Sarcoïdose: *atteinte pulmonaire*

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DU Médecine Interne, 19 01 18

COI disclosure

- Pas de COI avec la présentation
- Membres de conseils scientifiques français et internationaux sur la FPI (Bohringer-Ingelheim, Roche)
- PI et Membre de *steering committee* sur le traitement de la FPI
- Lecture aux « avancées de pneumologie » (Astra)

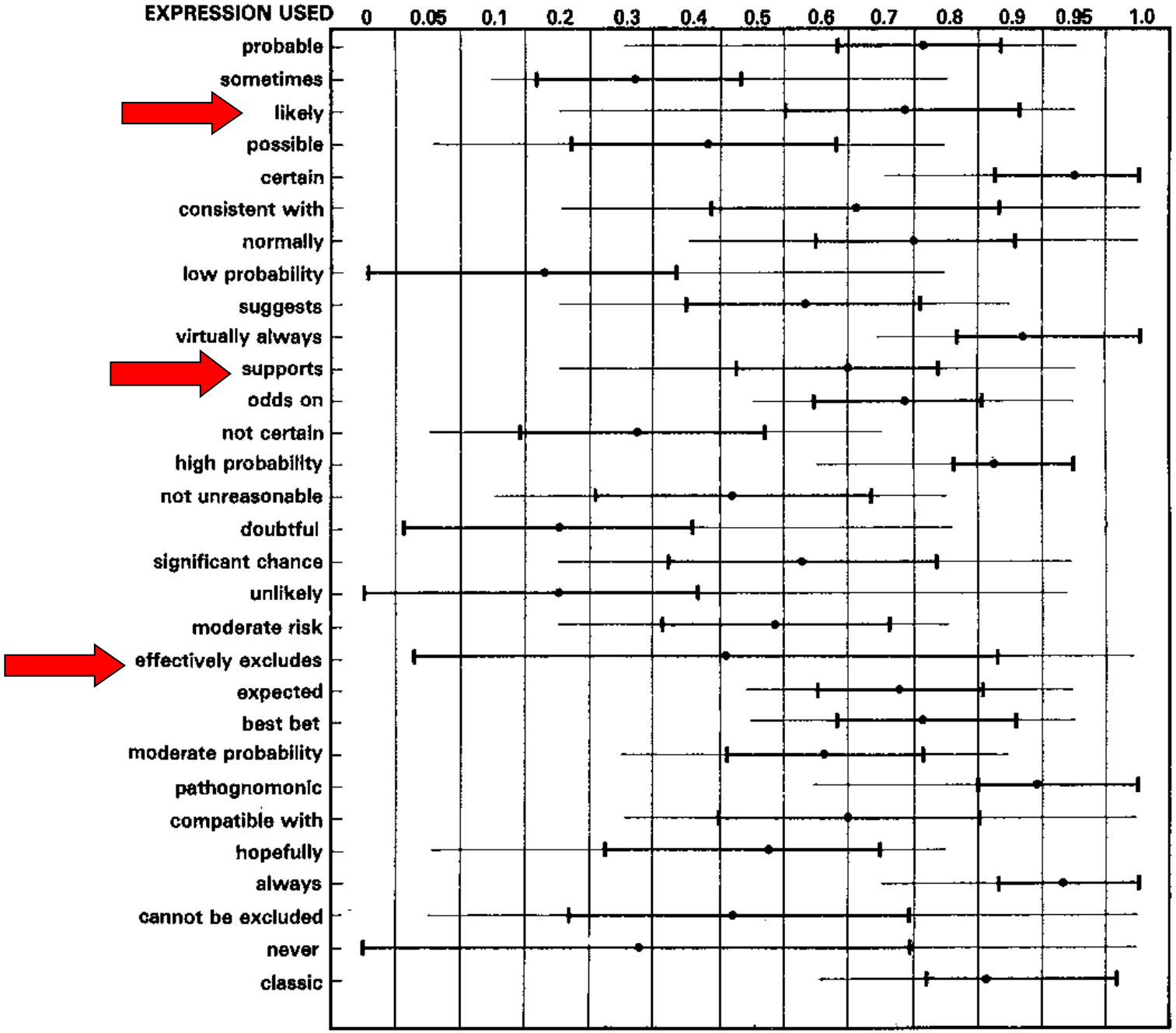
Introduction

- Diagnostic
- Work-up
- Diagnostic d’une dyspnée
- Monitorage du suivi
- Evolution sévère
  - HTP
  - CPA
  - Exacerbations aiguës
  - Critères pronostiques péjoratifs: algorithme de Walsh
- Conclusion

Diagnosis of sarcoidosis *per se*

- The diagnosis of sarcoidosis is based on the following*:
  - A compatible clinical and/or radiological picture
  - Histological demonstration of noncaseating granulomas
  - Exclusion of other diseases capable of producing a similar histological or clinical picture
- The diagnosis rests on**:
  - the correct clinical setting, typical chest radiograpic or CT appearances and
  - a biopsy showing non-caseationg granulomas

**Statement, AJRCCM 1999; **BTS guidelines, Thorax 2008*


EXPRESSION USED
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probable
sometimes
likely
possible
certain
consistent with
normally
low probability
suggests
virtually always
supports
odds on
not certain
high probability
not unreasonable
doubtful
significant chance
unlikely
moderate risk
effectively excludes
expected
best bet
moderate probability
pathognomonic
compatible with
hopefully
always
cannot be excluded
never
classic

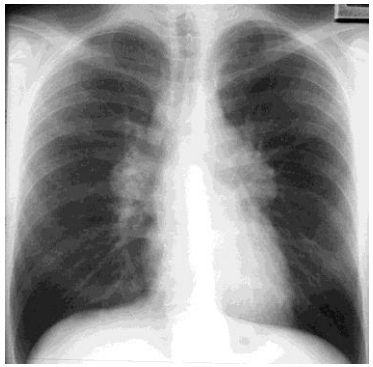
NEJM 1980

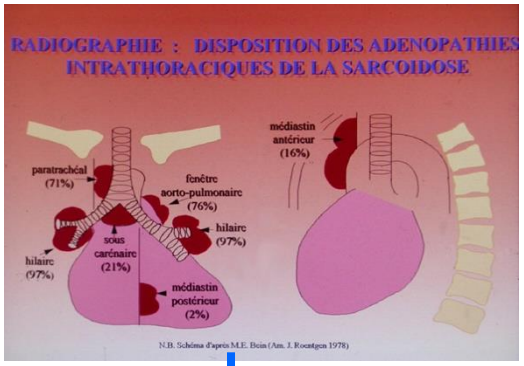
Diagnostic

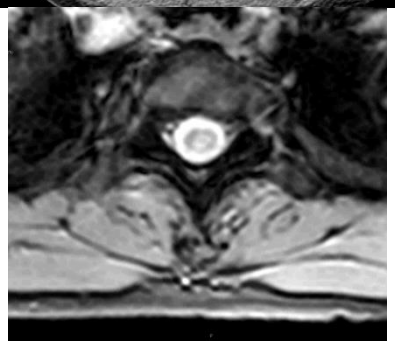
- 3 critères mais leur poids respectif dépend du scenario au Dc
- Retard Dc et recours à x Médecins avant un Dc
- « working diagnosis » +++: probabilité plus précise avec le temps
- Sites de prélèvements
  - Algorithme
  - EBUS (↕ médiastinoscopie)
  - Biopsie de GG périphériques sous échographie (PYB, SVDLD 2016)
  - Biopsie de nodule conjonctival
  - Site orienté par TEP

Judson Chest 2004; Baughman AJRCCM 2010; Culver Curr Opin Pulm Med 2015

Thoracic lymphadenopathy

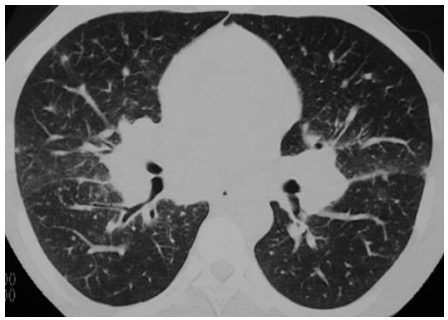






EN, uveitis, isolated

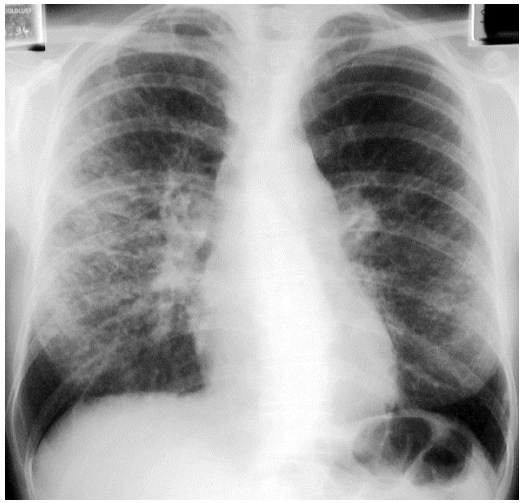
+ -

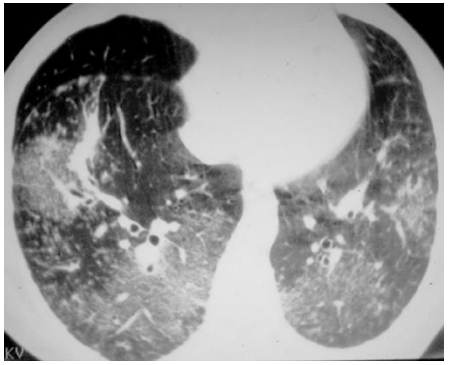


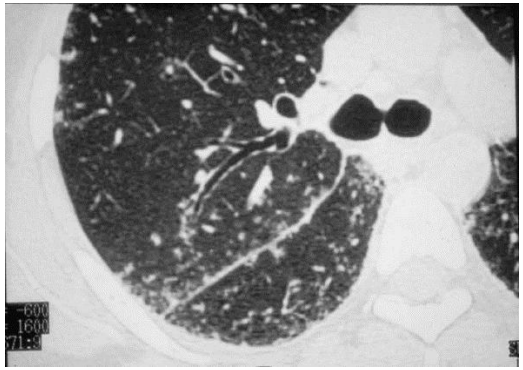
Bein AJR 1978: Neville OJM 1983: Butt SVDLD 2011

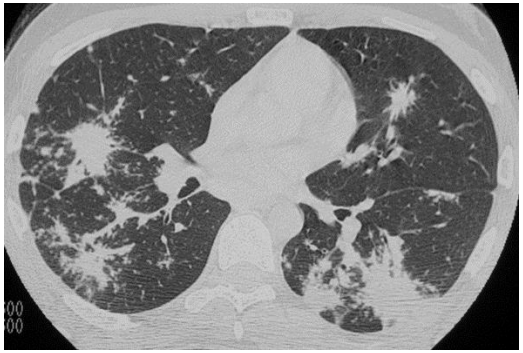
Lung perilymphatic micronodules

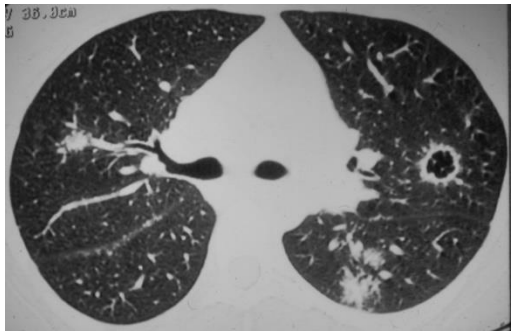
80% with diagnosis probability >95% using C + X Ray + CT*





