Chronic respiratory diseases

Pediatric chronic respiratory infections

Chronic respiratory infections

- **Chronic bronchitis**
  - Cystic fibrosis
  - Immunodeficiencies
  - Disorders of the local defenses
  - Consequences of acute respiratory infections

Allergic diseases

- Asthma bronchiale

Congenital respiratory tract anomalies

Consequences of perinatal pathologies

Diffuse parenchymal lung diseases

- Lung fibrosis
- Systemic diseases

Definition

Recurrent respiratory infections

> 4 - 6 epizodes/year

Chronic cough

> 3 weeks for no apparent reason

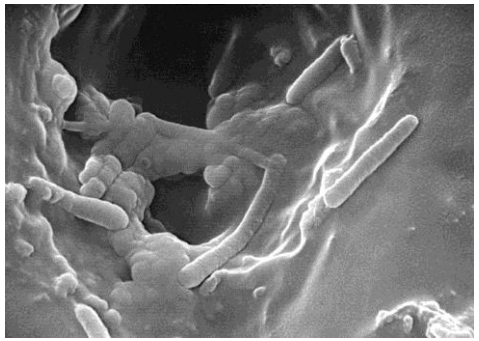
Chronic bronchitis

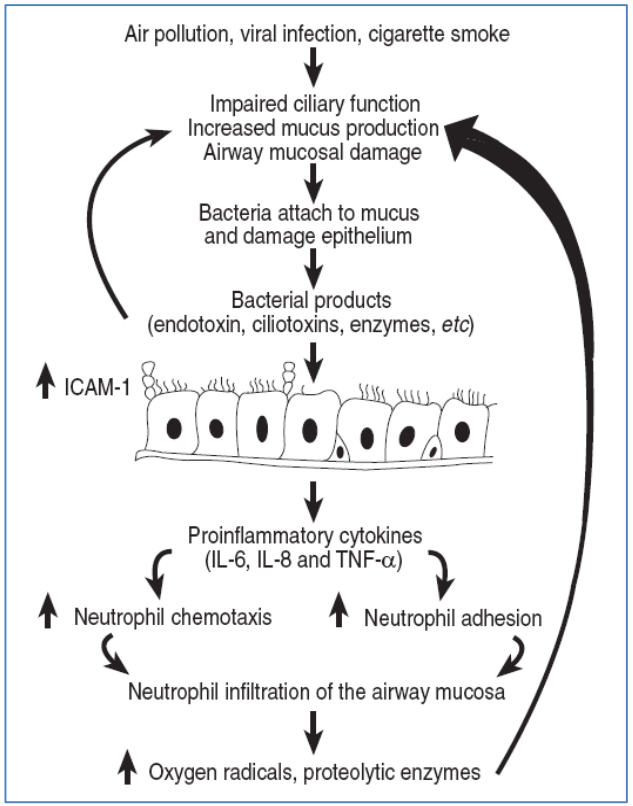
Recurrent cough and bronchial auscultation, lasting longer than 3 months per year for 2-3 years + insufficient recovery

Bacteria induced inflammatory mediators

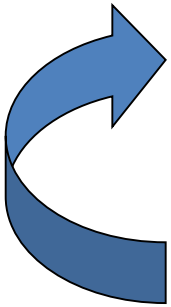
Initiating factors
Bacterial infection
Inflammation
Decreased bronchial clearance

Properties of bacteria
Irreversible changes

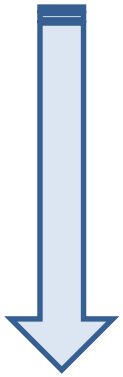




Chronic inflammation



Damage to the epithelium → destruction of ciliary function
Damage to the bronchial wall → bronchiectasis
Increase in secretory elements → increased mucous secretions
Increased bacterial load
Persistent inflammatory reaction



Bronchiectasis

Chronic bronchitis

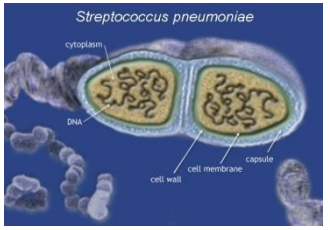
Etiology

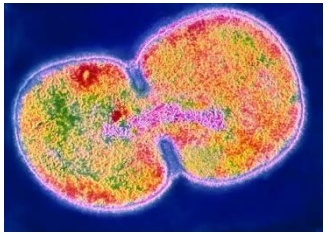
- ***Haemophilus influenzae sp*** (cca 50%)
- *Streptococcus pneumoniae* (cca 20%)
- ***Moraxella catarrhalis*** (cca 20 %).
- *Staphylococcus aureus* (cca 12%)

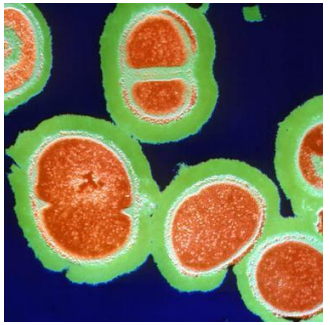
Zgherea D, Pagala S, Mendiratta M, Marcus MG, Shelov SP, Kazachkov M. Bronchoscopic findings in children with chronic wet cough. Pediatrics. 2012 Feb;129(2):e364–9.

