ATHENA
International Conference
Approaching The Severely Infected Patient
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Let's talk about inhaled antibiotics

Ongoing clinical studies

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Faculty disclosure (2012-15)

Advisory Boards

- MERCK USA, Bayer Europe, MSD Europe, Clinigen UK, Cardeas USA, Virogates Denmark, Cempra USA, Tetraphase USA, Gilead UK

Lectures fees

- Pfizer Asian Pacific / USA, Pfizer Korea, Pfizer Taiwan/Australia, MediaHealth New Delhi -India Astellas UK / Japan, Baxter France

Research Grants

- EU-FP_7 Project
- EU-Horizon FP_8 Project

Societies

- ESICM, ERS, ESCMID, International Society of Chemotherapy Asian-Pacific Society of Infectious Diseases

Outcomes in pneumonia in the ICU remain suboptimal with current treatments

Morbidity and mortality in intubated and mechanically ventilated patients with pneumonia remain high, even when using current standard of care antibiotic therapy

↓

Effective empiric initial treatment is required in order to improve clinical outcomes

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MDR gram-negative pneumonia is increasing

↓

Treating MDR gram-negative pneumonia may be compounded in the future by a lack of new antibiotics in development

↓

Success of systemic treatment in critically ill patients may be limited by altered pharmacokinetics (e.g. accelerated plasma clearance)

ATS/IDSA. Am J Respir Crit Care 2005;171:388-416, Kollef KE et al. Chest 2008;134:281-287, Iregui M, et al Chest 2002;122:262-268, Luna CM, et al. Eur Respir J 2006;27:158-164, Dey A, et al. Annals Thorac Med 2007;2:52-7, Boucher HW et al. Clin Infect Dis 2009;48:1-12, Smith B, et al. Chest 2012;141:1327-36, Blot SI, et al. Adv Drug Del Rev 2014;17:3-11.

Inhaled antibiotics could help to improve outcomes !!!

- **Aerosolized antibiotics for inhalation in pneumonia are attractive to:**
  1. Optimize **drug delivery** at the site of infection
  2. Achieving **concentrations in the lung >*in vitro* MIC** of infecting bacteria
  3. Minimize systemic **adverse events**

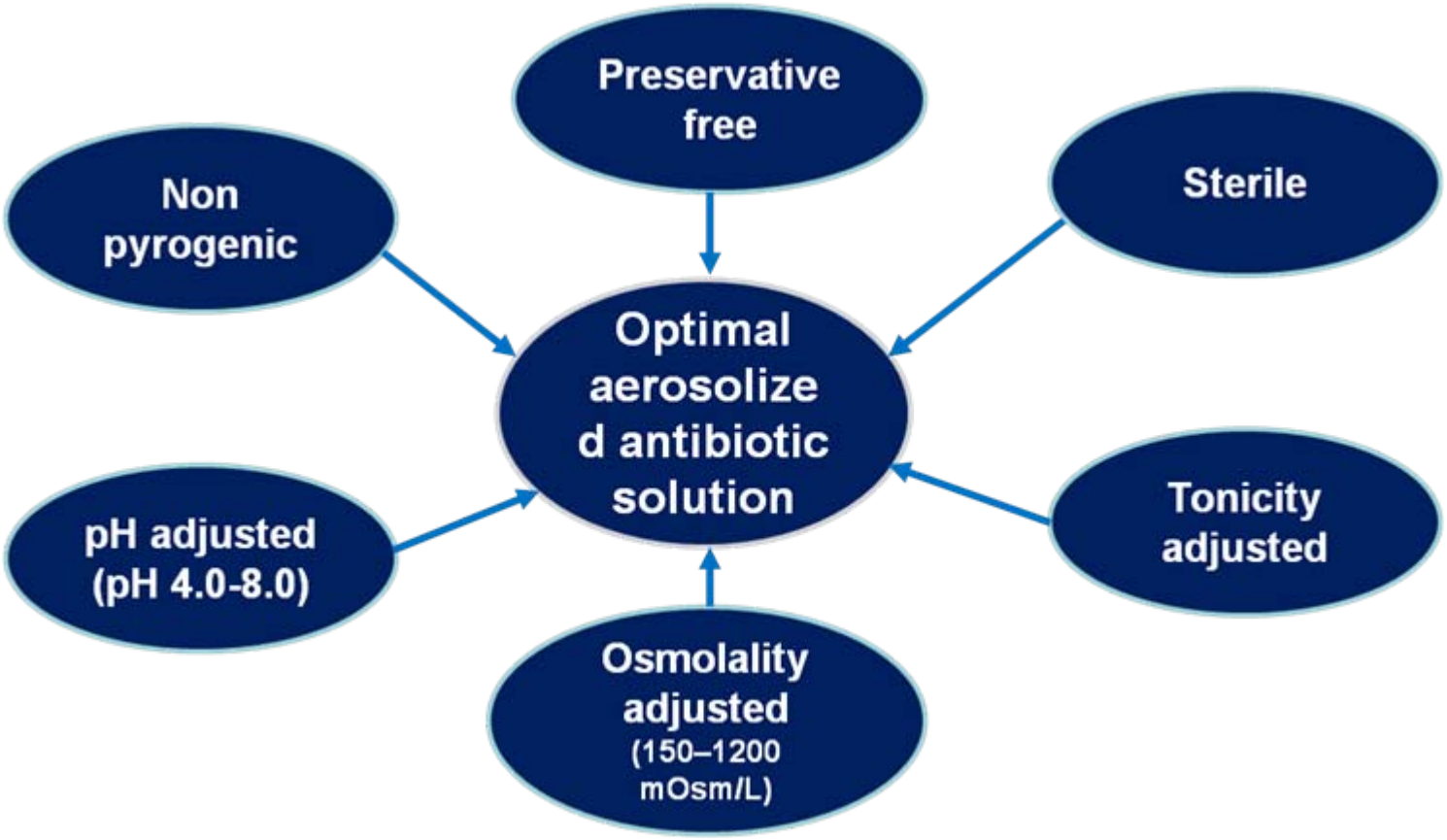
Wood CG. *Exp Rev Anti Infect Ther* 2011;9:993-1000,
Lu Q et al. AJRCCM 2011;184:106-15;

