

Pulmonary guidelines & current practice updates in treatments of CF lung disease



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The 'guidelines'

The writers team mix

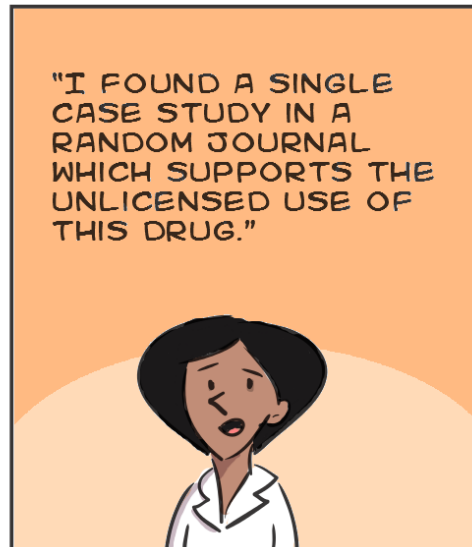
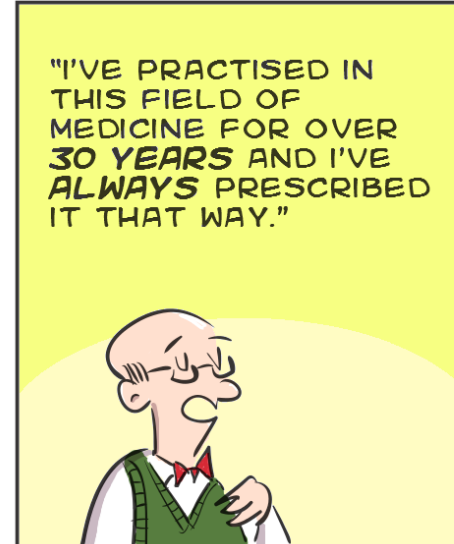


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N=16

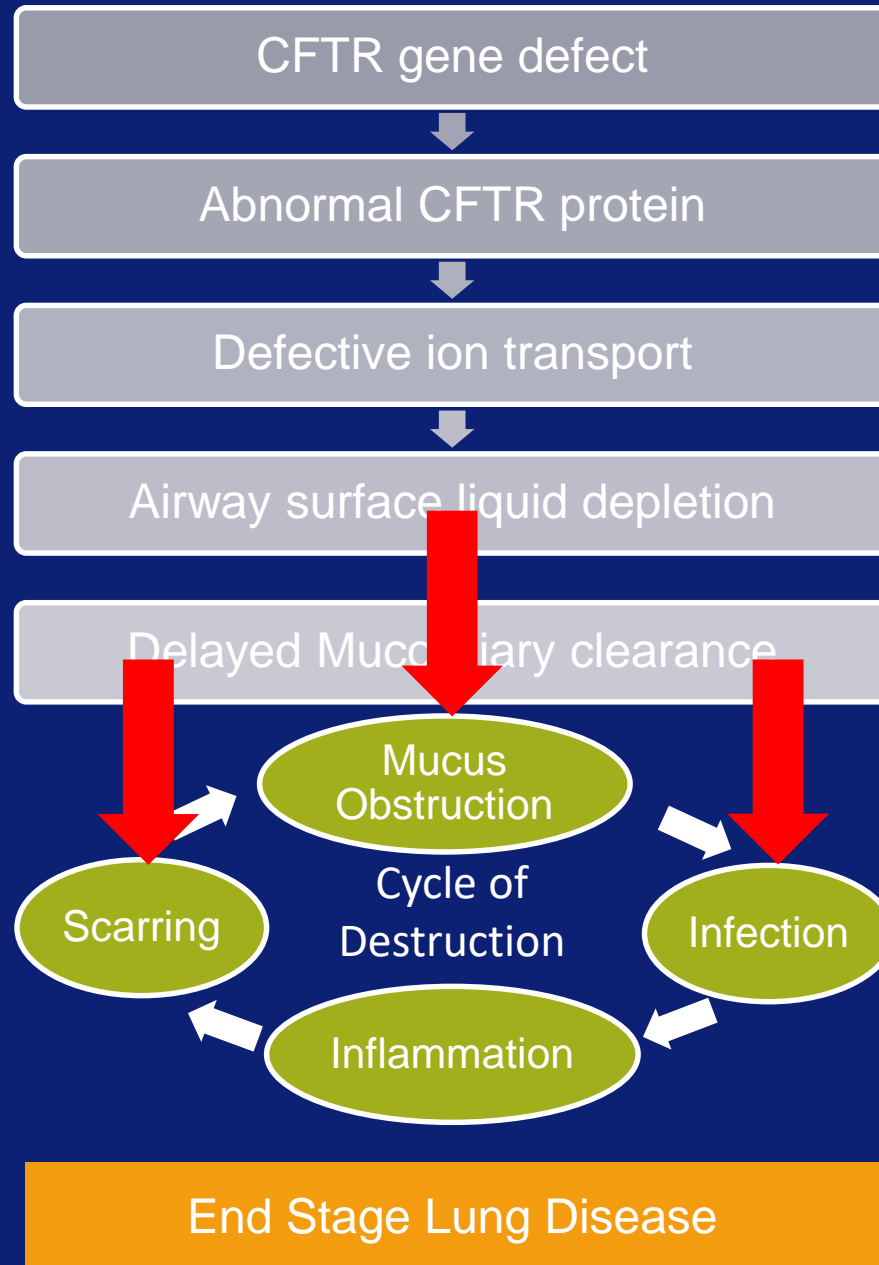
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**Cystic
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'What are the recommended chronic maintenance therapies to maintain lung health?: Mucolytics

