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DIAGNOSIS OF VENTILATOR-ASSOCIATED PNEUMONIA

SUMMARY

Bronchoalveolar lavage (BAL) is the most accurate method for quantitatively diagnosing the presence of ventilator-associated pneumonia (VAP). Tracheal aspirate (TA), which provides only a qualitative culture, may overestimate the incidence of VAP and lead to over-treatment. Mini-bronchoalveolar lavage (mini-BAL) and protected brush specimen (PBS) are alternate modalities for obtaining quantitative cultures. The overuse of antibiotic therapy carries significant risk for the patient, leads to development of resistant organisms, and increases healthcare costs. BAL facilitates appropriate antibiotic use and this benefit often outweighs the additional cost of BAL and the small risk of this invasive procedure.

RECOMMENDATIONS

- **Level 1**
 - **None**
- **Level 2**
 - **Early, broad-spectrum antimicrobial coverage should be instituted in patients clinically suspected of having ventilator-associated pneumonia (VAP).**
 - **Cultures should be obtained in a timely fashion and antibiotic coverage adjusted based upon culture results.**
- **Level 3**
 - **Quantitative culture is the diagnostic method of choice in the work up of fever in mechanically ventilated patients and should be performed when there is clinical suspicion of VAP.**
 - **Traditional tracheal aspirate cultures should not be used to diagnose VAP in mechanically ventilated patients.**
 - **Bronchoalveolar lavage (BAL) cultures growing more than 100,000 (10^5) colony forming units (cfu)/ml indicate a positive culture for pneumonia.**
 - **Mini-bronchoalveolar lavage (Mini-BAL) cultures growing more than 10,000 (10^4) colony forming units (cfu)/ml indicate a positive culture for pneumonia.**
 - **Patients with a Clinical Pulmonary Infection Score (CPIS) ≥ 6 should undergo either BAL or Mini-BAL.**
 - **The inner cannula of a tracheostomy tube should be changed before sputum specimens are collected.**

INTRODUCTION

Ventilator-associated pneumonia (VAP) is the most widespread infection encountered in the intensive care unit and is associated with significant morbidity, mortality and cost (1). Ten to 20 percent of patients mechanically ventilated for greater than 48 hours will develop VAP, increasing mortality two-fold (1). Timely, appropriate antibiotic therapy improves patient survival in the presence of infection. Such

EVIDENCE DEFINITIONS

- **Class I:** Prospective randomized controlled trial.
- **Class II:** Prospective clinical study or retrospective analysis of reliable data. Includes observational, cohort, prevalence, or case control studies.
- **Class III:** Retrospective study. Includes database or registry reviews, large series of case reports, expert opinion.
- **Technology assessment:** A technology study which does not lend itself to classification in the above-mentioned format. Devices are evaluated in terms of their accuracy, reliability, therapeutic potential, or cost effectiveness.

LEVEL OF RECOMMENDATION DEFINITIONS

- **Level 1:** Convincingly justifiable based on available scientific information alone. Usually based on Class I data or strong Class II evidence if randomized testing is inappropriate. Conversely, low quality or contradictory Class I data may be insufficient to support a Level I recommendation.
- **Level 2:** Reasonably justifiable based on available scientific evidence and strongly supported by expert opinion. Usually supported by Class II data or a preponderance of Class III evidence.
- **Level 3:** Supported by available data, but scientific evidence is lacking. Generally supported by Class III data. Useful for educational purposes and in guiding future clinical research.

treatment, however, can foster antibiotic resistance and incur the associated risks of antibiotic therapy itself. Accurate and timely diagnosis of VAP is crucial to appropriate treatment.

Commonly used clinical VAP criteria include the presence of a new or progressive pulmonary infiltrate on chest radiograph, fever (greater than 38.3°C), leukocytosis or leukopenia, or purulent tracheobronchial secretions. These non-specific findings, however, can lead to antibiotic treatment of non-infectious processes and correlate poorly with microbiologic cultures. Although originally intended to help differentiate between VAP and pulmonary colonization, the Clinical Pulmonary Infection Score (CPIS) has been used to assist in the clinical diagnosis of VAP. While using CPIS to diagnose the presence of VAP results in fewer missed VAP episodes, its' use can result in patients being treated with antibiotics unnecessarily. As a result, sputum cultures are most commonly utilized to confirm the presence of VAP. Several of the most commonly employed techniques are outlined below.

