MEDLON
MEDISCHE DIAGNOSTIEK

Diagnostiek ILD in het kader van systeemziekten

Leontine Mulder

Interstitiële longziekten

- Grote groep verschillende aandoeningen
- Grove verdeling in bekende oorzaak versus onbekende oorzaak
- Bekende oorzaak bijvoorbeeld: inhalatie irriterende stoffen als asbest, talk, silica, schimmels, medicatie

Vaak oorzaak van buiten

- Onbekende oorzaak bijvoorbeeld: sarcoïdose, idiopathische fibrose etc.
- Ook interstitiële longziekten bij systeemziekten

Oorzaak van binnen? Immuunbalans?

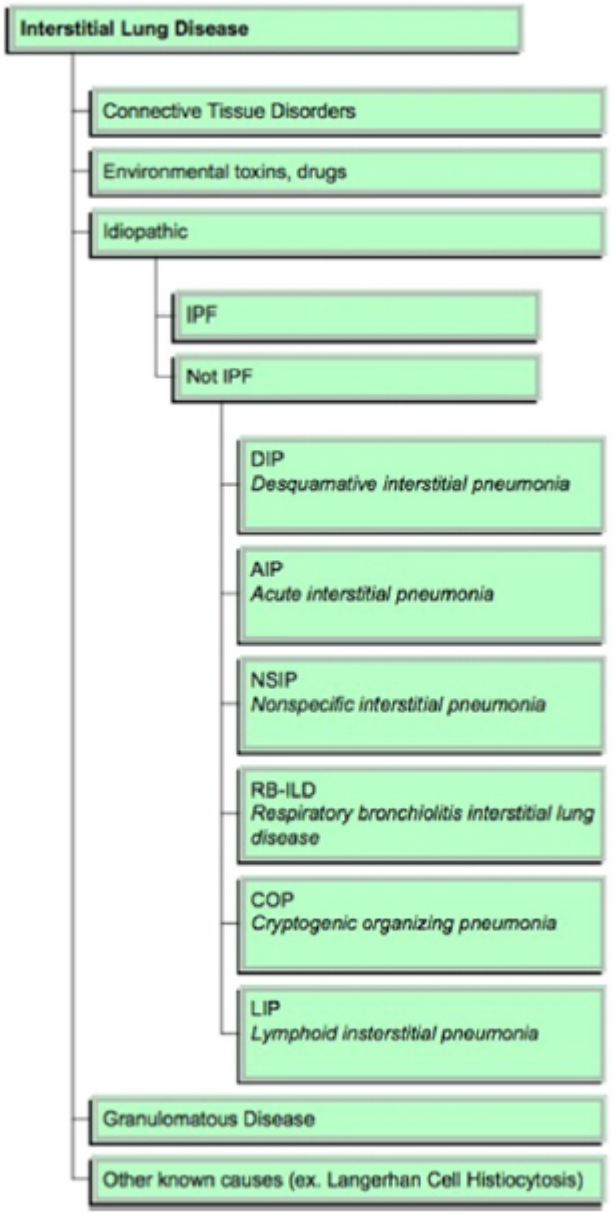


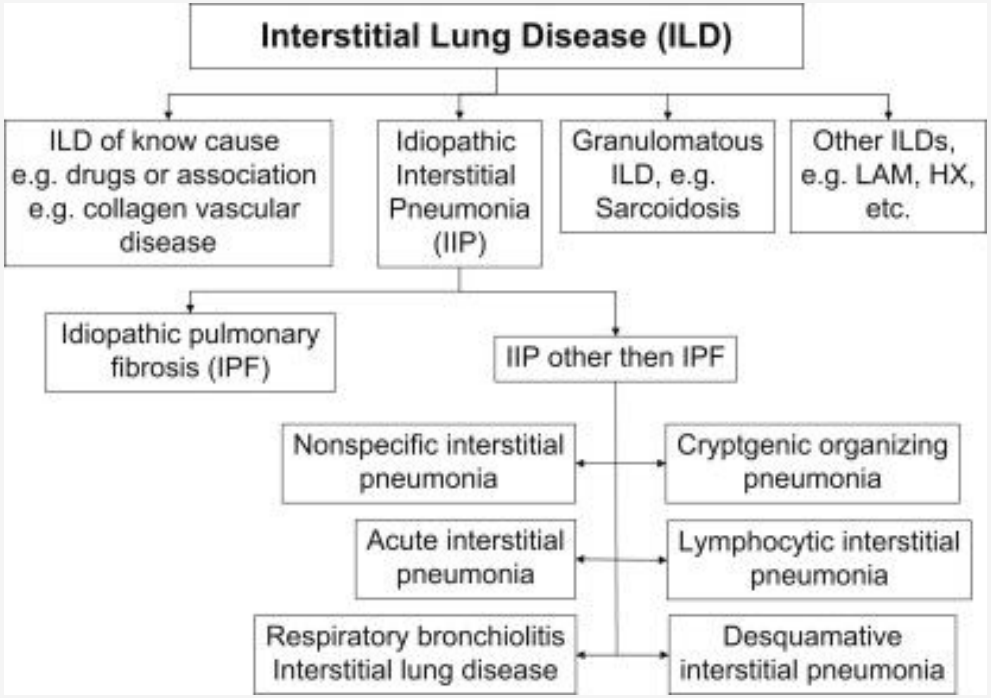
Fig. 1. A classification system for interstitial lung disease.

De ILDs bij systeemziekten maken dus onderdeel uit van het spectrum van de ILDs

Presentatie van symptomen in de tijd kan het lastig maken om de ILD goed te classificeren.

Diagnostiek ILDs

- HRCT
- Lavage met kweek en cytologie
  - Aandacht voor factoren van buitenaf!
- Immunologische BAL
  - Toegevoegde waarde soms diagnostisch, vaker richtinggevend



Clinics in Chest Medicine.