2014

3.7.1. Mucolytics

The only mucus degrading agent that has proven efficacy in CF is dornase alfa. Studies have demonstrated improvements in lung function and a reduction in pulmonary exacerbations in patients regardless of disease severity [32]. Recent evidence from an analysis of a large data base suggests that dornase alfa reduces lung function decline [33]. Treatment effects are lost when treatment is ceased, therefore long term maintenance therapy is required. Other mucolytics, such as N acetyl cysteine, have not been proven to be effective in CF patients [34].

Over 50 papers on dornase alfa since 2014?!
What is lung function?

2018

5.7.1. Mucolytics

The only mucus degrading agent that has proven efficacy in CF is dornase alfa. Studies have demonstrated improvements in lung function and a reduction in PEX in patients regardless of disease severity [45]. Recent evidence from an analysis of a large data base suggests that dornase alfa reduces lung function decline [46]. Treatment effects are lost when treatment is ceased therefore long-term maintenance therapy is required. Other mucolytics, such as N acetyl cysteine, have not been proven to be effective in CF patients [47].

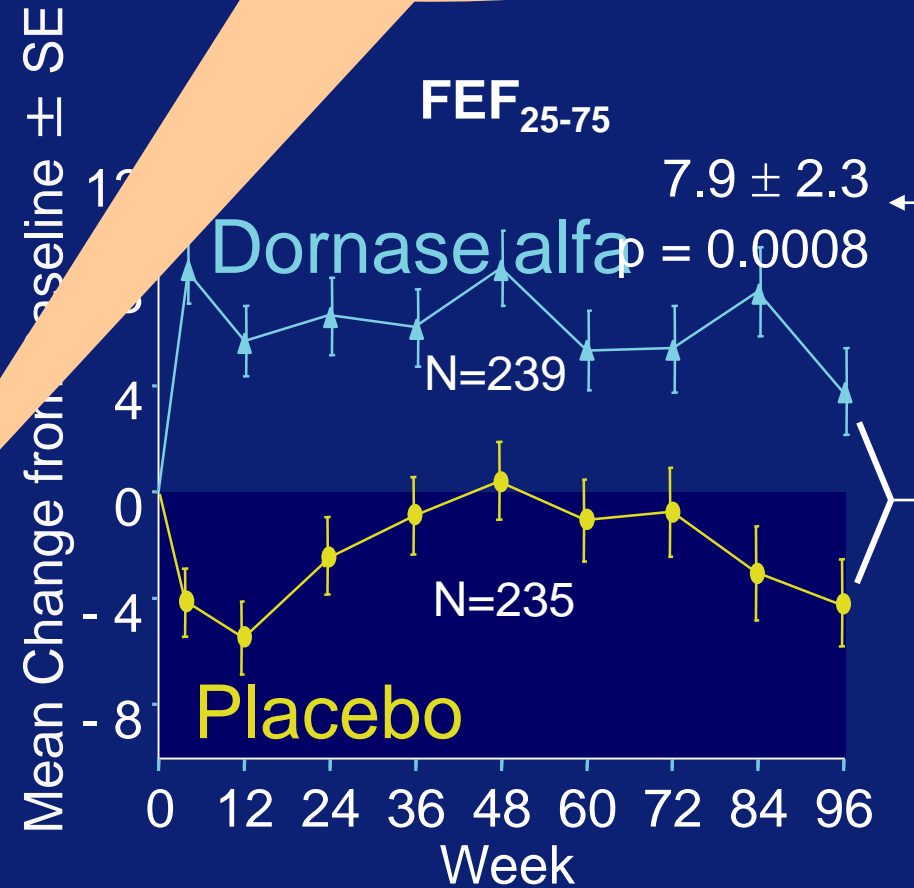
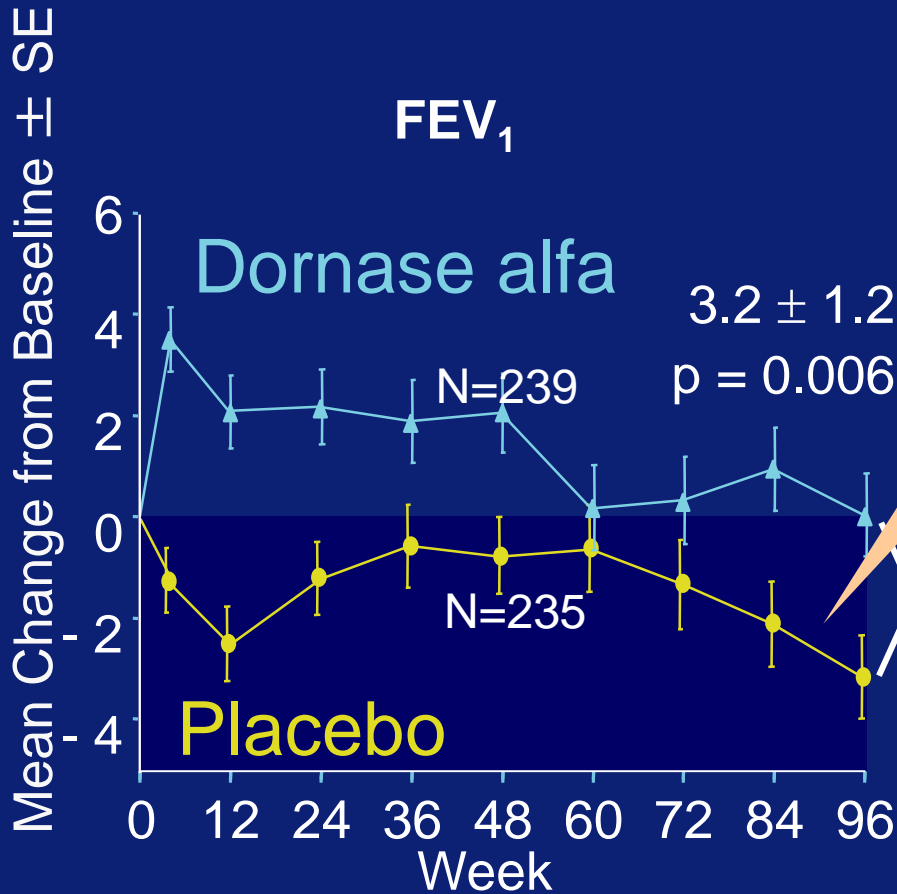
Yang C, Dornase alfa for CF: Improves lung function compared to placebo, reduces exacerbations *Cochrane: 2018*

