Earlier Appropriate Antibiotics Treatment of Ventilator Associated Tracheobronchitis: Now or Wait?

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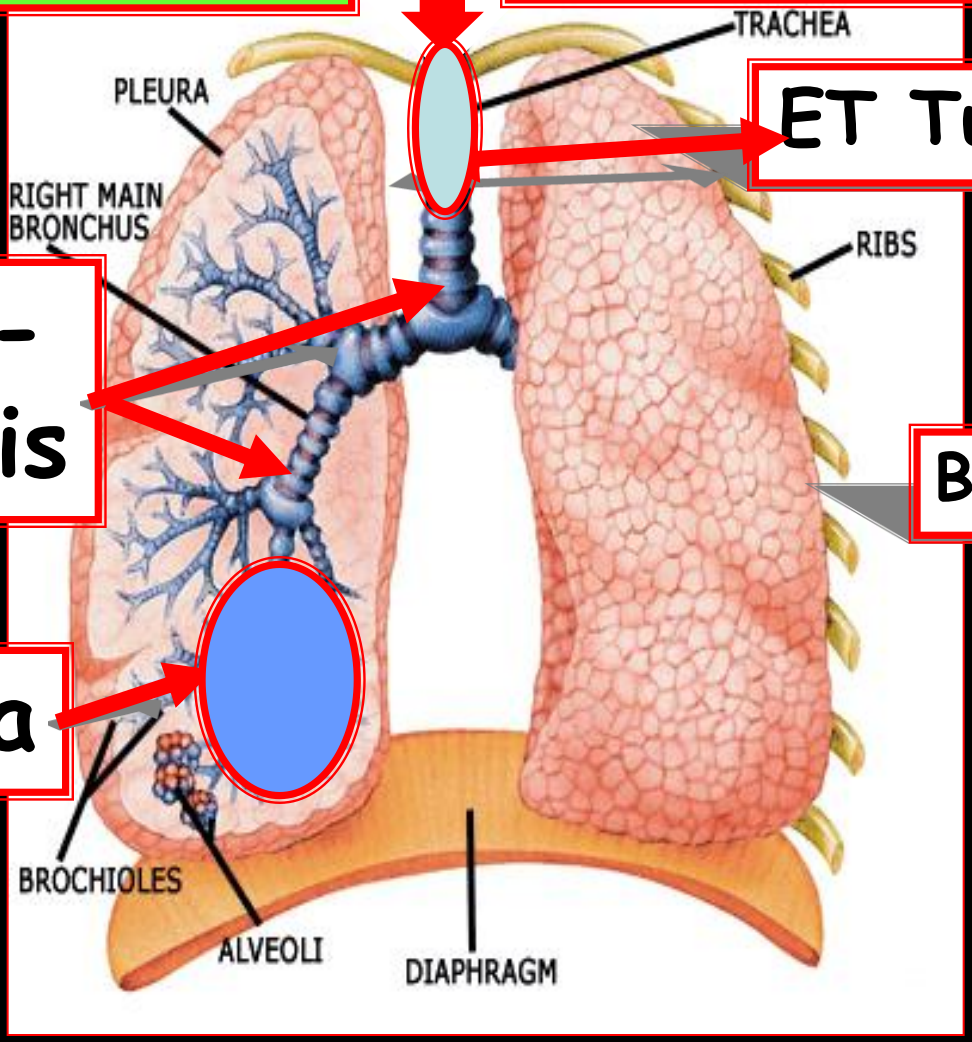
Craven DE, Hudcova J, Rashid J Antibiotic therapy for ventilator-associated tracheobronchitis: a standard of care to reduce pneumonia, morbidity and costs? *Curr Opin Pulm Med* **2015**; **21**: 250-9.

Craven DE, Hudcova J, Craven KA, Scopa C, **Lei Y** Antibiotic treatment of ventilator-associated tracheobronchitis: to treat or not to treat? *Curr Opin Crit Care* **2014**; **20**: 532-41.