Tracheal Aspirate (TA): The least invasive method. This technique does not require specialized training or equipment. The practitioner suctions the upper airway through a sterile catheter and collects the sputum specimen. As the catheter is inserted blindly, organisms from the biofilm coating the endotracheal or tracheostomy tube may contaminate the culture results obtained. The technique is sensitive, but not specific (sensitivity 38-100% and specificity 14-100%) (6). Quantitative cultures are rarely performed on these samples (2).

Bronchoalveolar Lavage (BAL): A fiberoptic bronchoscope is directed to the area of concern within the lung, which is flushed with sterile fluid. The fluid and specimen it carries with it are then suctioned, collected and cultured. BAL may be both diagnostic and therapeutic as mucous plugs and excessive secretions may be subsequently aspirated during the same procedure. Quantitative cultures are usually obtained. The large volume of the specimen makes it useful for detecting non-bacterial pathogens. Sensitivity ranges from 42-93% Specificity 45-100% (6). Bronchoscopy carries a procedural risk of hypoxia. (2)

“Mini-BAL” or Non-Bronchoscopic Bronchoalveolar Lavage: A specialized catheter is inserted into the endotracheal tube. A plug or telescoping catheter system protects the end of the catheter from contamination during insertion. The catheter is advanced approximately 30 cm and the inner cannula is then gently advanced until it meets resistance. Thirty mL of sterile saline is injected and suctioned. This is repeated a second time and the combined aspirate sent for culture. Semi-quantitative or quantitative cultures are usually performed. Sensitivity and specificity are similar to BAL (sensitivity 63-100% and specificity 66-96%) (2,6).

Protected Brush Specimens (PBS): A specialized catheter containing a brush is either blindly advanced until gentle resistance is met or inserted during bronchoscopy through the forceps port. When the area to be sampled is visualized, the brush is pushed through a plug and a sample obtained by gentle scraping. The brush is retracted, the catheter or bronchoscope is removed, and a quantitative culture is obtained. Because the sample is low volume, it is not appropriate for detection of non-bacterial pathogens. Results are less sensitive, but more specific than BAL (sensitivity 33-100% and specificity 50-100%) (2,6).

The role of invasive testing to obtain specimens for microbiologic diagnosis and the appropriate diagnostic criteria for VAP continues to be debated. TA is consistently the least specific of the diagnostic techniques. Reliance upon it as a diagnostic technique may lead to over-diagnosis and unnecessary treatment of VAP, increasing both patient care costs and the rise of resistant organisms. BAL is emerging as a test with a good balance of sensitivity and specificity. The initial cost of the equipment and of the procedure itself may be offset by the benefits of more accurate VAP diagnosis.

LITERATURE REVIEW

Clinical outcomes when invasive vs. non-invasive methods are utilized for the diagnosis of VAP

In a large, multicenter study, patients who had been in the ICU for at least 4 days and were suspected of having VAP were randomized to either BAL with quantitative culture or TA with qualitative culture (3).

Both groups received the same empiric antibiotics, which were subsequently tailored to appropriate monotherapy or double-drug coverage by a second randomization if an organism was identified. There were no significant differences between the groups in terms of 28-day mortality, targeted antibiotic therapy, days alive without antibiotics, maximum organ dysfunction scores, length of stay in the ICU or length of stay in the hospital. The authors attribute the lack of difference primarily to the early and standardized empiric antibiotic therapy given to both groups. This study concluded that similar outcomes and use of antibiotics result whether the diagnosis of VAP is made by TA or BAL (Class I). Of note, the study population had a low prevalence of *MRSA* and *Pseudomonas spp.* and so may not be applicable in populations with a high incidence of these infections. In a commentary regarding this study, Fagon et al. express several concerns (10). They reiterate that the relative lack of “high-risk” pathogens in the patients studied makes it difficult to extrapolate these results to many ICUs. They note that many patients received antibiotics within 3 days prior to randomization and that this might particularly interfere with quantitative culture results. A relatively high rate of inappropriate initial therapy was reported in both groups (11% of BAL patients and 10.5% of TA patients). This may be related to a concurrent randomization to dual or monotherapy among these patients and, though it occurred evenly between the groups, may obfuscate the results of the study as a whole. Finally, targeted therapy was achieved in only 74.2% of BAL patients and 74.6 % of TA patients by day 6. This makes the true benefit of the techniques in allowing early de-escalation or targeted therapy difficult to accurately assess.

