Guidelines of the Papanicolaou Society of Cytopathology for the Examination of Cytologic Specimens Obtained from the Respiratory Tract

Papanicolaou Society of Cytopathology Task Force on Standards of Practice*

Cytologic examination of specimens obtained from the respiratory tract is a primary and frequently the initial diagnostic technique performed in patients with respiratory symptoms or in those presenting with a pulmonary abnormality. While occasional cytologic specimens are obtained from the upper respiratory tract, the majority of pulmonary diagnostic cytology involves the study of the lower respiratory tract. The guidelines contained within this document will address evaluation of specimens relating to the lower respiratory system (trachea, bronchi, bronchioles, and alveoli).

Due to the complexity of the respiratory tract and the location of various target lesions, a variety of cytologic techniques have been developed for the study of diseases involving the respiratory system. Both exfoliative cytology techniques and fine-needle aspiration (FNA) are used extensively for diagnosis of pulmonary lesions. While respiratory cytology is used predominantly for the study of neoplastic or potentially neoplastic disease, it is also variably useful in the investigation of a variety of benign diseases including opportunistic infections, tuberculosis, sarcoidosis, industrial disease (e.g., asbestosis), and lung transplant rejection.1–24

Safety at Work

Laboratory staff processing pulmonary cytologic materials are at particular risk of exposure to aerosol infections. They must protect themselves from this potential hazard by wearing protective masks and gowns, handling the material within an appropriate cabinet equipped with a laminar flow biohazard containment hood, and following standard laboratory hygienic procedures.

Exfoliative Cytology of the Respiratory Tract

Each of the techniques used for obtaining exfoliative specimens from the respiratory tract has associated limita-
tions, advantages, and diagnostic accuracy. Diagnostic accuracy can be optimized by selecting the most appropriate technique for a given clinical situation. Sputum cytology is noninvasive and is the most easily obtainable of the techniques available.

Sputum Cytology

The spontaneous production of significant amounts of sputum often indicates pulmonary disease. Sputum is composed predominantly of mucoid substances, as well as variable numbers of inflammatory and epithelial cells. Variations in the numbers of macrophages, neutrophils, and epithelial cells and morphologic alterations in the latter elements can yield significant insight into the underlying pathologic process. Similarly, the level of pigmentation within macrophages and the presence or absence of Cur- schmann's spirals indicate much about the underlying pulmonary pathophysiology.

Specimen Adequacy

Adequate sputum samples must contain alveolar macrophages. Absence of such cells indicates the presence of only saliva. No numerical cutpoint for number of macrophages is consistently reported in the literature, but an adequate specimen should have numerous easily identifiable cells of this type. Greenberg stated that the “adequacy of a sputum sample is directly proportional to the number of alveolar macrophages it contains.” In addition, a sputum sample should be large enough to prepare 2–4 slides. Bardales et al. showed that the preparation of four smears from a sputum specimen increased the diagnostic yield, but significantly increased the screening and turnaround times and, hence, was not cost-effective. At present, it appears that a sputum specimen increased the diagnostic yield, but significantly increased the screening and turnaround times and, hence, was not cost-effective. At present, it appears that a sputum specimen should be considered adequate for evaluation if a minimum of two smears can be prepared, and microscopic evaluation reveals numerous alveolar macrophages. In addition, the cytologic material should be well-preserved and well-stained.

Bronchial Washings and Brushings

Indications

Bronchial brushings and washings are complementary to sputum cytology in the diagnosis of pulmonary lesions. The most common indications for bronchoscopy are persistent cough, radiographic documentation of a new solitary pulmonary nodule, hemoptysis, bronchial obstruction, atelectasis, persistent localized wheezes, and persistent infiltrates on chest X-ray. Bronchoscopy may also be used to confirm an abnormal sputum cytology. Bronchoscopy is of questionable value for nodules occurring within peripheral lung fields. However, bronchial brushing appears to have greater sensitivity than either bronchial washings or sputum cytology for peripheral tumors, necrotic carcinomas, and metastatic cancer.

