Delivery During Mechanical Ventilation

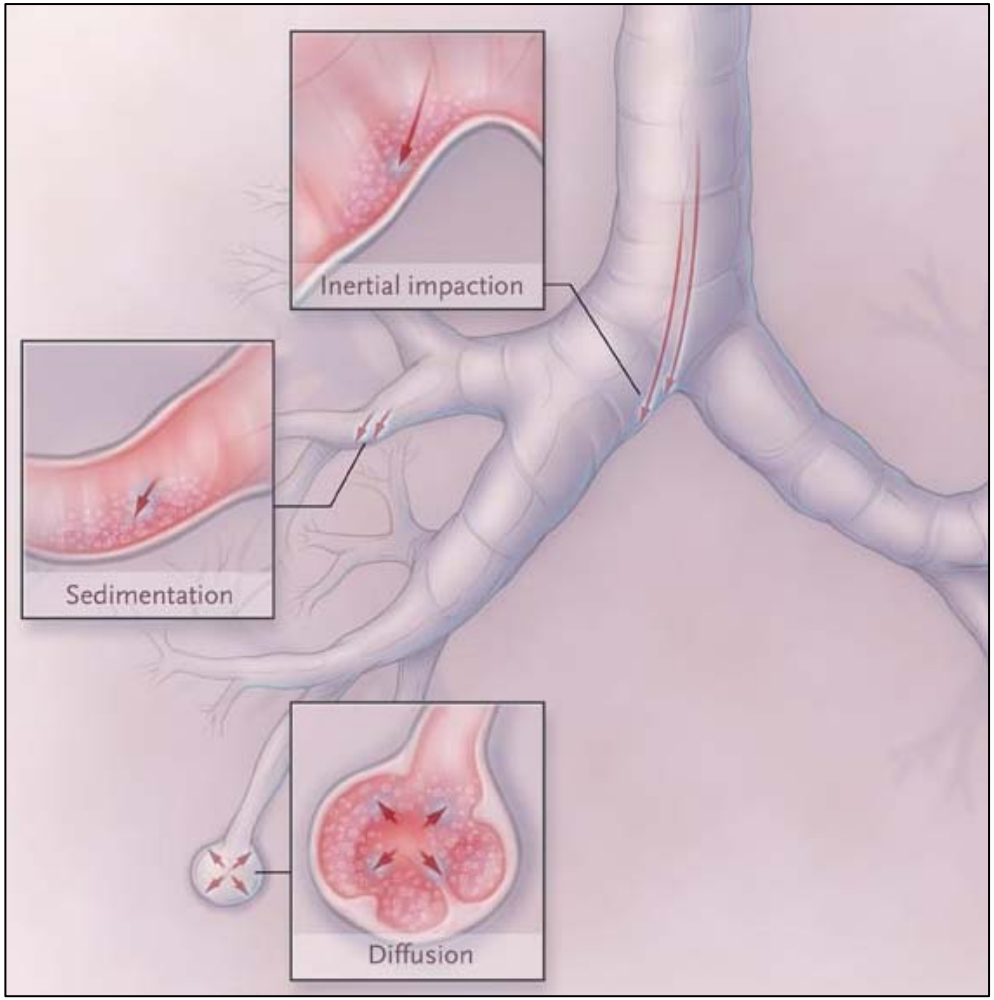
- Better understanding of physiological factors influencing lung deposition of aerosolized particles together with improvement in technology have contributed to optimize the delivery of nebulized antibiotics to the deep lung.

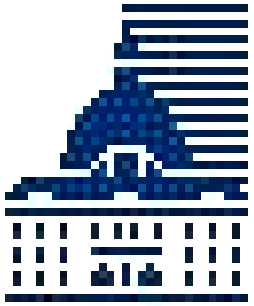
Depositing Drugs in the Lung

Coates A. N Engl J Med 2008;358:304-305

The deposition of an inhaled aerosol occurs through 3 mechanisms:

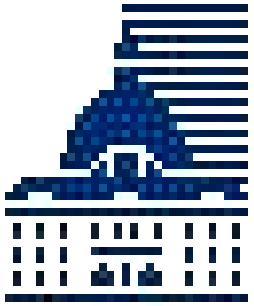
- by inertial *impaction*, in which a droplet fails to turn a corner and impacts the wall of the airway.
- by *sedimentation*, in which the droplets "rain out" under the influence of gravity.
- by *diffusion* caused by Brownian motion, which results in collisions of the droplets with the airway wall





Optimizing Aerosol Delivery During Mechanical Ventilation

- A number of factors influence lung deposition of antibiotics during mechanical ventilation:
  - aerosol particle size,
  - type of nebulizer,
  - and respiratory settings.



