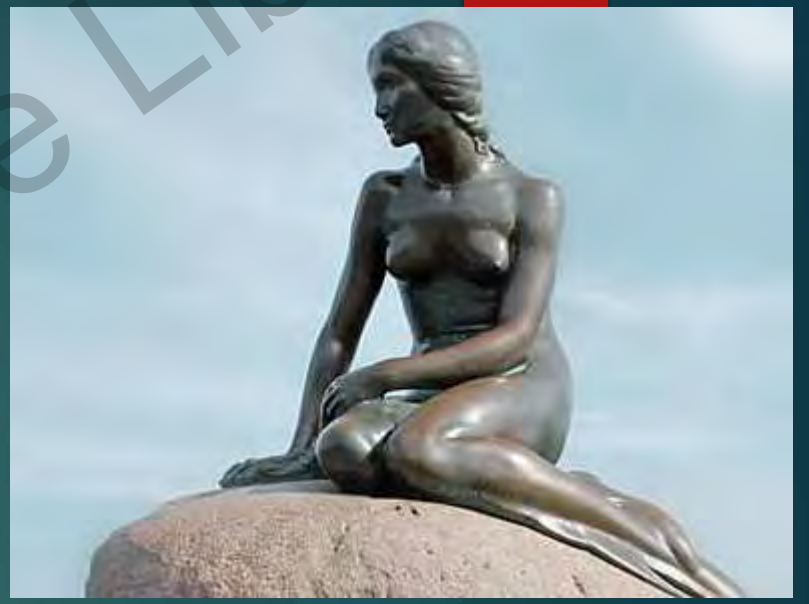
Meet the expert session, Tuesday - April 28, 2015 08:15 - 08:45

25th ECCMID Copenhagen, Denmark 25 - 28 April 2015

ESCMID EUROPEAN SOCIETY OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES



When to start treatment:
VAT (ventilator-associated tracheobronchitis) or VAP (pneumonia)?

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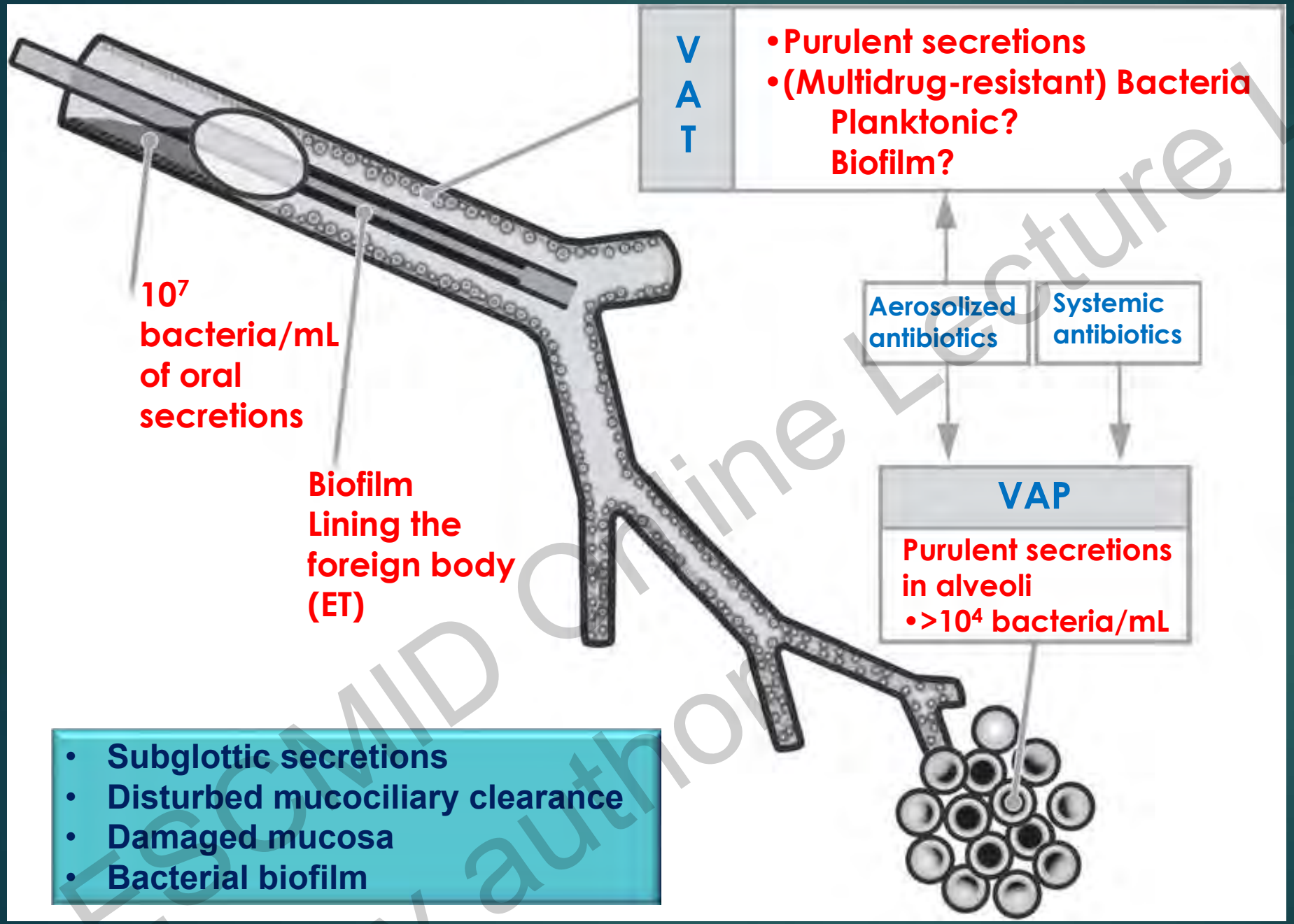
Conflict of interest