The indications for repeat bronchial cytology specimens are poorly formulated, but include initial negative bronchial cytology associated with positive sputum cytology, and highly suspicious clinical or radiographic findings in the face of negative sputum cytology and a negative first bronchial cytology. Some authorities believe that an unequivocal positive sputum cytology associated with clinical findings of cancer is adequate to proceed directly to treatment. Ng and Horak demonstrated that diagnostic
sensitivity increased from 70% to 90% when two bronchial cytologic specimens were obtained instead of one.

**Specimen Procurement**

Technical aspects of the bronchoscopic procedure are beyond the scope of these guidelines but have been well-summarized by Walloch. In general, both washings and brushings are taken of any clinically suspicious areas. Washings are obtained by repetitive instillation of 3–5 ml of a sterile balanced salt solution through the bronchoscope and reaspiration of fluid. Brushings are obtained by the use of a small circular stiff-bristle brush. Brushings must be obtained before “bite” biopsies are performed to avoid excessive and obscuring blood.

Smears are prepared by immediately rolling the end of the brush on a glass slide. The smears are fixed immediately in 95% alcohol. Any delay in fixation will result in severe air-drying artifacts and an uninterpretable specimen. In many institutions, clinicians are discouraged from preparing direct smears from endoscopic samples. The disposable brush is cut off its shaft, placed in a tube containing balanced salt solution or Saccomanno fixative, and transported to the laboratory where more uniform and high-quality preparations can be made. In the laboratory, the brush is rolled between two frosted glass slides. The smears are air-dried to increase cell adhesion and stained by the Papanicolaou technique. The brush is placed back in the tube, the tube with the brush is vortexed, the brush is discarded, and a cytocentrifugation specimen and/or cell block is prepared from the cell-enriched fluid.

The aspirated washing material should be immediately transported to the cytopathology laboratory, where they are centrifuged and smears prepared from the cell buttons. The buttons may also be fixed in 10% neutral-buffered formalin and embedded in paraffin for histologic sectioning. Alternatively, material from the washings can be prepared by cytocentrifuge techniques, membrane filtration preparations, or one of the new monolayer methods. In general, a combination of techniques yields the most satisfactory diagnostic sensitivity.

**Specimen Adequacy**

A bronchial washing/brushing specimen is considered satisfactory when cells or agents diagnostic of a pathologic process are present, but in the absence of such cells or infectious agents, specimen adequacy is less easily defined. In general, a satisfactory specimen should contain a large number of well-preserved, optimally stained ciliated bronchial epithelial cells and macrophages. Specimens which contain few cells or are heavily contaminated and obscured by large numbers of oral squamous cells or oral saprophytes should be deemed unsatisfactory. Similarly, specimens in which the cellular details are obscured by blood, inflammation, or air-drying artifacts should be considered unsatisfactory for definitive evaluation. The reasons for the inadequacy should be documented in the report. A specimen can be considered less than adequate if there is inadequate clinical information provided.

**Diagnostic Accuracy**

Bronchoscopic samples can achieve a sensitivity of up to 90% when multiple brushings are performed during one bronchoscopic examination. Multiple brushings not only increase diagnostic sensitivity but also decrease the need for rebronchoscopy or other invasive procedures, including FNA. Overall sensitivity depends on a number of factors, including skill of the endoscopist and the location, size, and histologic type of the neoplasm.

**Bronchoalveolar Lavage**

Although invasive, bronchoalveolar lavage (BAL) has such low morbidity that it can be safely used in critically ill patients. BAL, along with fine-needle aspiration, represent the only cytologic techniques which can study the contents and composition of the most terminal air spaces. While fine-needle aspiration cytology generally requires a localized and circumscribed target, BAL can successfully investigate diffuse pulmonary disease.

**Clinical Applications of BAL**

Bronchoalveolar lavage is most widely and effectively used in immunosuppressed patients with pulmonary infiltrates for the diagnosis of opportunistic infections. Many infectious microorganisms can be diagnosed by cytologic examination of BAL fluid on conventional smears or with the aid of special stains. If indicated, BAL fluid can be submitted for microbiologic cultures. In addition to the identification of microorganisms, BAL shows specific recognizable features in the following conditions: alveolar proteinosis, alveolar microlithiasis, presence of malignant cells, and dust exposure, such as asbestos bodies, and silica and talc particles.

