Bronchoalveolar lavage as a diagnostic procedure: a review of known cellular and molecular findings in various lung diseases

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Abstract: Bronchoalveolar lavage (BAL) is a commonly used procedure in the evaluation of lung disease as it allows for sampling of the lower respiratory tract. In many circumstances, BAL differential cell counts have been reported to be typical of specific lung disorders. In addition, more specific diagnostic tests including molecular assays such as polymerase chain reaction (PCR) or enzyme-linked immunosorbent assay, special cytopathologic stains, or particular microscopic findings have been described as part of BAL fluid analysis. This review focuses on common cellular and molecular findings of BAL in a wide range of lung diseases. Since the performance of the first lung irrigation in 1927, BAL has become a common and important diagnostic tool. While some pulmonary disorders have a highly characteristic signature of BAL findings, BAL results alone often lack specificity and require interpretation along with other clinical and radiographic details. Development of new diagnostic assays is certain to reinforce the utility of BAL in the future. Our review of the BAL literature is intended to serve as a resource to assist clinicians in the care of patients with lung disorders.

Keywords: Bronchoalveolar lavage (BAL); bronchoscopy; cell count differential; lung disease; pneumonitis; signature

Introduction

Bronchoalveolar lavage (BAL) is a common and relatively safe diagnostic procedure for the evaluation of patients with lung disease. It often provides valuable diagnostic information when clinical history, physical exam, routine laboratory testing, pulmonary function testing and radiographic imaging are insufficient to reach a definitive diagnosis. Compared to sputum analysis, BAL allows for targeted sampling of the lower respiratory tract with less microbial contamination from the upper aerodigestive tract.

Since the first lung irrigation was performed through a rigid bronchoscope in 1927, the procedure of BAL has advanced to become safer and better tolerated (1,2). Development of the flexible bronchoscope in 1966 was a major breakthrough as bronchoscopy and BAL are now typically performed under conscious sedation. BAL is frequently paired with other bronchoscopic procedures such as endobronchial or transbronchial biopsies, transbronchial needle aspiration, bronchial brushings, and endobronchial ultrasound-guided needle aspirations. The lavage fluid can be evaluated with a variety of analytical tests including cell counts and differential, cytopathologic analysis, and cultures in addition to specific molecular and immunologic diagnostic tests.

BAL as a diagnostic procedure

Several characteristics of BAL fluid have been recognized to predict—with varying degrees of confidence—specific lung disorders. For example, with compatible clinical history and imaging, a lymphocytic-predominant BAL is adequate to support a diagnosis of pulmonary sarcoidosis or hypersensitivity pneumonitis; or in a patient with an acute alveolar opacification on chest imaging, the presence of significant BAL eosinophils can indicate acute eosinophilic pneumonia with a fair degree of certainty (3-6). However, in most instances, although the cell differential findings on BAL often lack specificity, they still may be useful in excluding certain disorders such as diffuse alveolar hemorrhage, eosinophilic lung diseases, and to a lesser degree, certain infections, thus narrowing the differential diagnosis (7). The differential cell count may even be normal in many pulmonary disorders such as chronic obstructive pulmonary disease, asthma, or some cases of drug-induced pneumonitis (8,9). Creating greater complexity, the BAL cell count differential may evolve over time depending on the stage of the disease process such as in hypersensitivity pneumonitis and cases of acute respiratory distress syndrome (ARDS) (10,11). Nevertheless, the BAL cell count and differential pattern often assists clinicians in supporting a particular diagnosis or excluding others, thereby providing helpful clues in challenging cases and improving diagnostic accuracy. In some circumstances, no characteristic cell count and differential patterns are discernable either because of variability of cell counts seen in the disease process or limited data on BAL cell counts reported in the literature. Transbronchial biopsy and especially surgical lung biopsy retain a prominent role in the formal diagnosis of several lung diseases where BAL findings are nondiagnostic (12,13).

BAL is often performed to obtain respiratory samples in suspected infections for microbiologic culture and analysis when patients are unable to expectorate sputum even after attempt at sputum induction. However, after the initiation of antibiotics, even BAL loses sensitivity for many bacterial pathogens and becomes insensitive for fastidious microbes (14). Newer diagnostic techniques including polymerase chain reaction (PCR) and other molecular assays enhance the role of BAL for identifying specific microbial infections. Among immunocompromised patients who are vulnerable to a wider range of pathogens and may not exhibit classic symptoms or radiographic findings, BAL is particularly useful; e.g., for the diagnosis of pneumocystis pneumonia.

Additionally, more recent diagnostic techniques such as matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF) and PCR coupled to electrospray ionization mass spectrometry (PCR/ESI-MS) both show potential to provide rapid microbiologic results of BAL fluid that will enable clinicians to target particular organisms far sooner than conventionally possible (15,16). More recently, whole-genome sequencing, including real-time metagenomic sequencing, of BAL fluid has been used to diagnose and manage viral, bacterial, and fungal pneumonias in critically ill patients with and without immunosuppression (17,18). In addition, shotgun sequencing of BAL fluid has been used to characterize the metagenomics and microbiome of the respiratory tract of lung transplant recipients (19) and patients with chronic lung diseases (20). As whole-genome sequencing becomes more readily available in clinical laboratories, its role in the analysis of BAL fluid will likely increase.

The technique by which BAL is performed, while similar globally, may have geographic variations depending on the institution and region of the world (21). In the United States and Europe, there are efforts to standardize the collection of BAL according to consensus guidelines (13,22,23). The bronchoscope is advanced distally into the bronchopulmonary segment of interest until it occludes the bronchus, thereby "wedging" the scope. Sequential aliquots of normal saline totaling at least 100 mL (and no more than 300 mL) should be instilled and at least 30% returned for optimal sampling. A minimum 5 mL (and ideally 10–20 mL) is needed for cellular analysis (13). Strict safety standards are advised including the use of sedatives and anesthetics and diligent monitoring of patients' vital signs, respirations, and oxygenation during the procedure (24). BAL fluid should be collected in a labeled sterile container and transported expediently to the laboratory for analysis (21). Depending on laboratory capabilities, differential cell counts are performed by flow cytometry or manually after filtration or cytocentrifugation techniques (25).

Topical anesthetics such as lidocaine are administered universally in the upper airway, larynx, and lower respiratory tree to provide comfort and decrease cough. Theoretically, there have been concerns that high levels of topical anesthetics could reduce the sensitivity of microbial cultures from the BAL (26). This appears to be true of bronchial washings, but not of BAL (27). Such discrepancy is accounted for by the much higher volumes of sterile saline used during BAL in comparison to bronchial washings, thereby diluting the concentration of any residual

Table 1 Healthy subjects

Smoking status	Bronchoalveolar lavage fluid findings
Healthy non-smokers	Macrophage predominant ~85% of all white blood cells. Lymphocytes ~10%, ~5% neutrophils, <1% eosinophils, <1% basophils (28-30)
Healthy smokers	Smokers have increased cellularity compared to non-smokers. They also have an increased fraction of pigmented macrophages and decreased fraction of lymphocytes (29,31)

Table 2 Airway diseases

Diseases	Bronchoalveolar lavage fluid findings
Allergic bronchopulmonary aspergillosis/ mycosis (ABPA/ABPM)	Increased cellularity with eosinophils, lymphocytes, or neutrophils, but often remaining macrophage predominant (32). BAL *Aspergillus fumigatus* IgE and BAL galactomannan can also be elevated (33)
Asthma	Frequently increased proportion of eosinophils; but an elevated mixed pattern with increased proportions of neutrophils, lymphocytes and mast cells are also reported (9)
Bronchocentric granulomatosis	No data available
Chronic obstructive pulmonary disease (COPD)	May reveal increased cellularity and pigmented macrophages among smokers. Otherwise, no particular pattern is seen. Stable COPD may show small increases in neutrophils, eosinophils, and lymphocytes (8,34). Patients with more severe COPD may have increased percentage of neutrophils (25). Among patients with acute exacerbations of COPD, increases in neutrophils, eosinophils, and lymphocytes may be seen
Cystic fibrosis	Typically remain neutrophil predominant even between exacerbations (35)
Mournier-Kuhn syndrome (tracheobronchomegaly, bronchiectasis, and airway diverticula)	No data available
Primary ciliary dyskinesia	Often neutrophilic from increased frequency of recurrent bacterial infections due to the presence of bronchiectasis (36)
Williams-Campbell syndrome	No data available

topical anesthetic.

