Broncho alveolar lavage in Interstitial lung diseases – A useful tool or an out dated concept ?

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AIMS

1. Technical Considerations in performing BAL

2. Role of BAL in ILD
    1. Diagnosis
        - Confirms the diagnosis
        - Assists in diagnosis
        - Ruling out differentials
    2. Prognosis
    3. Monitoring

TECHNICAL CONSIDERATIONS IN PERFORMING BAL

Semin Respir Crit Care Med 2007;28:475–485

Am J Respir Crit Care Med 2012 ;185(9):1004-1011

Eur Respir J 2011; 38: 761–769

1. Choosing the segment

- Segment or segments on HRCT which show maximum changes
  - Ground Glass opacities
  - Nodules
  - Fine reticulation
- If the lung is diffusely and uniformly involved, BAL may be performed from the Right middle lobe or the lingula.
- HRCT should have been done within 6 weeks of the BAL procedure

NUMBER OF AREAS TO SAMPLE

- Various options available:
  - One segment which is maximally involved
  - Lavage multiple segments and pool the return
    (Gives a picture of the generalized response of the lung)
  - Lavage multiple segments and analyze independently (More useful for research purposes)
- All are acceptable and no definite consensus

POSITIONING THE SCOPE

- The bronchoscope should be wedged into a segmental or a subsegmental bronchus and the seal maintained through out the procedure.
- To prevent the contamination by proximal airway epithelial cells.

VOLUME OF FLUID TO BE INSTILLED

- ATS 2012 recommendation :
  - 100-300 ml of total fluid to be instilled divided into three to five aliquots.

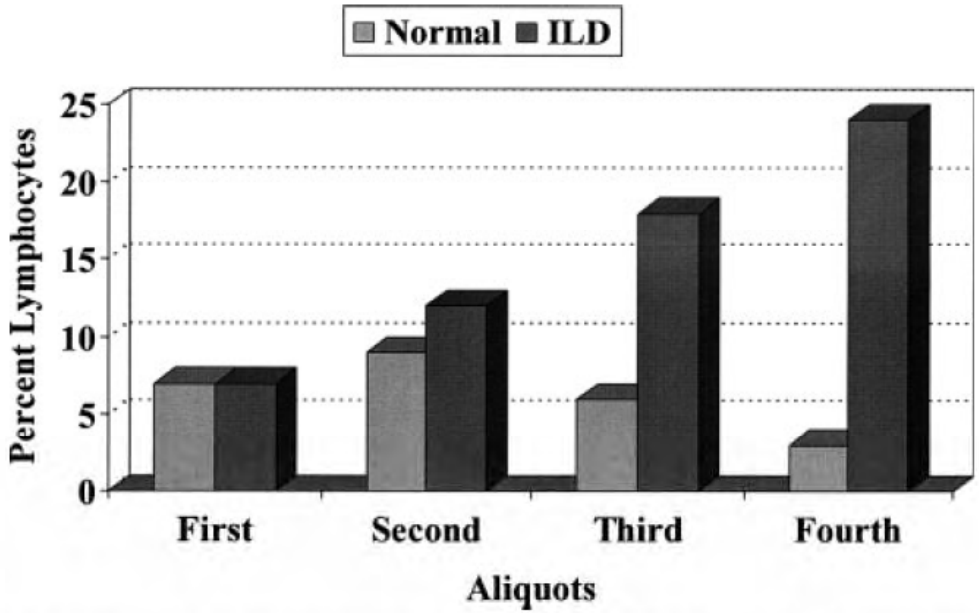


Figure 2 Percentage of lymphocytes in the aspirated fluid after each 60 mL aliquot of a bronchoalveolar lavage in either healthy volunteers or patients with interstitial lung disease, mostly sarcoidosis. The percentage of lymphocytes is significantly higher after the second aliquot (a total of 120 mL instilled). The differences become larger with larger volumes instilled, but the percent lymphocytes was not significantly different between aliquots three and four.[27]

Am Rev Respir Dis 1985;132:390–392

SUCTION PRESSURE TO BE APPLIED

- Negative suction can be applied either by
  - Hand held syringe
  - Suction wall mount
- Recommendation is to use negative pressure less than 100 mm Hg so as to avoid visual collapse of the airways.
- Most centers use pressures less than 60 mm Hg

VOLUME OF RETURN FLUID

- Optimal BAL sampling retrieves >30 % of the instilled aliquot. (Total retrieved volume >30% of total instilled volume)

- Atleast 5 % of the instilled fluid should be retrieved or else the procedure should be abandoned.
- Some consider stopping BAL in a particular segment if the difference between the instilled and retrieved volumes exceeds 100 ml (for safety reasons)

- Volume of fluid retrieved is immaterial when the BAL purpose is to diagnose malignancy or infection.
- When BAL is used for cell counts, it is important to have a good and adequate alveolar sample which is ensured by having a good BAL return.

Semin Respir Crit Care Med 2007;28:475–485.

Am J Respir Crit Care Med Vol 185, Iss. 9, pp 1004–1014, May 1, 2012

FACTORS AFFECTING LAVAGE RETURN

- Diseases causing airway obstruction decrease the return as the airways are narrower and are more easily collapsible.
- The volume of return also decreases with old age again due to more collapsible airways.
- Smokers also have less return as compared to non smokers.

PROCESSING FIRST SAMPLE

- Some consider the first aliquot as Bronchial sample and the remaining aliquots as Alveolar samples.
- This is because the first aliquot contained more epithelial cells and protein lactoferrin from the bronchiolar walls.

Am Rev Respir Dis 1990;141:208-217

- However, further studies have shown no effect of pooling all the aliquots.

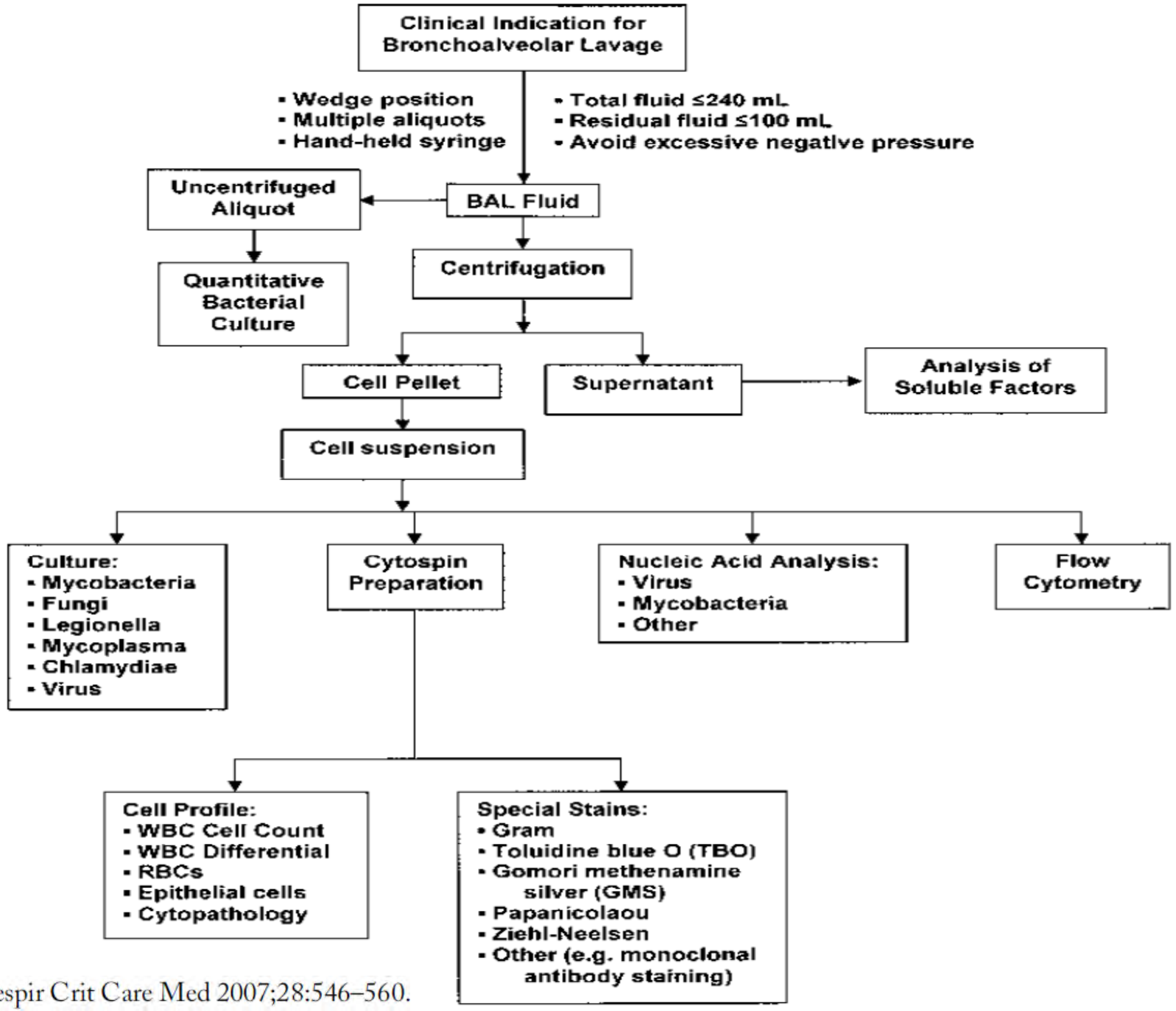
- Current recommendation : No need to separately analyze or discard the first sample. Can be pooled with the rest.