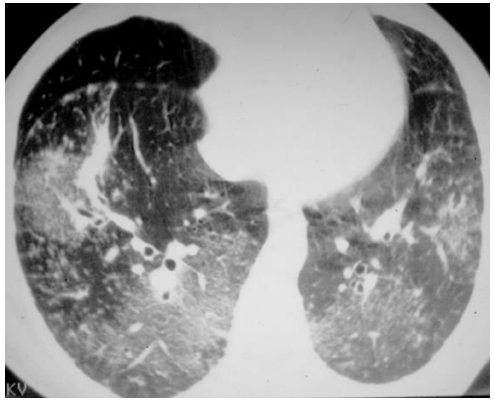




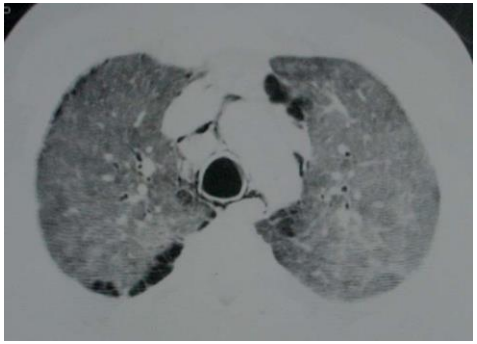


**Grenier Radiology 1994; Nakatsu AJR 2002; Martin Eur Radiol 2010; Criado RadioGraphics 2010; Hours Medicine 2008; Nunes ERJ 2013; Silva 2016; de Margerie-Melon SVDLD 2016*

Sarcoidosis vs other

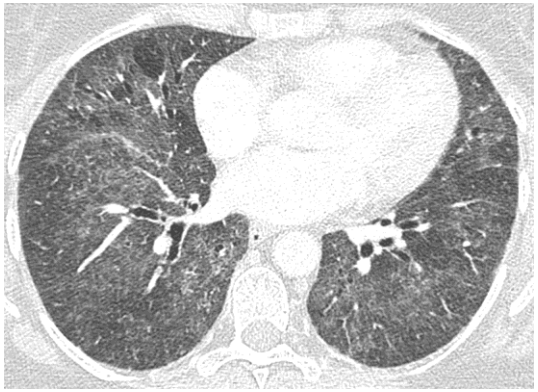


Sarcoidosis



Berylliosis

HP

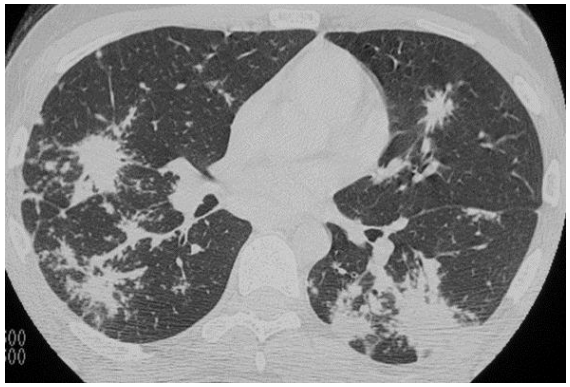


DIP

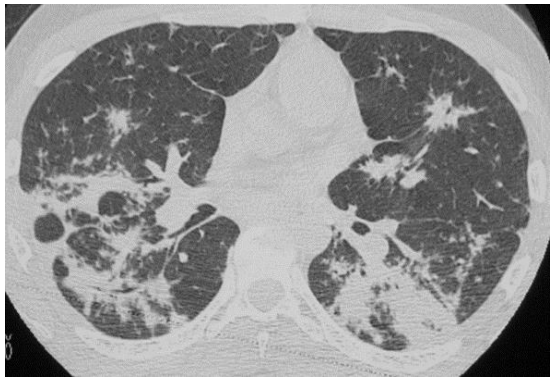
Drug-induced

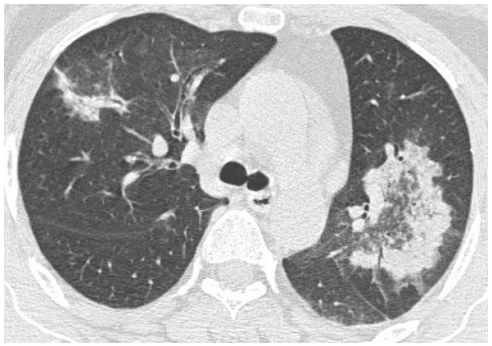
NSIP

Sarcoidosis vs other diagnoses (2)

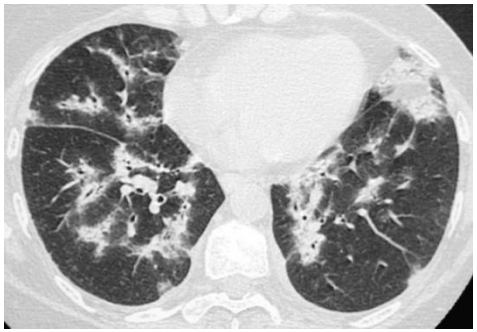


Sarcoidosis

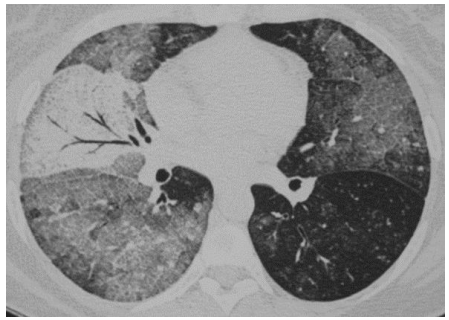




COP



BAC



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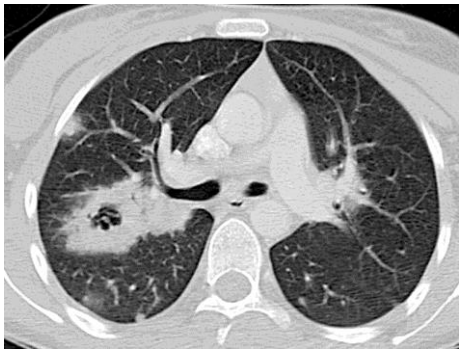
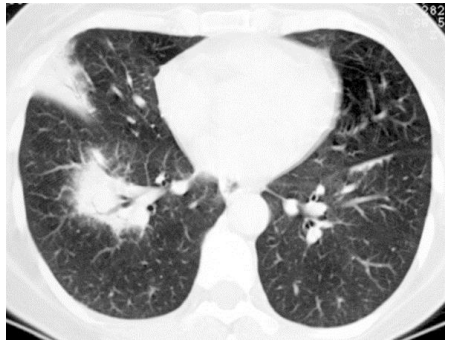
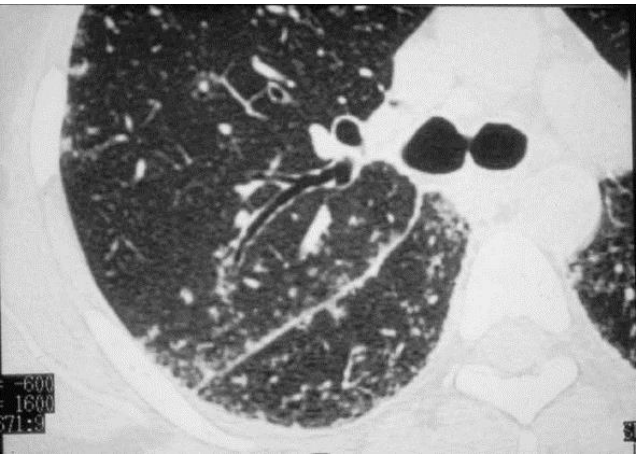


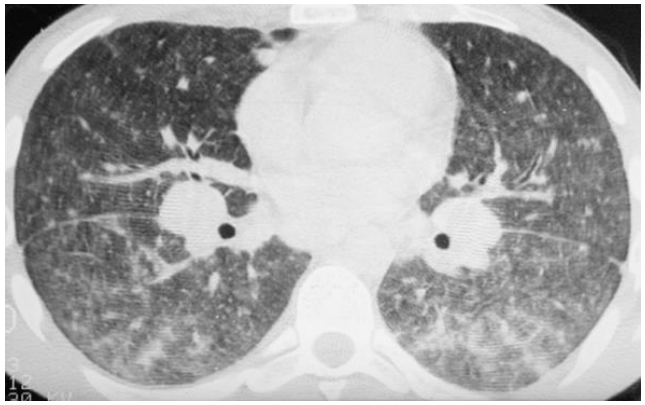


lymphoma

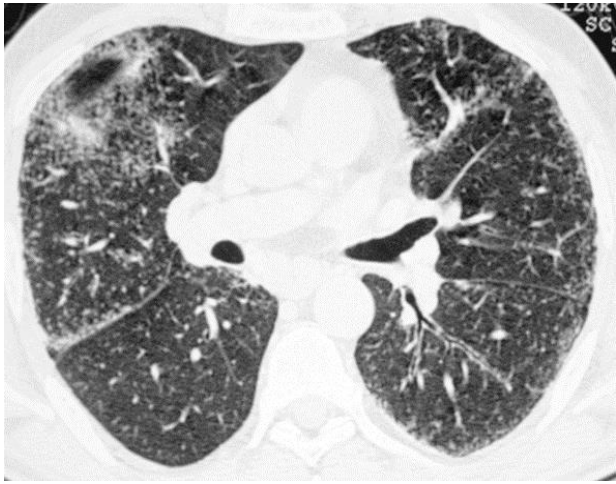
Sarcoidosis vs other diagnoses (1)