Setting: A 1,000,000 Room Hotel

Bacteria

Primary Entry



ET Tube & Cuff

Tracheo-Bronchitis

Bacteremia

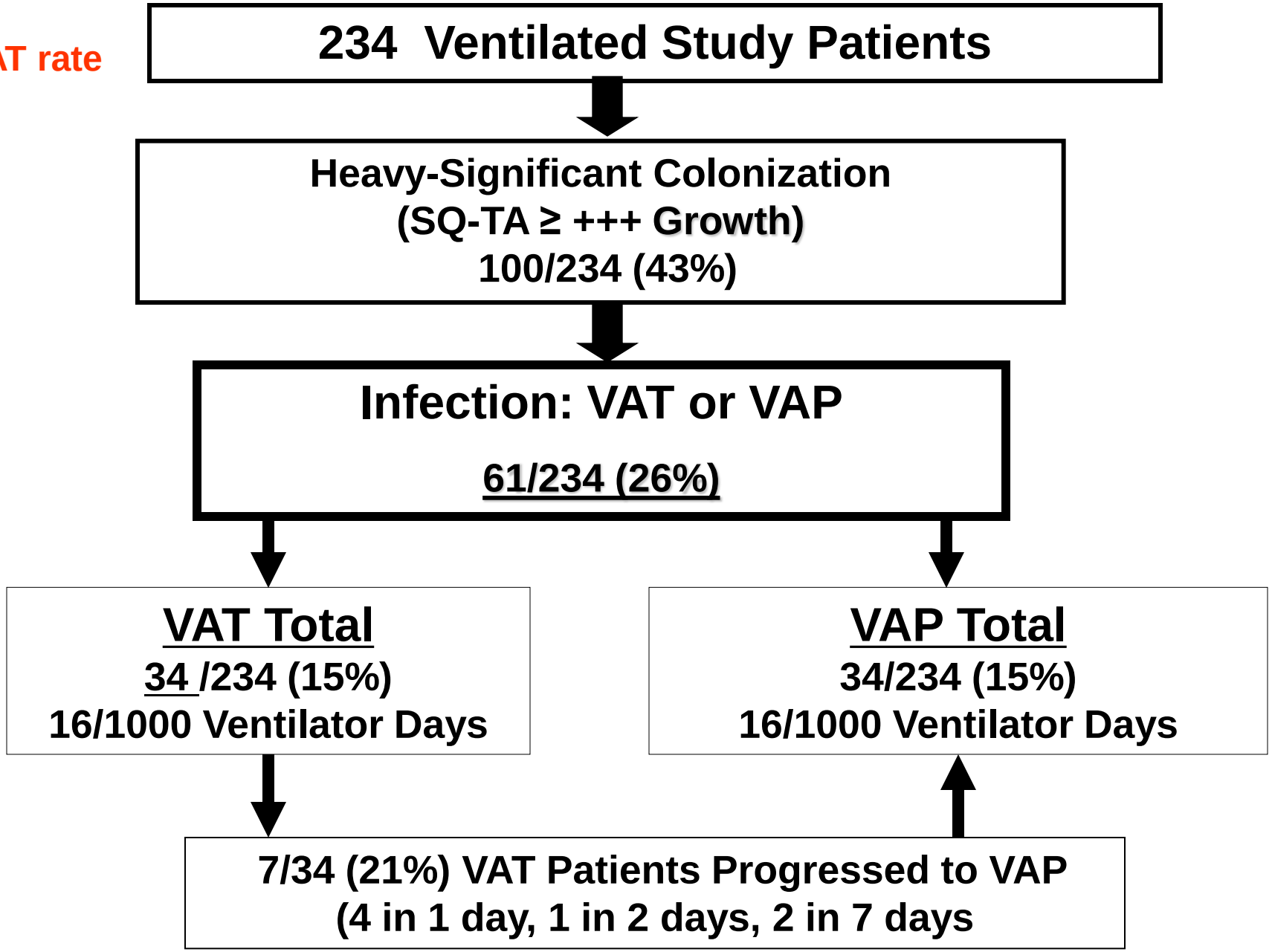
Pneumonia

Diagnosis

	Clinical signs and symptoms[a]	Chest X-Ray or CT scan	Microbiology lung culture methods	
VAT	Temperature: >38°C WBC: >12 000/mm^3 or <4000/mm^3 and purulent sputum[b]	No new lung infiltrate	B-BAL or NB-BAL <10^4 cfu/ml	ETA
			OR	Q-ETA > 10^5 cfu/ml or SQ-ETA > moderate (+++) growth
			NB-PSB < 10^3 cfu/ml	OR
VAP	At least two of the following: 1. Temperature > 38°C 2. WBC: > 12 000/mm^3 or <4000/mm^3 3. Purulent sputum[b] 4. Hypoxia[c]	New and persistent lung infiltrate	B-BAL ≥10^4 cfu/ml	
			OR	Q-ETA > 10^5 cfu/ml or SQ-ETA > moderate (+++) growth
			B-PSB ≥10^3 cfu/ml	

VAT=Ventlator-associated tracheobronchitis VAP=Ventilator-associated pneumonia
WBC=White blood cell B-BAL=Bronchoscopic bronchoalveolar lavage
NB-BAL=Nonbronchoscopic bronchoalveolar lavage B-PSB=Bronchoscopic protected specimen brush
NB-PSB=Nonbrochoscopic protected specimen brush Q-ETA=Quantitative endotracheal tube aspirates
SQ-ETA=Semiquantitative endotracheal tube aspirates

VAT rate



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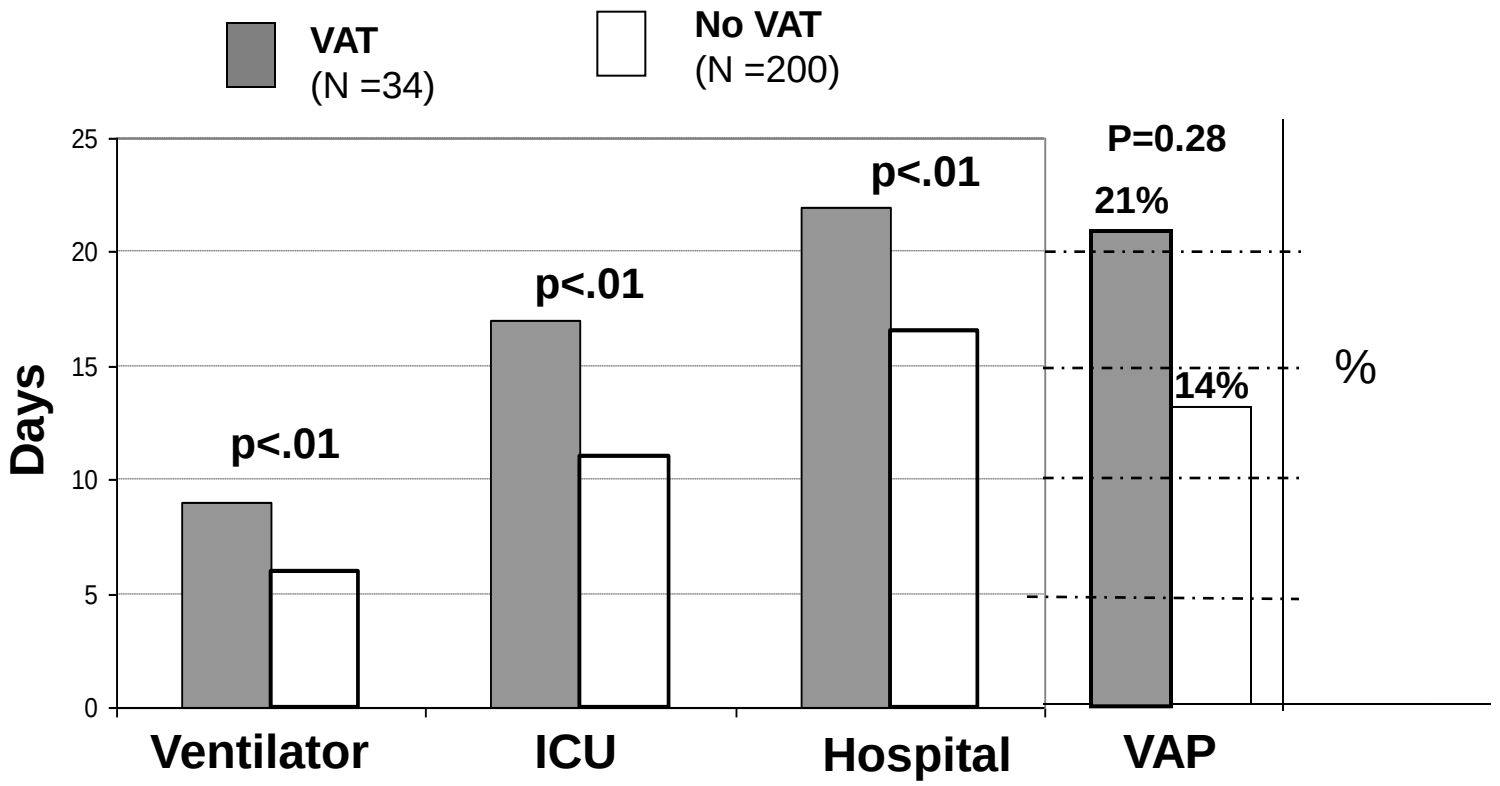
Craven DE, **Lei Y**, Ruthazer R, Sarwar A, Hudcova J., Incidence and outcomes of ventilator-associated tracheobronchitis and pneumonia. *Am J Med* 2013; **126**: 542-9.

