

Diagnosis of Ventilator-Associated Pneumonia: Where are we now?

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BSAC Guideline 2008

Masterton R, Galloway A, French G, Street M, Armstrong J, Brown E, Cleverley, Dilworth P, Fry C, Gascoigne A, Knox A, Nathwani D, Spencer R, Wilcox M.

Guidelines for the management of hospital-acquired pneumonia in the UK: report of the working party on hospital-acquired pneumonia of the BSAC

J Antimicrob Chemother 2008;62:5-34.

Available from www.bsac.org.uk

Definition of VAP

- Usually defined as pneumonia developing 48 h after implementing ET intubation and/or mechanical ventilation that was not present or before intubation

The fundamental questions

- How to diagnose VAP?
- What are the causative organisms?
 - Can this guide therapy?
 - Can this improve outcome?

SIGN Levels of Evidence

High quality meta-analyses, systematic reviews of RCTs, RCTs with very low risk of bias	1++
Well conducted meta-analyses, systematic reviews of RCTs, RCTs with low risk of bias	1+
Meta-analyses, systematic reviews or RCTs, RCTs with high risk of bias	1
High quality systematic reviews of case-control/cohort studies <i>or</i> High quality case-control/cohort studies with very low risk of confounding, bias, or chance and high probability of causal relationship	2++
Well conducted case-control/cohort studies with low risk of confounding, bias, or chance and moderate probability of causal relationship	2+
Case-control/cohort studies with high risk of confounding, bias, or chance and significant risk that relationship is not causal	2
Non-analytic studies, e.g. case reports, case series	3
Expert opinion	4

Grades of Recommendation

At least one meta-analysis, systematic review, or RCT rated as 1++ <i>or</i> Systematic review of RCTs or body of evidence mainly rated 1+ and demonstrating overall consistency	A
A body of evidence including 2++ demonstrating overall consistency <i>or</i> Extrapolated evidence from studies rated as 1++ or 1+	B
A body of evidence including 2+ and demonstrating overall consistency <i>or</i> Extrapolated evidence from studies rated as 2++	C
Evidence level 3 or 4 <i>or</i> Extrapolated evidence from studies rated as 2+	D

GPP

Grades of Recommendation for Diagnosis of VAP

- 4 A, 2 C, 2 D, 9 GPP

4 A:

Quantification of intracellular organisms in BALs is rapid and specific and can guide initial therapy

No one invasive sampling method is better than any other

PSB and BAL should not be relied on for diagnosis

EA cultures should not be used diagnosis

Michaud S, Suzuki S, Harbarth S. Effect of design-related bias in studies of diagnostic tests for VAP. *Am J Respir Crit Care Med* 2002;166:1320–1325.

The fundamental problem 1: No gold standard

- There appears to be no 'gold standard' for the diagnosis of VAP
- Since there is no reliable reference, it is difficult to judge papers which compare one diagnostic technique with another
 - This also affects studies of other aspects of VAP such as treatment

Q: Is lung histology a suitable reference standard for VAP diagnosis?

- **Histology: VAP in Baboon model**

Moderate/severe pneumonia was associated with high bacterial concentrations in lungs

- **But in humans**

Pathologists vary, distribution of changes in lungs variable, not all studies show a good relationship between cultures & histology

Q: Is lung histology a suitable reference standard for VAP diagnosis?

Quantitative airway or lung cultures do not accurately separate histological pneumonia & non-pneumonia groups

Fundamental Problem 2: Clinical & Radiological diagnosis

- There are no distinguishing clinical, radiological or other imaging features that can be used to reliably diagnose VAP
- If the clinical signs & XRay changes are suggestive of VAP this should be treated

Q: What are the clinical diagnostic criteria for VAP?

Recommendation	Grading
The clinical diagnosis of VAP is difficult but can be based on the following criteria:	C
New and/or persistent infiltrate on chest radiograph; Pyrexia; Purulent respiratory secretions; Peripheral leucocytosis or leucopenia; Increased oxygen requirement; Cough; Increased respiratory rate; Sometimes confusion; Other organ failure.	
CPIS may be useful for selecting patients for short-course therapy and monitoring response.	GPP

Q: Are there key imaging investigations for diagnosing VAP?

