AIP, COP: diagnosis, differential diagnosis and treatment

Ulrich Costabel

Department Pneumology/Allergology
Ruhrlandklinik – University Hospital
Essen

Revised classification of IIP

CATEGORY	CLINICAL-RADIOLOGIC-PATHOLOGIC DIAGNOSES	ASSOCIATED MORPHOLOGIC PATTERN
Chronic fibrosing IP	Idiopathic Pulmonary fibrosis	Usual Interstitial pneumonia
	Idiopathic Nonspecific Interstitial Pneumonia	Nonspecific Interstitial Pneumonia
Smoking related IP	Respiratory Bronchiolitis Interstitial Lung Disease	Respiratory Bronchiolitis
	Desquamative Interstitial Pneumonia	Desquamative Interstitial Pneumonia
Acute/subacute IP	Cryptogenic organizing Pneumonia	Organizing Pneumonia
	Acute Interstitial Pneumonia	Diffuse Alveolar Damage

AIP

AIP

- 1935 Hamman and Rich: „fulminating diffuse interstitial fibrosis of the lung“ (4 cases)
- 1986 Katzenstein et al: „acute interstitial pneumonia“, considered as distinct form of IIP (8 cases)

Proposed diagnostic criteria for AIP

1 Acute symptomatic lower respiratory tract illness < 60 days

2 Diffuse bilateral radiographic infiltrates

3 Exudative, organizing, or proliferative diffuse alveolar damage (DAD) on lung biopsy

4 Exclusion of any known inciting event (infection, sepsis, toxic exposure, CTD, previous ILD...)

5 Absence of previously abnormal radiograph

Modified from Vourlekis JS et al, 2001

AIP: Clinical presentation
(n=252, published case series)

- Age 56 years
- M:F 1.2:1.0
- Dyspnoe, cough, fever, crackles, leukocytosis, hypoxemie

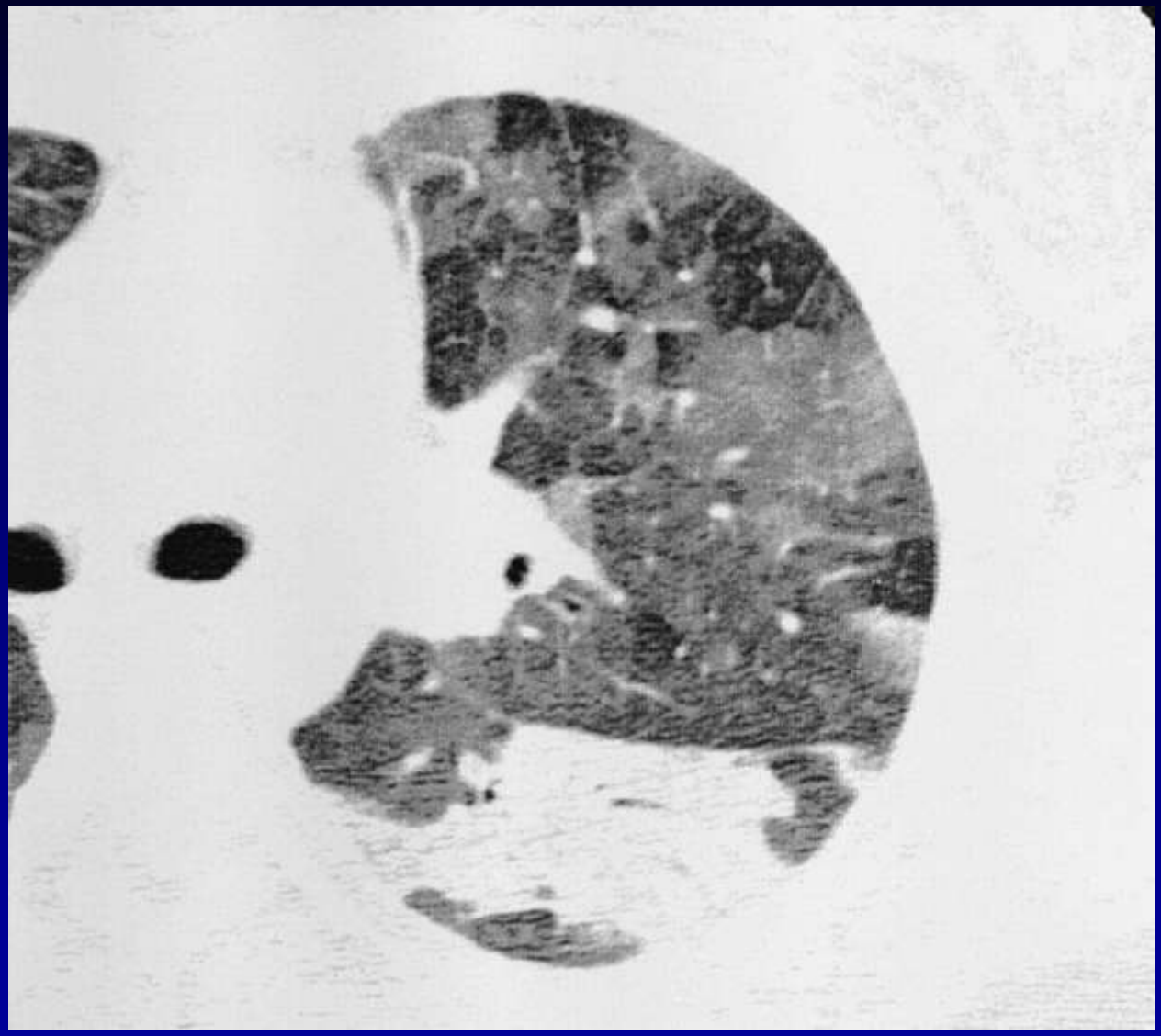
From Collard and Brown, in Schwarz/King: Interstitial Lung Disease, 2011

AIP: CT

- ground glass, partially in geographic distribution
- consolidation
- traction bronchiectasis
- cysts (late stage)

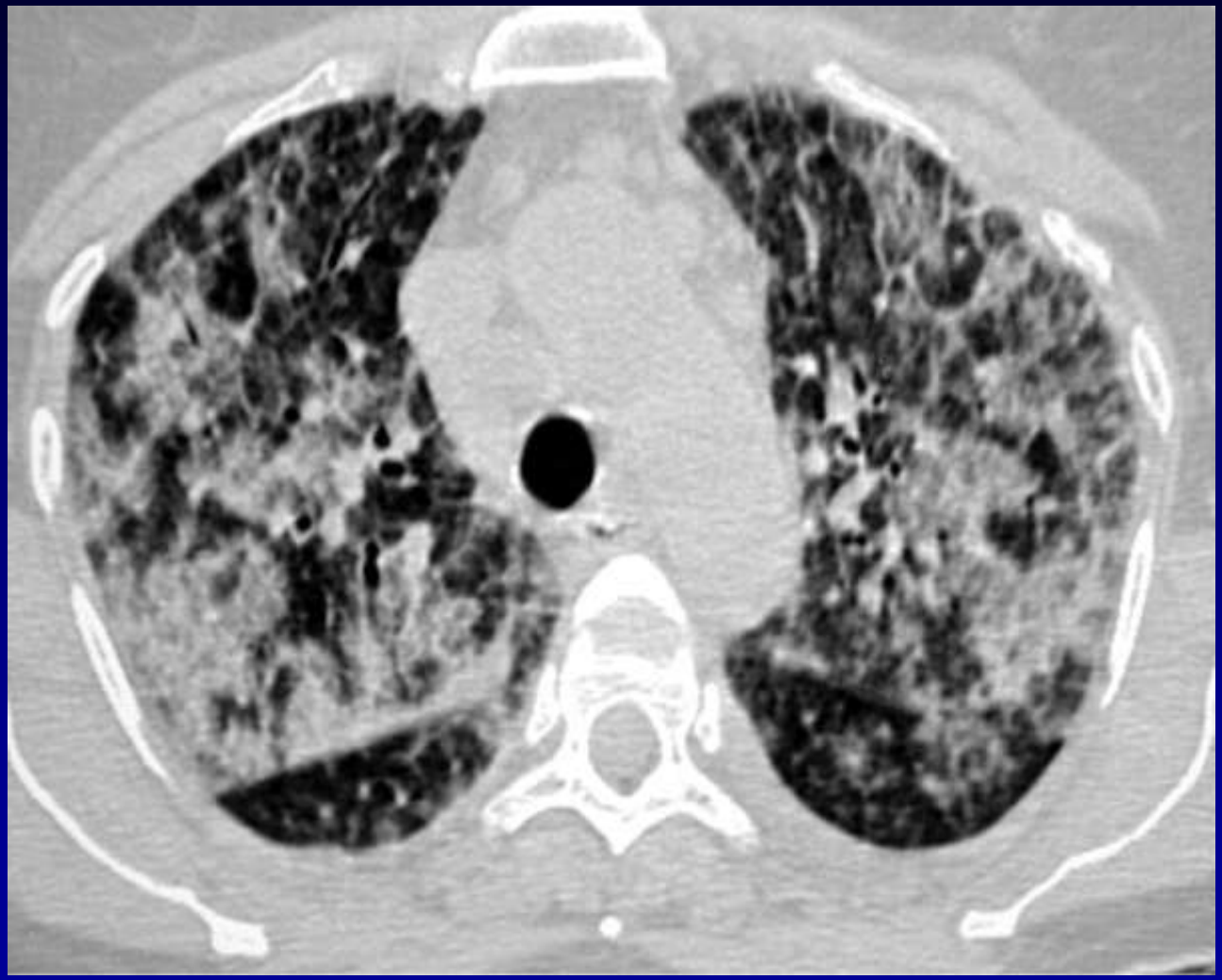
From Collard and Brown, in Schwarz/King: Interstitial Lung Disease, 2011