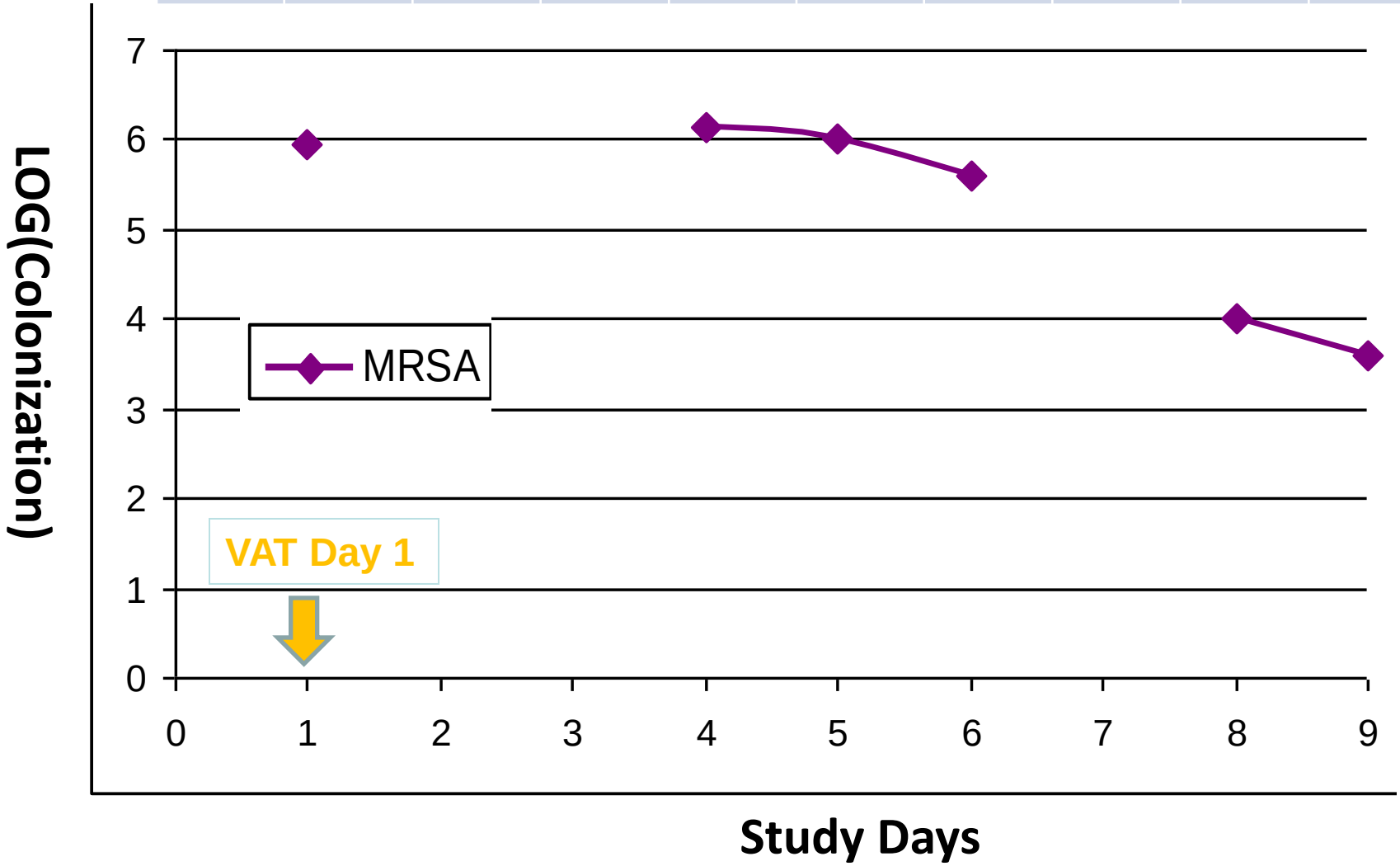
Outcomes


VAT
(N =34)
No VAT
(N =200)
Days
25
20
15
10
5
0
p<.01
p<.01
p<.01
P=0.28
21%
14%
%
Ventilator
ICU
Hospital
VAP

Pathogens	All VAT patients (N=34)	VAT did not progressed to VAP (N=27)	VAT progressed to VAP (N=7)
Gram-Positive Cocci Methicillin-resistant *Staphylococcus aureus*	13 (38%)	12 (44%)	1(14%)
Methicillin-sensitive Staphylococcus aureus	6 (18%)	2 (7%)	4 (57%)
Enterococcus species	2 (6%)	2 (7%)	0
Gram -Negative Pathogens *Psudomonas aeruginosa*	3 (9%)	2 (7%)	1(14%)
Escherichia coli	2 (6%)	1 (4%)	1(14%)
Klebsiella pneumoniae	5(15%)	4(15%)	1(14%)
Klebsiella oxytoca	1 (3%)	0	1 (14%)
Enterobacter species	1(3%)	1(4%)	0
Serratia marcescens	2 (6%)	2 (7%)	0
Proteus mirabilis	1 (3%)	1 (4%)	0
Stenotrophomonas maltophilia	2 (6%)	1 (4%)	1(14%)
Acinectobacter baumannii	1 (3%)	1 (4%)	0
Chryseobacterium species	1 (3%)	1 (4%)	0
Haemophilus influenza	2 (6%)	1 (4%)	1 (14%)
One Pathogen	27 (79%)	23 (86%)	4 (57%)
Two Pathogens	4 (12%)	2 (7%)	2 (29%)
Three Pathogens	3 (9%)	2 (7%)	1 (14%)

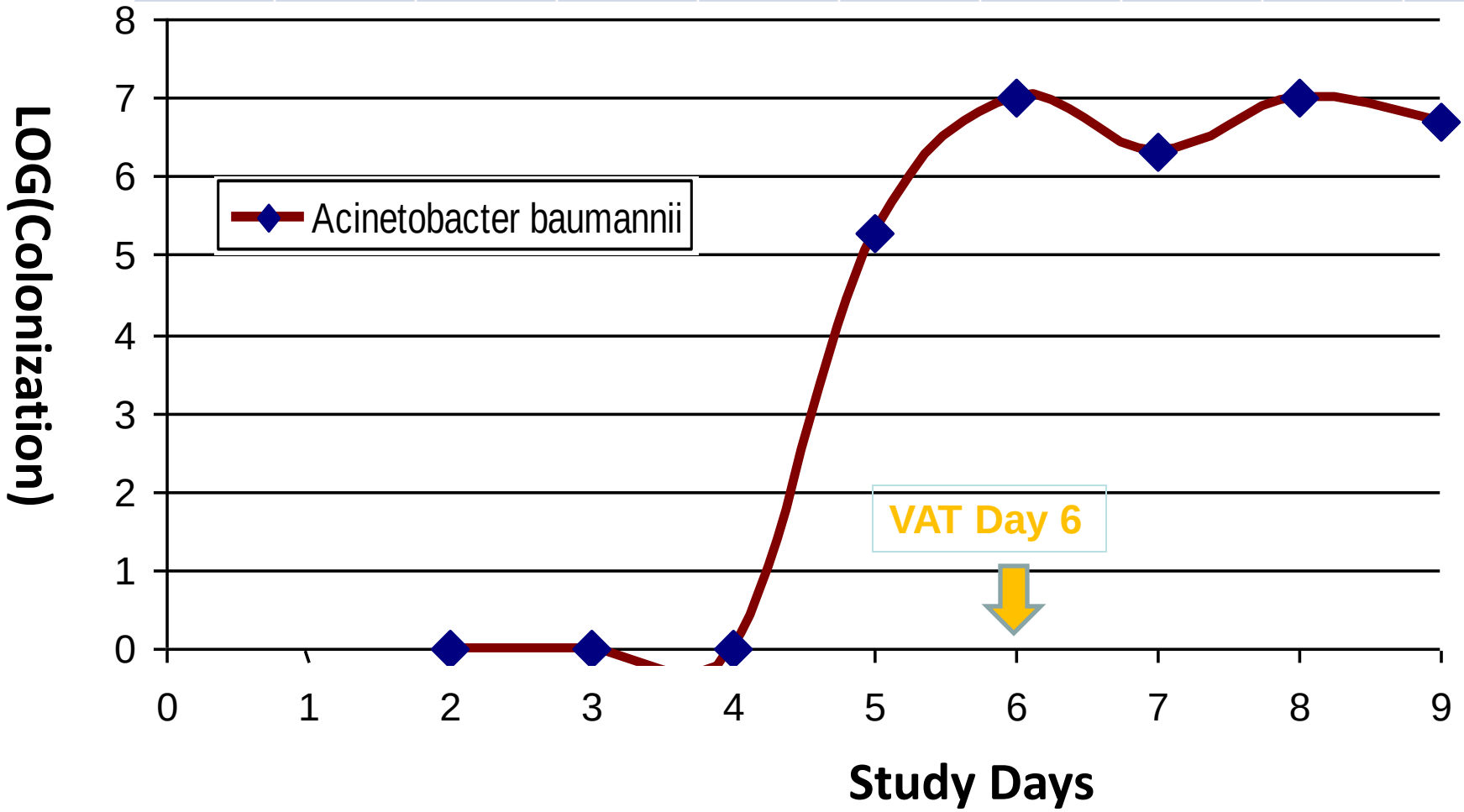
Susceptibility: Vancomycin mic=1 S Linezolid mic=2 S