- Pseudomonas aeruginosa
- Stenotrophomonas maltophilia
- Alcaligenes xylosoxidans
- Burkholderia cepacia

- Aspergillus fumigatus



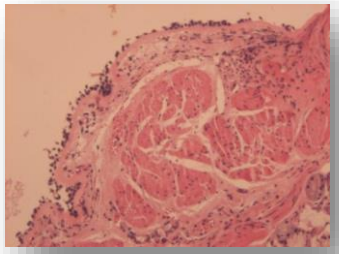


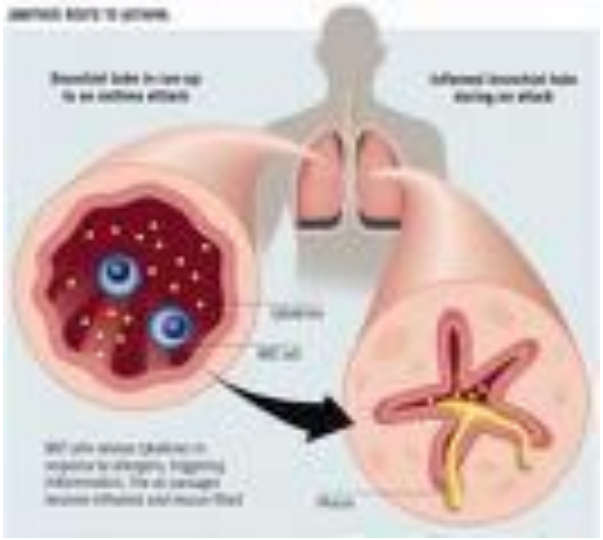


Bronchial hyperreactivity (BHR)

Ability of bronchial wall to develop bronchial obstruction
Reversibility and variability of obstruction

Remodeling





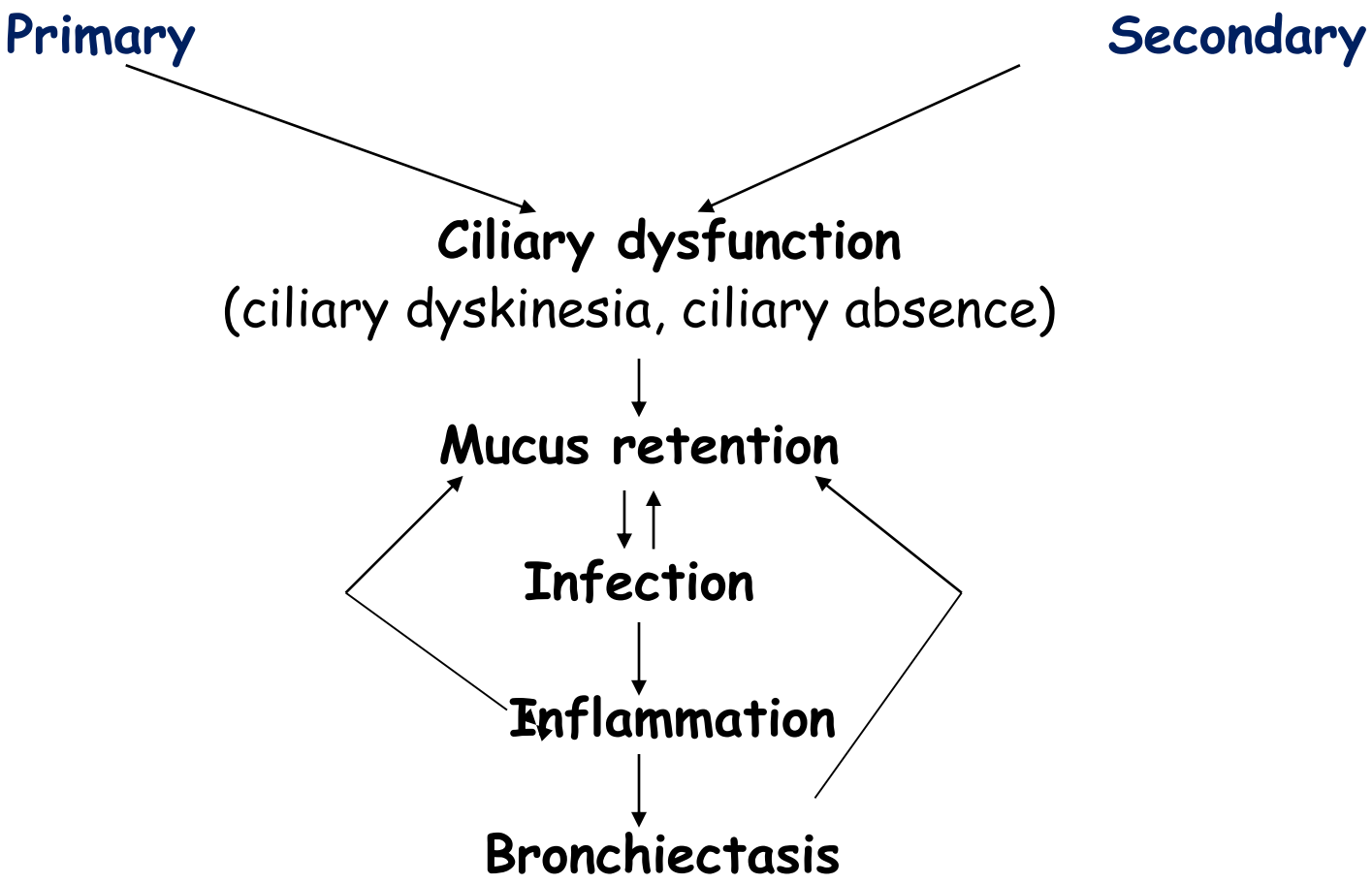
Evidence of BHR

- Variability of obstruction
- Reversibility of obstruction
- Positive metacholin challenge test