TRANSPORT AND PROCESSING BAL

- Bal should be collected in containers that do not promote cell adherence to surfaces (Silicone coated glass, polypropylene or other plastics).

- Bal fluid should be transported immediately at room temperature.
- If delay beyond 30 minutes is anticipated, should be transported at 4^{o} C.
- Samples obtained more than 24 hours earlier are not suitable for analysis even when stored at 4^{o} C.

- If BAL fluid analysis cannot be done within 1 hour, then the cells should be transferred to a tissue culture medium(MEM+25mM HEPES or RPMI 1640+25mM HEPES).



Semin Respir Crit Care Med 2007;28:546–560.

Normal BAL findings

BAL IN HEALTHY NON SMOKER

- Presence of squamous epithelial cells indicate upper airway contamination / aspiration.

Status	Cell profile	Noncellular components
Normal nonsmokers	Differential cell count (mean %): AM, 85%; lymphocytes, 7–12%; PMN, 1–2%; eosinophils-basophils, <1%; ciliated cells, 1–5%; dendritic cells, 1%	95% as IgA (40% as IgA_2), almost no IgM, IgG (IgG1-3/albumin ratios similar to serum), increased IgG4
	Lymphocytes subsets: CD4 helper, 50%; CD8 suppressor or cytotoic, 30%; CD4/CD8 ratio, 1.5; B lymphocytes (plasma cells), 5%	Low concentrations of cytokines (IL-6, IL-8)
		Adhesion molecules detectable
		Histamine detectable
		Surfactant present
Normal moderate smokers	3-fold increase of total cells, 95% AM, 3–5-fold increased AM, PMN approximately 3%, lymphocytes 3% in differential cell count	Increased IgG as IgG/albumin ratio with serum, increased IgG3 and IgG4, decreased FSC, less surfactant recovered (lipid component profile same as that of nonsmoker)
		Decreased A_1AT elastase inhibitory activity
		Increased ACE (in AM) may be found

Lung (2011) 189:87–99

BAL ANALYSIS – HEALTHY SMOKERS

BAL Cooperative study : A large multicentric study done on healthy adult volunteers . Included 191 subjects. (published in 1990)

- Current Smokers : Actively smoking
- Ex Smokers : Left 1 year ago
- Never smokers : Less then 1 cigarette pack in lifetime

BAL – DIAGNOSIS OF ILD?

BAL – Establishing the diagnosis

- Only in a very few conditions, can BAL definitely establish the diagnosis.

1. Diffuse Alveolar Hemorrhage
2. Pulmonary Alveolar Proteinosis
3. Chronic Beryllium Disease (BAL lymphocyte proliferation test)
4. Pulmonary Langerhan Cell Histiocytosis (>5% CD1a +ve cells)

Diffuse Alveolar Hemorrhage

- Grossly bloody BAL return, especially if the sequentially retrieved aliquots do not show any decrease on the bloody discolouration of lavage fluid or there is increase in bloody discolouration.
- Microscopy shows fresh RBCs or hemosiderin laden macrophages(if bleed occurred >48 hrs).

Diffuse Alveolar Hemorrhage

- Hemosiderin score is calculated after staining with prussian blue stain.
- Score >100 suggests Alveolar hemorrhage
- Normal controls have scores between 0-20.

Table 4 Golde Score for the Quantification of Alveolar Hemorrhage

Hemosiderin Scale[a]	Blue Staining of Macrophage Cytoplasm
0	No blue color
1	Faint staining
2	Dense in minor portion or medium throughout cytoplasm
3	Deep blue in most parts of cytoplasm
4	Dark blue throughout cytoplasm

[a]200 to 300 macrophages are counted, and each cell is graded on the Golde scale. The mean score for 100 cells is calculated, with 400 being the maximum (if all cells are graded with 4).

(Chest 1992; 102:1794-99)

Hemosiderin Laden Macrophages or Siderophages:

- Most specific finding of DAH
- More commonly used as Golde score is time consuming
- Seen if the bleed occurred anywhere between 2 days to 2 weeks prior to the procedure.
- It takes 2-4 weeks for the siderophages to clear off.
- Presence of >20% Siderophages or Golde score >100 suggests significant DAH

- Note:
  - Caution in interpreting in patients with bleeding tendencies, renal failure and cardiac transplant, CCF with pulmonary venous congestion.

Pulmonary Alveolar Proteinosis

- Milky BAL fluid which sediments by gravity even without centrifugation suggests PAP.
- Microscopy of the sediment shows PAS positive macrophages.

PLCH

- Diagnosis established by
  - Detecting CD1a positive cells > 5% in BAL
  - Demonstration of Birbeck granules by electron microscopy.
- Smoking and other ILDs can also have increased LCH but always <5%.
- In a patient suspected to have PLCH, mere absence of >5% LCH does not rule out PLCH (sensitivity only -50%) as the involvement can be patchy, but warrants a biopsy.

PLCH

- Langerhan cells in the BAL fluid can be detected by IHC using
  - S-100
  - CD1 a
  - Langerin (CD207)

BAL – EXCLUDING DIFFERENTIALS

- An important role of BAL is to rule out infection and malignancy as both can sometimes mimic ILD.

- Examples :

  - Tuberculosis and Sarcoidosis
  - Bronchoalveolar carcinoma can mimic ILD
  - Lymphangitis carcinomatosis
  - Pulmonary lymphoma can mimic organizing pneumonia.

