Cross Canada Rounds
Long Case Presentation

Hasan Ghandourah
Pediatric Respiratory medicine
1st year fellow Fellow

SickKids®

Overview

- Case Presentation
- Diagnosis
- Review of the current literature

Case

- 13 year old girl with:
  - Chest tightness and exertional dyspnea, without improvement on inhaled corticosteroids and short acting beta agonists
  - Unremarkable exam, other than mild tachypnea and labored breathing on exam.
  - Restrictive defect on spirometry revealed restriction, with diffusion impairment
  - Chest CT showing ground glass opacity and intralobular septal thickening (crazy paving)
  - Bronchoscopy revealed positive PAS staining, with cholesterol and myelin inclusions

Pulmonary Alveolar Proteinosis (PAP)

Objectives

- Understand the pathophysiology of PAP
- Differentiate between the Classes of PAP
- To be able to Recognize the clinical presentation
- Identify the Treatment options according to the underlying pathology.

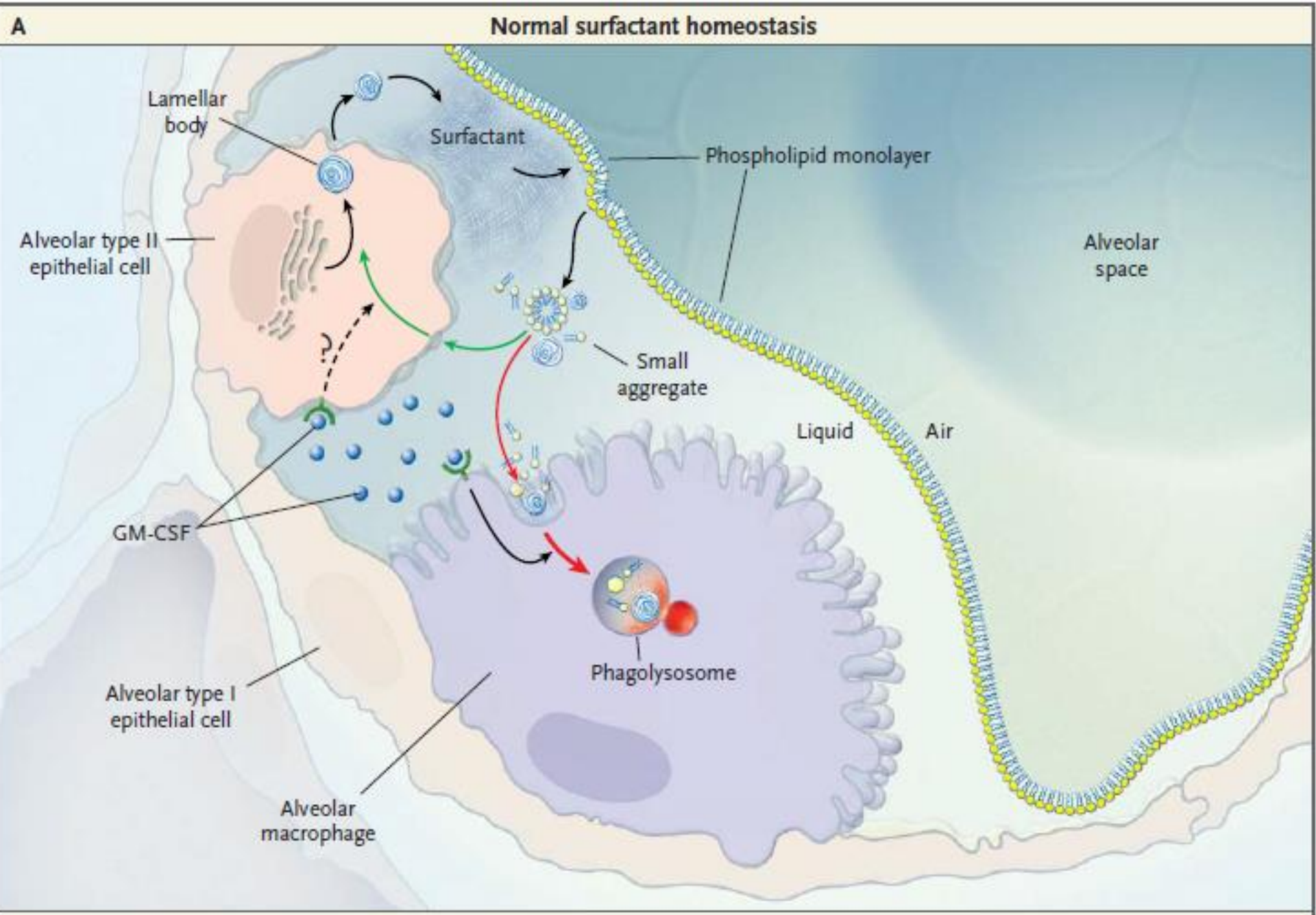
PAP

- First described by Rosen et al in 1958.
- Diffuse lung disease characterized by the accumulation of phospholipo-proteinaceous material in the alveoli.
- Pulmonary infiltrates with varying degrees of hypoxemia.

Rosen SH, Castleman B, Liebow AA. Pulmonary alveolar proteinosis. N Engl J Med 1958; 258:1123–1142

