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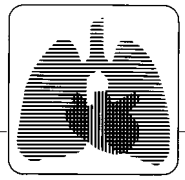

The Diagnosis of Ventilator-Associated Pneumonia*

A Comparison of Histologic, Microbiologic, and Clinical Criteria

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Study objective: **To evaluate histologic, microbiological, and clinical criteria in the recognition of ventilator-associated pneumonia (VAP) in patients who died while mechanically ventilated.**
Methods: **The study group consisted of 39 patients who died after a mean of 14 days of mechanical ventilation. Postmortem fiberoptic bronchoscopy (FOB) and open lung biopsy were performed with collection of specimens initiated <1 h after death. The microbiological specimens included suction catheter aspirate of tracheal secretions, FOB-guided protected specimen brush (PSB) of tracheal secretions, blindly placed PSB in a distal airway, FOB-guided PSB in a distal airway, and FOB-guided BAL fluid (BALF) in a distal airway. Qualitative bacteriologic study was performed on all specimens, and quantitative bacteriologic study was performed on all but the suction catheter aspirate of the trachea. A biopsy specimen of peripheral lung parenchyma from the same region sampled by FOB was sent for quantitative culture and histologic analysis. The BALF was analyzed for cell population and percent of neutrophils containing intracellular organisms. The clinical criteria selected for comparison with histologic and microbiological results included a temperature 38.5°C during the 48 h prior to death, a WBC count 15,000/mm^3 in the 48 h prior to death, presence of a bacterial or fungal pathogen on the last sputum culture, radiographic worsening in the week prior to death, and worsening gas exchange defined as a 15% decrease in the PaO_2/fraction of inspired oxygen ratio in the 72 h prior to death.**
Results: **None of the quantitative cultures had a reliable positive predictive value for histologic pneumonia. None of the five clinical criteria tested showed agreement with the presence or absence of histologic pneumonia. There was a significant correlation between qualitative and quantitative microbiological results from the distal airway/FOB-guided PSB, distal airway/BALF, and quantitative culture of the lung parenchyma. Also, suction catheter aspirate of the trachea had a sensitivity of 87% in recognizing the bacterial species simultaneously present in lung parenchyma. None of the patients with histologic pneumonia had <50% neutrophils in the BALF.**
Conclusions: **Neither the bacterial density from the four airway quantitative cultures, nor the bacterial density from quantitative culture of lung parenchyma accurately separated the histologic pneumonia and nonpneumonia groups. No clinical criteria or combination of clinical criteria correlated with the presence or absence of histologic pneumonia. A BALF with <50% neutrophils had a 100% negative predictive value for histologic pneumonia. A BALF quantitative culture had a sensitivity of 63%, specificity of 96%, and positive predictive value of 91% in recognizing sterile lung parenchyma. Thus, BALF may have a role in excluding pneumonia/infection in the ventilated patient. Antibiotic choice for the empiric therapy of VAP can be accurately guided by the microbial population recognized through culture of a tracheal suction catheter aspirate.** ***(CHEST 1997; 112:445-57)***

Key words: clinical criteria; diagnosis; postmortem histology; quantitative bacteriology; ventilator-associated pneumonia

Abbreviations: BALF=BAL fluid; FIO_2=fraction of inspired oxygen; FOB=fiberoptic bronchoscopy; HP-con=histologic pneumonia-consensus; HP-pre=histologic pneumonia-preselected criteria; PSB=protected specimen brush; VAP=ventilator-associated pneumonia

The development of pneumonia is a frequent and serious complication in mechanically ventilated patients.[1] Clinical criteria for the diagnosis of ventilator-associated pneumonia (VAP) have proved inadequate, and cultures of respiratory secretions obtained through the endotracheal tube lack specificity because of the high incidence of bacterial colonization of the airway.[2-7] Specialized techniques such as quantitative culture of secretions obtained by protective specimen brush (PSB) and quantitative culture of BAL fluid (BALF) have been developed to improve diagnostic accuracy.[8-10] In a seminal study, Chastre and colleagues[8] in 1984 reported validation of a distal airway/fiberoptic bronchoscopy (FOB)-directed PSB in recognizing histologic pneumonia in ventilated patients. This study was the foundation for subsequent investigations that utilized PSB as the diagnostic criterion for the presence or absence of VAP.

In 1991, we began a study of the diagnosis of VAP following the recommendations of an international consensus conference by using lung histologic study and culture of lung parenchyma as a basis for assessing various microbiological diagnostic techniques and clinical criteria in recognizing VAP.[11] The microbiological techniques chosen included culture and Gram's stain of a tracheal suction catheter aspirate and quantitative cultures of tracheal secretions obtained by FOB-guided PSB, distal airway secretions obtained by a blindly passed PSB, distal airway secretions obtained by FOB-guided PSB, BALF, and peripheral lung parenchyma obtained by postmortem lung biopsy. The population studied consisted of patients dying while receiving mechanical ventilation. The vast majority of patients evaluated were receiving antibiotics at the time of death as mechanically ventilated patients in our hospital almost inevitably receive such therapy for either a perceived VAP or extrapulmonary infection.

Materials and Methods

Study Design

The study, a prospective cross-sectional study of 40 patients dying while receiving mechanical ventilation, was approved by our institutional review committee on human research.

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Patient Population

The patients were recruited from the combined medical and surgical ICU of a 234-bed teaching hospital. The criteria for inclusion were as follows: (1) the patient had ≥24 h of mechanical ventilation prior to death; (2) the patient had been hospitalized for ≥72 h prior to death; and (3) specimen collection could be completed within 2 h of death. Patients were excluded from the study if there was premortem evidence of bilateral pleural infection, the patient had bilateral chest tubes, or the patient was known to be infected with HIV. Informed consent for the study was obtained from legally responsible family members after the purpose and design were carefully explained.

Specimens Collected

Prior to FOB, the patients' chest radiographs were reviewed to identify the location of the most recent airspace disease. All specimens were obtained by only two physicians (S.H.K. or D.E.C.). Collection was initiated as soon as possible after death. The following sequence was performed.

(1) Trachea/Suction Catheter Aspirate: A sterile 14F suction catheter (Kendall; Mansfield, Mass) was advanced through the endotracheal tube to a depth measured to be 2 cm distal to the tip. Once in position, suction was applied and the catheter removed with a rotary motion. The secretions obtained were collected in a sterile 40-mL sputum trap (Medical Marketing Group Inc; Decatur, Ga). If no respiratory secretions were obtained on the first pass, 5 mL of sterile saline solution was injected through the endotracheal tube and the aspirate repeated.

(2) Distal Airway/Blindly Placed PSB: A PSB (No. 1607, 3-mm PSB; Microvasive; Milford, Mass) was blindly passed through the endotracheal tube. Effort was made to manipulate the brush into the lung with the greatest radiographic abnormality by turning the patient's head opposite the affected lung and advancing the sheathed catheter 50 to 60 cm or until resistance was felt. The inner brush was then advanced 2 cm beyond the tip of the catheter jettisoning the protective polyethylene glycol plug. With rotation of the brush, secretions were collected and the brush withdrawn into the catheter to protect it from contamination. The catheter was left in place until FOB was performed to determine its location. After visual localization, the sheathed PSB was removed and quantitative culture performed.