BAL – TOTAL CELL COUNT

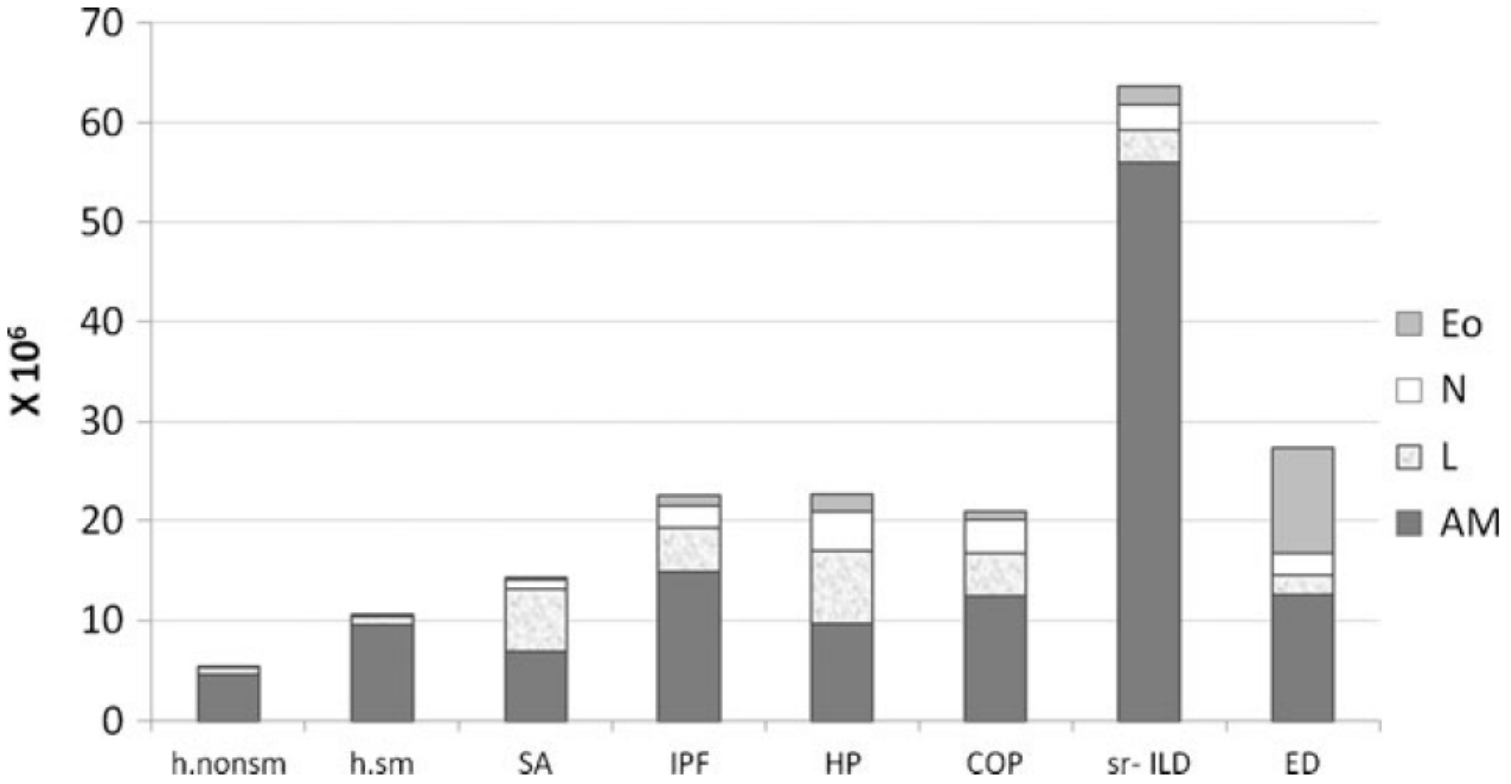
- Expressed either as
  - Total number of cells recovered per lavage
  - Concentration of cells per ml of lavage fluid

BAL TCC (mean ± S.D)	Total cells ($x10^6$)	Cells/ml ($x10^4$)
Healthy non smokers	18.1 ± 1.9	12.9 ± 2.0
Healthy smokers	59.9±7.3	41.8±4.5
Healthy former smokers	20.01 ± 1.5	13.9± 1.1

Am Rev Respir Dis 1990 ;141: S169

Inflammation, Vol. 35, No. 3, June 2012 (© 2011)
DOI: 10.1007/s10753-011-9378-5

Bronchoalveolar Lavage Total Cell Count in Interstitial Lung Diseases—Does It Matter?



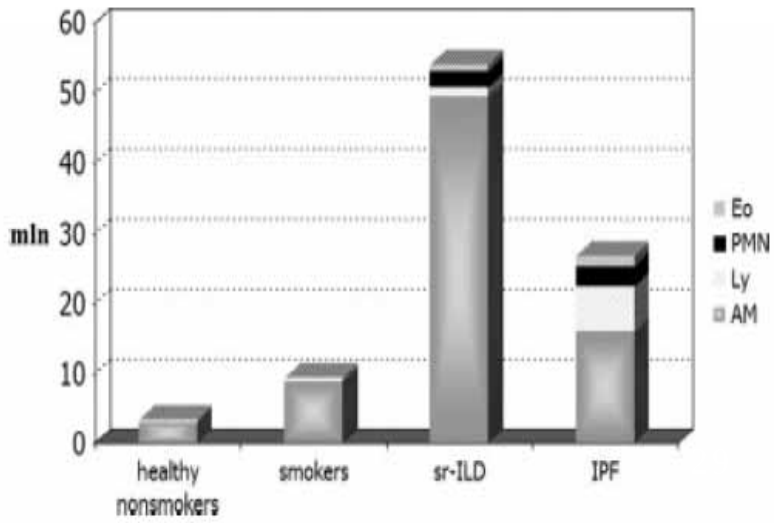
- 237 patients of ILD and 30 healthy controls examined.
- Mean TCC in healthy controls was 6.7 x 106
- Reporting DLC alone without TCC may lead to under diagnosis of certain ILDs such as SR-ILDs in which the percentages of inflammatory cells would remain the same.

BAL in the Diagnosis of Smoking-Related Interstitial Lung Diseases:
Review of Literature and Analysis of Our Experience

Joanna Domagała-Kulawik, M.D., Ph.D.*

Diagnostic Cytopathology, Vol 36, No 12 909

- An extremely high BAL TCC with preponderance of pigmented alveolar macrophages is very characteristic of DIP/RBILD



Pigmented macrophage Vacuolated macrophage

n=700 , sr-ILD = 18

BAL – Differential cell count

- The slides for differential count assessment are prepared by
  - Cytocentrifugatioin technique
  - Millipore filter smeared slide (Time consuming)
- Atleast 300 cells and preferable 400-500 cells to be counted for a reasonable estimation of BAL differential cell count.
- Expressed as percentage of the total nucleated WBCs. (RBCs and epithelial cells not included in the denominator)

BAL – DIFFERENTIAL CELL COUNT

- Differential usually expressed as percentages.

BAL lymphocytosis	: >15% lymphocytes
BAL neutrophilia	: > 3% Neutrophils
BAL Eosinophilia	: > 1 % Eosinophils
BAL Mastocytosis	: >0.5% Mast cells

- Finding a particular BAL immune cell pattern is non specific and can occur in a variety of conditions both in ILDs and other diseases.

BAL Lymphocytosis

- >15 % lymphocytes :
  - Sarcoidosis
  - Hypersensitivity Pneumonitis
  - NSIP
  - COP
  - Drug reactions
  - LIP/Lymphoma
  - Radiation pneumonitis

- >50% lymphocytes :
  - Hypersensitivity pneumonitis
  - Cellular NSIP

BAL Neutrophilia

- >3% Neutrophils :
  - Infection
  - ARDS
  - IPF
  - Collagen vascular disease
  - Asbestosis
  - Aspiration pneumonia
  - Bronchitis

- >50% Neutrophils :
  - Aspiration pneumonia
  - Suppurative infection

BAL Eosinophilia

- >1 % Eosinophils
  - Eosinophilic lung disease
  - Asthma, ABPA
  - Churg strauss syndrome
  - Drug reactions
  - Bone marrow transplant
  - Hodgkins disease

- >25 % Eosinophils
  - Acute eosinophilic pneumonia
  - Chronic Eosinophilic pneumonia (>40%)
  - Tropical Pulmonary Eosinophilia (40-70 %)
  - Churg strauss Syndrome with active alveolitis

EPITHELIAL CELLS

- Always important to also count the percentage of epithelial cells.

- >5 % squamous or columnar epithelial cells indicate poor sampling and an unrepresentative BAL sample.