The objectives here are to compile available BAL data categorized by different classes of lung diseases and also to highlight lung disorders where insufficient BAL data exist. We performed comprehensive searches on PubMed to find available data on particular BAL profiles for a given disease using the keywords of BAL, lung lavage, and the names of specific disorders. A further goal is to provide clinicians with a succinct and referenced resource to aid in the evaluation of patients who undergo BAL albeit we acknowledge that in some resource-poor countries, many of the specific molecular tests may not be readily available. The data assembled are focused on the particular patterns of BAL cellularity seen within each disease state. In many cases, there were few published studies and when present, often limited to case reports and series. Not surprisingly, we

found very few published articles on BAL data of rare lung diseases or pulmonary toxicities associated with recently developed medications.

The BAL data are organized into the following categories: healthy subjects (*Table 1*), airways diseases (*Table 2*), cystic lung diseases (*Table 3*), pulmonary vasculitides (*Table 4*), interstitial lung diseases (*Table 5*), occupational and environmental lung diseases (*Table 6*), radiation-induced pneumonitis (*Table 7*), infectious pneumonias (*Tables 8-12*), drug-induced pneumonitis (*Table 13*), and miscellaneous lung diseases (*Table 14*). For infectious pneumonias, we focused primarily on microbiologic and molecular diagnostic testing available. Additionally, we tabulated diseases characterized by particular BAL cell differential (eosinophilic, lymphocytic, or neutrophilic predominance) (*Table 15*), diffuse alveolar hemorrhage (DAH) due to non-

Table 3 Cystic lung diseases

Diseases	Bronchoalveolar lavage fluid findings
Birt-Hogg-Dubé syndrome	No data available
Lymphangioleiomyomatosis (LAM)	No specific pattern, although may have increased pigment-laden macrophages (37). Transbronchial biopsies show positivity for HMB45 and smooth muscle actin as well as nodular infiltration of pulmonary lymphatics with LAM cells (38)
Neurofibromatosis	Macrophage predominance (~80%) with low level eosinophilia and mast cells described in single cases of neurofibromatosis-associated lung fibrosis (39)
Pulmonary Langerhans cell histiocytosis (PLCH, formerly eosinophilic granuloma)	Similar to smokers, shows increased cellularity with macrophage predominance. There may also be lymphocytosis, slight neutrophilia or eosinophilia but these changes are inconsistent. Cells demonstrating +CD1a (OKT6) in ≥5% of cells are highly specific for PLCH; although sensitivity for this cutoff value is low because only ~50% of patients show this elevation of CD1a(+) cells (7,40-42). On immunohistochemistry, cells are typically also CD68 positive and langerin (CD207) positive (43). S-100 may also be positive but is nonspecific (44). Transbronchial biopsy is insensitive (10–40% sensitivity) given patchy lung involvement in PLCH (37). Langerhans cells with distinguishing Birbeck granules may be seen on electron microscopy of biopsy specimens (45)

Table 4 Pulmonary vasculitides*

Diseases	Bronchoalveolar lavage fluid characteristics
Behçet's disease	Increased cellularity with increased proportion of lymphocytes. Neutrophils may also be increased (46)
Cryoglobulinemia	Associated with lymphocyte predominance and overall increased cellularity including subtle elevations in proportions of neutrophils and occasionally eosinophils (47,48)
Eosinophilic granulomatosis with polyangiitis (EGPA, formerly Churg-Strauss syndrome)	Typically with increased fraction of eosinophils (≥25%) (49). Transbronchial lung biopsy has low yield
Granulomatous polyangiitis (GPA, formerly Wegener's granulomatosis)	Neutrophil predominance with slight elevation in lymphocytes or eosinophils is seen in analysis of BAL fluid (50,51). Bleeding may also be present
Goodpasture syndrome	Lavage confirms hemosiderin-laden macrophages or acute DAH (52)

*, all will likely have a BAL consistent with diffuse alveolar hemorrhage (DAH).

infectious and infectious causes (*Table 16*), foamy alveolar macrophages (*Table 17*), and a tabulation of disorders in which a signature of BAL cellular findings may be diagnostic or relatively so (*Table 18*). Abbreviations in the tables are defined at the bottom of *Table 18*. We have elected not to discuss cytologic analysis of BAL to diagnose primary lung cancer or metastatic disease in detail in the scope of this paper.

BAL as a therapeutic procedure

BAL is almost exclusively used as a diagnostic tool. But a modified BAL—really more of a bronchial wash—using smaller aliquots of saline to help dislodge distal mucous plugs is likely the most common therapeutic use, especially in those with a secured airway (endotracheal tube or tracheostomy) but too debilitated to self-expectorate successfully. The best evidence for therapeutic use of BAL is for pulmonary alveolar proteinosis. In this instance, the BAL technique is modified with high volumes of sterile normal saline via a dual lumen endotracheal tube to perform a therapeutic whole lung lavage with removal of heavy lipoproteinaceous sediment from the lungs. This procedure was first described in 1963 with subsequent modifications in technique to optimize patient safety, yield of removed protein and therapeutic benefit (320). Other rare reports of therapeutic lung lavage have been described for exogenous lipoid pneumonia from milk aspiration (321) and another