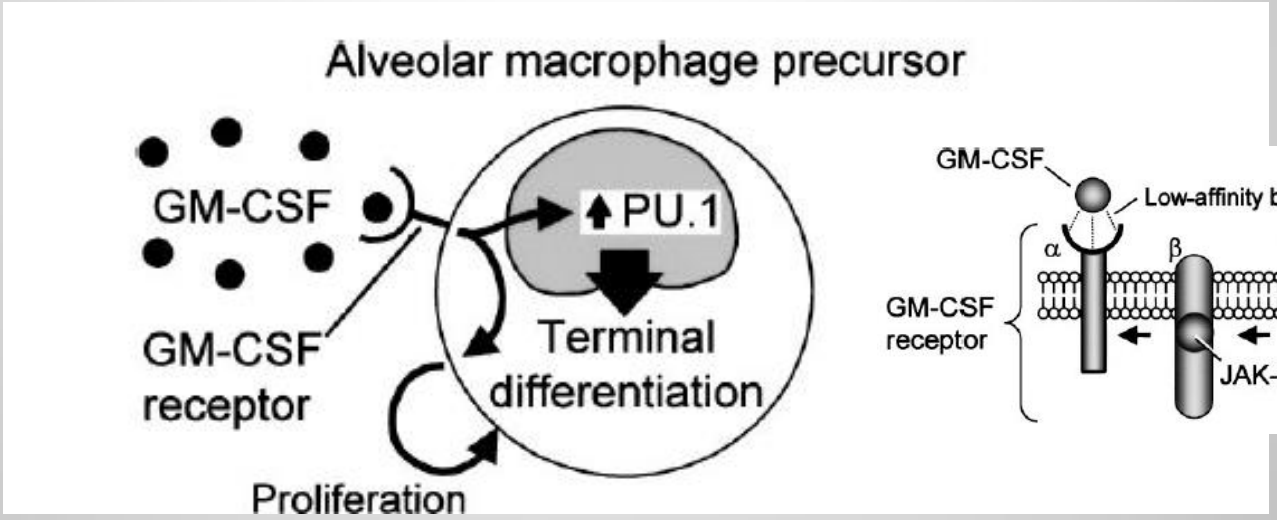
Pathology

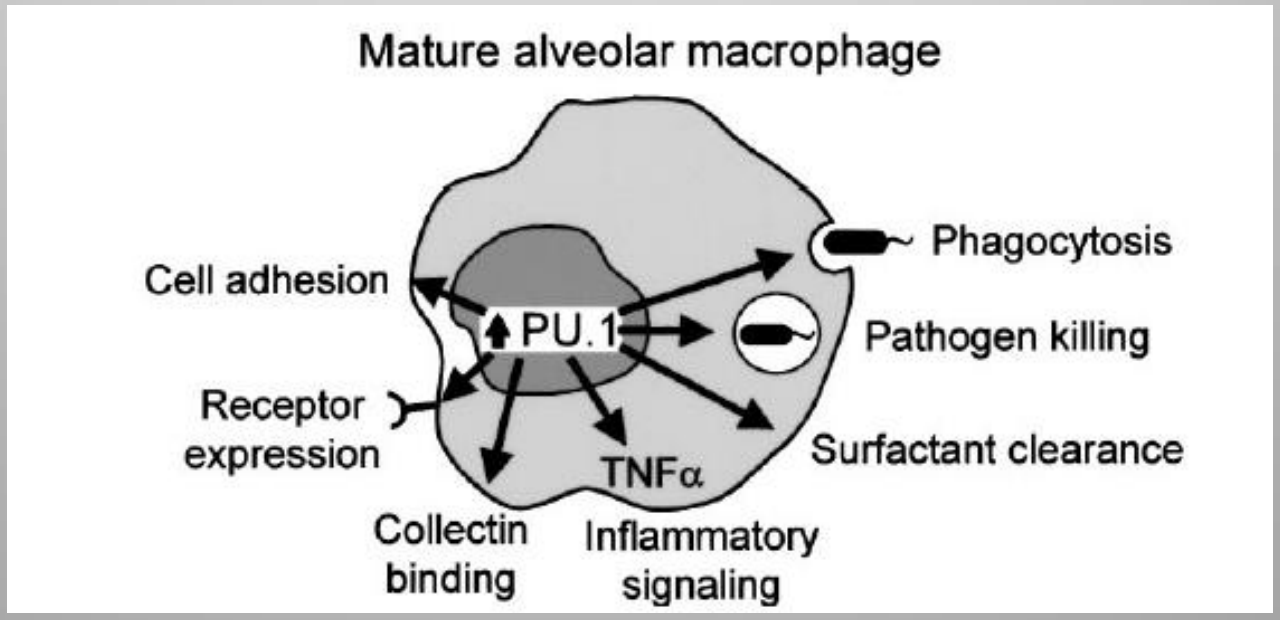
- Surfactant homeostasis:
  - Complex dynamic process involving
    - Alveolar type II cells.
    - Macrophages.


A
Normal surfactant homeostasis
Lamellar body
Surfactant
Phospholipid monolayer
Alveolar type II epithelial cell
Alveolar space
Small aggregate
Liquid
Air
GM-CSF
Phagolysosome
Alveolar type I epithelial cell
Alveolar macrophage

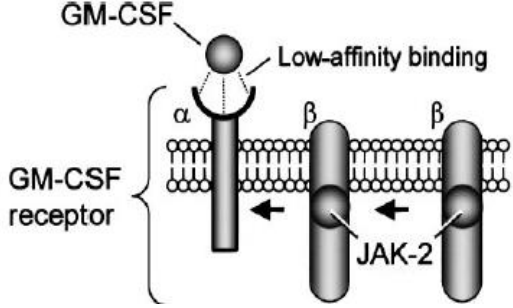
Alveolar Macrophages

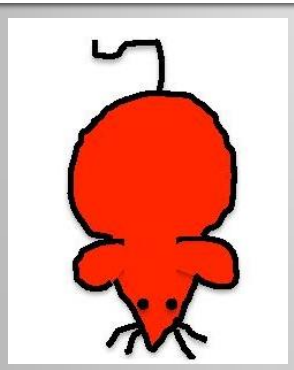
- Serving as the front line of cellular defense against respiratory pathogens.
- Important role in uptake, degradation, and recycling of surfactant.
- To do that, they need GM-CSF to:
  - Stimulate the terminal differentiation of alveolar macrophages principally by raising the levels of PU.1.


Alveolar macrophage precursor
GM-CSF
GM-CSF receptor
PU.1
Terminal differentiation
Proliferation
GM-CSF
Low-affinity binding
α
β
β
GM-CSF receptor
Plasma membrane
JAK-2

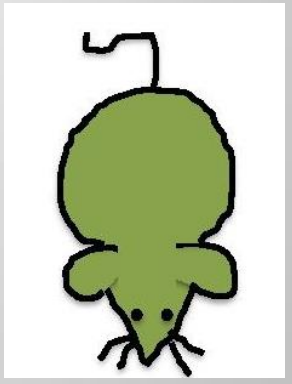

Mature alveolar macrophage
Cell adhesion
PU.1
Receptor expression
TNFα
Collectin binding
Inflammatory signaling
Phagocytosis
Pathogen killing
Surfactant clearance

Mouse models





Knockout mice that were deficient in GM-CSF

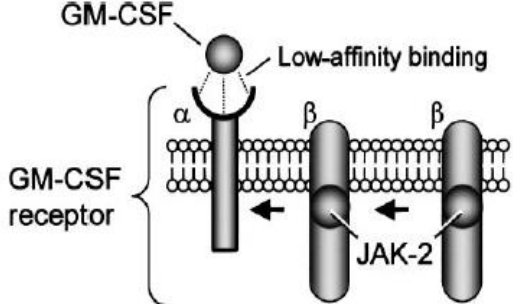


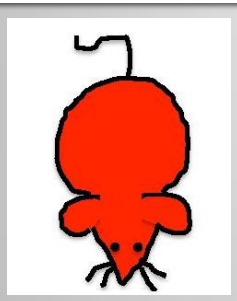
Targeted disruption of the gene encoding the Beta chain of the GM-CSF receptor .

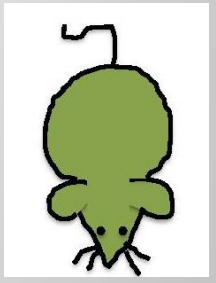
- Accumulations of lipoproteinaceous material and large, foamy macrophages in the alveoli.