Sarcoidosis



Berylliosis



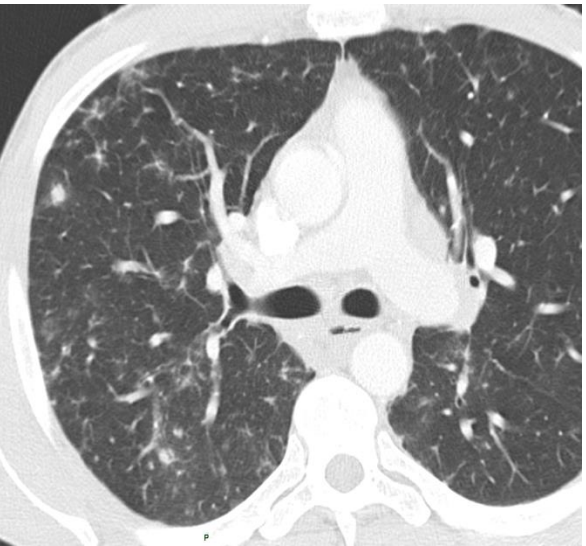
IFNβ-induced

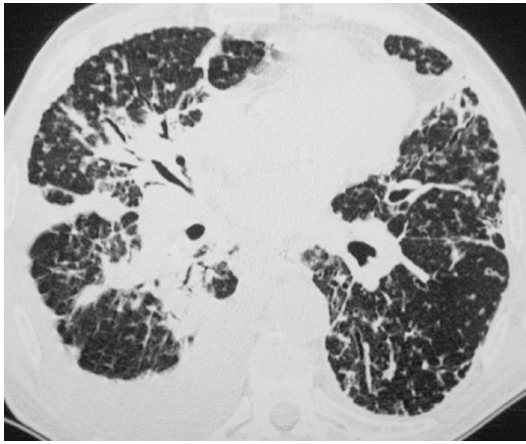
CVID

Bouvry ERJ 2013

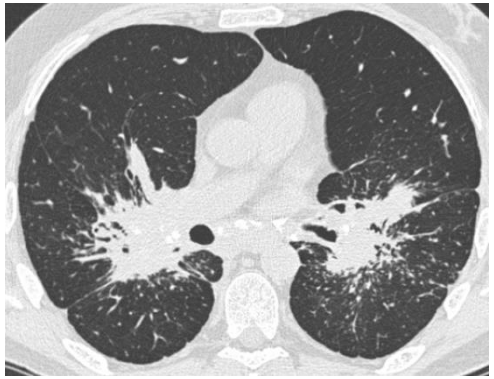
AL Amylosis

lymphoma



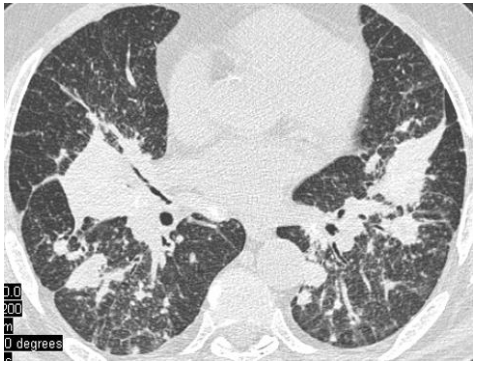


Sarcoidosis or not

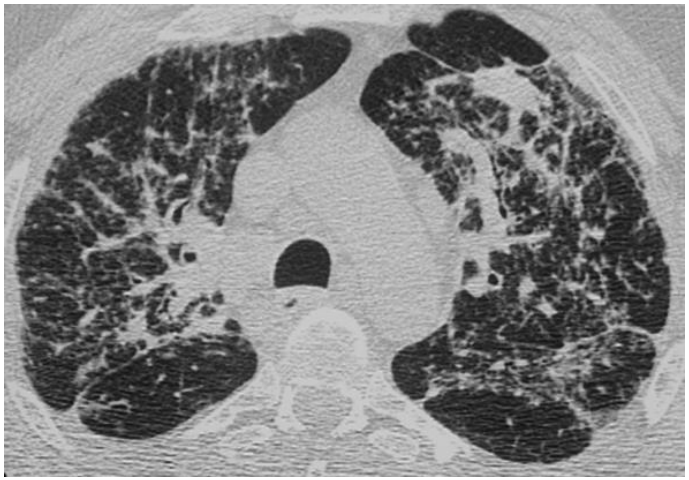


sarcoidosis

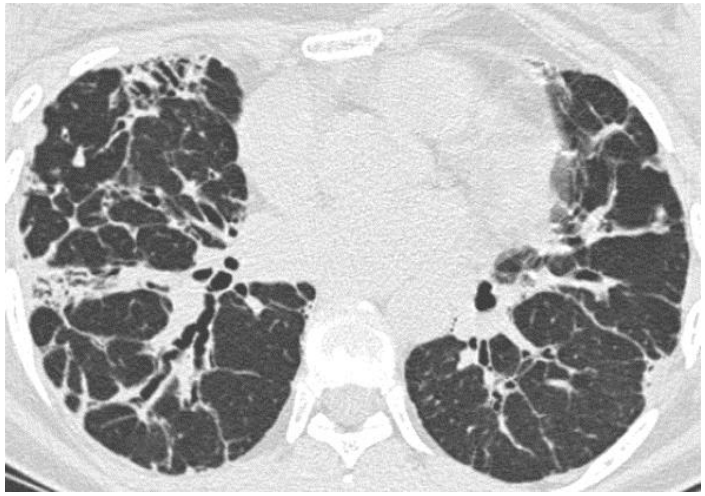
Sarcoidosis



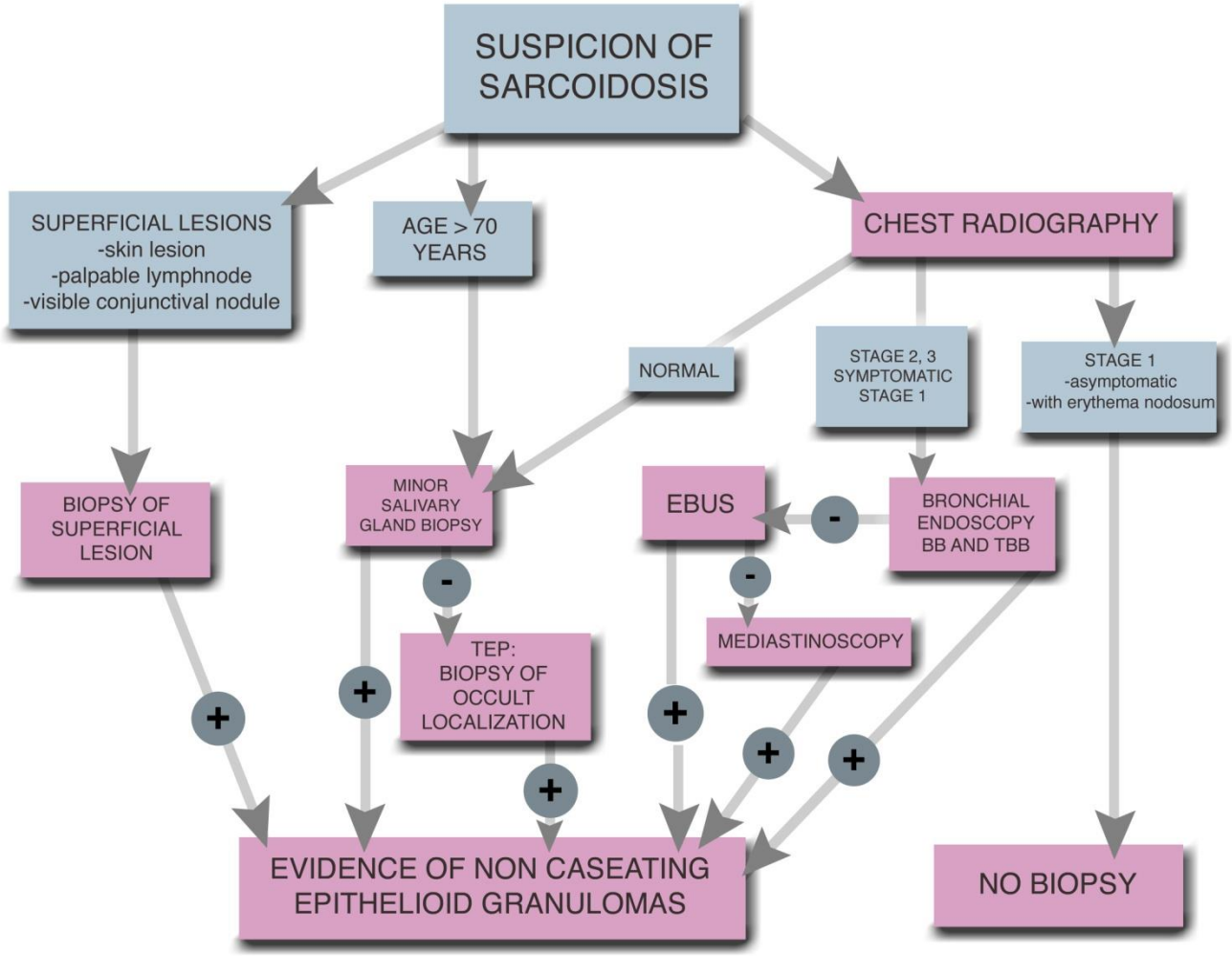
Silicosis



Sarcoidosis



PINS



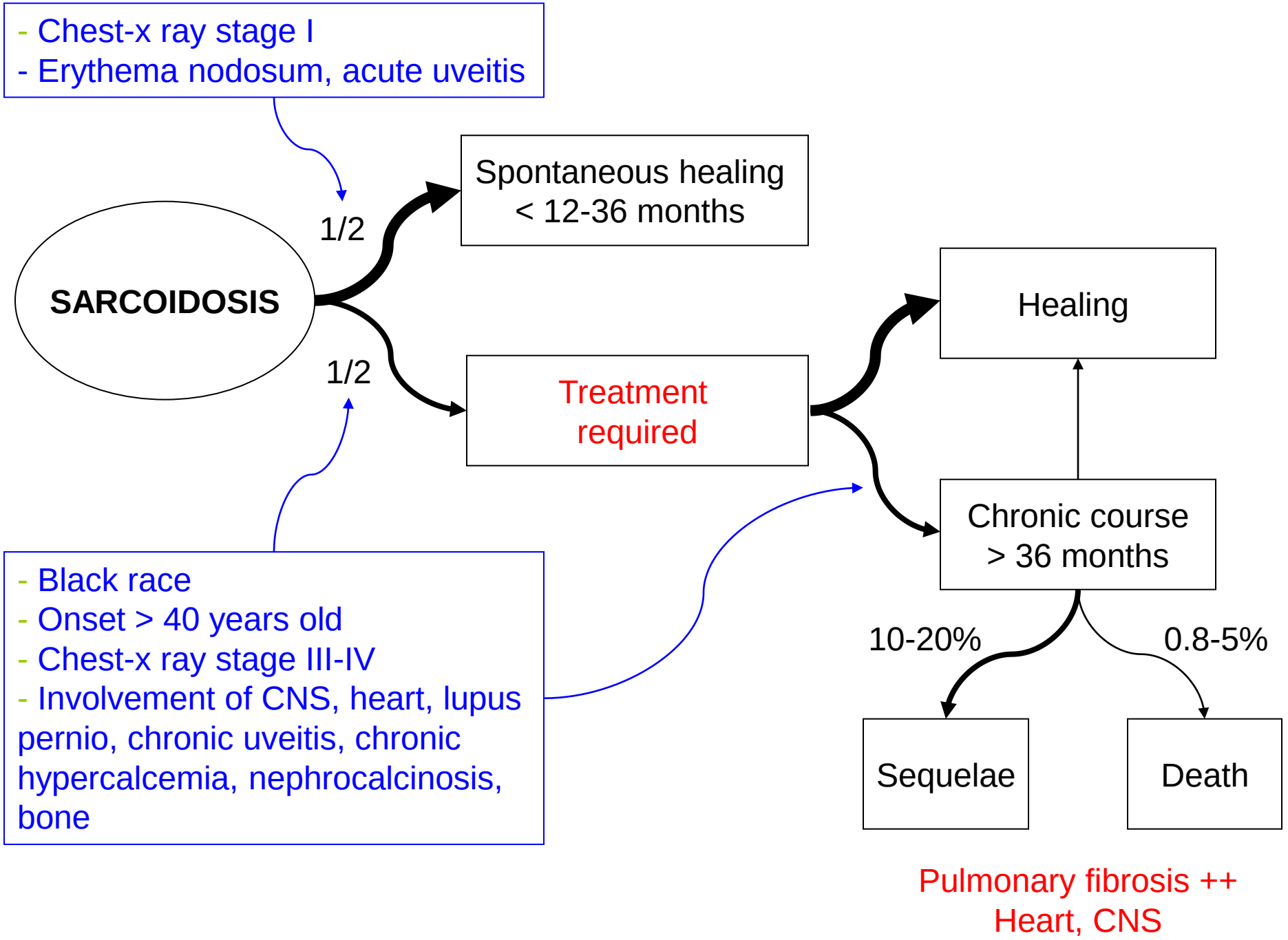
Valeyre Lancet 2014; Benouar SVDLD 2016

Diagnostic différentiel

	Main diseases	Etiological agent	Diagnosis criteria
Infections	Tuberculosis, histoplasmosis, leprosy, Whipple's disease	Infectious agents	Epidemiologic factors, microbiology
Environmental agents	Chronic beryllium disease	Beryllium	Exposure to beryllium; beryllium hypersensitivity
Drugs	Drug-induced granulomatosis	IFN α and β; anti-TNFα; intravesical BCG-therapy; natalizumab; alemtuzumab; inhibiteurs CTLA4; inhibiteurs PD1 et PDL1	Anamnesis
Immuno-deficiency	Common variable immuno-deficiency; Chronic granulomatous disease	-	Recurrent infections ; hypogammaglobulinemia Recurrent pyogenic infections ; defective respiratory burst in phagocytes
Genetic disease	Blau's syndrome	-	Presentation; familial history; genetic investigation
Proliferations	Lymphomas Solid neoplasias	-	Pathology; molecular biology
Unknown origin	Wegener's granulomatosis Crohn's disease Primiray biliary cirrhosis	-	Presentation; ANCA Presentation Presentation ; anti-mitochondrial antibodies ; pathology

Examens respiratoires lors du workup Dc

- Incontournables
  - Rx simple thorax
  - Spirométrie + DLCO: Courbe débit-volume +++
  - Endoscopie (presque toujours)
- Dans certains cas
  - TDM (le plus souvent non injecté)