(3) Trachea/FOB-Guided PSB: Postmortem FOB was performed with a bronchoscope (Olympus BF20D; Mellville, NY) passed through the patient's endotracheal tube. The FOB was passed into the lower trachea to the tip of the endotracheal tube. A PSB was extended and secretions collected under direct vision for quantitative culture from the lower trachea 1 to 3 cm distal to the endotracheal tube tip.

(4) Distal Airway/FOB-Guided PSB: The FOB was then used to pass a PSB under direct vision into a subsegmental airway. The site of bronchoscopic sampling was determined by the presence of new airspace disease on a recent chest radiograph. In patients without radiographic change, the presence of endobronchial purulence was used to determine the sampling site. When infiltrates and purulence were absent or diffuse, specimens were collected from the right middle lobe. The tip of the brush was extended beyond the field of vision into a subsegment and secretions were obtained. The brush was removed and quantitative culture performed.

(5) Distal Airway/BAL: BAL was performed in the same segment/subsegment from which the distal airway/FOB-guided PSB was obtained. Mechanical ventilation was continued and the tip of the FOB was wedged in the selected segmental or subsegmental airway. BALF was performed using six sequential

20-mL aliquots of sterile, nonbacteriostatic saline solution with returns aspirated by gentle suction applied to the side channel of the bronchoscope. The return from the first 20 mL was discarded and returns from the subsequent five 20-mL aliquots were pooled and submitted for quantitative culture and cell analysis.

(6) Lung Parenchymal Biopsy: Following collection of bronchoscopy specimens, the chest wall was prepared for thoracotomy. A region extending from sternum to posterior axilla was painted with antiseptic (Clinidine Povidone-Iodine Solution; Guilford, Conn) and surrounded with sterile drapes. An intercostal incision was made extending from midclavicular line to midaxillary line. A sterile rib-spreader, forceps, and scalpel were then used to obtain the lung biopsy specimen. The region from which the biopsy specimen was to be taken was identified by leaving the FOB in place after the BALF with the light source illuminating the region eventually sampled. A piece of lung parenchyma measuring at least 2×3 cm with a depth ≤1 cm was obtained from the subsegment from which the distal airway/FOB-guided PSB and BALF were obtained. Care was exercised to avoid obtaining tissue more than 1 cm below the lung surface so that only distal lung parenchyma would be included.

Microbiology

(1) Tracheal Aspirate: A Gram's stain of the tracheal aspirates was prepared and examined for WBCs and microorganisms. The specimen was cultured on sheep's blood, chocolate agar, and MacConkey plates and all bacterial species isolated were identified by standard microbiological technique.

(2) Protected Specimen Brush: Our technique for quantitative brush culture has been reported previously in detail.[12] Processing of the PSB began with severing the distal 2 cm of plastic sheath using sterile scissors. The brush was then advanced, aseptically removed, and dropped into 1 mL of trypticase soy broth. The solution was vortexed for 30 s and loops containing 0.01 mL of the solution were plated onto sheep's blood, chocolate agar, and MacConkey plates for aerobic and anaerobic culture. Following a minimum incubation period of 3 days, plates were assessed for bacterial or fungal growth. Each distinct colony was counted separately, multiplied by 100, and recorded as colony forming units per brush. All bacterial species isolated by quantitative culture were identified by standard microbiological technique.

(3) Quantitative Culture of BALF: A 0.1-mL aliquot of undiluted lavage solution was plated onto sheep's blood, chocolate agar, and MacConkey plates for aerobic and anaerobic culture. Each distinct colony was counted separately, multiplied by 10 and recorded as colony forming units per milliliter BALF.

(4) Quantitative Culture of Lung Parenchyma: Using sterile technique, lung biopsy specimens were halved lengthwise with one specimen examined histologically and the other submitted for microbiological analysis. The specimen for culture was weighed, crushed, and 1 g of tissue was emulsified in 5 mL of trypticase soy broth. A Gram's stain of the preparation was performed and the presence or absence of microorganisms noted. Lung parenchyma emulsion (0.25 mL) was inoculated by pipette onto sheep's blood, chocolate agar, and MacConkey plates. Each distinct colony was counted separately, multiplied by 20, and recorded as colony forming units per gram of lung parenchyma.

(5) Lung Histology: Tissue was fixed in formaldehyde solution and representative sections mounted onto slides. The details of the histologic analysis are reported in an accompanying article.[13]

BALF Cell Populations

Our method of BALF cell analysis has been reported previously in detail.[14,15] The volume of the return was recorded and a small aliquot of fluid was taken for estimation of cell viability by trypan blue dye exclusion. A hemocytometer chamber count was performed to determine the total number of nucleated cells in the BALF. The lavage fluid was then centrifuged at 450 *g* for 10 min to separate cellular elements. The supernatant was decanted, and the pellet was resuspended in 5 to 10 mL of balanced salt solution (RPMI-1640 with 10% fetal calf serum (FCS); Gibco Laboratories; Grand Island, NY). Morphologic analysis of the cell population was performed on a Wright-Giemsa-stained cytocentrifuged preparation. Pulmonary alveolar macrophages were identified by nonspecific esterase stains. Neutrophils, lymphocytes, eosinophils, basophils, alveolar macrophages, bronchial epithelial (columnar) cells, and squamous cells were quantitated, and results were recorded as a percentage of the total nucleated cells in the differential cell count. Three hundred or more cells from each BALF were counted. Also, the number of neutrophils with intracellular microorganisms was recorded and expressed as a percent of total neutrophils present.

Clinical Data

Patient charts were reviewed with the following clinical and laboratory data recorded: age, sex, respiratory diagnoses at the time of intubation, duration of mechanical ventilation, type and duration of antimicrobial therapy, results of the most recent culture of respiratory secretions, the maximum temperature in the 48 h prior to death, the highest WBC count in the 48 h prior to death, and arterial blood gas results from the last week of life. In this study, ARDS was defined as follows: (1) presence of bilateral pulmonary infiltrates; (2) a PaO_2 fraction of inspired oxygen (FIo_2) ratio <200 regardless of positive end-expiratory pressure; and (3) pulmonary capillary wedge pressure <18 mm Hg when measured, or no clinical evidence of left atrial hypertension.[16]

The chest radiographs from the last week of life for each patient were reviewed by a radiologist blinded to all other patient information. A chest radiograph obtained in the 48 h prior to death was compared to one taken approximately 7 days earlier, and graded as showing progressive airspace disease, improvement in airspace disease, or unchanged over this interval.