Reed JA, Ikegami M, Cianciolo ER, et al. Am J Physiol 1999;276:L556-L563.

Mouse models







Knockout mice that were deficient in GM-CSF

Targeted disruption of the gene encoding the Beta chain of the GM-CSF receptor in mice.

GM-CSF

BMT from normal mice corrected the defective metabolism of surfactant

Resulted in resolution of PAP

Resulted in resolution of PAP

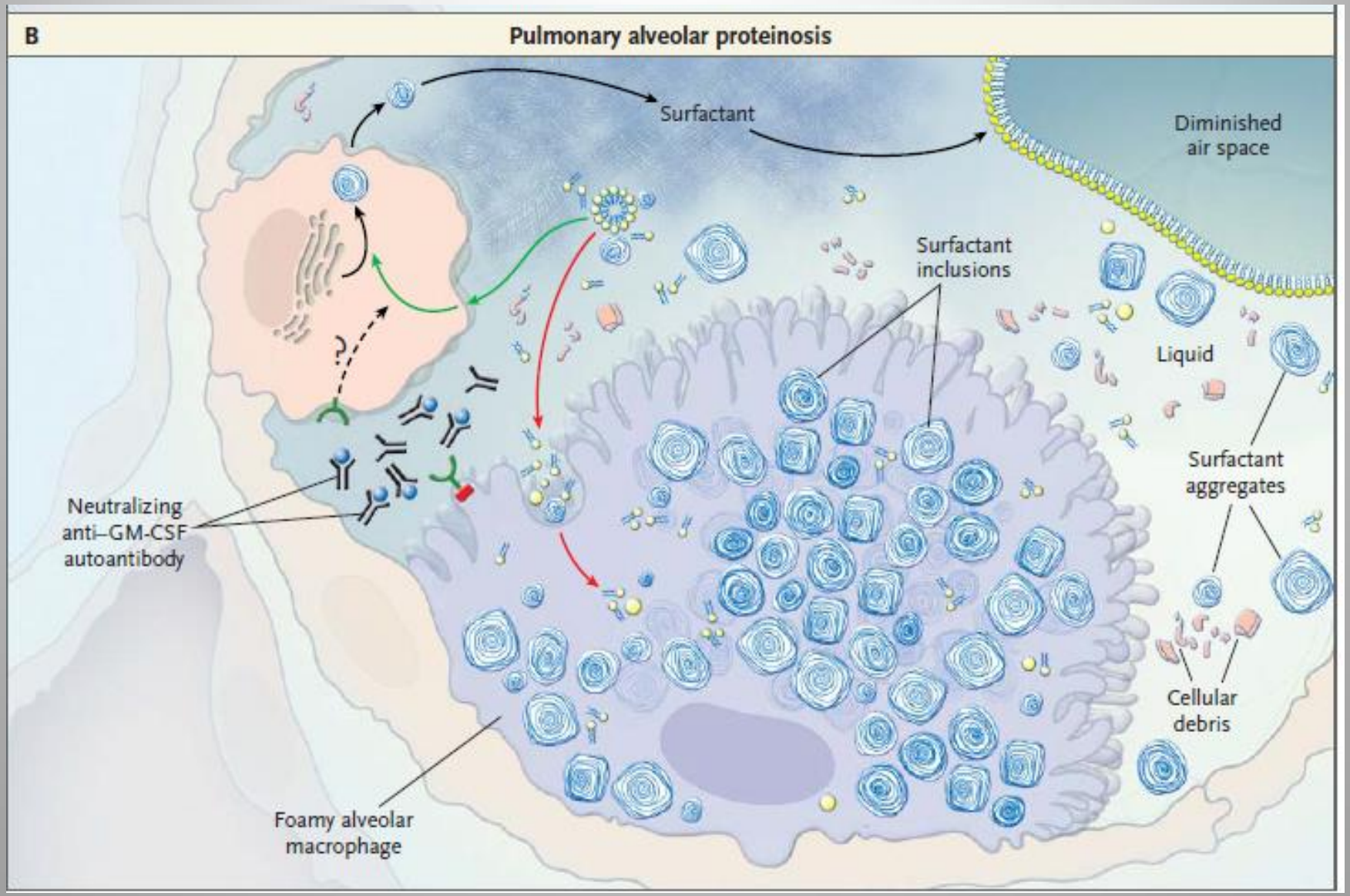
Reed JA, Ikegami M, Cianciolo ER, et al. Am J Physiol 1999;276:L556-L563.

Antibodies against GM-CSF

- BAL from patients, inhibited the ability of GM-CSF dependent cell from binding to GM-CSF.
- This inhibitory activity was due to a neutralizing IgG antibody against GM-CSF.

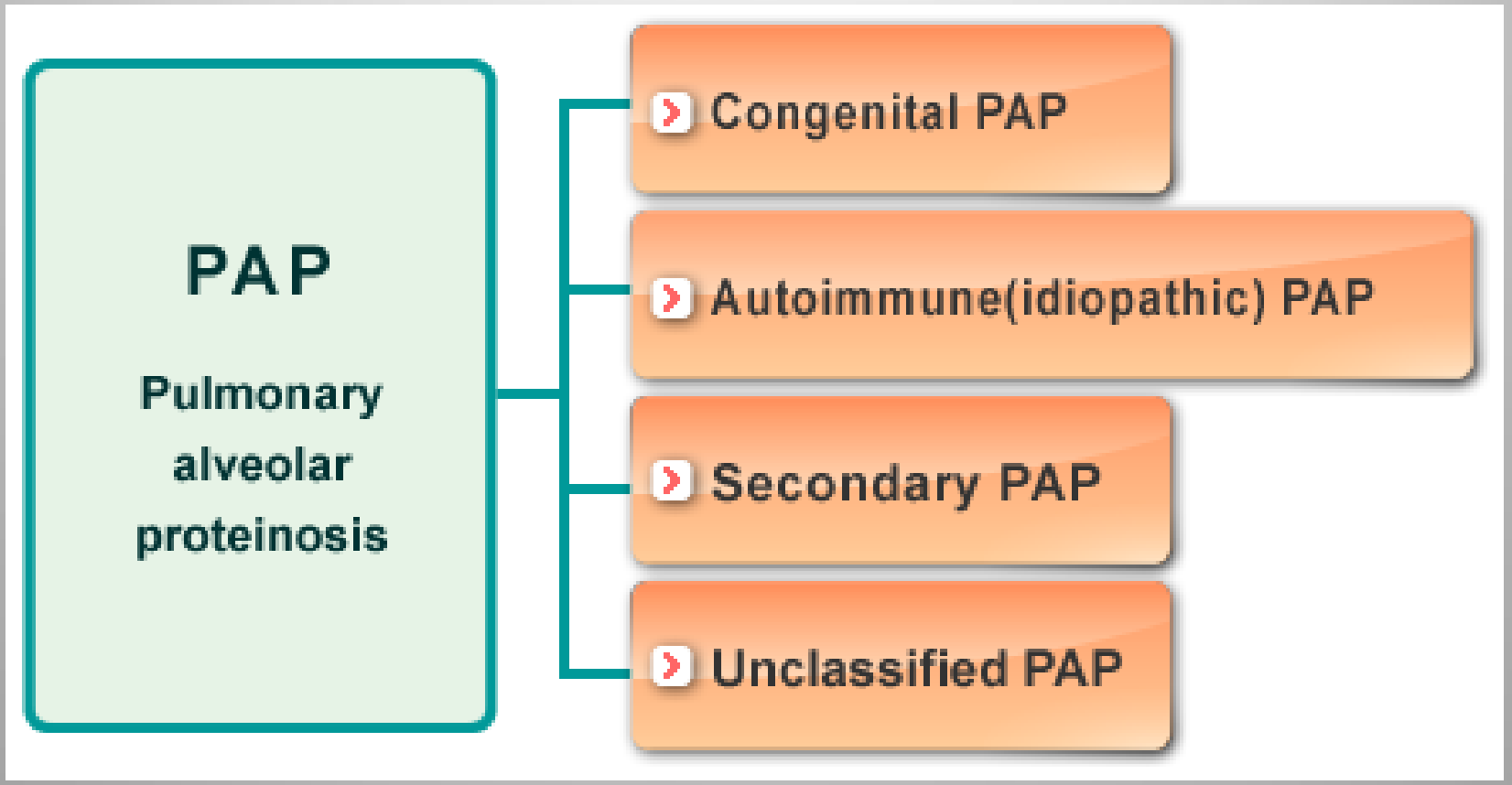
Ruben FL, Talamo TS. Am J Med 1986;80:1187-90.