Inhaled antibiotics could help to improve outcomes !!!

- **However…**
  - Optimal means of delivery via aerosol required to overcome potential limitations of IV therapy in this patient population
  - Traditional nebulizers limited by poor delivery efficiency
- **But, recent advances in nebulizer technology have enabled significant improvements**
  - Vibrating mesh technology presents the possibility of highly efficient pulmonary antibiotic administration for critically ill patients with severe respiratory tract infections

Wood CG. *Exp Rev Anti Infect Ther* 2011;9:993–1000, Lu Q et al. AJRCCM 2011;184:106-15, Dhand R. *Respir Care* 2007;52:866–884, Le Brun PP et al. *Pharm World Sci* 2000;22:75–81, Watts AB. *Drug Dev Indust Pharm* 2008;34:913–22

Ideal inhaled antibiotic formulation for aerosolization



Le J et al. *Pharmacother* 2010;30:562-8; Wood C et al. *Pharmacother* 2000;20:166-81; Wood CG. *Exp Rev Anti Infect Ther* 2011;9:993-1000; Abu-Salah T, et al. *Adv Ther* 2011;29:728-47

Amikacin Inhale program

BAYER®

Drug–device combination designed to improve clinical outcomes in gram-negative pneumonia in intubated and mechanically ventilated patients in the ICU in combination with standard of care therapy

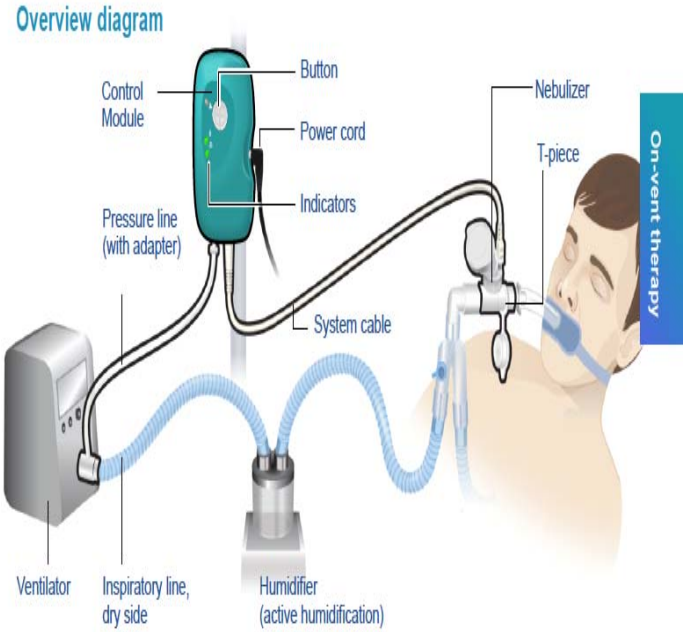
- Amikacin Inhalation Solution is
  - **preservative-free**, and
  - **pH-adjusted** to the lung environment to minimize the risk of bronchospasm