In another prospective trial, data were collected on all infectious complications in mechanically ventilated burn/trauma patients for the calendar year 2001 (4). Sixty-eight patients clinically suspected of having VAP based on clinical findings (fever, leukocytosis greater than 10,000 mm³, purulent sputum, new infiltrate on chest radiograph or increased oxygen requirements) were further evaluated for VAP. In the initial 37 patients, this was done by sputum culture and Gram’s stain of a specimen obtained by the respiratory therapist using an in-line suction catheter (TA). In the subsequent 29 patients, cultures were obtained first as described above and immediately following by BAL. BAL was done by the trauma attending physician or by a surgical resident. All patients were started on empiric antibiotics after cultures were obtained and these were adjusted at the discretion of the attending physician. Initial empiric antibiotic coverage did not differ between the two groups. There were no statistical differences in Injury Severity Score, number of patients correctly treated with empiric antibiotics, hospital length of stay, ventilator days, rate of recurrent pneumonias, antibiotic or respiratory/ventilator costs, or mortality between the groups. There was a trend towards a shorter time before initial treatment in the BAL group, but this was not statistically significant (Class I).

A meta-analysis was performed including four randomized, controlled trials from 1998 to 2000 that compared non-invasive to invasive methods of VAP diagnosis in terms of antibiotic management and overall mortality (5). Together, the studies included 628 patients. Invasive specimens were obtained by BAL and PSB or BAL alone. The overall quality of these studies was rated as moderate and they found clinical and statistical heterogeneity among the trials. Ninety-three percent of all patients received early, appropriate antibiotic therapy. Invasive testing did not alter mortality (Odds ratio 0.89, 95% confidence interval 0.56–1.41), but did lead to tailoring of antibiotic therapy (Odds ratio for change in antibiotic management after invasive sampling, 2.85, 95% confidence interval 1.45–5.59). The authors also reviewed five prospective, observational studies that included 635 patients. This analysis supported the data showing antibiotic alterations resulting from invasive diagnostic techniques in more than half of patients (pooled estimate for rate of alteration in antibiotic prescription, 50.3%, 95% confidence interval 35.9–64.6%). The authors conclude that invasive techniques are useful in adjusting antibiotic therapy; however, this does not lead to a difference in mortality (Class II).

Mini-BAL has been found to have some practical advantages over BAL in that it can be performed by a trained respiratory therapist and may decrease costs without significantly affecting the diagnostic sensitivity and specificity. In a prospective study by Marik et al (13) comparing mini-BAL and blind PBS (b-PSB) to diagnose VAP in medical and surgical intensive care patients, sequential b-PSB followed by mini-BAL was performed by trained respiratory therapists. One hundred and ninety paired specimens were obtained from 175 patients. The diagnostic agreement between the two techniques was 90%. In 6 episodes, mini-BAL was negative and b-PSB was positive. In 13 episodes, b-PSB was negative and mini-BAL was positive. The authors conclude that both PSB and mini-BAL can be performed safely by

respiratory therapists. Neither diagnostic method was clearly superior (Class II). For a discussion of cost, see below.

The quantitative culture threshold for the diagnosis of VAP

The number of colony forming units (cfu) that determines a positive culture varies depending upon the technique by which it was obtained. The cutoffs listed below have been determined based on the volume sampled and a desired sensitivity and specificity:

- For TA, a threshold of more than 1,000,000 cfu/ml (10^6) is accepted as positive (2).
- For BAL, thresholds ranging between 1,000 (10^3) and 100,000 cfu/mL (10^5) have been reported (6); however, a value of 100,000 cfu (10^5) is gaining clinical acceptance.
- For Mini-BAL a threshold of more than 10,000 cfu/ml (10^4) is considered positive (2).
- For PBS, a threshold of more than 1000 cfu/ml (10^3) is considered positive (2).