CT in AIP



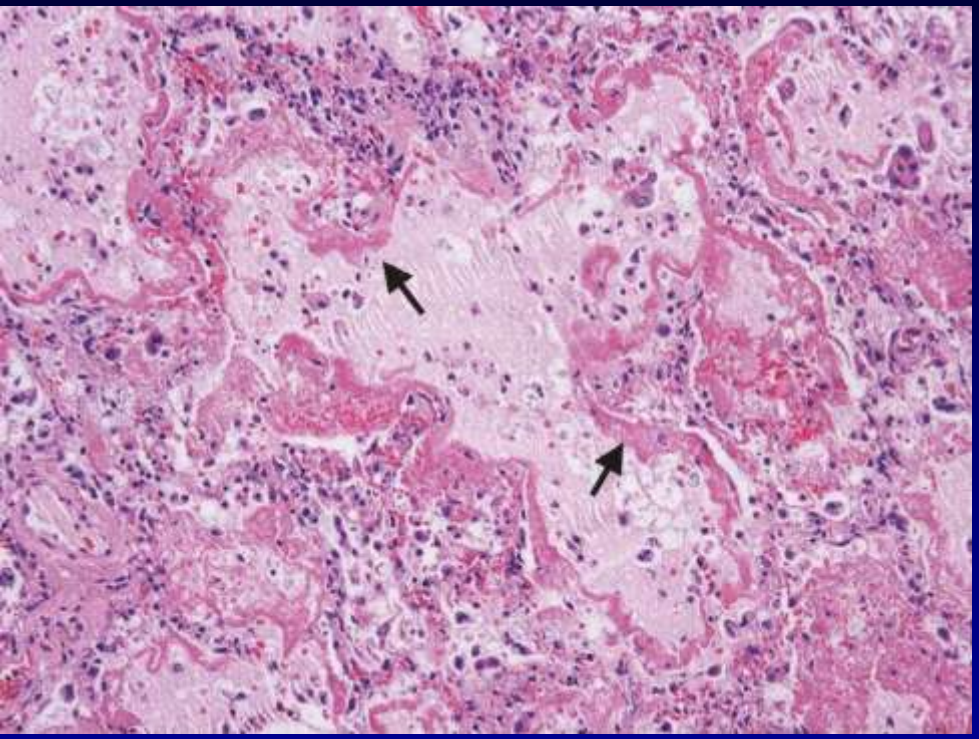
From ATS/ERS IIP Statement, AJRCCM 2002

CT in AIP

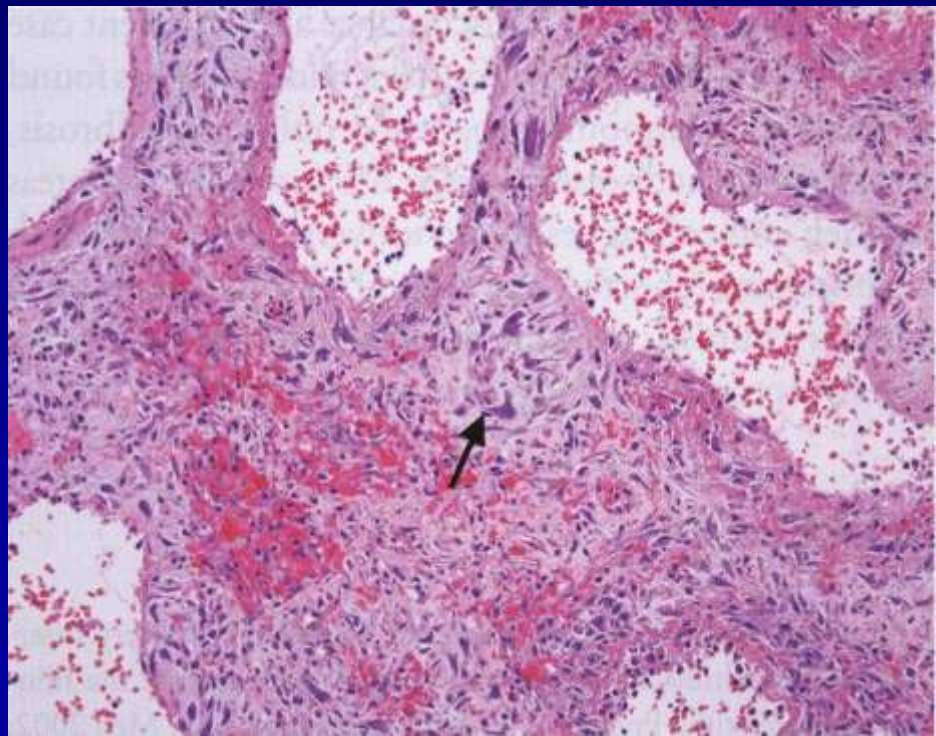


From Gotwell et al, Thorax 2005

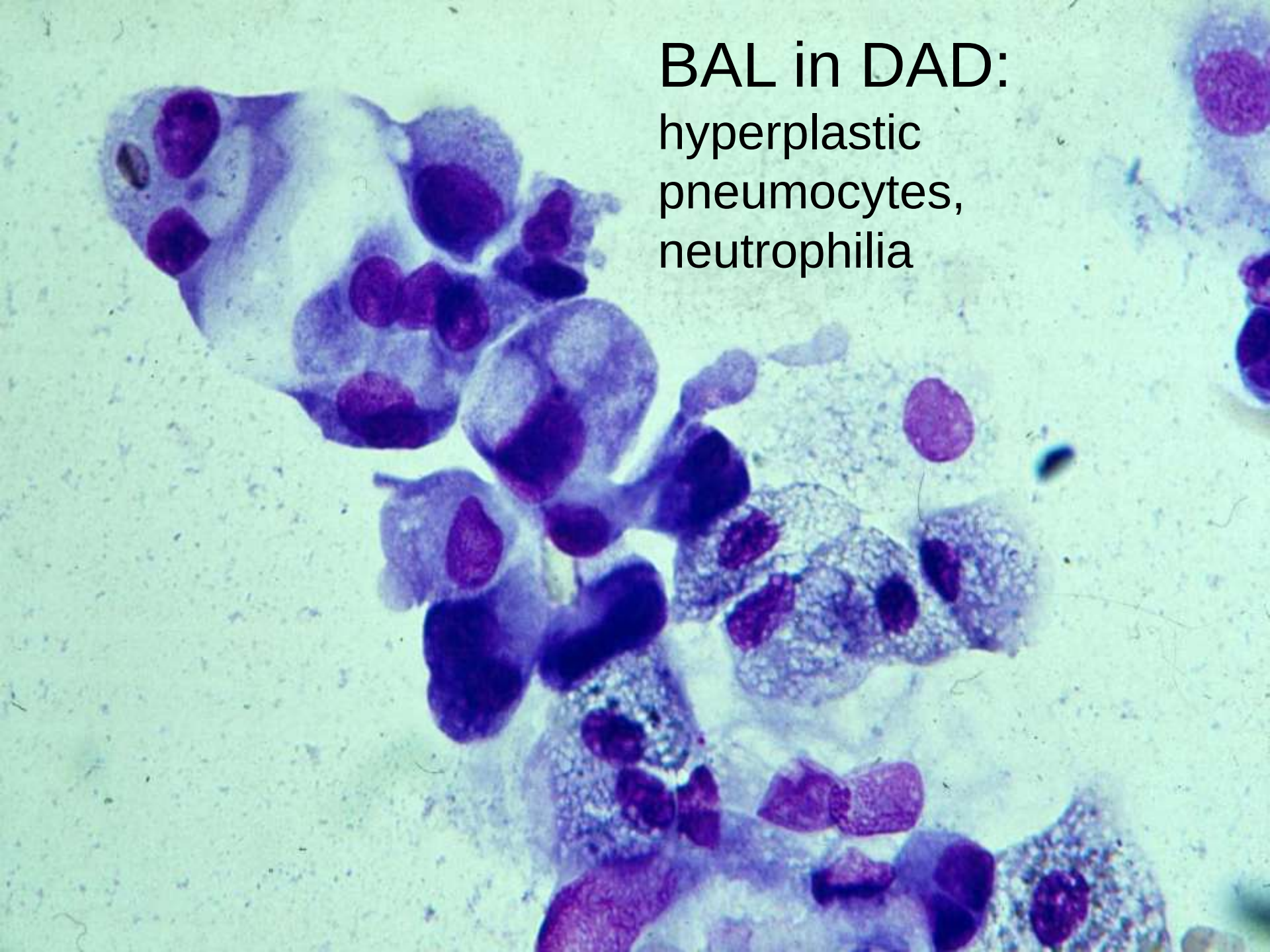
Histopathology of AIP



Diffuse alveolar damage (DAD)



From Collard and Brown, in Schwarz /King: Interstitial Lung Disease, 2011


BAL in DAD:
hyperplastic
pneumocytes,
neutrophilia

Therapy of AIP

- M-prednisolone pulse: 500 mg-1000 mg/day i.v. for 3 days
- +/- Cyclophosphamide i.v.