Predictive value of BAL cell differentials in the diagnosis of interstitial lung diseases

Eur Respir J 2004; 24: 1000–1006

L. Welker*, R.A. Jörres*, U. Costabel#, H. Magnussen*

- A total of 3975 BAL samples from 3118 patients were analyzed.
- Final diagnosis was either clinical or HPE based.
- Pre and Post test probabilities were calculated using Bayes rule.

Results :

- Likelihood of sarcoidosis increased from 33.7% to 68.1% if
  - Lymphocyte percentage between 30-50% and
  - Granulocyte percentage low (<4%)

- Likelihood of IPF increased from 15.8% to 33.3 % if
  - Granulocyte percentage high (4-20%) and
  - Lymphocyte percentage low (<30%)

- CD4 /CD8 ratio aids in the diagnosis of Sarcoidosis and EAA.

TABLE 1 Bronchoalveolar lavage (BAL) findings that are useful in interstitial lung disease diagnosis

BAL finding	Consistent interpretation/suggested diagnosis
Eosinophils ⩾25%	Eosinophilic pneumonia
Lymphocytes ⩾25%	Sarcoidosis, HP, cellular NSIP, drug reaction, CBD, LIP, lymphoproliferative disorder
Neutrophils ⩾50%	AIP, DAD, AEIPF, pulmonary infection
Bloody fluid	Pulmonary haemorrhage, DAH
High haemosiderin score	DAH, DAD
CD1a+ cells >4%	PLCH
Milky BAL fluid with PAS-positive amorphous debris	PAP
Monotypic lymphocytes	Pulmonary lymphomatous malignancy
Malignant cells	Pulmonary malignancy
Squamous epithelial cells >5%	Unsuitable sample due to upper airway secretion contamination
Bronchial epithelial cells >5%	BAL sample may be unsuitable for cell analysis

Eur Respir J 2011; 38: 761–769

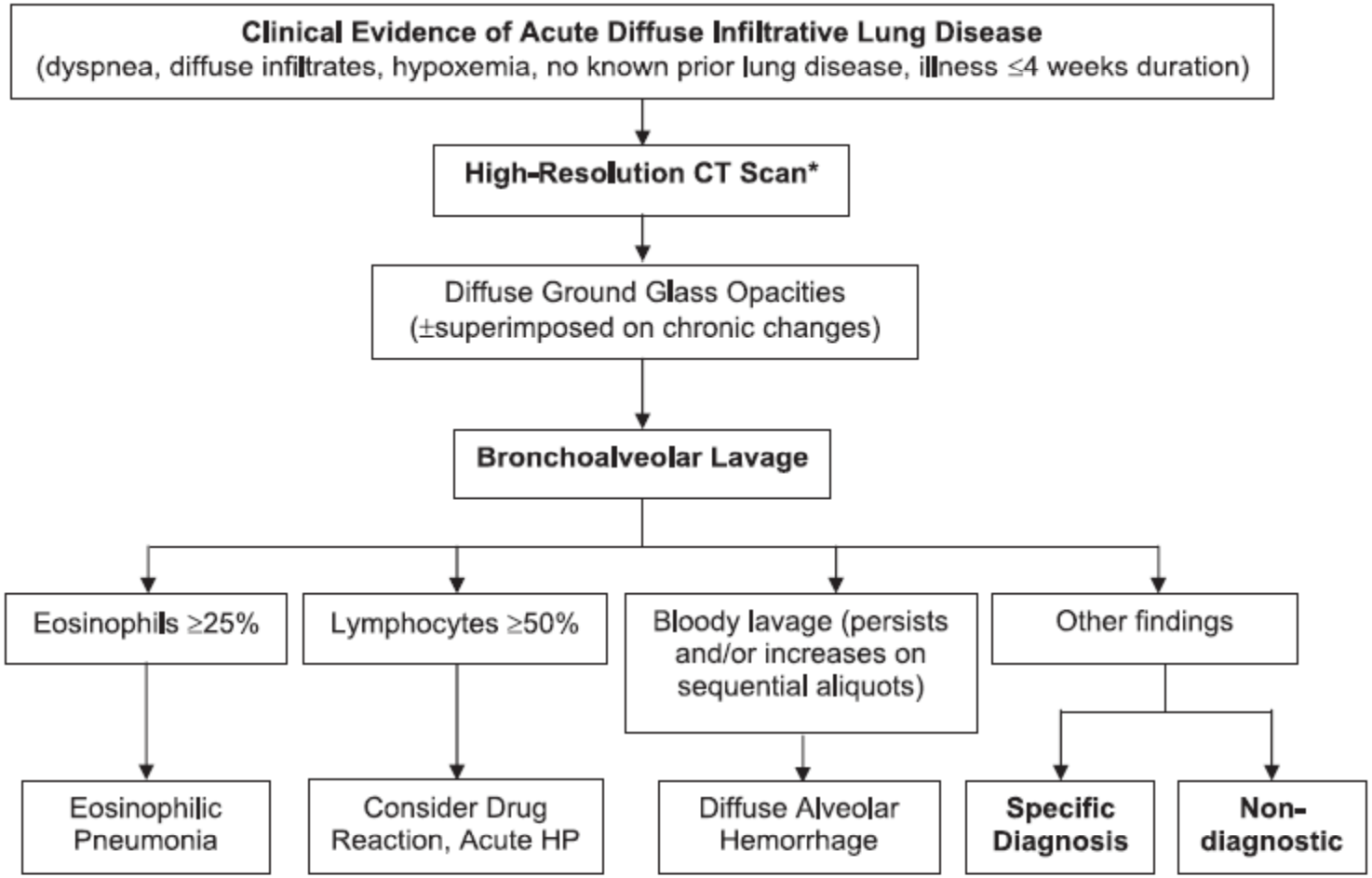
CONCLUSIONS

- ATS 2012 guidelines recommend performing a BAL differential in patients suspected of ILD.

- Finding a pattern of BAL cell count abnormality is non specific and should always be interpreted in concordance with the clinical scenario and the HRCT imaging findings.

- More often, BAL cell counts will either narrow the differential diagnosis or strengthen the probability of a particular ILD rather than helping in definite diagnosis.

BAL- Acute ILD



Am J Respir Crit Care Med Vol 185, Iss. 9, pp 1004–1014, May 1, 2012

BAL CD 4/CD8 ratio

- Sarcoidosis
- Hypersensitivity pneumonitis

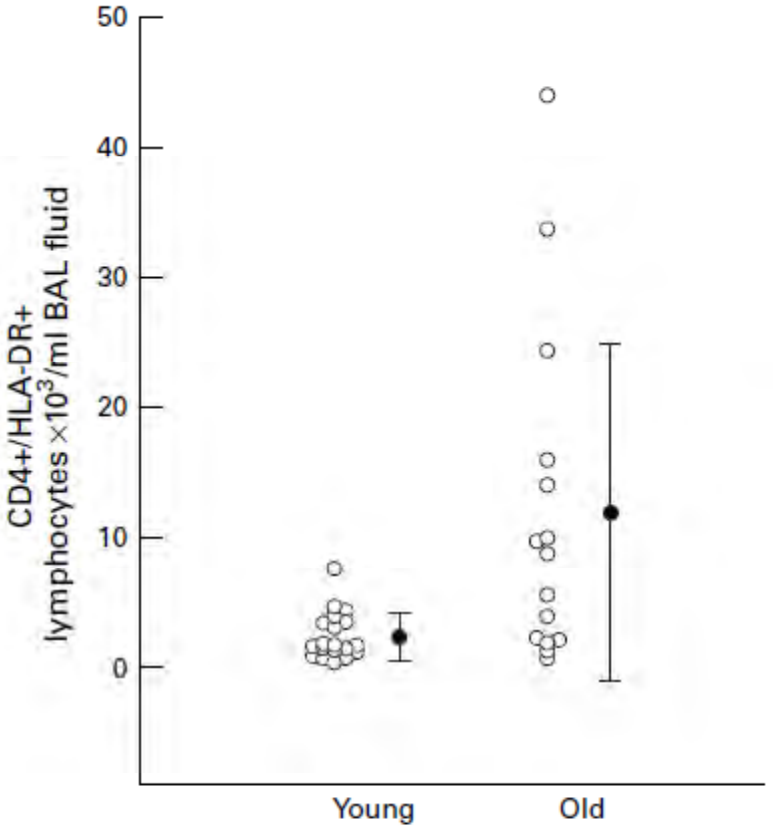
BAL – T CELL SUB TYPING (CD4/CD8)