A prospective study was performed to identify the optimal BAL threshold (7). Two hundred fifty-seven BALs were performed in 168 patients. Subdiagnostic quantities of bacteria (≥ 100 , but $< 10,000$ cfu/mL) were seen in 98 BALs. Of these, only 16 episodes (16%) of VAP with the same organism were seen later during hospitalization. At a threshold of $\geq 10,000$ cfu/mL, 4 of 28 patients (14%) went on to develop pneumonia. A similar pattern was seen at diagnostic thresholds of ≥ 1000 cfu/mL (10 of 72 [14%]) and ≥ 100 cfu/mL. The authors conclude that a threshold of $\geq 100,000$ cfu/mL (10^5) for VAP diagnosis carries a low false-negative rate. At least 80% of patients who would have been treated had a threshold of $\geq 10,000$ cfu/mL been used recovered without treatment and thus would have undergone unnecessary antibiotic exposure. A similar pattern is seen at all lower thresholds (Class II).

In a prospective trauma database study, BAL culture results over a 46-month period were reviewed (8). A false negative BAL was defined as any patient with $< 100,000$ cfu/mL who then developed VAP with a culture of $> 100,000$ cfu/mL with the same organism within seven days. The authors found 43 episodes of VAP with a false negative rate of 3%. The data were then reviewed using 10,000 cfu/mL as a diagnostic threshold. They found 106 cases of VAP with a false negative rate of 9%.

Colony Count (organisms/mL)	Mortality (%)		$\geq 10^5$ (%)	$\geq 10^4$ (%)
$\geq 10^5$	17	Sensitivity	95	99
10^4	15	Specificity	100	70
10^3	13	Positive predictive value	100	80
$\leq 10^2$	13	Negative predictive value	97	98

The authors conclude that with a change in the diagnostic threshold from 100,000 cfu/mL to 10,000 cfu/mL, there are minimal gains in sensitivity, but large drops in specificity and positive predictive value. This might lead to over treatment of some patients and thus 100,000 cfu/mL (10^5) is the appropriate clinical diagnostic threshold (Class II).

Use of BAL results to tailor antibiotics

This 2007 study by Muller et al found that repeating BAL to monitor success of treatment in cases of VAP may reduce the duration of antibiotic use (9). The duration of antibiotic in the control arm of the trial was dependant on physician discretion and averaged 16.7 ± 7.4 days. The other group was managed with a BAL clinical pathway that utilized BAL on day 4 after initiation of adequate antibiotic therapy. If BAL quantitative cultures grew $< 10,000$ cfu/mL, the antibiotics were discontinued. The mean antibiotic use was 9.8 ± 3.8 days. There were no differences in pneumonia relapse, ventilator-free ICU days, ICU-free hospital days or mortality (Class I). While this study demonstrated a significant reduction in antibiotic use, which may help to decrease resistance over the long-term, the mean days of antibiotic use in the control group was considerably longer than the 8-10 day course that is gaining acceptance (9). Further studies are needed to determine the role of BAL as a guide to antibiotic duration.

In a large, multicenter trial, the use of BAL to determine antibiotic therapy did not result in significant differences in antibiotics administered or days alive without antibiotics (3). As described above, this may be related to the early and standardized empiric antibiotic therapy initially given to both groups.

In the meta-analysis discussed above, BAL did lead to tailoring of antibiotic therapy (Odds ratio for change in antibiotic management after invasive sampling, 2.85, 95% confidence interval 1.45–5.59) (5). In three of the four trials that reported antibiotic changes, 20.8% of all patients undergoing BAL and 12.8% of the non-invasively managed patients had initially inadequate antibiotic therapy that was then adjusted. However, this difference was not statistically significant (Odds ratio 1.96 95% CI 0.91-4.20). The fourth study reported antibiotic-free days and found that invasive testing significantly increased the number of antibiotic free days. Unfortunately, none of the reports consistently describe the reasons for antibiotic changes. The authors conclude that invasive techniques may be used to adjust antibiotic therapy; however, there is no difference in mortality (Class II).