NONE RELATED TO THIS PRESENTATION

Overview of the presentation
Ventilator-Associated Tracheobronchitis/VAT

1. What is VAT
    1. Definition,
    2. Pathophysiology
    3. Diagnosis
2. Why treat VAT
    1. Clinical consequences
    2. Mortality of untreated VAT
3. Current therapeutic approaches
4. Current challenges and considerations

The multifactorial process that leads to VAT and VAP



Adapted from
Palmer LB
Curr Opin Pulm Med
2015, 21:239–249

A model of descending infection for VAT proposed by Craven DE et al

Critical Care 2014, 18:627

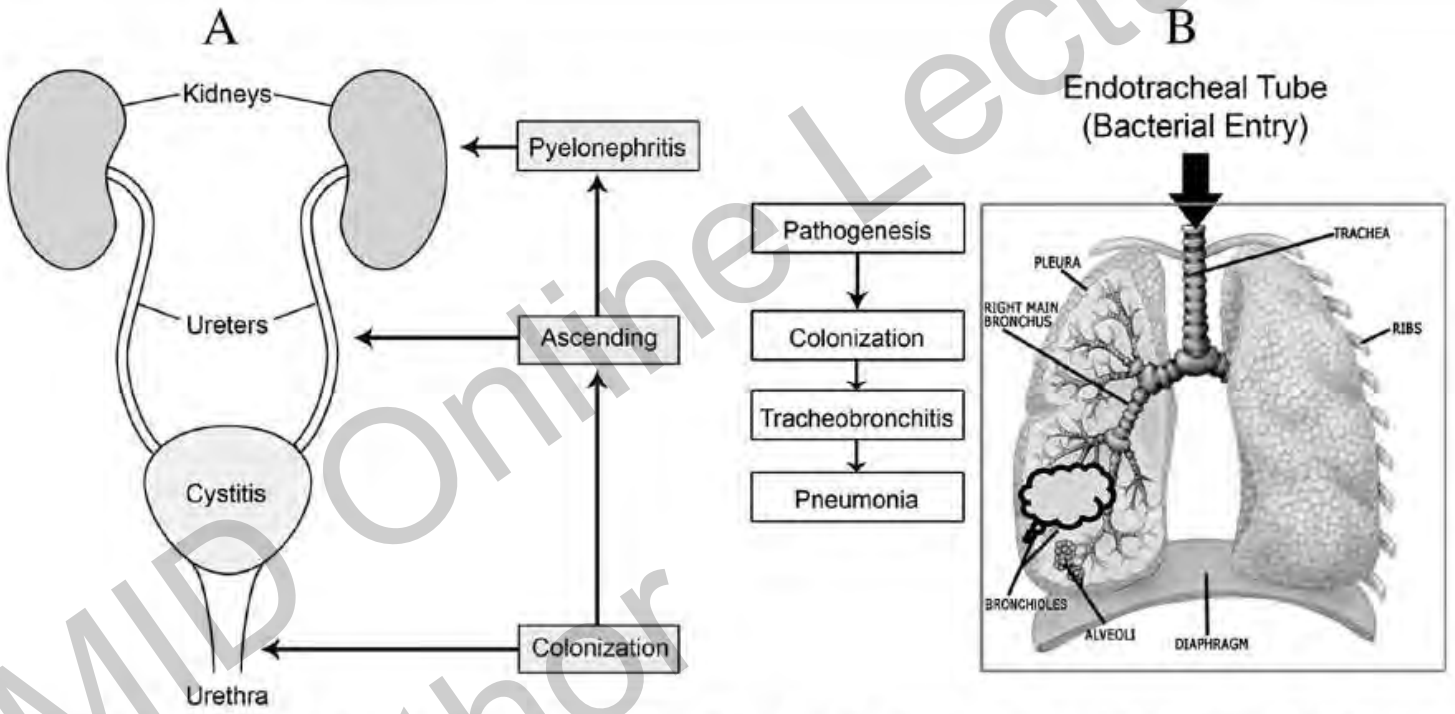


Figure 1 Pathogenesis and routine antibiotic therapy for urinary tract infections versus ventilator-associated pneumonia and tracheobronchitis. **(A)** The pathogenesis of 'ascending' urinary tract infection due to cystitis or pyelonephritis or both, which are currently treated with antibiotics as a 'standard of care'. **(B)** The pathogenesis of 'descending', primarily 'one-way' respiratory tract infection manifests as ventilator-associated tracheobronchitis or pneumonia, for which we would recommend treatment with intravenous or aerosolized antibiotic therapy or both. Reprinted with permission from Lippincott Williams & Wilkins [12].