Behr, Jürgen, MD. Published March 1, 2012. Volume 33, Issue 1. Pages 1-10.

Table 1. Pattern of respiratory involvement in connective tissue disease

	Airways	Pleura	PAH	Muscle	ILD	ILD pattern
SSc	−/+	−/+	+++	−	+++++	NSIP>>>UIP
RA	++++	+++	−/+	−	++	UIP>NSIP>OP=DAD
PM/DM	−/+	−	−/+	++	++++	NSIP=OP>DAD>UIP
Sjögren's	+++++	−/+	+	−/+	+++	NSIP>LIP>OP=UIP=DAD
SLE	−/+	++++	++	+	+	NSIP>DAD=LIP=OP=UIP

Abbreviations: SSc: systemic sclerosis, RA: rheumatoid arthritis, PM/DM: polymyositis/dermatomyositis, SjS: Sjögren's syndrome, SLE: systemic lupus erythematosus, NSIP: non-specific interstitial pneumonia, UIP: usual interstitial pneumonia, OP: organizing pneumonia, DAD: diffuse alveolar damage, LIP: lymphocytic interstitial pneumonia.

Radio- en histologische patronen en klinische aandoeningen

TABLE 6. CLINICAL CONDITIONS ASSOCIATED WITH USUAL INTERSTITIAL PNEUMONIA PATTERN

Idiopathic pulmonary fibrosis/cryptogenic fibrosing alveolitis
Collagen vascular disease
Drug toxicity
Chronic hypersensitivity pneumonitis
Asbestosis
Familial idiopathic pulmonary fibrosis
Hermansky–Pudlak syndrome

TABLE 8. CLINICAL CONDITIONS ASSOCIATED WITH NONSPECIFIC INTERSTITIAL PNEUMONIA HISTOLOGIC PATTERN*

No detectable cause (idiopathic NSIP)
Collagen vascular disease
Hypersensitivity pneumonitis
Drug-induced pneumonitis
Infection
Immunodeficiency including HIV infection

* Adapted from Reference 23.

Am J Respir Crit Care Med Vol 165. pp 277–304, 2002

Wanneer aan ILD denken bij patient met CTD?

Wanneer aan CTD denken bij patient met ILD?

Wanneer aan ILD denken bij CTD patient met longklachten?

DD
-infectious (immuunsuppressiva)
-medicamenteus
-complicatie CTD bijv bij hartfalen

Retrospectieve studie Mayo Clinics

	ILD 1235 (35%)	No ILD 2317 (65%)
CTD 450 (13%)	326 (72%)	124 (28%)
No CTD 3123 (87%)	930 (30%)	2193 (70%)

Respir Med. 2015 March ; 109(3): 397–405.

Slechts 9% van totale cohort

	ILD 1235 (35%)	No ILD 2317 (65%)
CTD 450 (13%)	326 (72%)	124 (28%)
No CTD 3123 (87%)	930 (30%)	2193 (70%)

Wel 26% van alle ILD patiënten

CTD should be considered in every patient with ILD, particularly females and subjects <50 years of age.

Cottin V. Eur Respir Rev. 2013 Sep 1;22(129):273-80

Voor diagnose IPF moet CTD expliciet uitgesloten worden.

Wanneer aan ILD denken bij patient met CTD? *Vaak/altijd*

Wanneer aan CTD denken bij patient met ILD? *bij ILD van onbekende oorzaak altijd*

Patient M

- Sinds een half jaar toenemend kortademig.
- Inspanning gerelateerd
- Tevens droge hoest
- Afwijkende X-thorax daarop HRCT
- Interstitieel beeld, possible UIP, geen honeycombing, progressief

Diagnostisch dilemma

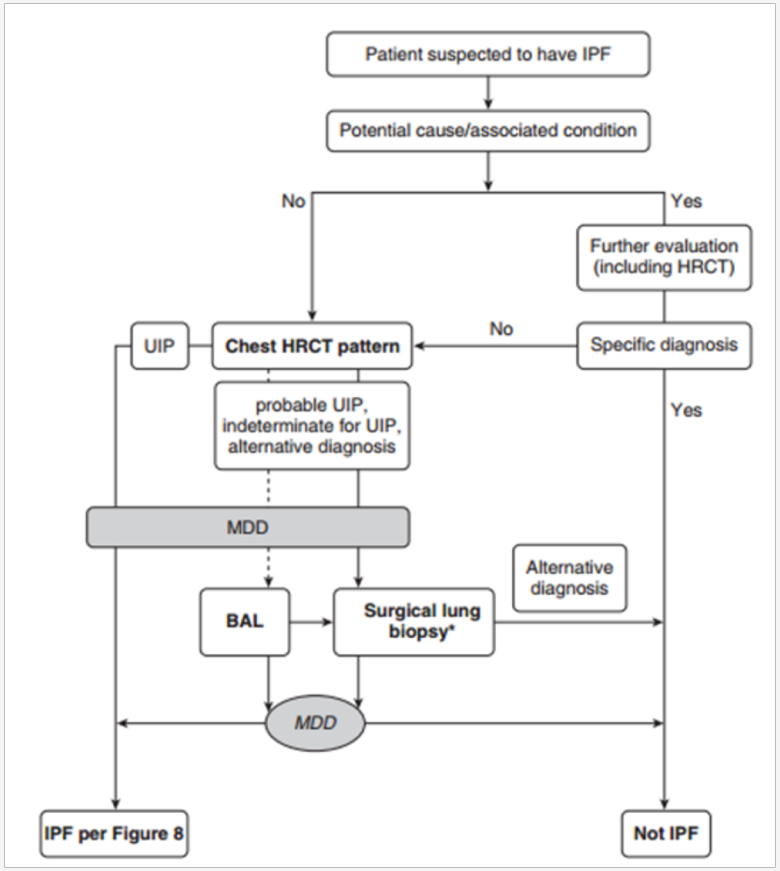
- Anamnestisch geen aanknopingspunten
- Indien IPF dan fibroseremmers
- Indien secundaire fibrose dan immuunsuppressiva