  - Diagnostic difficile; complication; signe non univoque
  - Ne pas répéter sauf exception
  - TM6
- Rarement
  - Pet/FDG


- Chest-x ray stage I
- Erythema nodosum, acute uveitis
SARCOIDOSIS
1/2
1/2
Spontaneous healing
< 12-36 months
Treatment
required
Healing
Chronic course
> 36 months
10-20%
0.8-5%
Sequelae
Death
- Black race
- Onset > 40 years old
- Chest-x ray stage III-IV
- Involvement of CNS, heart, lupus pernio, chronic uveitis, chronic hypercalcemia, nephrocalcinosis, bone
Pulmonary fibrosis ++
Heart, CNS

Causes of dyspnea during sarcoidosis

- Lung (restrictive)
- Lower airways involvement (A.O.)
- Pulmonary hypertension
- Congestive heart disease
- Abnormal sympathic control of heart frequency
- Neuro-muscular causes
- Co-morbidities: asthma; pulmonary embolism etc…

Wallaert Respiration 2011

Lower airways involvement

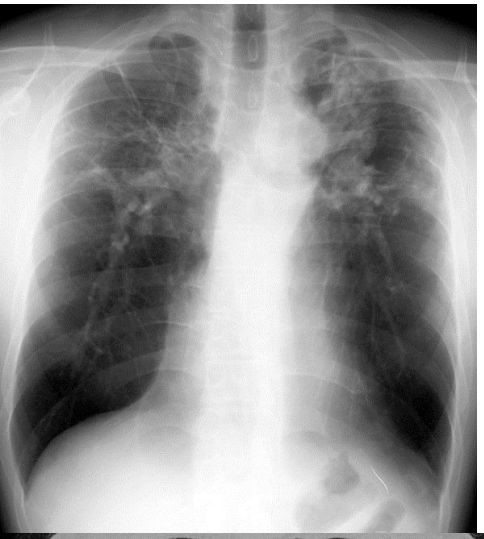
- Symptoms
  - Dry cough (19% → 89%); dyspnea (out of proportion/Chest X-ray); wheezing; hemoptysis; recurrent infections
- Investigations → help diagnosis of severe involvement
  - Chest X Ray and CT
  - Bronchial endoscopy
  - Pulmonary function

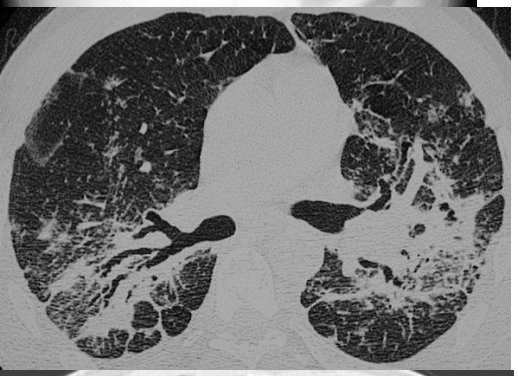
Airflow obstruction

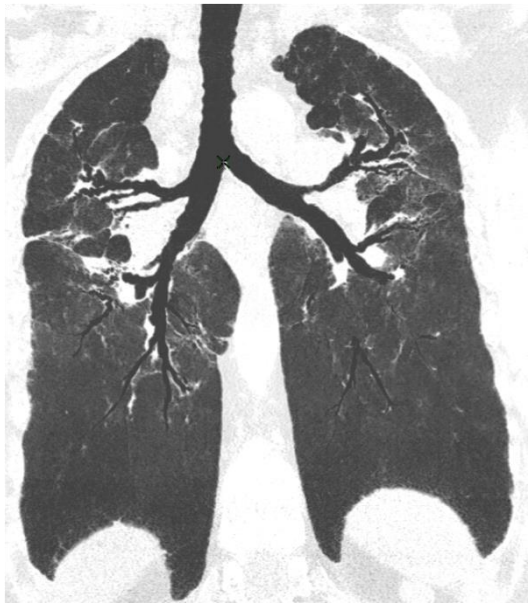
- Multiple mechanisms of A.O. even for a single patient
- Easy detection of two main mechanisms
  - Bronchial distorsion (stage IV)
  - Bronchial granulomatosis (stage I–III)
- Other less frequent mechanisms
  - Bronchial compression by Adenopathies
  - Localized bronchial stenosis (stage I-III)
  - Distal bronchiolitis
  - Airways hyperreactivity
  - Bronchomalacia

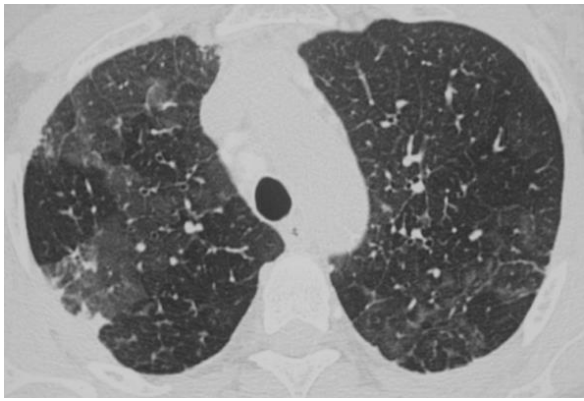
Hansell Radiology 1998; Lavergne Chest 1999; Chambellan Chest 2005; Handa Chest 2006; Naccache JCAT 2008; Abehsera AJR 2000