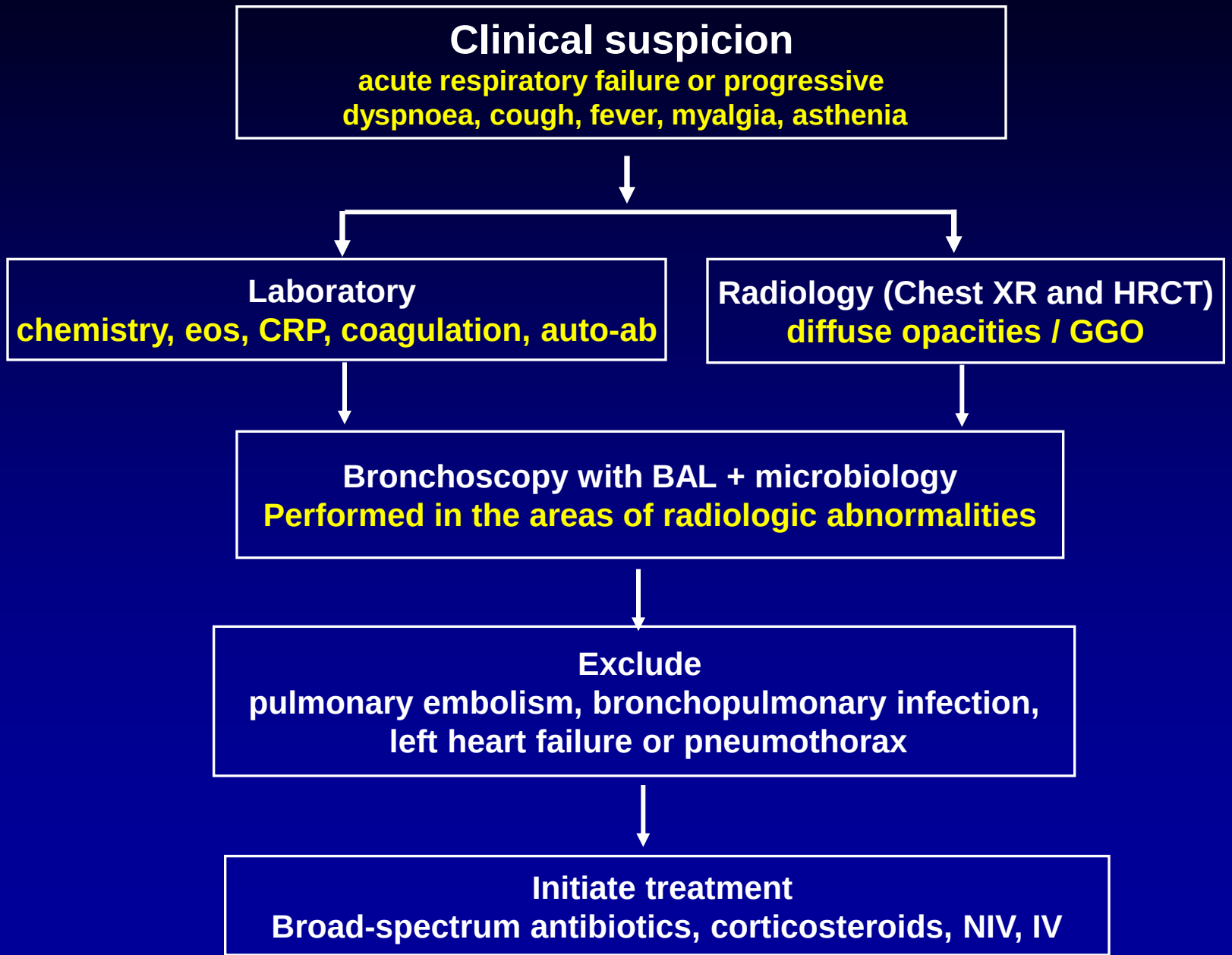
- Cyclosporine (Inase et al 2003, Sakamoto et al 2010)

- Hemoperfusion (Neutrophilenelimination) (Seo et al 2006)

- Sivelastat (Anti-neutrophil-elastase) (Nakamura et al 2007)

- Tacrolimus (Horita et al 2011)

Management of acute ILDs



Course of AIP

(n=252, published case series)

- Symptom duration 1 day to 4 months
- Mortality 70 %
  (compare: ARDS 40%)
- Long term prognosis of survivors good (60-100%)
  (similar to ARDS)

From Collard and Brown, in Schwarz/King: Interstitial Lung Disease, 2011

Summary: AIP

- Clinical/radiological: ARDS of unknown etiology
- Histology: DAD
- Diagnosis: usually BAL+/- TBB, no surgical biopsy
- Very rare emtity: most cases acute exacerbations of previously undiagnosed IPF?

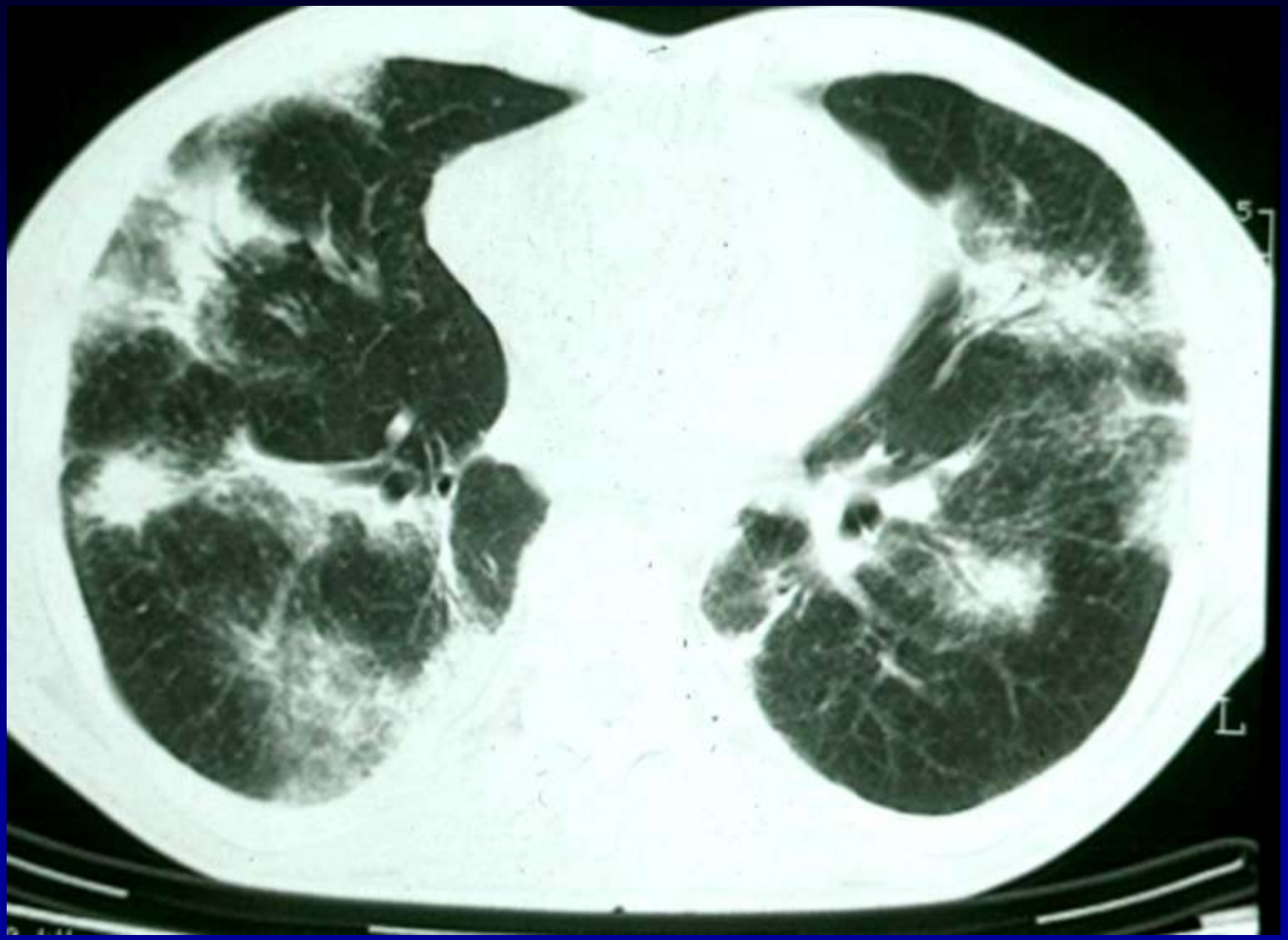
COP

Definition of COP or (idiopathic BOOP)