Erasmus MC

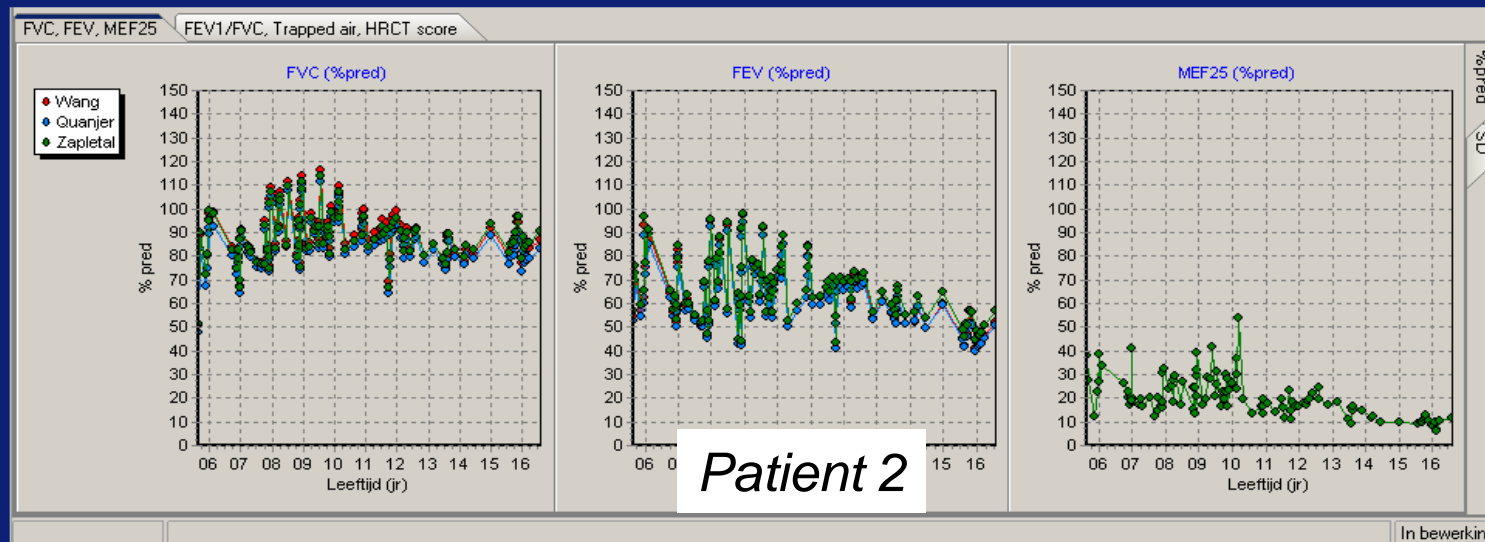
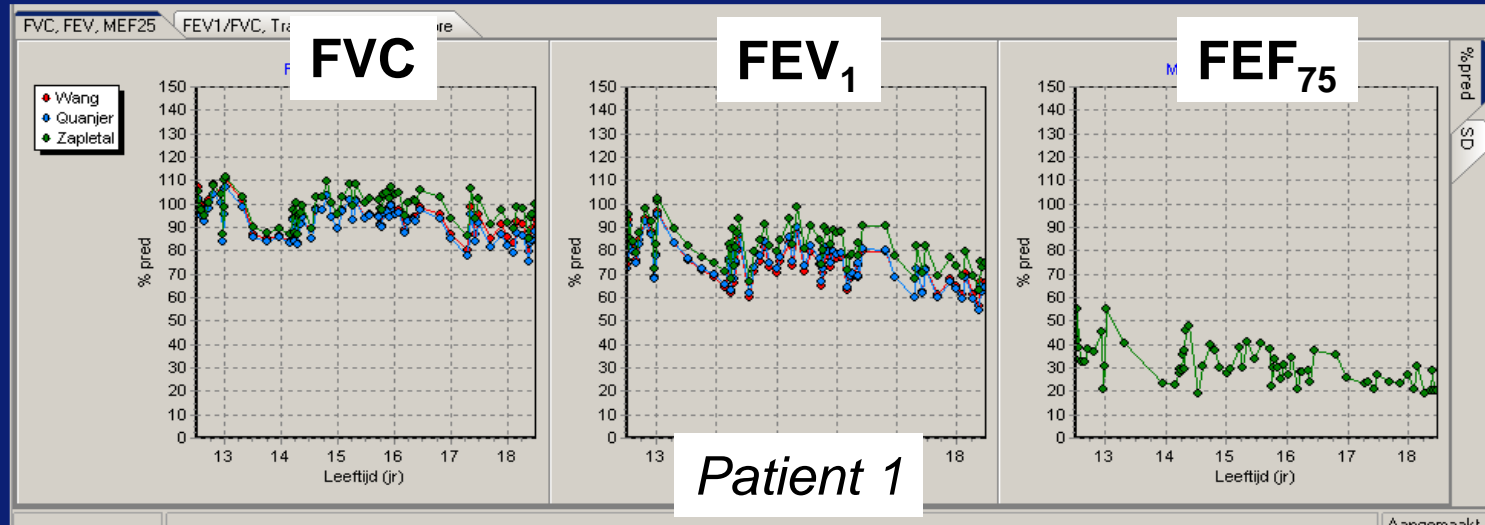


