Fibroza Chistica

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Ce este fibroza chistica (FC)?

"Cystic fibrosis (CF) is a hereditary disease of the *mucus, saliva and sweat glands. It affects organs such as lungs, pancreas, liver, intestines, sinuses, and sex organs"* (MedicineNet Inc)

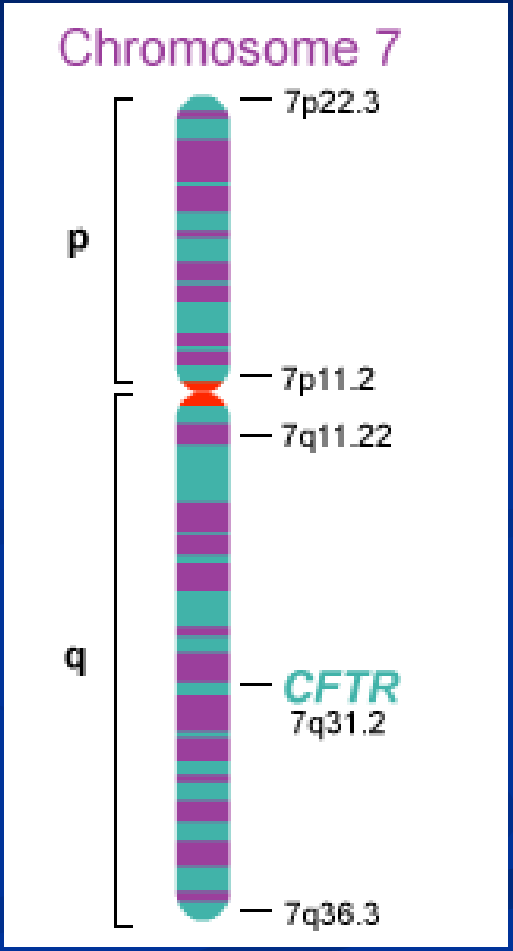
"Cystic fibrosis is the most common inherited, life limiting, incurable condition amongst Caucasians" (Royal Children's Hospital)

Importanta FC

- Cea mai fecventa boala genetica ce scurteaza viata la Caucazieni
  - 1 la 3500 nou-nascuti in USA
  - 1 la 15000 nou-nascuti afro-americani
  - 1 in 25500 nou-nascuti asiatici
- 80% cazuri dg < 2 ani
- 10% cazuri dg > 18 ani (forme mai usoare)

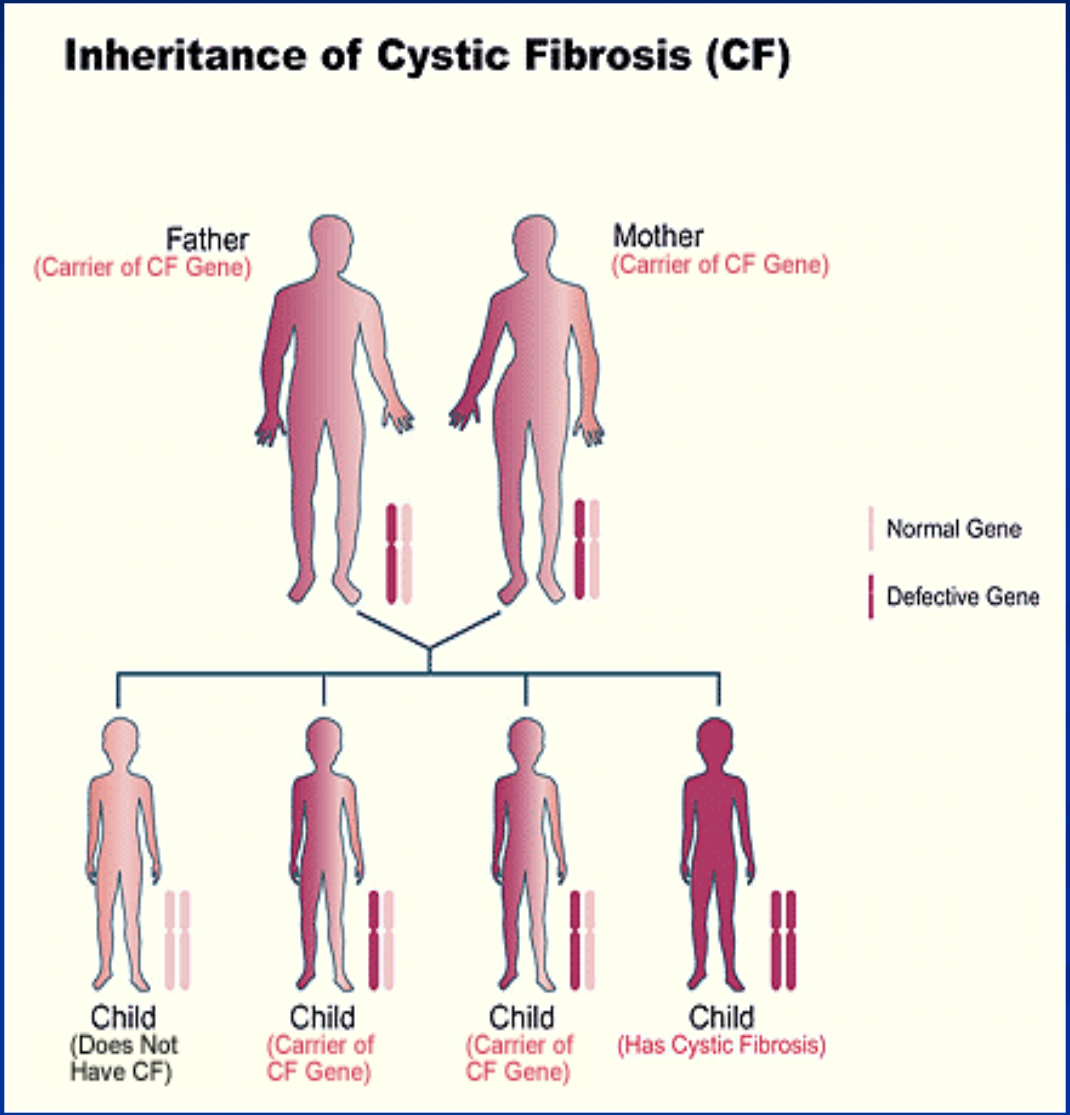
Ce este fibroza chistica (FC)?