Risk faktors in children

- Ciliary dysfunction
- Tracheobronchomalacia
- Chronic aspirations
- Imunodeficiency
- Enviromental factors

Ciliary dysfunction



Primary ciliary dyskinesia

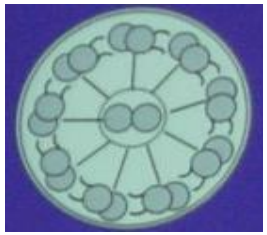
Brain Ependyma

Respiratory tract

Reproductive tract

Oviduct

Sperm flagella



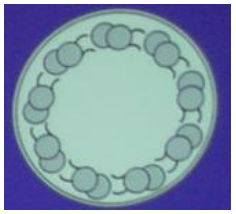
Motile (9+2)

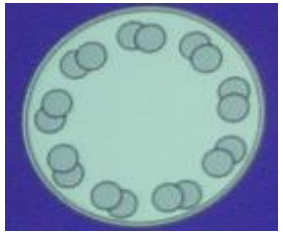
Cilia

Motile (9+0)

„nodal”

(embryonic development)





Non-motile(9+0)

„primary”

Kidney Tubule

Bile duct

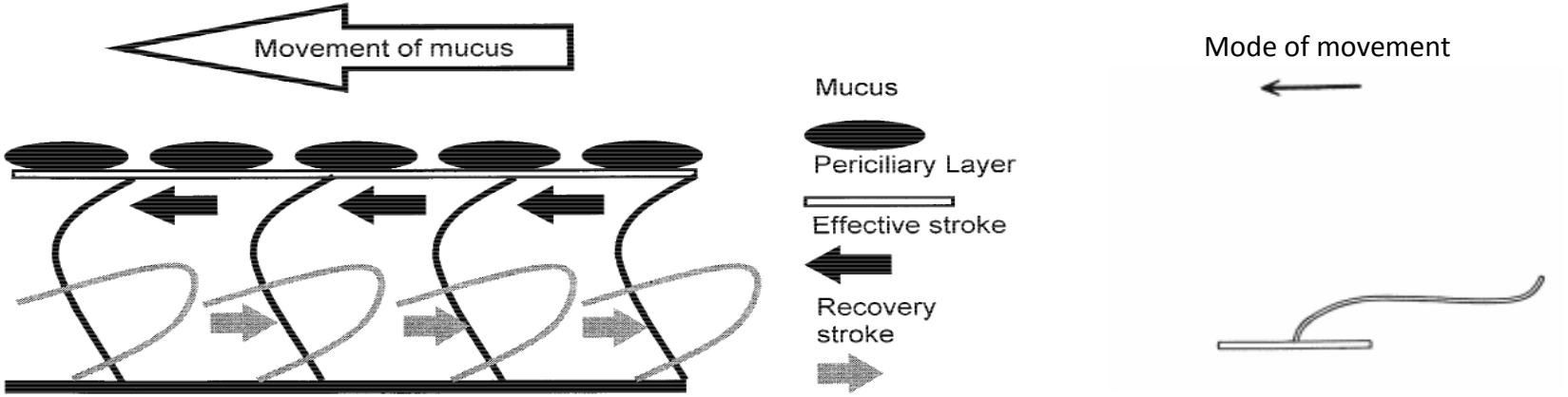
Pancreatic duct

Bone cartilage

Eye

Structure and function 9+2

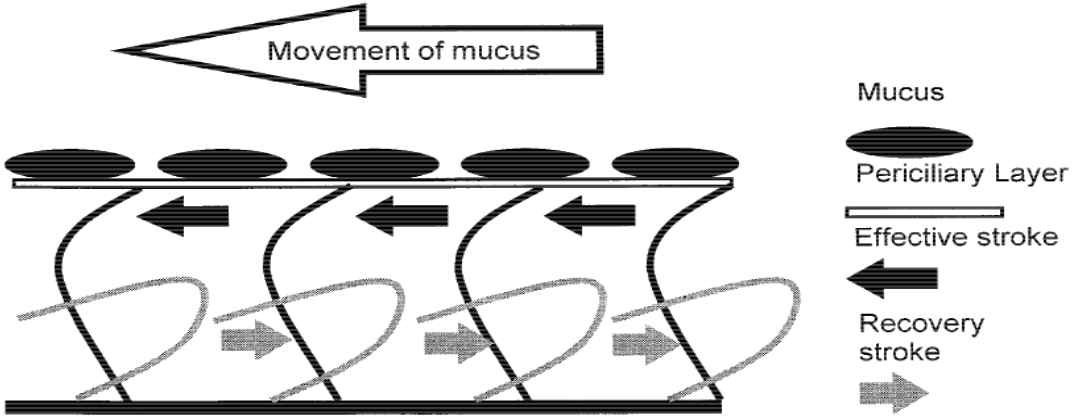
Rare genetic condition (1:16000 – 1:32000 live-born neonates)

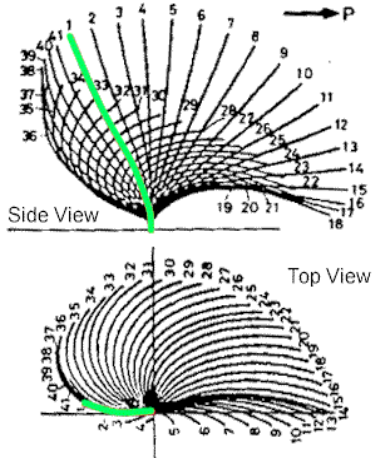


Mucus speed: 4 mm/min
Direction of movement: orally
Number of cilia : $10^9/cm^2$
Ciliary cell: 250 cilia