Day	1	2	3	4	5	6	7	8	9
ABX	Vanco	Vanco	Vanco	Vanco	Vanco	Vanco	Vanco Ceftriaxone	Vanco	Vanco

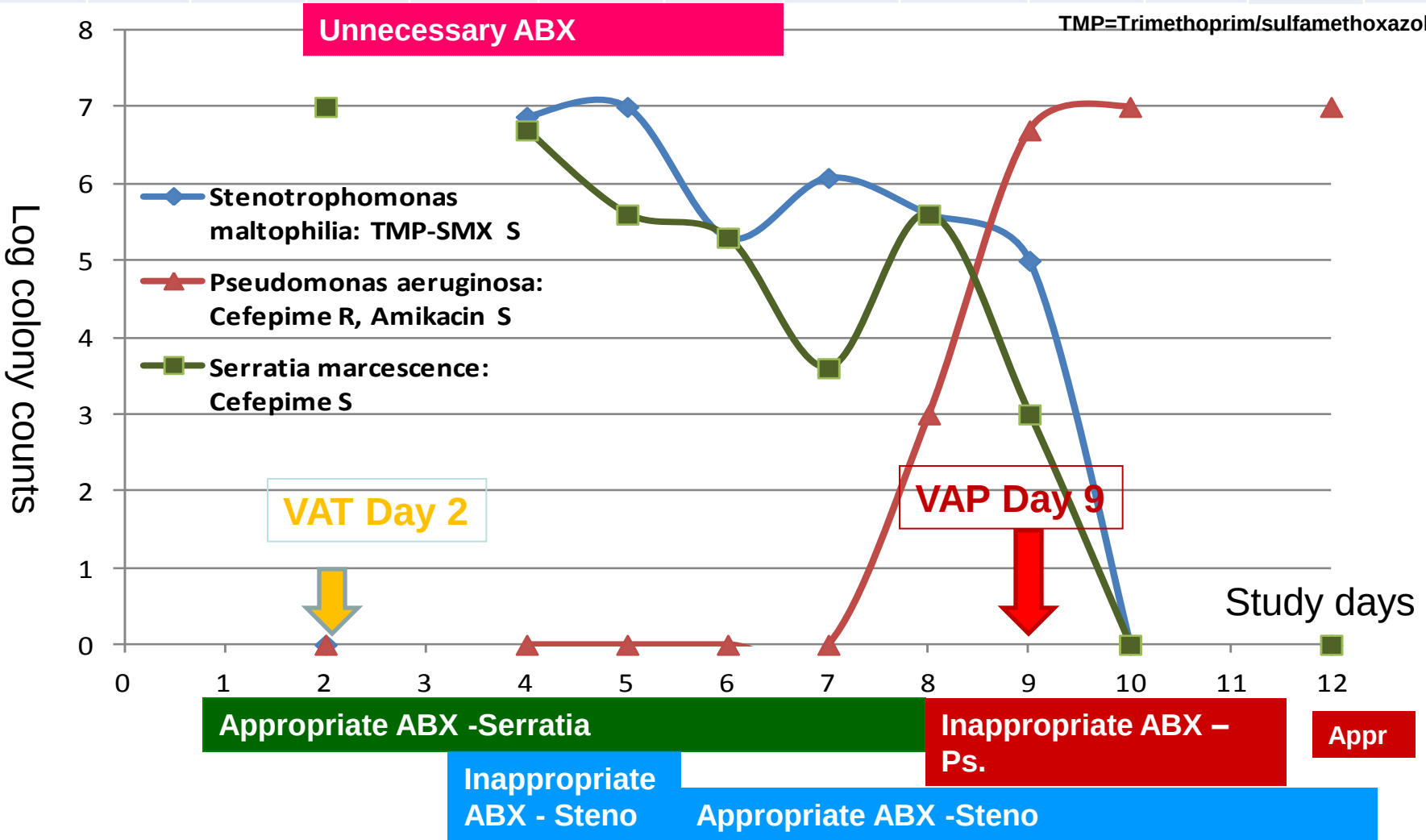


Susceptibility test not available.

Day	1	2	3	4	5	6	7	8	9
ABX	Cef	Cef Vanco	Cef	Cef Vanco	Cef	Cef	Cef N-acetylcystein	Cef N-acetylcystein	N-acetylcystein