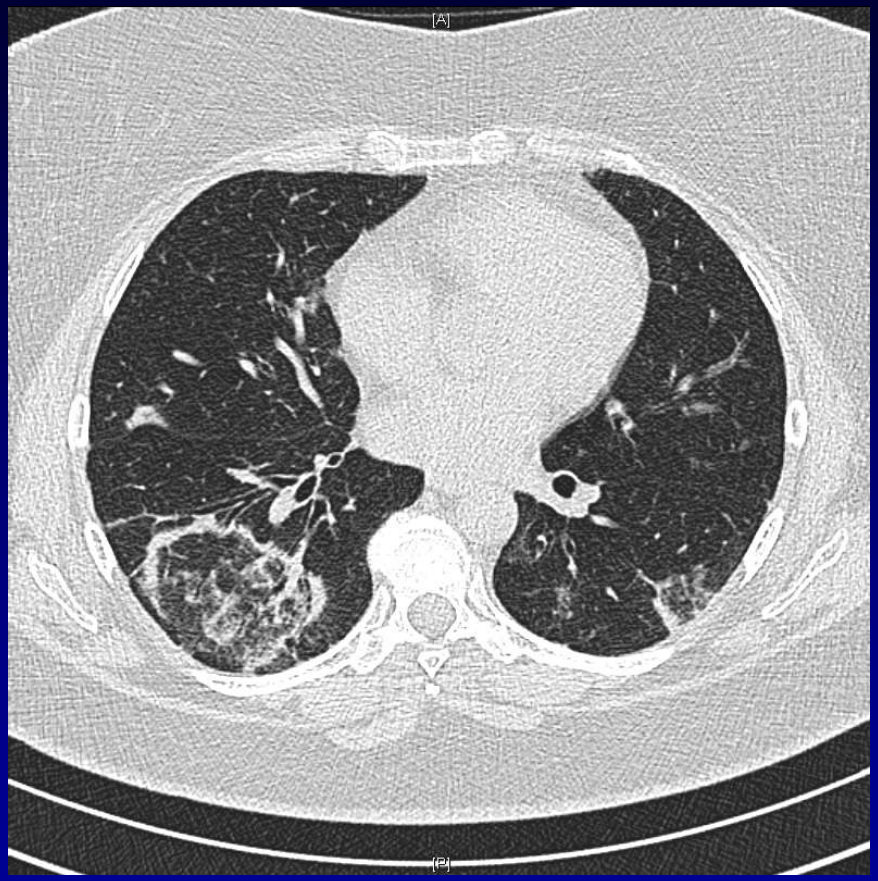
Cryptogenic organizing pneumonia (COP) or idiopathic BOOP is a clinicopathological syndrome of unknown cause or association characterized by

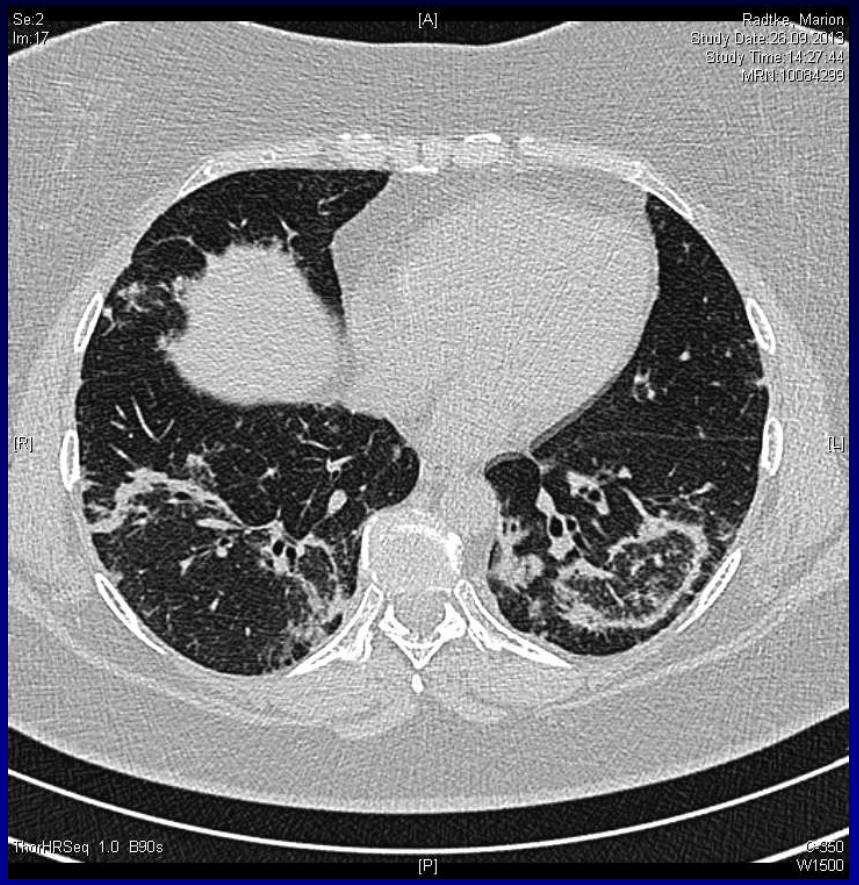
- the clinical presentation with a subacute influenenza-like illness
- multiple patchy infiltrates on chest X-ray and/or CT scan
- the histopathological pattern of intraluminal organization predominantly in the alveolar ducts