Semiqualitative methods for counting the number of hemosiderin-laden macrophages in BAL have been published. In one study, the finding of >20% hemosiderin macrophages in BAL was indicative of significant alveolar hemorrhage. Alveolar hemorrhage has diverse causes, and the physician must therefore interpret this information in the context of clinical or other laboratory findings. Similarly, semiqualitative methods for counting the number of oil red-O-stained lipid-laden macrophages in BAL have been used for the diagnosis of aspiration pneumonia.
with a high risk of functional deterioration, whereas a high percentage of lymphocytes in BAL correlates with a better outcome. In sarcoidosis, a study of the number of T-helper lymphocytes or the ratio of helper lymphocytes to suppressor lymphocytes in BAL fluid can predict clinical activity and response to steroid therapy. Phenotyping of alveolar lymphocytes can be done by flow cytometry, or immunofluorescent or immunocytochemical techniques.

**Specimen Procurement**

While techniques of BAL differ, it is usually performed under local anesthesia with a 5-mm bronchoscope. The bronchoscope is advanced into a subsegmental bronchus and wedged into position. In the absence of a localized lesion, the right middle lobe or lingula is usually selected for sampling because of technical convenience and associated high yields of fluid and cells. The lavage is performed with warm saline, using a total volume of 100–300 ml to sample each site. Several sequential fluid instillations are performed with 20–100-ml aliquots. This fluid floods the airspace distal to the bronchoscope and is then reaspirated by the bronchoscopist.

Standardization of the amount of fluid used and the number of aliquots is important because these factors influence cytologic yield. It appears to be preferable to use five 20-ml aliquots, with fractionation for lavage specimens. The first aliquot is usually separated from the subsequent four, which are pooled. This technique optimizes the separation of bronchial epithelial cells from truly alveolar material. Fractionation decreases the number of unsatisfactory specimens when percentages of bronchial epithelial cells are used as a rejection criterion.

The BAL specimen should be rapidly transported to the cytopathology laboratory, where it may be processed by either a filtration method or cytocentrifugation. Chamberlain et al. suggested that the filtration technique may be superior to cytocentrifugation because there are fewer unsatisfactory specimens with this technology. If conspicuous amounts of mucus are present, most laboratories begin processing of the specimen with passage through a loose nylon gauze mesh to trap mucous aggregates. Alternatively, the specimen may be treated by sputolysin. Passage through mesh leads to some loss of epithelial cells, but generally to a degree insufficient to affect sample interpretation. Following mesh filtration, the fluid is subjected to low-speed (1,800 g) centrifugation to obtain a cell pellet. This is resuspended in balanced salt solution, and aliquots (100,000–200,000 cells are desirable) are used to prepare cytocentrifuge slides or membrane filtrates. For routine evaluation, some slides are stained by the Romanowsky technique, and others by the Papanicolaou method. Some authorities have recommended preparation of hematoxylin-eosin (H&E) eosin stained slides. Additional cytocentrifuge slides should be prepared if special stains (acid fast bacteria, Grocott, methenamine silver) are required for identification of microorganisms. Issues of cytocentrifugation speed and the potential superiority of membrane filtration over cytocentrifugation are discussed in a number of recent publications.

**Specimen Adequacy**

Bronchoalveolar lavage fluids must be assessed for adequacy. Excessive numbers of ciliated or squamous epithelial cells (greater than 5%) are indicative of contamination by bronchial or oral material, indicating that the specimen may not be representative of the distal portions of the respiratory tract. Chamberlain et al. suggested specific criteria for judging specimens as unsatisfactory for evaluation. Criteria for rejection included: 1) paucity of alveolar macrophages on the prepared glass slides (less than 10 alveolar macrophages per 10 high-power fields or less than 25 alveolar macrophages per high-power field in combination with either criterion two or three); 2) excessive numbers of epithelial cells, either showing morphologic degenerative changes or exceeding the number of alveolar macrophages present; 3) a mucopurulent exudate of polymorphonuclear cells; 4) numerous red blood cells in combination with at least one of the other criteria for inadequacy; or 5) degenerative changes or artifacts obscuring cell identity. In addition, a specimen should be considered adequate if it demonstrates a specific pathologic process (viral infection, neoplasia, or fungal or bacterial disease).