Table 5 Interstitial lung diseases

Diseases	Bronchoalveolar lavage fluid characteristics
Acute eosinophilic pneumonia (AEP)	Eosinophilia >25%, often ranging 37–54% (6,53,54)
Acute interstitial pneumonia (AIP)	Neutrophil predominance with occasional evidence of hemorrhage related to DAD and resultant capillary leak (13,55)
Chronic eosinophilic pneumonia (CEP)	Eosinophilia, often >40%, along with relatively normal percentages of lymphocytes and neutrophils, although mild to moderate increase in lymphocytes with reduced CD4:CD8 ratio may be seen (6,7,56)
Cryptogenic organizing pneumonia (COP)	Findings are nonspecific. Typically, there is increased cellularity in a mixed pattern with variable increases in lymphocytes, neutrophils, eosinophils, and foamy macrophages as well as occasional increases in plasma cells and mast cells (57,58). Acute fulminant cases are often neutrophilic whereas more chronic cases tend to be lymphocytic (59). Classically, the CD4:CD8 ratio is reduced, but this finding is variable (60)
Desquamative interstitial pneumonia (DIP)	Increased cellularity along with increases in pigmented alveolar macrophages. An increase in eosinophils and increase in neutrophils may also be seen but lymphocyte levels tend to be low (13,61,62)
Granulomatous lymphocytic interstitial lung disease (GLILD)	Lymphocytosis >20% was seen among 85% of patients in a small case series (63). 50% of these cases have a low CD4:CD8 ratio
Interstitial pneumonia with autoimmune features (IPAF), Connective tissue associated interstitial lung disease (CT-ILD, ILD associated with rheumatoid arthritis, Sjögren's syndrome, scleroderma, dermatomyositis)	Forms of lung disease are associated with many systemic rheumatologic conditions; these have been loosely grouped together as IPAF or CT-ILD. Although findings are highly variable, increased lymphocytes are frequently reported (64). Among patients with dermatomyositis-associated ILD, lymphocytosis is often reported and more frequent in patients with MDA-5 antibody positivity (65,66). Increases of neutrophils with rheumatoid arthritis and ILD are seen and increases in neutrophils and eosinophils can be seen in ILD associated with CREST syndrome (67,68). Sjögren's syndrome associated ILD is also frequently associated with lymphocytosis; however, presence of neutrophils is associated with worsened disease (69). Scleroderma patients with ILD frequently have variable increases in neutrophils, eosinophils, or lymphocytes (70-72)
Lymphocytic interstitial pneumonia (LIP)	In one series of 15 patients, average lymphocyte counts were 30% (73). Within this series 11 were diagnosed with open lung biopsy, 3 with video-assisted thoracoscopic surgery, and 1 with transbronchial lung biopsy. Molecular testing for monoclonal gene rearrangements can confirm pulmonary lymphoma (74)
Niemann-Pick disease	Foamy histiocytes that are Periodic acid Schiff (PAS)-positive (75)
Nonspecific interstitial pneumonia (NSIP)	Typically a lymphocytosis, but highly variable (76,77). There is reduced CD4:CD8 ratio, but cases of fibrotic NSIP often do not adhere to this pattern (78). Compared to UIP, NSIP typically have greater proportion of lymphocytes and similar or less percentage of neutrophils (79)
Pleuroparenchymal fibroelastosis (PPFE)	Normal cell counts with slight lymphocyte elevation and low levels of neutrophils and eosinophils (80)
Respiratory bronchiolitis interstitial lung disease (RBILD)	Identical to smokers; increased overall cellularity with heavy pigmented macrophage predominance (13,81)
Usual interstitial pneumonia (UIP), idiopathic pulmonary fibrosis	Increased total number of cells with a mixed pattern, often macrophage predominant with <30% total lymphocytes, variable increases in neutrophils and small increase in eosinophils (13,28,77,82). Although elevated BAL neutrophils can be associated with worsened survival, there is no consensus that BAL results portend prognosis (83)

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Table 6 Occupational & environmental lung diseases

Diseases	Bronchoalveolar lavage fluid characteristics
Asbestosis	Increased cellularity with overall increased macrophages along with increased percentages of neutrophils, eosinophils, or lymphocytes. Iron staining of sediment may show ferruginous bodies (asbestos bodies), which appear as rod-like, or elongated dumbbell shaped crystals. However, presence of these forms only confirms exposure and not necessarily the development of clinical asbestosis (84-87)
Berylliosis	Blood beryllium (Be) lymphocyte proliferation test (BeLPT) is used as a screening test to confirm Be exposure. Typically, there is lymphocyte predominance with characteristically positive BeLPT (88). However, smokers and immunosuppressed patients with chronic berylliosis may have a negative BAL BeLPT. Biopsy characteristically shows granulomas.
Byssinosis	Increased cellularity of both neutrophils and lymphocytes (89)
Caplan's syndrome (rheumatoid pneumoconiosis) associated with both rheumatoid arthritis and occupational pneumoconiosis	No cell profile available other than findings of heavily pigmented macrophages (90). Biopsy shows layer of anthracotic pigment surrounding central necrotic core
Coal worker's pneumoconiosis	Increased cellularity with anthracotic-pigmented macrophages. A small increase in neutrophils may be seen, especially in those with progressive massive fibrosis (91-93)
Hard metal lung disease (cobalt, molybdenum, nickel, titanium, tungsten exposure)	Multinucleated giant cells are typically seen, but not always. Cell count may be increased in a mixed pattern or have relative lymphocytosis or eosinophilia. Transbronchial biopsies may be analyzed for heavy metals (94-97)
Hypersensitivity pneumonitis (HP, also known as extrinsic allergic alveolitis)	Lymphocytosis (often >50%) with moderate neutrophilia, modest eosinophilia and mast cells. Classically, a low CD4:CD8 ratio was believed to be helpful in differentiating HP from sarcoidosis but high variability in the CD4:CD8 ratio may be seen (4,5,98-101). Levels of neutrophils in BAL decline with time after antigen exposure (10). Foamy macrophages may be seen
Siderosis	Hemosiderin-laden macrophages but otherwise a normal differential cell count (102,103). Elevated BAL ferritin levels have also been reported (104)
Silicosis	In acute silicosis, lavage is often milky appearing similar to alveolar proteinosis. Foamy macrophages with positive periodic acid Schiff (PAS) staining are characteristic. Birefringent particles consistent with silica may be seen with polarized microscopy. In chronic silicosis, biopsy may show pigmented macrophages along with silicotic nodules and parenchymal fibrosis. Abundant macrophages with an increase in lymphocytes and neutrophils can be seen. Lesions can develop into progressive massive fibrosis where the cores may become necrotic (105-107)

Table 7 Radiation-induced pneumonitis

Diseases	Bronchoalveolar lavage fluid characteristics
Radiation-induced pneumonitis—may be a primary lung injury in a radiation treatment field or secondary injury outside the field due to radiation-primed, immune-mediated inflammation	Increase in several cell types but often a lymphocyte predominance both in irradiated and non-irradiated, contralateral lung (108,109). Radiation-induced organizing pneumonia may be seen with contralateral radiotherapy for breast cancer with a mixed pattern of increases in lymphocytes, neutrophils, eosinophils, and mast cells (7)

