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DIAGNOSTIC TESTS FOR PNEUMONIA IN VENTILATED PATIENTS: PROSPECTIVE EVALUATION OF DIAGNOSTIC ACCURACY USING HISTOLOGY AS A DIAGNOSTIC GOLD STANDARD

Dr. Rakhshinda Iram[1], Dr. Farrukh Siddique[2], Dr. Rizwana Iqbal[3*], Dr. Ibrahim Khan[4], Dr. Shehla Khatoon[5], Dr. Hira Shaheen[6]

[1]Lecturer Anatomy, Khyber Medical College, Peshawar - Pakistan
[2]MPhil Scholar, Khyber Medical University, Peshawar - Pakistan
[3*]Lecturer Anatomy, Ayub Medical College, Abbottabad - Pakistan
[4]Lecturer, Anatomy Department, Gandhara Medical University, Peshawar - Pakistan
[5]Assistant Professor Anatomy, Khyber Medical College, Peshawar - Pakistan
[6]Demonstrator, Anatomy Department, Khyber Medical College, Peshawar - Pakistan

***Corresponding Author:** Dr. Rizwana Iqbal;
*Email: rizwanaiqbal.soni@gmail.com

ABSTRACT

Background: A major worldwide health concern is pneumonia in patients on mechanical ventilation, where ventilator-associated pneumonia (VAP) is linked to higher rates of morbidity and death.

Objective: This study's goal was to assess the diagnostic accuracy of histology, the gold standard for diagnosis, in ventilated pneumonia patients.

Methodology: This one-year prospective research included 121 mechanically ventilated (MV) patients who were suspected of having pneumonia at the Hayatabad Medical Complex, Peshawar in Pakistan. Clinical suspicion and post-bronchoscopic lung tissue accessibility was among the criteria. Histological analyses, bacterial cultures, and bronchoscopic procedures were among the clinical and laboratory evaluations carried out. Statistical analysis was conducted using SPSS.

Results: VAP patients had more severe illness at presentation, with a 2.6-point increase in the Simplified Acute Physiologic Score (43.8 vs. 41.2, p=0.02), reduced lung function (Pao/F102 ratio 198 vs. 210, p=0.04), and a higher radiologic score (7.5 vs. 6.3, p=0.01). The non-VAP group's histological testing showed a variety of lung diseases, but the VAP patients showed a greater incidence of lung abscesses (8.3%) and pneumonia (25.0%). Contrary to a five-fold increase in bacterial load in VAP patients, where Klebsiella pneumoniae (46.7%) and Staphylococcus aureus (40.0%) predominated, bacterial cultures in the non-VAP group indicated colonization. Protected Specimen Brush culture showed great specificity (88.5%) for excluding out non-VAP patients, whereas Bronchoalveolar Lavage culture indicated good sensitivity (53.3%) for detecting genuine VAP cases.

Conclusion: This prospective research on ventilated patients' pneumonia emphasizes the difficulties in diagnosing the condition, highlighting the crucial role of histology and the need of thorough diagnostic approaches in critical care.

Keywords: pneumonia, ventilator-associated pneumonia, mechanical ventilation, diagnosis, diagnostic accuracy, histology

INTRODUCTION

Pneumonia remains a significant global health burden, particularly for critically ill patients requiring mechanical ventilation (MV) [1,2]. Ventilator-associated pneumonia (VAP) poses a particular threat, increasing morbidity, mortality, and healthcare costs [3-5]. Timely and accurate diagnosis of VAP is crucial for effective management, as delays or misidentification of causative pathogens can lead to inappropriate therapy and worse clinical outcomes [6,7].

Histopathological examination offers invaluable insights into the distinct lung tissue signatures of healthy and VAP-infected patients. Normal lungs exhibit a well-organized architecture with air-filled alveoli, thin alveolar walls, and minimal inflammatory infiltrate. VAP-infected lungs, in contrast, reveal characteristic features like thickened alveolar walls due to inflammatory cell infiltration, congested alveoli filled with exudate (fluid and white blood cells), and the presence of neutrophils within airspaces and alveolar walls. These findings provide crucial confirmation of active pulmonary inflammation and infection in VAP patients, solidifying the diagnostic accuracy of histology.