Optimizing Aerosol Delivery During Mechanical Ventilation

- Jet nebulizers have serious drawbacks when used during mechanical ventilation.
- When operated continuously by an external gas flow, a high-speed turbulent gas flow is produced that promotes particles impaction on ventilator circuits.
- Using such devices, lung deposition varies between 1 and 15 % of the nominal dose.

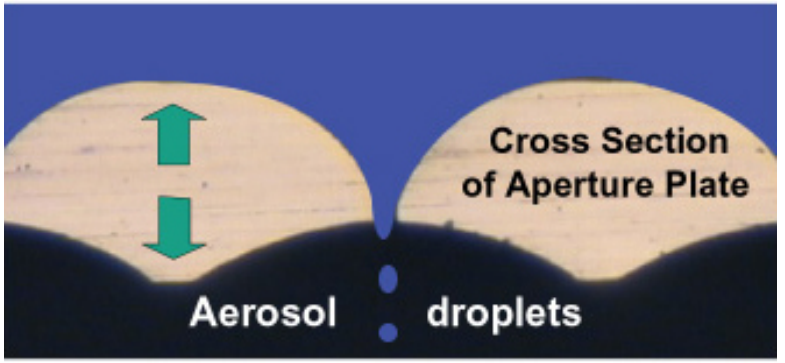
Optimizing Aerosol Delivery During Mechanical Ventilation

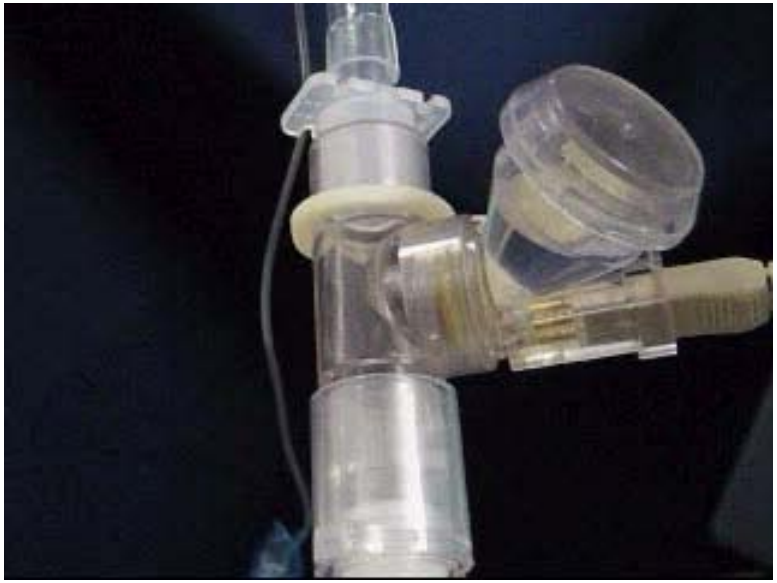
- Compared with jet nebulizers, *in vitro* and *in vivo* data suggest that ultrasonic devices provide higher lung tissue deposition:
  - they are generally equipped with a large reservoir;
  - they generate particles whose diameter is < 5 μ;
  - the aerosol is continuously generated, allowing the inspiratory administration of a bolus of aerosolized particles that accumulate within the inspiratory limb during the expiratory phase.

Optimizing Aerosol Delivery During MV: The Vibrating Plate Aerosol (Nektar-Aerogen®)

Potential advantages:

- The aerosol is generated by a ceramic vibrating element and a domed aperture plate through which the solution is micropumped;
- the antibiotic solution is not heated;
- the aerosol generation can be synchronized with inspiration minimizing aerosol waste during exhalation.