- **On-vent** or **hand-held configuration**
- Air pressure feedback tube and adaptor detect patient's breathing and allow **synchronization of nebulization** to first 75% of inspiration
- PDDS generates **particles with a consistent size** (3–5 µm)
  - suited to deposition throughout airway, including **into deep lung**

Dhand R. Respir Care 2007;52:866-884; Kadrichu N, et al. Critical Care 2013;17(Suppl 2):S29-30; Kadrichu N et al., RDD 2014, Puerto Rico; Kadrichu N et al. ISAM 2013, P-055; Kadrichu N et al. ISAM 2013, P-055; Corkery K et al. ECCMID 2013, P-1636

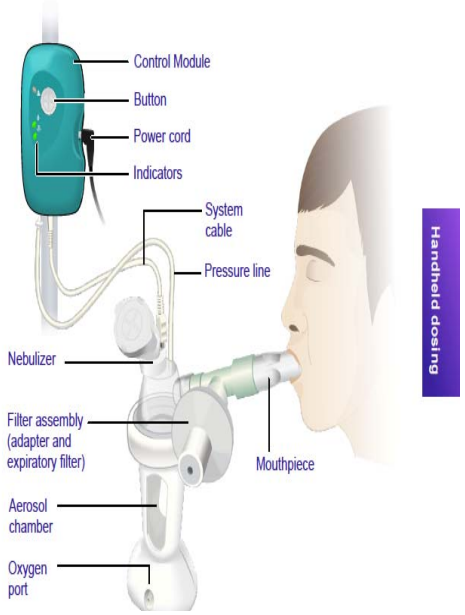
Specially formulated Amikacin Inhalation Solution - Pulmonary Drug Delivery System

On-Vent Configuration



Mesh Nebulizer and Amikacin Inhalation Solution

Hand-held Configuration



Amikacin Inhale, in combination with IV therapy, is currently in Phase 3 clinical studies powered to demonstrate superiority over current IV therapy AND be the first licensed aerosolized antibiotic for use in intubated and mechanically ventilated patients with gram-negative pneumonia

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Current development program for Amikacin Inhale: INHALE

Number of Trials	**Two identical superiority Phase III trials** INHALE 1 – US, CA, CO, BR, MX, AU, PH, KR, CZ, TH, TR, TW INHALE 2 – EU (9), RU, UA, CN, JP (PK sites included)
Trial Design	Prospective, randomized, double-blind, **placebo-controlled** safety and efficacy trial
Indication	Adjunctive treatment of intubated and mechanically ventilated patients with Gram-negative pneumonia
Primary Endpoint	Statistically significant improvement of an absolute change of **14%** of clinical cure rate over Standard of Care (SOC) at TOC visit (assumed clinical cure rate of SOC: 55%)