Clinical criteria arbitrarily selected to compare with histologic and microbiological results were as follows: (1) temperature ≥38.5°C in the 48 h prior to death; (2) WBC count ≥15,000 in the 48 h prior to death; (3) presence of a bacterial or fungal pathogen on the most recent sputum culture; (4) progression of radiographic infiltrates over the 7 days prior to death; and (5) worsening gas exchange as evidenced by a decrease in the PaO_2/FIo_2 ratio of at least 15% in the 72 h prior to death.

Statistical Analysis

In accord with previous studies of quantitative bacteriology and histologic pneumonia, a bacterial density $\geq 10^4$ cfu of a single organism from lung parenchyma or BALF and a bacterial density of $\geq 10^3$ cfu of a single bacterial species on PSB were considered as "positive for pneumonia" in our analysis.[8,9]

The correlation of microbiology results with histology was measured by sensitivity, specificity, positive predictive value, and negative predictive value calculated using standard formulas. The number of microbial species from various specimens was compared using the Wilcoxon rank sum test assuming nonrandom distribution. The relationship between quantitative culture results was explored with linear regression. BALF cell populations were expressed as the mean±SD and compared using a two-tailed Student's *t* test. The correlation among clinical, histologic, microbiological, and BALF results was calculated by Kappa statistics.[17,18] A p value ≤0.05 was considered significant.

Results

From August 1991 to October 1994, 40 patients were prospectively entered. The pathology specimen from one patient was lost in the course of the study and the related data were excluded from analysis. The study group of 39 patients consisted of 20 women and 19 men with a mean age of 66 years (range, 38 to 85 years). The duration of mechanical ventilation ranged from 1 to 134 days with a mean of 14 days and median of 8 days. Thirty-six of 39 patients had airspace disease on the chest radiograph taken most recent to the time of death and 38 patients had received antibacterial and/or antifungal therapy in the 48 h prior to death. Collection of specimens was initiated 57±26 min after death.

The primary pulmonary disease present at the time of intubation included ARDS in 24 patients, COPD in four patients, congestive heart failure in three patients, alveolar hemorrhage in two patients, and bronchiolitis obliterans organizing pneumonia (BOOP), pulmonary emboli, and interstitial lung disease in single patients. Three patients had no pulmonary disease at the time of intubation.

Histologic Results

One hundred forty-six slides from 39 patients were examined independently by a panel of four pathologists.[13] The pathologists were blinded to microbiological results, clinical information, and the interpretation of their peers. No *a priori* criteria for recognition of pneumonia were used for the initial analysis. There was considerable variation between pathologists in the identification of patients with pneumonia. Arbitrarily we used a consensus of three or more pathologists to separate the study group into nine patients with pneumonia and 30 patients without pneumonia. In addition, the slides were reviewed by a single pathologist and graded as severe, moderate, mild, or no pneumonia according to the criteria of Johanson et al.[19] This produced a group of 14 patients with pneumonia (one severe, five moderate, and eight mild), and included eight of the nine patients selected by consensus. These two histologic groups will be referred to as HP-consensus (HP-con) and HP-preselected (HP-pre) in the results. Patients without pneumonia are designated no-HP-con and no-HP-pre, respectively.

Correlation Between Histology and Quantitative Cultures

Table 1 lists the microbiological results from all 39 patients. A comparison of quantitative bacteriology results with the presence or absence of pneumonia is shown in Figure 1. The scattergrams demonstrate extensive overlap in bacterial populations in patients with and without pneumonia in both the groups selected by consensus of pathologists and preselected criteria. There was no clear separation of pneumonia from nonpneumonia by any of the five quantitative culture specimens obtained. Quantitative culture of the lung parenchyma and quantitative culture of secretions obtained by a FOB-guided PSB in a distal airway are the specimens previously most extensively studied and are shown on the right-sided panels of Figure 1. Only one of nine patients of the HP-con group had $\geq 10^4$ cfu/g of lung parenchyma and none of the 14 HP-pre group achieved this microbial density (Fig 1, *bottom right*). However, 2 of the 30 no-HP-con patients and 3 of the 25 no-HP-pre patients had $\geq 10^4$ cfu/g of tissue. The distal airway/FOB-guided PSB yielded $\geq 10^3$ cfu per brush in three patients in both pneumonia groups (Fig 1, *top right*). However, 11 patients in both the no-HP-con and no-HP-pre groups had $\geq 10^3$ cfu on this culture. Forty-four percent of the HP-con and 43% of the HP-pre patients had sterile peripheral lung parenchyma (Fig 1, *bottom right*). Quantitative culture from distal airway/FOB-guided PSB was sterile in 56% of HP-con and 57% of HP-pre patients (Fig 1, *top right*). The distal airway/BALF was sterile in 33% of HP-con patients and 36% of HP-pre patients (Fig 1, *bottom left*).

The sensitivity, specificity, and predictive values of the five quantitative bacteriological specimens in recognizing histologic pneumonia are listed in Table 2. The greatest sensitivity was 50% in HP-con patients with $\geq 10^3$ cfu from a tracheal/FOB-guided PSB. The specificity of this culture was 59% and positive predictive value was 25%. Greater than or equal to 10^4 cfu of a microbial species on culture of peripheral lung parenchyma had a specificity of 93% for HP-con but was found in only one of nine patients for a sensitivity of 11%. The negative predictive value was greater than positive predictive value for all five specimens. The sensitivity, specificity, and positive predictive values of quantitative bacteriology showed a trend to be higher for HP-con than HP-pre patients for all specimens except distal airway BALF.

The correlation between quantitative culture results of peripheral lung parenchyma and endobronchial quantitative cultures was examined by linear regression. There was a significant correlation with distal airway/FOB-guided PSB bacterial density ($r=0.53$, $p=0.001$), distal airway BALF bacterial density ($r=0.51$, $p=0.001$), and the bacterial burden of lung parenchyma. The correlation between tracheal FOB-guided PSB and lung parenchyma culture results just missed statistical significance ($r=0.32$, $p=0.054$). There was no correlation be-

Table 1—*Bacteriology Results From 39 Patients Dying When Mechanically Ventilated*