Rationale for treating VAT and/or VAP

- VAT and VAP are 'descending, one-way infections
- Impaired tracheobronchial clearance
- Bacteria-loaded secretions constantly fight the gravity
- Reflux of ventilator tubing concentrate may also wash bacteria down into the bronchioles and alveoli
- Removal of bacteria is limited to suctioning through the ETT lumen. This procedure is blind, and may dislodge pathogens or biofilm-encased bacteria into the lower airway.
- Age, comorbidities, concurrent medications, and nutrition are representative risk factors that may further increase total bacterial lung burden

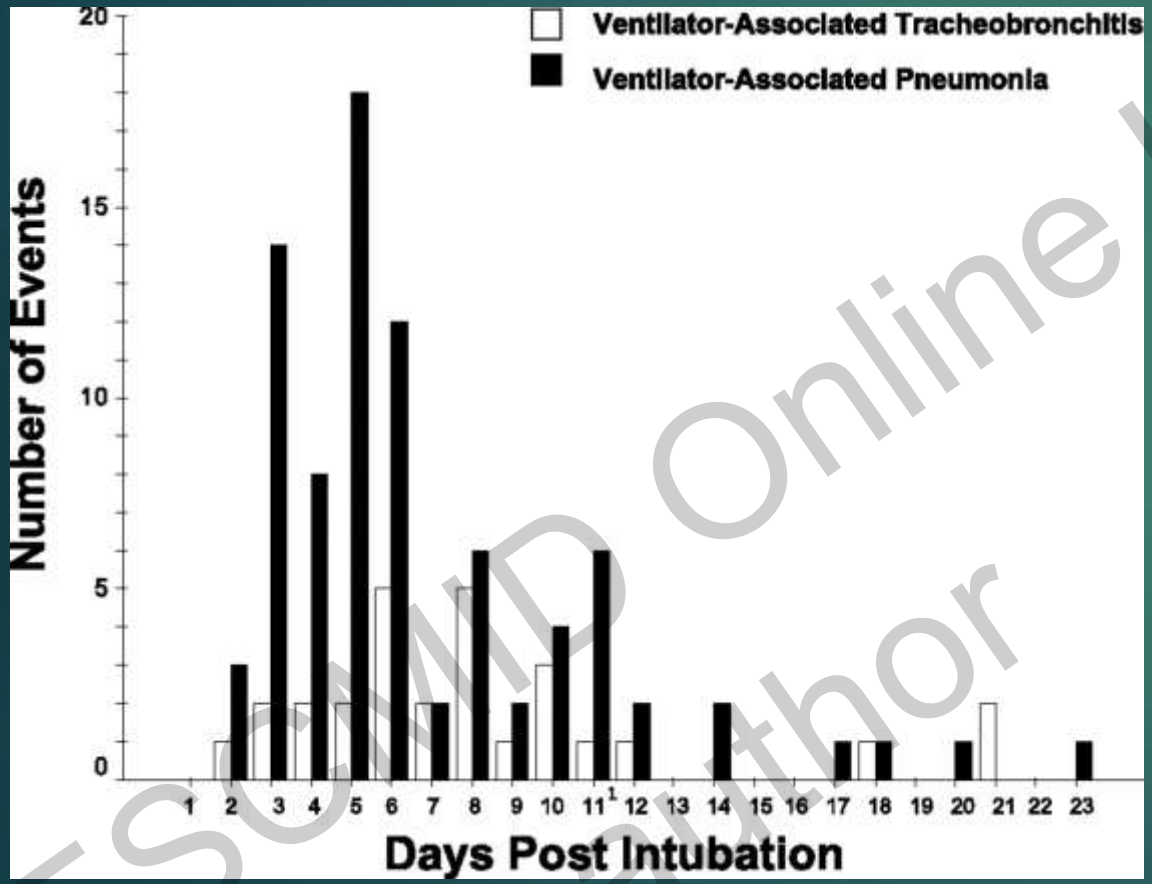
General concepts …debated

- Ventilator-associated tracheobronchitis (VAT) is believed to be an intermediate stage between colonization of the lower respiratory tract and VAP
- However, more recent data suggests that VAT may be a separate entity that may contribute to increased length of ICU stay and longer duration of MV

Craven DE, Chest. 2009;1352:521-528
Dallas J, Chest. 2011;139(3):513-518

Ventilator-Associated Tracheobronchitis in a Mixed Surgical and Medical ICU Population

Is VAT really a precursor of VAP?



- Incidence of VAT was 1.4%, and the overall incidence of VAP was 4.0%
- Rate of 3.2 cases of VAT per 1,000 mechanical ventilator days and 9.4 cases of VAP per 1,000 mechanical ventilator days
- The mean onset of VAT was 8.3 ± 4.8 days (median 7.5 days; interquartile range, 5.25-10.0 days), and the mean onset of VAP was 6.7 ± 4.1 days (P = .052) (median 5.0 days; interquartile range, 4.0-8.0 days).