Structure and function 9+2

Rare genetic condition (1:16000 – 1:32000 live-born neonates)





Mucus speed: 4 mm/min
Direction of movement: orally
Number of cilia : $10^9/cm^2$
Ciliary cell: 250 cilia

Symptoms of PCD

Antenatally

Situs inversus, situs ambiguus + VCC vascular anomalies
Mild ventriculomegaly

Neonates

Tachypnoe or neonatal pneumonia in term newborns without risc factors and congenital infection
Rhinitis (permanent variable)
Situs viscerum inversus, ambiguus
Hydrocephalus
Heart defects, esophageal atresia, biliary atresia

Children

Chronic wet cough,
Repeated pneumonia, atelectasis
„ **Unresponsive astma"**
Rhinosinusitis
Otitis media with effusion
Bronchiectasis
Persistent airways colonization with patogens

Adults: similar to children

Women **subfertility,** ectopic pregnancy
Men **infertility** with dysmotility or immotility of sperms

Kartagener syndrom : Situs viscerum inversus + sinusitis + bronchiectasis

Diagnostic algorithm

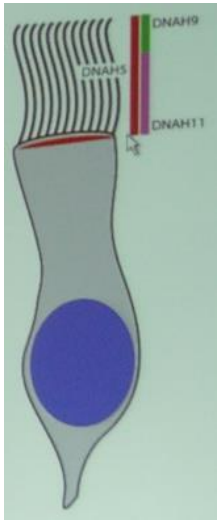
- **Ciliary motility**
  - Saccharine test (low objectivity)
  - Tc-albumin scan (technical equipment)
  - **High speed videomicroscopy**
- **Electron microscopy**
  - **Ciliary structure**
  - **Ciliary orientation**
- Nasal exhaled NO
- **Genetics**

PCD genetics

Table 2: Mutations in the Genes that cause Human PCD

Human Gene	Human Chromosomal Location	*Chlamydomonas* Ortholog	Ciliary Ultrastructure in Subjects with Biallelic Mutations	Presence of Laterality Defects	% of individual with biallelic mutations	MIM#	References
DNAH5	5p15.2	*DHC*	ODA defect	yes	15-21% of all PCD, 27-38% of PCD with ODA defects	608644	2,16
DNAI1	9p21-p13	*IC78*	ODA defect	yes	2-9% of all PCD, 4-13% of PCD with ODA defects	244400	2,16
DNAI2	17q25	*IC69*	ODA defect	yes	2% of all PCD, 4% of PCD with ODA defects	612444	16
DNAL1	14q24.3	*LC1*	ODA defect	yes	na	614017	16,81
CCDC114	19q13.32	*DC2*	ODA defect	yes	6% of PCD with ODA defects	615038	83,84
TXNDC3 (NME8)	7p14-p13	*LC5*	Partial ODA defect (66% cilia defective)	yes	na	610852	16
DNAAF1 (LRRC50)	16q24.1	*ODA7*	ODA+IDA defect	yes	17% of PCD with ODA+IDA defects	613193	16
DNAAF2 (KTU)	14q21.3	*PF13*	ODA+IDA defect	yes	12% of PCD with ODA+IDA defects	612517, 612518	16
DNAAF3 (C19ORF51)	19q13.42	*PF22*	ODA+IDA defect	yes	na	606763	75
CCDC103	17q21.31	*PR46b*	ODA+IDA defect	yes	na	614679	77
HEATR2	7p22.3	Chlre4 gene model 525994 Phytozyme v8.0 gene id Cre09.g39500.t1	ODA+IDA defect	yes	na	614864	79
LRRC6	8q24	*MOT47*	ODA+IDA defect	yes	11% of PCD with ODA+IDA defects	614930	80
CCDC39	3q26.33	*FAP59*	IDA defect + Axonemal disorganization	yes	36-65% of PCD with IDA defects + Axonemal disorganization	613798	16,82
CCDC40	17q25.3	*FAP172*	IDA defect + Axonemal disorganization	yes	24-54% of PCD with IDA defects + Axonemal disorganization	613808	16,82
RSPH4A	6q22.1	*RSP4, RSP6*	Mostly normal, CA defects in small proportion of cilia	no	na	612649	16
RSPH9	6p21.1	*RSP9*	Mostly normal, CA defects in small proportion of cilia	no	na	612648	16
HYDIN	16q22.2	*hydin*	Normal, very occasionally CA defects	no	na	610812	75
DNAH11	7p21	*DHC β*	Normal	yes	6% of all PCD, 22% of PCD with normal ultrastructure	603339	16
RPGR	Xp21.1	na	Mixed	no	PCD co-segregates with X-linked Retinitis Pigmentosa	300170	16
OFD1	Xq22	*OFD1*	nd	no	PCD co-segregates with X-linked mental retardation	312610	16
CCDC164 (C2ORF39)	2p23.3	*DRC1*	Nexin (N-DRC) link missing; axonemal disorganization in small proportion of cilia	no	na	312610	85