Patient No.	Peripheral Lung Parenchyma/Lung Biopsy, cfu/g*	Distal Airway/FOB-Guided PSB, cfu/Brush†	Distal Airway/BALF, cfu/mL‡	Distal Airway/Blindly Placed PSB, cfu/Brush†	Trachea/FOB-Guided PSB, cfu/Brush†	Trachea/Suction Catheter Aspirate
1§‖	10 *Staphylococcus aureus* 3 *Candida albicans*	Sterile	108 *S aureus*	200 *S aureus*	3,200 *S aureus* 200 *C albicans*	*S aureus* *C albicans*
2§‖	67 *Aspergillus fumigatus*	Sterile	9 *S epidermidis* 27 *A fumigatus*	Sterile	Sterile	*S epidermidis* *A fumigatus*
3§‖	Sterile	Sterile	Sterile	Sterile	Sterile	Sterile
4§‖	882 *Pseudomonas aeruginosa*	2,300 *P aeruginosa*	1,200 *P aeruginosa*	7,000 *P aeruginosa*	10,000 *P aeruginosa*	*P aeruginosa*
5§‖	Sterile	Sterile	Sterile	Sterile	Sterile	Sterile
6§‖	40 *Staphylococcus epidermidis*	1,500 *S epidermidis*	10,000 *S epidermidis* 10,000 *S viridans* 10,000 *Eikenella corrodens* 140 *A fumigatus*	1,000 *S epidermidis* 100 *A fumigatus*	1,800 *S epidermidis* 100 *S viridans*	*S epidermidis* *A fumigatus*
7§‖	Sterile	Sterile	250 Diphtheria 300 *S epidermidis* 200 *S viridans*	Sterile	Not done	Diphtheria *S epidermidis* *S aureus* *S viridans*
8§	10,000 *S epidermidis* 150 Mucor 1,750 *C albicans*	10,000 *S epidermidis* 200 Mucor	100 *S epidermidis*	Sterile	3,000 *S epidermidis*	*S epidermidis* *C albicans* Proteus sp Mucor
9§‖	Sterile	400 *C albicans*	Sterile	Sterile	600 *C albicans*	*C albicans*
10‖	Sterile	Sterile	Sterile	Sterile	Sterile	*S epidermidis*
11	220 *S epidermidis*	Sterile	Sterile	Sterile	Sterile	*S epidermidis* *C albicans* *S marcesans*
12	Sterile	Sterile	Sterile	Sterile	Sterile	*C glabrata*
13§	73 Enterobacter 545 *C albicans*	200 Enterobacter	100 Enterobacter 10 *C albicans*	Sterile	300 Enterobacter	Enterococcus *C albicans* *S epidermidis*
14	178 *Enterobacter cloacae* 44 Enterobacter 89 *Streptococcus viridans*	3,500 *E cloacae* 200 *K pneumoniae* 700 Enterobacter 600 *S viridans*	3,500 *E cloacae* 800 *K pneumoniae* 3,000 Enterobacter	8,000 *E cloacae* 2,500 *K pneumoniae* 5,000 Enterobacter 2,000 *S viridans*	10,000 *E cloacae* 4,000 *K pneumoniae* 10,000 Enterobacter 5,000 *S viridans*	*E cloacae* *K pneumoniae* Enterobacter *S viridans*
15	117 Diphtheria 1,167 *Klebsiella pneumonia*	2,700 Diphtheria 2,000 K pneumonia 100 *E cloacae*	150 Diphtheria 330 *K pneumoniae* 10 *E cloacae*	10,000 Diphtheria 1,200 *K pneumoniae* 500 *E cloacae*	6,000 Diphtheria 200 *K pneumoniae*	Diphtheria *K pneumoniae* E cloacae
16‖	Sterile	Sterile	Sterile	Sterile	Sterile	Sterile
17‖	50 *S epidermidis*	700 *S epidermidis*	700 *S epidermidis* 50 *C albicans*	300 *S epidermidis*	6,500 *S epidermidis* 300 Proteus sp	*S epidermidis* Proteus sp *C albicans*
18‖	62 *S epidermidis*	Sterile	10,000 *S epidermidis*	Sterile	300 *S epidermidis*	*S epidermidis*
19‖	150 *C albicans*	1,700 *C albicans*	60 *C albicans*	Sterile	Sterile	*C albicans*
20	100,000 *S epidermidis*	10,000 *S epidermidis*	10,000 *S epidermidis*	Sterile	Not done	*S epidermidis*

continued

Table 1—*Continued*

Patient No.	Peripheral Lung Parenchyma/Lung Biopsy, cfu/g*	Distal Airway/ FOB-Guided PSB, cfu/Brush†	Distal Airway/BALF, cfu/mL‡	Distal Airway/Blindly Placed PSB, cfu/Brush†	Trachea/FOB-Guided PSB, cfu/Brush†	Trachea/Suction Catheter Aspirate
21	4,300 *S epidermidis*	Sterile	10,000 *S epidermidis*	Sterile	10,000 *S epidermidis*	*S epidermidis*
	200 Enterobacter		1,500 *C glab*		1 *C glabrata*	*C glabrata*
	100 *C glabrata*		300 *S aureus*			
22	50,000 *S viridans*	10,000 *S viridans*	10,000 *S viridans*	9,000 *S viridans*	10,000 *S viridans*	*S viridans*
	800 *B streptococcus*	400 *B streptococci*	800 *B streptococci*	100 *B streptococci*	1,000 *B streptococci*	Micro
		100 Fusobacterium	50 Fusobacterium		100 Fusobacterium	
23	300 *C albicans*	Sterile	20 *C albicans*	Sterile	300 *C albicans*	*C albicans*
						S viridans
24	Sterile	Sterile	Sterile	Sterile	Sterile	Sterile
25	Sterile	Sterile	Sterile	Sterile	Sterile	*S epidermidis*
						Saccharomyces cerevisiae
26	1,695 *Acinetobacter calcoaceticus*	600 *A calcoaceticus*	2,000 *A calcoaceticus*		1,400 *A calcoaceticus*	*A calcoaceticus*
	3,390 Enterobacter	1,300 Enterobacter	3,200 Enterobacter	300 Enterobacter	3,500 Enterobacter	Enterobacter
	1,017 *S viridans*	700 *S viridans*	800 *S epidermidis*	100 *S viridans*	1,000 *S viridans*	*S viridans*
	339 *C albicans*	100 *S epidermidis*		100 Yeast	1,200 *S epidermidis*	*C albicans*
	339 *S epidermidis*				700 *C albicans*	*S epidermidis*
27	Sterile	100 *S viridans*	50 *K pneumoniae*	100 *K pneumoniae*	200 Hafnia	*S epidermidis*
		100 *S epidermidis*	10 Hafnia	100 Hafnia		*K pneumoniae*
			50 *S viridans*	500 *S viridans*		Hafnia
			70 *S epidermidis*	100 *S epidermidis*		*S viridans*
			30 *Haemophilus parainfluenzae*			*H parainfluenzae*
28	125 *C krusei*	10,000 *Escherichia coli*	10,000 *E coli*	6,500 *E coli*	10,000 *E coli*	*E coli*
29	Sterile	Sterile	Sterile	Sterile	Sterile	*H influenzae*
						C albicans
30	Sterile	Sterile	40 *Staphylococcus haemolyticus*	Sterile	2,100 *S haemolyticus*	*S haemolyticus*
31	292 *S epidermidis*	10,000 *S epidermidis*	10,000 *S epidermidis*	Sterile	10,000 *S epidermidis*	*S epidermidis*
	92 *S viridans*	4,500 *S viridans*	10,000 *S viridans*		10,000 *S viridans*	*S viridans*
	1,000 Lactobacillus	1,500 Lactobacillus	10,000 Lactobacillus		10,000 Lactobacillus	Lactobacillus
32	233 *C albicans*	Sterile	160 *C albicans*	600 *C albicans*	2,400 *C albicans*	*C albicans*
33	46 *C albicans*	2,600 *C albicans*	160 *C albicans*	Sterile	Sterile	*C albicans*
34	Sterile	Sterile	Sterile	Sterile	Sterile	Sterile
35	64 *S viridans*	300 Enterobacter	1,200 Enterobacter	4,000 Enterobacter	6,000 Enterobacter	*S epidermidis*
	2 S *epidermidis*	3,000 *E cloacae*	1,800 *E cloacae*	10,000 *E cloacae*	10,000 *E cloacae*	*S epidermidis*
	156 *E cloacae*					*E cloacae*
36	Sterile	Sterile	100 *S epidermidis*	1,000 *S epidermidis*	300 *S epidermidis*	*S epidermidis*
			30 Enterobacter	500 Enterobacter		*S viridans*
			30 *C albicans*	200 *C albicans*		Enterobacter
						C albicans