Dallas J, Chest. 2011;139(3):513-518

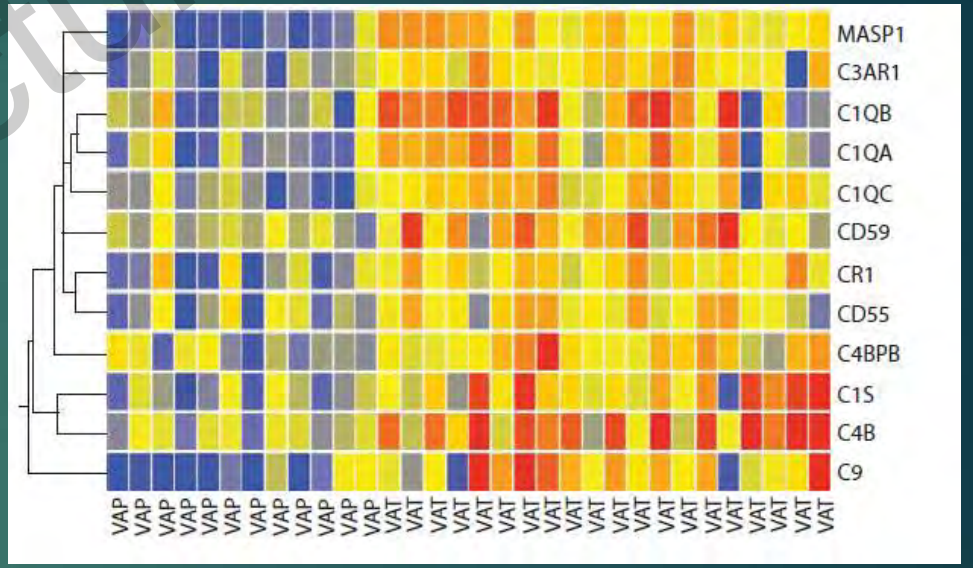
Are VAT and VAT really a continuum?

Comparison of VAP/VAT gene expression "signatures" using genomewide oligonucleotide microarrays

Translational study, 8 patients

Gene expression profiles in the pre-infection period identified a significant depression of the complement system pathway in the VAP group compared to the VAT group, affecting the classical pathway along with the final common pathway

red, upregulated; blue, downregulated



- **This suggests that intubation by itself is associated with different degrees of immunocompromise**
- **Early development of immunocompromise in the post-intubation period suggests that not all episodes of VAP are preventable**

I. Martin-Loeches et al Med Intensiva 2012

Incidence of VAT in the literature

Study	Incidence %	Population
Nseir/2002	10	Mixed
Hortal/2010	10	CVS
Ninan/2010	16	Respiratory stepdown unit
Dallas/2011	1.4	Mixed
Craven/2013	11	Mixed
Karvouniaris/2014	18	Mixed

Frequency, prevention, outcome and treatment of ventilator-associated tracheobronchitis: Systematic review and meta-analysis

- 10 randomized controlled trials (RCTs), 5 cohorts, and 2 case control studies involving 7056 patients
- VAT affected 386 (11.5%) out of 3,362 patients (5 reports)

Agrafiotis M et al, Respiratory Medicine (2010) 104, 325e336

Incidence may vary according to the patient population

- 236 patients observed; 42 patients (18%) presented with VAT
- Patients with a neurosurgical admission presented with VAT significantly more often than did other ICU patients (28.5% vs 14.1%; *P* = .02).

Karvouniaris M et al, Infect Control Hosp Epidemiol 2013;34(8):800-808

Rate of progression of VAT to VAP

Study	Rate %	Population
Nseir 2002	9	Mixed
Nseir 2008	34	Mixed
Dallas 2011	32.1	Mixed
Craven 2013	29	Mixed
Karvouniaris 2014	16.7	Mixed

Diagnostic criteria for ventilator-associated tracheobronchitis and ventilator-associated pneumonia

They vary significantly among studies!

	Clinical signs and symptoms	Chest radiograph or CT scan	Microbiology lung culture methods	
VAT	Temperature >38° WBC >12 000/μl or <4000/μl purulent sputum[a]	No new lung infiltrate	B-BAL or N-BAL $< 10^4$ cfu/ml	SQ-ETA: ≥ +++
			OR	OR
			B-PSB $< 10^3$ cfu/ml	Q-ETA $\geq 10^5$ cfu/ml
VAP	Temperature >38° WBC >12 000/μl or <4000/μl purulent sputum[a]	New and persistent lung infiltrate	B-BAL or N-BAL $\geq 10^4$ cfu/ml	SQ-ETA: ≥ +++
			OR	OR
			B-PSB $\geq 10^3$ cfu/ml	Q-ETA $\geq 10^5$ cfu/ml

Craven DE et al, Curr Opin Crit Care 2014, 20:532–541
Am J Respir Crit Care Med 2005; 171:388–416; 2005