- Boala sistemica, genetica, autosomal recesiva
- Cauza: mutatii ale genei "cystic fibrosis transmembrane conductance regulator (CFTR)"
  - cromosomul 7
  - codifica un canal membranar de Cl reglat de c-AMP



Rosenstein, BJ and Zeitlin, PL. Cystic fibrosis. The Lancet. 351: 277-82.

Transmiterea genei FC



Patogenie

- Clearance-ul mucusului depinde de :
  - Functia ciliara
  - Secretia de mucina
  - Volumul de liq de la suprafata CAI
    - Formeaza strat periciliar de lichid
    - “Entrapment” al bacteriilor
    - Reglat de absorbtia Na+ si secretia Cl-

Volumul de liq de la suprafata CAI

- CFTR normala inhiba si un canal de Na
  - CFTR mutanta----canal ne-inhibat
    - Absorbtia Na e crescuta
    - Apa urmeaza Na
    - Volumul liq supraf CAI scade
- CFTR normala --- Cl- e secretat atunci cind Vol liq supraf CAI e mic
  - CFTR mutanta --- Cl- nu e secretat

Consecinte

- Scade miscarea cililor
- Mucina e aderenta – eliminare dificila
- Mucusul devine concentrat
  - Aderenta crescuta la mucoasa
  - Favorizeaza infectia cronica

Clinic:

- Boala cronica sino-pulmonara
- Deficiente nutritionale/afectare GI
- Infertilitate
- Diselectrolitemie

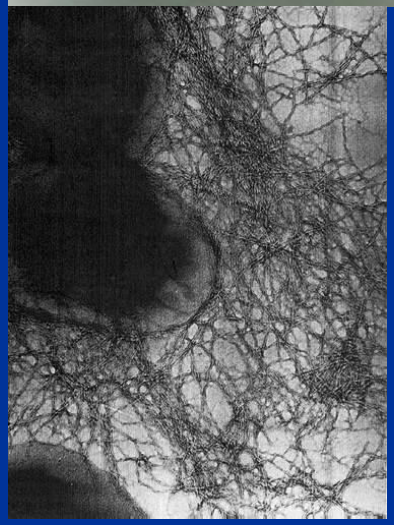
Boala Cronica Sino-Pulmonara

- Infectie cronica cu patogeni
- Boala endobronsica
  - Tuse productiva
  - Boala obstructiva (wheezing; disfunctie obstructiva la PFR)
  - Anomalii Rx
  - “Digital Clubbing”
- Boala sinusala
  - Polipi nazali
  - “gaselnita” la CT / Rx-ray

Infectia---*Pseudomonas aeruginosa*

- 80% pacienti fac cindva infectie cu pseudomonas
- Determina deteriorare clinica
- Biofilm (cresc lent, Ac ineficienti, rezistenta Ab)
- Genom mai mare decit tulpinile de laborator