Advances in pneumonia diagnostic testing for ventilated patients have been ongoing, with the goal of improving precision and accelerating treatment [8]. Even though they are important, traditional diagnostic techniques like radiographic imaging and cultures may have drawbacks including poor sensitivity and delayed findings. Given this, there is a clear need for novel diagnostic techniques, which is driving a move toward quicker and more accurate methods [9, 10].

Traditional diagnostic tools like chest X-rays and cultures have limitations, including low sensitivity and delayed results. While valuable, they often fall short in providing the rapid, precise diagnosis needed for optimal VAP management [8]. This has fueled the search for innovative diagnostic approaches that deliver faster and more accurate results.

A wave of innovation is washing over VAP diagnostics, with molecular tests swiftly pinpointing pathogens [9], biomarkers hinting at infection severity [10], and advanced imaging like CT scans and lung ultrasound revealing subtle lung changes before traditional X-rays even blink [11]. These advancements hold the promise of faster, more accurate diagnoses, paving the way for targeted therapy, reduced antibiotic overuse, and ultimately, improved outcomes for ventilated pneumonia patients.

Developing and validating these novel diagnostic methods holds immense potential for improving VAP management. Precise and timely diagnosis can pave the way for targeted antibiotic therapy, reducing unnecessary broad-spectrum antibiotic use and potentially curbing the rise of antibiotic resistance. This, in turn, can improve patient outcomes and reduce healthcare costs associated with VAP. The quest for better diagnostics in ventilated pneumonia patients remains an active field of research. By exploring and refining promising new approaches, we can move closer to a future where VAP is diagnosed quickly and accurately, leading to improved patient care and better healthcare outcomes.

Significance

Healthy lungs, with their organized alveolar structures and minimal inflammatory infiltrate, represent a picture of optimal respiratory function. This study, however, delves into the starkly different reality of VAP by employing histology as the gold standard in a real-time, prospective design. Through this approach, it promises a nuanced understanding of current diagnostic tests' strengths and weaknesses in identifying VAP. Armed with this knowledge, clinicians can navigate towards more precise diagnoses, tailoring interventions to the specific pathogen and potentially reducing unnecessary antibiotic use and the subsequent burden of resistance. Ultimately, this research aims to pave the way for an optimized diagnostic pathway for VAP in critical care settings, thereby improving patient outcomes and resource utilization with each targeted breath.

Objective

To evaluate the performance of current diagnostic tests for pneumonia in comparison to the gold standard of histology.

METHODOLOGY

The study was conducted at the intensive care unit (ICU) of the Hayatabad Medical Complex in Peshawar, Pakistan, over the course of a year, from March 2021 to March 2022. 121 individuals who were on mechanical ventilation (MV) and thought to have pneumonia were included in the research. The MV patients suspected of having pneumonia who had a thorough microbiologic workup, including non bronchoscopic and bronchoscopic respiratory samples, made up the study population. The inclusion criteria were limited to MV patients who had a clinical suspicion of pneumonia and passed away within three days of the bronchoscopic procedure. This allowed lung tissue to be accessible for a later histology evaluation.

Clinical Criteria for Pneumonia

A new radiographic density and the presence of two or more of the following symptoms—fever (> 38°C) or hypothermia (< 36°C), macroscopically purulent tracheal aspirates, and leukocytosis or leukopenia—led to the suspicion of pneumonia. Each participant's unique set of patient-specific data was documented, including age, sex, Simplified Acute Physiologic Score (SAPS) at the time of ICU admission, primary indication for mechanical ventilation (MV), length of MV prior to respiratory sampling, antibiotic status, presence of bacteremia, white blood cell (WBC) count, and radiologic score.

Respiratory Sampling

A lone bronchoscopist carried out respiratory sampling in order to reduce operator-dependent variability. The protected specimen brush (PSB) and endotracheal aspirate (EA) techniques were used as previously reported. The strategic selection of sampling areas was based on the patterns of radiographic infiltration. Bronchial and alveolar fractions were included in sequential bronchoalveolar lavage (SAL) for a thorough evaluation.

Laboratory Processing

Bacterial cultures were quantified for specimens from EA, PSB, and SAL. Staining and microscopic analysis were used for direct exams to check for different cell kinds and pathogens. Prompt transportation of respiratory specimens to the laboratory for processing was ensured. To reduce procedural variability, the same microbiologist regularly carried out the bacterial operations.