Samples Images: Volunteer #1

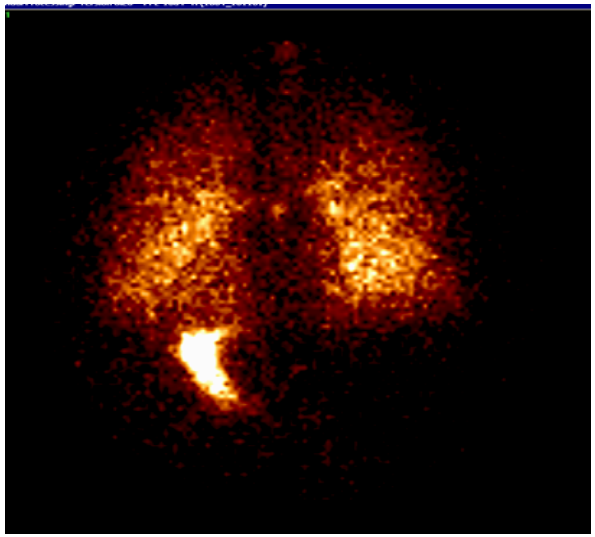


Image of posterior thorax

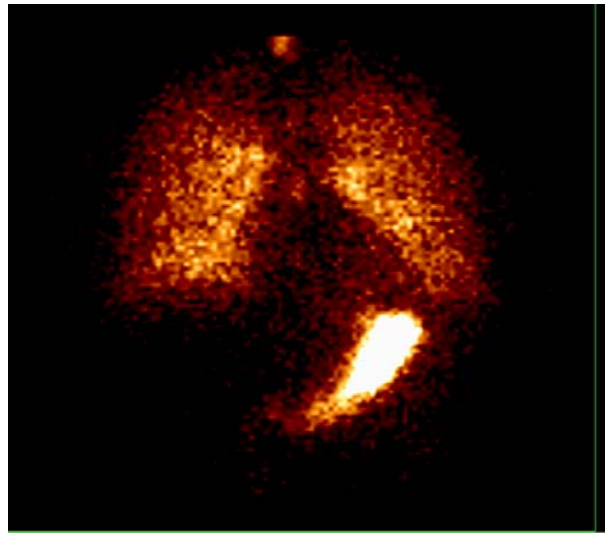


Image of anterior thorax

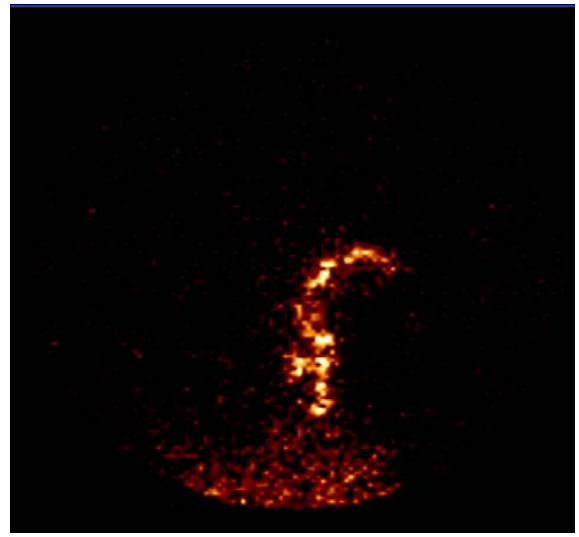


Image of right lateral head

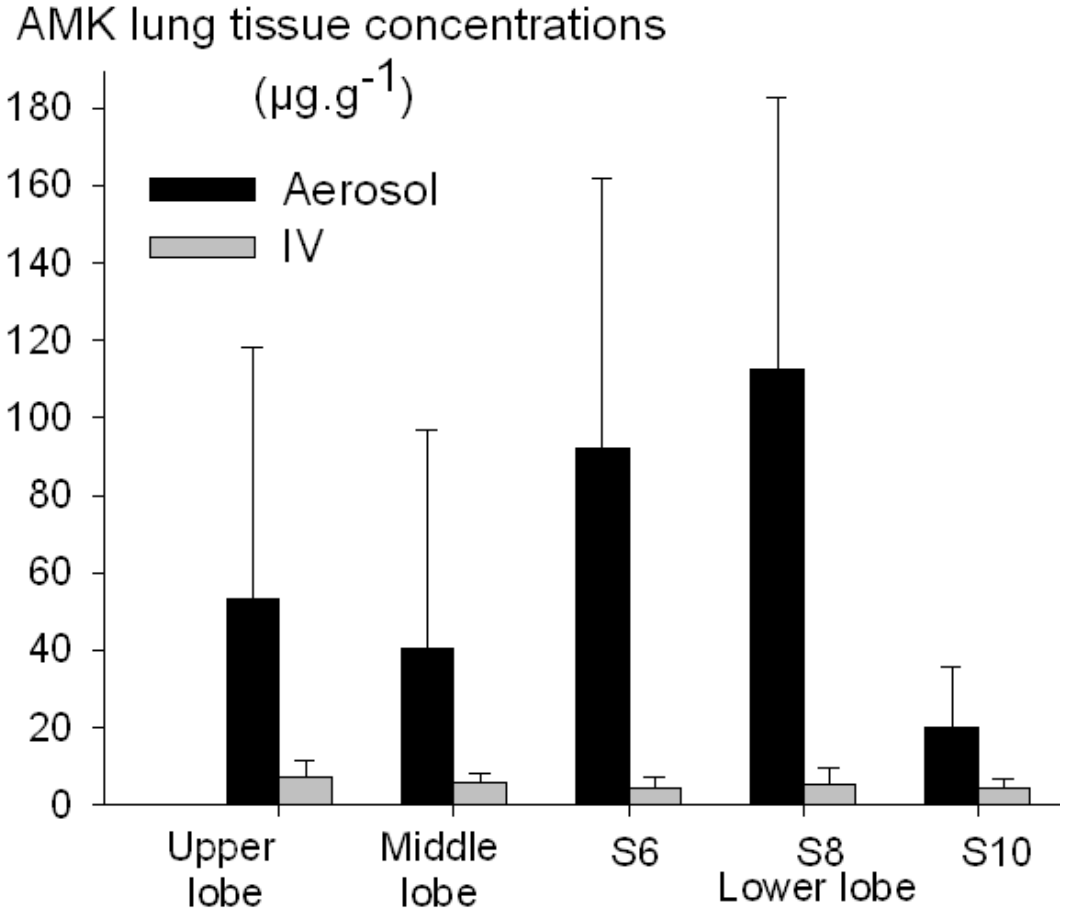
06-IN-AK003 Deposition Data

N =13	Whole lung (%)	Oropharyngeal (%) Includes mouth and stomach	Device (%)	Exhaled air (%)
Mean	43.0	29.4	16.1	11.5
SD	6.1	7.3	4.8	5.5
Median	43.2	31.5	17.4	10.2