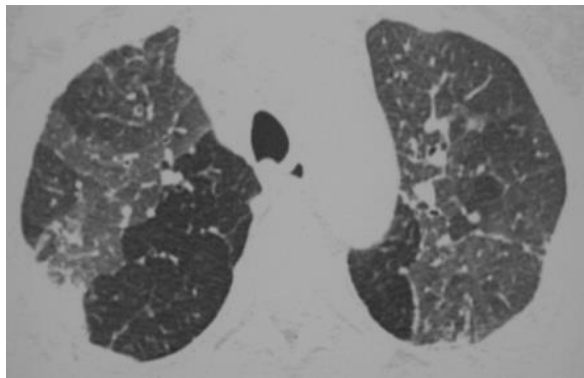
CT imaging of lower airways





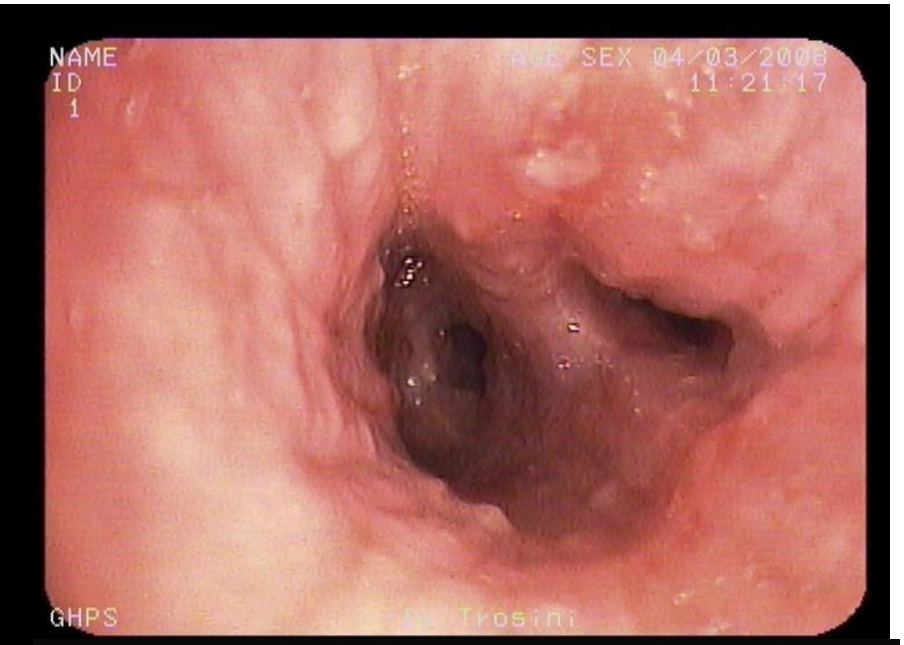


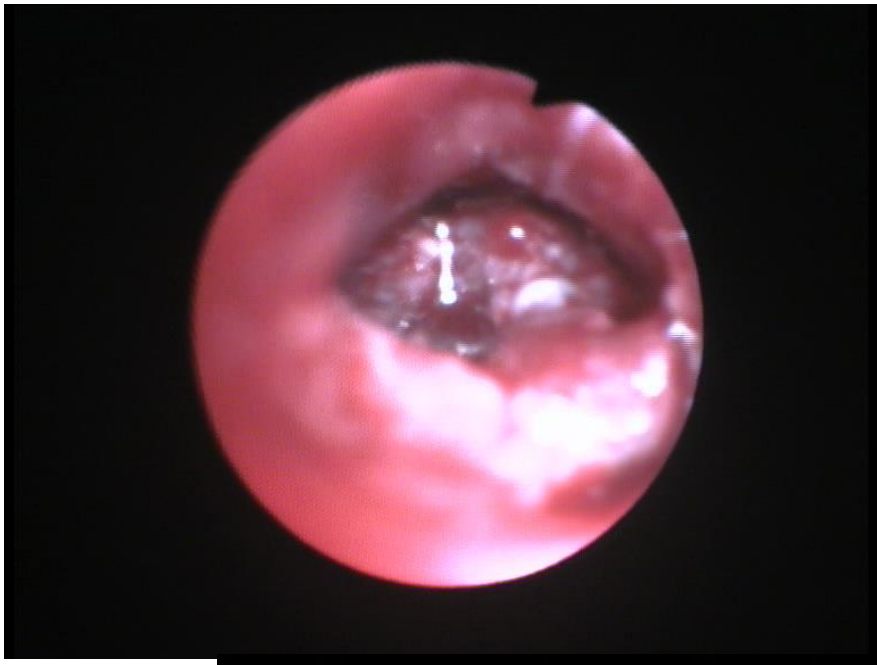


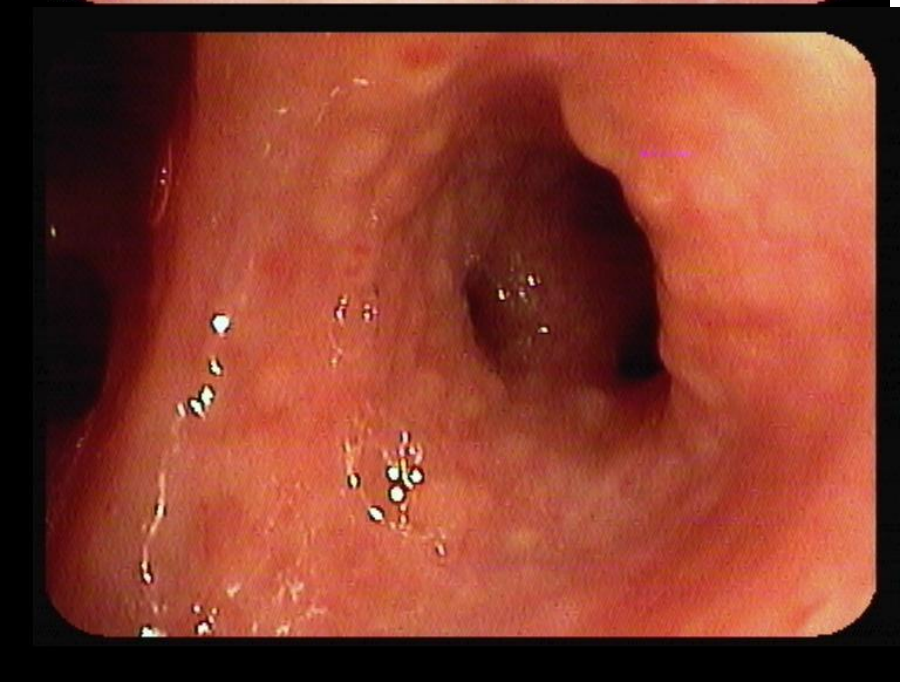


Remeciements: Pr M Brauner

Endoscopic aspects







Remerciements:
Valery Trosini,
JM Vergnon

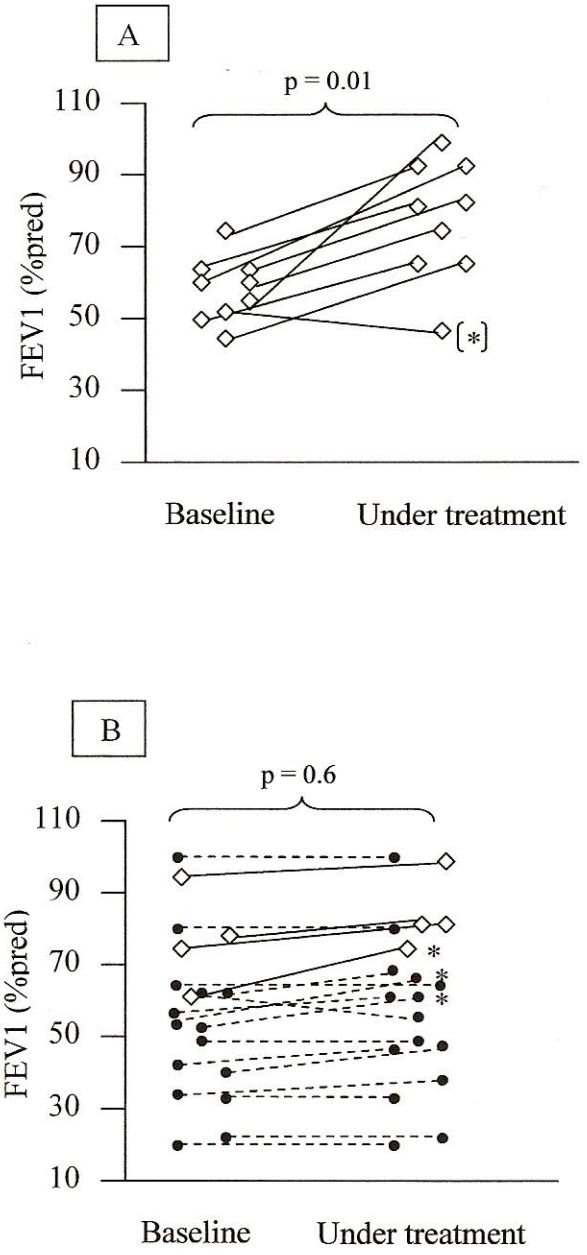
Predictive value of CT on FEV1 response to treatment

Predominant perbronchic thickening

Predominant bronchial distorsion

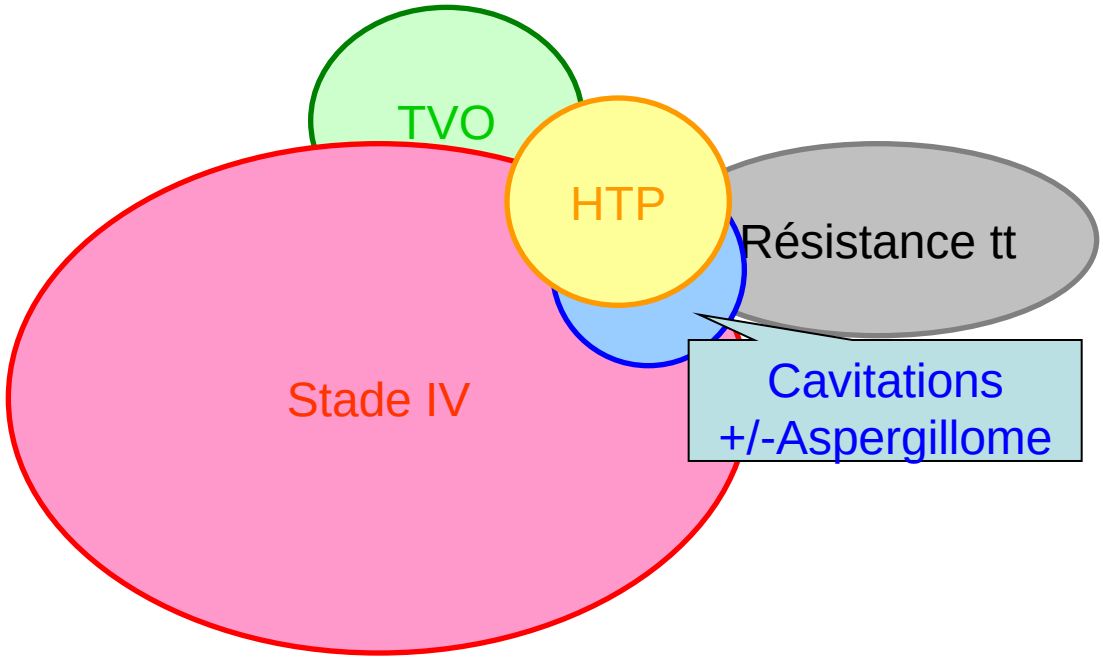
Naccache JCAT 2008

Figure 6:



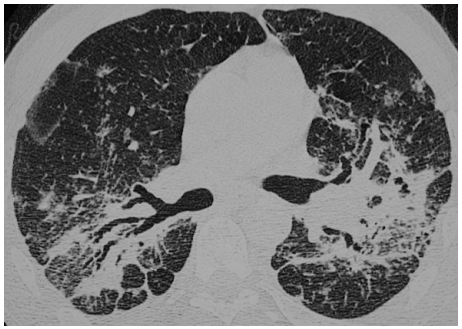
Sarcoïdose pulmonaire sévère

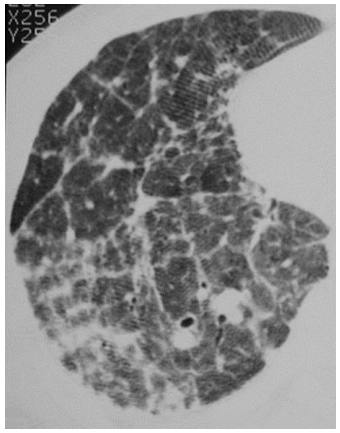
Formes particulières

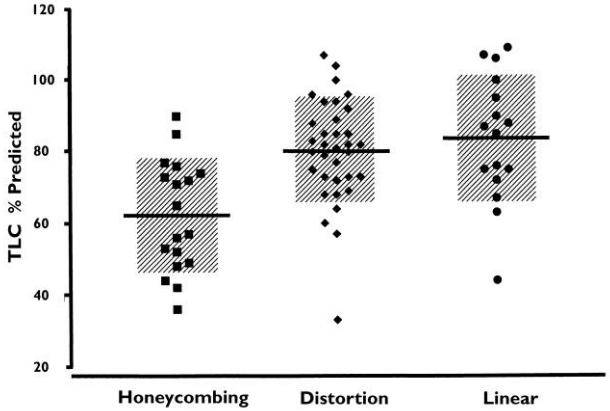


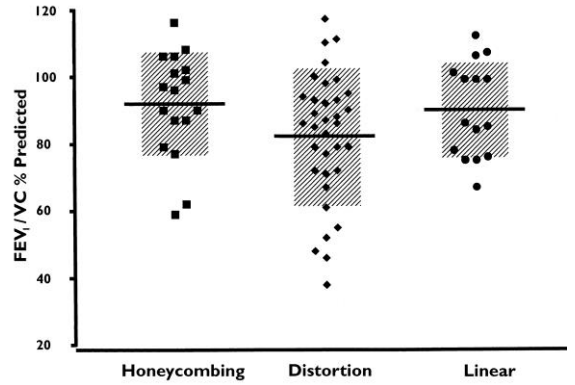
Sarcoïdose stade IV
Patterns TDM et profil EFR

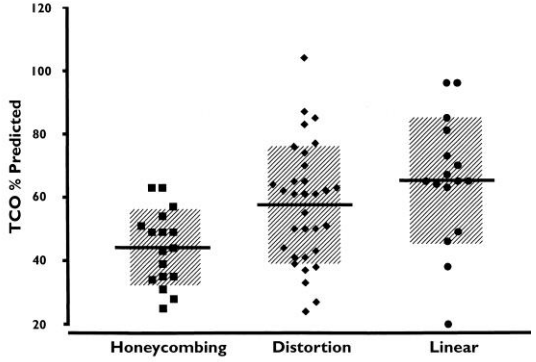
Fréquence: 5.5% au Dc et 10% lors suivi











Baughman 2001; Ianuzzi 2007; Abesehra AJR 2000; Nardi ERJ 2011

Sarcoïdose et HTP

- Prévalence 5-74%
- Disproportionnée
- Mécanismes ≠
  - –Destruction of the capillary bed by lung fibrosis
  - –Hypoxaemia
  - –External compression of pulmonary arteries
  - –Portal hypertension due to sarcoid liver localization
  - –Specific vascular involvement (69 -100 %)
- Venous involvement is predominant by far:
  - ✓Venous involvement: 92%, exclusive: 61%
  - ✓Mixed involvement: 31%
  - ✓Exclusive arterial involvement: 8%