Vervolg patiënt M

- Analyse door reumatoloog:
  - Mild last van ochtendstijfheid
  - Anti-CCP is negatief
  - Autoimmuunserologie: positieve ANA met negatieve CTD screen
- Conclusie: Onvoldoende aanwijzingen voor onderliggende autoimmuunziekte

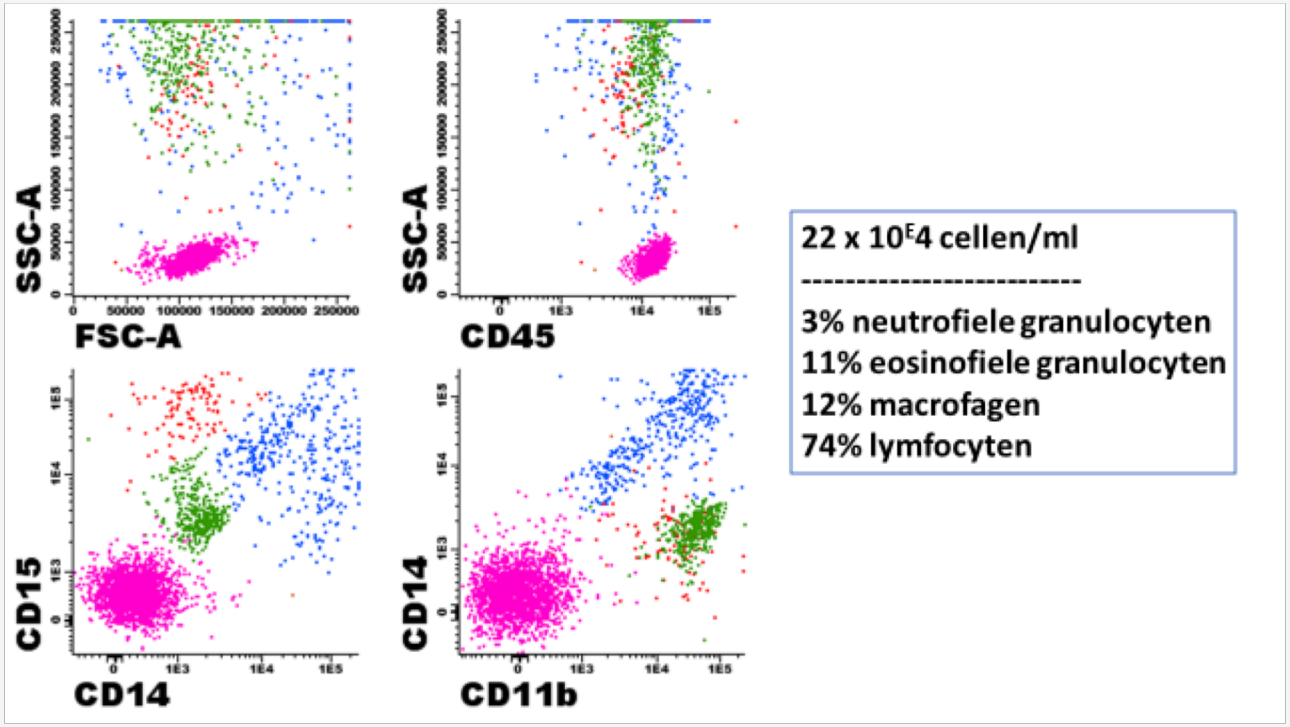
MDO ILD-ziekten

- Autoimmuunserologie nog uitbreiden?
- Toch BAL verrichten met het oog op de consequenties voor behandelen:
  - Indien lymfocytair beeld dan immuunsuppressiva



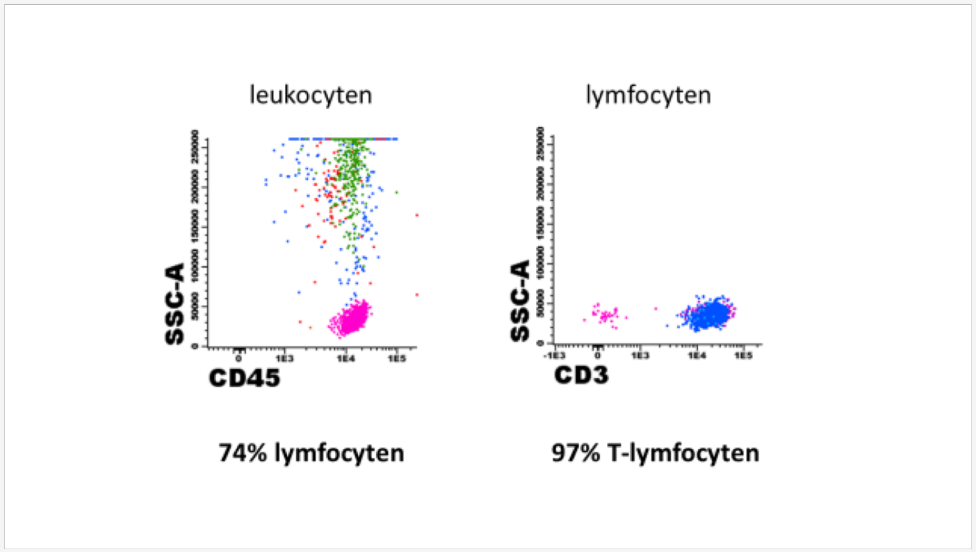
Mevrouw N

- Niet opknappende pneumonie, dyspnoe bij inspanning
- Nav afwijkende X-thorax HRCT: bilaterale peribronchovasculaire consolidaties, matglas, geen fibrose (DD infectieus, OP, eosinofiele pneumonie, UIP)
- Diffuus gewrichtspijnen, droge mond en Raynaud
- Reumatoloog icc en BAL verrichten