**Fine-Needle Aspiration**

Fine-needle aspiration (FNA) cytology is a widely used technique for the diagnosis of localized pulmonary pathology and is the most effective cytologic technique for establishing a definitive diagnosis of lung carcinoma. Transthoracic FNA is successful at diagnosing both primary and metastatic disease, and is associated with an overall diagnostic sensitivity between 75–95%. Both transthoracic percutaneous needle aspiration and transbronchial (Wang) needle aspiration biopsy are used for investigation of pulmonary nodules.

**Percutaneous Transthoracic Biopsy**

Percutaneous transthoracic aspiration biopsy is the more widely used of the two procedures. In many centers, if sputum cytology is negative and the pulmonary lesion is present at the periphery or apex of the lung, transthoracic FNA will be performed without bronchoscopy. In the majority of cases, a 22-gauge Chiba or Greene needle will optimize specimen procurement.

The fine needle is guided to the desired location by fluoroscopy or CT imaging, and once the needle tip is confirmed to be in position, the stylet is removed and a syringe is attached. Suction is applied and the needle moved rapidly forwards and backwards in the lesion. The vacuum is then released, and the needle removed while the patient...
holds his breath. A portion of the sample is expelled onto
glass slides and smears prepared. Some are allowed to
air-dry, while others are fixed in 95% ethanol. The needle
may be washed out in either a balanced salt solution or
formalin. The air-dried material is stained by the Wright-
Giemsa technique (Diff-Quik) and immediately assessed as
to specimen adequacy. Alternatively, rapid evaluation can be
achieved using smears appropriately fixed and stained by the
rapid Papanicolaou stain or a frozen section-type H&E stain.
If diagnostic material is not obtained, repeat aspirations are
performed until satisfactory material is obtained or the
radiologist or patient chooses to end the procedure. Immedi-
ate microscopic assessment of material also allows the
performance of additional passes when the cytopathologist
on immediate review deems special studies, including
immunohistochemistry, flow cytometry, electron micro-
copy, or microbiologic culture, necessary for complete
evaluation.86,87 Specimens submitted (other than smears) can
be processed by either cytocentrifugation or cell-block
techniques. When cytocentrifugation is preferred, the needle
should be rinsed in 1–2 ml of balanced salt solution or RPMI
medium. Blood clot and visible tissue fragments are best
processed as cell-block preparations, and these are obtained
by rinsing the needle in 2–3 ml of 10% neutral-buffered
formalin. The cell blocks are routinely processed through
paraffin, and H&E sections are prepared. In selected cases, immuno-
histochemistry can be performed on the cell block or
cytocentrifuge specimens.81 Many centers prefer using
cell-block material for immunohistochemistry.

Transbronchial (Wang) Needle Biopsy
While transbronchial aspiration biopsy via flexible broncho-
scope was originally used to detect metastases within
mediastinal lymph nodes, it has become popular with
pulmonologists for the workup of lung nodules in or near the
major bronchi.82–84 The procedure is used less frequently
because it is relatively time-consuming and requires a
skilled bronchoscopist. It is, however, a low-risk procedure
and may provide diagnostic information when other tech-
niques fail, such as bronchial brushing, washing, and biopsy.
It is useful for investigating external bronchial compression
or submucosal lesions and for evaluating mediastinal lymph
nodes in staging of bronchogenic carcinoma. The addition of
transbronchial needle biopsy to bronchoscopy increases the
overall sensitivity of that technique to nearly 100% for
tumors located in large bronchi.85 Wang needle biopsy
should be obtained prior to performing other diagnostic
procedures, including bronchial washings, brushings, and
grasp biopsy.86,87 Processing and interpretation are per-
formed by a technique identical to that used for percutane-
ous aspirations. An adequate specimen usually contains
many diagnostic cells. Unsatisfactory specimens include
samples with much blood, with low cellularity, or with many
benign bronchial mucosal cells and macrophages represent-
ing contaminants from tracheobronchial secretions on the
mucosal surface. A malignant aspirate may be obtained by
inadvertent aspiration of endotracheal secretions containing
neoplastic cells from the more distal airways. Similarly, in
mediastinal staging of pulmonary neoplasms, the aspirate
may be contaminated by inadvertent sampling of tumor in
the lung parenchyma rather than in the lymph nodes.88 In this
situation, the cytopathologist should ascertain that the
smears contain lymphocytes as evidence of accurate sam-
pling of the peribronchial or tracheal lymph nodes. It seems
prudent for the cytopathologist to interpret with caution
specimens containing only a few tumor cells, no lympho-
cytes, and abundant respiratory cells or mucus.88