- Done by either
  - Flow cytometry
  - Immunocytochemistry
- Useful in sub classifying patients with BAL lymphocytosis
  - Sarcoidosis (Increased CD4/CD8 ratio >3.5)
  - Hypersensitivity Pneumonitis (Decreased CD4/CD8 ratio <1)

Variation of bronchoalveolar lymphocyte phenotypes with age in the physiologically normal human lung

Thorax 1999;54:697–700

Parameter	Group I		Group II
	BAL fluid	Blood	BAL fluid
%CD3+	79.7 (3.3)	70.1 (1.9)	79.8 (3.0)
%CD19+	2.2 (0.4)	11.4 (0.8)	1.2 (0.2)*
%CD16+/56+	3.4 (0.5)	11.8 (1.3)	3.1 (0.5)
%CD4+	46.4 (2.9)	40.3 (1.4)	68.4 (4.2)*
%CD8+	31.6 (3.5)	31.8 (1.4)	12.6 (1.7)*
CD4/CD8 ratio	1.9 (0.3)	1.4 (0.1)	7.6 (1.5)†
%γδ TCR+	2.9 (0.3)	4.5 (0.5)	0.97 (0.19)*
%CD5+/IgM+	0.93 (0.20)	0.19 (0.03)	1.26 (0.23)
%CD4+/DR+	20.3 (2.1)	2.9 (0.2)	33.8 (3.8)*
%CD4+/CD69+	33.8 (3.5)	8.3 (1.6)	51.5 (7.0)*



Predictive value of BAL cell differentials in the diagnosis of interstitial lung diseases

Eur Respir J 2004; 24: 1000–1006

L. Welker*, R.A. Jörres*, U. Costabel#, H. Magnussen*

Table 5. – Probability of interstitial lung disease (ILD) as a function of CD4/CD8 in suspected ILD

CD4/CD8 ratio	Subjects n	*A priori*	*A posteriori*			
			No value#	<0.5	0.5–3.5	>3.5
Sarcoidosis	239	33.7	16.3***	9.1*	40.3	69.1***
UIP	112	15.8	22.7*	13.6	12.2	5.2*
EAA	66	9.3	1.5***	27.3*	17.2*	12.5
NSIP	46	6.5	7.6	18.2	5.4	3.7
Connective tissue disease	18	2.5	2.7	0.0	3.2	1.5
Others	229	32.2	49.2***	31.8	21.7*	8.1***
Total n	710		331	22	221	136

BAL - SARCOIDOSIS

- The predominant BAL findings of sarcoidosis

  - Elevated BAL –TCC , predominantly lymphocytes
  - Nearly normal eosinophils and neutrophils
  - Absence of plasma cells
  - Increased BAL CD4/CD8 ratio
  - Decreased BAL CD103 CD4/CD4 ratio

- All these findings have poor sensitivity and specificity and when assessed alone have little diagnostic value.

Table 1 Predictive Value of CD4:CD8 Ratio in Bronchoalveolar Lavage for the Diagnosis of Sarcoidosis

Study	CD4:CD8 Ratio	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
Costabel et al 1988[14]	>3.5	53	93	75	85
	>5.0	47	98	89	84
Winterbauer et al 1993[15]	>3.0	67	89	86	74
	>4.0	59	96	94	71
Thomeer, Demedts 1997[16]	>3.0	64	89	73	84
	>4.0	55	94	82	82
Korosec et al 2010[17]	>3.3	70	88	na	na

Semin Respir Crit Care Med 2010;31:404–408

In long standing and fibrotic sarcoid patients, the CD4/CD8 ratio may return to normal with an increase in the percentage of neutrophils.

Evaluation of CD103 as a cellular marker for the diagnosis of pulmonary sarcoidosis

Table 3 Cut-off values, sensitivity, specificity, PPV, and NPV for different parameters in patient cohort assembled by the Dutch BAL working party (n=119; 56 sarcoidosis, 63 other ILDs)

Patient cohort (n=119)	Selected cut-off	Sensitivity, %	Specificity, %	PPV, %	NPV, %
BAL $CD4^+/CD8^+$ [a]	2.5	73	67	66	74
BAL $CD4^+/CD8^+$ and $CD103^+/CD4^+$ [a]	2.5 and 0.31	57	91	84	70
BAL $CD4^+/CD8^+$	3	68	73	69	72
BAL $CD4^+/CD8^+$ or $CD4^+/CD8^+$ BAL/PB and $CD103^+CD4^+/CD4^+$	3 or 2 and 0.2	66	89	82	74

Clinical Immunology (2008) **126**, 338–344

Value of s-ACE, BAL lymphocytosis, and CD4+/CD8+ and CD103+CD4+/CD4+ T-cell ratios in diagnosis of sarcoidosis

Eur Resp J 2012 ;39 : 1037-39

TABLE 1 Diagnostic values of single parameters

	Cases		Controls		Optimal cut-off	Sensitivity %	Specificity %	PPV %	NPV %	p-value
	Subjects n	Mean (95% CI)	Subjects n	Mean (95% CI)						
Lymphocyte fraction %	17	28.1 (18.9–37.4)	73	15.7 (12.1–19.3)	13	71	68	34	91	<0.05
CD4+/CD8+	19	6.1 (5.2–7.0)	83	3.7 (2.9–4.5)	3.8	68	73	37	91	<0.02
CD103+CD4+/CD4+	19	0.23 (0.20–0.27)	82	0.32 (0.28–0.36)	0.22	63	76	29	88	0.064
s-ACE $U \cdot L^{-1}$	17	119.0 (86.6–151.4)	54	57.2 (49.2–62.2)	84	82	89	70	94	<0.001

Combinations	Cases n	Controls n	Sensitivity %	Specificity %	PPV %	NPV %
CD103+CD4+/CD4+ <0.22 and lymphocyte fraction >13%	17	68	35	93	55	85
CD103+CD4+/CD4+ <0.22 and CD4+/CD8+ >3.8	19	78	42	91	53	87
s-ACE >84 $U \cdot L^{-1}$ and CD103+CD4+/CD4+ <0.22	17	50	53	96	82	86
CD103+CD4+/CD4+ <0.22, CD4+/CD8+ >3.8 and s-ACE >84 $U \cdot L^{-1}$	17	48	35	100	100	81

Diagnostic value of CD103 expression in bronchoalveolar lymphocytes in sarcoidosis

Respiratory Medicine (2012) 106, 1014–1020

Table 2 Sensitivity (Sn) and specificity (Sp) of the BALF $CD103^+CD4^+/CD4^+$ ratio for sarcoidosis diagnosis in the study population (left column), and in a subgroup of sarcoidosis with a BALF CD4/CD8 <3.5 (right column) all with histological confirmation, comparatively with the other ILD.

All sarcoidosis patients ($n = 41$)			Sarcoidosis with BALF $CD4^+/CD8^+$ <3.5 ($n = 12$)		
$CD103^+CD4^+/CD4^+$	Sn (%)	Sp (%)	$CD103^+CD4^+/CD4^+$	Sn (%)	Sp (%)
0.05	12	100	0.15	25	93
0.15	42	93	0.25	42	91
0.25	63	91	0.35	58	80
0.35	76	80	0.45	75	78
0.45	81	78	0.55	75	71
0.55	83	71	0.65	83	64
0.65	88	64	0.75	83	60
0.75	88	60	0.85	83	56
0.85	90	56	0.95	83	53
0.95	93	53	1.05	83	49

Sn, sensitivity; Sp, Specificity.