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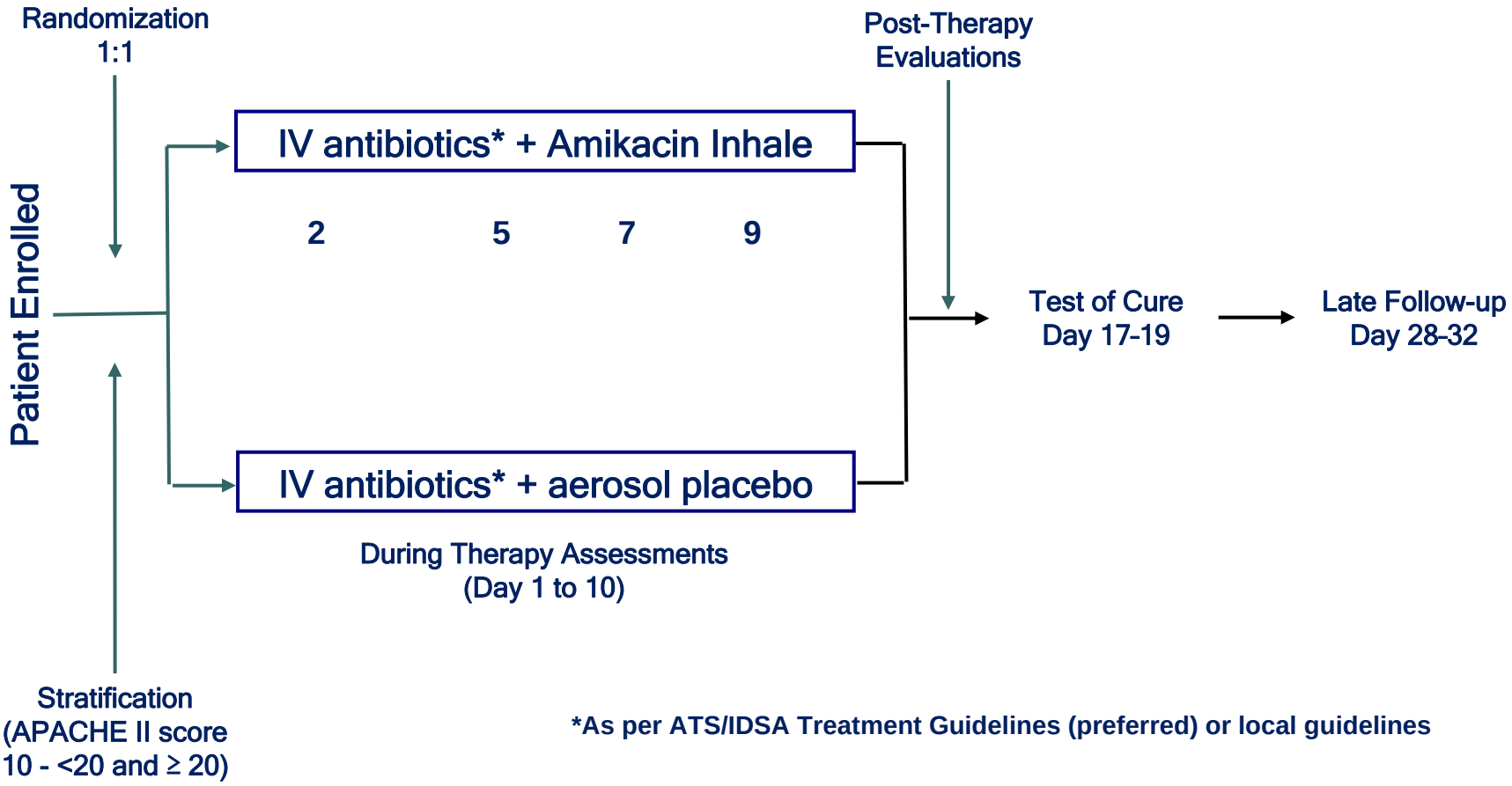
INHALE trial schematic



*As per ATS/IDSA Treatment Guidelines (preferred) or local guidelines

Amikacin INHALE: summary

- Amikacin Inhale is being developed to improve the outcome of intubated and mechanically ventilated patients with gram-negative pneumonia
- The PDDS is a delivery system that can be used in both on-vent and hand-held configurations
  - Both configurations are associated with high amikacin deposition in the lungs
- Amikacin Inhalation Solution has been specially developed
  - To facilitate deposition of amikacin to the deep lung
  - To minimize side effects such as bronchospasm
- Phase 3 clinical trials commenced in 2013

Kadrichu N, et al. Critical Care 2013;17(Suppl 2):S29-30; Kadrichu N et al., RDD 2014, Puerto Rico; Kadrichu N et al. ISAM 2013, P-055; Kadrichu N et al. ISAM 2013, P-055; Corkery K et al. ECCMID 2013, P-1636; Luyt CE et al. J Aero Med Pulm Drug Delivery 2011;24:183-190; Niederman MS et al. Int Care Med 2012;38:263-271