Table 8 Infectious pneumonia: viruses

Diseases/agent	Bronchoalveolar lavage fluid characteristics
Adenovirus	PCR is highly specific and sensitive (110). One case report with acute infection revealed neutrophil predominance (111)
Anellovirus	Whole-genome shotgun DNA sequencing can reveal higher abundance in lung transplant receipt compared to healthy controls; high viral load correlates with dysbiotic communities in the allograft BAL and may indicate anellovirus lung infection and portend adverse transplant outcome (19)
Coronavirus, Middle East respiratory syndrome strain (MERS-CoV)	Detection of coronavirus with various strain-specific PCR (112). BAL and tracheal aspirates yielded greater viral loads for MERS-coronavirus than nasopharyngeal swabs or sputum samples (113). No cell data available
Coronavirus, COVID-19	Single cell RNA sequencing of BAL fluid demonstrated depletion of tissue-resident alveolar macrophages and increased monocyte-derived inflammatory macrophages (in severe disease), and increased clonal expansion of CD8+ T cells (in mild cases) (114). Increasing levels of neutrophils were associated with worsened severity of disease (114)
Cytomegalovirus	PCR of BAL specimens is rapid and sensitive (115). Cytopathologic changes can show characteristic Cowdry owl's eye inclusion bodies. Serum pp65 antigen detection may be a better test for active infection than CMV PCR (116). Metagenomic next-generation sequencing showing ≥50% unique reads or any read of the virus not detected by convention means may indicate infection in critically ill patients (17)
Hantavirus pulmonary syndrome (Sin Nombre virus)	Capillary leak pulmonary edema with relative acellularity; immunoblasts found are activated lymphocytes with plasmacytoid features (117,118)
Hemorrhagic fever with renal syndrome with pulmonary involvement (Seoul hantavirus or Puumala virus)	Increased lymphocytes comprised of CD8 T cells and natural killer cells with increased expression of HLA-DR and CD25 (activation markers) as well as increased granzymes A and B (119-121). For Puumala hantavirus, alveolar macrophages with greenish, intracytoplasmic inclusions. With Seoul hantavirus, plasmacytoid and plasmablastic cells (immunoblasts) are seen (122)
HIV-associated pneumonitis	Lymphocytosis with associations with either LIP or NSIP (123-126)
Human metapneumovirus (hMPV)	No BAL cell profile available. Epithelial cell degenerative changes with eosinophilic inclusions may be seen within in the cytoplasm. hMPV RNA is detected by RT-PCR (127,128)
Herpes simplex (HSV-1) bronchopneumonitis	Macroscopic bronchial lesions may present as mucosal erythema and superficial ulcerations. Non-specific increases in all types of inflammatory cells are described (129-131). Multinucleated epithelial cell metaplasia (Tzanck cells) and the presence of eosinophilic nuclear inclusions with a surrounding clear halo (Cowdry bodies) that may also be seen with varicella zoster virus and cytomegalovirus infections. PCR for HSV-1 can be diagnostic. Quantitation of DNA load may predict respiratory insufficiency and perhaps mortality (132,133). Metagenomic next-generation sequencing can be used to diagnose infection in critically-ill patients (17)
Influenza	Neutrophilia in first week followed by subsequent lymphocytosis (134). Limited data from a series of patients with ARDS from influenza
Parainfluenza	Elevations in both neutrophils and lymphocytes from one case report (135)
Respiratory syncytial virus	Neutrophilic predominance has been described (136)
Varicella zoster pneumonia	Elevated cellularity and an increase in lymphocytes with a low CD4:CD8 T-cell ratio (137). Detected by PCR (138)

Table 9 Infectious pneumonia: bacteria

Diseases/organisms	Bronchoalveolar lavage fluid characteristics
Q fever (*Coxiella burnetii*)	PCR positive for C. *burnetii* DNA (repetitive element IS1111) (139)
Legionella	Severe *L. pneumophila* pneumonia revealed marked neutrophilia with increased number of lymphoblasts and activated T cells (140). BAL for *Legionella* DNA (16S rRNA gene) by PCR, direct fluorescent antibody test, and culture may complement urine antigen testing (141). *L. pneumophila* may also stain acid-fast positive (142)
Leptospirosis	DAH may occur with minimal or no apparent abnormality on chest radiograph and with or without renal or hepatic involvement. No definitive data on differential cell count although histopathologic findings indicate relatively modest infiltration of alveolar spaces with monocytes and neutrophils. Dark-field examination may show the spirochetes (143-146)
Mycoplasma pneumoniae	Increased neutrophils and T lymphocytes with greater T_H2 cytokine expression; i.e., increased IL-4 and IL-4/IFN ratio compared to pneumococcal pneumonia and controls (147). PCR targeting phosphotransferase system I gene, P1 cytadhesin gene, and *M. pneumoniae* repetitive element (RepMP1) all have similar and good accuracy on various respiratory specimens including BAL fluid (148). DAH has also been reported (149). BAL cell profile not available
Plague (*Yersinia pestis*)	No data available
Tularemia (*Francisella tularensis*)	No data available. Culture has lower sensitivity than PCR (150)

Table 10 Infectious pneumonia: fungi

Diseases	Bronchoalveolar lavage fluid characteristics
Aspergillus pneumonia	BAL galactomannan increases the sensitivity of test when compared to serum galactomannan (151). However, BAL galactomannan is not routinely recommended among non-immunocompromised patients due to risk of false-positive results (152). Angioinvasive aspergillosis is diagnosed based on tissue biopsy. Metagenomic next-generation/whole genome sequencing can be used to diagnose infection (17)
Blastomyces pneumonia	Yeast forms are ~8–15 μm in diameter with broad-based budding. Fungal culture adds to diagnostic yield of cases not diagnosed on BAL cytopathology alone (153). Specific antigen testing in BAL fluid is only 62.5% sensitive (154)
Candida pneumonia	Colonization frequency is quite high among critically ill and mechanically ventilated patients. No formal quantitative thresholds exist to differentiate infection from colonization (155)
Coccidioides pneumonia	*Coccidioides immitis* spherules can be seen on Papanicolaou stain. Culture of BAL fluid has higher sensitivity than microscopy alone (156). BAL cellular profiles tend to have elevations in neutrophils and may have very mild elevations in eosinophils (157). Eosinophilia is more commonly seen in peripheral blood
Cryptococcus pneumonia	Encapsulated yeast can be seen on microscopy, particularly when stained with India ink (158). Cryptococcal antigen testing on BAL is highly specific (159)
Histoplasma pneumonia	Delicate smooth branching microconidia, 2–3 μm in diameter with narrow-based budding can be seen on microscopy. Histoplasma antigen enzyme immunoassay (EIA) in BAL fluid is quite sensitive (94%) when tested in a cohort of mostly immunocompromised patients (160)
Pneumocystis jirovecii pneumonia (PJP) or PCP pneumonia	Cell count is nonspecific and may show relative increases in lymphocytes, neutrophils, and eosinophils. Foamy alveolar casts and *P. jirovecii* clusters are seen on Giemsa stain. PCR and DFA can also be sent on BAL fluid with improved yield in comparison to sputum alone (161-163)
Pulmonary mucor (Zygomycosis)	Ribbon-like fungal hyphae with non-septated, right-angle branching seen on Papanicolaou stains (164). In a small case series, 60% of cases were diagnosed on BAL alone and the remaining 40% were diagnosed based on transbronchial biopsy (165). Fungal stain on microscopy has higher yield than fungal culture

Table 11 Infectious pneumonia: parasites

Diseases	Bronchoalveolar lavage fluid characteristics
Angiostrongyliasis	Eosinophilia with nematode larvae on microscopy (166)
Leishmaniasis	Amastigotes can be found on microscopy (167)
Paragonimiasis	Ova & parasite exam reveals ova which are golden yellow in color, 80 µm in length and 40–50 µm in diameter with a flat operculum (168,169)
Strongyloidiasis	Neutrophil predominant with rhabditiform larvae on microscopy (170,171)
Toxocariasis	Eosinophilia (172)
Toxoplasmosis	Trophozoites can be seen with Giemsa-stain (173)

Table 12 Infectious pneumonia: mycobacteria

Diseases	Bronchoalveolar lavage fluid characteristics
Tuberculosis	Acid-fast bacilli on stain and subsequent culture. Increased total number of cells and percentage of lymphocytes (174,175). *Mycobacterium tuberculosis* PCR can provide rapid diagnosis prior to culture results. Higher percentage of CD4+ T cells and lower percentage CD8+ T cells (and opposite findings in peripheral blood) of patients with higher clinical grade of pulmonary TB-defined by extent of lung involvement and presence of fever and weight loss (176)
Non-tuberculous mycobacteria (NTM)	Acid-fast bacilli on Ziehl-Neelsen stain may be seen but unusual unless mycobacterial burden is high. A single case report in a patient with Hodgkin's lymphoma and *Mycobacterium mucogenicum* had a lymphocyte predominance (177). NTM lung disease is typically associated with increased percentage of lymphocytes and neutrophils (178). With *Mycobacterium avium* complex (MAC)-associated nodular bronchiectasis, those who were "not deteriorating" (n=8) had increased lymphocyte and neutrophils but macrophages > lymphocytes > neutrophils; in contrast, of those who were "deteriorating" (n=13), the relative percentages were neutrophils ≥ macrophages > lymphocytes (179). In 37 MAC lung disease subjects, those with neutrophil-dominant BAL had more severe radiographic disease and greater clinical deterioration than those with lymphocyte-dominant BAL (180)