Evidence statement:	Grading
There are no key investigations but a normal chest radiograph excludes VAP.	2++
The presence of an alveolar infiltrate on the chest radiograph raises the possibility of VAP as well as other differential diagnoses.	2-
Ventilated patients may have an abnormal chest XRay secondary to other pathology (including acute lung injury or LVF). The presence of new infiltrates may indicate VAP.	2-

Fundamental problem 3: Microbiological investigations

- Sputum and tracheal aspirates may be contaminated with upper respiratory organisms that do not contribute to the pneumonic process
- When organisms are isolated from respiratory secretions, it is necessary to distinguish between contamination, colonisation and infection

Fundamental problem 3: Microbiological investigations

- Several techniques have been introduced to obtain lower respiratory specimens protected from upper respiratory contamination
- There is no evidence that any one is better than another
- There is limited evidence that these tests are successful in helping diagnose VAP or identifying true pathogens

Q: What organisms are isolated from respiratory specimens in patients with suspected VAP?

Evidence statement:	Grading
Many organisms have been isolated from respiratory specimens of patients with VAP, predominantly aerobic bacteria and often in mixed culture,	1++
However, there are no agreed criteria to distinguish contamination, colonisation and infection.	

Q: What organisms are isolated from respiratory specimens in patients with suspected VAP?

Evidence statement:	Grading
The distribution of isolates varies with time and place but the commonest are <i>Pseudomonas aeruginosa</i> , enterobacteria and <i>Staphylococcus aureus</i>	2+
Patients are more likely to have multi-resistant opportunistic organisms if they stay longer in hospital, have more intensive therapy and receive prior antimicrobial therapy.	2+

Q: What organisms are isolated from respiratory specimens in patients with suspected VAP?

Recommendation:	Grading
Surveillance data, especially local data, should be used to guide therapy in potentially infected patients.	2+

Q: Can quantitative and qualitative microbiology aid the diagnosis of VAP?

- **Optimism**
- Chastre J et al. (1984) *Am Rev Resp Dis* 130:924-29
 - PSB is specific & sensitive
 - Can identify causative organisms in VAP
 - Distinguishes between colonization & infection
- Chastre J et al. (1995) *Am J Resp Crit Care Med* 152:231-40
 - BAL & PSB reliably identify organisms of VAP
 - Even in patients on antibiotics for several days

Q: Can quantitative and qualitative microbiology aid the diagnosis of VAP?

- **More specific than sensitive**
- Marquette CH *et al.* (1995) *Am J Resp Crit Care Med* 151:1878-88
 - Quantitative BAL, cutoff of 10^6 cfu/mL :
Sensitivity 47%, specificity 100%
 - Intracellular organisms: sensitivity 37%, specificity 100%
- Papazian L *et al.* (1995) *Am J Resp Crit Care Med* 152:1982-91
 - 12/18 patients with histological VAP had positive lung cultures
 - 6/18 were negative

Q: Can quantitative and qualitative microbiology aid the diagnosis of VAP?

- **Pessimism**
- **Torres A et al. (1994)** *Am J Crit Care Med* 149:324-31
 - Quantitative microbiology in patients on antibiotics is “of poor help in managing VAP”
- **Rouby JJ et al. (1992)** *Am Rev Respir Dis* 146:1059-66
 - Blind protected BAL was “not reliable in critically ill patients receiving antibiotics”
- **Kirtland SH et al. (1997)** *Chest* 112:445-57.
 - There was “no meaningful correlation between histologic features & microbiological results”

Q: Can quantitative and qualitative microbiology aid the diagnosis of VAP?

Evidence statement:	Grading
<p>They cannot.</p> <p>They have a wide range of accuracy and a high likelihood of false-ve and false+ve results compared with reference standards. They misdiagnose VAP in 20% or more of cases.</p>	1++
<p>However, the detection of intracellular organisms in BAL specimens is a rapid test with high specificity.</p>	1++

Q: Should invasive and quantitative microbiological results be used to direct therapy of VAP?

- Failure to isolate organisms from either respiratory secretions or blood does not exclude VAP
- There is limited evidence to confirm that use of an appropriate antibiotic therapy guided by microbiological findings affects clinical outcome, but this is an evolving issue

Noninvasive versus invasive microbiological investigation in VAP.

Ruiz M et al. *Amer J Resp Crit Care Med* 2000;162:119-125.

- Single ICU; ~39 patients suspected of VAP in each arm
- Compared outcomes with invasive & non-invasive microbial investigation
- Assessed by length of stay on ICU, length of ventilation, mortality
- No difference in outcome between two groups

Impact of quantitative invasive techniques in the management and outcome of ventilated patients with suspected VAP.

Sole Violan J et al. Crit Care Med 2000;28:273-41.

- Single ICU; ~43 patients suspected of VAP in each arm
- Compared outcomes with invasive & non-invasive microbial investigation
- Assessed by length of stay on ICU, length of ventilation, mortality
- No difference in outcome between two groups

Invasive & non-invasive management of suspected VAP

Fagon J-Y et al *Ann Intern Med.* 2000;132:621-630.