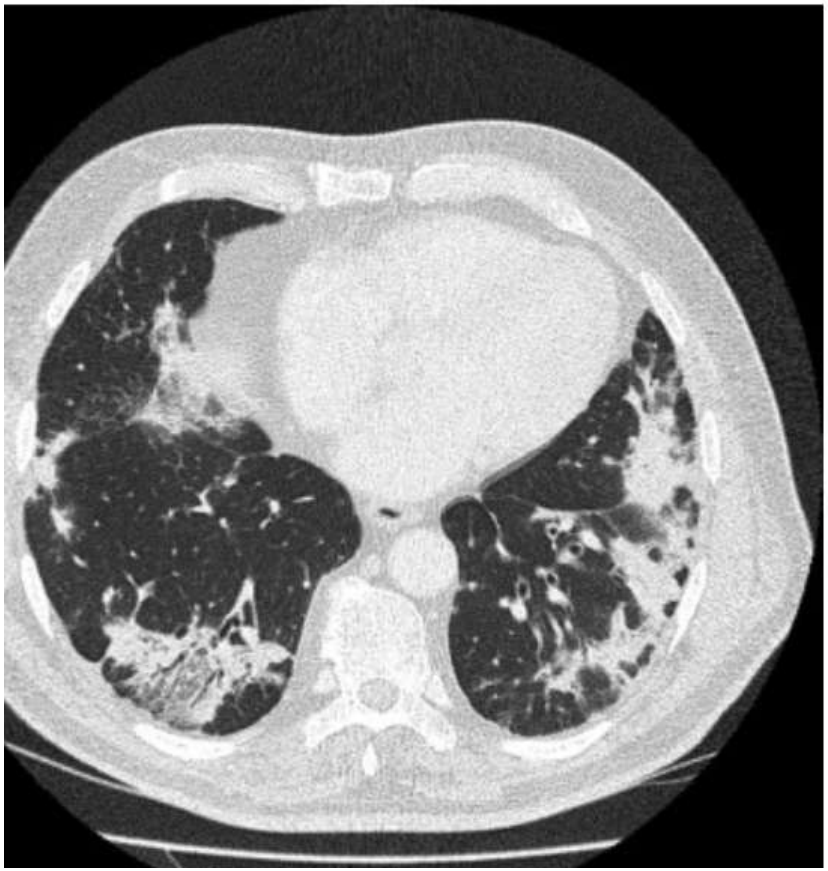
OP

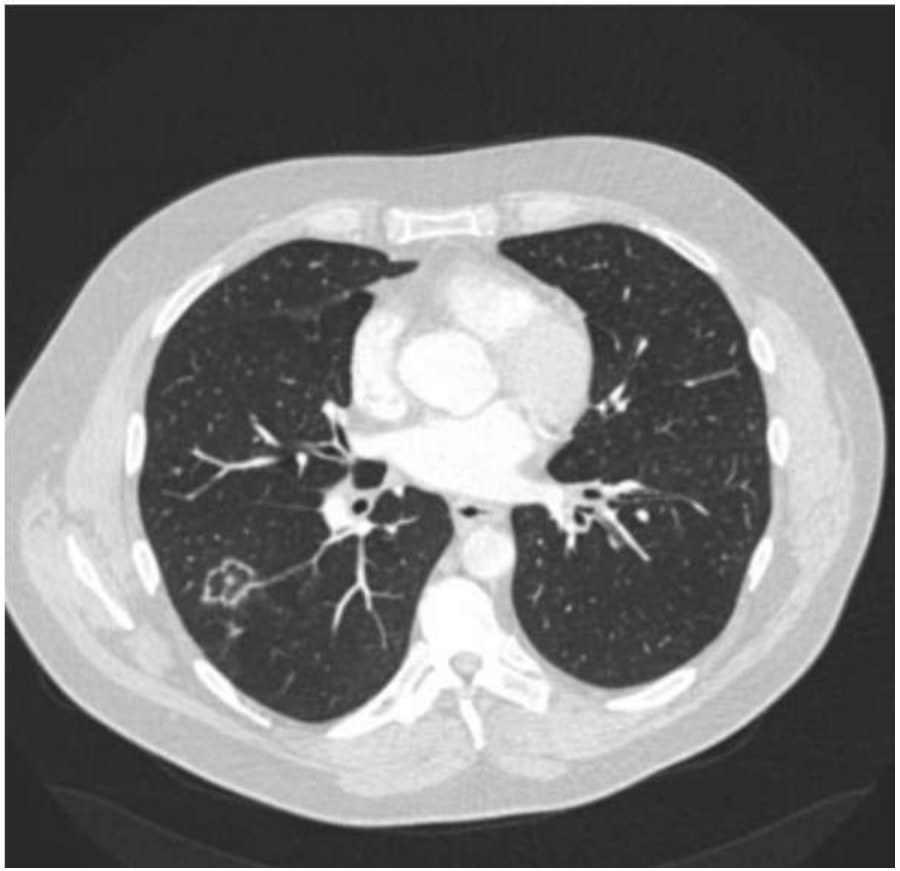


OP: reverse halo



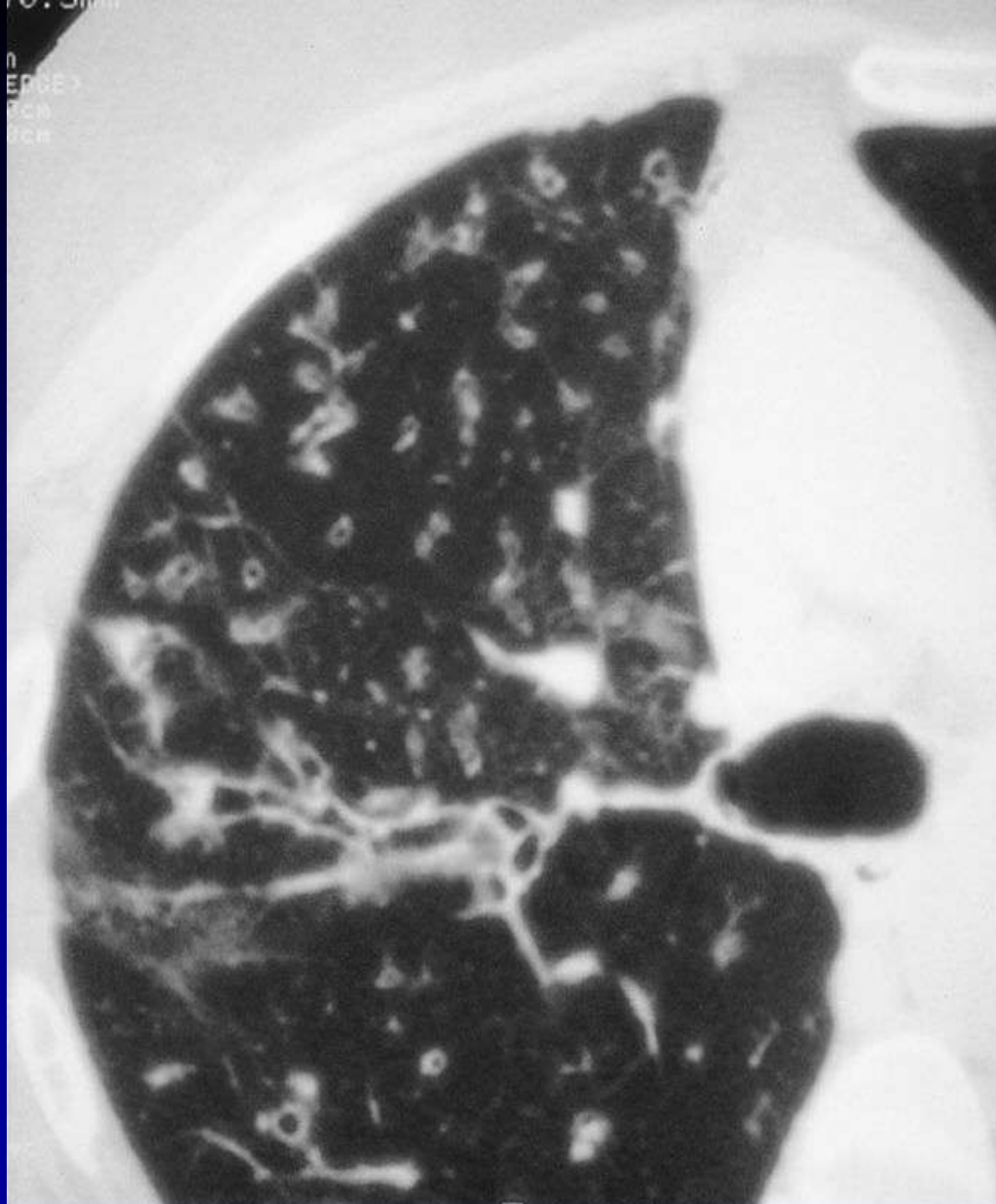


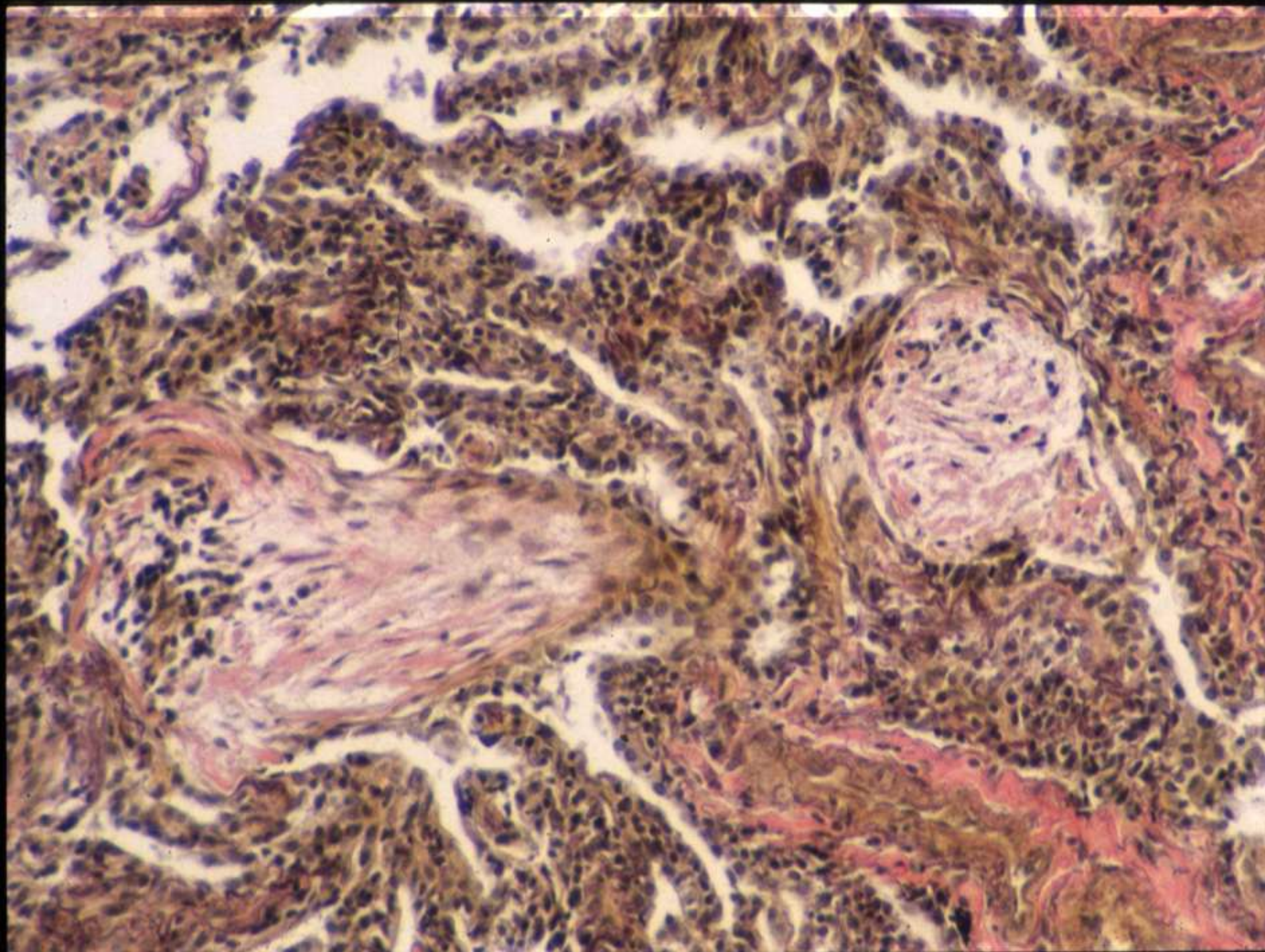




Cottin & Cordier, *Sem Respir Crit Care Med 2012*

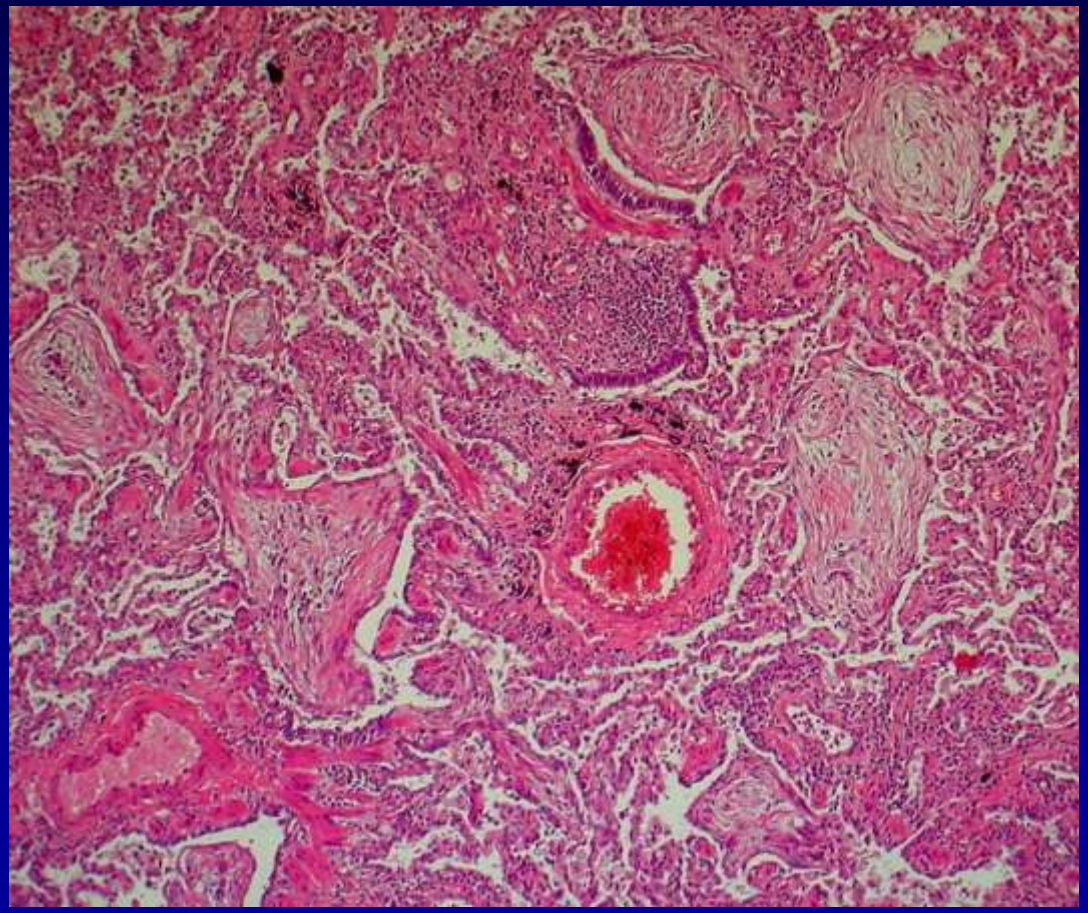
OP: micronodules, peribronchial consolidation





OP pattern

- Adjacent airspaces obliterated by these fibroblastic plugs
- A characteristic variation in shape from round or oval to elongated or serpiginous formed intraluminal plugs



OP

Clinicopathologic entity

- Idiopathic, COP
- collagen-vascular diseases
- autoimmune disorders
- drugs
- cocaine inhalation
- HIV infection
- bone marrow transplation
- Radition therapy for breast cancer

Second. histol. lesion

- organizing infections
- chronic aspiration
- extrinsic allergic alveolitis
- chronic eosinophilic pneumonia
- irradiation pneumonitis
- Wegener's granulomatosis
- collagen-vascular disorders
- organizing diffuse alveolar damage

Diagnostic value of BAL and TBB in Cryptogenic Organizing Pneumonia

(Poletti et al. ERJ 9:2513)

	BAL	TBB
Sensitivity	63%	64%
Specificity	57%	86%
Positive predictive value	85%	94%
Negative predictive value	29%	40%
Diagnostic Accuracy	62%	69%

Study population: n = 35

Differential diagnosis of COP

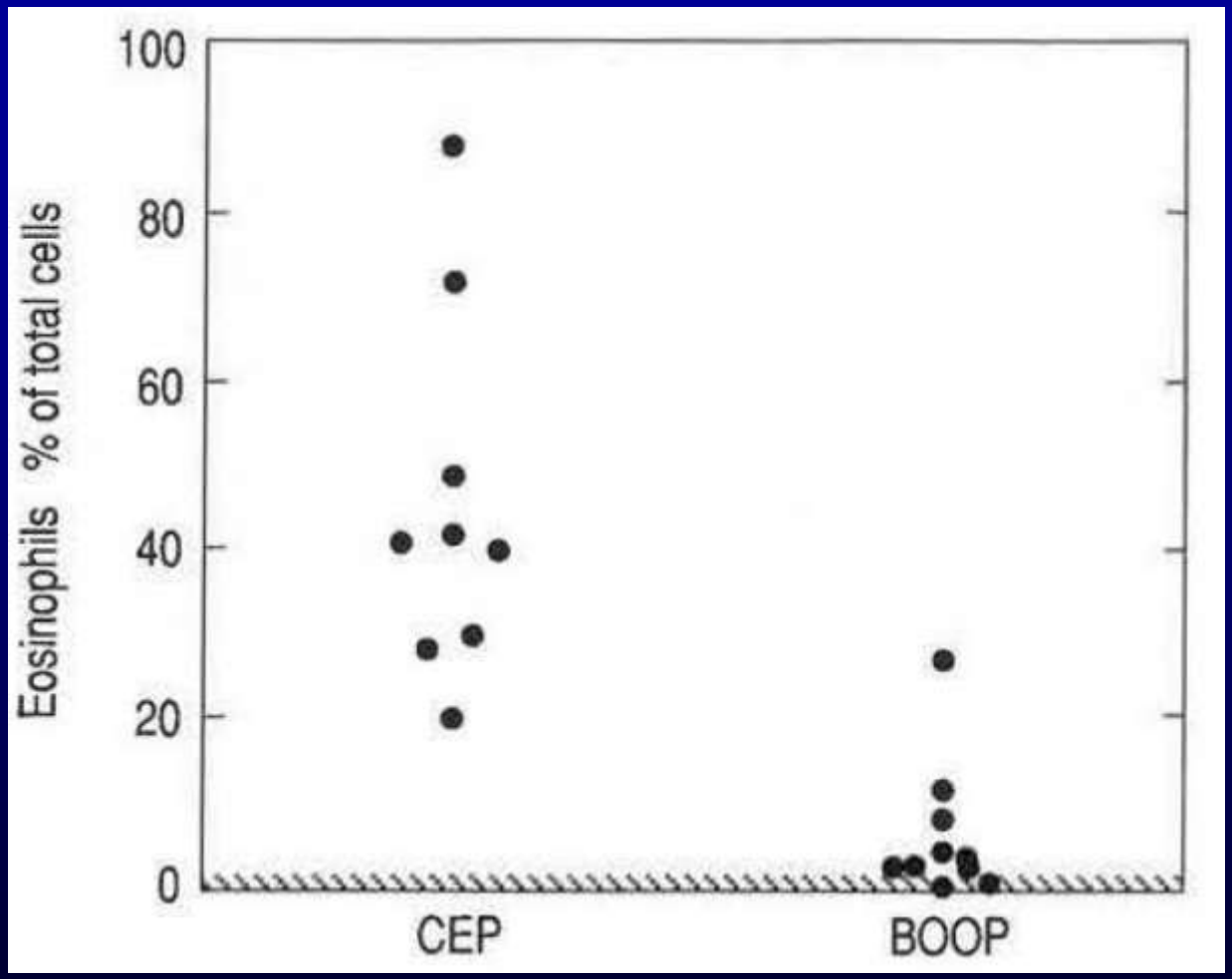
Multiple patchy alveolar opacities

- Bronchoalveolar carcinoma
- Malignant lymphoma
- Infectious pneumonia
- Aspiration pneumonia
- Pulmonary embolism with infarction
- Chronic eosinophilic pneumonia

Differential diagnosis COP versus chron. eosin. pneumonia (CEP)

	CEP	BOOP