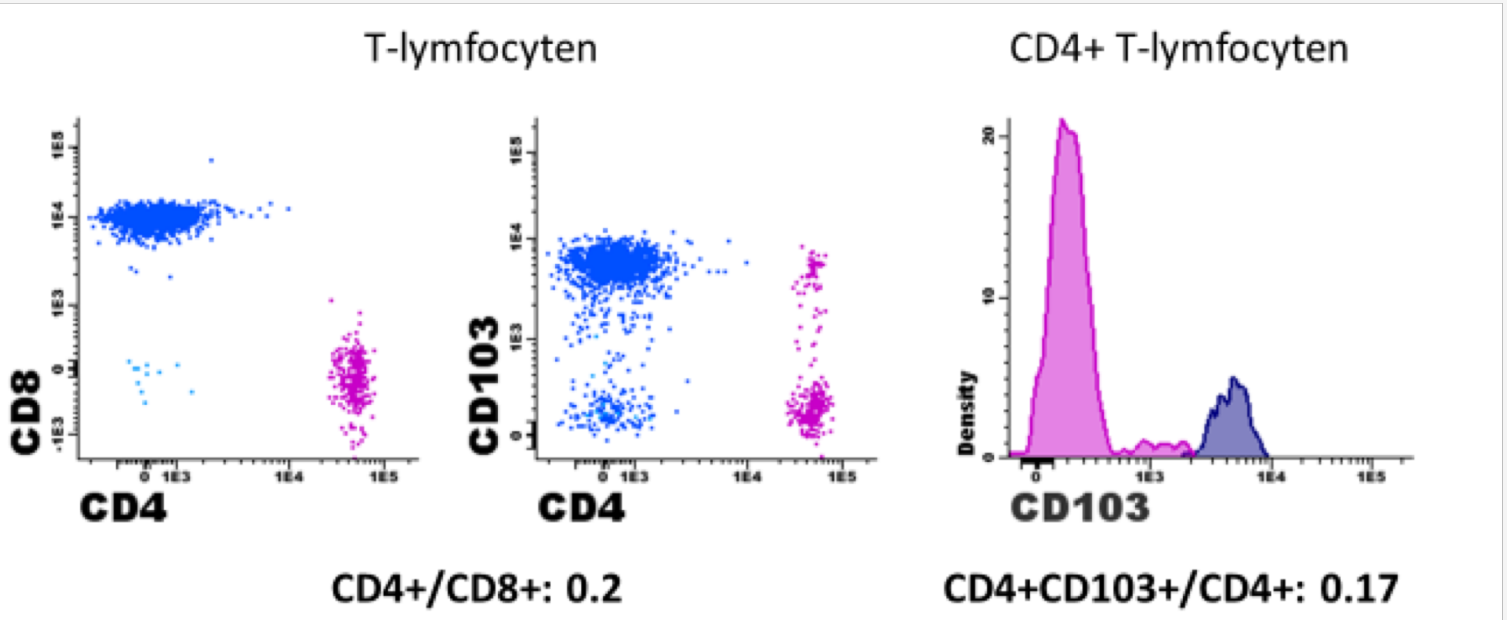


22 x $10^{E}4$ cellen/ml

3% neutrofiele granulocyten
11% eosinofiele granulocyten
12% macrofagen
74% lymfocyten



Klinische informatie:
Bilaterale afwijkingen
DD OP, eosinofiele pneumonie



BAL vloeistof met een CD8+ T-cellymfocytose en verhoogd percentage neutrofiele- en eosinofiele granulocyten. Beeld kan passen bij EAA.

Reumatoloog

- Artritis rechterpols en MCP2, hydrops rechter knie
- Geen huid/nagelafwijkingen
- ANA neg, Rf-IgM pos, anti-CCP neg
- aanvullend lab (antidsDNA, ENA's, IgG4, cryoglobuline, ACE, etc..)

Longarts

Reumatoloog

- DD: ILD bij RA, MCTD, Sjogren, Sclerodermie, anti-synthetase syndroom, sarcoidose

Medisch immunoloog

- Kan passen bij EAA

Beleid

- Start prednison:
  - goede respons X-thorax
  - Minder benauwd, minder zuurstof behoeftig
  - Wel verminderde diffusie

Vervolg

- Anti-Jo1 en anti-SSa positief
- Werkdiagnose was RA met ILD, wordt nu uitgebreid met anti-synthetase syndroom of Sjogren

- Overleg academie: start plaquenil en MTX

Nog verdere differentiatie?

- ILD RA
- ILD inflammatoire myopathie – groepen antistoffen zijn geassocieerd met ILD.
- ILD Sjogren – voorkomen is geassocieerd met de ziekteduur SS

Table 5
Prevalence of interstitial lung diseases in systemic autoimmune rheumatic diseases.

Diseases	ILDs	Comment
Classical connective tissue diseases		
Systemic sclerosis (SSc)	55–65% [34,48]	Clinically overt ILD; mainly in diffuse cutaneous SSc subset [49]; NSIP pattern more frequently reported [50]
Systemic lupus erythematosus (SLE)	1–15% [51]	Mainly in long-lasting disease duration and older patients; possible evolution from SLE pneumonitis [52]
Sjögren's syndrome (SS)	2–45% [53-55]	ILD prevalence directly correlated with SS duration [55]
Inflammatory myopathies (DM/PM)	up to 75% [56]	Anti-synthetase antibodies mark the presence/development of ILD [56]
Mixed connective tissue disease	35–66% [57,58]	
Undifferentiated connective tissue disease (UCTD)	n.a.	ILD is not reported in UCTD cohort studies [16-24]
Other systemic autoimmune diseases		
Rheumatoid arthritis	4–68% [59]	Smoking, male gender, and long-standing disease are frequently reported as risk factors for ILD [59]; UIP pattern present in 2/3 cases [60]
Ankylosing spondylitis	35–65% [61]	data from small case series
Behçet's disease	n.a.	nodular or reticular opacities have been occasionally described and considered residuals of lung hemorrhage/infarcts [62]
Cryoglobulinemic vasculitis	Anecdotal [63]	Subclinical lymphocytic alveolitis (BAL) [64,65]
ANCA-associated vasculitides[a]	~3 [66]	Association with MPO-ANCA antibodies [66]

ILDs: interstitial lung diseases; NSIP: Non Specific Interstitial Pneumonia; UIP: Usual Interstitial Pneumonia; DM/PM: dermatomyositis/polymyositis; n.a.: not available; BAL: broncho-alveolar lavage; MPO-ANCA: anti-myeloperoxidase-antineutrophil cytoplasmic autoantibodies.