continued

Table 1—*Continued*

Patient No.	Peripheral Lung Parenchyma/ Lung Biopsy, cfu/g*	Distal Airway/FOB-Guided PSB, cfu/ Brush†	Distal Airway/BALF, cfu/mL‡	Distal Airway/Blindly Placed PSB, cfu/Brush†	Trachea/FOB-Guided PSB, cfu/Brush†	Trachea/Suction Catheter Aspirate
37	Sterile	10,000 staphylococcus	1,600 *S viridans*	400 *S viridans*	800 *S viridans*	*S viridans*
			1,200 *H parainfluenzae*	5,000 *H parainfluenzae*	1,500 *H parainfluenzae*	*C albicans*
			10 *C albicans*			*H parainfluenzae*
38	Sterile	Sterile	60 *C albicans* 250 *S epidermidis*	Sterile	Sterile	*C albicans*
39	20 *S epidermidis*	100 *S epidermidis*	450 *S epidermidis*	300 *S epidermidis*	100 *S epidermidis*	*S epidermidis*
	5 *S viridans* 5 *C albicans* 20 Diphtheria	200 *S viridans*	600 *S viridans* 300 Diphtheria 50 *C albicans* 10 Enterobacter	200 *S viridans* 100 Diphtheria		S viridans Diphtheria *C albicans*

*CFU per gram of lung parenchyma.
†PSB specimens are recorded as CFU per brush.
‡CFU per mL of BALF returned.
§HP-con.
‖HP-pre.

tween quantitative bacteriology results from the distal airway/blindly placed PSB and culture of lung parenchyma ($r=0.15$, $p=0.37$).

Sixteen of 39 patients had sterile lung parenchyma by quantitative culture. Table 3 shows the sensitivity, specificity, and predictive values of the four endobronchial quantitative cultures in recognizing these 16 patients. An endobronchial culture must also be sterile to be a true positive. The distal airway/FOB-guided PSB had a sensitivity of 81%, specificity of 70%, and positive predictive value of 65%. Distal airway/BALF had a sensitivity of 63% but sterile BALF had a specificity of 96% and positive predictive value of 91% for sterile lung parenchyma.

Comparison of Five Culture Techniques in Identifying the Microbial Species Found on Culture of Lung Parenchyma

In total, 44 different microbial species were isolated from peripheral lung parenchyma culture in 39 patients. The number of microbial species isolated on culture of the lung parenchyma was variable among the patient group. For example, in the nine patients with HP-con, one had three microbial species on culture of the lung parenchyma, one had two microbial species, three had a single isolate, and the lung culture was sterile in four (Table 1). The isolates included 13 fungi and 31 bacteria. Fungi were isolated from 12 different patients and were the only microbiologic isolate in six and the predominant isolate in one additional patient (Table 1).

The mean number of bacterial species isolated by six different culture specimens is listed in Table 4. Culture of a tracheal suction catheter aspirate had a mean of 2.00 bacterial species per patient, and BALF had a mean of 1.64 species per patient. Both specimens had a significantly greater number of bacterial species than the 1.12 bacterial species found on culture of lung parenchyma. All PSB specimens approximated one isolate per patient and were not statistically different from the number of species isolated from lung parenchyma.

The sensitivity of the five culture specimens in recognizing microbial species isolated from culture of the lung parenchyma of all 39 patients is listed in Table 5. A lung biopsy specimen was considered positive when it was not sterile. An airway culture was considered positive when it recognized the same or more microbial species than present in the biopsy culture. The sensitivity from Table 5 is the probability that the airway culture is positive given that the biopsy culture is positive. The positive predictive value is the probability that a biopsy culture is positive given that the airway culture is positive. Although the tracheal suction catheter aspirate was frequently polymicrobial, 38 of the 44 microbial isolates from lung parenchyma were also isolated on tracheal aspirate for a sensitivity of 87% and specificity of 31%. The distal airway/BALF had a sensitivity of 65% in recognizing the microbial species present in lung parenchyma and specificity of 63%.

The distal airway/blindly placed PSB had the lowest sensitivity in recognizing lung parenchymal microbes at 30%. The distal airway/blindly passed