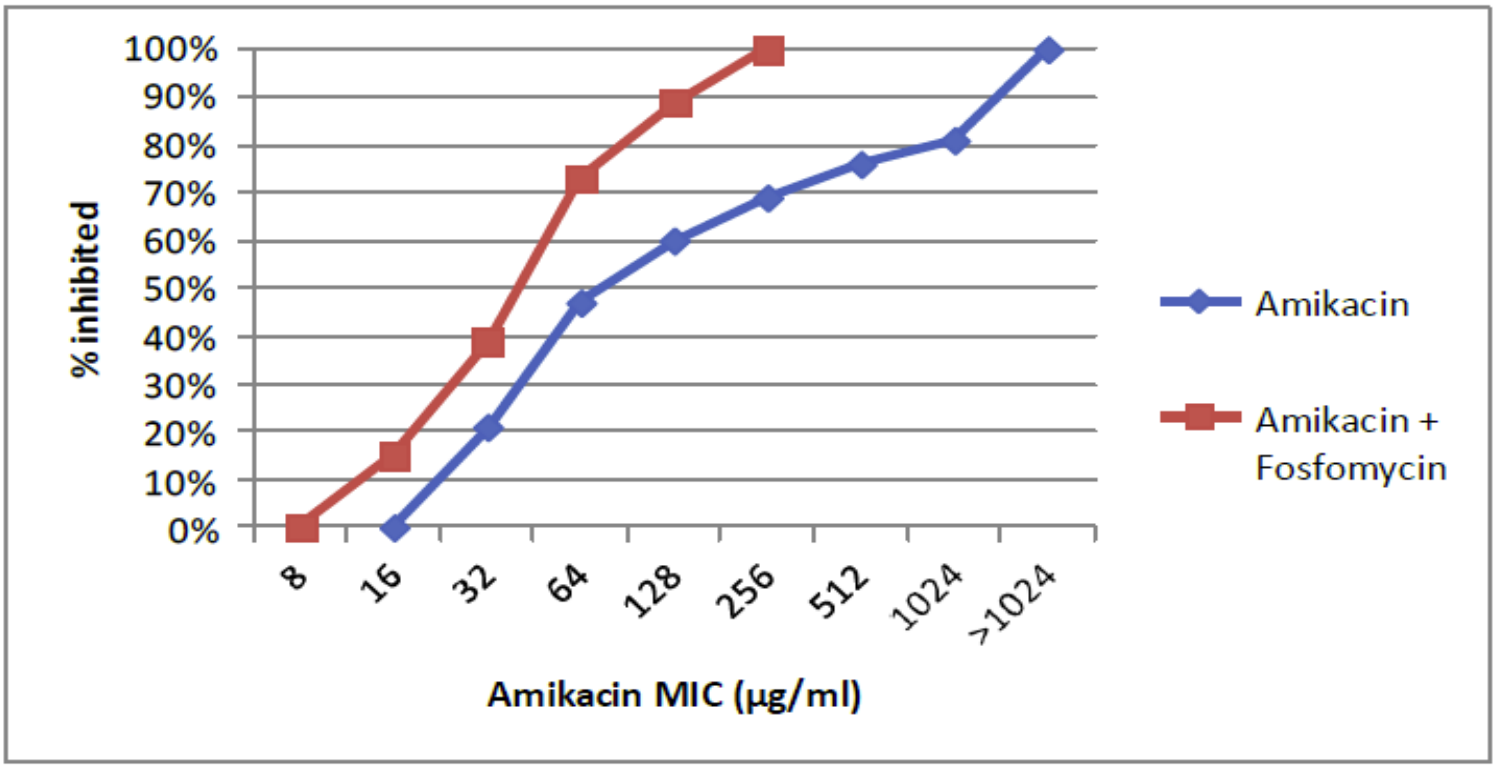
Amikacin/Fosfomycin Synergy

- **Amikacin**
  - Gram negative activity, superior to other aminoglycosides
  - Decreases resistance mutation rate of fosfomycin
  - Known to be safe to airway, low systemic absorption
- **Fosfomycin**
  - Inactivates the first step of cell wall biosynthesis
  - No other antibiotic shares this mechanism of action
  - Gram negative, Gram positive (including MRSA), and anaerobic activity
  - Bactericidal, potentiates amikacin activity in Gram negative bacteria
  - Improves aminoglycoside biofilm activity, improves MIC's in sputum
  - Known to be safe to airway, low systemic absorption

Antimicrob. Agents Chemother. July 2014, 58: 3714-3719.

Amikacin/Fosfomycin Synergy

Cumulative percent inhibited for all 62 amikacin non-susceptible strains tested against amikacin alone (blue) and in a 5:2 ratio with fosfomycin (red).