DIAGNOSIS OF VAT: a difficult task

- Diagnosis of VAT and/or VAP requires similar clinical signs and microbiologic criteria
- VAP requires evidence of a new and persistent infiltrate on chest X-ray or computed tomography scan
- Portable chest X-rays often lack sensitivity and specificity, making it difficult for clinicians to differentiate VAP from noninfectious causes, such as congestive heart failure, pulmonary emboli or neoplastic disease

Craven DE et al, Curr Opin Crit Care 2014, 20:532–541
Am J Respir Crit Care Med 2005; 171:388–416; 2005
Wunderink RG, Chest 2000; 117 (4 Suppl 2):191S–194S

A novel approach to VAP definition

- The Centers for Disease Control's (CDC) National Health Safety Network has proposed new surveillance definitions for possible and probable ventilator-associated pneumonia
- The new definitions rely on changes in oxygenation, clinical signs, and microbiologic criteria
- Chest radiograph criteria were not included for the diagnosis of "probable or possible VAP."
- They focus on ventilator-associated infections and would not discriminate between ventilator-associated tracheobronchitis and pneumonia!

http://www.cdc.gov/nhsn

Incidence and diagnosis of ventilator-associated tracheobronchitis in the intensive care unit: an international online survey

- 288 ICUs from 16 countries answered the survey: 51% from the Latin American (LA) group and 49% from Spain, Portugal, and France (SPF group)
- The majority of respondents (n = 228; 79.2%) make the diagnosis of VAT on the basis of both clinical and microbiological criteria
- 13.9% reported diagnosis using clinical criteria alone

Rodríguez et al. Critical Care 2014, 18:R32

Techniques used for the diagnosis of ventilator-associated tracheobronchitis

Technique	Global n = 288 n (%)
Endotracheal aspirate (ETA)	171 (59.4)
Bronchoalveolar lavage (BAL)	40 (13.9)
ETA plus other techniques	35 (12.2)
Mini-BAL	21 (7.3)
Protected specimen brush	4 (1.4)
No response	17 (5.9)

- **Endotracheal aspirates were reported to be the most frequently used technique followed by bronchoalveolar lavage (BAL)**
- **BAL and mini-BAL techniques were more frequently employed by the LA group, whereas multiple sample techniques were more commonly used by the SPF group**

Rodríguez et al. Critical Care 2014, 18:R32

Diagnosis of VAT according to an international survey
Diverse use of laboratory parameters

- More than 50% of physicians requested a computed tomography (CT) scan, 48.3% of them when CXR is inconclusive
- Although the majority of respondents (n = 276; 95.8%) use microbiological findings to guide ATB treatment, more than half (59.0%) do not perform a Gram stain on the respiratory sample
- 22.9% do not routinely request quantitative cultures of respiratory secretions

Rodríguez et al. Critical Care 2014, 18:R32

Diverse methods of microbiologic diagnosis and criteria

- In 16 of the included studies the authors used tracheal aspirates
- Bronchoscopic cultures (bronchoalveolar lavage and protected specimen brush) have additionally been employed in 5 studies
- Cultures were quantitative in 10 studies
- Cutoff point of bacterial concentration for positivity in tracheal aspirates was 10^6 cfu/ml in 6 studies, 10^5 in 2 studies, 10^3 cfu/ml in 1 study and 10^2 cfu/ml in one study

Agrafiotis M et al, Respiratory Medicine (2010) 104, 325e336

How feasible and easy is to obtain optimal imaging?

- The diagnosis of a NEW infiltrate on CT scan precludes a baseline examination in suspicion of VAP
- Intrahospital transport can be a life-threatening endeavor
- A recent case–control study identified intrahospital transport (OR 2.9; 95%CI 1.4–5.7) as an independent risk factor for VAP
- Cost effectiveness of CT scan for all VAP suspected patients has not been thoroughly evaluated

Syrjiala H, Clin Infect Dis 1998;27:358–363.
Am J Respir Crit Care Med 2005; 171:388–416

Warren J, Crit Care Med 2004; 32:256–262.
Bercault N, Crit Care Med 2005; 33:2471–2478.
Lorente L, Eur Respir J 2007; 30:1193–1207.

Is VAT associated with increased mortality?
Be cautious about comparator arms…

- In two case-control studies excluding patients who eventually developed VAP, the presence, as opposed to the absence of VAT was not associated with higher attributable mortality (OR: 1.02, 95% CI: 0.57-1.81)
- In an observational cohort crude mortality was significantly higher in VAT patients, but this difference disappeared after exclusion of patients who subsequently developed VAP
- In another report by Bouza et al, in which patients who also developed VAP were not excluded, crude mortality of VAT was significantly higher compared to non-colonized patients

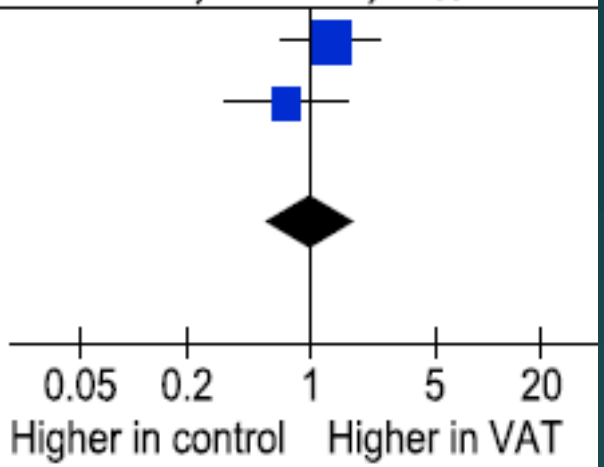
Agrafiotis M et al, Respiratory Medicine (2010) 104, 325e336