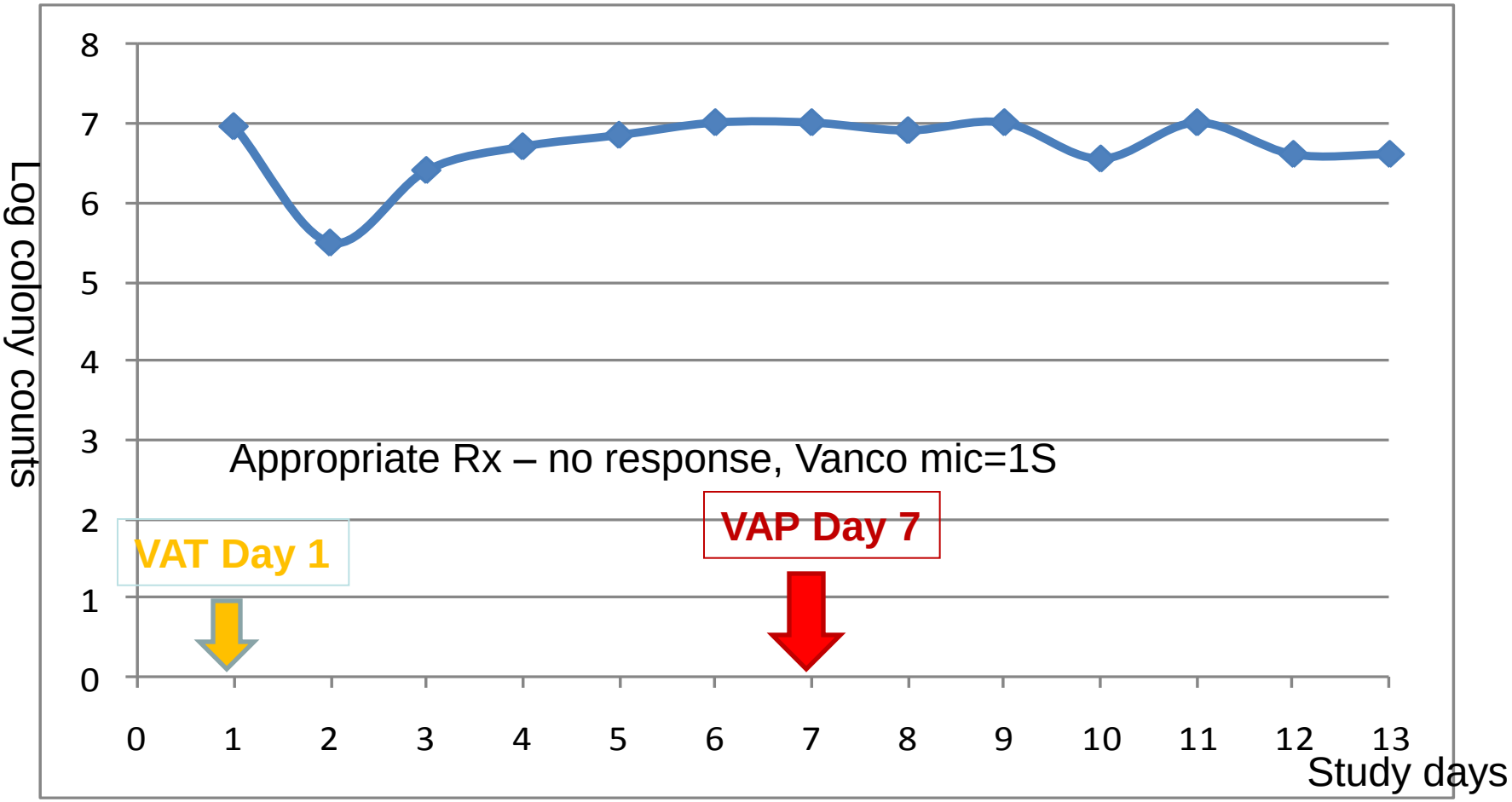


Study Day	1	2	3	4	5	6	7	8	9	10	11	12
ABX	none	CEF	CEF Vanco	CEF Vanco	CEF Vanco	CEF Vanco TMP	TMP	TMP	TMP	TMP	TMP	CEF TMP AMIK
BAC	No specim	Serr.	No specim	Serr. Steno	Serr. Steno	Serr. Steno	Steno	Serr. Steno	Steno	Psa	No specim	Psa



4-Vancomycin 10-Ciprofloxacin 13-flagyl

Day	1	2	3	4	5	6	7	8	9	10	11	12	13
ABX	4,10, 13	4,10, 13	4,10, 13	4,10, 13	4,10, 13	4,10, 13	4,10, 13	4,10, 13	4,10, 13	4,10, 13	4,10, 13	4,5,10, 13	4,5,10, 13
BAC	MSSA	MSSA	MSSA	MSSA	MSSA	MSSA	MSSA	MSSA	MSSA	MSSA	MSSA	MSSA	MSSA



Timely and appropriate antibiotics

VAT → VAP

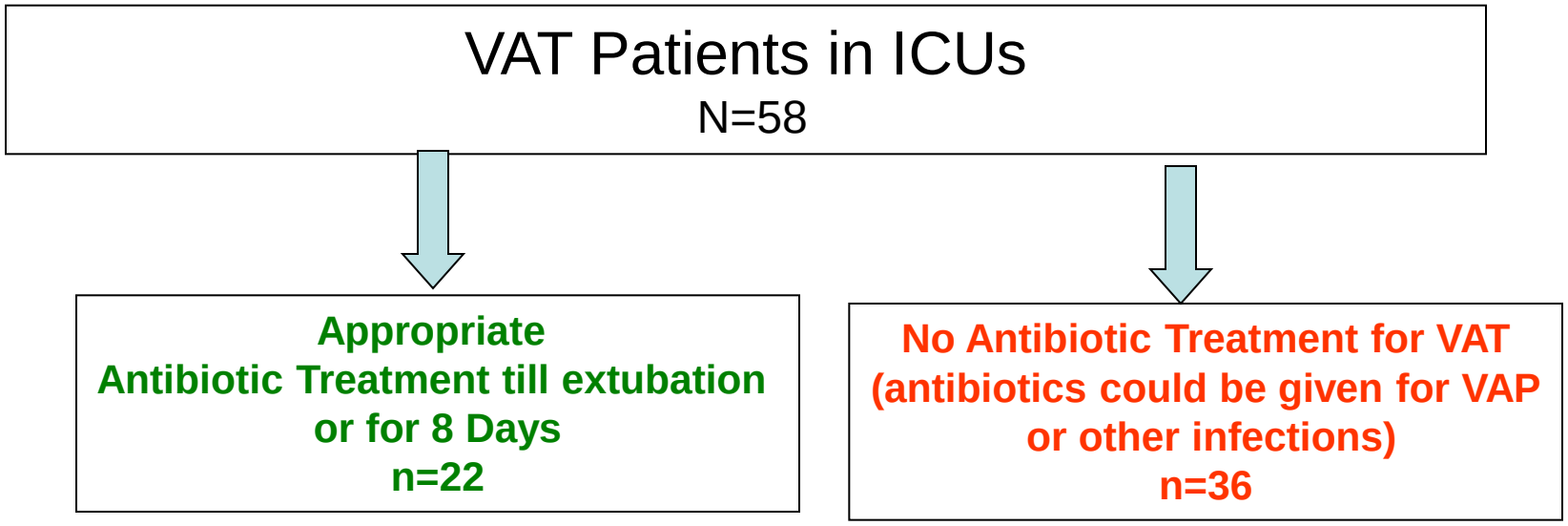
Ventilator days, ICU days, Hospital stay and Mortality?

Systemic antibiotics---Retrospective data analysis

Outcomes	All VAT (N=34)	VAT did not progress to VAP (N=27)	VAT progressed to VAP (N=7)	p value
Ventilator Days (min-max)	10 (4-22)	10 (4-21)	14 (5-22)	0.07
ICU[b] Days (min-max)	18 (6-56)	17 (6-56)	20 (13-52)	0.26
Hospital Days (min-max)	23 (7-107)	23 (7-107)	23 (13-53)	0.69
Mortality	8 (23.5%)	5 (18.5%)	3 (42.9%)	0.18

Timely Appropriate Antibiotics within 24 hours Total N=34 VAT	Yes N=25	No N=9	P Value
VAP rate	**5/25 (20.0%)**	**2/9 (22.2%)**	**1.00**
Ventilator Days (min-max)	11 (4-22)	10(6-18)	0.91
ICU Days (min-max)	20 (6-56)	15 (10-31)	0.14
Hospital Days (min-max)	25 (7-107)	19 (11-51)	0.30
Mortality	6/25 (24.0%)	2/9 (22.2%)	1.00
Average CPIS[c]	5 (4-8)	5 (4-8)	0.75
CPIS at VAT diagnosis	6 (4-10)	5 (4-8)	0.20

Systemic antibiotics-Randomized trial



VAP rate:	**13%**	vs	**47%**	p=0.011
Vent-Free:	**12 days**	vs	**2 days**	p<.001
ICU Mortality:	**18%**	vs	**47%**	p=0.047

Nseir S, Favory R, Jozefowicz E *et al.* Antimicrobial treatment for ventilator-associated tracheobronchitis: a randomized, controlled, multicenter study. *Crit Care* 2008; **12**: R62.