ECONOMIC ANALYSIS

In a prospective study, patient charges associated with BAL and quantitative cultures were compared to those of TA (12). Over 14 months, the study enrolled 107 trauma patients based on clinical suspicion of pneumonia (at least 3 of fever > 101 F or < 96 F, leukocytosis >10,000 or immature forms > 10%, purulent sputum, new or worsened infiltrate on chest X-ray). In each case, a TA, PBS and BAL specimen were obtained in that order. One hundred thirty-six sets of cultures were obtained during the study period. Patients were then started on empiric antibiotics of ceftazidime and vancomycin. Antibiotics were tailored according to TA results as cultures returned. The incidence of nosocomial pneumonia by each method was TA (73%), PSB (34%), BAL (25%). Charges were calculated to include the overall charges associated with a diagnosis of nosocomial pneumonia. Based on a 14 day course of antibiotics, the charges associated with diagnosis by TA was \$302,830. Charges associated with PSB were 58% of that and those for BAL were 43%. The authors conclude that the charges incurred by the initial BAL may be offset by the antibiotic savings associated with a lower rate of diagnosis of VAP.

An interesting thought experiment by Ost et al compared the theoretic costs and benefits of empiric treatment alone, TA, mini-BAL, BAL, and BAL with PSB. They constructed a decision tree for the diagnosis and treatment of VAP and created a hypothetical cohort of immunocompetent patients in the intensive care unit, intubated for 7 days, with evidence of late-onset VAP and an estimated mortality rate of 20% for use in a decision analysis model. The initial decision was whether to do a diagnostic test immediately. The second decision was how many initial antibiotics to give. Two separate aspects of cost were considered: financial cost and antibiotics used. Effectiveness was measured in terms of hospital survival. A decision analysis model that examined 16 strategies in the management of VAP was constructed. Initial coverage with three antibiotics was better than expectant management or one or two antibiotic approaches, leading to both improved survival (54% vs. 66%) and decreased cost (\$55,447 vs. \$41,483 per survivor). Testing with mini-BAL did not improve survival, but did decrease costs (\$41,483 vs. \$39,967) and antibiotic use (63 vs. 39 antibiotic days per survivor). From the perspective of minimizing cost, minimizing antibiotic use, and maximizing survival, the best strategy was three antibiotics with mini-BAL (Class III).

CONCLUSIONS

Early, appropriate antibiotic therapy is essential to decreasing the mortality associated with VAP. Though BAL has not been shown to improve mortality in VAP patients, it offers several advantages in the diagnosis and management of these patients. It provides greater specificity in the diagnosis and thus reduces unnecessary antibiotic use. By allowing direct visualization of the airway, BAL may also facilitate the diagnosis of other pulmonary pathology. Its costs compare favorably with the cost of overuse of antibiotics. Mini-BAL may have advantages in some situations in that it can be performed by trained respiratory therapists and may minimize cost. It has become our practice to perform BAL to obtain a sputum specimen when there is clinical suspicion of VAP and as part of a fever work-up.

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Clinical Pulmonary Infection Score (CPIS)

Parameter	Score
<u>Temperature (°C)</u>	
≥36.5 and ≤ 38.4	0
≥38.5 and ≤ 38.9	1
≥39.0 or ≤ 36.5	2
<u>White Blood Cell (WBC) Count</u>	
≥4,000 and ≤ 11,000	0
<4,000 or >11,000	1
<4,000 or > 11,000 & band forms ≥ 50%	2
<u>Tracheal Secretions</u>	
None or scant	0
Non-purulent	1
Purulent	2
<u>PaO₂/FiO₂</u>	
>240, ARDS* or pulmonary contusion	0
≤240 and no ARDS*	2
<u>Chest Radiograph</u>	
No infiltrate	0
Diffuse (or patchy) infiltrate	1
Localized infiltrate	2

Total CPIS	Action
≤6 and low suspicion for VAP	Evaluate for other potential sources of infection
≤6 and high suspicion for VAP	BAL or mini-BAL
>6	BAL or mini-BAL

* ARDS is defined as a PaO₂/FiO₂ ≤200, PAOP ≤18 mmHg, and acute bilateral infiltrates

Figure 1: Ventilator Associated Pneumonia (VAP) Evaluation Algorithm