Ventilator-associated tracheobronchitis attributable mortality

Study or Subgroup	VAT Events	VAT Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
Nseir 2004	33	81	28	81	58.6%	1.30 [0.69, 2.46]
Nseir 2005	16	55	20	55	41.4%	0.72 [0.32, 1.60]
Total (95% CI)		**136**		**136**	**100.0%**	**1.02 [0.57, 1.81]**
Total events	49		48			

Heterogeneity: Tau² = 0.04; Chi² = 1.30, df = 1 (P = 0.25); I² = 23%

Test for overall effect: Z = 0.06 (P = 0.95)



Agrafiotis M et al, Respiratory Medicine (2010) 104, 325-336

VAT and patients' outcomes

Table 2 Impact of ventilator-associated tracheobronchitis on outcome in medical and surgical patients

	Medical patients ($n=1655$)			Surgical patients ($n=234$)		
	Yes ($n=165$)	No ($n=1490$)	P	Yes ($n=36$)	No ($n=198$)	P
Duration of MV	26 ± 17 (22)	8 ± 7 (6)	<0.001	32 ± 31 (23)	13 ± 12 (10)	<0.001
Length of ICU stay	33 ± 20 (28)	12 ± 19 (9)	<0.001	39 ± 31 (31)	18 ± 15 (14)	<0.001
ICU mortality	64 (38)	479 (32)	0.051	20 (55)	112 (56)	>0.999

Data are numbers (%) or mean ± SD (median). MV, mechanical ventilation. Adapted from [3].

Table 3 Impact of ventilator-associated tracheobronchitis on outcome in matched case–control studies

	COPD patients			Patients without chronic respiratory disease		
	Yes ($n=81$)	No ($n=81$)	P	Yes ($n=55$)	No ($n=55$)	P
Duration of MV	21 ± 12 (20)	19 ± 15 (12)	0.015	21 ± 16 (17)	13 ± 13 (8)	<0.001
Length of ICU stay	27 ± 13 (25)	24 ± 20 (18)	0.022	28 ± 15 (24)	17 ± 16 (12)	<0.001
ICU-mortality	33 (40)	28 (34)	0.480	16 (29)	20 (36)	0.294

Data are numbers (%) or mean ± SD (median). COPD, chronic obstructive pulmonary disease; MV, mechanical ventilation. Adapted from [32,33].

Nseir S: Curr Opin Infect Dis 2009; 22:148–153
Eur Respir J 2002; 20:1483–1489

Nseir S: Infection 2004; 32:210–216
Crit Care 2005; 9:R238–R245

Ventilator-Associated Tracheobronchitis Increases the Length of Intensive Care Unit Stay

TABLE 5. Results of Multiple Logistic Regression Analyses of the Study

	ICU mortality		ICU stay[a]	
Variable	OR (95% CI)	*P*	OR (95% CI)	*P*
Age	1.04 (1.01–1.06)	.02	1.01 (0.98–1.02)	.83
Medical cause of ICU admission	1.85 (0.76–4.49)	.17	1.33 (0.94–1.9)	.10
SOFA	1.14 (0.97–1.32)	.11	−0.95 (0.85–1.01)	.58
APACHE II	1.08 (1.01–1.16)	.02	1.04 (0.98–1.1)	.14.
CRP	1.05 (1.01–1.09)	.02	0.95 (0.90–1)	.03
PaO_2/FiO_2	1.0 (0.99–1.01)	.75	...	
VAT[b]	...		3.04 (1.35–6.85)	.01
VAP	0.41 (0.14–1.18)	.10	5.5 (2.8–10.88)	<.001

NOTE. APACHE, Acute Physiology and Chronic Health Evaluation; CI, confidence interval; CRP, C-reactive protein; ICU, intensive care unit; OR, odds ratio; SOFA, Sequential Organ Failure Assessment; VAT, ventilator-associated tracheobronchitis; VAP, ventilator-associated pneumonia.