Highly resistant Gram negative bacteria from 2011 worldwide surveillance study with over 35,000 isolates

Antimicrob. Agents Chemother. July 2014, 58: 3714-3719.

More Details on Synergy Study

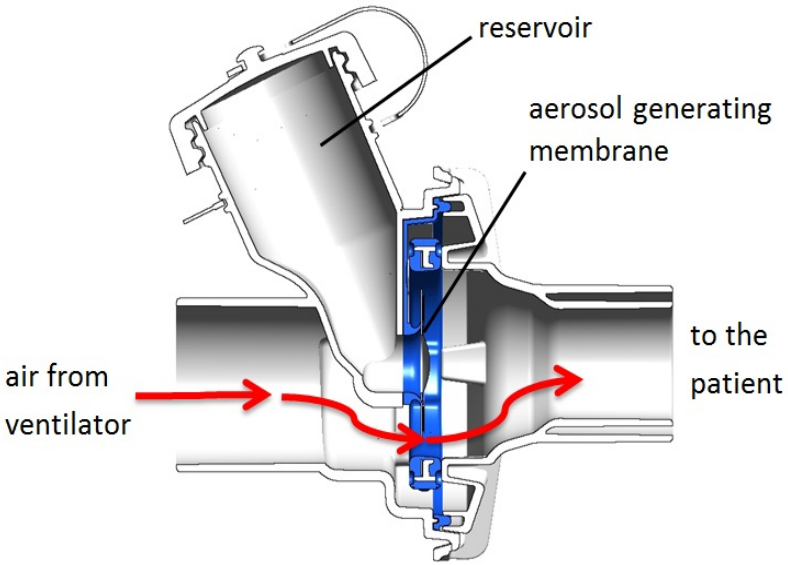
- **Highly resistant organisms**
  - *A. baumannii* (n=21)
    - Includes OXA 23, 24, 51, and 58 resistance genes
  - *K. pneumoniae* (n = 20)
    - Includes KPC 2 and 3 resistance genes
  - *P. aeruginosa* (n=21)
    - Includes GES-1, VIM-2, VIM-4, OXA-2, and OXA-10 resistance genes
- **Fosfomycin MICs max 204 µg/mL in all isolates**
  - However, time above MIC needed for bactericidal activity
  - On average 2X synergy with amikacin
  - Would require 6X administrations per day as monotherapy due to rapid airway clearance

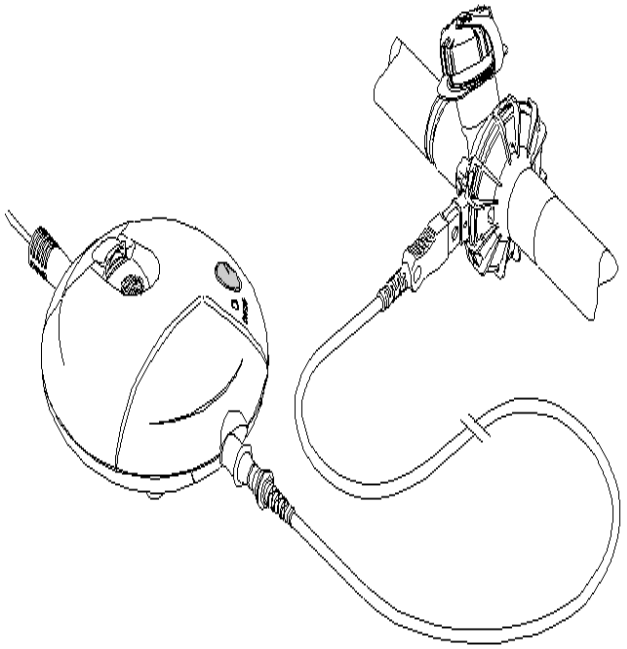
Mucin Inhibition of Antibiotic Activity

Organism	Compound	Standard MIC (MHB)	MIC 2% Mucin
K. pneumoniae **ATCC 700603**	Colistin Sulfate	≤0.06	>128
	Fosfomycin	>128	>128
	Amikacin	0.25	0.5
	FOS/AMK	≤0.25	<0.25
A. baumaunii **ATCC 19606**	Colistin Sulfate	<0.06	>128
	Fosfomycin	32	128
	Amikacin	4	32
	FOS/AMK	2	2