Infectia ---*Burkholderia cepacia*



Holmes, A, Govan, J, and Goldstein, R. Agricultural Use of Burkholderia cepacia:
A Threat to Human Health?
Emerging Infectious Diseases. 4(2):221-227; 1998

- Sindromul *B. cepacia* : febra, pneumonie necrotica rapid progresiva, deces
- Infectia cronica—functie pulmon scazuta, mortalitate crescuta
- Mai multe specii inrudite genomovari
  - III – boala mai severa

Boala endobronsica

- Hiperinflatie
- Bronsiectazie
- Fibroza difuza
- Atelectazie

Polipi nazali

- Mari – obstructie nazala – cefalee, sforait
- Asociati cu inflamatia cronica
- Pot necesita interventie chirurgicala
- Rata mare de recurenta

“Digital Clubbing”

From: Fawcett et al., 2004

- Stergerea unghiului normal dintre unghie si patul unghial---semnul Schamroth
- Se pot asocia cu boli pulmonare, colita ulceroasa, neoplazii

Deficiente nutritionale

- Insuficienta pancreatica
  - Autopsii 1938 --- "cystic fibrosis of the pancreas" : obstructia ductelor glandulare cu mucus[1]
  - "impermeabilitatea" pt Cl- afecteaza secretia de HCO3- si apa in ductele pancreatice
    - Enzimele pancreatice ramin in ducte si se activeaza intraductal
      - Autoliza pancreasului
      - Obstructia ductelor, inflamatie, calcificari, fibroza
  - Malabsorbtie
    - Deficite de vitamine liposolubile

1. Davis, P. Cystic Fibrosis Since 1938. AJRCCM Articles in Press. Doi: 10.1164/rccm.200505-840OE; 2005.

Boala GI

- Afectare intestinala
  - Ileus cu meconiu
  - Obstructie intestinala distala
  - Prolaps rectal
- Boala hepatobiliara (10-40%)
  - A doua cauza de deces
  - Enzime crescute
  - HTPortala
  - Ciroza biliara (focala / multilobulara)
- Disfunctie a pancreasului endocrin
  - Diabet zaharat

Infertilitate

- Barbati
  - Dezvoltare embriologica anormala a ductului epididimar si a canalului deferent
  - Absenta bilaterala congenitala a canalului deferent — 97-98% din barbatii cu FC
- Femei
  - Mucus cervical : viscos si redus cantitativ
  - Sarcina nu influenteaza prognosticul bolii

Diselectrolitemia

- Alcaloza metabolica hipochloremica:
  - CFTR la capătul luminal ductului gld sudoripare
    - Cl- trece in celule din lumen via CFTR
    - Na+ trece via canalul de Na
  - CFTR anormala--- “miscarea” Na+ si Cl- in lumen este alterata l

Diagnostic paraclinic

Masurarea Cl- in sudoare

- Tehnica descrisa de Gibson si Cooke in 1950
  - Subst ce stimuleaza transpiratia pusa sub electrod; ser fiziologic sub alt electrod, pe brat
  - Curent electric de intensitate mica intre
  - Colectarea traspiratiei si masurarea Cl-

- Pozitiv : 60-165 meq/L
- "Borderline" (incert) : 40-60 m
- Normal : 0-40

Testare genetica

- A celor mai frecventa mutatii / secventializarea completa a genei

- Screening prenatal :
  - Am Coll OBG - 23 cele mai frecvente mutatii
  - Sensibilitate ~ 75%

Tratament multidisciplinar

- Clearance-ul cailor aeriene
- Infectia
- Inflamatia
- Nutritia
- Infertilitatea
- Gastrointestinal
- Probleme sociale

Tratament: “toaleta pulmonara” / clearance-ul cailor aeriene

- Fizioterapie
  - Drenaj postural / tapotare
  - Dispozitive diverse (High frequency chest wall oscillation)
- Albuterol
  - Bronhodilatatie
  - Creste eficienta cililor
  - Nebulizari cu SF hieprton

Tratament: infectia cronica

- Antibiotice inhalatorii
  - Tobramicina inhalator la pacienti cu pseudomonas
- Dupa antibiograma culturii sputei
- Tratamentul exacerbarilor
  - Exacerbare---modificarea simptome / semne fata de nivelul "obisnuit" (tuse, productia de sputa, PFR, crackles >)
  - Necesita spitalizare pt Ab IV si crestera clearance cai aeriene

Tratament: anti-inflammatorii

- Ibuprofen
  - Konstan et al., 2003
  - 85 pacienti, virsta 5-39, boala pulm usoara, placebo sau ibuprofen doza mare 4 ani
    - Grupul ibuprofen :
      - Scadere anuala a FEV1 mai lenta; mentin mai bine nutritia
      - Fara diferenta in frecventa spitalizarilor
      - Efect optim la pacientii < 13 ani

Konstan et al., Effect of High Dose Ibuprofen in Patients with Cystic Fibrosis. NEJM. 332:848-54; 2003.