Lung Deposition and Efficiency of Nebulized AMK during *E. coli* Pneumonia in Ventilated Piglets

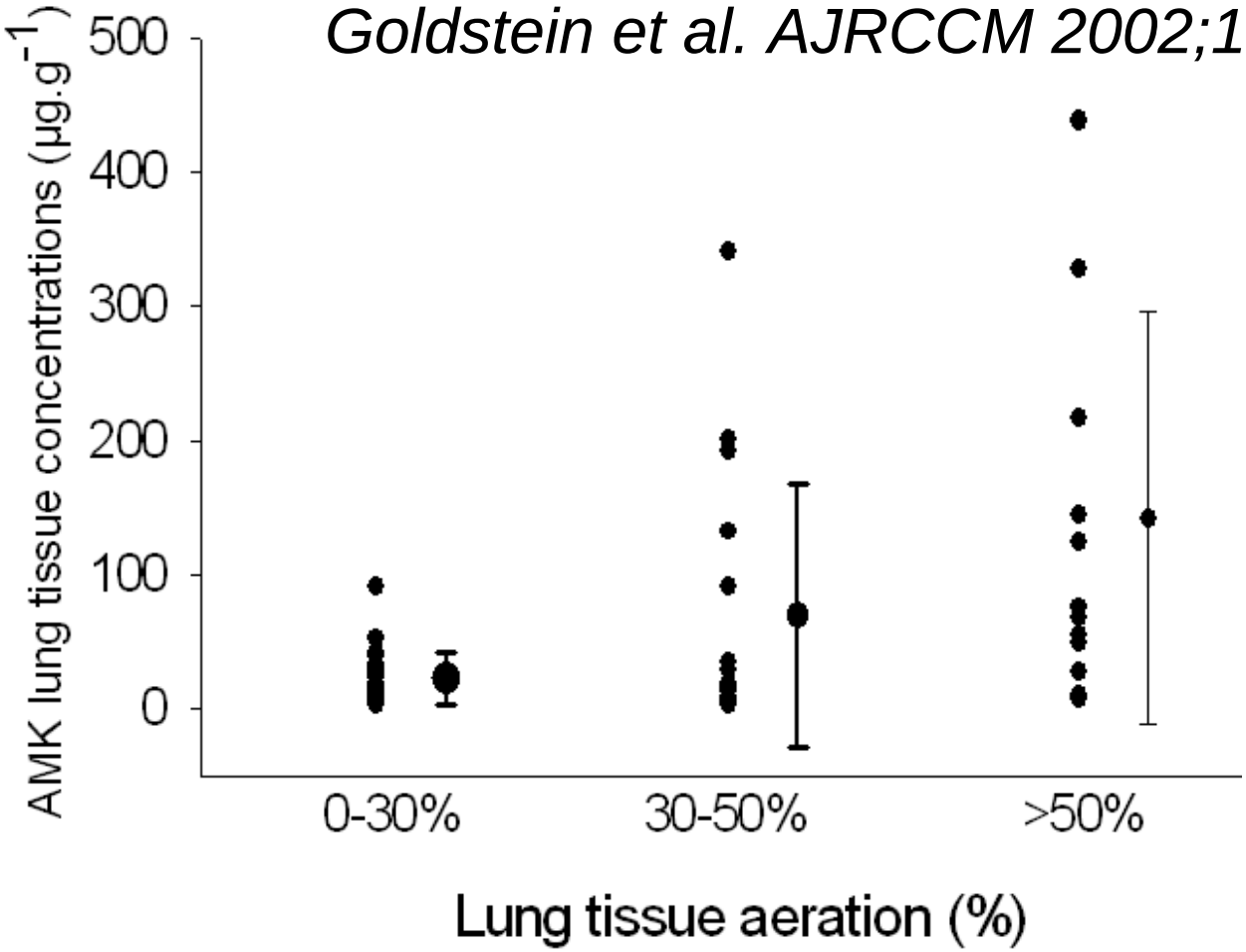
- Piglets on prolonged MV for a severe *E. coli* pneumonia received either a 15 mg/kg IV infusion of amikacin or a nebulization of 45 mg/kg. through an ultrasonic aerosol.
- AMK lung tissue conc. were markedly higher following aerosol, compared to IV.
- Lung deposition following aerosol was less in the more severely infected regions.