Imaging	Predominant ULF More ground glass Air bronchogram rare	Predominant LLF More consolidation Air bronchogram
BAL	Eosinophils > 25%	Mixed cellularity
Histology	No fibrosis Foamy cells rare BO rare	Fibroblasts Foam cells frequent BO frequent

BAL: CEP vs BOOP



Costabel et al. *ERJ 1992*

Diseases associated with OP

- Rheumatoid arthritis
- Polymyositis and dermatomyositis
- Systemic lupus erythematosus
- Progressive systemic sclerosis
- Sjögren's syndrome
- Mixed connective tissue disease
- Polymyalgia rheumatica
- Behcet's disease
- Polyarteritis nodosa
- Ulcerative colitis

Drugs associated with OP

- Gold
- Methotrexate
- Bleomycin
- Naproxen
- Sulphasalazine
- Sulindac
- Cephalosporins
- Amphotericin B
- Amiodarone
- Acebutolol
- Interferon
- L-Tryptophan
- Cocaine

Conditions associated with BOOP
Miscellaneous associations

- HIV infection
- Common variable immunodeficiency syndrome
- Radiation therapy
- Myelodysplastic syndrome
- Leukaemia
- Paint aerosol inhalation
- Chronic thyroiditis
- Alcoholic cirrhosis
- Malaria
- Bone marrow / lung transplantation
- Seasonal syndrome with cholestasis

Radiation-induced BOOP

- 15 cases in a retrospective series *(Crestani et al, AJRCCM 1998;158:1929)*
- All in women with breast cancer having received radiotherapy with 45 to 55 Gy
- Always fever and recurrent and migrating infiltrates outside the radiation field within 12 months after completion of radiotherapy
- BAL (n=10): Ly > 20% in all,
  Neutro > 5% in 8, Eos > 5% in 5
- Good and fast response after corticosteroid therapy but relapses may occur while tapering or stopping (mean total duration of steroids 49 wk)