Tratament: Nutritia

- Element important de urmarit
- Enzime pancreatice (A! colopatie fibrozanta)
- Suplimentare vitaminica
- Alte suplimentari - dupa nevoi

Tratament: afectarea hepatica

- Ursodiol
  - Creste fluxul biliar
  - Scade toxicitatea acizilor biliari
- Scleroterapie, sunturi portosistemice
- Transplantul hepatic – singurul tratament curativ pt HTPortala

Tratament: infertilitatea

- "Microsurgical epididymal sperm aspiration"
- "Percutaneous epididymal sperm aspiration"
- "Testicular sperm extraction"

Probleme psihosociale

- Calitatea vietii
  - Spitalizari frecvente
  - Timpul petrecut in spitale
  - Morbiditatea legata de boala
  - Restrictiii legate de boala
- Aderenta la terapie
- Planning familial
- “End of life issues”

Supravietuirea

- Tendinta la imbunatatire
- La femei – mai mica ca la barbati (intre 2-20 ani)
- 35% din pacienti au peste 18 ani la diagnostic
- Supravietuirea medie - 36.8 ani (1930 - 6 luni)

Pneumoniile de hipersensibilitate (alveolita alergica extrinseca)

- Boli pulmonare interstitiale, mediate imun
- Produse de expunerea la prafuri organice sau alti antigeni profesionali sau nu
- Dupa frecventa, durata, intensitatea expunerii si durata bolii sunt acute, subacute, cronice

Forma acuta

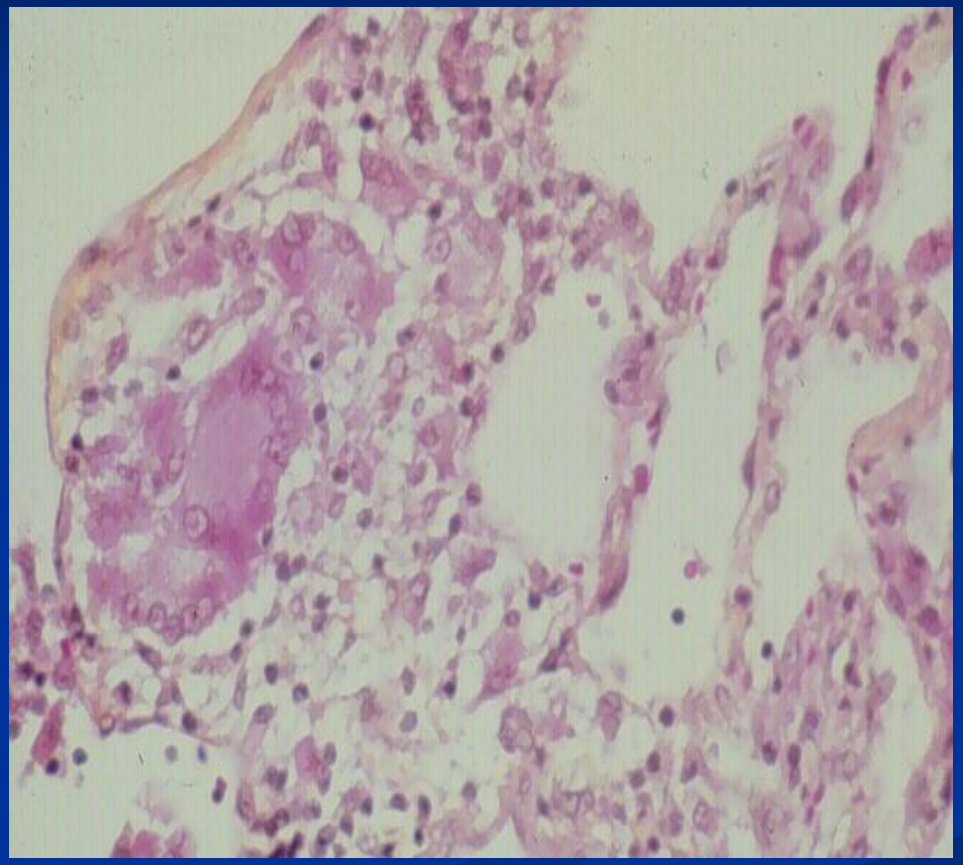
- Cea mai frecventa
- Dupa expunere masiva
- Mimeaza infectia bacteriana sau virala
  - Febra, frison, tuse, dispnee, greata, varsatura; fara wheezing
- Clinic :
  - Polipnee si raluri crepitante uscate fine
- A fost initial tratata antibiotic
- Inlaturarea expunerii - remisiune completa in 12h-zile
- Poate reapare la reexpunere