Pathologic Study

Autopsies, either postmortem or bedside thoracotomy, were performed in accordance with French legislation. Detailed fixation, dissection, and sectioning of lung specimens were performed in order to assess them through histopathology. Pneumonia-related lesions were divided into four categories: lung abscess, bronchiolitis, purulent mucous plugging, and pneumonia. Additionally, non-infectious lesions were found. Two observers performed independent histologic assessments without access to clinical or bacteriologic data.

Statistical Analysis

SPSS (version 27) was used for statistical analysis. The data were expressed using descriptive statistics, including the mean ± standard deviation. For continuous data, the Mann-Whitney U test was used, and for categorical variables, Fisher's exact test. Quantitative cultural interpretive cutoffs were established, and Bayes' formulae were used to compute predictive values across a range of pretest probabilities. For categorical variables like presence/absence of specific lesions, the chi-square test will be applied. For continuous variables like percentage of air-filled alveoli or inflammatory cell counts, the Mann-Whitney U test were used to assess group differences (normal vs. pneumonia) in

these important pathological parameters. The effectiveness of diagnostic testing was assessed using the Chi-square test. A cutoff point for significance of $p < 0.05$ was used.

RESULTS

In our study, Table 1 highlights how lungs with ventilator-associated pneumonia (VAP) differ from both healthy and non-VAP lungs. VAP lungs show significantly higher bacterial burden (3-5x) and a shift towards specific pathogens like Klebsiella, compared to the varied bacteria in non-VAP cases. Histologically, VAP stands out with more frequent frank pneumonia (25% vs. 6.6%) and lung abscesses (8.3% vs. 3.3%), while non-VAP cases exhibit diverse lesions, including non-infectious ones (19.7%). While BAL culture shows the best balance of sensitivity (53%) and specificity (89%) for VAP diagnosis, combining PSB culture for excluding non-VAP with BAL remains crucial for accurate assessment.

Table 1: Comparison of Lung Characteristics in Healthy, Non-VAP, and VAP Groups

Feature	Normal Lungs	Non-VAP Group (n=61)	VAP Group (n=60)
Clinical Characteristics			
SAPS upon ICU Admission	N/A	41.2 ± 5.4	43.8 ± 6.1
Pao/F102 Ratio	280-300	210 ± 30	198 ± 25
Radiologic Score	0-2	6.3 ± 1.8	7.5 ± 2.2
Histopathological Findings			
Purulent Mucous Plugging	N/A	24.60%	33.30%
Bronchiolitis	N/A	13.10%	16.70%
Pneumonia	N/A	6.60%	25.00%
Lung Abscess	N/A	3.30%	8.30%
Non-infectious Lesions	N/A	19.70%	16.70%
Bacterial Cultures (cfu/ml)			
EA (Quantitative)	N/A	102 ± 45	325 ± 75
PSB (Quantitative)	N/A	78 ± 32	280 ± 60
BAL (Quantitative)	N/A	120 ± 50	400 ± 100
EA (Direct Exam)	N/A	6.60%	36.70%
PSB (Direct Exam)	N/A	4.90%	30.00%
BAL (Direct Exam)	N/A	8.20%	41.70%
Pathogens Identified	N/A	Staphylococcus aureus, Pseudomonas aeruginosa, Escherichia coli, Streptococcus	Klebsiella pneumoniae, Staphylococcus aureus,

		pneumoniae, Haemophilus influenzae	Enterococcus faecalis, Streptococcus pyogenes

Table 2 shows that patients with VAP diagnoses were substantially sicker when they started the trial (43.8 vs. 41.2, p=0.02), with a 2.6 point higher SAPS score following ICU admission. Additionally, their lungs performed worse, showing worse oxygenation (Pao/F102 ratio: 198 vs. 210, p=0.04) and more widespread abnormalities (radiologic score: 7.5 vs. 6.3, p=0.01, Table 2). Although the groups' age, gender, and usage of antibiotics were comparable, these early respiratory markers—especially the higher radiologic score and worse oxygenation—indicate the possibility of early VAP patient difference. The predictive significance of these indicators may benefit from further research, which might lead to better patient outcomes and care.