Antibodies against GM-CSF



N ENGL J MED 349;26 WWW.NEJM.ORG DECEMBER 25, 2003

Classification of PAP



Congenital PAP

- Caused by congenital defects in the surfactant generation or degeneration process.
  - Surfactant protein B, C, or $ABCA_3$ deficiency.
  - Mutation (GM-CSF) receptor α or β.

Secondary PAP

- Develops secondarily to :
  - Rheumatologic/ Autoimmune diseases (e.g.Behcet disease, ADA deficiency)
  - Hematological disorders (e.g. myelodysplastic syndrome)
- Constitutes 6% of PAP.

Autoimmune (Acquired) PAP

- Constitutes 90% of PAP.
- Prevalence of 0.37 per 100,000 people and a median age at diagnosis of 39 years.
- Male : Female ratio 3:1
- 72 % have a history of smoking

Inoue Y, Trapnell BC, Tazawa R, et al. Am J Respir Crit Care Med 2008; 177: 752–762.

Trapnell BC, Whitsett JA, Nakata K. Pulmonary alveolar proteinosis. N Engl J Med 2003; 349:2527–2539

Clinical presentation

- Dyspnea is the most common presenting symptom.
- Less commonly,
  - Cough (often trivial).
  - Fever.
  - Chest pain.
  - Hemoptysis , especially if secondary infection is present.

Opportunistic infection in PAP

Pathogen	*n* (%)
Nocardia (*n* = 32)	
N. asteroides	19 (59%)
N. brasiliensis	1 (3%)
N. farcinica	1 (3%)
Nocardia spp.	11 (34%)
Mycobacteria (*n* = 28)	
M. tuberculosis	21 (75%)
M. kansasi	4 (14%)
M. avium intracellulare	3 (11%)
Fungi (*n* = 15)	
Aspergillus spp.	4 (27%)
Cryptococcus spp.	5 (33%)
Histoplasma capsulatum	4 (27%)
Aspergillus spp. and *Cryptococcus* spp.	1 (7%)
Zygomyces	1 (7%)
TOTAL	75

Punatar, Ankit D. ; Kusne, Shimon ,Holenarasipur R. Journal of Infection, 2012, Vol.65(2),

Clinical presentation

- Physical examination can be unremarkable:
  - Inspiratory crackles 50%.
  - Cyanosis in 25%
  - Digital Clubbing 1/3 of cases.

Laboratory findings

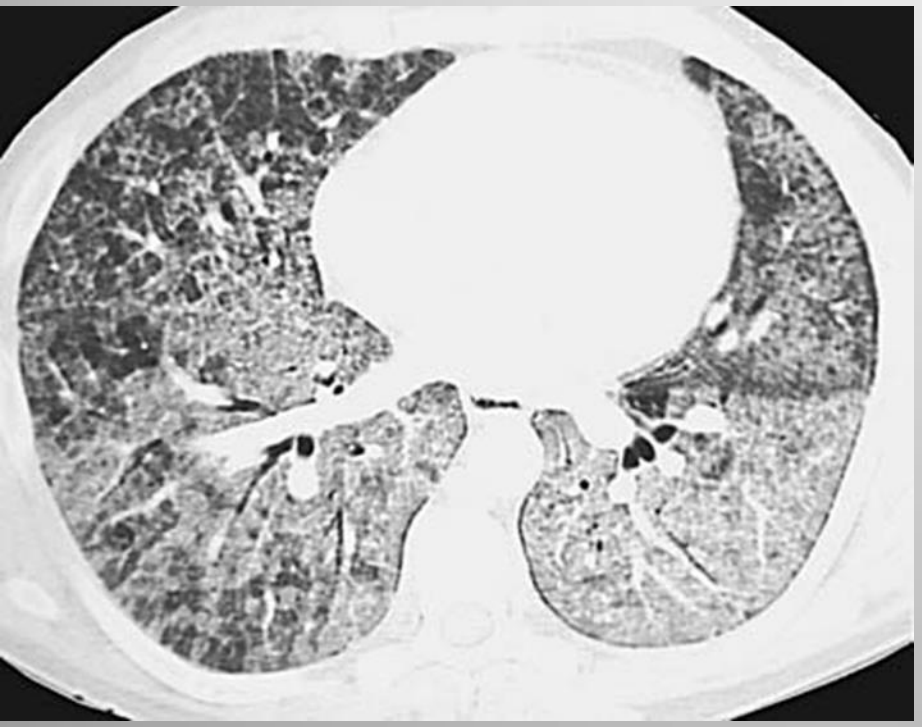
- Routine chemical analysis and urinalysis are usually normal.
- The serum level of LDH is frequently elevated.
- Elevations in the serum levels of:
  - Carcinoembryonic antigen (CEA)
  - Cytokeratin
  - Mucin KL-6