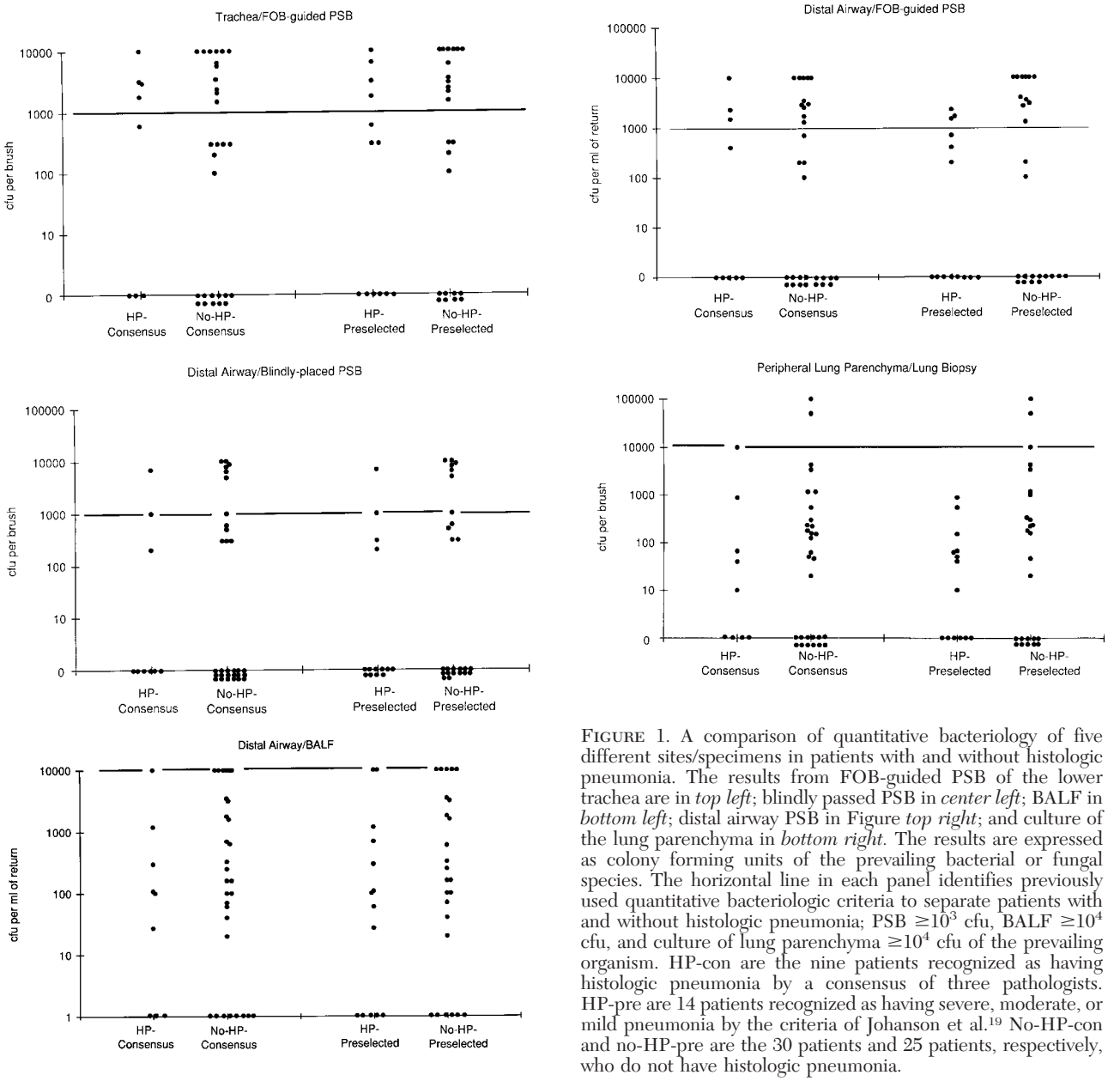

FIGURE 1. A comparison of quantitative bacteriology of five different sites/specimens in patients with and without histologic pneumonia. The results from FOB-guided PSB of the lower trachea are in *top left*; blindly passed PSB in *center left*; BALF in *bottom left*; distal airway PSB in Figure *top right*; and culture of the lung parenchyma in *bottom right*. The results are expressed as colony forming units of the prevailing bacterial or fungal species. The horizontal line in each panel identifies previously used quantitative bacteriologic criteria to separate patients with and without histologic pneumonia; PSB $\geq 10^3$ cfu, BALF $\geq 10^4$ cfu, and culture of lung parenchyma $\geq 10^4$ cfu of the prevailing organism. HP-con are the nine patients recognized as having histologic pneumonia by a consensus of three pathologists. HP-pre are 14 patients recognized as having severe, moderate, or mild pneumonia by the criteria of Johanson et al.[19] No-HP-con and no-HP-pre are the 30 patients and 25 patients, respectively, who do not have histologic pneumonia.

PSB was located in the right lower lobe in 23 patients, the right middle lobe in two patients, the left lower lobe in 12 patients, and coiled in the left mainstem bronchus in two patients. The blindly passed PSB sampled from the side intended in 20 of 39 patients.

BALF Cell Populations and Histologic Pneumonia

The percentage of neutrophils in the lavage of patients with HP-con ranged from 50 to 96% with a mean of 75±17% (Fig 2, *top*). This was significantly higher than no-HP-con patients who had a range of 1 to 96%, and mean of 46±28% (p=0.006). In contrast, the mean percent neutrophils with intracellular bacteria on Gram's stain in the HP-con patients ranged from 0 to 32% with a mean of 8±11% and was not significantly higher than in no-HP-con patients who had a range 0 to 61%, and a mean of 5±13% (p=0.58) (Fig 2, *bottom*). Less than 50% neutrophils in BALF was 100% predictive of the absence of pneumonia in no-HP-con patients.

Correlation of Clinical Criteria With Histology, Quantitative Culture of Lung Parenchyma, and BAL Cell Populations

The clinical criteria selected were temperature ≥38.5°C during the 48 h prior to death, a WBC count ≥15,000/mm^3 in the 48 h prior to death,

Table 2—*Sensitivity, Specificity, and Predictive Value of Quantitative Bacteriology in Recognizing Histologic Pneumonia*

Culture Site and Type	Peripheral Lung Parenchyma		Distal Airway FOB-Guided PSB		Trachea FOB-Guided PSB		Distal Airway Blindly Placed PSB		Distal Airway BALF	
	HP-con	HP-pre	HP-con	HP-pre	HP-con	HP-pre	HP-con	HP-pre	HP-con	HP-pre
Sensitivity in recognizing pneumonia,* %	11	0	33	21	50	31	22	14	11	14
Specificity, %	93	88	63	56	59	50	77	72	80	80
Positive predictive value, %	33	0	21	21	25	25	22	22	14	29
Negative predictive value, %	78	61	76	56	81	57	77	60	75	63

*$\geq 10^4$ cfu regarded as positive for quantitative culture of lung parenchyma and BALF; $\geq 10^3$ cfu regarded as positive for all PSB specimens.

presence of a bacteria or fungal pathogen on the last sputum culture, radiographic worsening in the week prior to death, and worsening gas exchange defined as a ≥15% decrease in the PaO_2/FIO_2 ratio in the 72 h prior to death.

The results are shown in Table 6. None of the five clinical criteria tested showed agreement with the presence or absence of histologic pneumonia, the results of quantitative culture of lung parenchyma, or the presence or absence of ≥50% neutrophils on BAL. For example, progression of radiographic infiltrates was seen in 55% of HP-con patients, and 64% of HP-pre patients, but also 50% of no-HP-con and 61% of no-HP-pre patients. One of three patients with $\geq 10^4$ cfu of organisms per gram of lung parenchyma had progressive radiographic infiltrates while 21 of 36 patients (58%) with $<10^4$ cfu showed radiographic progression over the last week of life.