Forma acuta

- Laborator si paraclinic (valoare limitata)
  - VSH, CRP, CIC crescute
  - LDH crescut ; scade cu ameliorarea
  - LBA – posibil limfocitoza
  - Gaze arteriale : hipoxemie usoara
  - PFR : restrictie in timpul episoadelor simptomatice

Forma acuta

- Histopatologie
  - Granuloame interstitiale necazeoase, prost delimitate
  - Infiltrat mononuclear peribronsic cu celule gigante
- Imagistic
  - Pattern micronodular interstitial cimpuri inf erior si mijlociu (HRCT)
  - Rx - normal



Forma subacuta

- Instalare insidioasa
- Simptome
  - Tuse productiva, dispnee, oboseala
- Examen clinic
  - Polipnee si raluri difuze
- Indepartarea expunerii – rezolutie completa (saptamini, luni)
- Poate fi necesara corticoterapia

Forma subacuta

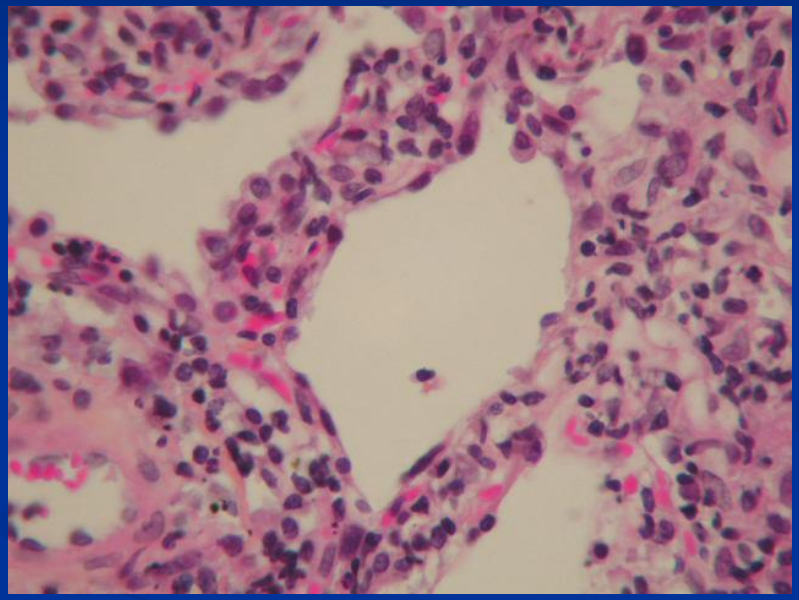
- Laborator si paraclinic
  - LBA - limfocitoza
  - Hipoxemie usoara
  - PFR :
    - Pattern restrictiv / mixt
    - DLCO scazut
- Imagistica
  - Rx : opacitati micronodulare sau reticulare cimp mijl si sup
  - HRCT : micronoduli, aspect de "pseudo sticla mata", fibroza minima
- Histopatologic
  - Granuloame interstitiale necazeoase bine delimitated
  - Bronsiolita
  - Fibroza interstitiala putina

Forma cronica

- Fara istoric de episoade acute
- Debut insidios cu tuse, dispnee, oboseala, scadere ponderala
- Stadii avansate – hipocratism, fibroza pulmonara ireversibila
- Indepartarea expunerii – ameliorare partiala, necesita corticoterapie

Forma cronica

- Laborator, paraclinic (utilitate minima)
  - LBA – limfocitoza, neutrofilie, eozinofilie
  - PFR : orice pattern
  - DLCO scazuta
  - Hipoxemie de efort / repaus
- Imagistica
  - Modificari fibrotice progresive cimp superior
  - "fagure de miere" si/sau emfizem
- Diagnosticul
  - Necesita biopsie pulmonara
  - Aspect : pneumonita interstitiala difuza, distructie alveolara ("fagurele"), bronsiolita obliteranta, fibroza densa



Eozinofilia pulmonara

- Boli caracterizate prin cresterea numarului eozinofilelor din parenchimul pulmonar

- Caracteristici necesare pentru diagnostic:
  - Eozinofilie periferica + anomalii pulmonare
  - Eozinofilie pulmonara (biopsie pulmonara)
  - Eozinofilie in LBA