[a] Granulomatosis with polyangiitis, eosinophilic granulomatosis with polyangiitis, microscopic polyangiitis.

Table 1. Pattern of respiratory involvement in connective tissue disease

	Airways	Pleura	PAH	Muscle	ILD	ILD pattern
SSc	−/+	−/+	+++	−	+++++	NSIP>>>UIP
RA	++++	+++	−/+	−	++	UIP>NSIP>OP=DAD
PM/DM	−/+	−	−/+	++	++++	NSIP=OP>DAD>UIP
Sjögren's	+++++	−/+	+	−/+	+++	NSIP>LIP>OP=UIP=DAD
SLE	−/+	++++	++	+	+	NSIP>DAD=LIP=OP=UIP

Abbreviations: SSc: systemic sclerosis, RA: rheumatoid arthritis, PM/DM: polymyositis/dermatomyositis, SjS: Sjögren's syndrome, SLE: systemic lupus erythematosus, NSIP: non-specific interstitial pneumonia, UIP: usual interstitial pneumonia, OP: organizing pneumonia, DAD: diffuse alveolar damage, LIP: lymphocytic interstitial pneumonia.

THE CLINICAL UTILITY OF BRONCHOALVEOLAR LAVAGE CELLULAR ANALYSIS IN INTERSTITIAL LUNG DISEASE: AN ATS CLINICAL PRACTICE GUIDELINE 2012

The committee concludes the following regarding the clinical utility of BAL cellular analyses for **RA** :

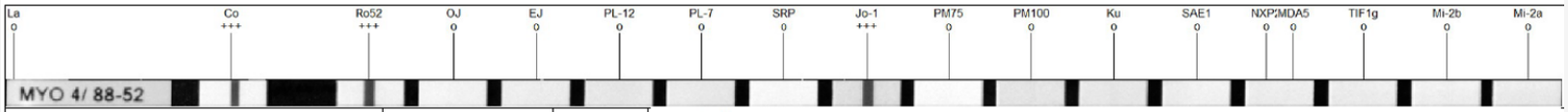
- Lymphocytes are a more prominent feature in RA than in SSc.
- Good studies to correlate BAL with HRCT patterns of disease are lacking

The committee concludes the following regarding the clinical utility of BAL cellular analyses for **Primary Sjögren's syndrome**:

- Lymphocytosis is prominent and usually associated with good outcome.
- Excessive neutrophils, when present, are associated with persistent disease.

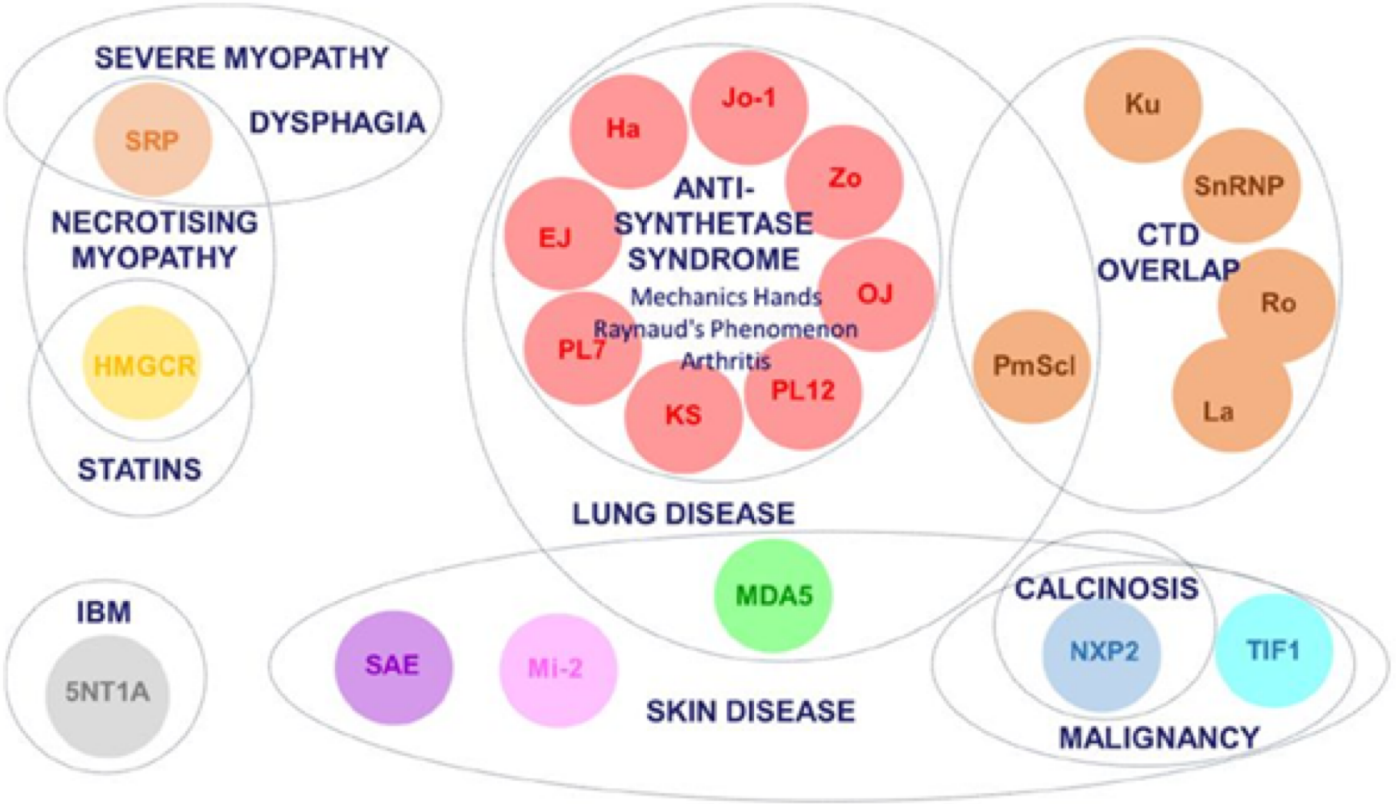
The committee concludes the following regarding the clinical utility of BAL cellular analyses for **dermatomyositis/polymyositis:**