Discussion

The diagnosis of pneumonia in the ventilated patient remains elusive. Chastre and colleagues[8] in 1984 were the first to use postmortem lung biopsy specimens for validation of the diagnosis of pneumonia, comparing histologic features with results from quantitative culture of lung parenchyma and an FOB-guided PSB of distal airway secretions. Twenty-six patients ventilated for a mean 11 days were studied, 14 of whom were receiving antibiotics. The lung biopsy specimen consisted of six 5-mm^3 specimens for culture and a 1-cm^3 specimen for histologic study. The histologic criteria for pneumonia was "foci of consolidation with intense polymorphonuclear leucocyte accumulation in bronchioles and adjacent alveoli." Six patients had histologic pneumonia. The authors found a statistically significant correlation between quantitative culture of lung parenchyma and quantitative culture of distal airway PSB. The correlation was stronger in the 12 patients who received no antibiotics for 1 week preceding death than in the 14 receiving antibiotics. A PSB culture with $\geq 10^3$ cfu was 100% sensitive in recognizing histologic pneumonia in patients with or without antibiotics with a negative predictive value of 100%. In patients receiving antibiotics, the specificity was 42% and positive predictive value was 22% compared with 87% and 80%, respectively, in patients not receiving antibiotics. The authors concluded that histologic pneumonia was characterized by $\geq 10^4$ cfu of one or more bacterial species in the lung parenchyma and that PSB of distal airway secretions reliably recognized the same bacteria although at a density of $\geq 10^3$ cfu per brush.[8]

There now have been five additional studies using postmortem histology as "the gold standard" to establish the accuracy of various quantitative cultures in recognizing VAP.[9,20-23] A comparison of these six studies is shown in Table 7. The studies vary in sample size, minimum duration of ventilation required for inclusion, mean duration of ventilation, frequency of pneumonia, frequency of antibiotic use,

Table 3—*Sensitivity, Specificity, and Predictive Value of Endobronchial Quantitative Bacteriology in Recognizing Sterile Lung Pneumonia*

Culture Site and Type	Tracheal Suction Catheter Aspirate	Trachea FOB-Guided PSB	Distal Airway Blindly Placed PSB	Distal Airway FOB-Guided PSB	Distal Airway BALF
Sensitivity, %	31	53	81	81	63
Specificity, %	100	73	52	70	96
Positive predictive value, %	100	57	54	65	91
Negative predictive value, %	68	70	80	84	79

Table 4—*Number of Microbial Species Isolated by Different Culture Specimens*

Site	Specimen	No. of Microbial Species per Patient (n=39) Mean±SD	Comparison to Peripheral Lung Parenchyma Culture (Wilcoxon Rank Sum Test, p Value)
Trachea	Suction catheter aspirate	2.00±1.43	0.004
Trachea	FOB-guided PSB	1.05±1.20	0.55
Distal airway	Blindly placed PSB	0.87±1.26	0.18
Distal airway	FOB-guided PSB	0.90±1.07	0.77
Distal airway	BALF	1.64±1.48	0.02
Peripheral lung parenchyma	Lung biopsy	1.12±1.32	—

microbiological specimens studied, and the size of the histologic specimen. The variation in histologic criteria is examined in detail in our companion article.[13] The extremes varied from the use of preselected criteria and a consensus of two pathologists to no criteria stated at all.[9,21] The conclusions from these studies were also variable. Chastre and colleagues[8] stated that "PSB offers a rather sensitive and specific approach to establish the causative organisms in cases of pneumonia and in differentiating between colonization of the upper respiratory tract and distal lung infection." In a second study using quantitative culture of BALF and PSB, the authors state "both samples very reliably identify both quantitatively and qualitatively microorganisms present in lung segments with bacterial pneumonia, . . . even in a patient already receiving antimicrobial therapy for several days."[9] In contrast, Torres and colleagues,[21] using similar specimens, concluded that "diagnostic procedures performed upon patients receiving antibiotic treatment are of poor help in managing ventilator-associated pneumonia." Rouby et al[20] also concluded that blindly passed protected BALF was "not reliable in critically ill patients receiving antibiotics."

In contrast to four of the six previous studies, we can find no meaningful correlation between histologic features and microbiological results. There are several possible explanations for the lack of correlation. First, the histologic features of VAP are not nearly as distinct as portrayed in a recent consensus conference. The definition offered at the conference was accumulation of polymorphonuclear leukocytes with confirmation of infection by demonstration of the infecting microorganism.[24] However, the pulmonary neutrophil population has many modifiers. A number of noninfectious pulmonary diseases, including ARDS, congestive heart failure, pulmonary hemorrhage, ischemia, and possibly atelectasis may result in neutrophil accumulation. At the opposite extreme, neutropenia, corticosteroids, malnutrition, and diffuse alveolar damage may reduce the neutrophil response to infection. Antibiotic therapy is the principal factor affecting the recovery of the offending organism from lung parenchyma. The invading organism may produce pneumonia with a typical neutrophilic response but then be unrecoverable because of the use of antibiotics.

There are several observations of clinical importance made by this study.

(1) An aspirate of the lower trachea via a sterile suction catheter introduced through the endotracheal tube had a 87% sensitivity in recognizing the bacterial species simultaneously present in lung parenchyma. This means that in patients suspected of having pneumonia, the antibiotic selection for possible parenchymal pathogens can be accurately directed by the suction catheter aspirate. Although the sensitivity was excellent at 87%, the specificity was only 31% as there are multiple bacteria isolated from trachea and endotracheal tube that probably are not pathogens.

(2) We found a significant correlation between peripheral lung parenchyma quantitative culture and quantitative culture results from both distal airway/FOB-guided PSB and distal airway BALF, although

Table 5—*Sensitivity, Specificity, and Predictive Value of Endobronchial Cultures in Recognizing the Microbial Species Isolated From Culture of the Lung Parenchyma in 39 Patients*

Site	Specimen	Sensitivity, %	Specificity, %	Positive Predictive Value, %	Negative Predictive Value, %
Trachea	Suction catheter aspirate	87	31	65	63
Trachea	FOB-guided PSB	55	67	71	50
Distal airway	Blindly placed PSB	30	81	70	45
Distal airway	FOB-guided PSB	44	81	77	50
Distal airway	BALF	65	63	72	56

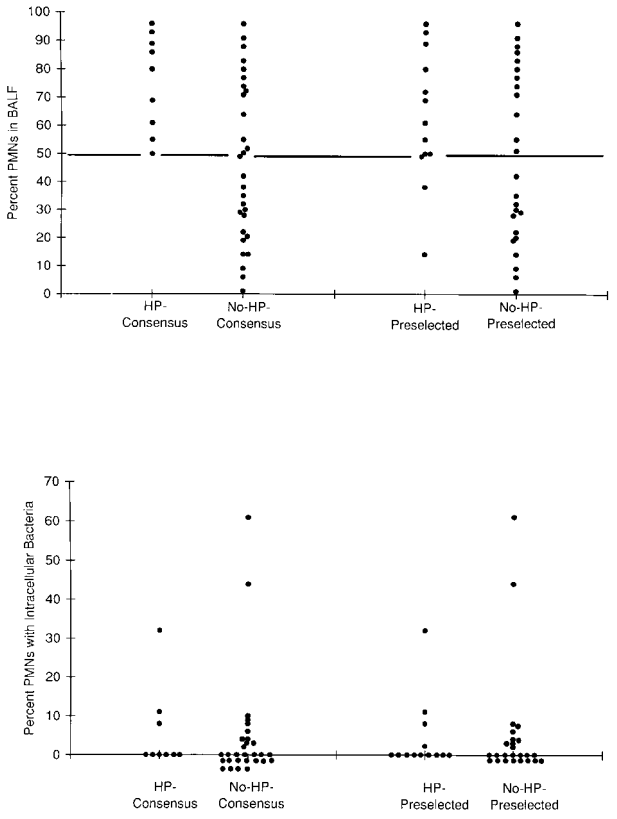

FIGURE 2. Scattergrams showing percent BALF neutrophils (*top*) and percent neutrophils with intracellular bacteria (*bottom*) in patients with and without histologic pneumonia.