eFlow Inline Nebulizer

- Utilizes the PARI eFlow technology
- Very low increased resistance to flow





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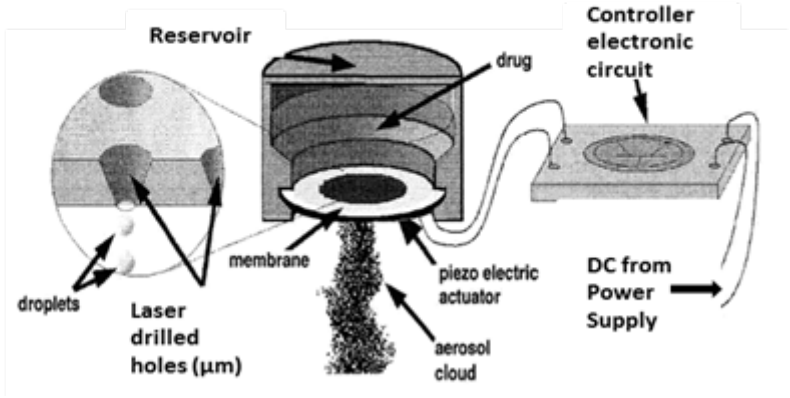
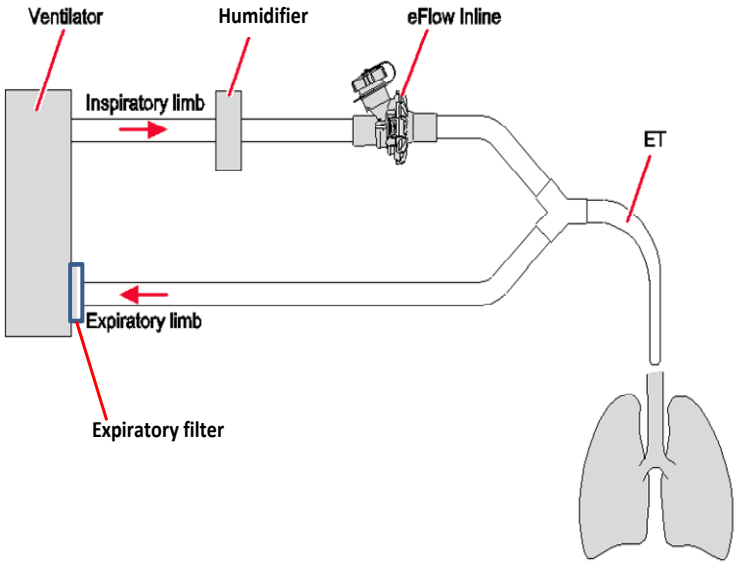
Details on PARI eFlow Inline





- Vibrating membrane containing thousands of micron size holes (laser drilled)
- Membrane excited and oscillates at ~120kHz
- Particle size 3.2 µm with humidity
- Monodispersed aerosol (much tighter distribution than conventional jet nebulizers)
- Fast, silent operation
  - ✓ Treatment time for 6mL ~ 12 minutes
- Single patient use, multiple treatment nebulizer
- Continuous nebulization