- Multicenter trial of patients suspected clinically of VAP
 - Clinical management (209 pts)
 - Invasive management (204 pts)
- Invasive management was significantly associated with
 - fewer deaths at 14 days, earlier improvement of organ dysfunction, less antibiotic use

Q: Should invasive and quantitative microbiological results be used to direct therapy of VAP?

Evidence statement:	Grading
There is conflicting evidence as to whether the use of invasive and quantitative microbiology to diagnose VAP and direct therapy is associated with improved outcomes.	1-

Q: Should invasive and quantitative microbiological results be used to direct therapy of VAP?

Recommendation:	Grading
There is inadequate evidence to support the use of invasive and quantitative microbiology for diagnosis and initial therapy to improve outcome of VAP in individual patients.	C
But these techniques can be used for de-escalation	C

Muscedere J, Dodek P, Keenan S, et al.
Comprehensive Evidence-Based Clinical Practice
Guidelines for VAP: Diagnosis and Treatment.

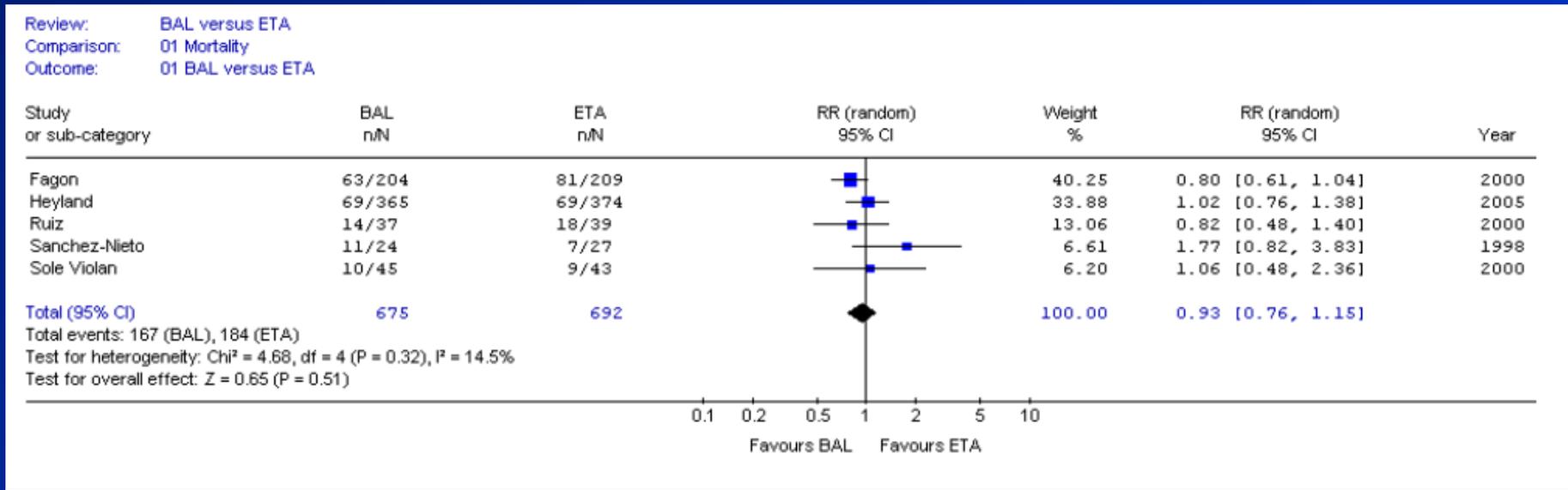
J Crit Care 2008;23(1): 138-147.

There was no evidence that using quantitative BAL and/or PSB to diagnose VAP improved hospital mortality, LOS or ventilator time compared to ETAs with non-quantitative cultures.

Recommendation: if empiric antibiotic therapy is being initiated at the time VAP is suspected, ETAs with nonquantitative cultures should be used as the initial diagnostic strategy

Muscedere J et al. J Crit Care 2008;23(1): 138-147.