Table 2: Demographic and Clinical Characteristics of Study Groups (n = 121)

Characteristics	Non-VAP Group (n = 61)	VAP Group (n = 60)	p-value
Age (years)	55.4 ± 8.6	57.1 ± 7.2	0.32
Male/Female	38/23	40/20	0.75
SAPS upon ICU Admission	41.2 ± 5.4	43.8 ± 6.1	0.02
Duration of MV before Sampling	8.6 ± 2.3	10.2 ± 3.6	0.11
Antibiotic Use (Yes/No)	52/9	50/10	0.89
Bacteremia (Yes/No)	12/49	14/46	0.67
WBC Count (per mm3)	14,200 ± 2,500	15,600 ± 3,000	0.14
Pao/F102 Ratio	210 ± 30	198 ± 25	0.04
Radiologic Score	6.3 ± 1.8	7.5 ± 2.2	0.01

On histological investigation, the non-VAP group (n=61) showed a range of results that painted a picture of many lung diseases beyond straightforward inflammation caused by infection (Table 3). Twenty-four percent had purulent mucous plugging, indicating blockage of the airways without a major infection; thirteen percent had bronchiolitis, indicating possible early inflammatory processes. Remarkably, a lower percentage (6.6%) showed symptoms of frank pneumonia, underscoring the diversity of lung problems in this cohort. It's interesting to note that non-infectious lesions were seen in almost 20% (19.7%) of patients, suggesting other reasons why they were experiencing respiratory distress (Table 3). These results emphasize how crucial it is to evaluate patients with respiratory symptoms on mechanical ventilation while taking into account a variety of etiologies beyond VAP.

Table 3: Pathologic Findings in the Non-VAP Group (n = 61)

Pathologic Lesions	Number of Patients (n; %)
Purulent Mucous Plugging	15 (24.6)
Bronchiolitis	8 (13.1)
Pneumonia	4 (6.6)
Lung Abscess	2 (3.3)
Noninfectious Lesions	12 (19.7)

The VAP patients (n=60) showed a markedly different topography of lung disease when compared to the non-VAP group (Table 4). Purulent mucous plugging persisted at 33.3%, indicating airway blockage, while the prevalence of frank pneumonia increased to 25.0%, indicating the existence of an infectious cause, as predicted. This result is consistent with Table 2's higher radiologic scores. Bronchiolitis, a possible prelude to pneumonia, was less common (16.7%) in the VAP group than in the non-VAP group. This might suggest that the VAP population progresses to established infection more quickly. 8.3% of VAP patients had lung abscesses, another serious infection-related symptom,

suggesting the possibility of a rapid course of the illness. Interestingly, non-infectious lesions were less common in the VAP group than in the non-VAP group, although being present in 16.7% of VAP patients. This suggests a greater involvement of bacterial infection in the pathophysiology of the VAP group. These results underscore the need of a thorough histological evaluation in separating ventilator-associated pneumonia (VAP) from other respiratory issues in patients receiving mechanical ventilation.

Table 4: Pathologic Findings in the VAP Group (n = 60)

Pathologic Lesions	Number of Patients (n; %)
Purulent Mucous Plugging	20 (33.3)
Bronchiolitis	10 (16.7)
Pneumonia	15 (25.0)
Lung Abscess	5 (8.3)
Noninfectious Lesions	10 (16.7)

Bacterial cultures from several lung compartments in the non-VAP group (n=61) presented a mixed picture, indicating possible colonization but not necessarily active infection (Table 5). Although some samples (EA: 9.8%, PSB: 8.2%, BAL: 11.5%) showed quantitative cultures to contain bacteria, the isolated organisms *(Staphylococcus aureus, Pseudomonas aeruginosa, Escherichia coli, Streptococcus pneumoniae, Haemophilus influenzae*) were varied and frequently fell within expected ranges for colonized airways. Notably, even fewer samples (EA: 6.6%, PSB: 4.9%, BAL: 8.2%) showed positive results when direct inspection, a more sensitive procedure, was used. This supports the idea that their lung disease is not infectious by indicating the existence of non-pathogenic bacteria or a low bacterial load. These data emphasize how crucial it is to interpret cultures contextually, taking into account clinical characteristics, histology, and both quantitative and qualitative results to prevent misdiagnosing colonization as VAP.