Radiation-Induced BOOP

- Incidence: 4 of 157 patients (2.5%) in a Japanese series (Takigawa et al, 2000)
- No risk factors: no difference between patients with and without BOOP
- Relapses: in all patients at 0 to 2.5mg prednisone after a treatment period of 2 to 5 months
- My conclusion: treatment for one year (like idiopathic BOOP) to avoid relapse

COP may present as an acute and life-threatening syndrome

Nizami et al, CHEST 1995; 108: 271

- 5 patients with ARDS-like presentation
- 4 required mechanical ventilation
- 3 survived due to early corticosteroid treatment, in one case started before results of open biopsy were obtained

➔ early corticosteroid treatment may be life-safing

COP with multiple cavitary nodules

- Two case reports
  - Haro et al, ERJ 1995; 8: 1975
  - Froudarakis et al, ERJ 1995; 8: 1972

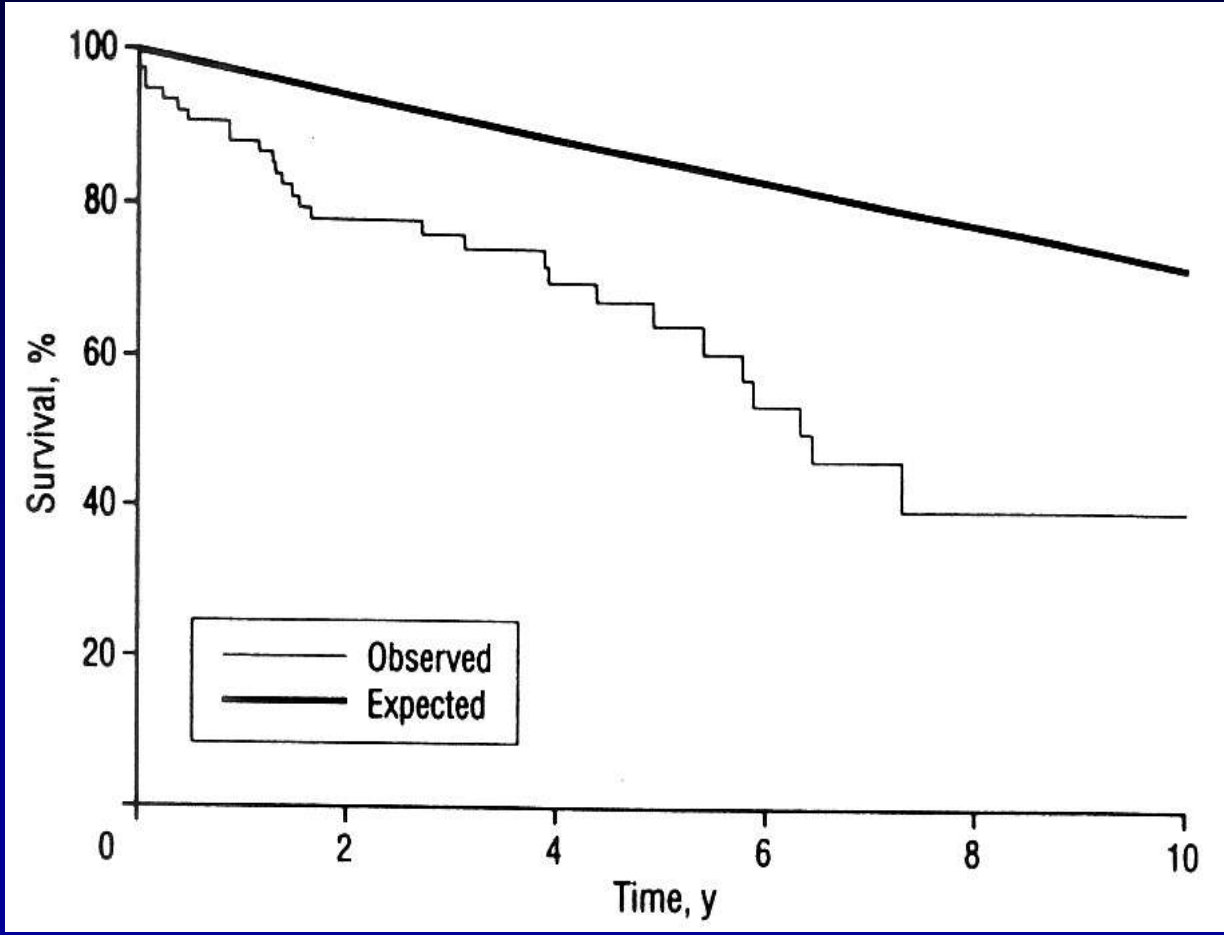
➔ COP should be added to the list of diseases with multiple cavitary nodules

Organising Pneumonia - Mayo Clinic

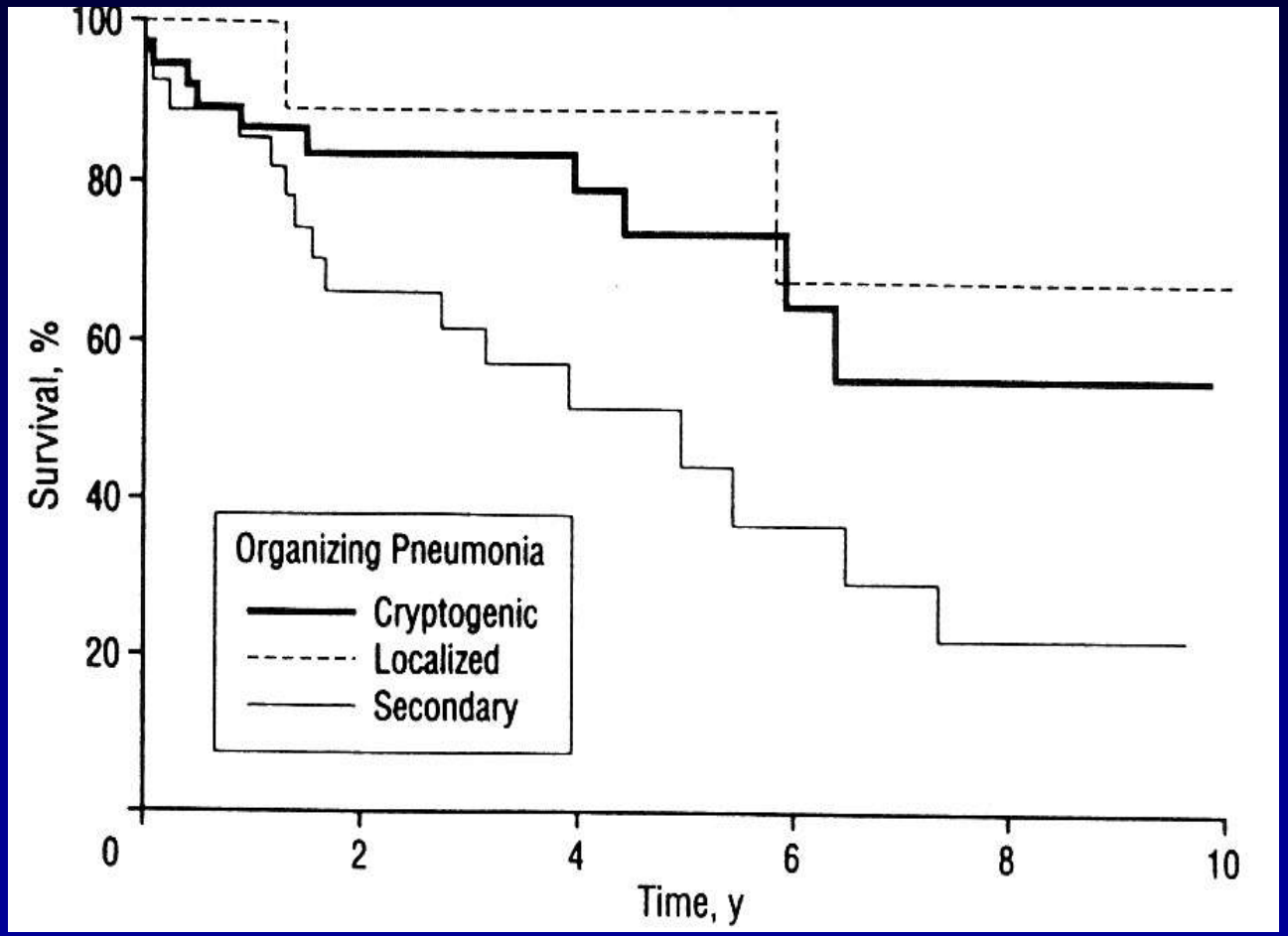
Lohr et al. Arch Intern Med 1997; 157: 1323

- 74 patients from 1984 - 1994
  - 37 (50%) cryptogenic OP
  - 27 (36%) secondary OP
  - 10 (14%) asymptomatic focal nodule
- Relapse rate
  - 13% in cryptogenic
  - 17% in secondary
- 5-year survival
  - 73% in cryptogenic
  - 44% in secondary

Organizing Pneumonia, Survival *(n=74)*



Organizing Pneumonia, Survival *(n=74)*



Prognosis of COP

- Complete Recovery 40 - 60%
- Recovery with some residuals 30%
- Progressive disease and death 8 - 12%