Systemic antibiotics

A prospective observational multicenter study

A largest multicentre study that prospectively follows VAT as the main ventilator-associated complication occurring in the critically ill patient

Antibiotic treatment was considered **appropriate** when at least one antibiotic active *in vitro* on all organisms causing VAT was administrated to treat VAT.

Antibiotic treatment for VAT was at the discretion of attending physicians.

Selective digestive decontamination, and prophylactic aerosolized antibiotics were not used during the study period.

VAT N=122	Appropriate antibiotics N=58	Not appropriate antibiotics N=64	P value
VAP rate	2(3.4%)	15(23.4%)	0.003

OR [95% CI] 0.12[0.02-0.59], *P* = 0.009

Nseir S, Martin-Loeches I, Makris D *et al.*
Impact of appropriate antimicrobial treatment on transition from ventilator-associated tracheobronchitis to ventilator-associated pneumonia.
Crit Care 2014; **18**: R129.

Aerosolized antibiotics

Choice of aerosolized antibiotic in the randomization arm was defined on the basis of the Gram stain of the aspirated tracheal secretions. Gram-positive bacteria were treated with vancomycin HCL, 120 mg in 2mL normal saline every 8 hrs, and Gram negative organisms were treated with gentamicin-sulfate, 80 mg in 2 mL normal saline every 8 hrs. Both antibiotics were administered serially if Gram-positive and Gram negative organisms were present. Medication and placebo were nebulized via an AeroTech II nebulizer (CIS-US, Bedford, MA).

Decrease VAP rate

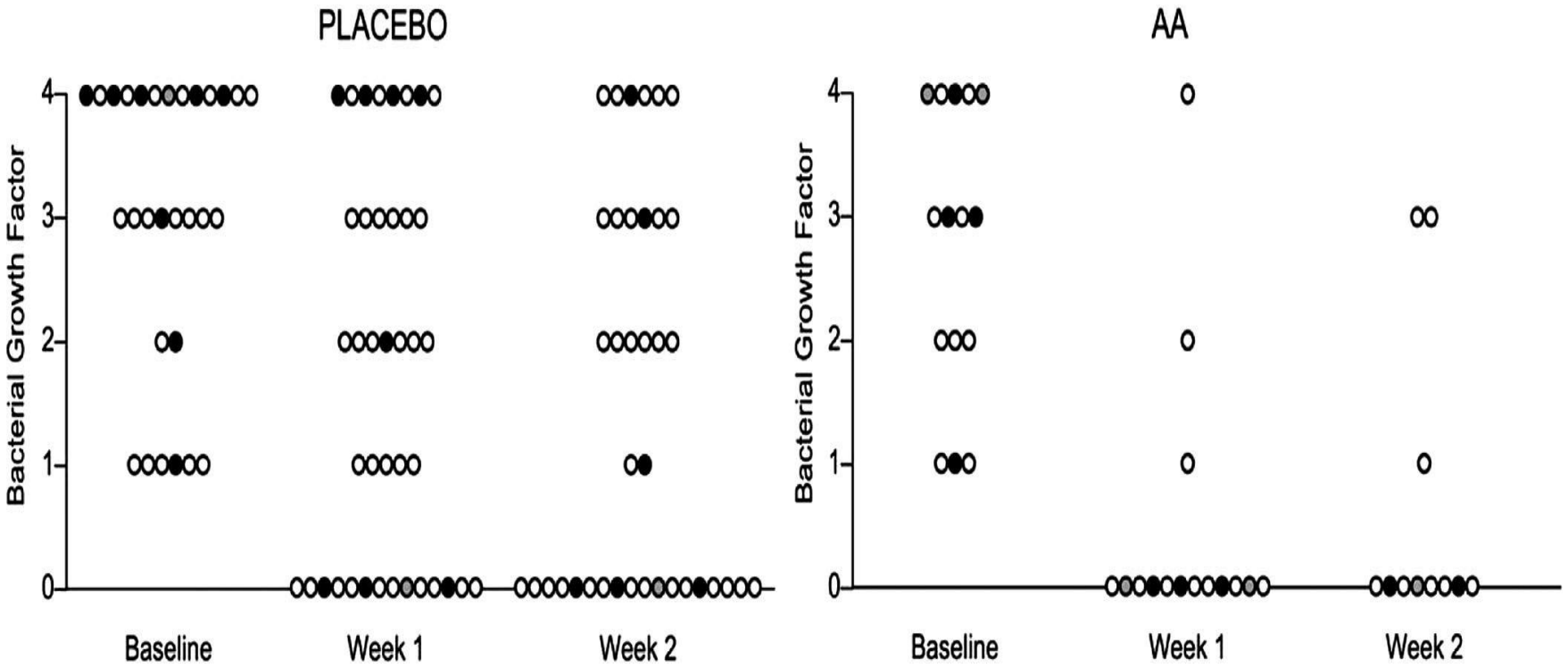
	Aerosolized Antibiotics N=19		**Placebo N=24**		P value
	n(%)	P value	n(%)	P value	
Treatment Day 1	14/19(73.6)		18/24(75.0)		1.00
End of treatment	6/19(31.6)	0.007	14/24(58.3)	0.28	0.12
Treatment Day 14	5/14(35.7)	0.06	11/14(78.6)	1.00	0.05

Palmer LB, Smaldone GC, Chen JJ *et al.*
Aerosolized antibiotics and ventilator-associated tracheobronchitis in the intensive care unit.
Crit Care Med 2008; **36**: 2008-13.

Aerosolized antibiotics

- Gram negative organisms
- Staphylococcus aureus
- Other gram-positive organisms

Decrease bacterial growth



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Aerosolized antibiotics and ventilator-associated tracheobronchitis in the intensive care unit.
Crit Care Med 2008; **36**: 2008-13.

Aerosolized antibiotics

- **Decrease white blood cell count**

AA: 13.6→ 9.2
Placebo: 12.4→ 14.9

P=0.016

- **Decrease use of systemic antibiotics**

AA: 8/19 (42%)
Placebo: 17/24 (71%)

P=0.042

- **Improve weaning from mechanical ventilation**

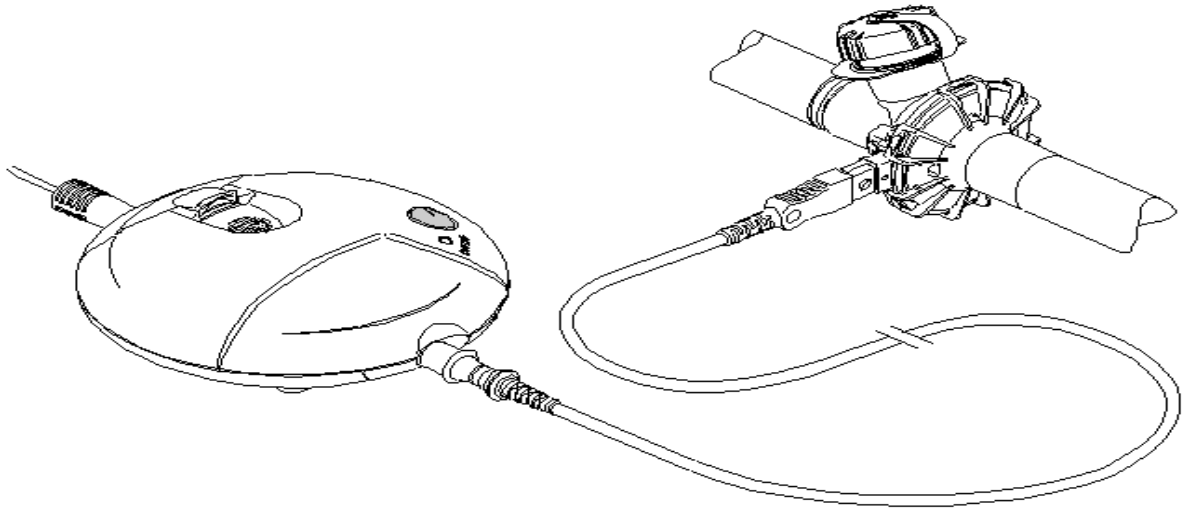
AA: 80%
Placebo: 45%

P=0.042

Palmer LB, Smaldone GC, Chen JJ *et al.*
Aerosolized antibiotics and ventilator-associated tracheobronchitis in the intensive care unit.
Crit Care Med 2008; **36**: 2008-13.