none of the three correlated with the presence or absence of histologic pneumonia. Of particular note was the ability of sterile endobronchial cultures to recognize sterile lung parenchyma; distal airway/FOB-guided PSB had a sensitivity of 81%, specificity of 70%, positive predictive value of 65%, and negative predictive value of 84%, and BALF had a sensitivity of 63%, specificity of 96%, positive predictive value of 91%, and negative predictive value of 79%. Reliable recognition of sterile lung parenchyma is of major clinical importance. In patients not receiving antibiotics, sterile lung parenchyma would indicate the absence of infection and similar findings in patients receiving antibiotics would at least indicate no need to change to new antimicrobials and in some instances, facilitate a decision to stop antibiotic therapy.

(3) None of the patients with <50% neutrophils in the BALF had histologic pneumonia. BALF is another measure of the neutrophil population within lung parenchyma. BAL samples up to 5% of total lung volume and thus a far greater area than represented by our 2×3×1-cm peripheral lung biopsy specimen. BALF may avoid some of the sampling error inherent in a small peripheral biopsy specimen. Our finding creates the possibility that BALF with <50% neutrophils could be an indication that the patient need not be treated for bacterial pneumonia. However, this will have to be substantiated in future studies.

Marquette and colleagues[22] also found increased neutrophils in patients with pneumonia (87±13%) in comparison to patients without pneumonia (49±32%). They concluded that "the large range of values within each group precludes the use of a high neutrophil count as a reliable clue for establishing the diagnosis of pneumonia." Our data suggest the role of BALF neutrophils lies in its negative predictive value for histologic pneumonia in those patients with <50%. Chastre et al[9] observed 77±27% neutrophils in lung segments with $\geq 10^4$ bacteria/per gram of tissue and that the presence of intracellular bacteria correlated with lung bacterial burden. Ten

Table 6—*Correlation of Clinical Findings With Histologic Diagnosis of Pneumonia, Microbial Population of Lung Parenchyma, and BALF Neutrophil Content*

	Histologic Diagnosis of Pneumonia		≥10,000 cfu of Bacteria or Fungus on Culture of Lung Parenchyma	Sterile Lung Parenchyma Culture	≥50% Neutrophils in BALF
	HP-con	HP-pre			
Temperature ≥38.5°C in previous 48 h	0.15*	0.14	−0.15	0.00	0.03
WBC count ≥15,000 in the previous 48 h	−0.03	0.17	−0.07	0.10	0.07
Presence of a bacterial or fungal pathogen on recent sputum culture	−0.06	−0.10	0.02	0.21	−0.08
Increasing air space disease on CXR†	0.04	0.12	−0.09	0.10	−0.04
Decrease in PaO_2/FIO_2	0.11	−0.03	−0.04	−0.04	0.09

*Kappa statistic <0.4 reflects very poor agreement between the two measurements.
†CXR=chest radiograph.

Table 7—*Studies of VAP in Humans With Histologic Confirmation of Pneumonia*

Source	Year	Total No. of Patients	No. (%) of Patients With Pneumonia	No. (%) of Patients Receiving Antibiotics	Duration of Ventilation Required for Inclusion, h	Biopsy Specimen Size for Histologic Study	Microbiological Specimens*	Days of Ventilation, Mean±SD
Chastre et al[8]	1984	26	6 (23)	14 (54)	>1	1×1×1 cm	(1) PSB distal airway (2) Lung parenchyma	16±21
Rouby et al[20]	1992	83 (only 33 with quantitative bacteriology)	43 (52)	67 (81)	>48	Unilateral pneumonectomy	(1) Protected mini-BALF passed blindly (2) Lung parenchyma	17±13
Torres et al[21]	1994	30	18 (60)	30 (100)	>72	Bilateral 2×2×2 cm	(1) PSB distal airway (2) BALF (3) Bronchial aspirate through FOB channel (4) FOB needle aspirate (5) Lung parenchyma	9±7
Marquette et al[22]	1995	28	19 (67)	13 (46)	>48	Bilateral pneumonectomy in 22 patients, lobectomy in 5 patients	(1) PSB distal airway (2) BALF (3) Endotracheal aspirate	11±8
Chastre et al[9]	1995	20	11 (55)	18 (90)	>72	5×5×5 cm from each of two lobes	(1) PSB distal airway (2) BALF (3) Lung parenchyma	16±9
Papazian et al[23]	1995	38	18 (47)	25 (66)	>72	Unilateral pneumonectomy	(1) Blind distal airway suction catheter (2) Blind mini-BALF (3) PSB distal airway (4) FOB BALF (5) Lung parenchyma	23.4±27.5

*All are quantitative cultures unless stated otherwise.

of 11 segments with $\geq 10^4$ bacteria/per gram of lung tissue had >5% of cells with intracellular organisms while <1% of cells contained intracellular bacteria in eight of nine noninfected lung segments.[9] We found no correlation between percent of neutrophils with intracellular bacteria and either the presence of histologic pneumonia or the bacterial burden of lung parenchyma.

We conclude that none of the quantitative bacteriology specimens used were predictive of the histologic presence of pneumonia, nor did they correlate with specific clinical symptoms. However, a BALF with <50% neutrophils did correlate with the absence of histologic pneumonia. Also, sterile BALF and sterile distal airway/FOB-guided PSB correlate with sterile lung parenchyma. These specimens may be helpful in excluding lung infection. These are potentially important observations but must be substantiated by further study assessing the risk-benefit and cost-benefit ratios of FOB in mechanically ventilated patients. For now, the choice of when to treat or not to treat remains a clinical one. Good clinical habits currently will create a bias to overtreat and give antibiotics to a number of patients who do not have pneumonia. The choice of antibiotics can be settled by suction catheter aspirate of the trachea and is not enhanced by any quantitative culture technique.

The experience from this study has pointed out the fallacies inherent in the postmortem histology model for recognition of pneumonia. Equating neutrophilic infiltrate with bacterial infection or a paucity of neutrophils as absence of infection seems an oversimplification. At the very least, we need to develop common histologic criteria so that variation in histologic interpretation can be avoided as a potential variable between different investigators. Even with standardization of observation, we question whether this model truly holds additional answers. Recognition of sterile lung parenchyma probably should replace histologic pneumonia as the "gold standard." However, the use of antibiotics similarly makes bacteriologic results in postmortem studies inconsistent and difficult to interpret. Antibiotics in the ventilated patient are almost a certainty. Even if FOB and quantitative bacteriology

could recognize pneumonitis in the absence of antibiotics, the technique would apply only to a brief period in the course of the ventilated patient.

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