- Increased lymphocytes and neutrophils represent the most common BAL abnormality.



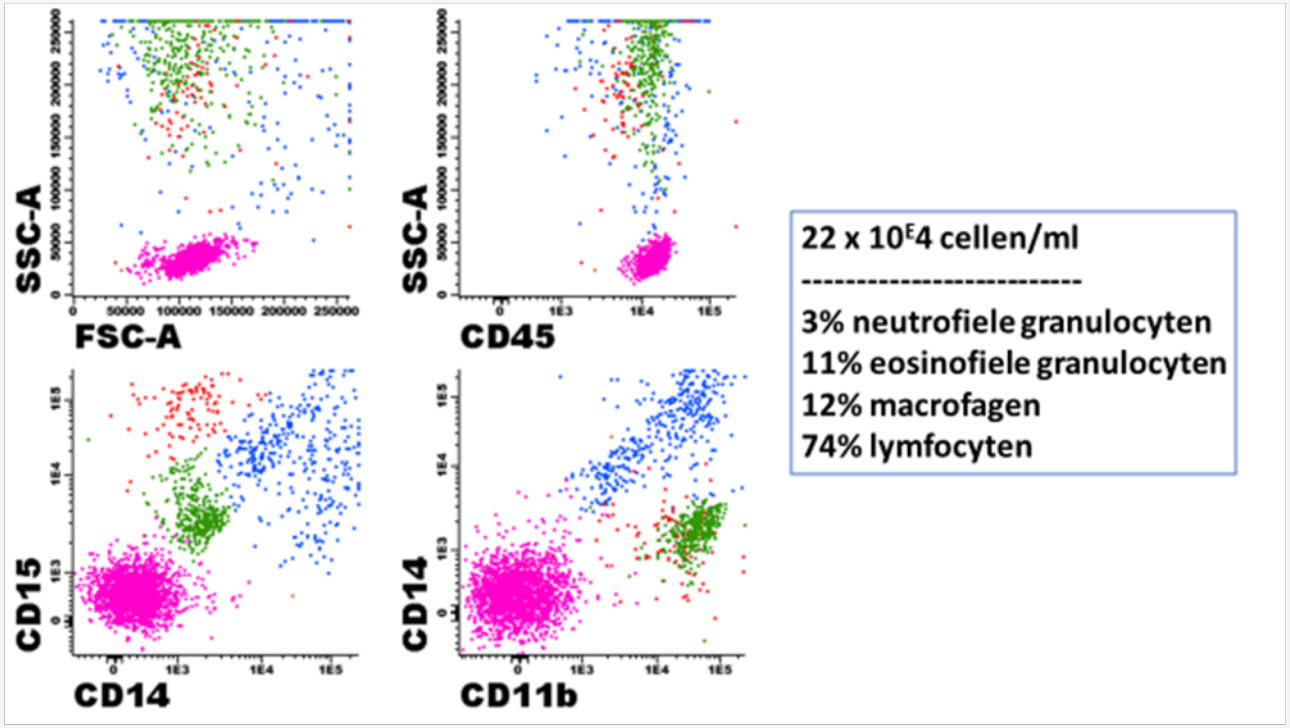
Antigen	Intensity	Class
Mi-2alpha (Mi-2a)	1	o
Mi-2beta (Mi-2b)	2	o
TIF1gamma (TIF1g)	1	o
MDA5 (MDA5)	1	o
NXP2 (NXP2)	2	o
SAE1 (SAE1)	0	o
Ku (Ku)	3	o
PM-Scl100 (PM100)	2	o
PM-Scl75 (PM75)	1	o
Jo-1 (Jo-1)	141	+++
SRP (SRP)	2	o
PL-7 (PL-7)	1	o
PL-12 (PL-12)	2	o
EJ (EJ)	2	o
OJ (OJ)	1	o
Ro52 (Ro52)	160	+++
Control (Co)	163	+++