BAL-SARCOIDOSIS DIAGNOSIS

- BAL lymphocytosis occurs in 90% of the patients at diagnosis.
- There is a considerable overlap between patients with active and inactive disease.

- BAL CD4/CD8 ratio is increased in 50-60% of the patients. A ratio >3.5 has good specificity (80-95%)
- However there is considerable variability and the ratio can even be decreased in upto 15% of the patients.

- BAL CD103 is a new marker and needs further validation

Semin Respir Crit Care Med 2007;28:486–495.

BAL-Sarcoidosis prognosis

- Bal lymphocytosis or CD4/CD8 ratios have poor prognostic value and do not represent severity of alveolitis or response to corticosteroids.

- Infact, patients with Lofgrens syndrome, who have self remitting disease have high lymphocyte percentages and CD4/CD8 ratios.

- BAL neutrophils >3% may correlate with clinical deterioration and may indicate the need for corticosteroids.

Semin Respir Crit Care Med 2007;28:486–495.

BAL- Hypersensitivity Pneumonitis

- BAL findings in HP include
  - BAL lymphocytosis
  - Decreased BAL CD4/CD8 ratio <1
  - BAL Neutrophils (Increased in acute exposure and in long standing fibrotic disease)
  - BAL Mast cells (>1%) increase with acute exposures
  - BAL eosinophilia (accompanies neutrophils)
  - Presence of Plasma cells and increased Ig G,A M

- If BAL differential shows
  - Lymphocytes >50%
  - Mast cells >1 %
  - Neutrophils > 5 %
- Diagnostic of ACUTE HYPERSENSITIVITY PNEUMONITIS

Am J Respir Crit Care Med 2012 ;185(9):1004-1011

BAL- Hypersensitivity Pneumonitis

- Effect of the time of antigen exposure on BAL findings.

A landmark study in 1993 on 57 patients of HP

1. Group1 (<24 hrs) : Increase in lymphocytes, neutrophils, eosinophils and mast cells.
2. Group 2 (2-7 days) : Neutrophils return to normal. Increase in lymphocytes, mast cells, plasma cells and Ig A,M,G.
3. Group 3 (8-30 days) : All values except lymphocytosis gradually return to normal.
4. Group 4 (1-12 months) : Only lymphocytosis

Eur Respir J 1993; 6: 1276–1281.

BAL – Hypersensitivity pneumonitis

- BAL Lymphocytosis
-
  - Included in the diagnostic criteria of HP
  - Has a good Negative Predictive Value
  - Cannot differentiate symptomatic HP from asymptomatic but sensitized individuals.

- Presence of BAL lymphocytosis with decreased CD4/CD8 ratio increases the specificity.

- Role of BAL neutrophilia in predicting prognosis is still not established.

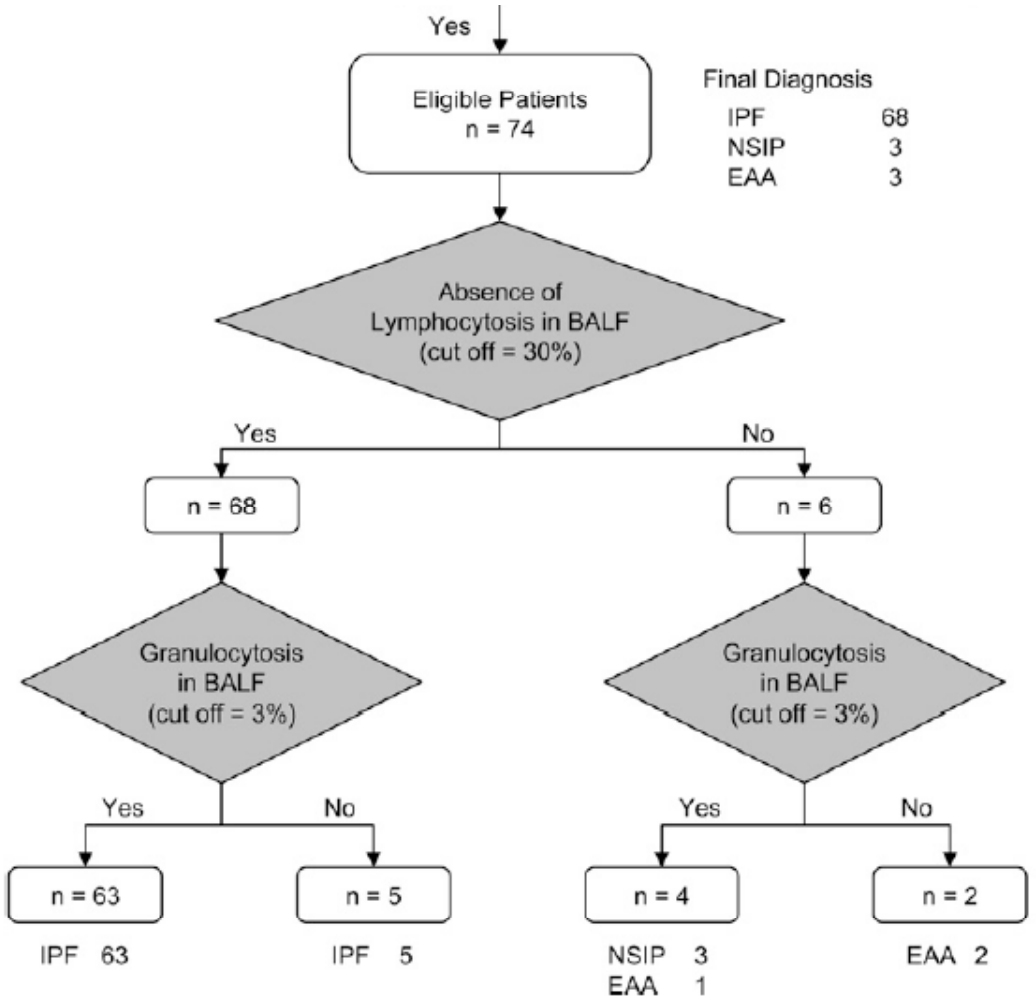
BAL in IPF/NSIP – Does it have any role?

ROLE OF BAL IN IIP

Idiopathic Pulmonary Fibrosis :

- No role in diagnosis or management of patients with IPF.
- According to the latest ATS/ERS 2011 guidelines
  - The most important application of BAL is to rule out chronic hypersensitivity pneumonitis. BAL lymphocytosis suggests the latter.
  - BAL cellular analysis should not be performed in the diagnostic workup of patients with suspected IPF in the majority of patients, but may be appropriate in a minority.
  - BAL cellular analysis should be considered at the discretion of the treating physician based on the availability and expertise.

Significance of Bronchoalveolar Lavage for the Diagnosis of Idiopathic Pulmonary Fibrosis



Am J Respir Crit Care Med Vol 179. pp 1043–1047, 2009

BAL- IPF PROGNOSIS

Author	Journal /Year	No. of patients	Results
Veeraraghavan et al	Eur Respir J 2003	35	BAL findings cannot discriminate UIP from NSIP and have no prognostic value
Rollin P Tabuena et al	Respiration 2005	81	Increase in number of BAL neutrophils and lymphocytes are poor prognosticators in current smokers only.
Brent W Kinder etal	CHEST 2008	156	BAL neutrophilia at diagnosis is an independent predictor of early mortality. Every doubling in neutrophil percentage increases the risk of death by 30%. No role of BAL lymphocytes or Eosinophils

BAL-NSIP

- BAL findings are also non specific !!