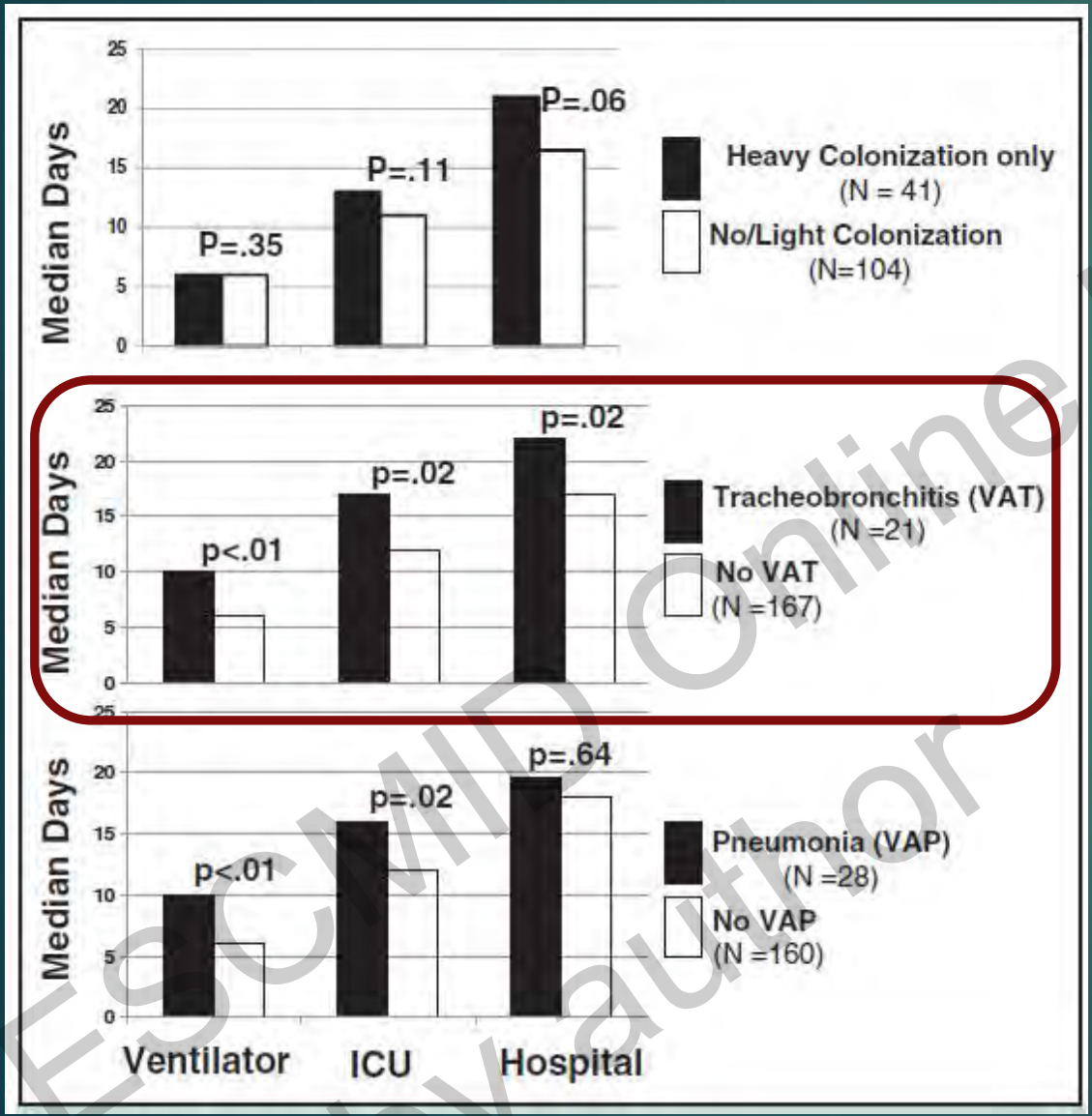
[a] ICU stay was assessed as greater of the median value.

[b] Patients with VAT who subsequently presented with VAP are included in the VAP group.

- The occurrence of VAT was a significant risk factor for increased duration of ICU stay but not of mortality

Karvouniaris M et al, Infect Control Hosp Epidemiol 2013;34(8):800-808

Outcomes of patients



Craven DE et al, The American Journal of Medicine (2013) 126, 542-549

Prescribing behaviours about VAT according to an international survey

- Half of physicians reported prescribing broad-spectrum systemic antibiotics for the treatment of VAT

Rodríguez et al. Critical Care 2014, 18:R32

Prescribing behaviours about VAT according to an international survey

- Intravenous (IV) monotherapy (62.5%) is the first choice of ATB treatment for VAT, followed by IV ATB combination (20.8%) and then IV and nebulized ATB.
- The use of nebulized ATB is more frequently reported by the LA group compared with the SPF group

Rodríguez et al. Critical Care 2014, 18:R32

Prescribing behaviours about VAT according to an international survey

- More than half (66.7) favored ATB treatment with a duration of between 7 and 10 days
- Half of the respondents preferred to de-escalate therapy when the results of microbiology tests are available
- Surprisingly, only 24% indicated a preference for a short course of ATB treatment (<7 days).