Table 13 Drug-induced pneumonitis

Drugs	Bronchoalveolar lavage fluid characteristics
Adalimumab (anti-TNF monoclonal antibody)	Macrophage predominance with slight elevations in eosinophils and lymphocytes (181). Transbronchial biopsy with thickening in alveolar septa and mild to moderate lymphocytic interstitial cellularity consistent with ILD and OP
Alemtuzumab (anti-CD52 monoclonal antibody)	Associated with DAH and interstitial pneumonitis (182). No BAL cell profile available
Amiodarone	Highly variable pattern: normal to increased levels of lymphocytes, neutrophils, and eosinophils. Lymphocytosis and foamy intracytoplasmic vacuoles in alveolar macrophages (due to accumulation of phospholipids) may indicate only exposure and not necessarily toxicity (183-186). On electron microscopy, the foamy cytoplasmic vacuoles correspond to surfactant-like lamellar bodies. Cellular differential is not prognostic of outcome
Anagrelide	Hypersensitivity pneumonitis with BAL showing predominance of lymphocytes as well as fibrotic changes are reported (187)
Azathioprine	Rare association with usual interstitial pneumonitis, organizing pneumonia or DAD (188). No BAL cell profile available

Table 13 (*continued*)

Table 13 (*continued*)

Drugs	Bronchoalveolar lavage fluid characteristics
Bevacizumab (anti-VEGF monoclonal antibody)	Associated with development of hemoptysis, pulmonary embolus, pulmonary hemorrhage and interstitial pneumonitis (189). With interstitial pneumonitis, BAL may reveal elevated lymphocytes (190)
Bleomycin	Neutrophilia from limited data (191)
Bortezomib (proteasome inhibitor)	Associated with a pattern of organizing pneumonia, bronchiolitis obliterans, pleural effusions, or DAD (192-194). No BAL cell profile available
Bromocriptine	Associated with pulmonary fibrosis (195). No BAL cell profile available
Busulfan (alkylating chemotherapeutic)	Both increases in lymphocytes or neutrophils have been reported along with atypia in type I pneumocytes (196)
Captopril and perindopril	Rarely, diffuse interstitial/alveolar pneumonitis has been reported which may have lymphocytic infiltration or eosinophilic pneumonia (197,198)
Carbamazepine	Associated with an acute pattern of hypersensitivity pneumonitis or eosinophilic pneumonia from limited data (199)
Carmustine (BCNU) (alkylating chemotherapeutic)	Associated with development of pulmonary fibrosis that may be early-onset or delayed. No BAL cell profile exists on patients with early-onset fibrosis. Among patients with delayed-onset, they had upper lobe predominant fibrosis and either a normal BAL differential or increase in lymphocytes (200)
Cetuximab (anti-EGFR monoclonal antibody)	Associated with infusion-related bronchospasm, pneumonitis, bronchiolitis, organizing pneumonia and pulmonary fibrosis (201,202). Pneumonitis was more common in patients also receiving radiation therapy for non-small cell lung cancer (203). No BAL cell profile available
Checkpoint inhibitors (anti-PD-1, anti-CTLA-4, anti-PD-L1)	Risk of checkpoint inhibitor pneumonitis (CIP)—consolidation, organizing pneumonia, GGO, interlobular septal thickening, and traction bronchiectasis—greater with anti-PD-1 and anti-PD-L1 than anti-CTLA4. In a meta-analysis of nearly 4,500 patients on anti-PD-1 inhibitor, the overall incidence of pneumonitis was 2.7% and the pneumonitis was more frequent and severe in patients with lung cancer or renal cell carcinoma than melanoma (204,205). In 22 patients with CIP, the mean BAL lymphocyte count was 14% (range 4–90%) (206). Another study of 30 patients with CIP determined the mean BAL lymphocytes to be 34% (1–70%) (207). High-grade CIP is associated with poor prognosis (208)
Chlorambucil (alkylating chemotherapeutic)	Associated with a hypersensitivity pneumonitis pattern with increased lymphocytes (209). However, if leukemic pulmonary infiltration is suspected as cause of radiographic abnormality, BAL is insensitive and lung biopsy is recommended (210)
Cyclophosphamide (alkylating chemotherapeutic)	Both early-onset acute pneumonitis is described along with a late-onset fibrotic disease associated with pleural thickening and DAD (211). Limited BAL cell profile data exists for either form; a patient with chronic cyclophosphamide toxicity and associated fibrosis was reported to have macrophage predominance (212)
Dasatinib (Tyrosine kinase inhibitor)	Pneumonitis with lymphocytosis is most commonly reported (213). Also associated with lymphocytic, typically exudative pleural effusions. Another single report with BAL neutrophilia was also reported (214)
Docetaxel (anti-mitotic chemotherapeutic)	Associated with a capillary leak syndrome 8–14 days after administration (215,216). No BAL cell profile available
Doxorubicin (topoisomerase inhibitor)	Possible association with organizing pneumonia from limited data (217). Associated with radiation recall effect
Erlotinib (tyrosine kinase inhibitor)	Associated with acute development of ILD with either a DAD or OP pattern (218-220). BAL with neutrophilic predominance
Etanercept (soluble p75 TNF receptor subunit)	Associated with development of granulomatous inflammation and a sarcoidosis-like reaction or organizing pneumonia with lymphocytic BAL (221-223)

Table 13 (*continued*)

Table 13 (*continued*)