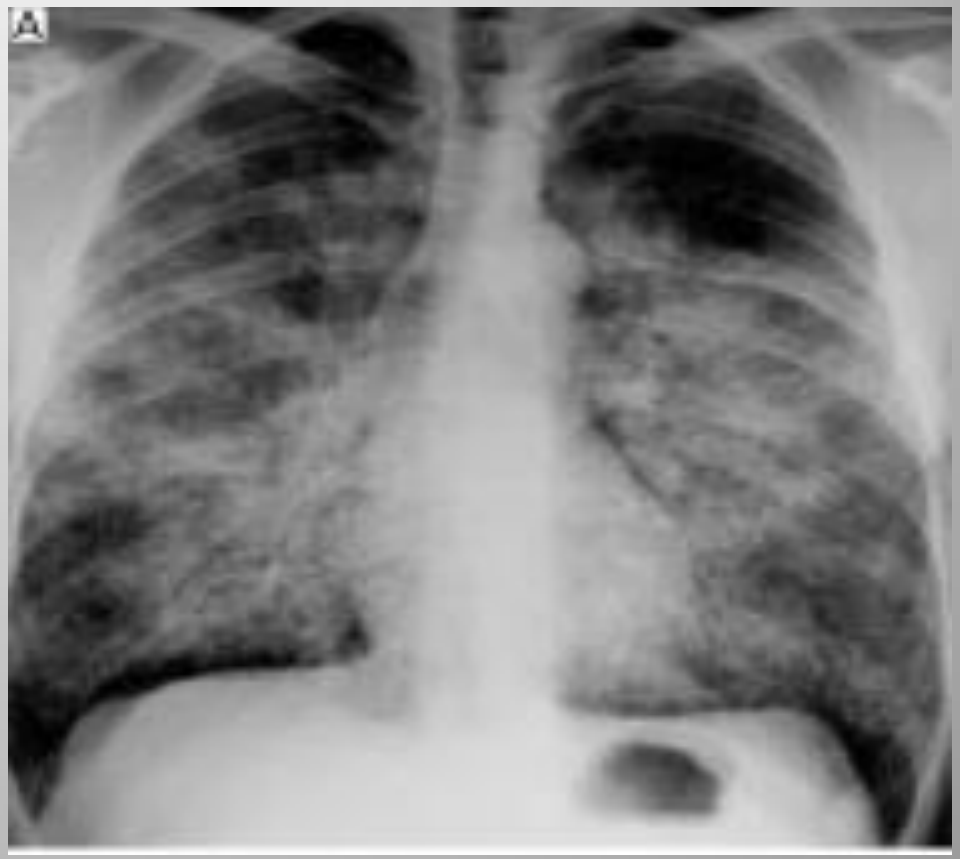
GM-CSF autoantibodies

- The latex-agglutination test has a sensitivity (100 %) and specificity (98 %) for the diagnosis of acquired PAP.

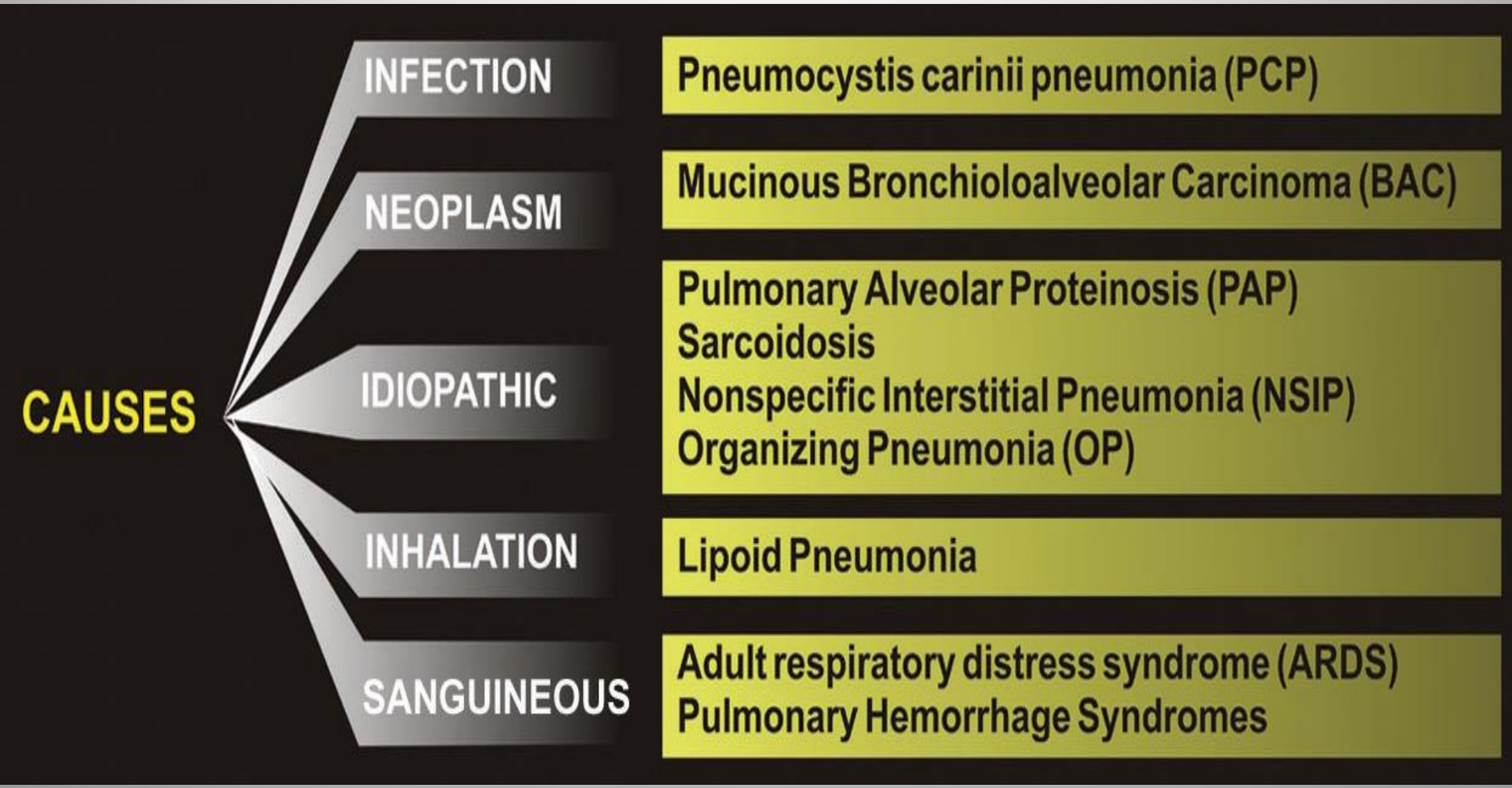
TAKAYUKI KITAMURA, KANJI UCHIDA, NAOHIKO TANAKA, and KOH NAKATA ", American Journal of Respiratory and Critical Care Medicine, Vol. 162, No. 2 (2000), pp. 658-662