Goldstein et al. AJRCCM 2002



Influence of lung aeration on lung tissue penetration of nebulized AMK in piglets with *E. coli* bronchopneumonia

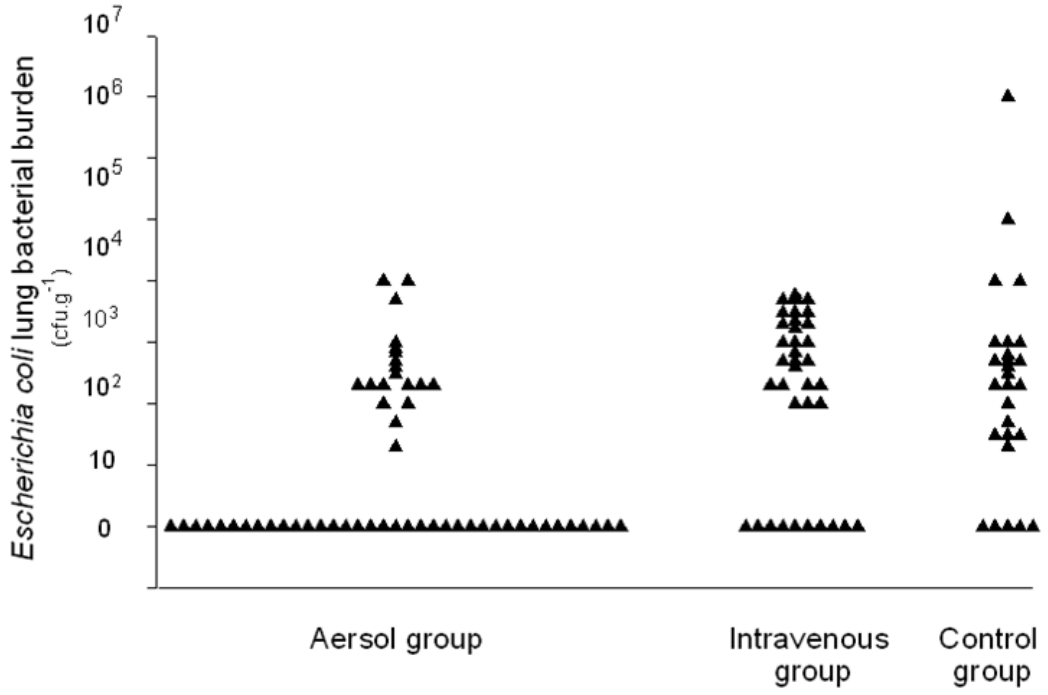
Goldstein et al. AJRCCM 2002;166:1375-81