MSA/MAAS AND CLINICAL ASSOCIATIONS IN ADULT MYOSITIS

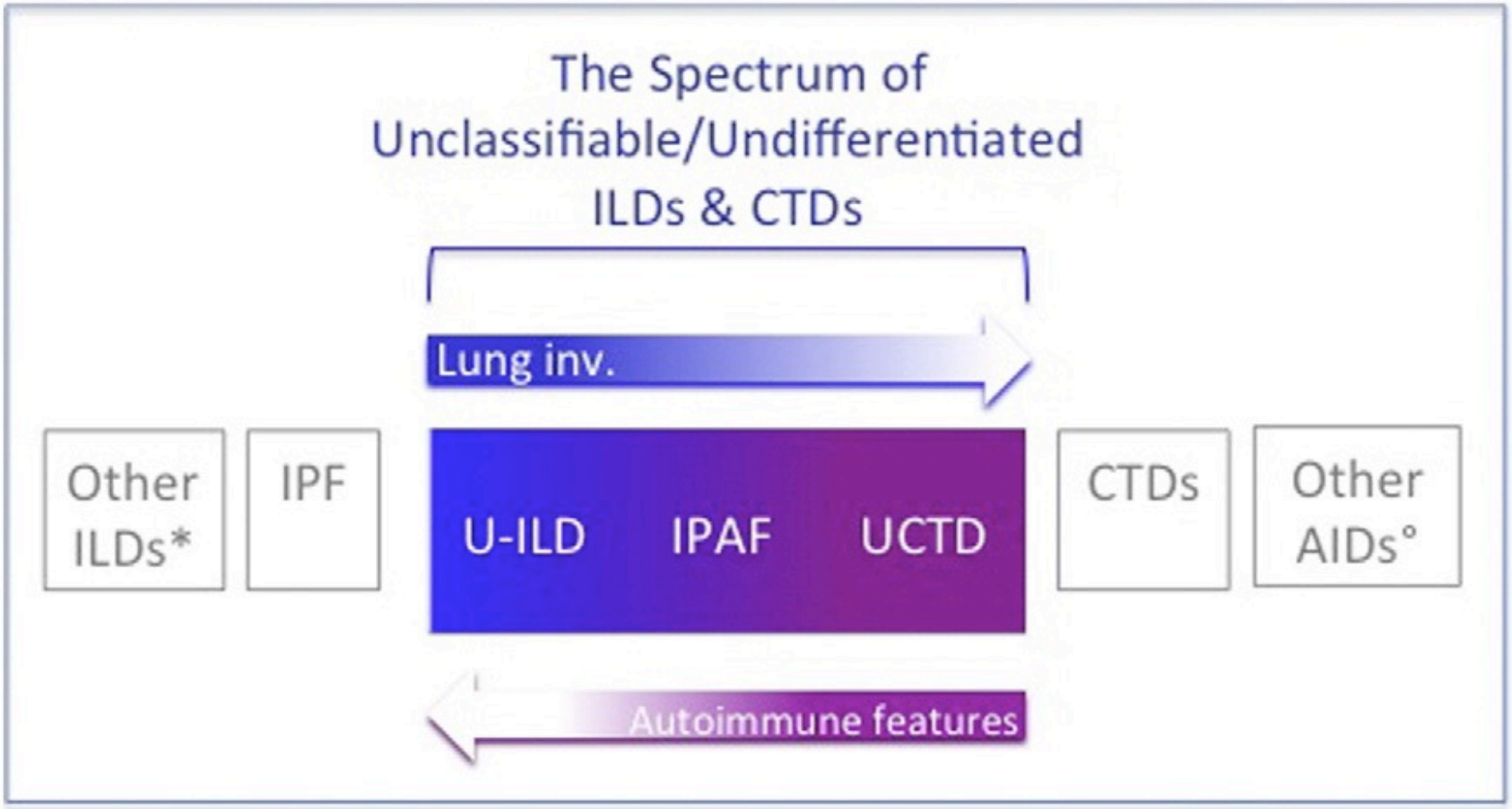


The committee concludes the following regarding the clinical utility of BAL cellular analyses for **dermatomyositis/polymyositis**:

- Increased lymphocytes and neutrophils represent the most common BAL abnormality.



Er ontstaat een spectrum
Links de ILDs met bekende oorzaken en de granulomateuze ILDs

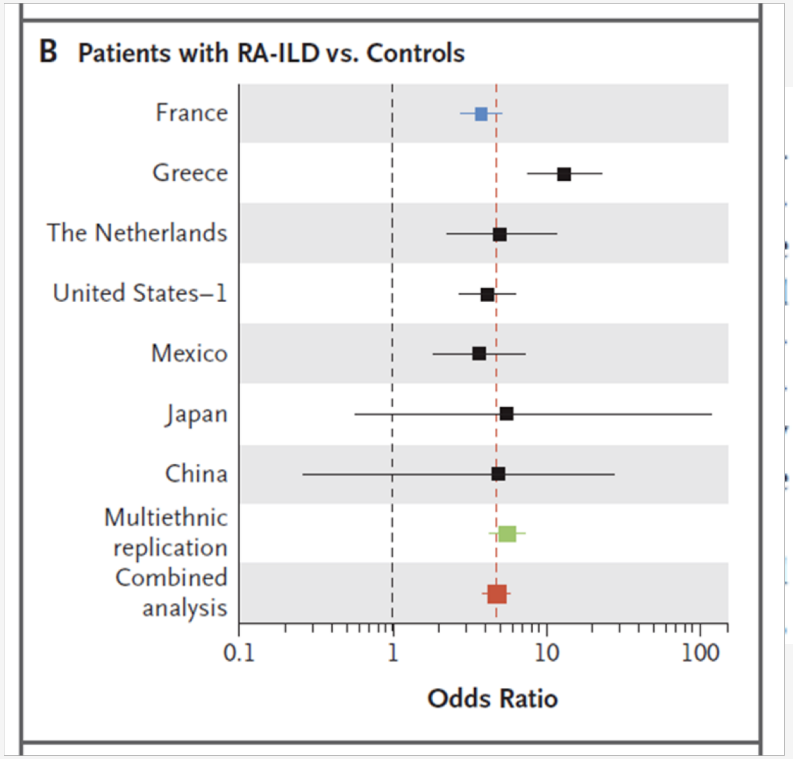


Rechts de autoimmuunziekten en de connective tissue diseases

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

MUC5B Promoter Variant and Rheumatoid Arthritis with Interstitial Lung Disease



The common gain-of-function variant rs35705950[16] in the promoter of *MUC5B*, encoding mucin 5B, is the strongest genetic risk factor for idiopathic pulmonary fibrosis; it is observed in at least 50% of patients with idiopathic pulmonary fibrosis and accounts for 30% of the risk of developing this disease.[17-25] This variant is associated with increased expression of *MUC5B* in lung parenchyma of unaffected controls and of persons with idiopathic pulmonary fibrosis.[16,17] Conse-

MUC5B promoter variant

- Specifiek geassocieerd met RA-ILD met UIP patroon
- Niet geassocieerd met ILD bij SSc of inflammatoire myopathie.
- Specifieke subgroup?