- Cellular NSIP : Increase in lymphocytes
- Fibrotic NSIP : Increase in Neutrophils

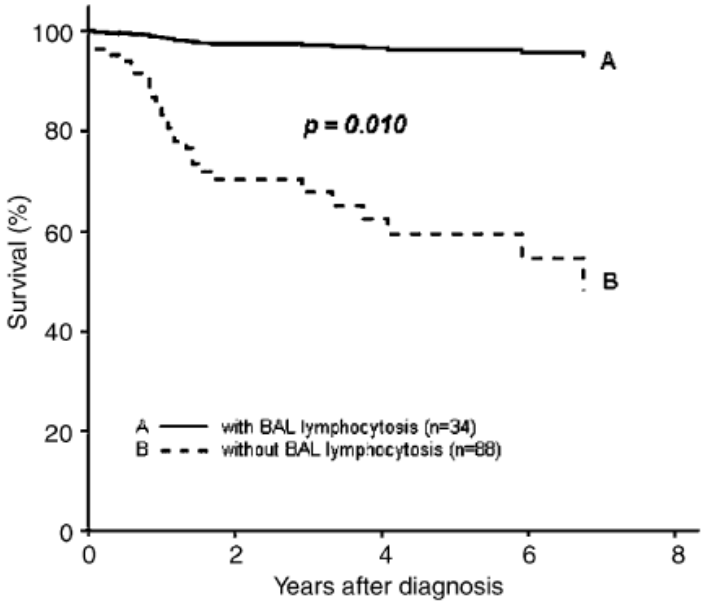
Table 4. Bronchoalveolar lavage cells in nonspecific interstitial pneumonia versus usual interstitial pneumonia*

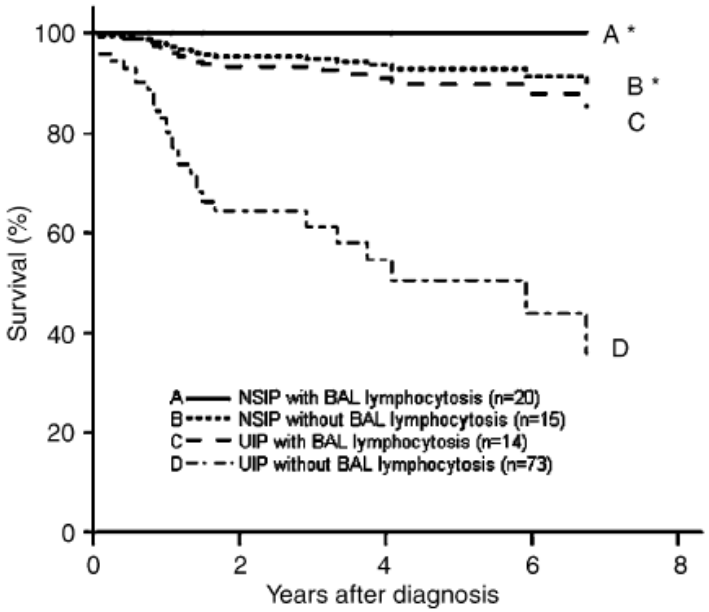
	Lymphocytes, %		Neutrophils, %	
Study	NSIP	UIP	NSIP	UIP
Nagai *et al.*	37	7	8	6
Daniil *et al.*	9	8	8	10
Park *et al.* [	46	8	23	13
Suga *et al.*	21	6	7	7

Bronchoalveolar lavage in fibrotic idiopathic interstitial pneumonias

Respiratory Medicine (2007) **101**, 655–660

Variables	IPF ($n = 87$)	Idiopathic NSIP			*P*-value*
		Cellular ($n = 6$)	Fibrotic ($n = 29$)	Both ($n = 35$)	
BAL neutrophils					
Counts (%) (ranges)	7.0(0–85)	3.5(1–25)	3.0(0–38)	3.0(0–38)	<0.05
Neutrophilia (+) (n)	49	2	10	12	<0.05
BAL lymphocytes					
Counts (%) (ranges)	5.5(0–68)	40.5(29–76)	19.0(4–71)	29.0(4–76)	<0.05
Lymphocytosis (+) (n)	14	6	14	20	<0.05





Conclusions

- BAL does not have a role in the diagnosis of IPF/NSIP. The diagnosis is based on radiology/ histopathology.

- BAL however can help in differentiation between IPF and NSIP which may have prognostic implications.

- The role of BAL cell counts as predictors of prognosis needs to be further validated in larger prospective studies

Role of BAL in Pneumoconiosis

DIAGNOSIS

- BAL findings can identify exposure to mineral dusts.

  - Asbestos bodies : Asbestos exposure
  - Coal dust engulfed macrophages : Coal dust exposure
  - Silica particles by optical/electron microscopy : Silica exposure

- Exposure is not same as Disease
- BAL findings cannot differentiate Exposure from Disease

BAL-Asbestosis

- Gold standard for diagnosis is demonstration of asbestos bodies(AB) in the lung tissue.

- Good correlation between BAL AB and lung asbestos burden.
- More than 1 AB/ ml BAL fluid correlates with >1000 AB/gm lung tissue and is considered significant.

- However, significant overlap seen between those exposed without disease and those who have disease.

Asbestos Bodies

occupational and environmental lung disease

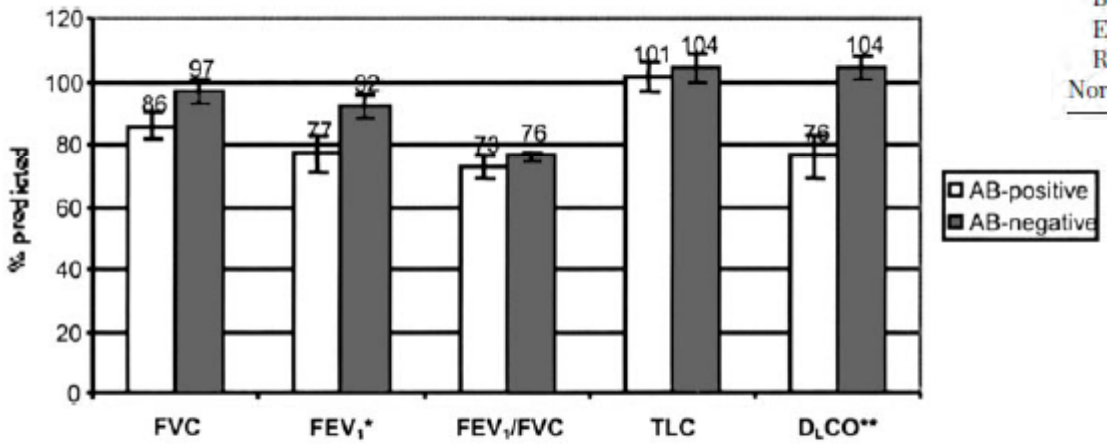
Clinical Correlation of Asbestos Bodies in BAL Fluid*

(CHEST 2004; 126:966–971)

Table 2—*Respiratory Symptoms

Variables	Asbestos-Exposed Subjects (n = 29)		
	AB Positive (n = 10)	AB Negative (n = 19)	p Value
Any respiratory symptoms	7 (70)	5 (26)	0.023†
Chronic cough	6 (60)	1 (5)	0.001†
Sputum production	4 (40)		0.002†
Dyspnea	2 (20)	4 (21)	0.95
Wheeze	1 (10)	1 (5)	0.65

*Data are presented as No. (%).



* FEV_1; p value < 0.05
** D_LCO; p value < 0.01

Table 4—*HRCT Scan Results in Asbestos-Exposed Subjects

Variables	Asbestos-Exposed Subjects (n = 29)		
	AB Positive (n = 10)	AB Negative (n = 19)	p Value
Abnormal	9 (90)	15 (79)	0.47
Pleural plaques	6 (60)	11 (58)	0.92
Diffuse pleural thickening		1 (5)	
Parenchymal disease	7 (70)	5 (26)	0.023†
Subpleural reticular changes	2 (20)	5 (26)	0.72
Subpleural lines	1 (10)		
Fibrosis	4 (40)		0.002†
Bronchiectesis	2 (20)	1 (5)	
Emphysema		2 (10)	
Rounded atelectesis		1 (5)	
Normal	1 (10)	4 (21)	

Conclusion

- In the appropriate clinical scenario and presence of radiological abnormalities, the presence of BAL abnormalities may support the diagnosis of pneumoconiosis.