Efficiency of nebulized AMK in piglets with *E. coli* bronchopneumonia

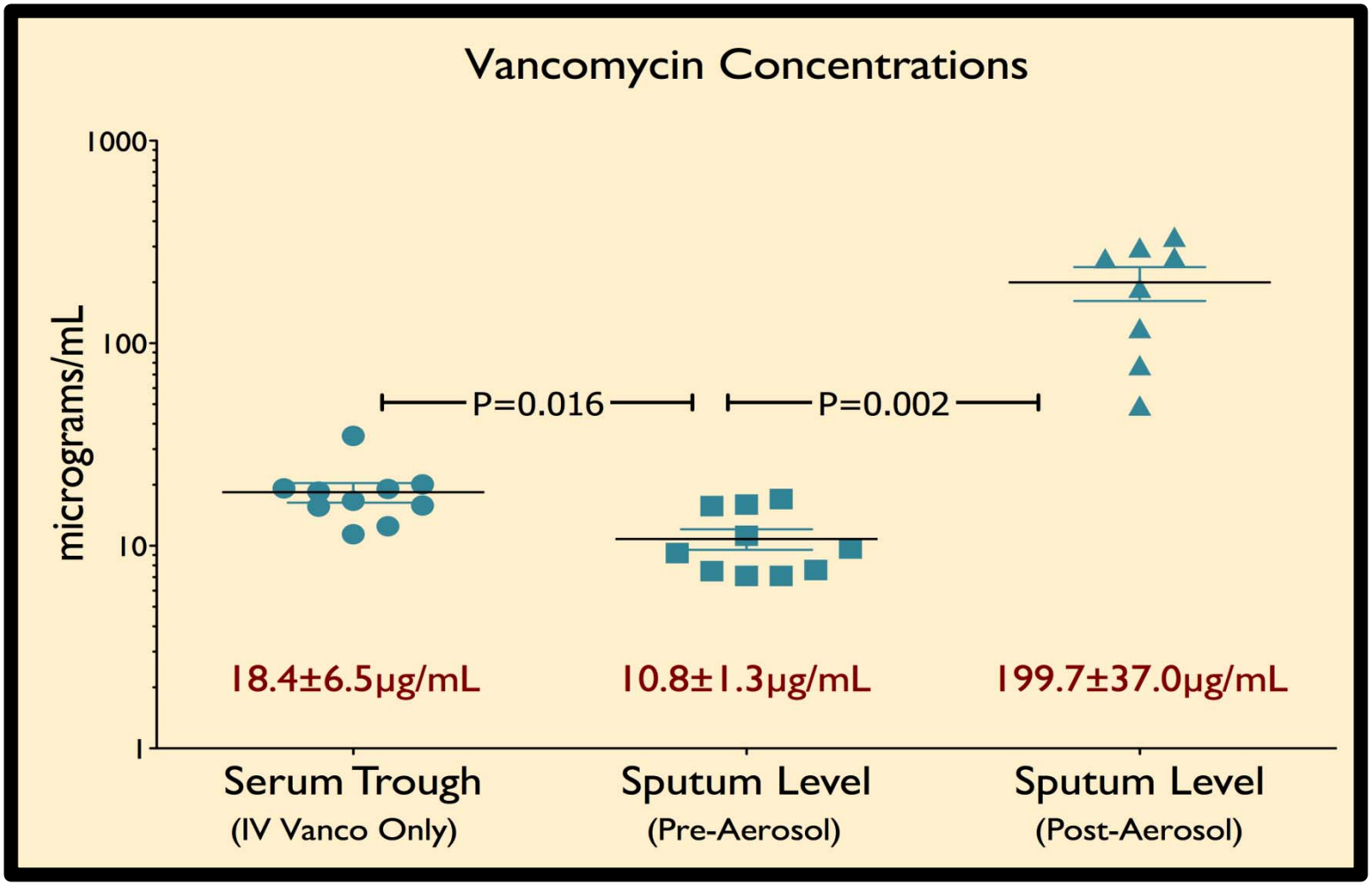
Goldstein et al. AJRCCM 2002;166:1375-81