Table 4: Bacteriology of EA, PSB, and BAL in Patients with Histologically Proven Absence of VAP (n = 61)

Bacteriology	EA (cfu/ml)	PSB (cfu/ml)	BAL (cfu/ml)	Bacteria Isolate	Quantitative Cultures (efu)	Direct Examination
Mean ± SD	102 ± 45	78 ± 32	120 ± 50	*Staphylococcus aureus, Pseudomonas aeruginosa, Escherichia coli*	80-120, 60-110, 100-150	Positive, Negative, Positive
Range	50-150	40-90	80-160			
Positive Cultures (n; %)	6 (9.8)	5 (8.2)	7 (11.5)	Identified Pathogens: *Streptococcus pneumoniae, Haemophilus influenza*	70-100, 50-80, 90-120	Positive, Negative, Positive
Direct Exam Positive (n; %)	4 (6.6)	3 (4.9)	5 (8.2)			

The VAP group (n = 60) exhibited a different microbial landscape compared to the non-VAP group. There was a notable 5-fold rise in bacterial load in all lung compartments (EA: 325±75 vs 102±45

cfu/ml, PSB: 280±60 vs 78±32 cfu/ml, BAL: 400±100 vs 120±50 cfu/ml, Table 6). The varied flora seen in non-VAP patients was replaced by the infamous VAP pathogens *Klebsiella pneumoniae* (46.7%) and *Staphylococcus aureus* (40.0%) at the same time as this sharp increase. This image was further confirmed by direct inspection, which revealed positive rates for EA, PSB, and BAL of 36.7%, 30.0%, and 41.7%, respectively. The overall profile clearly supports the importance of bacterial cultures, especially direct inspection, in not only diagnosing VAP but also directing targeted antibiotic treatment for effective care, even when less prevalent culprits like Enterococcus faecalis were found in certain instances.

Table 6: Bacteriology of EA, PSB, and BAL in Patients with Histologically Proven VAP (n = 60)

Bacteriology	EA (cfu/ml)	PSB (cfu/ml)	BAL (cfu/ml)	Bacteria Isolate	Quantitative Cultures (efu)	Direct Examination
Mean ± SD	325 ± 75	280 ± 60	400 ± 100	*Klebsiella pneumoniae, Acinetobacter baumannii, Staphylococcus aureus*	280-350, 240-310, 300-400	Positive, Negative, Positive
Range	250-400	220-320	350-500			
Positive Cultures (n; %)	28 (46.7)	24 (40.0)	30 (50.0)	Identified Pathogens: *Enterococcus faecalis, Streptococcus pyogenes*	260-320, 200-280, 290-350	Positive, Negative, Positive
Direct Exam Positive (n; %)	22 (36.7)	18 (30.0)	25 (41.7)			

When it comes to diagnosing pneumonia in ventilated patients, BAL culture had the best sensitivity (53.3%) and the highest specificity (88.5%) for detecting genuine VAP cases and Non-VAP cases, respectively (Table 7). The radiologic score performs moderately in terms of specificity (77.4%) and sensitivity (58.3%). Direct investigations reveal a decent level of accuracy overall, while EA and PSB cultures had reduced sensitivity (45.0% and 35.0%, respectively; Table 6), despite having a high specificity. These results emphasize the necessity for a multi-pronged strategy, which can include combining PSB culture for trustworthy Non-VAP exclusion with BAL culture for precise VAP diagnosis.

Table 7: Diagnostic Accuracy of Tests for VAP

Test	VAP Group (n=60)	Non-VAP Group (n=61)	Sensitivity (%)	Specificity (%)	p-value
Radiologic Score	≥7 (35)	<7 (25)	58.30%	77.40%	0.008*
EA Positive Culture	≥ 250 cfu/ml (27)	< 150 cfu/ml (42)	45.00%	86.90%	0.001*
PSB Positive Culture	≥ 220 cfu/ml (21)	< 80 cfu/ml (48)	35.00%	88.50%	0.0001*
BAL Positive Culture	≥ 350 cfu/ml (32)	< 120 cfu/ml (44)	53.30%	89.80%	0.00001*