Causes of Pulmonary Eosinophilia

Drug- and toxin-induced eosinophilic lung diseases

- Nitrofurantoin
- Phenytoin
- L-tryptophan

Helminthic and fungal infection-related eosinophilic lung diseases

- Transpulmonary passage of larvae (Loffler's syndrome)
  - Ascaris lumbricoides
  - Hookworm
  - Strongyloides stercoralis
- Pulmonary parenchymal invasion — mostly helminths, eg, paragonimiasis
- Heavy hematogenous seeding with helminths
  - Trichinosis
  - Disseminated strongyloidiasis
  - Cutaneous and visceral larva migrans
  - Schistosomiasis
- Tropical pulmonary eosinophilia
  - Wuchereria bancrofti
  - Brugia malayi
- Allergic bronchopulmonary aspergillosis

Acute eosinophilic pneumonia

Chronic eosinophilic pneumonia

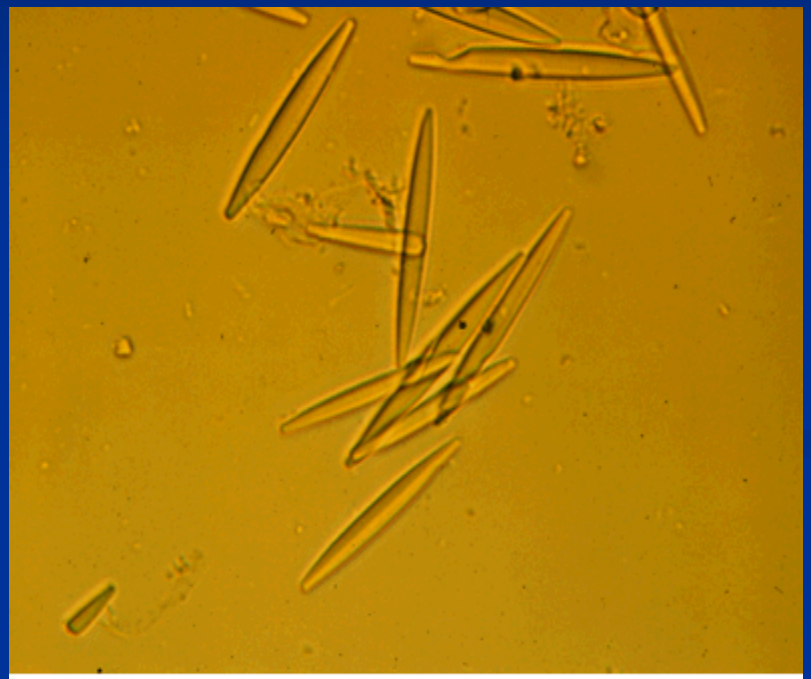
Churg-Strauss syndrome

Other

- Idiopathic hypereosinophilic syndrome
- Idiopathic lung diseases
- Neoplasms
- Nonhelminthic infections

Infectii paraziare

- Sdr Loffler
  - **Ascaris lumbricoides**, Strongyloides stercoralis
  - Simptome – tuse iritativa neproductiva, disconfort substernal agravat de tuse sau inspir profund
  - Posibil – dispnee, wheezing, febra, sputa hemoptoica cu cristale Charcot Leyden
  - Rx : infiltrate rotunde sau ovalare



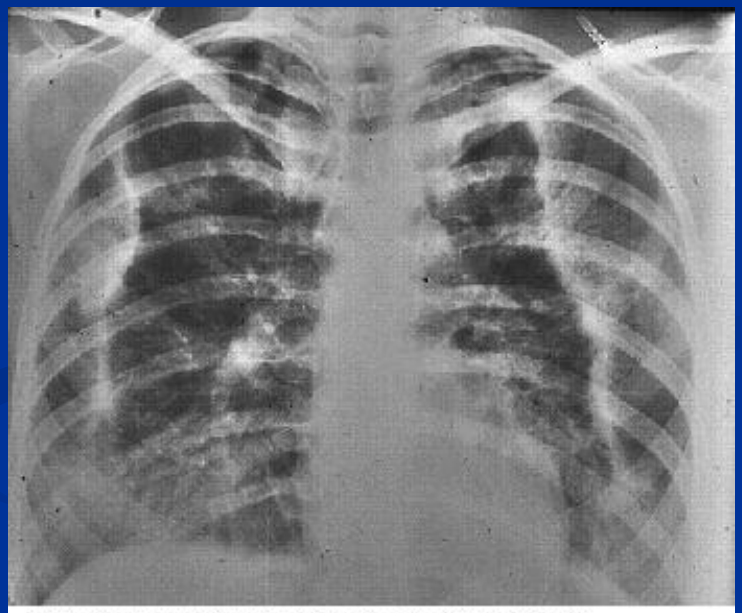
Charcot-Leyden crystals Charcot-Leyden crystals as found in sputum from a patient with ascariasis. These crystals, which are found in all eosinophilic parasitic lung infections consist of lysophospholipase, an eosinophil-derived enzyme. Courtesy of Peter F Weller, MD.