Dornase alfa has a substantial effect on the end expiratory volume

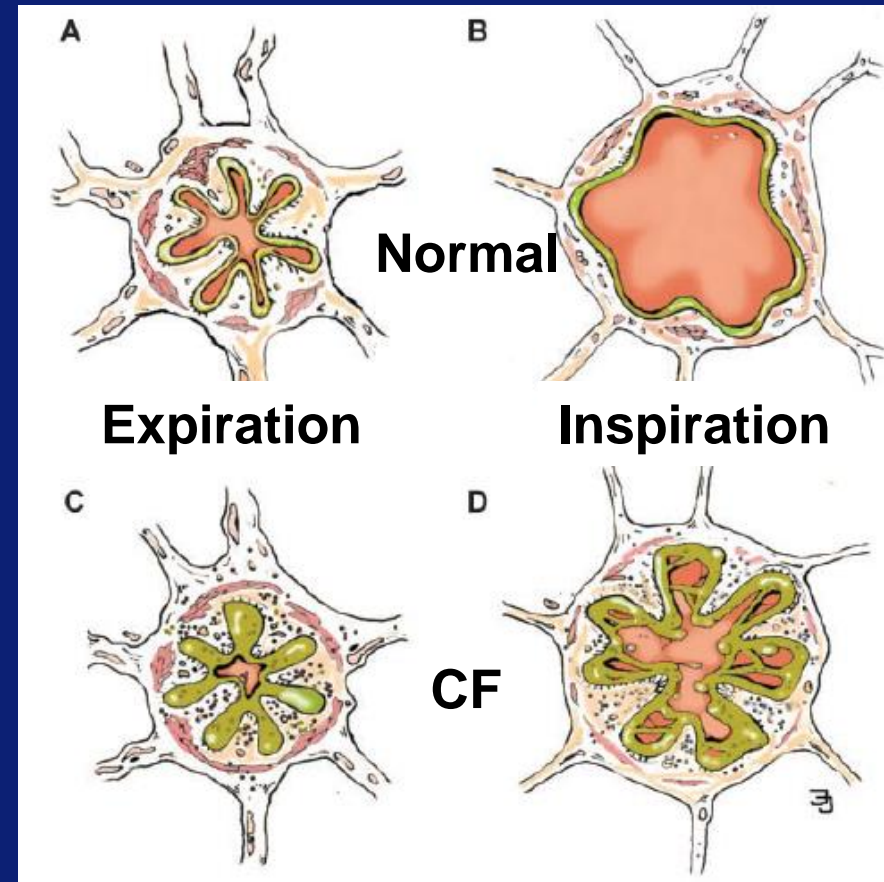
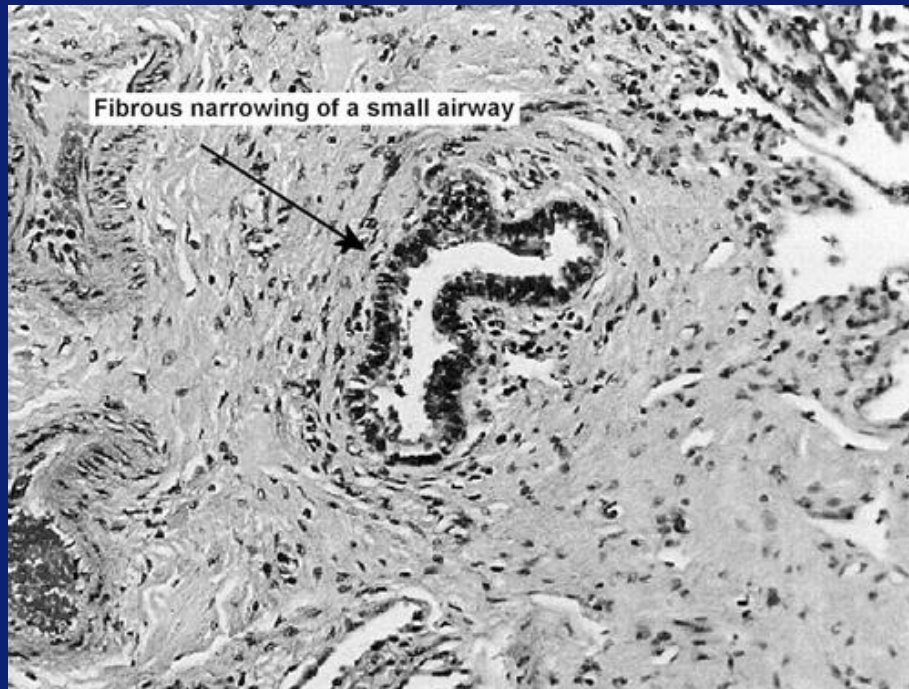
Represents the **average** response of a selected group