- Lung bacterial burden of *E. coli* in lung segments collected 1 hour after the 2nd aerosol or IV dose of AMK, or 48 hours after the bacterial inoculation in the untreated control group.
- Each symbol refers to a single lung specimen.
- The lung bacerial burden of lung segments is significantly lower in the aerosol group as compared with the IV or control groups



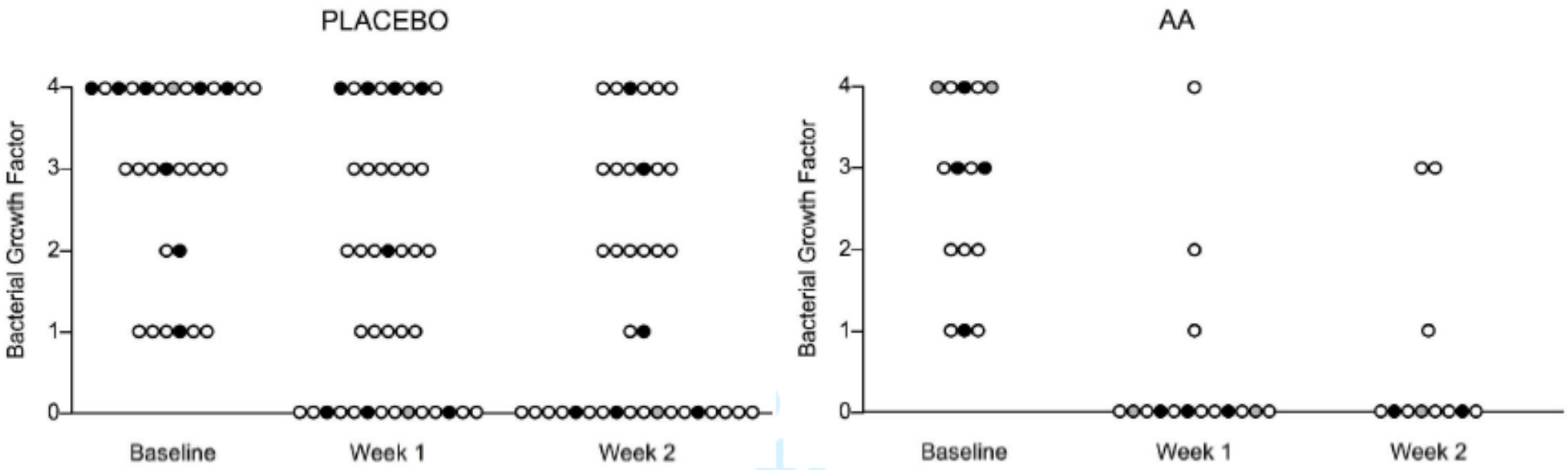
Systemic versus Aerosolized Delivery of Vancomycin (120 mg in 2 ml) in 10 Patients with MRSA Lung Infection

Zarrilli, et al. ATS 2008, A286



Effects of Aerosolized Antibiotics on Bacterial Growth in Tracheal Aspirates of 43 Patients with Ventilator Associated Tracheobronchitis

Palmer LB, et al. CCM 2008, in press



Each filled circle represents *S. aureus*, each shaded circle represents other Gram-positives, and open circles represent Gram-negatives

Effects of Aerosolized Antibiotics on Bacterial Growth in Tracheal Aspirates of 43 Patients with VAP and/or Tracheobronchitis

Palmer LB, et al. CCM 2008, in press

Intensive therapy of VAP/VAT with aerosolized therapy significantly:

- reduced signs of respiratory infection as assessed by CPIS scores (P=0.02),
- increased the number of ventilator free days (10±26 vs 0±26, P=0.07),
- decreased the number of patients who acquired resistant organisms (0/19 vs 8/24, P=0.006),
- and reduced the use of systemic antibiotics.

Inhaled Antibiotics for Ventilator-Associated Pneumonia. *Summary*

1. Better understanding of physiological factors influencing lung deposition of aerosolized particles together with improvement in aerosol technology has rendered possible to markedly increase the delivery of nebulized antibiotics to the deep lung.

Inhaled Antibiotics for Ventilator-Associated Pneumonia. *Summary*

2. However, and even if recent experimental studies are very encouraging, convincing clinical data are still lacking to support the *routine* administration of nebulized antibiotics for treating VAP.