Rosen, *Arch Pathol Lab Med* 1977

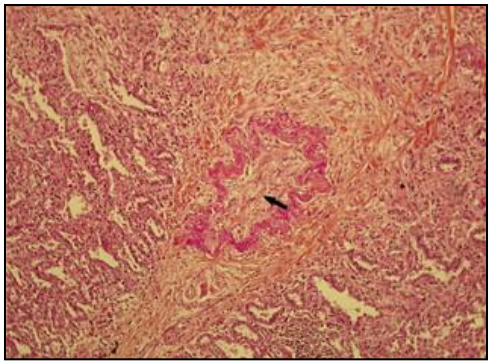
MVO

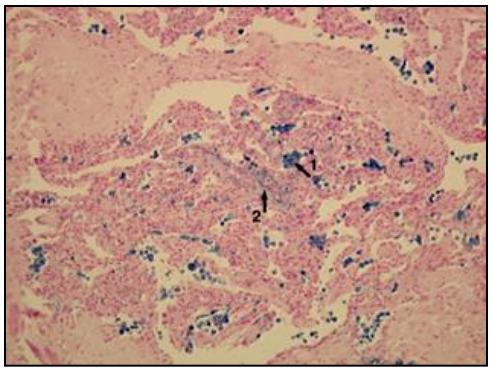
Septal veins intimal occlusive fibrosis: 5/5

n=5 (pulmonary explants)

Chronic hemosiderosis: 5/5

- ✓ Alveolar Haemorrhage
- ✓ Iron deposts in the elastic layer





Nunes, Thorax 2006, Boucly ERJ 2017

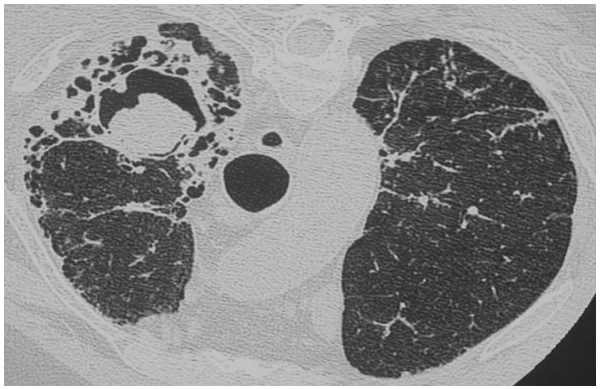
Sarcoïdose cavitaire

- ~4% des cas de sarcoïdose
- Phénotype:
  - chronique; 50% stade IV;
  - évolutivité; x-viscérale;
  - sévérité; traitement >12 mois
- Complications: 35% des cas
  - hémoptysies;
  - aspergillome;
  - autres surinfections;
  - pneumothorax

Hours Medicine 2007

Aspergillome

- Hemoptysis
- Poor survival
- Stage IV
- Variable prevalence
- Environemental factors ?



Tomlinson 1987; Wollschlager 1984; Israel 1982; Jones 1999; Uzunhan ERJ 2017

Explorations respiratoires lors du suivi

- Tous les 3-6-12 mois et après arrêt du tt
- Rx
- Explo fonctionnelles: courbe débit-volume: modification plus fiable que Rx: en fait clinique + Rx + EFR ++++
- Pas de TDM ++++ sauf argumentation

Monitoring change in pulmonary sarcoidosis

- Explore strategies with serial PFT and chest radiography against CT changes
- 63 patients with sarcoidosis with 2 x (concurrent Chest Rx + PFT + CT)
- Results:
  - Moderate agreement Rx-CT trends (Kw=0.46)
  - Good agreement PFT(alone)-CT trends (Kw=0.64)
  - No improvement with integrating Rx or DLCO
- Conclusion:
  - « PFT trends alone » constitute the best serial strategy to investigate changes in pulmonary sarcoidosis

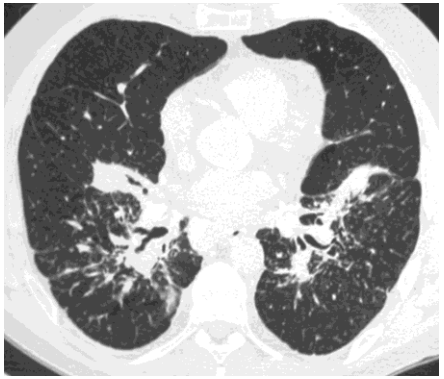
Zappala Chest 2014

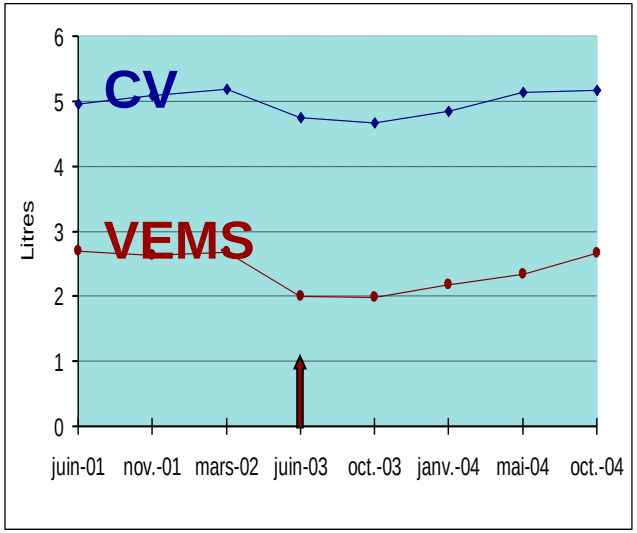
Acute worsening events in fibrotic pulmonary sarcoidosis patients*

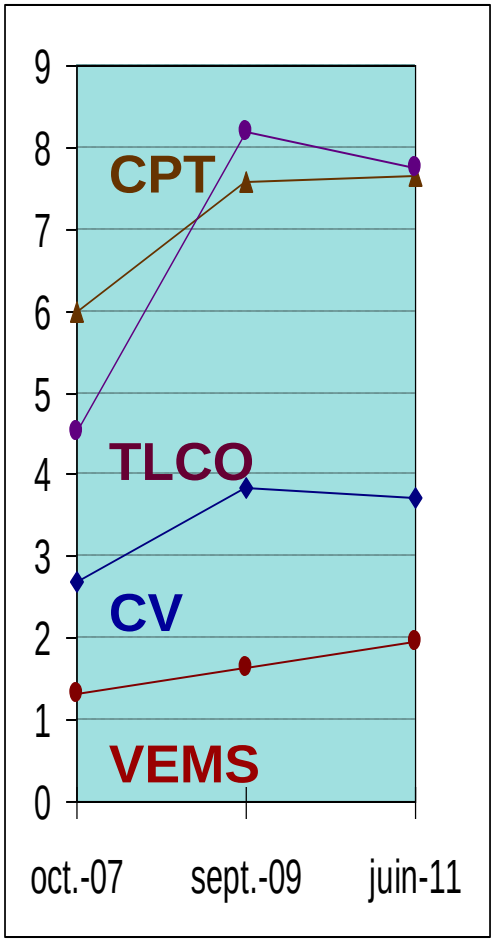
- Various causes of acute worsening in pulmonary sarcoidosis**
  - Worsening of underlying sarcoidosis
  - Infection
  - Acute bronchospasm
  - Extra-pulmonary causes
- fibrotic sarcoidosis (n=129) seen during a 4 month period (49% with bronchiectasis at CT)
- Definition of acute worsening: need for antibiotics or short duration increase of steroids
- mean=3 acute worsening episods (0-6) in the last year
- Bronchectasis or antiTNF treatment were associated with more frequent acute worsening events