Need more evidence

Aerosolized antibiotics trials in Lahey Hospital



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A Path to Treat Highly Resistant Bacteria

- Aerosolized antibiotics
  - Up to 1,000 fold higher concentrations of antibiotics
    - **Overcomes resistant mechanisms**
  - Low systemic absorption
    - **Safer than IV's**
- To succeed
  - **Need safe antibiotics that can kill bacteria**
  - **A delivery system that can get it into the lungs**
  - **A clinical plan to prove it**

Cardeas Study
Amikacin/Fosfomycin Inhalation System (AFIS)
vs
Placebo Therapy
For VAP Due to Gram-Negative Bacilli

All Patients Get Standard IV Antibiotics

A Randomized, Double-Blind

Placebo-Controlled Aerosol Therapy

Multicenter Trial

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Cardeas Study
Amikacin/Fosfomycin Inhalation System (AFIS)
vs
Placebo Therapy
For Gram-negative and/or Gram-positive Bacterial Colonization

- **Amikacin 300 mg + Fosfomycin 120 mg BID**

  Therapy for days 1-5

- **All patients: open label therapy: days 6-10**

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Why not Cephalosporins or Carbapenems as an Aerosol?

- Ceftazidime aerosols

  ---Fast airway clearance required q 3 h administration as mechanism is time above the MIC

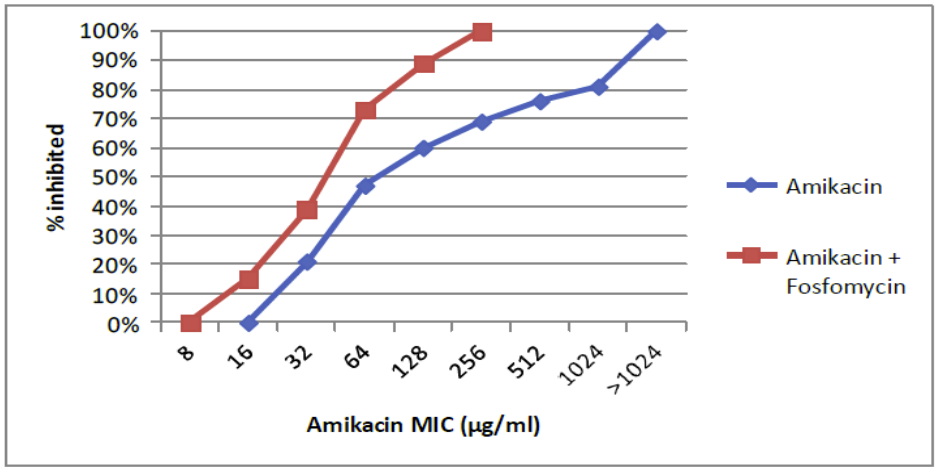
  – Requires propofol to prevent ventilator bucking
  – Large doses can clog expiratory filter, has caused respiratory arrests
- Carbapenems aerosols cause allergic reactions

Lu Q, Yang J, Liu Z, Gutierrez C, Aymard G, Rouby JJ **Nebulized ceftazidime and amikacin in ventilator-associated pneumonia caused by Pseudomonas aeruginosa.** *Am J Respir Crit Care Med* 2011; 184: 106-15.

Hilas O, Ezzo DC, Jodlowski TZ **Doripenem (doribax), a new carbapenem antibacterial agent**. *P T* 2008; **33**: 134-80.

Amikacin and Fosfomycin are Synergistic

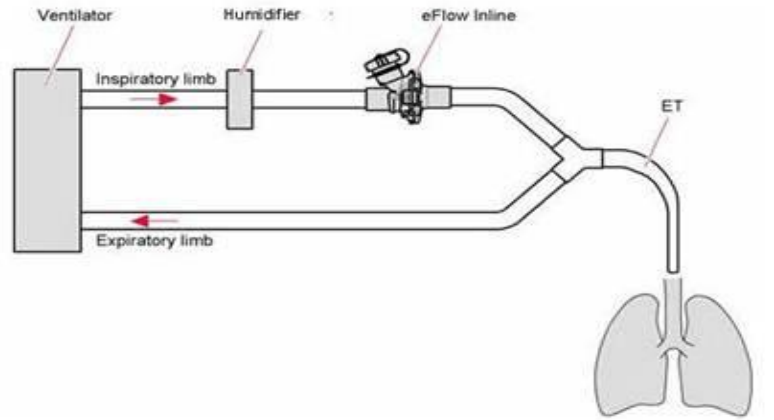
- Amikacin
  - Gram negative activity, superior to other aminoglycosides
  - Decreases resistance mutation rate of fosfomycin
  - After aerosol administration, safe to airway and low systemic absorption
- Fosfomycin
  - Inactivates the first step of cell wall biosynthesis
  - No other antibiotic shares 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, decreases sputum antagonism
  - Known to be safe to airway, low systemic absorption



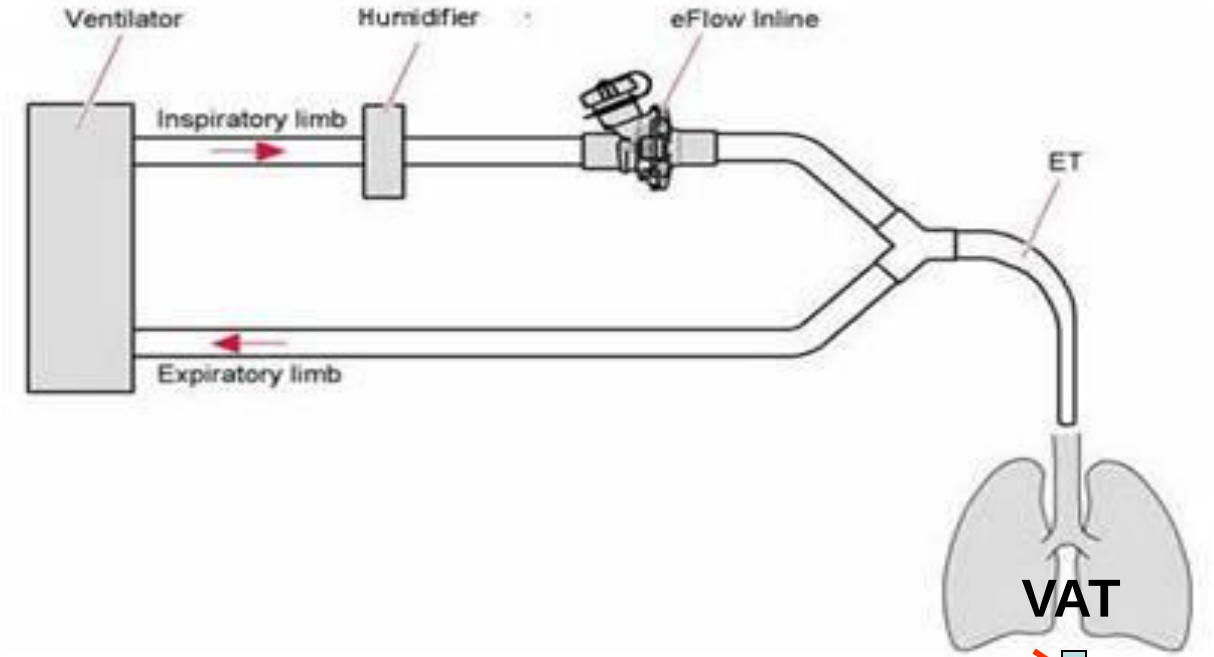
Am J Respir Crit Care Med 2013; 187:A3236