Drugs	Bronchoalveolar lavage fluid characteristics
Etoposide (topoisomerase II inhibitor)	Associated with DAD as well as radiation recall effect. BAL with lymphocytic predominance (224,225)
Everolimus (mTOR inhibitor)	HP pattern with lymphocytosis, in particular with increased CD4 cells (226,227). Biopsies may also show OP, LIP, non-necrotizing granulomatous inflammation, and vasculitis. Less commonly, an eosinophilic BAL is reported
Gefitinib (EGFR inhibitor)	Associated with acute ILD developing 3–7 weeks after initiating therapy. Increase in lymphocytes or eosinophils although some cases have normal cellularity and differential (228,229). Higher incidence in Japanese patients may be associated with increased EGFR mutations seen in Japan (230). Biopsies consistent with DAD
Gold	In one case series, 72% all had lymphocyte predominance (231). Cases can be associated with a pattern of NSIP, DAD or OP (231,232). Toxicity typically occurred 2–6 months after initiation on therapy
Hydroxyurea	Associated with a pattern of acute ILD or HP (233,234). No BAL cell profile available
Imatinib (BCR-ABL, c-Kit, and PDGFR tyrosine kinase inhibitor)	Pneumonitis. Can also cause pleural effusions and eosinophilic pneumonia. Limited BAL data reveals eosinophilia (235)
Ipilimumab (anti-CTLA4 monoclonal antibody)	Associated with inducing a sarcoidosis-like granulomatous disorder. Characteristically with elevated lymphocytes with a high CD4:CD8 ratio (236). Biopsy may show non-caseating granulomas or OP (237)
Isoniazid	Associated with a pattern of pneumonitis or lung fibrosis (238). No BAL cell profile available except for one case with eosinophilic pneumonia (239)
Lenalidomide	Patterns of HP, OP and eosinophilic pneumonia can be seen. Limited BAL data suggests a pattern with increased neutrophils (240,241)
Melphalan (alkylating chemotherapeutic)	Increased lymphocytes. Associated with development of interstitial pneumonitis and interstitial fibrosis (242,243)
Methotrexate	Lymphocytic predominance is quite common, but there can be a variable BAL pattern (244). Findings are nonspecific. NSIP pattern is common; however, OP and HP are also reported (245)
Methysergide	No BAL cell profile available. Associated with development of pulmonary and retroperitoneal fibrosis (246)
Nitrofurantoin	Associated with an acute and chronic form of drug injury. Acute toxicity occurs within 2 weeks often with fever, cough, dyspnea, and peripheral eosinophilia. In these acute cases, a relative increase in eosinophils was described. Chronic toxicity can occur months to years later with a pattern of NSIP and resultant fibrosis (247-249)
Nivolumab (anti-PD1 receptor monoclonal antibody)	Associated most frequently with pattern of OP but also HP, AIP/ARDS, and NSIP (250). Also associated with radiation recall (251). No BAL data available
Non-steroidal anti-inflammatory drugs (NSAIDS)	Associated with HP. No BAL data available (252)
Ofatumumab (anti-CD20 monoclonal antibody)	Associated with interstitial pneumonitis. Limited BAL data demonstrated lymphocyte predominance with low CD4:CD8 ratio (253,254)
Paclitaxel (anti-mitotic chemotherapeutic)	Increased proportion of lymphocytes and eosinophils (255,256). Pattern of HP is reported. Additionally, associated with radiation recall and may cause fibrosis
Pembrolizumab (anti-PD1 monoclonal antibody)	Associated with an OP pattern with increased cellularity including elevated lymphocytes and elevated neutrophils (257). One case of radiographic appearing NSIP has also been reported (258)
Penicillamine	Associated with interstitial pneumonitis, OP, HP and eosinophilic pneumonia (259). Hemorrhage can occur after prolonged therapy. No BAL data available

Table 13 (*continued*)

Table 13 (*continued*)

Drugs	Bronchoalveolar lavage fluid characteristics
Phenytoin	Normal differential reported in two case reports of pneumonitis (260,261)
Propylthiouracil	Associated with ANCA positive vasculitis, capillaritis, and DAD (262)
Rituximab (anti-CD20 monoclonal antibody)	Interstitial pneumonitis, OP and ARDS are all reported. Limited BAL data suggest lymphocytosis is a common feature (263-265)
Sirolimus (mTOR inhibitor)	Pneumonitis characterized by lymphocyte predominance and alveolar hemorrhage is described (266,267)
Sorafenib (tyrosine kinase inhibitor)	Pneumonitis including AIP has been described (268). Cases may have lymphocyte predominance
Sulfasalazine	Eosinophilic pneumonia, HP and OP patterns have been described (269-271)
Sunitinib (tyrosine kinase inhibitor which blocks receptors for PDGFR and VEGFR)	Associated with recall pneumonitis and increased risk of pulmonary embolism (272). No BAL data available
Trastuzumab (anti-HER2 monoclonal antibody)	Pneumonitis with neutrophil predominance (273)
Valproic acid	Neutrophil predominance (274). Valproic acid can also be associated with an eosinophilic pleural effusion or DAH (275,276)

Table 14 Miscellaneous lung diseases

Disease	Bronchoalveolar lavage fluid characteristics
Acute respiratory distress syndrome (ARDS)	BAL early in ARDS reveals extensive neutrophils (277). However, in later resolution phases, there are less neutrophils and restored numbers of macrophages (11). Relatively low numbers of lymphocytes are seen in both phases
Amyloidosis	No specific pattern seen; but, increased cellularity with relative elevations in lymphocytes are reported (278)
Chronic aspiration/lipoid pneumonia	Lipid laden macrophages are typical and can stain positive with lipid stains such as Oil Red O stain (279). Neutrophils may also be present depending on the burden of aspiration pneumonitis (280)
Crack-cocaine pneumonitis	Heavily pigmented turbid, gray, or black specimens due to carbonaceous material (281). Hemorrhage or elevations in eosinophils may be present in BAL (282)
Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH)	Lymphocytosis reported in a small case series (283)
Erdheim-Chester disease	Opalescent fluid predominantly comprised of foamy macrophage (histiocytes). Histiocytes are CD1a negative and langerin (CD207) negative, but positive for CD68, CD163, and Factor XIIIa (284,285). Some histiocytes are noted to have an additional intracytoplasmic membrane, termed a "double-contoured histiocyte."
Heřmanský-Pudlák syndrome	Increased cellularity with normal differential. Macrophages filled with ceroid, a lipofuscin-like lipopigment, which stains orange with lipid stains and deep blue with Schmorl's reaction (286,287)
Idiopathic pulmonary hemosiderosis	Consistent with DAH. In chronic pulmonary hemosiderosis, a brown-yellow tinged lavage is due to hemosiderin-laden macrophages (288)
Lung cancer	Historically, malignant cells in approximately 40% of cases with peripheral lesions based on older studies (289). More recently, BAL was shown to have reduced sensitivity of only 15% (290) and sensitivity declines rapidly with smaller and more peripheral lesions (291), reflecting changes in practice and advances in diagnostic bronchoscopy for suspected lung cancer

Table 14 (*continued*)

Table 14 (*continued*)

Disease	Bronchoalveolar lavage fluid characteristics
Pulmonary alveolar microlithiasis	May be cloudy with microliths that can be seen with microscopy. Transbronchial biopsy will yield concentric laminated microliths in alveolar space along with thickened interstitial septa (292,293). Microliths also seen with pulmonary tuberculosis and in healed varicella pneumonia
Pulmonary alveolar proteinosis (PAP)	Diagnostic in close to 100% of the cases. Fluid appears milky and if left standing, settles into a layer of lipoproteinaceous sediment. No particular cellular pattern on BAL is helpful for diagnosis although elevated lymphocytes or eosinophils have been reported (183,294). Cytology reveals foamy macrophages and globules that are PAS-positive for lipoproteinaceous material (295-298)
Pulmonary capillary hemangiomatosis	DAH with hemosiderin-laden macrophages (299). Transbronchial biopsy should be avoided given risk for hemorrhage
Pulmonary post-transplant lymphoproliferative disorder (PTLD), with spectrum ranging from polyclonal lymphoid hyperplasia to lymphoma with a variety of imaging findings	Typically, lymphocytic predominant that may be polyclonal or clonal B cells that are Epstein-Barr virus (EBV) positive by PCR. Screening for PTLD has been recommended by assaying for EBV by PCR in the blood or in the BAL (300,301)
Pulmonary veno-occlusive disease	DAH with hemosiderin-laden macrophages (302,303). Bronchoscopic appearance of intensely hyperemic lobar and segmental bronchi with longitudinal streaking has been reported. Transbronchial biopsy should be avoided given risk for hemorrhage (304)
Sarcoidosis	Majority of cases (90%) demonstrate increased lymphocytes with normal levels of neutrophils and eosinophils (3,5). Classically, CD4:CD8 ratio ≥2, but this ratio can be variable including cases with CD8 predominance (305). A combination of CD4:CD8 ratio ≥2, ≤1% neutrophils, and ≤1% eosinophils has a similar specificity and positive predictive value as multiple non-caseating granulomas on transbronchial biopsy in distinguishing sarcoidosis from non-sarcoidosis disease (306). BAL CD4:CD8 ratio does not predict prognosis or response to treatment
Electronic cigarette/vaping-associated lung injury (EVALI)	Majority of cases are linked with the use of marijuana oils or concentrates, associated with the presence of medium chain triglyceride, vitamin E acetate, and other lipids in the inhaled product (307-311). Lung diseases described with EVALI include DAD, AEP, OP, lipoid pneumonia, and HP and may present on chest CT as consolidation, GGO, and peripheral reticulations. In case series, BAL showed moderate increase in neutrophils (20–50%), mild increase in lymphocytes (0–25%), and high numbers of lipid-laden (Oil Red O stain positive) macrophages (25–75%) (312-314)

