Establishing the Etiologic Diagnosis of Pneumonia

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Abstract

Pneumonia is a serious entity with a mortality in the U.S. of from 6-24%. Many invasive and non-invasive procedures are used to establish an etiologic diagnosis. An acceptable sputum smear is characterized by a low number of epithelial cells, higher number of leukocytes, and the presence of alveolar macrophages. A gram-stain provides good clues about pneumococcal, Klebsiella, and mixed anaerobic infections. Common problems include interpretation of streptococci as S. pneumoniae and missing H. influenzae. A culture of sputum is frequently unreliable because of contamination by the upper airway bacteria. Transtracheal aspiration can minimize the upper airway contamination. Broncho-alveolar lavage is helpful in diagnosing pneumocystis infections in AIDS patients. Double lumen catheter systems can obtain secretions from the site of pneumonia without contamination. Transbronchial biopsy provides tissue specimens for stains and cultures. Transthoracic needle aspiration provides diagnostic yield of 56 to 82% of cases with a false negative rate of 22%. Open lung biopsy is usually done in very sick, immunocompromised patients if other diagnostic procedures have been unsuccessful.

Key words: *Nosocomial, pneumonia, lower airway infections, diagnosis*

Pneumonia continues to be a significant problem in clinical medicine. It is no longer described as the captain of death,[1] and is no longer associated with mortality rates of 83% as previously seen in baceremic pneumococcal pneumonia.[2] The current mortality rates in bacteremic pneumococcal pneumonia is 15% in patients treated with penicillin[3], however, mortality rates in nosocomial pneumonia vary from 20 to 50% and may be as high as 80% in patients with Pseudomonas penumonia.[4]

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Diagnostic procedures

In community acquired penumonia, therapy is either initiated empirically or based on the sputum examination.[5] In sicker patients further non-invasive and invasive investigations are usually undertaken.

Sputum examination: The value of sputum stains for establishing an etiologic diagnosis is controversial. Gram stain is a subjective analysis with significant variation based on individual microscopic expertise. A gram stain of the sputum is helpful when an adequate specimen can be obtained. In an adequately stained specimen characteristic features can be seen for S. pneumoniae, H. influenzae, Klebsiella, Staphylococci, and Nocardia. Streptococcus pneumoniae are lancet shaped gram positive diplococci, H influenzae are very small pleomorphic gram negative lightly staining Coccobacilli. Staphylococci are frequently seen in clusters and Klebsiella pneumoniae appear as plum gram negative rods. Members of the Nocardia genus are gram positive bacilli that appear as beaded and branching

filaments. Anaerobic infections are characterized by the presence of both gram negative and gram positive cocci and bacilli.

The three common problems associated with gram stains include the adequacy of the sputum specimen, false positive, and false negative results. In addition, the differentiation between colonization and infection remains a significant problem.

An adequate sputum specimen is essential for getting any useful information from gram stain and to distinguish oral contamination. A good specimen should have few squamous epithelial cells and many polymorphnuclear leukocytes. The presence of alveolar macrophages suggests that sputum's origin is the lower lung. Mayo Clinic was that a good specimen had to have at least 25 polymorphnuclear leukocytes and less than 10 squamous cells per low power field (X100). By utilizing these criteria they discarded 74% of the specimens.[6] Later they suggested including any specimen with more than 25 polymorphnuclear leukocytes but still had to discard about 25% of the specimens.[7]

The false positive results are usually related to over-interpretation of gram positive streptococci representing the normal flora as S. pneumoniae. Merrill et al compared the gram stain, cultures, and quelling reaction on sputums in acute pneumonia.[8] The gram stain interpretation by the housestaff had the highest sensitivity, identifying 26 of 27 culture positive specimens (sensitivity 96%). However, they also interpreted 23 of 26 specimens as showing pneumococci that did now grow pneumococci (specificity 12%). Alpha-hemolytic streptococci were isolated from all the specimens and were probably mistaken for pneumococci.