eFlow® Inline Investigational Nebulizer

- Single patient use, multiple treatment nebulizer
- Reusable controller
- Continuous nebulization
  - Inspiratory arm acts as reservoir chamber
  - Bias flow needs to be < 3 lpm
- Vibrating plate technology
  - Small particle size
  - Humidity left on
- Differences from other nebulizers
  - Multiple use
  - Does not require multiple circuit breaks
  - Small particle size provides less rain out and better peripheral delivery



Propose to treat VAT



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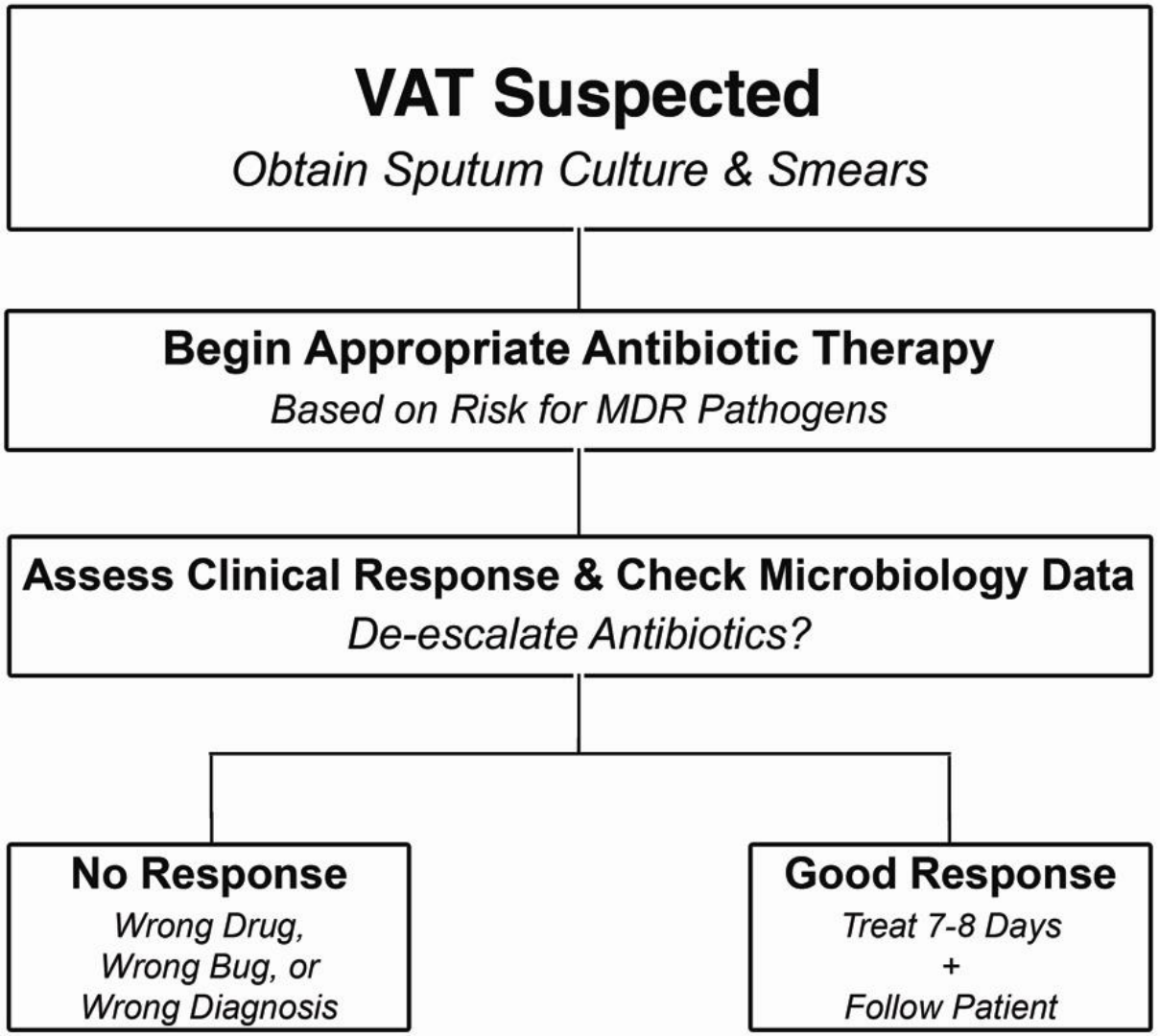
Recommendations for antibiotics for VAT/VAP

Bacterial pathogens	Combination antibiotic therapy
Gram-negative bacilli	
	Antipseudomonal cephalosporin
	(e.g., cefepime, ceftazidime)
	OR
Escherichia coli	Antipseudomonal carbapenem
	(e.g., imipenem or meropenem)
	Antipseudomonal penicillin
	(e.g. piperacillin–tazobactam)
Klebsiella pneumoniae	PLUS
	Antipseudomonal fluoroquinolone
	(e.g., ciprofloxacin or levofloxacin)
	OR
Enterobacter species	Aminoglycoside
	(e.g., amikacin, gentamicin, or tobramycin)

Bacterial pathogens	Combination antibiotic therapy
Pseudomonas aeruginosa	
Antibiotic Resistant Gram-negative bacalli (GNB)	
ESBL+ *Klebsiella pneumoniae* and other GNRs	Carbapenem
Acinetobacter baumannii	Carbapenem +/– aminoglycoside IV
	OR
	Colistin IV +/– aerosolized aminoglycoside
	Fosfomycin
Stenotrophomonas maltophilia	Trimethoprim–sulfamethoxazole
Legionella pneumophilia	Fluoroquinolone or macrolide
	(ciprofloxacin, levofloxacin or azithromycin)
Gram-positive cocci	
MSSA	Oxacillin or Cefazolin
MRSA	Vancomycin or linezolid


VAT Suspected
Obtain Sputum Culture & Smears
Begin Appropriate Antibiotic Therapy
Based on Risk for MDR Pathogens
Assess Clinical Response & Check Microbiology Data
De-escalate Antibiotics?
No Response
Wrong Drug,
Wrong Bug, or
Wrong Diagnosis
Good Response
Treat 7-8 Days
+
Follow Patient