Contraindications for Fine-Needle Aspiration
(Percutaneous and Transbronchial)
Relative contraindications for fine-needle aspiration of pul-
monary nodules include an uncooperative or unconscious
patient, an individual who is unable to control his or her
cough reflex, uncorrectable coagulation abnormalities, poor
lung function, severe emphysema, marked hypoxemia, pul-
monary hypertension, intrapulmonary vascular lesions, and
hydatid cyst.89–94 While none of these conditions is an
absolute contraindication for fine-needle aspiration of a
pulmonary lesion, the potential benefits should be substan-
tial before proceeding with the procedure. Because of the
potential hazards of transthoracic FNA, it may be best
performed in a setting where emergency services are imme-
diately available and where the services of a thoracic
surgeon are within reasonable proximity.

Complications associated with percutaneous fine-needle
aspiration include pneumothorax,95–100 intrathoracic hemor-
rhage with hemothysis,101,102 and air embolization,103–105 Up
to one third of patients may develop a clinically significant
pneumothorax, but only 5–10% will require treatment.95–100
Hemothysis occurs in between 2–8% of patients but is
usually not a significant clinical problem.101,102 Air embo-
lism is a very rare complication which may be fatal.
Transbronchial needle aspiration of pulmonary lesions is
associated with complications similar to those of percutane-
ous transthoracic fine-needle aspiration, but pneumothorax
is less frequent.

Specimen Adequacy
The assessment of specimen adequacy in fine-needle aspi-
rates from pulmonary nodules is a complex issue. The
presence of neoplastic cells in a specimen defines it as
adequate. However, there are no universally accepted mor-
phologic criteria defining a specimen as adequate in the
absence of malignant cells. Demonstration of etiologic
agents of infectious disease (e.g., fungal forms or AFB) may
also be indicative of the disease process. Other findings,
including those of pneumonia, do not necessarily guarantee
that the specimen represents the primary pathologic process.
Multiple samplings and immediate specimen assessment with repetitive sampling as indicated improve the satisfactory rate. Often factors other than the cytopathologist’s opinion of specimen adequacy will determine whether additional passes are attempted. In general, 2–3 passes optimize the relationship between sample adequacy rates and patient comfort. Williams et al. demonstrated that 80% of pulmonary malignancies were diagnosed within the first two passes, and all malignancies detectable were identified when six separate passes were performed.

Since specific morphologic or numeric criteria for specimen adequacy do not exist for pulmonary fine-needle aspiration cytology, we recommend the terms “adequate” and “nondiagnostic” in the evaluation of pulmonary FNA specimens. When a specimen yields material representative of a specific pathologic entity, the specimen is designated as “adequate.” A specimen composed of benign respiratory epithelium, macrophages, and inflammatory cells in the presence of a significant clinical or radiographic lesion is designated as nondiagnostic despite the presence of abundant cellular material. This category implies that clinical follow-up or further investigation should be considered. The assessment of a specimen as adequate or nondiagnostic probably occurs during the aspiration process and should be reported immediately. Additionally, the assessment of adequacy should be addressed in a comment contained within the final report. This is best done by inclusion of a section which addresses immediate evaluation of adequacy. Such a section has the benefit of documenting the performance of immediate assessment for billing purposes.