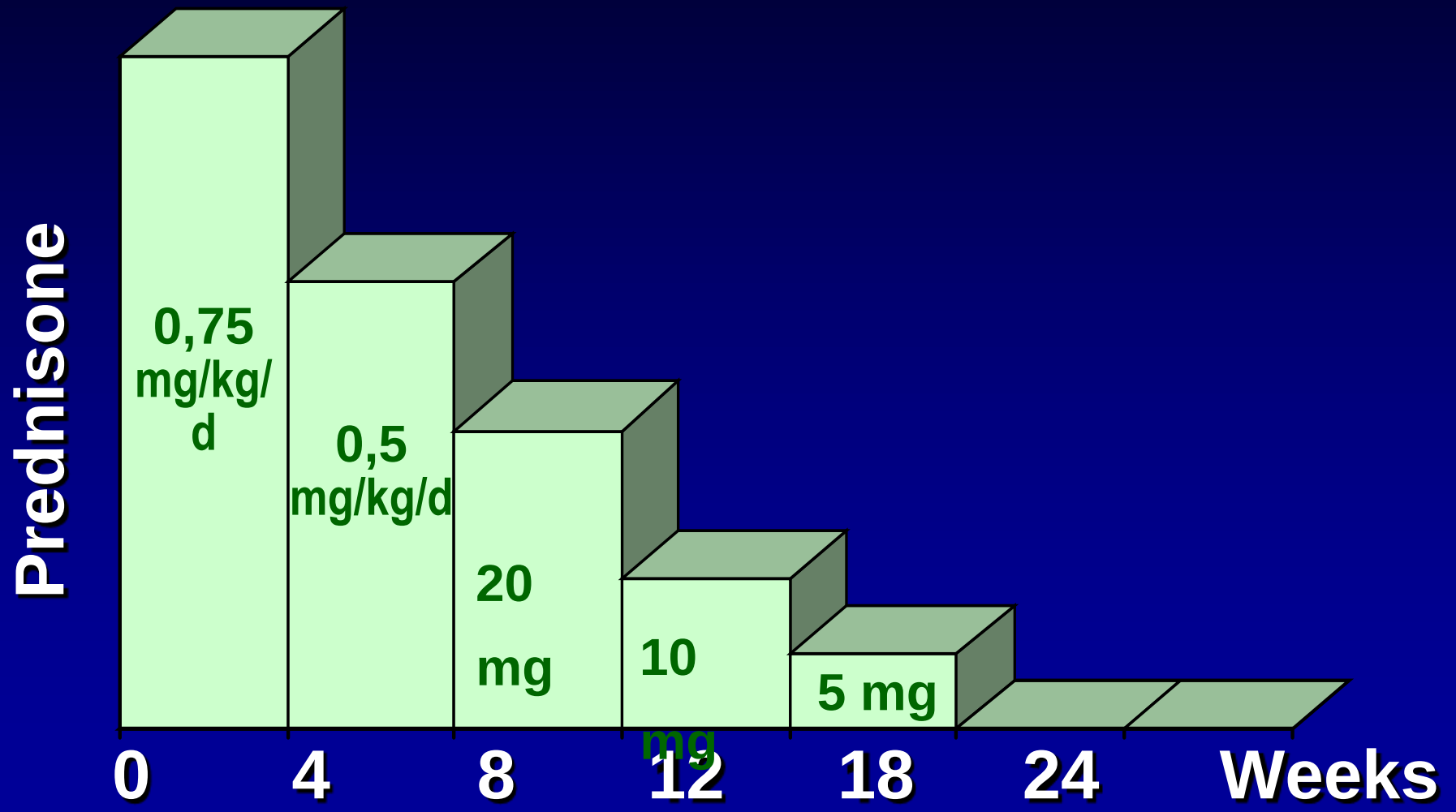
Risk factors for unfavourable outcome

- Interstitial pattern on radiography
- Lack of lymphocytosis in BAL fluid
- Features of UIP in biopsy
- Scarring and remodeling of lung parenchyma

Treatment of COP

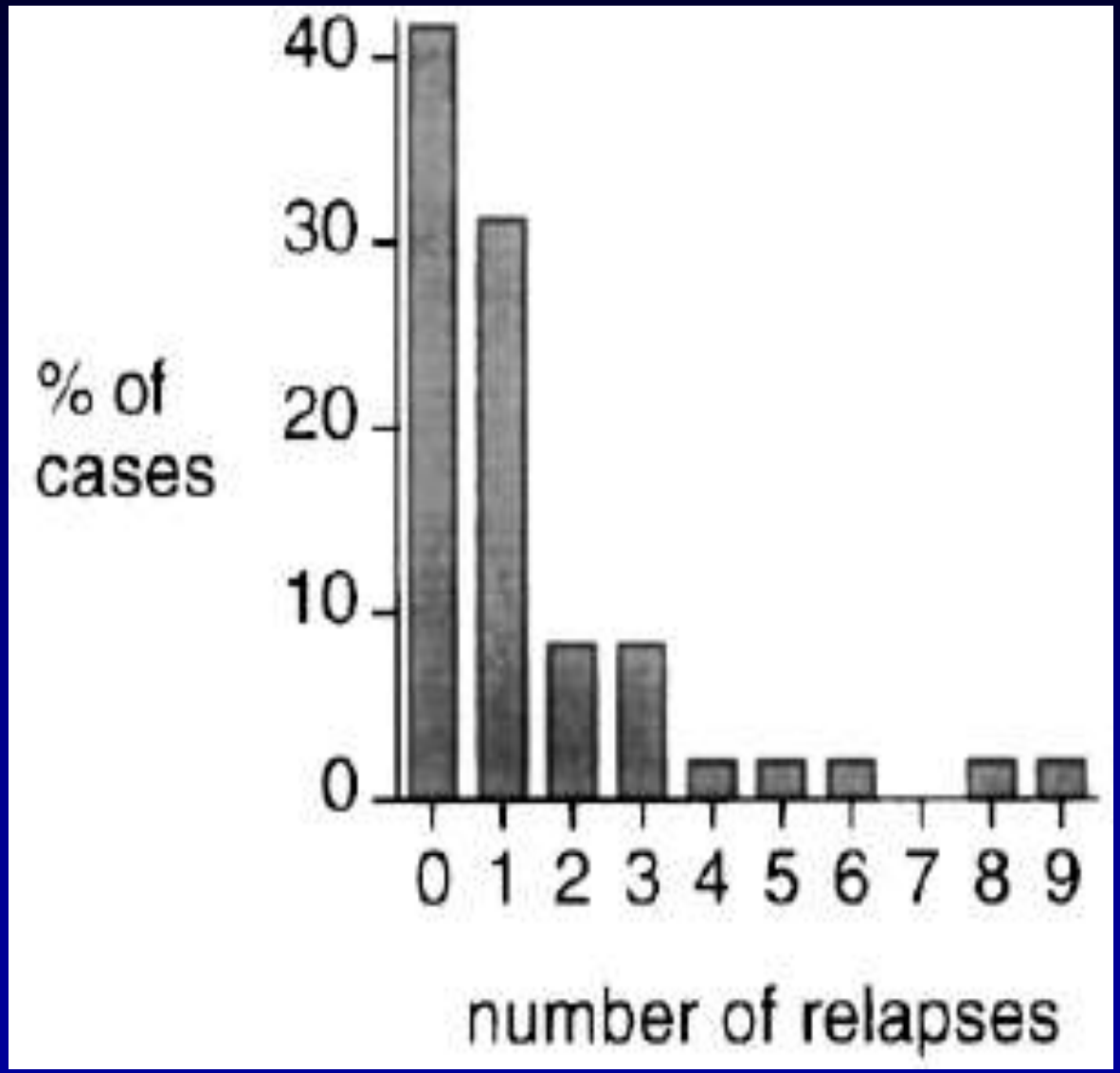
- Corticosteroids, e.g. prednisone
- Initial dosage 40 - 60 mg/day
- After 1 to 3 months tapering to 20 - 40mg
- After 4 to 6 months tapering to 7.5 - 10mg
- Duration of therapy: 9 - 12 months

Treatment of COP



Cordier JF. Germ"O"P 1996

Number of relapses in COP



Distribution of 48 cases of COP according to the number of relapses.

Values are expressed as percentage of the whole study population.

Lazor R. AJRCCM 2000

Macrolides – a treatment alternative for BOOP?

- 3 cases of idiopathic and 3 cases of radiation-related BOOP
- Clinical and radiographic response to clarithromycin 250-500 mg BID for 3-6 months

Stover DE. Chest 2005

Open question: in how many patients was this treatment NOT successful?

Clarithromycin for COP

- Report on three patients with COP.
- All three patients received clarithromycin 500 mg BID.
- Therapy ranged between 3-12 months.
- All of the patients showed improvement in their symptoms, together with radiological resolution.

Kastelik et al. ERJ 2006

Macrolides may have an immunomodulatory activity

1. Inhibition of the pulmonary influx of neutrophils
2. Reduction of inflammatory cytokines (*e.g.* IL-8)
3. Inhibition of T-cell activation
4. Protection of the epithelium from bioactive phospholipids
5. Improvement of the transportability of airway secretions

Rubin BK. Chest 2004

Summary: COP

- Clinical/radiological/pathological syndrome: OP of unknown cause
- Pneumonia-like presentation
- Diagnosis: usually BAL+/- TBB, no surgical biopsy
- Good response to corticosteroids, good prognosis, but relapses quite frequent