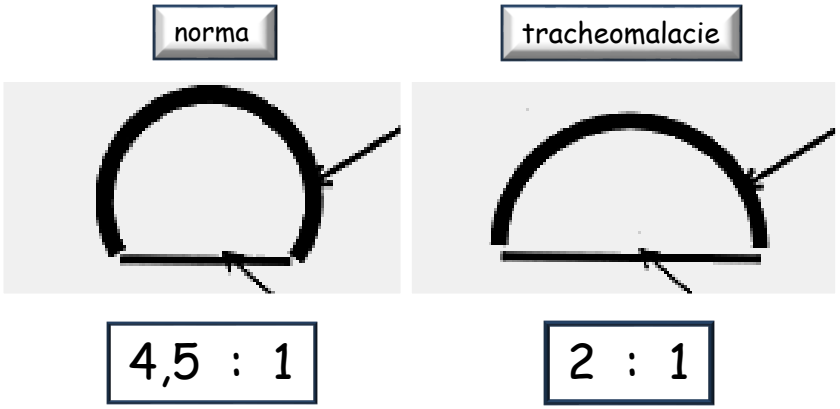
- Cilia require hundreds of different proteins necessary for a correct structure and/or function.
  - **Every mutation inside one of the genes encoding for one of these proteins may cause a pathological alteration in the structure and function of cilia**



Tracheo/bronchomalacia

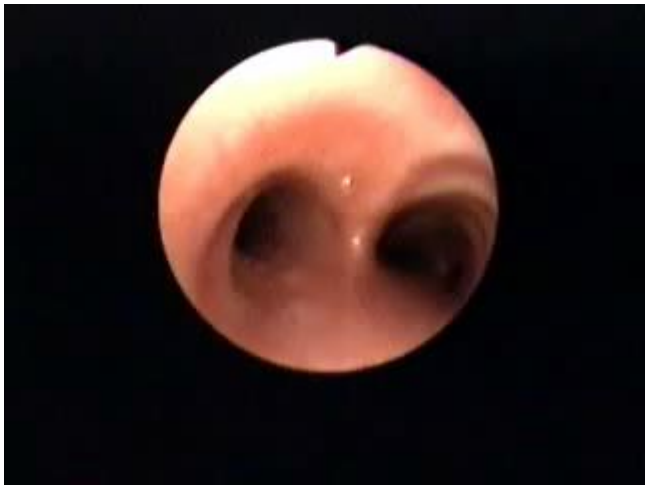
Weakness of the airways due :

- Reduction / atrophy of longitudinal elastic fibers pars membranacea
- Damage integrity of cartilaginous rings (immaturity))



Clinical symptoms

- Cough persisting after infection
- Typical irritating / whooping cough
- Mucus production
- Bronchodilation wit no effect
- Excercise intolerance



Tracheo/bronchomalacia

Etiology of tracheomalacia

Congenital

Acquired

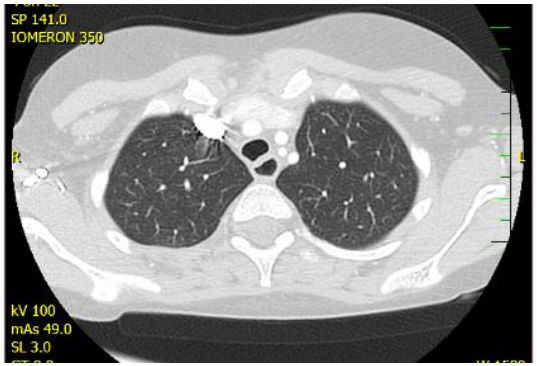
- Intubation
- Tracheotomy
- External pressure

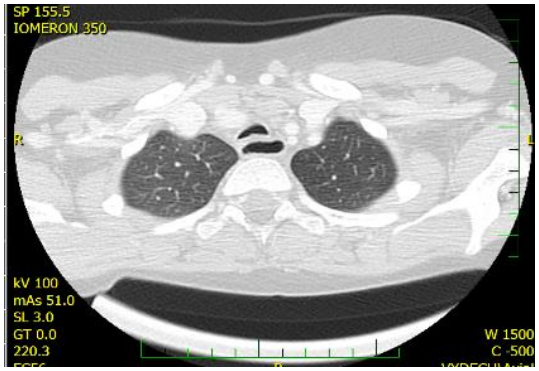
Risk patients

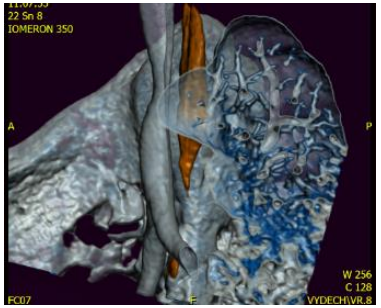
- Down syndrom
- Chronic bronchitis
- Extremely premature infants
- TOF
- Cardiovascular anomalies
- Marfan sy

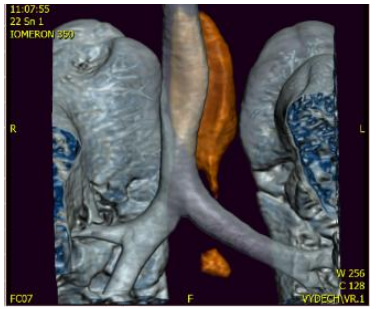
Diagnosis

- **Flexibil laryngotracheobronchoscopy** (modified anesthesia with spontanneous breathing)
- **Chest CT + angiography**