Chest radiograph





DDx of Crazy-Paving



RadioGraphics 2003; 23:1509–1519

Pulmonary function

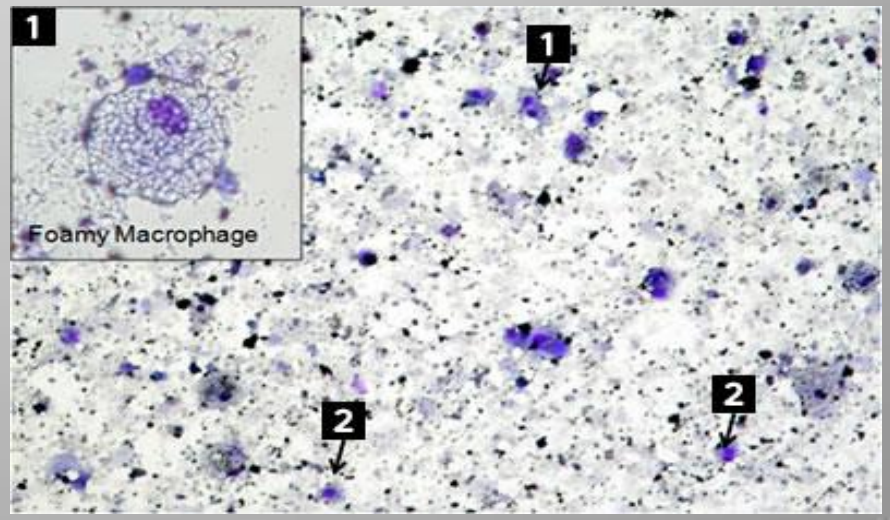
- Can be normal, but typically have a restrictive pattern.
- Slight impairments in the FVC & TLC.
- Severe reduction of the DLCO.

Hypoxemia

- Widened Alveolar– arteriolar gradient.
- This is thought to be due to:
  - Ventilation–perfusion inequality
  - Intrapulmonary Shunting.
  - Septal edema.
  - Interstitial fibrosis has been reported.

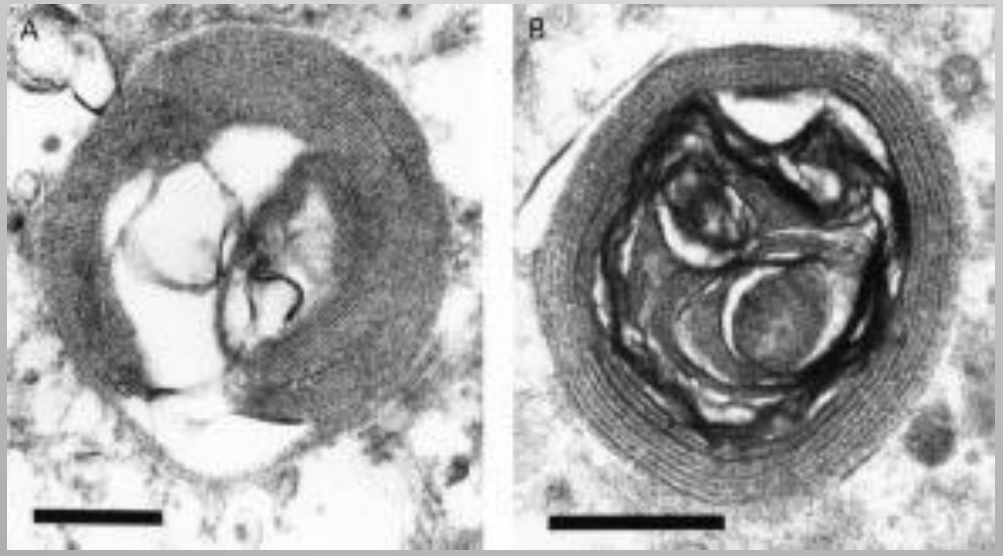
Broncho-alveolar Lavage

- The BAL fluid is opaque, milky appearance.
- Large eosinophilic bodies in a background of granular material that stains with (PAS).
  - Large, foamy alveolar macrophages



Electron microscopy

- BALF sediment shows the presence of lamellar bodies and tubular myelin aggregates.

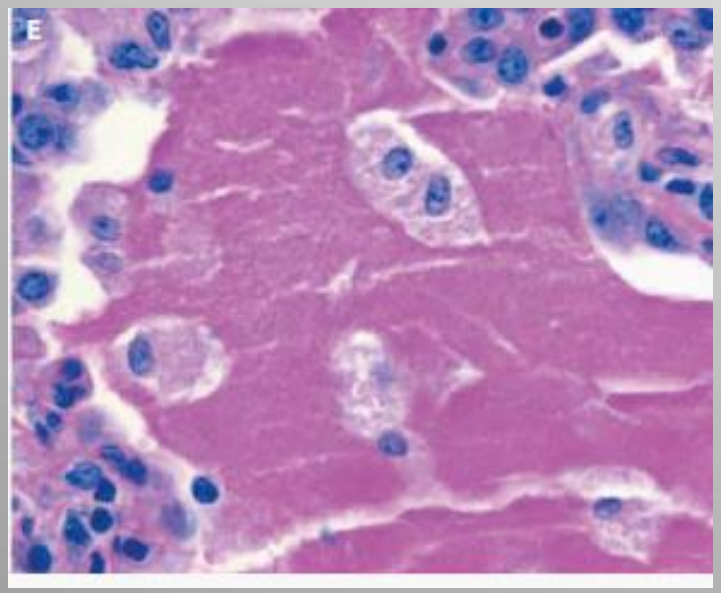


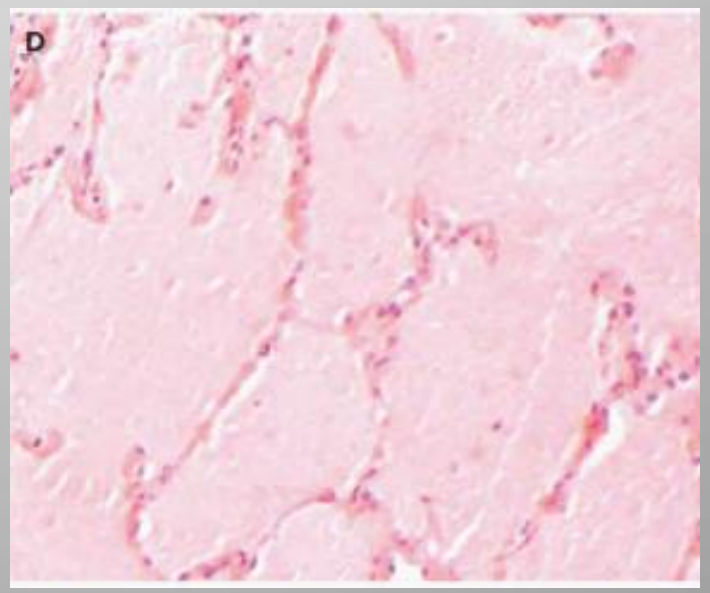
Open-lung biopsy

- The gold standard for the diagnosis of PAP, BUT:
- It is not always required.
- Can be false negative due to sampling error.