Table 15 Diseases characterized by particular BAL cell differential

Eosinophilic-dominant	Lymphocytic-dominant	Neutrophilic-dominant
Diseases: acute eosinophilic pneumonia, allergic bronchopulmonary aspergillosis, chronic eosinophilic pneumonia, eosinophilic granulomatosis with polyangiitis, parasitic pneumonias. Drug-induced: carbamazepine, sulfasalazine, others	Diseases: berylliosis, cryoglobulinemia, granulomatous lymphocytic interstitial lung disease, HIV-associated pneumonitis, hypersensitivity pneumonitis, lymphocytic interstitial pneumonia, non-specific interstitial pneumonia, sarcoidosis, tuberculosis. Drug-induced: checkpoint inhibitors (anti-PD-1 & anti-PD-L1 > anti-CTLA-4), dasatinib, etanercept, etoposide, everolimus, gold, pembrolizumab, radiation-induced pneumonitis, sirolimus	Diseases: acute interstitial pneumonia, ARDS, initial phase, bacterial pneumonia, cystic fibrosis, granulomatous polyangiitis. Drug-induced: bleomycin, erlotinib, trastuzumab, valproic acid

BAL, bronchoalveolar lavage.

Table 16 Diffuse alveolar hemorrhage

Diffuse alveolar hemorrhage due to non-infectious causes
DAH with pulmonary capillaritis
Isolated pauci-immune necrotizing pulmonary capillaritis
Granulomatous polyangiitis
Microscopic polyangiitis
Mixed cryoglobulinemia
Behcet's syndrome
Henoch-Schönlein purpura
Goodpasture's syndrome*
Pauci-immune glomerulonephritis
Immune-complex-associated glomerulonephritis
Collagen-vascular disease (systemic lupus erythematosus*, polymyositis, rheumatoid arthritis, mixed-connective tissue disease, scleroderma)
Primary antiphospholipid antibody syndrome
Acute lung transplant rejection
Autologous bone marrow transplantation
Drugs (e.g., propylthiouracil with positive anti-neutrophilic cytoplasmic antibody)
DAH without capillaritis
Idiopathic pulmonary hemosiderosis
Systemic lupus erythematosus*
Goodpasture's syndrome*
Diffuse alveolar damage—e.g., after cytotoxic drug preconditioning therapy for bone marrow transplantation
Penicillamine—bland hemorrhage; uncommon; occurs after 1 year of therapy
Tuberous sclerosis
Trimellitic anhydride
Mitral stenosis
Coagulation disorders
Pulmonary veno-occlusive disease
Pulmonary capillary hemangiomatosis
Lymphangioleiomyomatosis—due to rupture of postcapillary venules, which are infiltrated by smooth muscles
Pulmonary embolism with infarction
Diffuse alveolar hemorrhage due to infectious causes (315)
Immunocompromised patients
Adenovirus
Cytomegalovirus
Invasive aspergillosis
Legionella

Table 16 (*continued*)

Table 16 (*continued*)

Mycoplasma pneumoniae
Strongyloides
Immunocompetent patients
Dengue
Hantavirus
Influenza A (H1N1)
Leptospirosis
Malaria
Staphylococcus aureus

*, capillaritis may or may not be present. BAL typically shows bloody or pink to orange-brown color and hemosiderin-laden macrophages (which appear after 48 hours of bleeding) with intensity of the iron staining correlating well with histologic severity of DAH.

Table 17 Diseases with foamy alveolar macrophages

Diseases	Comments
Acute silicosis	Periodic acid-Schiff (PAS) positive foamy macrophages is likely due to phagocytosis of cellular debris of dying macrophages that have ingested silica and of damaged epithelial cells (316). Birefringent silica particles may be present
Amiodarone	Amiodarone interferes with the movement of phospholipids across intracellular membranes and inhibits phospholipid catabolism via inhibition of lysosomal phospholipase 2. Thus, in alveolar macrophages the accumulation of phospholipids as foamy vacuoles stain positive with Oil Red O
Chronic aspiration and lipoid pneumonia	Foamy macrophages that stain positive with Oil Red O stain
Erdheim-Chester disease	CD68 positive (and CD1a and S100 negative) foamy macrophages (considered to contain some form of lipid) although the precise cause of the accumulation is not known (317)
Hypersensitivity pneumonitis	Lymphocytic dominant background with foamy macrophages (318)
Niemann-Pick disease	Due to decreased sphingomyelinase activity, foamy histiocytes accumulate sphingomyelin and thus stain positive with Oil Red O; the sphingomyelin stain weakly positive with PAS although this may be increased with greater acidity of the periodic acid and longer time of oxidation by the acid
Pulmonary alveolar proteinosis	Large foamy macrophages due to accumulation of lipoproteinaceous sediment. The vacuoles stain for both lipids (Oil Red O) and polysaccharides (PAS stain) because lipids, polysaccharides, and glycolipids associate with surfactant proteins. With GM-CSF treatment, intracellular debris and extracellular lipoproteinacious material may resolve but foamy macrophages containing ingested lipoproteinacious material may remain (298). However, clinical efficacy of GM-CSF treatment is not universally proven (319)
Electronic cigarette/vaping-associated lung injury	Due to an acute lung injury associated with vitamin E acetate and other additives in the inhaled product