Diagnostic Categories for Cytology Specimens

The present guidelines do not attempt to describe the cytologic features related to various lesions occurring within the lung as sampled by multiple techniques. Rather, these guidelines are meant to establish a set of diagnostic categories which succinctly and uniformly transmit pathologic diagnostic information in a standardized format to the clinician. It must be stressed that FNA diagnosis of pulmonary lesions is a clinicopathologic interpretation, and correlation with clinical and radiographic findings is mandatory.

Nondiagnostic Specimens

This category is composed of specimens where no cellular material is obtained, the material is artifactually distorted by blood, poor preservation, or processing artifacts such that a diagnosis cannot be rendered, or a specific clinicopathologic entity cannot be diagnosed. Included in this category are specimens composed of benign cellular elements (respiratory epithelium, macrophages, inflammatory cells) which are insufficient to account for the lesion identified by bronchoscopic or radiographic study. When this diagnostic category is used, a comment should be included explaining the reason the specimen is assigned to this category.

Specific Benign Lesions

This category should include all benign neoplasms, inflammatory processes, and smears in which infectious (fungal, mycobacterial, and bacterial) agents are identified. Within this category each process should be described as specifically as possible. For example, the formulation might read “benign; pulmonary hamartoma” or “benign; granulomatous inflammation consistent with tuberculosis.” A comment should be issued when additional information further specifying the nature of the lesion would be helpful to the clinician.

Atypical Cells Present, Probably Benign

This category should be used when an epithelial or mesenchymal component is present with nuclear atypia believed by the cytopathologist to represent a reactive or reparative change. This diagnosis is not a “stand-alone” diagnosis but requires clinicopathologic correlation and additional investigation if clinically indicated.

Atypical, Suspicious for Malignancy

This category includes specimens that show atypical features believed by the cytopathologist to have a significant risk of representing a malignant neoplasm. This category also applies to cases in which severely abnormal cells may be present in numbers too low to permit a definitive diagnosis or the degree of atypia is below the threshold for a definitive diagnosis.

Malignancy Present

This category should contain all specimens in which a definitive diagnosis of malignancy can be made. If a specific histologic type of carcinoma is recognized it should be so diagnosed. Although since definitive pathologic tumor typing is not always possible, an attempt should be made to state whether the malignancy is of epithelial or nonepithelial origin, and if epithelial, whether it represents a small-cell or nonsmall-cell carcinoma or a metastasis. Correlation with clinical history is recommended.

Because some studies have reported only a 75% rate of correctly typing lung carcinomas, it may be prudent to separate lung carcinomas into small- and nonsmall-cell types. This division has clinical support in that most therapeutic decisions require only this level of subclassification. Raab and Silverman reviewed the accuracy and significance of cytologic typing of lung carcinomas.

Reporting of Findings in Cytologic Specimens

The cytologic report should be clear, concise, and clinically relevant, as discussed by Suen et al. in the Guidelines of the Papanicolaou Society of Cytopathology. A statement...
regarding the nature of the specimen reviewed should be
given to include the number of passes performed and the
number of slides received, and it should be documented if
materials were received for cytopsin or cell-block prepara-
tions. Terminology should be consistent, and the cytopatholo-
gist should attempt to render as specific a diagnosis as
possible. The Papanicolaou class system should not be used,
and whenever possible the cytologic diagnosis should closely
simulate the corresponding histopathologic diagnosis.

In many cases, a comment should address the adequacy of
the specimen, those factors limiting the diagnostic accuracy
of the specimen, and the reasons for the categorization of a
specimen as nondiagnostic, atypical and probably benign, or
atypical and suspicious for malignancy. A recommendation
for future action may be included in the report when the
cytopathologist feels that it is indicated. In other practice
circumstances, the cytopathologist may wish to report recom-
 mendations verbally to the clinician. The recommendation may
suggest further diagnostic studies, including bronchial bi-
opsy, mediastinoscopy, or thoracotomy with biopsy. This
recommendation need not be part of the report if a definitive
diagnosis is rendered. Comments and additional communica-
tion are most important when the cytopathologist is unfamil-
iar with the clinician or clinicians receiving the report.

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Discriminate analysis of lower respiratory tract components associ-
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