Toxine si medicamente

- Toxine
  - Silicat aluminiu si particule de metale
  - Veninul scorpionului
  - Heroina inhalatorie
  - Inhalarea de chimicale rezutind din cauciuc
- Medicamente frecvent utilizate : AINS, antibiotice
  - Mai rar - phenytoin, L-tryptophan, rantidine, trazodone

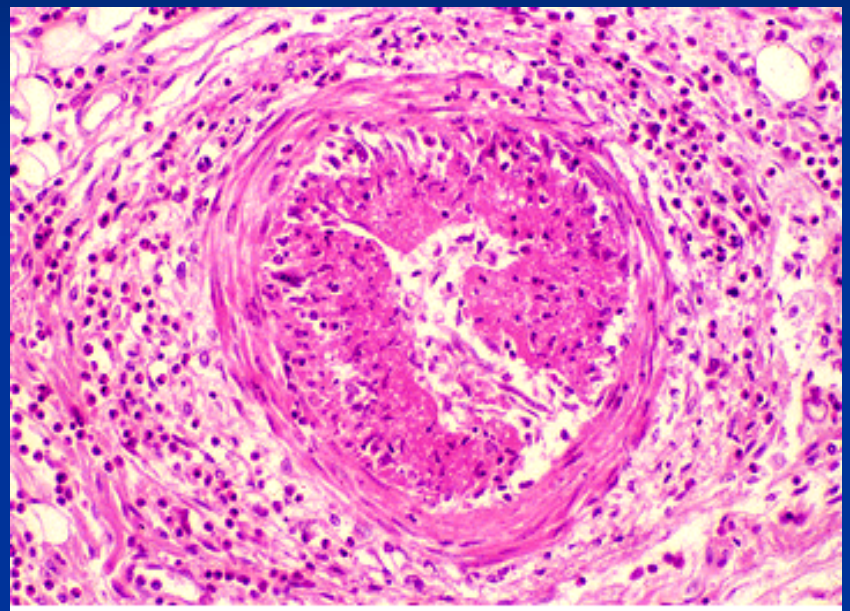
Forma acuta *vs* forma cronica

- Acuta (AEP)
  - Cauza de IResp acuta
  - Boala acuta febrila, <7 zile, tuse seaca, dispnee
  - Histopatologic : eozinofile multe interstitial si alveolar, membrane hialine, afectare alveolara difuza
- Cronica (CEP)
  - Afecteaza mai alea femeile si ne-fumatorii
  - Boala subacuta febrila cu tuse, dispnee progresiva, wheezing, scadere ponderala, transpiratii nocturne
  - In 50%, precedata sau insotita de tablou de astm
  - Rx : patognomonic – infiltrate periferice cu baza la pleura "negativul" edemului pulmonar



Chronic eosinophilic pneumonia Chest radiograph shows the so-called photographic negative pattern of pulmonary edema with selective consolidation of the outer periphery of the lung parenchyma. Courtesy of Paul Stark, MD.

Sdr Churg-Strauss



Vasculitis and eosinophilic infiltration in Churg Strauss Small artery in a patient with Churg Strauss syndrome showing intimal fibrinoid necrosis and mural infiltration by histiocytes consistent with a necrotizing granulomatous vasculitis. There is marked extravascular eosinophilia.

- Vasculita : sinuzita, astm, eozinofilie periferica mare
- Rx : opacitati parcelare tranzitorii, fara vreo distributie particulara
- Biopsia pulmonara : infiltrat eozinofilic, granulom interstitial si perivascular necrotizant, vasculita

Abordare diagnostica in eozinofiliile pulmonare

- Clinic
  - Istoric de expunere la noxe / medicamente
  - Examen pulmonar
  - Afectari extrapulmonare

- Eozinofilie sanghina
- Imagistica
  - Foarte utila in diagnosticul AEP, CEP
- Tehnici invazive
  - LBA – nr leucocite, tip leucocite
  - Idaca LBA irelevant, atunci biopsie pulmonara (transbronsica, pe torace deschis, video-asistata)

Tratament

- Inlaturarea expunerii
- “watchfull waiting”
- Corticoterapie (0,5-1mg/kgc)

Sdr de detresa respiratorie acuta (ARDS)

A.K.A.