The false negative results are mainly related to H. influenza.[9,10] Rein et al found a false negative rate of 38% for pneumococci.[11]

Sputum culture: The results of cultures of expectorated sputum can provide the identification of the causative organisms but there are problems similar to those of the gram stain. Fewer than 50% of sputum samples sent for culture yield reliable results.[12] The major problem is the differentiation between the organisms representing the colonization of the upper airways and those representing the lung infection. Colonization of the upper airways with gram negative organisms has been demonstrated in 2-18% of healthy subjects,[13,14] in 45% of patients in medical intensive care units, and in 75-100% of the patients with a pulmonary problem.[15,16] Similarly, the colonization of the central airways occurs rapidly in patients with endotracheal intubation or tracheostomy.[17]

Both false positive and false negative results are common. Gram-negative organism, and staphyllococci are easily recovered from sputum and hence their absence in a culture from purulent sputum makes it unlikely that the pneumonia was due to these organisms.[18] Routine cultures of sputum in patients with pneumococcal infections yield false positive and false negative rates of 25-44% and 50% respectively.[12] Pneumococci can be cultured in up to 50% of normal healthy adults.[19] In patients with pneumococcal pneumonia, the yield from routine cultures has varied between 41-51%.[20-25] The results of some of these studies are presented in Table 1. When specialized techniques are employed to identify pneumococci, the yield is significantly higher.[26-31] Data from a few studies utilizing these specialized techniques are shown in Table 2. These techniques are expensive, time consuming, and generally not available at most hospitals. Other newer techniques are increasingly being used to make an etiologic diagnosis. These includes counter-immunoelectrophoresis, coagglutination and latex agglutination.[32-34] Specific fluorescent antibody tests are being used to diagnose both Legionella and Chlamydia.[35,36]

Blood cultures: Positive blood cultures provide a definite etiology of pneumonia provided that patient does not have another infected site. The major problem appears to be the low yield of positive culuture results in most types of penumonias. Blood cultures are positive in approximately 25% of patients with pneumococcal pneumonia.[12] Positive culture with Klebsiella (14%) and anaerobic infections (4%) are even lower. In a study of 71 patients with community acquired pneumonias, blood cultures were found to be positive in only seven (10%) patients.[37] The authors suggested that blood culture results did not influence the choice of antibiotic therapy and are not indicated in the management of stable hospitalized patients with community acquired pneumonia. In patients with ARDS, positive blood cultures were found in only 27% of the patients with lung infections.[38] Similarly, positive pleural fluid cultures rarely provide a definite etiology.

Serologic diagnosis: In many diseases serology remains the primary method of diagnosis because the causative agents are difficult to culture. The two problems are the non-availability of serologic methods at many hospitals and the requirements of both acute and convalescent specimens. Furthermore, the serologic diagnosis is often made long after the initial treatment of the patient.

Mycoplasma pneumoniae can be diagnosed by serologic methods.[39] Two tests commonly done include a demonstration of cold agglutinins and the complement fixation test. Cold agglutinins are present at a titer of 1:32 in over 50% of cases but this test lacks specificity. The complement fixation test is more specific but serial determinations are neeeded

Table 1. Routine Sputum Culture Results in Patients with S. Pneumoniae Infection.

Reference	Comparison Source	Yield	%
Barrett-Connor (1971)	Blood Culture	28/51	55
Fiala (1969)	Blood Culture	11/25	44
Rathbun (1967)	Blood Culture	31/69	45
Hoeprich (1970)	TTA*	62/129	53
Kalinski (1967)	TTA*	47/102	48
Potter (168)	Double Catheter	41/100	41
Total		220/476	46

*TTA - Transtracheal Aspiration.

Table 2. Specialized Techniques for Detection of Pneumocci in Expectorated Sputum.

Reference	Comparison Source	Specialized Technique	Results	%
Tempest	Blood Culture	Mouse Inoculation	38/40	95
Drew	Blood Culture	Optochin Disk	29/31	94
Thorsteinsson	TTA*	Mouse Inoculation	13/13	100
Davidson	TTA*	Stereoscopic Microscopy	15/17	88
Benner	TTA*	Homogenation/ Quantitation	73/85	86
Bartlett	TTA*	Homogenation/ Quantitation	9/9	100
Total			177/195	91

**TTA - Transtracheal Aspiration.

to demonstrate a rise in antibody titer.

Invasive diagnostic procedures

When the diagnosis remains in doubt, an invasive procedure is frequently used. The decision for an invasive approach is determined by clinical circumstances. Four invasive procedures are commonly employed to establish the diagnosis of pulmonary infections: transtracheal aspiration, transthoracic needle aspiration, fiberoptic bronchoscopy, and open lung biopsy.