Microscopy

- Alveoli are filled with granular, eosinophilic material that stains with PAS.
- The architecture of the lung parenchyma is preserved.





Disease severity

- PFT can be used to assess disease
  - Severity.
  - Progression.
  - Response to treatment.

- P(A–a)O2 gradient on exercise is a better predictor of disease severity.

Rogers RM, Levin DC, Gray BA, et al. Am Rev Respir Dis 1978;118:255–64.
Kariman K, Kylstra JA, Spock A. Lung 1984;162:223–31.

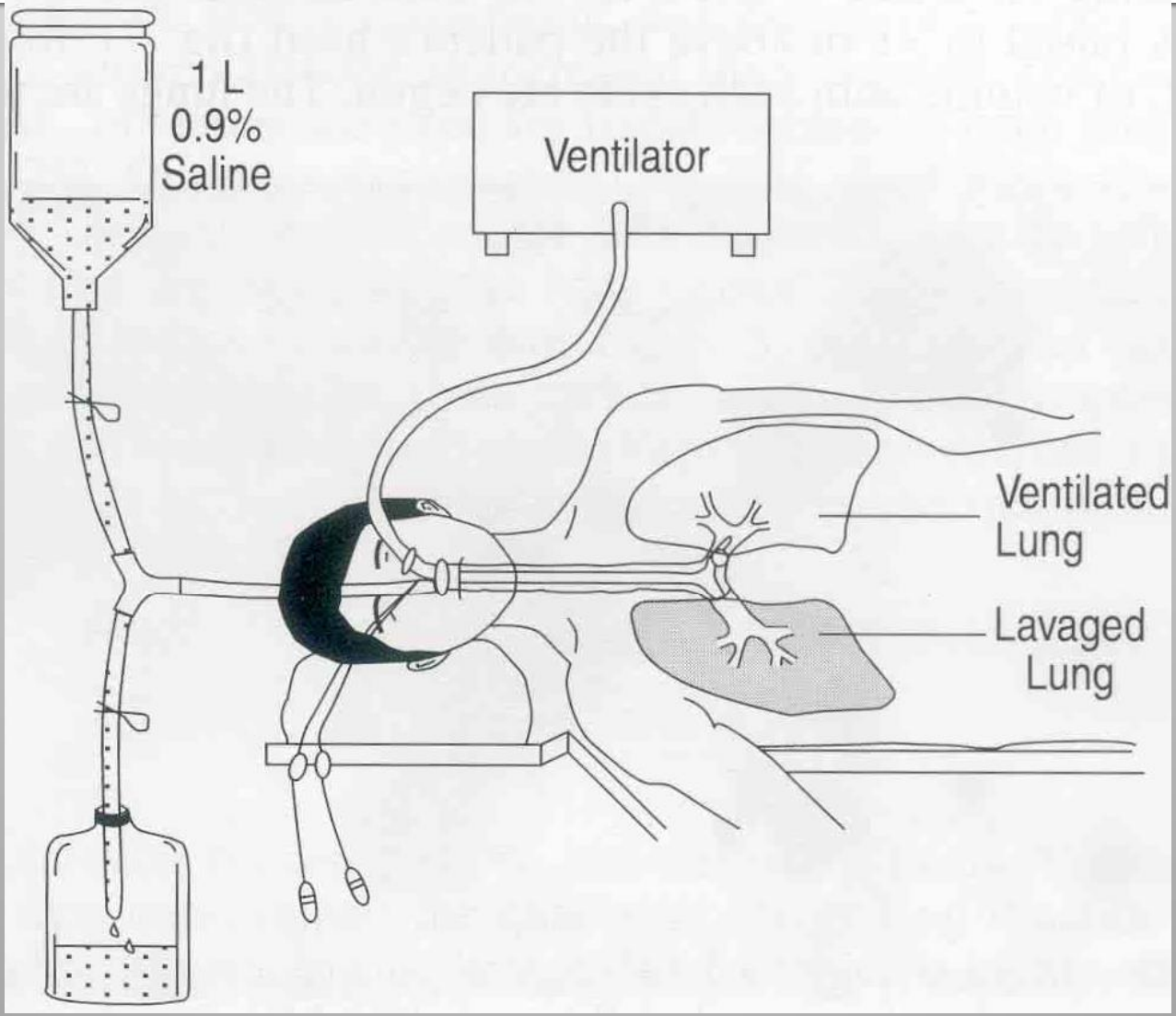
Therapeutic approaches

- Congenital form of the disorder:
  - Supportive
  - Lung Transplantation
  - BMT / Macrophage Transplantation
- Therapy for secondary PAP:
  - Treatment of the underlying condition

Acquired PAP

- Whole-lung lavage
- GM-CSF therapy
- Rituximab
- Others

Whole-lung lavage



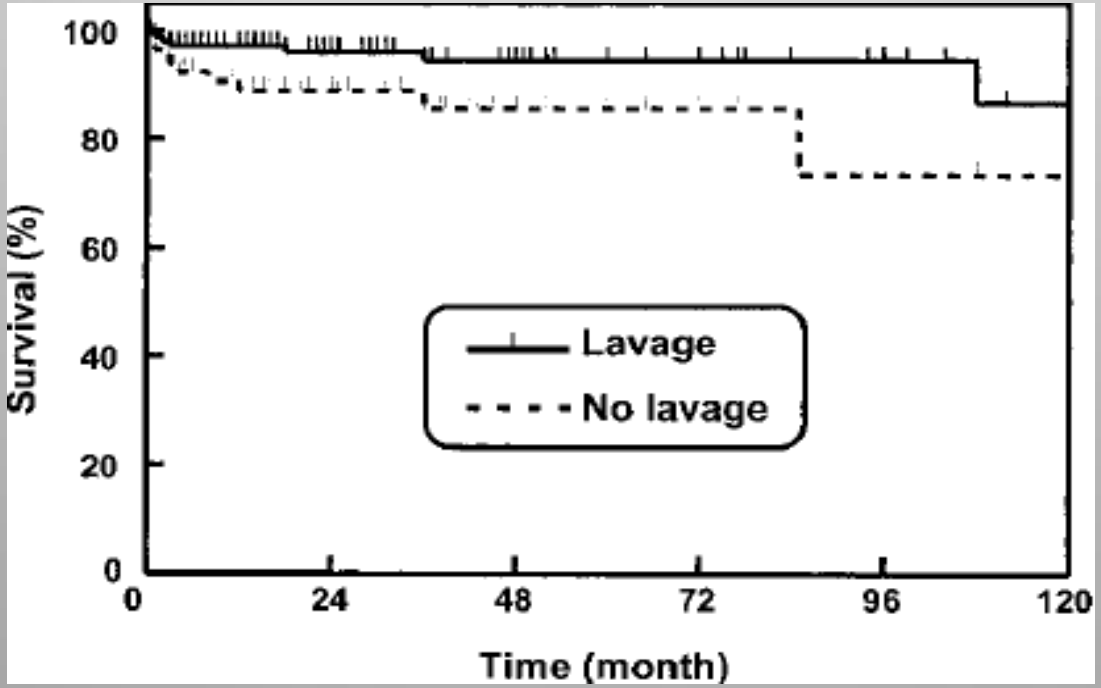
Whole-lung lavage

- A retrospective analysis of 231 cases found clinically significant improvement in :
  - Arterial oxygenation
  - Pulmonary function (FEV1, VC and DLCO).