The description of "foamy macrophages" refers to the multiple, relatively large vacuoles present in the cytoplasm of BAL cells, most often the alveolar macrophages. A stain may be a "negative stain" in that it stains the structures outside of the vacuoles that comprise the intracellular "foamy" characteristics (*Figure 1A,B*). Since the content of the foamy vacuoles are often lipid or lipoproteinaceous material, the content of the vacuoles may be stained positively with Oil Red O (*Figure 1C*). Peridic acid-Schiff (PAS) stains structures outside of the vacuoles but may also stain the contents within the vacuoles if they contain glycoproteins and glycolipids since PAS stains polysaccharides.
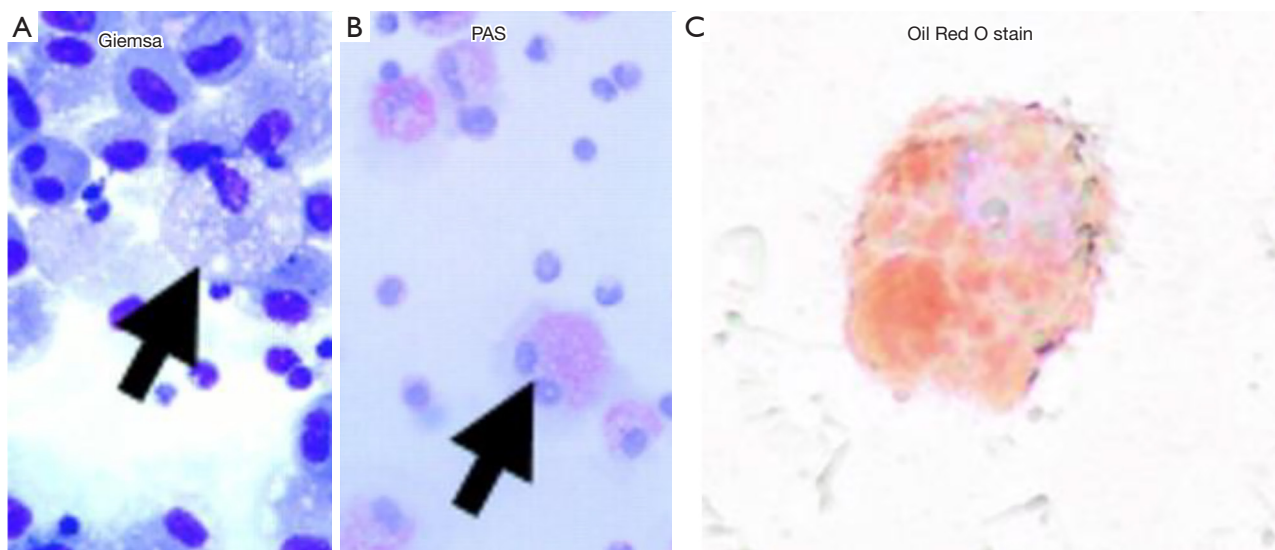
Figure 1 Visual detection of foamy macrophages. (A) Giemsa stain and (B) Periodic acid-Schiff (PAS) stain of BAL from a patient with pulmonary alveolar proteinosis demonstrating the "ghosts" of the foamy vacuoles [Figure modified from (298)]. A Wright-Giemsa stain is also a "negative stain" and will also accomplish the same visual effect. (C) Oil Red O stain of the BAL from a patient with electronic cigarette/vaping-associated lung injury (EVALI) showing lipid-filled vacuoles within an alveolar macrophage. Magnification: 1,000×. BAL, bronchoalveolar lavage.

with kerosene aspiration (322) utilizing low volume segmental lavage with good radiographic resolution. In children with refractory *Mycoplasma pneumoniae* pneumonia complicated by atelectasis, therapeutic BAL was shown to significantly shorten the duration of illness, time to radiographic resolution, and length of hospital stay (323).

Conclusions

Since the first bronchial irrigation by Stitt in 1927, BAL has evolved to become an often-used diagnostic procedure throughout most of the world. With development of additional assays for microbial product (e.g., galactomannan for invasive fungal disease), immunostaining for organisms (e.g., direct fluorescent antibody for pneumocystis), and nucleic acid amplification tests for specific microbes, BAL for diagnosis of infectious disorders has made significant progress and will continue to advance further with new technologies. While differential cell count profiles and ancillary testing on BAL fluid may in themselves not be specific or diagnostic, in the proper clinical context, the BAL findings may be the deciding factor in making a confident diagnosis. For example, in a patient with home bird exposure, significant lymphocytosis on BAL and

consistent imaging, a confident diagnosis of hypersensitivity pneumonitis can be made even in the absence of lung biopsy. Even when BAL results are non-diagnostic, their findings may help narrow the differential diagnosis. This review summarizes the vast array of additional characteristics and specific signature findings that can be a helpful aid to diagnosis. Herein, we present a current, succinct compilation of BAL data in a wide range of lung disease. In addition, we also listed those diseases and drug toxicities for which specific BAL data have not been reported.

In the future, it is likely that additional targeted diagnostics such as MALDI-TOF and PCR ES-M on BAL fluid will facilitate more rapid diagnosis of infectious pneumonia. Of particular interest is not only the ability to determine the etiology of infection but also to identify drug-resistant microbes. Such advances would transform the care of septic patients and also improve adherence to antibiotic stewardship. Additionally, genomic testing of BAL fluid may help clinicians differentiate patients with IPF from other forms of ILD as well as stratify patients with lung nodules into different risk groups for lung cancer. While surgical lung biopsy remains the gold standard for the diagnosis of various lung diseases, less

Table 18 Diagnostic or highly suggestive BAL cellular phenotypes

Diseases	Key BAL fluid findings and other clinical supporting features
Acute eosinophilic pneumonia	Eosinophils >25% in the setting of acute pneumonitis. Peripheral eosinophilia may be absent or mild initially
Asbestosis	Iron staining of may reveal ferruginous bodies with known exposure and compatible chest imaging
Berylliosis	Positive BeLPT with known or suspected beryllium exposure and compatible chest imaging
Diffuse alveolar hemorrhage	After instillation of lavage fluid, increasing bloodier return with aspiration of serial aliquots (grossly or by RBC count). However, does not inform the specific cause of the DAH
Hard metal lung disease	Multinucleated giant cells with known or suspected exposure and compatible chest imaging
Heřmanský-Pudlák syndrome	Alveolar macrophages may show yellow-brown staining of ceroid accumulation; the ceroid material may stain weakly acid-fast positive
Hypersensitivity pneumonitis	Lymphocytosis >50% with known or suspected exposure (typically elevated CD8+ T cells but elevated CD4+ T cells may be seen)
Niemann-Pick disease	Foamy histiocytes that are PAS positive and lipid stain positive with compatible imaging of ground-glass attenuation and thickening of the interlobular septae in the lower lung zones ("crazy paving sign"). Diffuse reticular and nodular infiltrates with basal predominance and honeycombing may also be seen
Pulmonary alveolar microlithiasis	Presence of microliths
Pulmonary alveolar proteinosis	Presence of milky and turbid appearance with a thick settling layer of sediment due to the lipoproteinaceous deposits
Pulmonary Langerhans cell histiocytosis	≥5% of cells positive for CD1a. S-100 positivity is supportive but less specific. Chest imaging shows cysts and nodules in an upper zone distribution in earlier phase and predominantly cysts in end-stage disease
Pulmonary post-transplant lymphoproliferative disorder (PTLD)	In the proper clinical context, increased B cells that are Epstein-Barr virus (EBV) positive by PCR (300,301)
Sarcoidosis	Lymphocyte predominant with CD4:CD8 ratio ≥2, neutrophils ≤1%, and eosinophils ≤1% may be as specific as transbronchial biopsy

BAL, bronchoalveolar lavage; AEP, acute eosinophilic pneumonia; AIP, acute interstitial pneumonitis; ANCA, antineutrophil cytoplasmic antibodies; ARDS, acute respiratory distress syndrome; BAL, bronchoalveolar lavage; COPD, chronic obstructive pulmonary disease; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; DAD, diffuse alveolar damage; DAH, diffuse alveolar hemorrhage; EGFR, epidermal growth factor receptor; GGO, ground glass opacities; HP, hypersensitivity pneumonitis; ILD, interstitial lung disease; LIP, lymphocytic interstitial pneumonitis; NSIP, non-specific interstitial pneumonitis; OP, organizing pneumonia; PAS, periodic acid-Schiff; PD-1, programmed cell death protein-1; PD-L1, programmed cell death ligand 1; PDGFR, platelet-derived growth factor receptor; PLCH, pulmonary Langerhans cell histiocytosis; VEGF, vascular endothelial growth factor.

invasive diagnostic techniques will become adopted if their yield becomes significantly more accurate. The ultimate goal would be to advance diagnostic techniques on BAL fluid to rival the sensitivity and specificity of the current gold standard of lung biopsy.

Footnote

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to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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