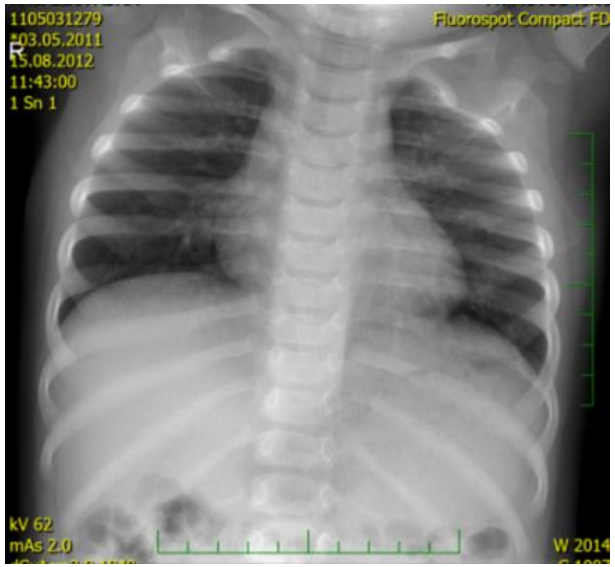
- **(MRI)**

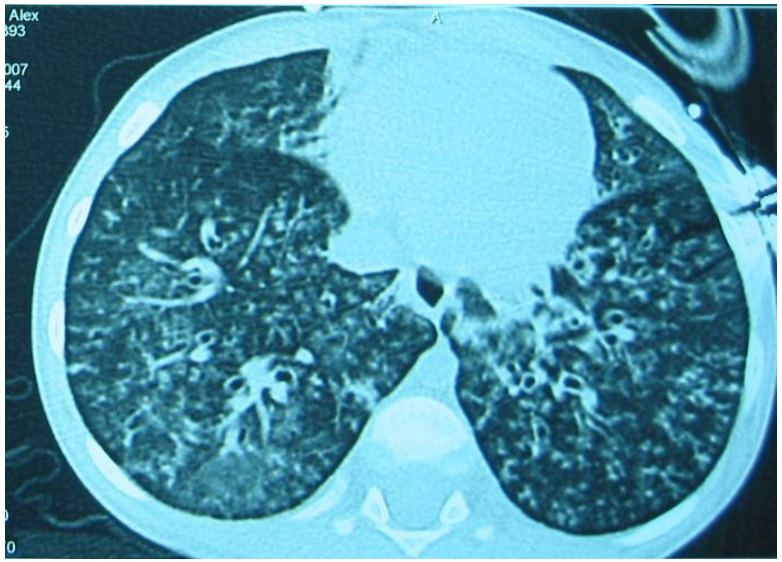
Chronic aspirations

Gastroesofageal reflux

Swallowing dyscoordination

Anatomical abnormalities

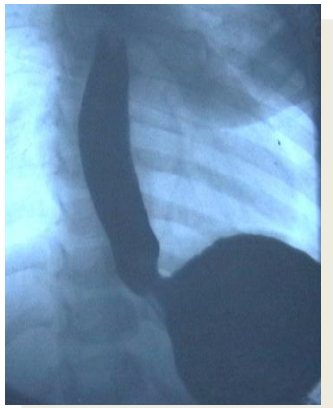




Gastroesophageal reflux

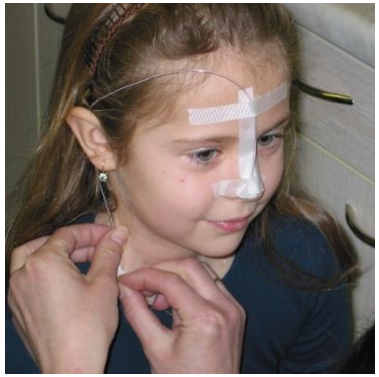
Ways of action

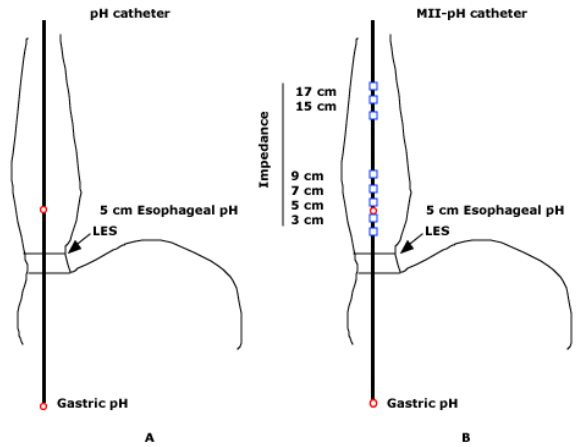
- Aspiration
- Microaspiration
- Vagal reflex



Diagnose

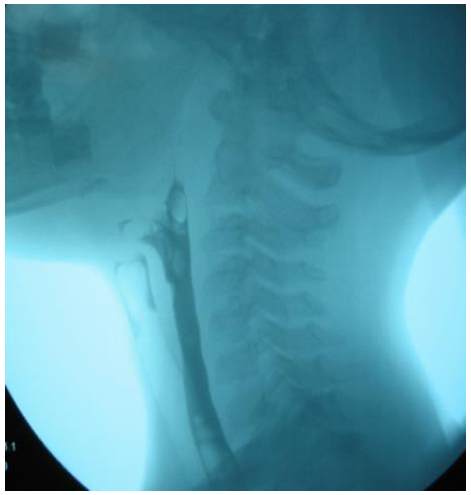
- Baryum swallow
- Scintigraphy
- (milk scan)
- pH-probe
- MLI-pH - multichannel intraluminal impedance