Rodríguez et al. Critical Care 2014, 18:R32

Response of VAT to Abx treatment is not always predictable

- **Concentrations in the airway may be lower than in the bloodstream**
- **The bacteria in this environment may require 10–25 times the minimum inhibitory concentration for bactericidal activity**
- **The presence of biofilm may decrease the efficacy of systemic antibiotics due to lack of penetration**

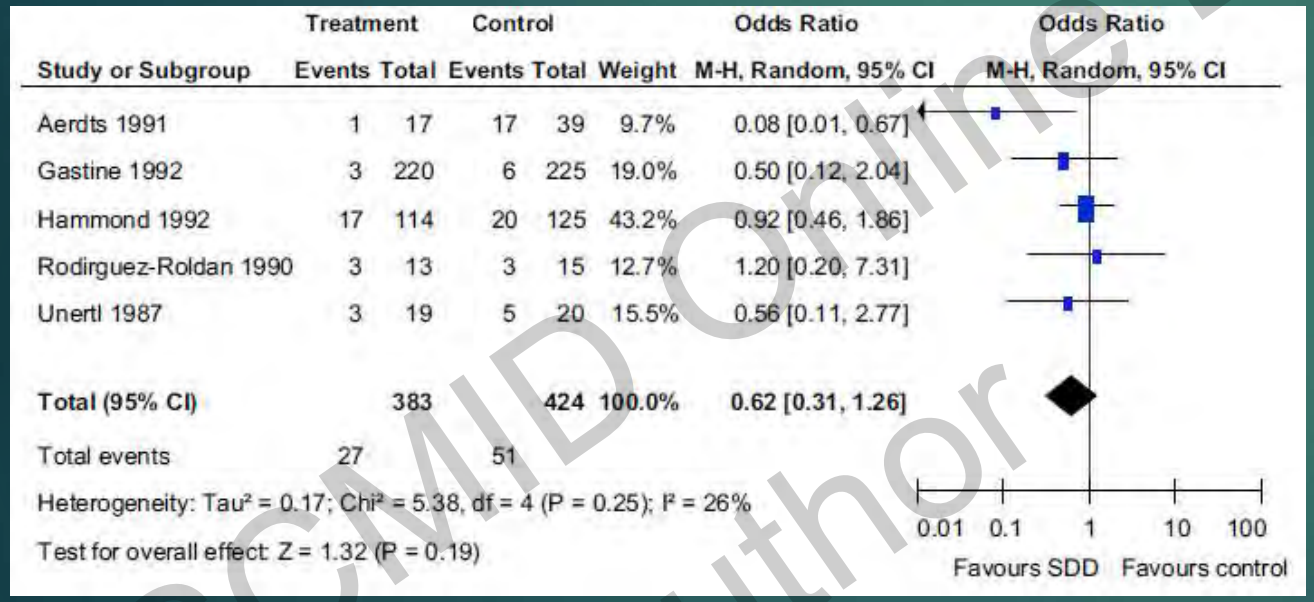
Gil-Perotin S, Crit Care 2012; 16:R93
Mendleman PM, Am Rev Respir Dis 1985; 132:761–765
Palmer LB, Curr Opin Pulm Med 2015, 21:239–249

Untreated VAT progresses to VAP? Timely treated VAT prevents VAP? Treated VAP eliminates VAT?

- When VAP is present and treated with systemic antibiotics, this more proximal area of infection may persist and lead to a vicious cycle of recurrent infections
- Alternatively, early treatment of ventilator-associated tracheobronchitis may prevent progression to VAP

Preventive measures of VAP may not be effective on VAT

Application of SDD as opposed to placebo, standard or no treatment did not reduce VAT frequency



Agrafiotis M, Resp Med 2010; 104:325-336
Gastinne H, N Engl J Med 1992;326:594-9
Hammond JM, Lancet 1992;340:5-9

The same stands true for automatic regulation of tracheal cuff pressure, oral cavity decontamination or bacterial filter in the ventilator circuit

Aerds SJ, Chest 1991;100:783-91
Rodriguez-Roldan JM, Crit Care Med 1990;18:1239-42
Unertl K, Intensive Care Med 1987;13:106-13

New therapeutic approaches

- Better understanding of pharmacokinetics of commonly used antibiotics in critically ill patients
  - Colistin (new treatment algorithms)
  - Aminoglycosides
  - B-lactams (continuous infusion, etc)
- An explosion of data with applications of nebulized antibiotics
- New devices to deliver antibiotics locally

Aerosolized antibiotics used in mechanically ventilated patients for respiratory infection

1. Amikacin and Amikacin with proprietary pulmonary drug delivery system (phase 3 study)
2. Amikacin/fosfomycin proprietary preparation (phase 1 completed; delivered with Pari investigational eFlow inline nebulizer)
3. Colistin and Colistin methanesulfonate (prodrug of colistin)
4. Ceftazidime
5. Gentamicin
6. Tobramycin and Tobramycin proprietary preparation (approved for spontaneous breathing cystic fibrosis patients)
7. Sisomycin
8. Vancomycin

Concern #1
Increase in overall antibiotic consumption

1. Diagnostic criteria need to be defined
2. Diagnostic techniques need to be confirmed
3. Imaging requirements should be defined
4. Impact on resistance trends should be investigated

Concern #2
What kind of treatment and for how long?

1. Intravenous
2. Intravenous +nebulized
3. Nebulized only
4. How to evaluate response to treatment?

Other Questions to be answered

1. What are the surrogates of success in this story apart from resolution of fever?
2. What are the concentrations of antibiotics needed to eradicate MDROs in the proximal airway in areas of thick purulent secretion
3. What are the best delivery devices to achieve the concentrations necessary to treat VAT and VAP?
4. Can inhaled antibiotics reduce or eliminate systemic antibiotic use and/or decrease the emergence of resistant organisms?

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