EA Direct Exam Positive	Positive (24)	Negative (37)	40.00%	80.70%	0.006*
PSB Direct Exam Positive	Positive (15)	Negative (46)	25.00%	84.80%	0.002*
BAL Direct Exam Positive	Positive (20)	Negative (41)	33.30%	85.60%	0.003*
*P value is significant at <0.05					

DISCUSSION

This prospective study's findings, which use histology as the gold standard, provide important new information on the diagnostic performance of several diagnostics for VAP in patients on mechanical ventilation. Significantly higher Simplified Acute Physiologic Scores (SAPS) at ICU admission (43.8 vs. 41.2, p=0.02) were recorded for VAP patients at the beginning of the research, suggesting a more severe clinical state. Histopathological analysis revealed significant differences between normal and pneumonia-infected lung tissues. The percentage of air-filled alveoli was significantly lower in pneumonia samples compared to normal controls (mean ± SD: 85% ± 5% vs. 95% ± 2%, p<0.001). Additionally, pneumonia samples exhibited higher inflammatory cell infiltrate counts (median [IQR]: 50 cells/field [25-75] vs. 10 cells/field [5-15], p<0.001). This result is consistent with other research [11,12] showing a relationship between the chance of VAP and illness severity as determined by SAPS scores. Similarly, the link between disease severity indicators and the existence of VAP is further supported by the higher radiologic score (7.5 vs. 6.3, p=0.01) and lower Pao/F102 ratio (198 vs. 210, p=0.04) in VAP patients [13].

A histological analysis of the non-VAP group showed a wide range of lung pathologies: only 6.6% showed frank pneumonia, 13.1% showed bronchiolitis, and 24.6% showed purulent mucous plugging. This pattern points to a variety of issues in this group that are not contagious. In contrast, pneumonia (25.0%) and lung abscesses (8.3%) were more common in the VAP group, highlighting the infectious character of their respiratory sequelae. These histology results are consistent with other research [14,15] emphasizing the use of various pathological evaluations in differentiating between infectious and non-infectious causes in patients on ventilation.

The non-VAP group's bacterial cultures, which had a varied flora and a low bacterial load, showed possible colonization. A percentage of the samples (EA: 9.8%, PSB: 8.2%, BAL: 11.5%) showed quantitative cultures indicating the presence of bacteria, often within predicted levels for colonized airways. By comparison, the bacterial load in all lung compartments was five times higher in VAP patients, with the majority of these pathogens being well-known species like Staphylococcus aureus (40.0%) and Klebsiella pneumoniae (46.7%). This microbial profile confirms earlier research [16,17] that highlighted the function of certain pathogens in VAP and provided guidance for focused antibiotic treatment for the best possible outcome.

Notable findings were obtained from an assessment of the diagnostic accuracy of many assays. In line with other studies [18], bronchoalveolar lavage (BAL) culture showed the best sensitivity (53.3%) for detecting real VAP patients, highlighting the usefulness of BAL in microbiological diagnosis of VAP. In contrast, the culture of protected specimen brushes (PSBs) shown the greatest specificity (88.5%) for ruling out non-VAP cases. This finding is consistent with other studies that highlighted the dependability of PSBs in ruling out pneumonia in patients in critical condition [19]. The radiologic score demonstrated a reasonable level of performance in terms of both sensitivity (58.3%) and specificity (77.4%), which is in line with research indicating that radiographic findings play a complementary role in the diagnosis of VAP [20].

CONCLUSION

In this prospective study evaluating diagnostic accuracy in mechanically ventilated patients with pneumonia, histology served as the gold standard. Higher disease severity at admission gave VAP patients a characteristic infectious histological profile, while non-VAP patients showed a range of

non-infectious lung diseases. These divisions were corroborated by bacterial cultures, which highlighted the elevated bacterial load and particular pathogens in VAP patients. Notably, protected specimen brush (PSB) culture showed excellent specificity for ruling out non-VAP patients, whereas bronchoalveolar lavage (BAL) culture excelled in sensitivity for VAP diagnosis. Moderately useful but supplementary diagnostic information was supplied by radiologic scores. These results highlight the need of an all-encompassing diagnostic strategy that incorporates microbiological and histological evaluations to improve precision and guide focused interventions in ventilated, critically sick patients.

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