Baughman RP Respiratory Medicine 2013; Panselinas Chest 2012***

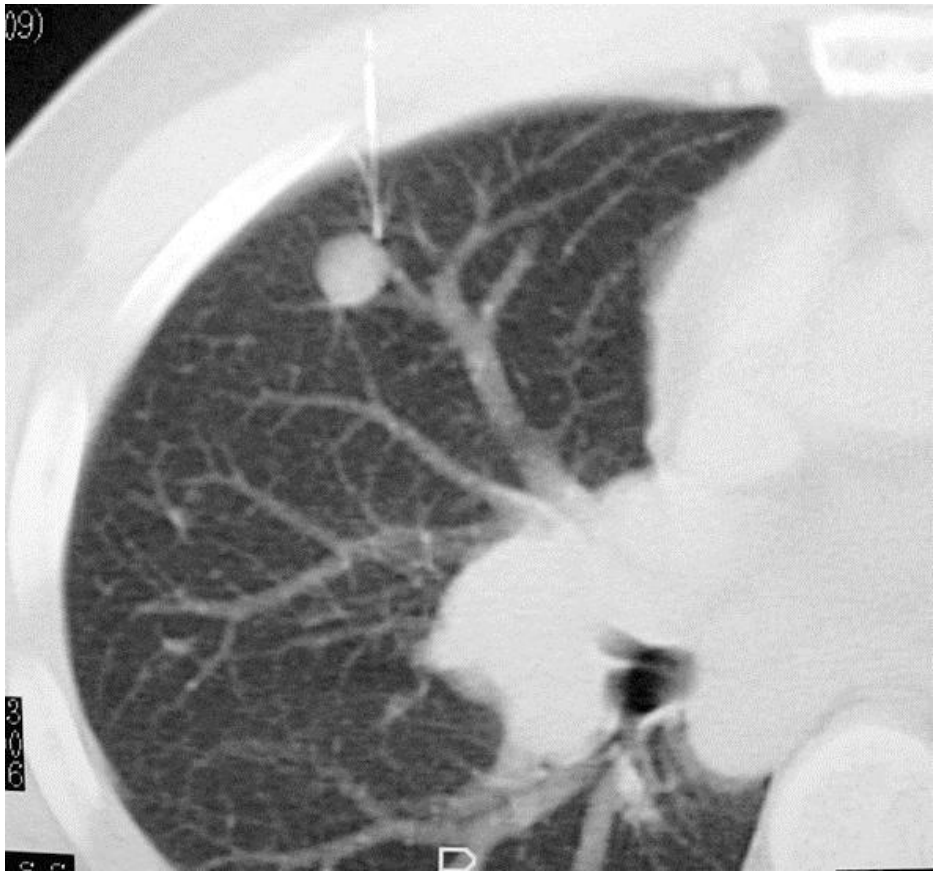
Pitfals when interpreting evolution



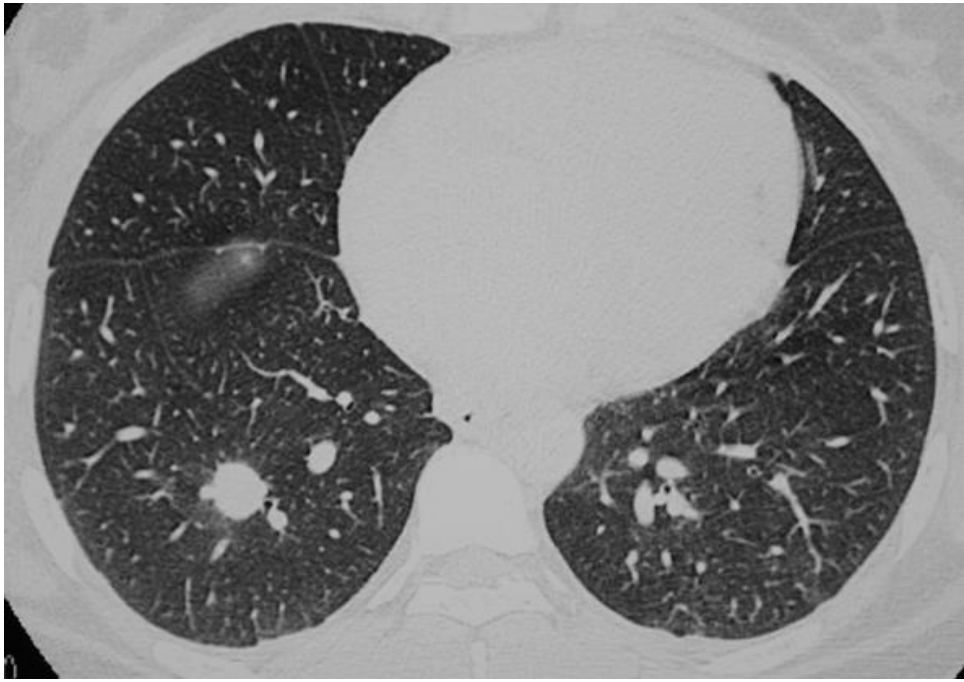




Judson Respirology 2008



Nodule unique sarcoïdien

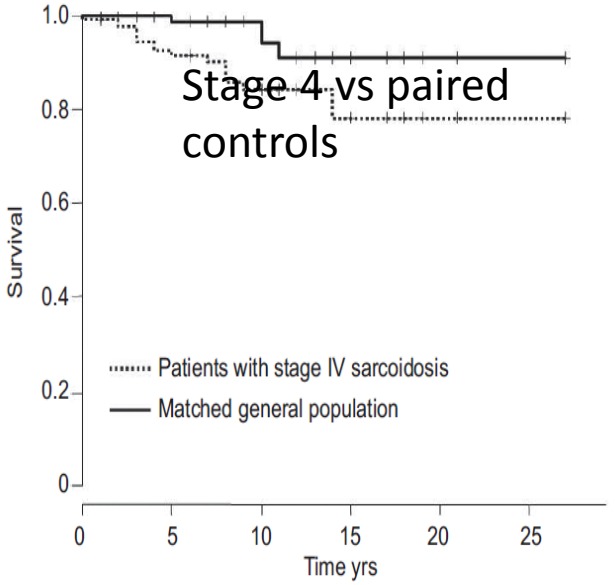


AdénoK

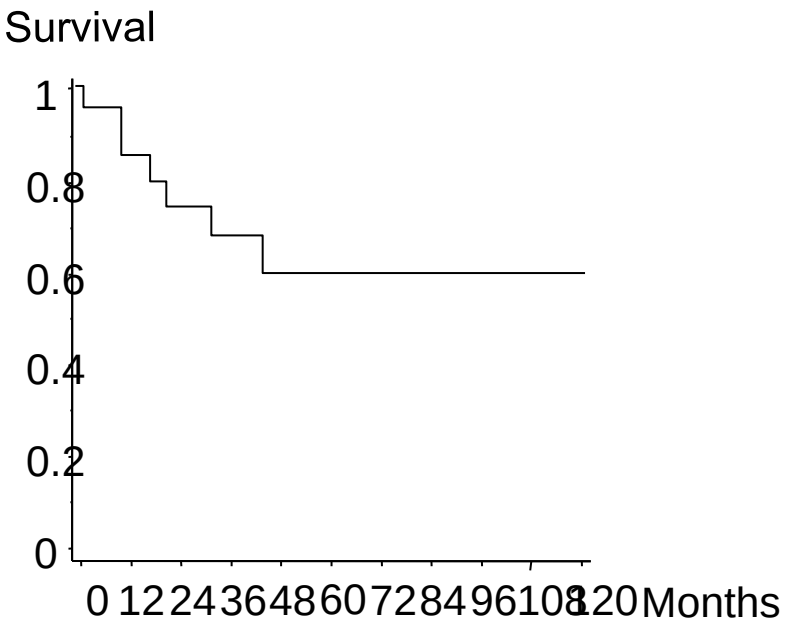
Predicting survival in advanced pulmonary sarcoidosis

- Factors known to be linked to mortality
  - PH both in patients listed for transplantation or not
  - Significant pulmonary fibrosis (stage 4)
  - FVC <1.500 mL
- Predicted survival using the integrated clinicoradiological staging system for pulmonary sarcoidosis
  - CPI (FVC, DLCO and FEV1)
  - CT: extent of fibrosis and main pulmonary artery diameter
    → algorithme de Walsh
- Confirmation
  - on a separate cohort … in the same center and in subgroups
  - Confirmed in two external cohorts
- Perspectives

Baughman SVDLD 1997; Nardi ERJ 2011; Walsh Lancet RM 2014; Kirkil Chest 2017



Sarcoidosis with PH



Advanced sarcoidosis with vs without aspergilloma

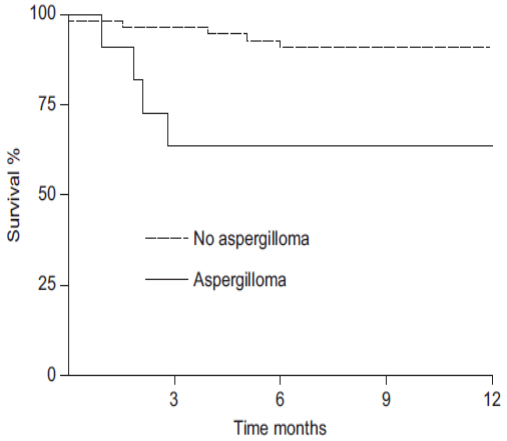
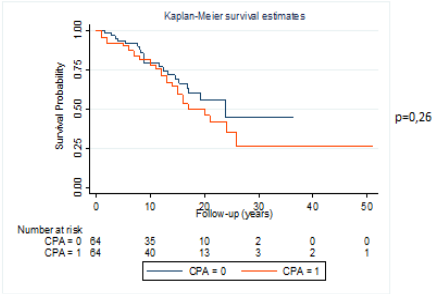


FIGURE 8. Kaplan–Meier survival curves of patients with advanced sarcoidosis stratified by the presence (n=11) or absence (n=57) of aspergillomas. Data from Inova Fairfax Hospital (Falls Church, VA, USA); September, 2006; p=0.009.



	Cases (n=64)	Controls (n=64)	p
Sex Male, N (%)	43 (67,1)	32 (50)	0,07
Geographic origin (SS or AC), N (%)	21 (32.8)	21 (32.8)	1
Age at stage 4 (mean)	43	41.8	0,66

Nardi ERJ 2011; Shorr Chest; Shlobin ERJ 2012; Uzunhan ERJ 2017

	Hazard ratio (95% CI)	p value
Extent of fibrosis	1·03 (1·01–1·04)	0·002
CPI	1·04 (1·02–1·06)	<0·0001

CPI=composite physiological index. HRCT=high-resolution computed tomography.

Table 2: **Mortality expressed as hazard ratios on multivariate analysis for HRCT patterns and pulmonary function tests including the CPI in sarcoidosis group A (n=251)**

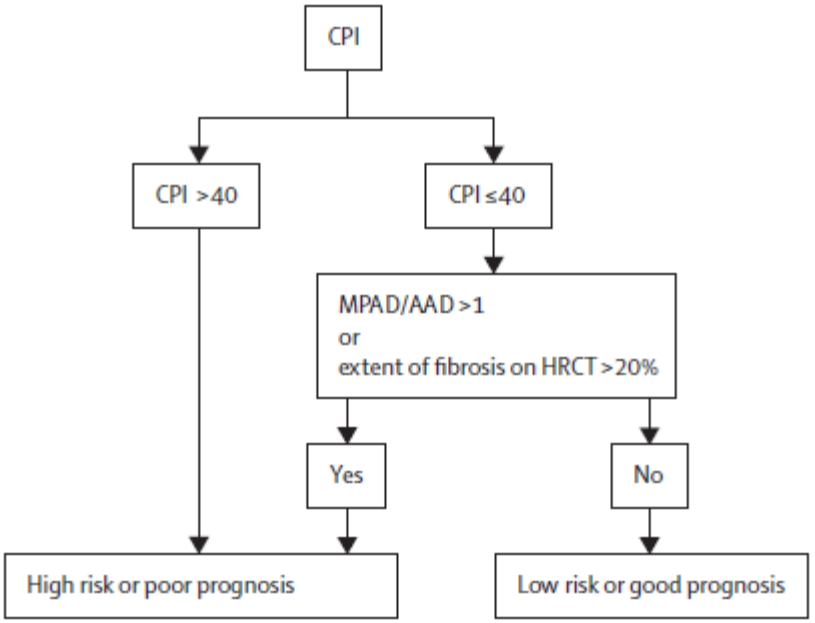


Figure 1: **Clinical staging algorithm for stratification of clinical risk in pulmonary sarcoidosis**

Walsh Lancet RM 2014

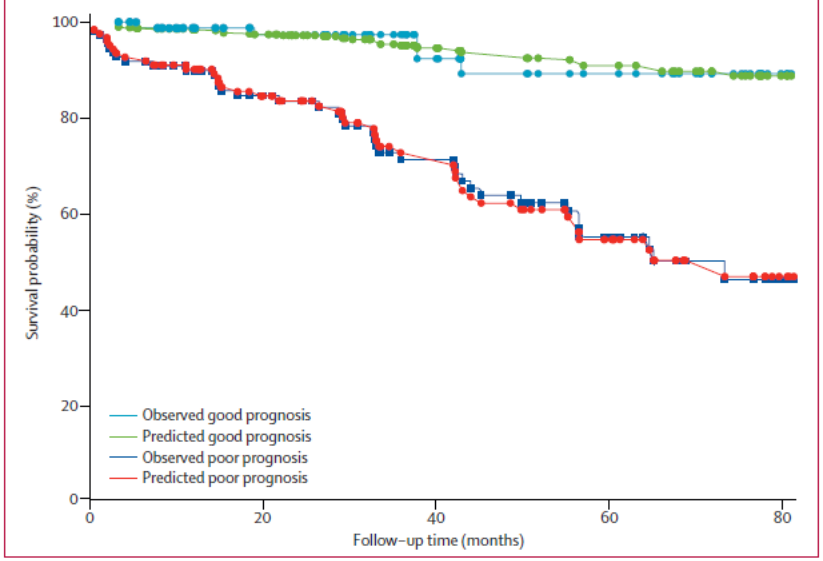
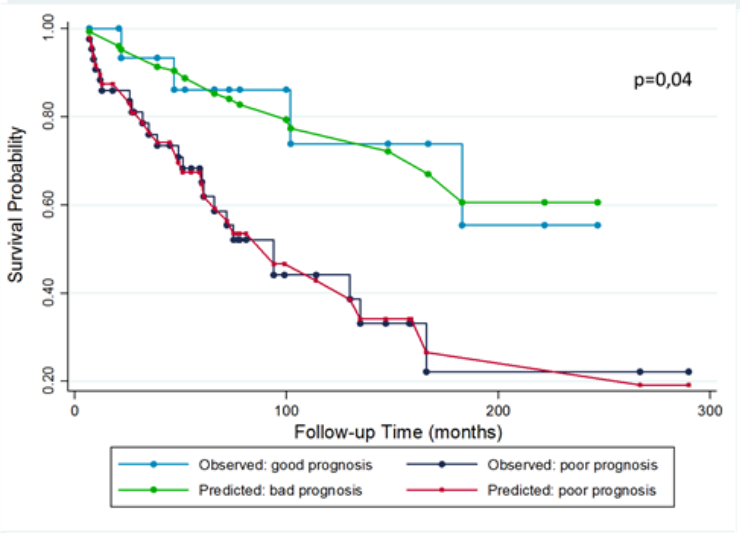