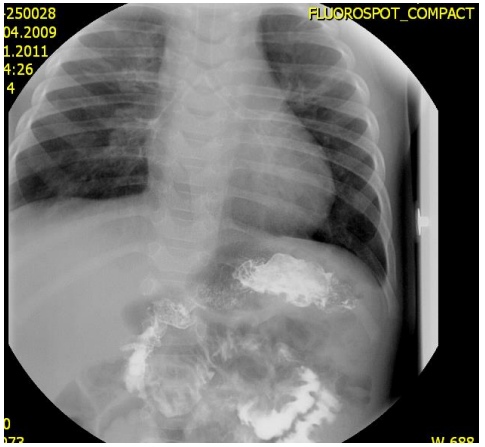
Swallowing dyscoordination

- Chronic wet cough
- Sputum production
- Persistent chest X ray infiltrations



Failure to thrive

Choking



Swallowing dyscoordination

History

Chest X-ray

pH probe/ MLI-pH often normal

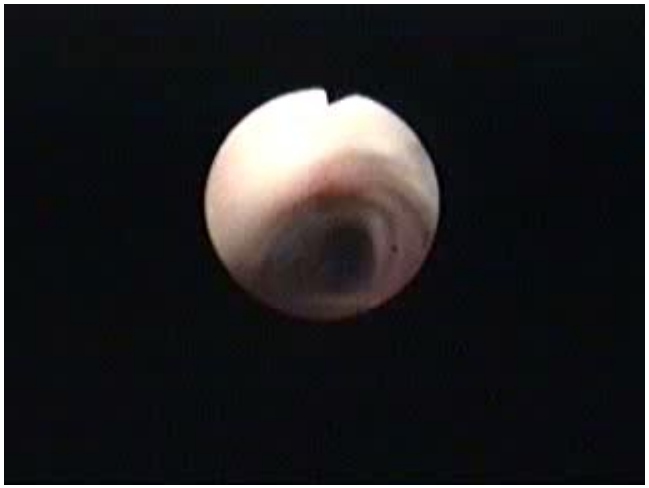
Swallowing examination

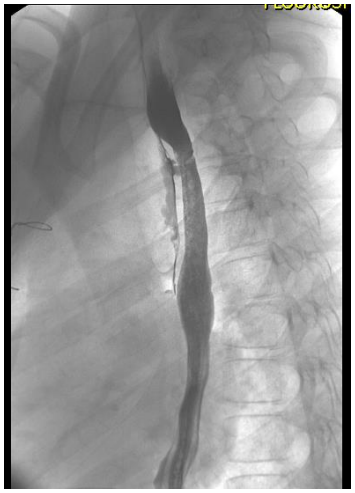
- Iomeron/baryum swallow
- **Videofluoroscopy** (fluid…mash.. solid consistence)
- FESS (flexible endoscopy swallow study)