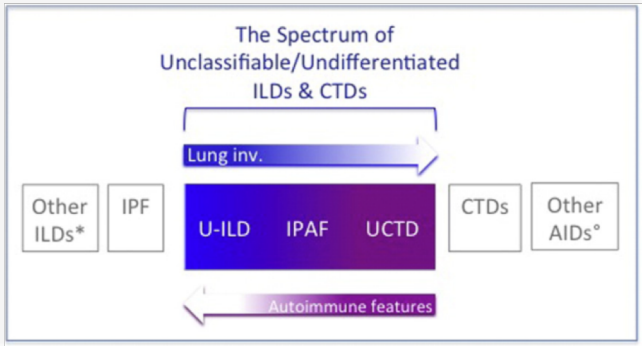
Take home

Systeemziekten en ILD verweven met elkaar

Toegevoegde waarde BAL tot nog toe beperkt maar niet nihil

Meer focus op mogelijk onderliggende systeemziekte dan in het verleden

Toekomst: meer inzicht in subgroepen



Dank aan

- Ellen van Lochem en Michiel Heron

Table 3. Classification of histological and radiological patterns developed for idiopathic interstitial pneumonias, applied to connective tissue disease-associated interstitial lung disease[8]

Pattern	Histology	CT features
UIP	Subpleural and peripheral fibrosis. Temporal and spatial heterogeneity. Scattered *fibroblastic foci* and honeycombing are key features.	Basal, subpleural reticulation and honeycombing; traction bronchiectasis; little, if any, ground-glass attenuation.
NSIP	Uniform interstitial involvement by variable degrees of fibrosis and inflammation. Honeycombing is rare.	Bilateral patchy ground-glass opacities admixed with reticulation and traction bronchiectasis / bronchiolectasis. Little or no honeycombing. Usually, predominantly basal.
OP	Connective tissue plugs within small airways and air spaces (Masson bodies). In its 'pure' form, little or no inflammation or fibrosis in the surrounding interstitium.	Airspace consolidation, with a predominantly basal/ peripheral or peri-bronchovascular distribution. Bands with air bronchograms and a perilobular pattern can also be seen.
DIP	Extensive macrophage accumulation within the distal air spaces. Mild interstitial involvement	Patchy ground-glass opacities. Microcystic change can be seen within the ground-glass. Basal, peripheral distribution frequent.
LIP	Bronchiolocentric lymphoid tissue hyperplasia.	Ground-glass attenuation is the predominant finding, with thin-walled cysts frequently present. Lung nodules and septal thickening may also be seen
RB-ILD	Bronchiolocentric macrophage accumulation. Mild bronchiolar fibrosis.	Centrilobular nodules, ground glass opacities. Diffuse or upper lung distribution
DAD	In the acute phase: hyaline membranes, edema. In the organizing phase: airspace and interstitial organization.	Acute phase: diffuse ground-glass opacities and consolidation in dependent areas. Organizing, phase: reticular pattern, traction bronchiectasis and architectural distortion

Abbreviations: DIP: desquamative interstitial pneumonia, NSIP: non-specific interstitial pneumonia, UIP: usual interstitial pneumonia, OP: organizing pneumonia, DAD: diffuse alveolar damage, RB-ILD: respiratory bronchiolitis interstitial lung disease, LIP: lymphocytic interstitial pneumonia.

Table 1
Clinical assessment of patients with interstitial lung diseases (ILDs).

General data	Signs/symptoms[a]	Laboratory examinations	Instrumental investigations
Demografic	Arthralgias	***First line***	
Occupational	Arthritis	ANA ≥ 1:320 titer	Chest HRCT
Environmental	Morning stiffness	Anti-ENA	PFTs (including DLco)
Avocational	Puffy fingers	ESR (>2 times normal)	
Medication	Raynaud's phen.	Abnormal CRP	
Smoking	Myalgias	Routine blood chemistry	
	Muscle weakness	Urinalysis	
	Rash	Infections	
	Photosensitivity	(HCV, HBV, HIV, EBV)	
	Alopecia	RF	
	Dermatitis	***Second line***	
	Mechanics' hand	Anti-CCP	Surgical lung biopsy
	Gottron's sign	Complement C3/C4	Doppler echocardiography
	Skin ulcers	AMA	Joint echography
	Oral/genital ulceration	ASMA	Nailfold capillaroscopy
	Oral dryness	ANCA	Schirmer's test
	Ocular dryness	Anti-phospholipid Ab/LAC	Salivary gland echography
	Dysphagia	Organ-specific autoAb	Minor salivary gland biopsy
	Recurrent fever	24 h-proteinuria	Muscle biopsy
	Weight loss		Electromyography
	Serositis		Skin biopsy
	Dyspnoea on exertion		
	Dry cough		

ANA: anti-nuclear antibodies; anti-ENA: anti-extractable nuclear antigen; (antibodies: anti-Scl-70, anti-Ro, anti-La, anti-dsDNA, anti-Smith, anti-RNP, anti-PM-Scl, and/or anti-tRNA synthetase); ESR: eritrocyte sedimentation rate; CRP: C-reactive protein; HCV: hepatitis C virus; HBV: hepatitis B virus; HIV: human immudeficiency virus; EBV: Epstein-Barr virus; RF: rheumatoid factor; anti-CCP: anti-cyclic citrullinated peptide antibodies; AMA: anti-mitochondrial antibodies; ASMA: anti-smooth muscle antibodies; ANCA: antineutrophil cytoplasmic antibodies; LAC: lupus anticoagulant; HRCT: high-resolution computed tomography; PFTs: pulmonary function tests; DLco: diffusion lung capacity for carbon monoxide.

[a] Past and/or present.