Seymour JF, Presneill JJ. Am J Respir Crit Care Med 2002;166: 215-35

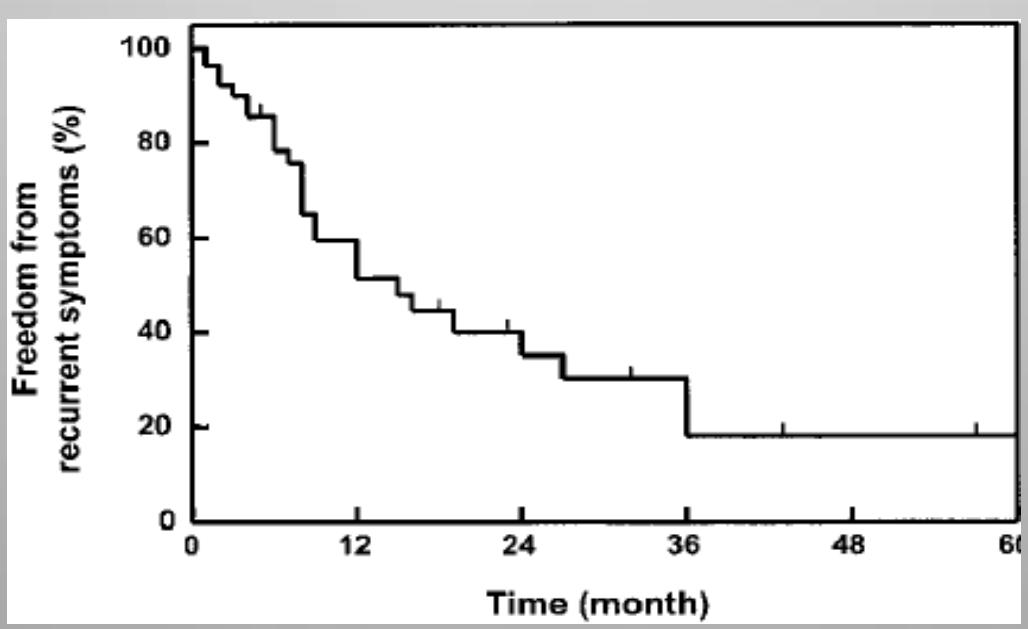
Whole-lung lavage

- The 5 years survival rate was 94±2 % with lavage, as compared with 85±5% without lavage (P=0.04).



Duration of response following lavage

- The median duration of clinical benefit from lavage was 15 months.
- Less than 20% of those patients followed beyond 3 years remaining free of recurrence.



In summary

- WLL is currently a safe procedure in an experienced setting.
- Immediate +ve outcome in >90% of cases.
- Recurrence rate ranging from 30 - 70%.
- No randomized controlled studies of WLL to determine the optimal strategy.

GM-CSF subcutaneously

- Multiple trials of subcutaneous GM-CSF treatment of patients with acquired PAP.

- Significant effect on:
  - PaO_2.
  - $P(A\text{-}a)O_2$.
  - DLCO.
  - CT scan.
  - 6-minutes walking test.

GM-CSF subcutaneously

	Trial	Intervention	Doses/repeats	Duration	Effect in % (patients)
1996	Seymour *et al.*[41]	GM-CSF subcutaneously	5 μg/kg/day (7,5–20)†	10–26 weeks	36% (*n* = 14)
2000	Kavuru *et al.*[42]	GM-CSF subcutaneously	250 μg/day; increased to 5–9 μg/kg/day†	12 weeks	75% (*n* = 4)
2002	Bonfield *et al.*[43]	GM-CSF subcutaneously	250 μg/day; increased to 18 μg/kg/day†	12–48 weeks	55% (*n* = 11)
2006	Venkateshiah *et al.*[44]	GM-CSF subcutaneously	250 μg/day increased to 5–18 μg/kg/day†	12–52 weeks	48% (*n* = 21)

GM-CSF subcutaneously

- Over all, was effective in about 50 – 70% of the cases with varying doses and treatment durations.

- Complications are considered minor:
  - Injection-site Erythema & edema
  - Malaise
  - Shortness of breath.
  - Neutropenia has been reported.

GM-CSF inhaled

	Trial	Intervention	Doses/repeats	Duration	Effect in % (patients)
2005	Tazawa *et al.*[45]	GM-CSF inhaled	250 μg/day; every second week	24 weeks	100% ($n = 3$)
2010	Tazawa *et al.*[46]	GM-CSF inhaled	250 μg/day; every second week for 12 week tapered to 4 days every second week for 12 weeks	24 weeks	62% ($n = 39$)

Improved:

- Arterial oxygen
- P (A-a)O2
- DLCO, and
- Forced vital capacity

Inhaled GM-CSF

- Over all , inhaled GM-CSF was effective in 4/5 patients.
- Complications include:
  - Fever
  - Otitis media
  - Upper respiratory infection
  - Diarrhea

Rituximab

	Trial	Intervention	Doses/repeats	Duration	Effect in % (patients)
2009	Borie *et al.*[47]	IV rituximab	1000 mg day 0 and 15	15 days	100% ($n = 1$)
2010	Amital *et al.*[48]	IV rituximab	rituximab 375 mg/m^2 administered weekly for 4 weeks	4 weeks	100% ($n = 1$)
2011	Kavuru *et al.*[49]	IV rituximab	1000 mg day 0 and 15	15 days	78% ($n = 9$)

Improvements were noted in

- P(A-a)O2
- Total lung capacity (TLC)
- High-resolution CT (HRCT) scans

Rituximab

- In conclusion, rituximab shows promising results in most of the treated patients.
- Adverse reactions were minor :
  - Fatigue
  - Headache
  - Dizziness
  - Anorexia
  - Upper respiratory infection

Other therapies

- Plasmapheresis
- Combination Therapy

Objectives

- Understand the pathophysiology of PAP
- Differentiate between the Classes of PAP
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References

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thanks,
photography