BAL- Connective Tissue related ILDs

- The main role of BAL in CT-ILD is to differentiate lung involvement due to primary disease per se from secondary causes of lung involvement.

  - Infections : CT-ILD are at increased risk of infections due to the disease per se (SLE) or because of the immunosuppressive therapies offered. BAL plays an important role in diagnosing TB, fungi, atypical infections like PCP.

  - Malignancy : Increased risk of bronchogenic malignancy in scleroderma, increased risk of lymphomas in SLE patients

  - DAH syndromes : BAL can differentiate DAH from Acute lupus pneumonitis

  - Drug toxicities : Increased Eosinophils and lymphocytes.

BAL- Systemic sclerosis

- Extensively studied
- Nearly 20 studies till date on the role of BAL in disease prognosis and monitoring.

Bronchoalveolar Lavage and Response to Cyclophosphamide in Scleroderma Interstitial Lung Disease

Am J Respir Crit Care Med Vol 177. pp 91–98, 2008

- Scleroderma lung study
- Only RCT published on the role of BAL and treatment response and monitoring

Methods: Patients underwent baseline lavage and/or high-resolution computed tomography as part of a randomized placebo-controlled trial of cyclophosphamide versus placebo (Scleroderma Lung Study) to determine the effect of therapy on forced vital capacity. Patients with 3% or greater polymorphonuclear and/or 2% or greater eosinophilic leukocytes on lavage and/or ground-glass opacification on computed tomography were eligible for enrollment.
Measurements and Main Results: Lavage was performed in 201 individuals, including 141 of the 158 randomized patients. Abnormal

Conclusions: The presence of an abnormal lavage in the Scleroderma Lung Study defined patients with more advanced interstitial lung disease but added no additional value to physiologic and computed tomography findings as a predictor of progression or treatment response.

SCLERODERMA
Semin Arthritis Rheum 40:73-88

Bronchoalveolar Lavage Fluid in Scleroderma Interstitial Lung Disease: Technical Aspects and Clinical Correlations: Review of the Literature

- 19 studies identified by pubmed search till 2008.

- Conclusions :
  - Alveolitis as detected by BAL is associated with poorer lung function as determined by PFTs and HRCT scores.
  - Insufficient evidence to recommend performing BAL cellular analysis as an independent predictor of outcome.

SERIAL BAL ASSESSMENT –ROLE?

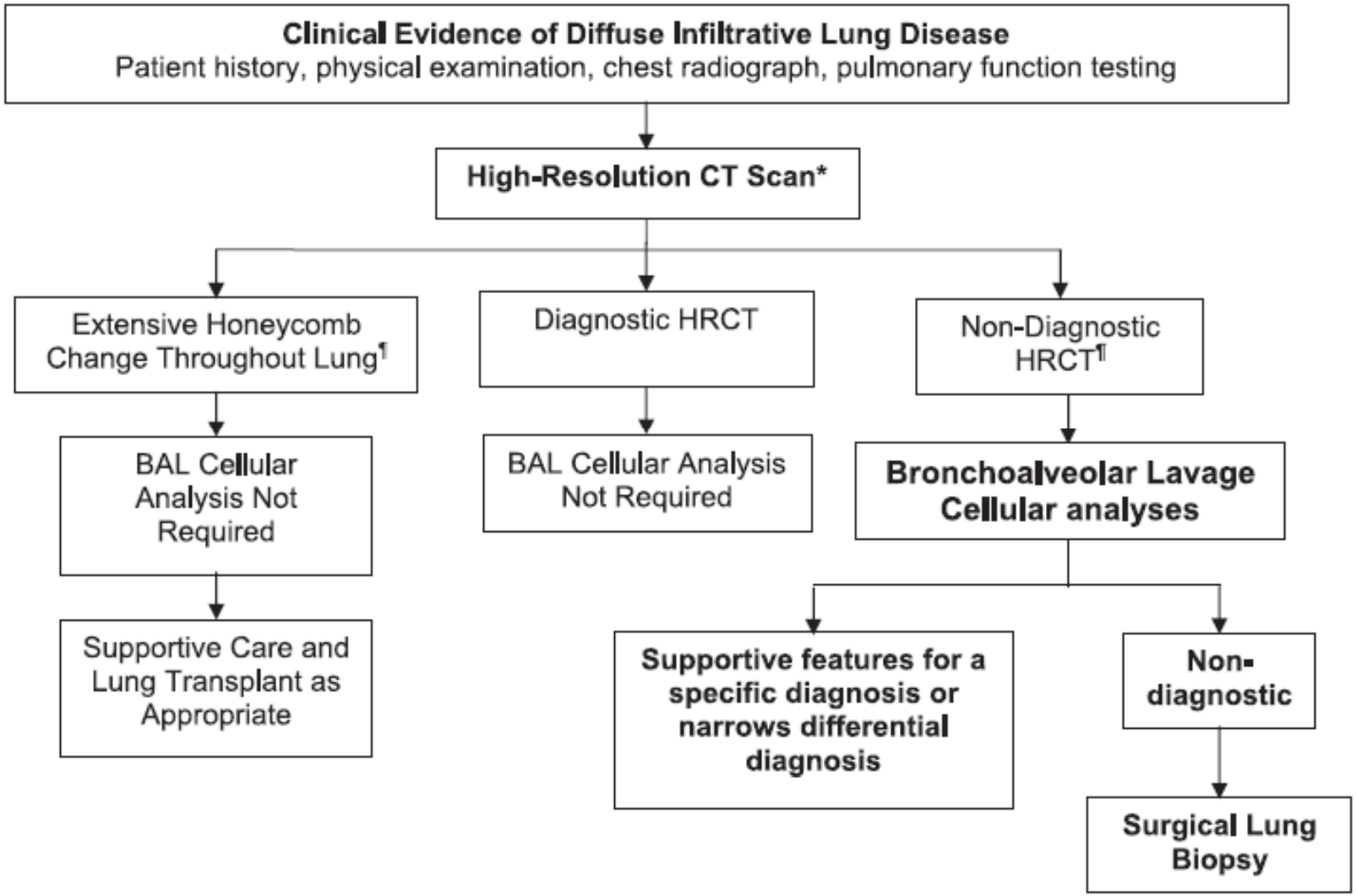
Author	Journal/Year	No. of patients	Results/Conclusions
Mittoo S etal	Arthritis Rheum 2007	25	Persistence of BAL alveolitis following CYC therapy does not predict future outcomes .
Colaci M et al	Scand J Rheumatol 2010	26	BAL fluid normalization following therapy predicts long term response whereas persistent alveolitis is a predictor of disease relapse.

Conclusions

- In CT-ILD, BAL is indicated mainly to rule out other differentials.
- Though BAL alveolitis has been consistently shown to be associated with worse disease outcomes, the additional benefit obtained over PFT and HRCT is minimal.
- Role of BAL in disease monitoring needs further research.

Take Home Message

- BAL findings alone cannot diagnose ILD and should be used in conjunction with the clinical history and radiological database.
- BAL total and differential cell counts will help to narrow the differential diagnosis and are indicated in the workup of suspect ILD patients.
- BAL lymphocyte sub typing is useful in select patients with BAL lymphocytosis.
- BAL also plays an important role in ruling out ILD mimics.
- BAL is not indicated for disease prognostication or disease monitoring.



Am J Respir Crit Care Med Vol 185, Iss. 9, pp 1004–1014, May 1, 2012