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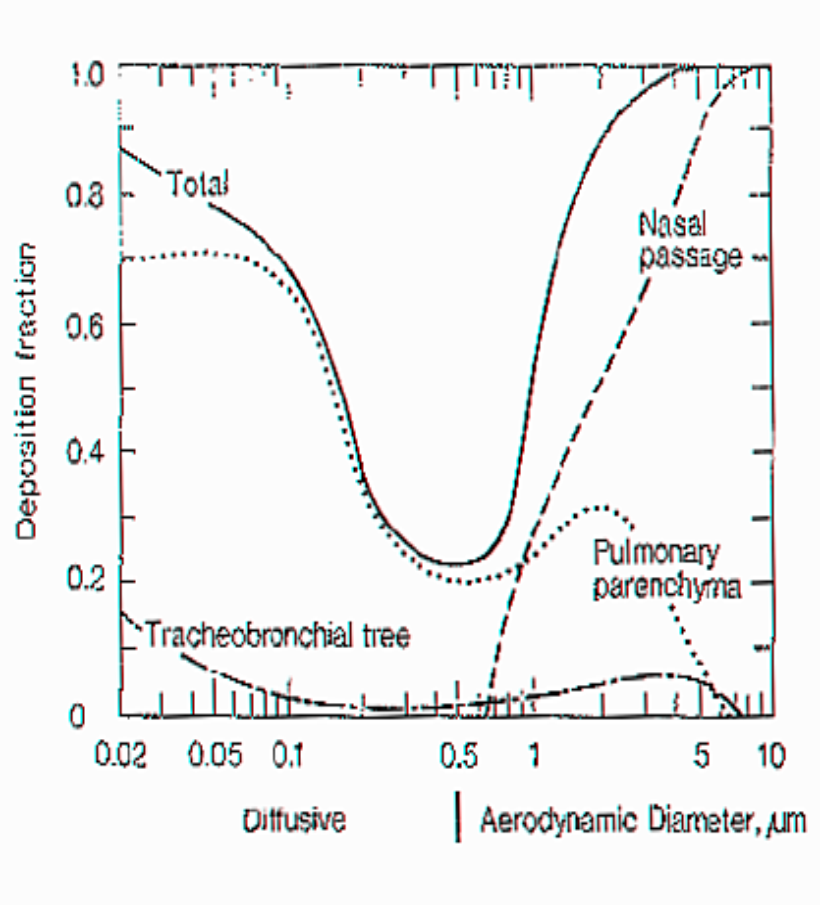
Smaller Particle Sizes Optimal for Lung Parenchymal Deposition



- Approximately 3 micron particle size is optimal for parenchymal delivery
- PARI Inline nebulizer formulation has MMAD of 3.2 microns after humidification
- Other vibrating plate nebulizers have larger MMAD
- Jet nebulizers have MMAD about 5 microns even if humidification turned off (and that takes an hour)

(WG Kreyling, adapted from International Commission on Radiological Protection)

Phase 1 : Design

- **Dose escalation study**
  - 3 patient cohorts of 3 VAP patients
  - Each patient received 3 escalating doses of study drug + 1 volume-matched dose of placebo
  - Also on IV antibiotics
- **Doses of amikacin 50 mg/mL + fosfomycin 20 mg/mL tested**
  - Cohort 1: 2 mL, 4 mL, 6 mL
  - Cohort 2: 4 mL, 6 mL, 8 mL
  - Cohort 3: 6 mL, 8 mL, 10 mL
- **Key endpoints**
  - Safety
  - Tracheal and systemic drug levels

Phase 1 : Results

1. **3/8 patients extubated within 48 hours**
   - Other 5 had underlying conditions keeping them on ventilator
   - VAP cured in all patients
   - No drug related adverse events or any respiratory effects
2. **Fosfomycin tracheal aspirate (6 mL)**
   - Mean peak (15 min) : 9000 µg/g
   - 24 hour: 20 µg/mL
   - MRSA MIC_{90}: 32 µg/mL
   - Twice daily therapy would give 24 hour coverage
3. **Amikacin tracheal aspirate (6 mL)**
   - Mean peak (15 min): 12985 µg/g
   - Gram negative highest MIC 256 µg/mL
   - 36x would overcome sputum inhibition
   - Peak level determines amount of bacteria killing
4. **Serum levels less than one-tenth seen at trough after a typical systemic dose**

J of Aerosol Med Pulm Drug Delivery 2014 27: 441-448

IASIS study : Clinical Design

- **Objectives**
  - Improve outcomes for patients with resistant bacteria
  - Shorten ventilator days for all patients
- **Trial**
  - Randomized placebo controlled study adjunctive to IV antibiotics
  - Gram negative pneumonia confirmed by quantitative culture BAL
  - Inclusion and exclusion criteria select for patients without severe underlying disease that would prevent recovery
  - Study will be completed in Q1 2016
  - ClinicalTrials.gov Identifier: NCT01969799
- **Sites with high incidence of resistant organisms**
  - 10-30% additive mortality in this group
- **Dose and patients**
  - 300 mg amikacin/120 mg fosfomycin for 10 days or placebo in 6 ml solution
  - N=150; 53 centers; international study

Conclusions

- **HAP/VAP**
  - Need to improve outcomes
- **Inhaled antibiotics**
  - promising
  - improve outcome ?
  - Delivery devices, the most important
- **Ongoing studies**
  - 2 RCTs
    - Inhale program : Amikacin through PPDS
    - IASIS study : Amikacin/Fosfomycin through PARI eFlow line
  - **Target : VAP due to MDR**