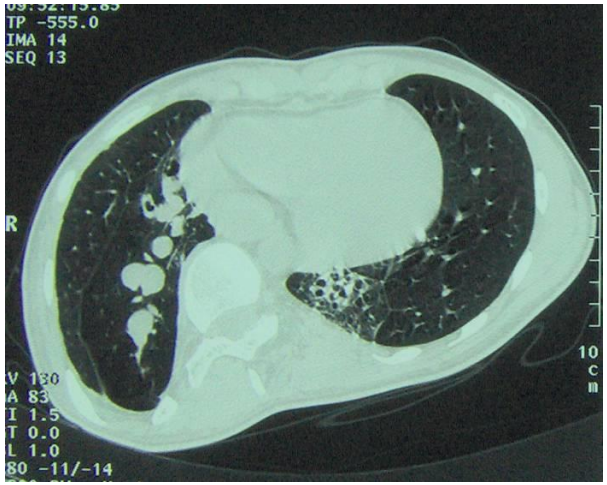
Anatomical abnormalities

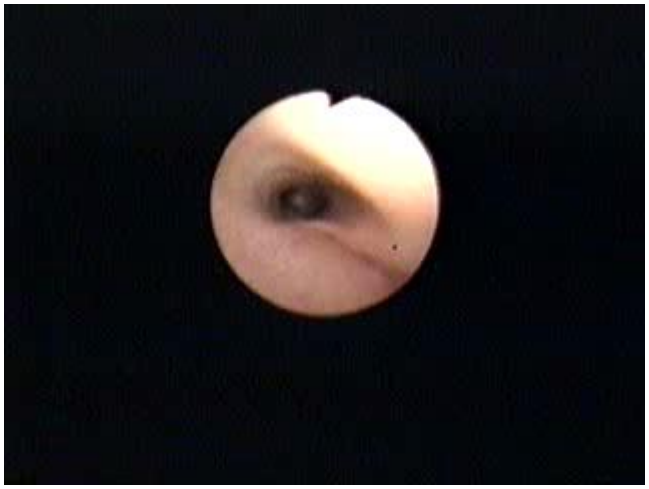
Anatomical abnormalities

- Cough wet….dry/whooping
- Protracted bronchitis
- X-ray
- Failure to thrive







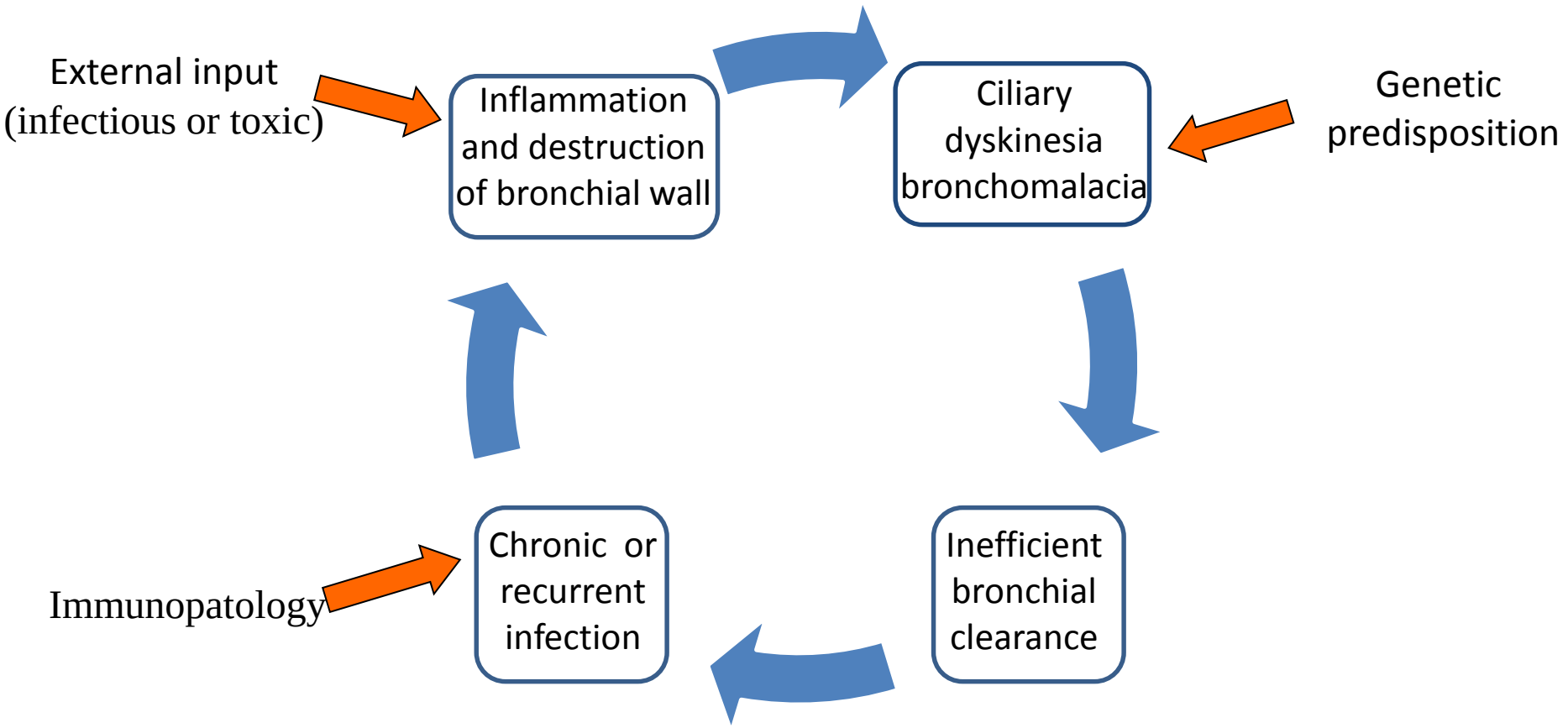


Bronchiectasis

Permanent abnormal dilatation of bronchial tree and the destruction of bronchial walls

- Cylindric
- Cystic
- Varicose

Patophysiology of bronchiectasis



Bronchiectasis

Aetiology

Postinfectious
- Whooping cough
- Measles
- Tuberculosis (TB)

Obstruction
- Foreign body
- Bronchial stenosis

Inherited
- **Cystic fibrosis**
- **PCD**
- **Imunodeficiency**

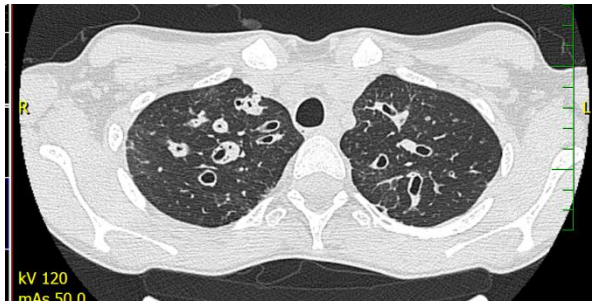
A-1- antitrypsin deficiency

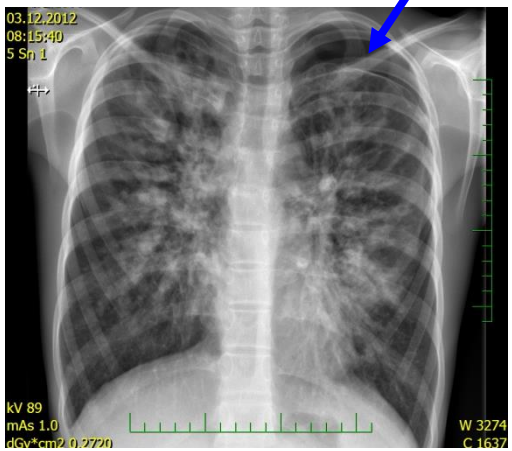
Chronic aspiration

Consequences

Growth failure
Osteopenia
Sleeping disorder
Hypoxemia

Pneumothorax
Source of infection





Therapy of chronic respiratory infections

Treatment of chronic inflammation and prevention of exacerbations

Inhalation + Physiotherapy

- Mucolytics
- Hypertonic saline NaCl

Antibiotics

- Acute exacerbations
- Long-term treatment
- Prophylaxis

Immunisation

- Haemophilus
- Streptococcus pneumoniae
- Influenza