Figure 2: Comparison of survival predicted by the sarcoidosis staging model with observed Kaplan-Meier estimates in the derivation cohort (group A, n=251)



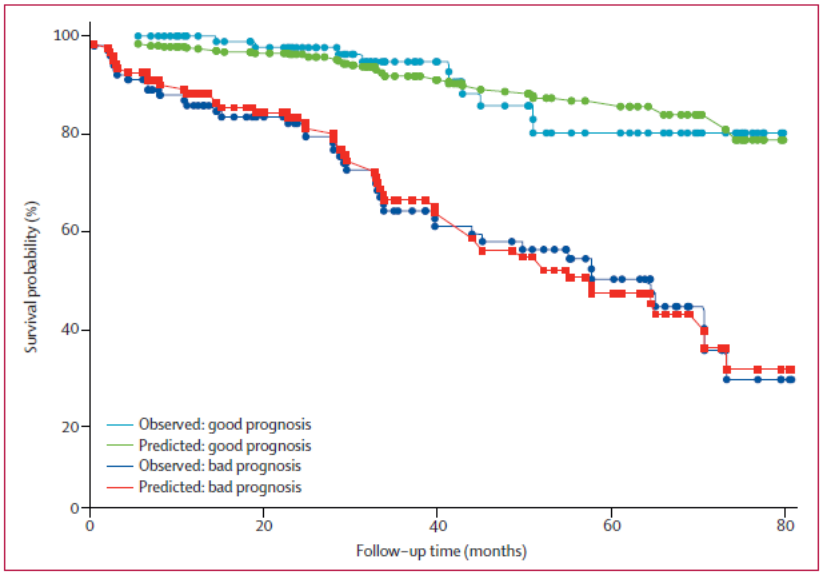


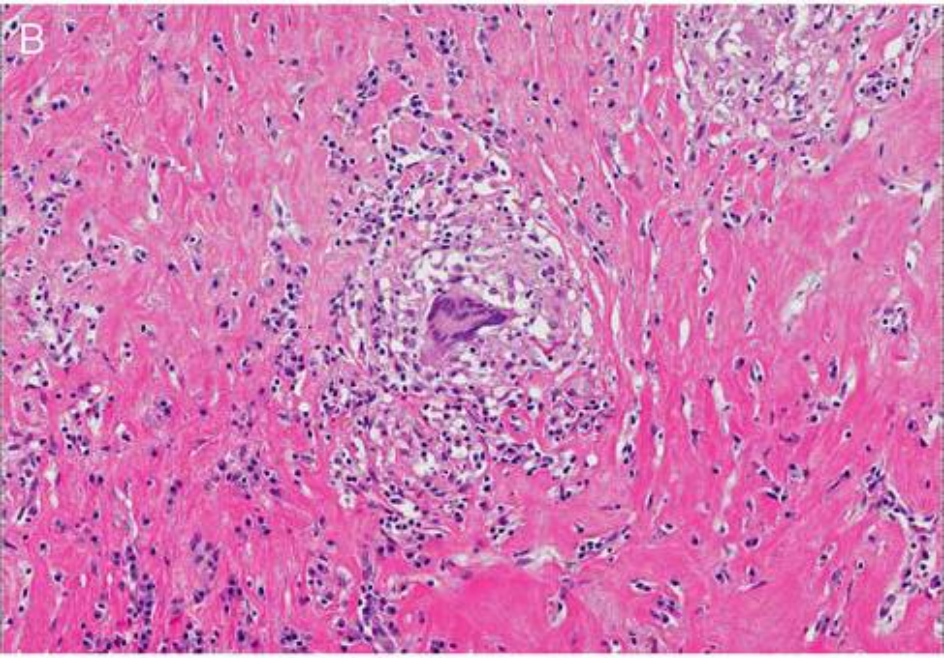
Figure 3: Comparison of survival predicted by the sarcoidosis staging model with observed Kaplan-Meier estimates in the test cohort (group B, n=252).

Walsh 2014; Uzunhan ERJ 2017 sous presse

End-stage sarcoid lung disease is distinct from UIP*

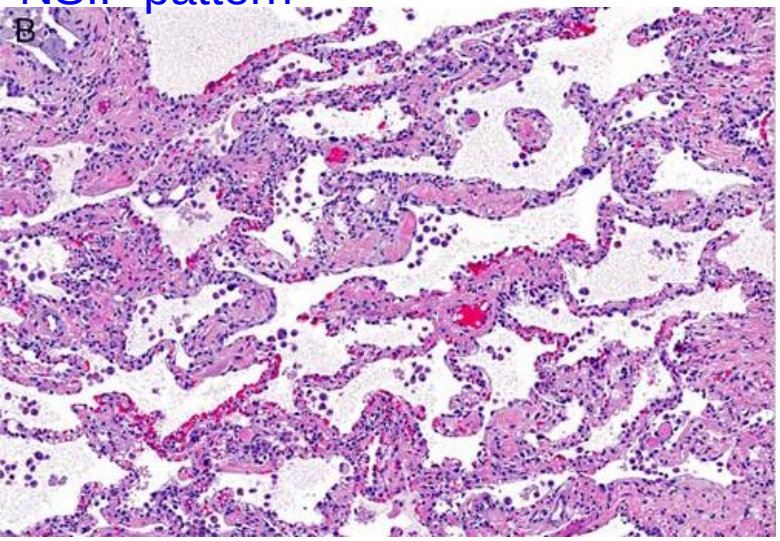
- UIP: due to sarcoidosis** or co-morbidity***?
- Histology from 9 lung explants with end-stage pulmonary sarcoidosis*
- 2 pathologic patterns
- Persistent of significant granulomatous components in half of cases
- Areas of NSIP (n=6)
- Fibrotic phase distinct from UIP
  - Post-granulomatous fibrosis may occur
  - HC in the middle and upper lung zone but sparing bases and more centrally
  - Mucin 5 B promoter polymorphism is associated to IPF but not sarcoidosis****

Xu Am J Surg Pathol 2013*; Shigemitsu ERJ 2010**;
Tachibana Internal Medicine 2012***; Stock Thorax 2013****; Valeyre Curr opin Pulm Dis 2014

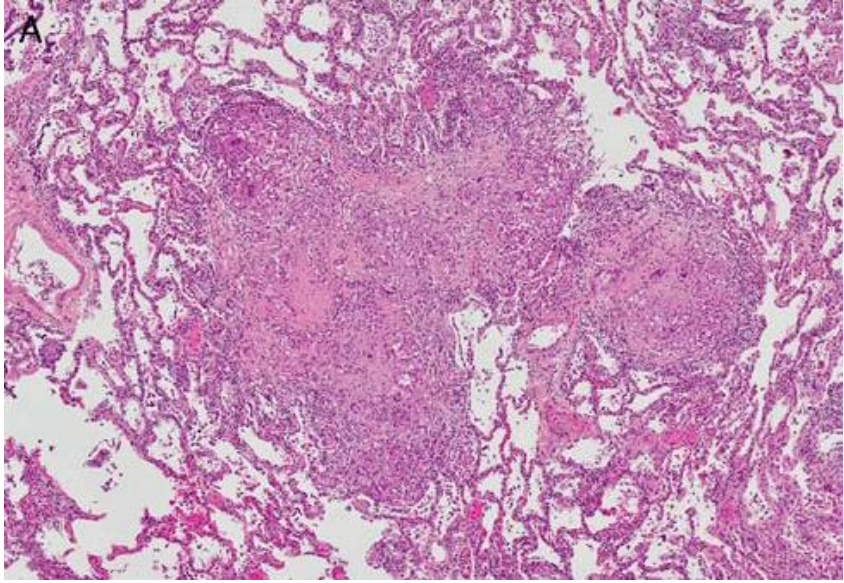


Granulomas embedded in dense scars

NSIP pattern



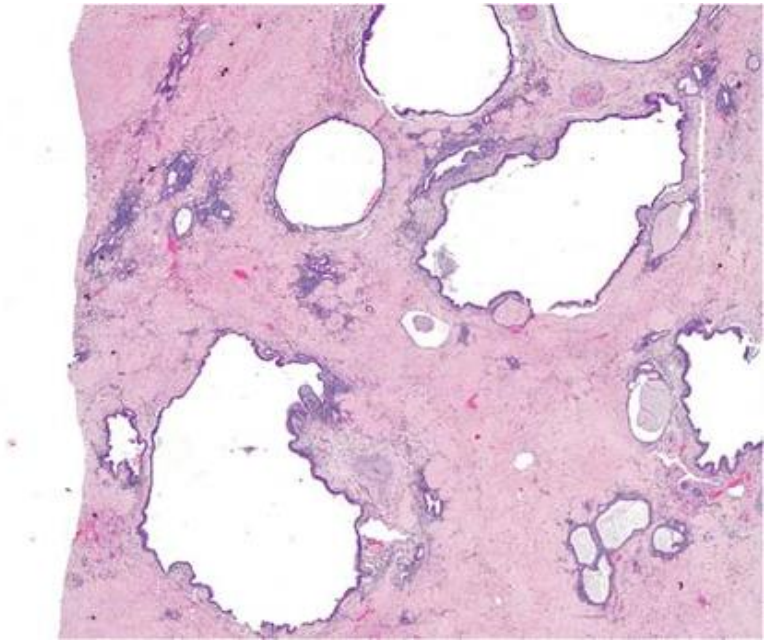
Xu Am J Surg Pathol 2013



Nodular granulomas

Remerciements
Pr JF Bernaudin

D



Peribronchic scars with HC

Conclusion

- L’atteinte pulmonaire de la sarcoïdose:
  - Présente dans 90% des cas
  - Le monitorage doit être adapté
  - Est la principale cause de mortalité prématurée
  - Enjeux thérapeutiques

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  - H Nunes; Y Uzunhan; D Bouvry; O Freynet; F Jeny
  - C Planès; PY Brillet; M Brauner; D Piver; M Kambouchner; JF Bernaudin
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