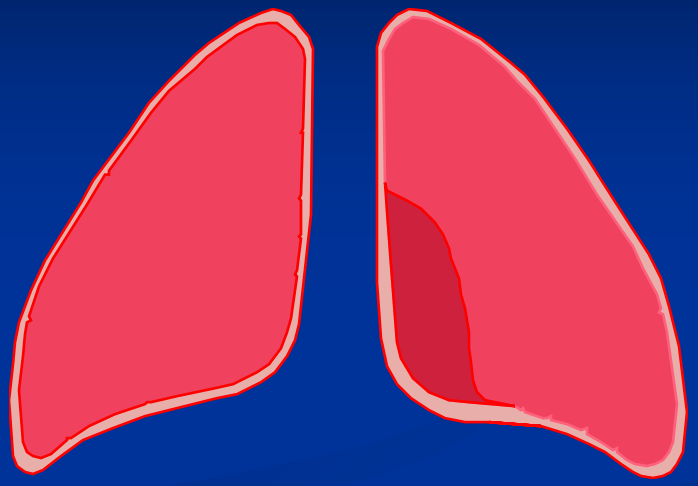
- "Adult Respiratory Distress Syndrome
- Da Nang Lung
- Transfusion Lung
- Post Perfusion Lung
- Shock Lung
- Traumatic Wet Lung"

ARDS
Definitie

- Afectare alveolara severa, acuta, difuza prin cresterea permeabilitatii microvasculare, cu edem pulmonar acut NEcardiogen
- Hipoxemie acuta refractare
- Incidenta anuala 75/100,000 in USA
- Prima descriere - 1967

Definitie CONSENS 1994

- Debut acut
- Infiltrate pulmonare bilaterale
- PCWP < 18 mm Hg
- ARDS - $PaO_2/FiO_2 \leq 200$
  - "Acute Lung Injury" - $PaO_2/FiO_2 \leq 300$



Factori declansatori

- Socul
- Traumatisme
- Infectii
- Inhalarea de gaze toxice
- Medicamente si otravuri
- Aspiratia continutului gastric
- Diverse

ARDS cauze

- Lezarea directa a plaminului :
  - a) pneumonia, aspiratia continutului gastric
  - b) embolia grasoasa
  - c) contuzia pulmonara
  - d) leziuni inhalatorii
  - e) leziunea de reperfuzie pulmonara dupa transplant

ARDS causes

- Lezarea indirecta a plaminului

  a) sepsis

  b) traumatisme severe cu soc hipovolemic

  c) supradozari medicamentoa

  d) “cardiopulmonary bypass”

  e) pancreatita acuta

  f) transfuziile multiple

Patogenie

- Evenimentul declansator
- Mediatori inflamatori
  - Lezarea endoteliului microvascular
  - Lezarea epiteliului alveolar
  - Acumulare de lichid bogat in proteine si cell inflamtorii
- Disfunctia surfactantului

ARDS

-

Stadii

- Acut (faza exudativa)
  - IRespA rapid instalata dupa trigger
  - Alveole pline cu lichid bogat in proteine
  - “ruperea” epiteliului alv si injurie capilara
  - Formarea de membrane hialine

Stadii

- Subacut (faza proliferativa)
  - Hipoxemie persistenta
  - Apare hipercarbia
  - Alveolita fibrozanta
  - HTPulmonara

Stadii

- Faza cronica
  - Obliterarea spatiilor alveolare, a bronhiolelor si a capilarelor pulmonare
- Faza de recuperare
  - Remisia graduala a hipoxemiei
  - Cresterea compliantei pulmonare
  - Remisia Rx

Fiziopatologic

- Anomalii ale schimburilor gazoase : hipoxemia = “MARCA” ARDS
- Interactiuni cardiopulmonare : HTPulmonara → creste postsarcina VD
- Afectari organice multiple : MSOF

ARDS
Tratament

- Ventilatie mecanica cu volum mic si frecventa mare (ARDSNet)
- Cauta si trateaza cauza / factorul declansator
- Fa preventia infectiilor nozocomiale
- Trateaza infectiile prompt (Ab ± chirurgie)
- Asigura nutritie parenterala adecvata
- Fa profilaxia TVP
- Eventual corticoterapie in doze mari, timp scurt (cazuri severe)

Cind astea dau gres…

ORICE altceva :

- Pozitia
- Oxid nitric inhalator
- Alte procedee de ventilatie mecanica
- Surfactant exogen
- …

Predictori ai evolutiei severe

- Prezenta lor la momentul dg, prezice riscul decesului

  a)boala cronica de ficat

  b)disfunctie organica preexistenta

  c)sepsis

  d)virsta inaintata

Mortalitate

- 40-60%
- Prin :
  - Insuficienta multipla de organ
  - Sepsis
- Mortalitate in scadere pt ca :
  - Strategia ventialtiei - ameliorata
  - Dg si tratament tot mai precoce

GATA !!!