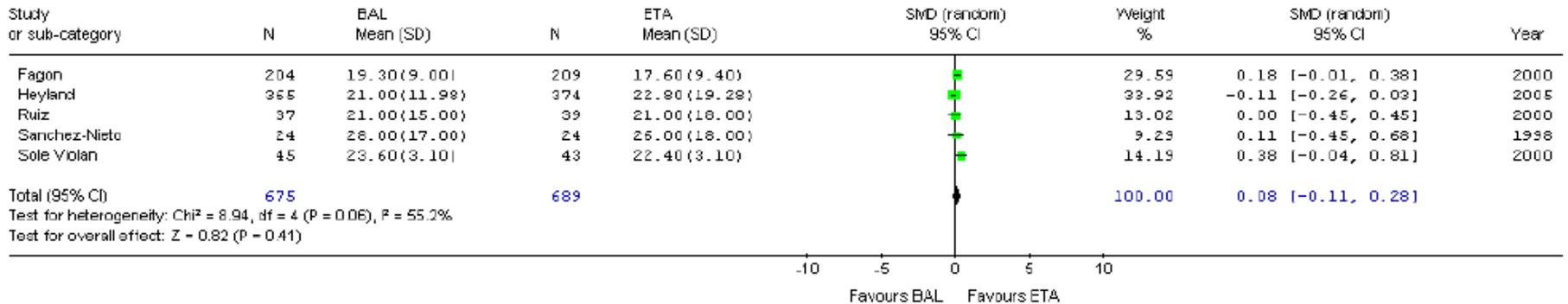
BAL Vs ETA: Mortality



Muscedere J et al. J Crit Care 2008;23(1): 138-147.

BAL Vs ETA: ITU LOS

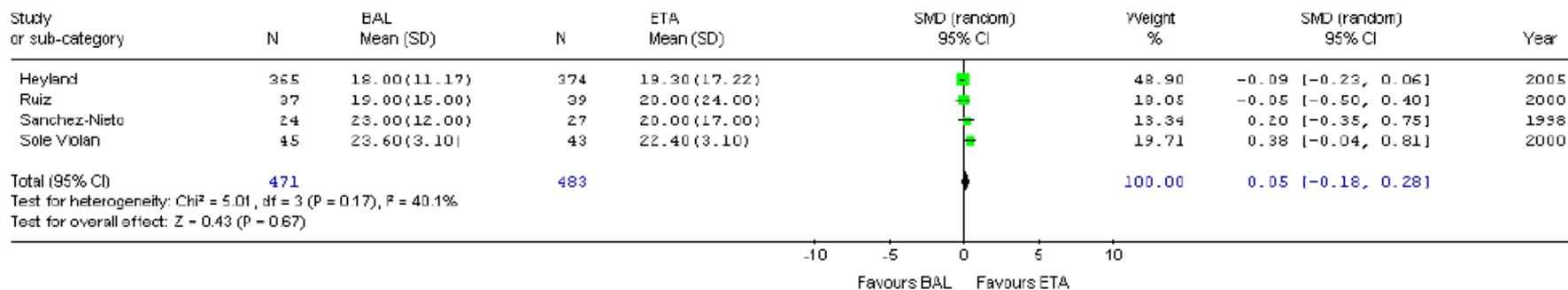
Review: BAL versus ETA
 Comparison: 02 ICU LOS
 Outcome: 01 ICU Length of Stay



Muscedere J et al. J Crit Care 2008;23(1): 138-147.

BAL Vs ETA: Ventilator Days

Review: BAL versus ETA
 Comparison: 03 Ventilator days
 Outcome: 01 Duration of Ventilation



American Thoracic Society. Guidelines for the management of adults with HAP, VAP & HCAP. Am J Respir Crit Care Med 2006; 171:388–416.

- Clinical assessment tends to over-diagnose VAP, leading to over use of antibiotics. Bacteriological assessment may give false-negative results, leading to failure to give necessary treatment.

ATS Guidelines 2005

- Collect LRT cultures before antibiotic therapy, but this should not delay initiation of therapy in critically ill patients.
- Quantitative cultures increase specificity of the diagnosis of HAP
- **Negative LRT cultures in absence of antibiotic change in prior 72 h can be used to stop antibiotics**
- Early, appropriate antibiotic therapy should be given; de-escalate in light of LRT cultures and clinical response

SUMMARY 1

- The assessment of diagnostic methods is complicated by the lack of a gold or reference standard for VAP
- Many studies are poorly designed and/or have limited numbers of cases

SUMMARY 2

- The diagnosis of VAP is difficult
 - There are no characteristic clinical and radiological features, but usually there are chest XRay changes
- Invasive and quantitative microbiological techniques do not improve diagnosis
 - Culture of endotracheal aspirates is unhelpful
 - But IC-BAL has a high specificity and supports clinical suspicion
 - Blind BAL is as good a sampling method as any

SUMMARY 3

- Many organisms can be cultured from secretions but it is difficult to distinguish colonisation, infection, contamination
- The organisms associated with VAP vary by time and place
 - However, microbiological surveillance can guide initial therapy
 - Multi-resistance is associated with prolonged stay, prior antimicrobial therapy, and admission to ITU

SUMMARY 4

- There is a lack of evidence that therapy directed by quantitative microbiology in individual patients improves outcome
- Early, appropriate therapy based on surveillance data improves outcome
- De-escalate antibiotics asap
- Do not delay therapy by waiting for microbiological results