Transtracheal aspiration has been successfully employed in community acquired pneumonias. The sensitivity of this technique is high but false positive cultures are found in 21% of patients.[40] The value of the technique in nosocomial infections remains unclear. Potential pathogens have been recovered in 85% of samples taken from patients with chronic lung disease even when these patients have no acute problem.[41] This technique does bypass the upper airway, thus avoiding oral flora but the samples obtained are from the central airways and not from the area of pneumonia. Complications occur in 4-19% of patients and are usually minor.[42,43] Serious complications can include bleeding, arrhythmias, subcutaneous emphysema, infection, and death.[44,45]

Transthoracic needle aspiration is usually performed by an 18-gauge needle under fluoroscopic guidance. False positive samples are uncommon. Diagnostic yields of 35% in pneumoccal pneumonia[46] and 75% in immunocompromised patients have been reported.[47] The diagnostic yield is higher in peripheral, localized and cavitary lesions. Pneumothorax has been reported in 9-26% of cases and hemorrhage in 3-18.%[46,48,49]

Many fiberoptic bronchoscopy techniques are used. Samples which are drawn through the suction channel are contaminated by upper airway

Table 3. Diagnosis of Pulmonary Infiltrates by Transbronchial Biopsy in Immunocompromised Patients.

Author	n	Diagnosis	Complications	
			Pneumothorax	Hemorrhage
Mathay et al (1977)	25	84%	8%	8%
Feldman et al (1977)	38	45%	11%	0%
Cunningham et al (1977)	31	48%	0%	6%
Poe et al (1979)	35	46%	19%	26%
Lauver et al (1979)	34	68%	7%	7%
Nishio and Lunch (1980)	47	30%	4%	4%

organisms.[50,51] Bartlett and co-workers found that all samples taken from 16 patients without lung infection were contaminated by upper airway organisms.[52] In order to overcome the problem of contamination, a double catheter system (also known as telescoping plugged catheter) was introduced.[53] The outer catheter, with a plug at the end, is introduced into the lesion. Then the inner catheter containing a brush comes out and finally the brush is pushed out. A gram stain of the brush sample is a good predictor of the culture results with 78% sensitivity.[54] Some contamination still occurs so quantitative cultures have been suggested. This plugged telescoping catheter has been extensively studied.[55-59] Most series have reported favorable results. Pollock et al performed this procedure in 144 patients and obtained bacterial growth at $> 10^3$ CFU/ml in 75 of 78 patients with typical pneumonia.[54] Only 2 of 35 control patients had organisms in this quantity. Two studies have reported a high rate of false positive results. Fletcher et al who reported unfavorable results had instilled lidocaine at the vocal cords via the suction channel that probably led to a high false positive rate.[59] Halperin et al employed semi-quantitative instead of quantitative cultures.[60]

Four recent studies have evaluated the usefulness of this protected brush technique in mechanically ventilated patients.[61-64] Fagon et al studied 147 patients on mechanical ventilation and were able to exclude the diagnosis of pneumonia in 72 patients and to establish a diagnosis in 45 patients.[61] They suggested that this procedure can help to avoid the unnecessary use of antibiotics thus reducing the cost of care. Torres et al introduced the telescoping plugged catheter into the lung via a radio-opaque Metras catheter instead of fiberoptic bronchoscopy and endotracheal aspirates.[62] The results were similar to those obtained through a bronchoscope and both of these procedures had high specificity (100%) compared to endotracheal aspiration (29%). In a subsequent study Torres et al compared the bronchoalveolar lavage and telescoping plugged catheter in mechanically ventilated patients with nosocomial pneumonia.[63] Culture results were similar with both techniques with specificity of 71% for lavage, 86% for catheter and only 14% for tracheal aspirate. This technique has been recently used as a standard to characterize the course of nosocomial pneumonia in patients on mechanical ventilation.[64]

Transbronchial biopsy is frequently employed when the diagnosis remains in doubt, particularly in immunocompromised patients. The availability of this procedure has reduced the need for open lung biopsy in establishing an etiologic diagnosis. The reported yields of transbronchial biopsy in immunocompromised patients varies as shown in Table 3.[65-70]

Transbronchial needle aspiration is a new technique. This technique has been successful in the diagnosis of malignancy. Lorch et al have found the results to be similar to plugged telescoping catheter in the diagnosis of pneumonia.[71]

Open lung biopsy is usually performed when other diagnostic methods have been unsuccessful and the patient is seriously ill. Mathay and Moritz reviewed the literature on open lung biopsies in immunocompromised patients.[72] The specific diagnostic yield in 288 patients varied between 55-91% with an average of 69%. The overall complication rate was 11% with pneumothorax being the commonest (8%) complication. Two studies have compared the open lung biopsy to the post-mortem findings and found that the open lung biopsy was accurate in only 40-60% of cases.[73,74] Open lung biopsy was diagnostically misleading in 6 of 15 patients (40%). Three patients had fungal disease, one patient had cytomegalovirus pneumonitis, and two patients had false positive results.[74]

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