End expiratory flows are more reduced compared to FEV₁ early in life



Large body of evidence that the small airways play an important role in onset + progression of CF lung disease



Refika Hamutcu et al, *AJRCCM* 2002
Loeve et al, *AJRCCM* 2012
Boon et al, *AJRCCM* 2017
Kuo et al, *Pediatric Pulmonology* 2017

Tiddens et al, *Ped Pulmonology* 2010

End expiratory flows are more reduced compared to FEV₁ early in life

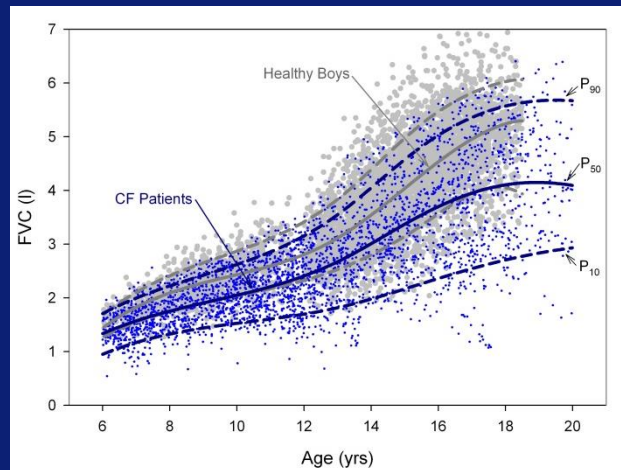
CF group:

Age 6 - 20 years
Boys (n=78) 2676 measurements
Girls (n=77) 3333 measurements

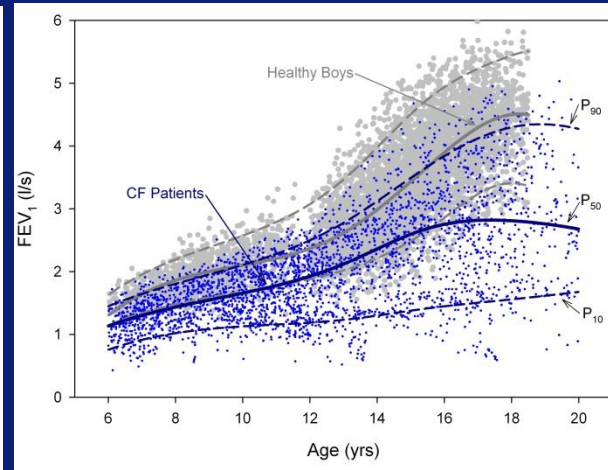
Healthy group:

Age 12 - 18.5 years
Boys (n=233) 2105 measurements
Girls (n=171) 1634 measurements

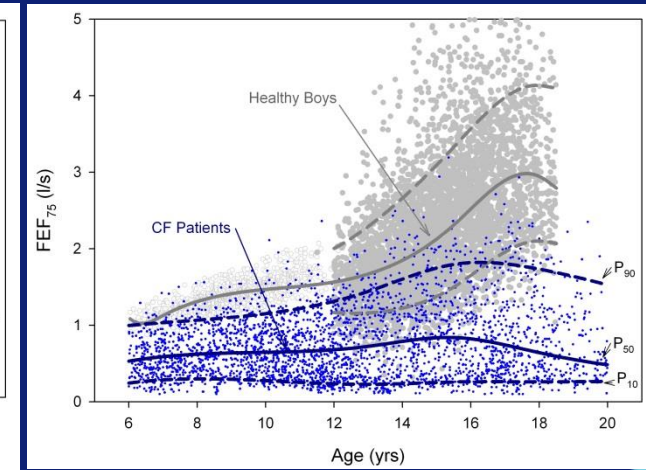
FVC



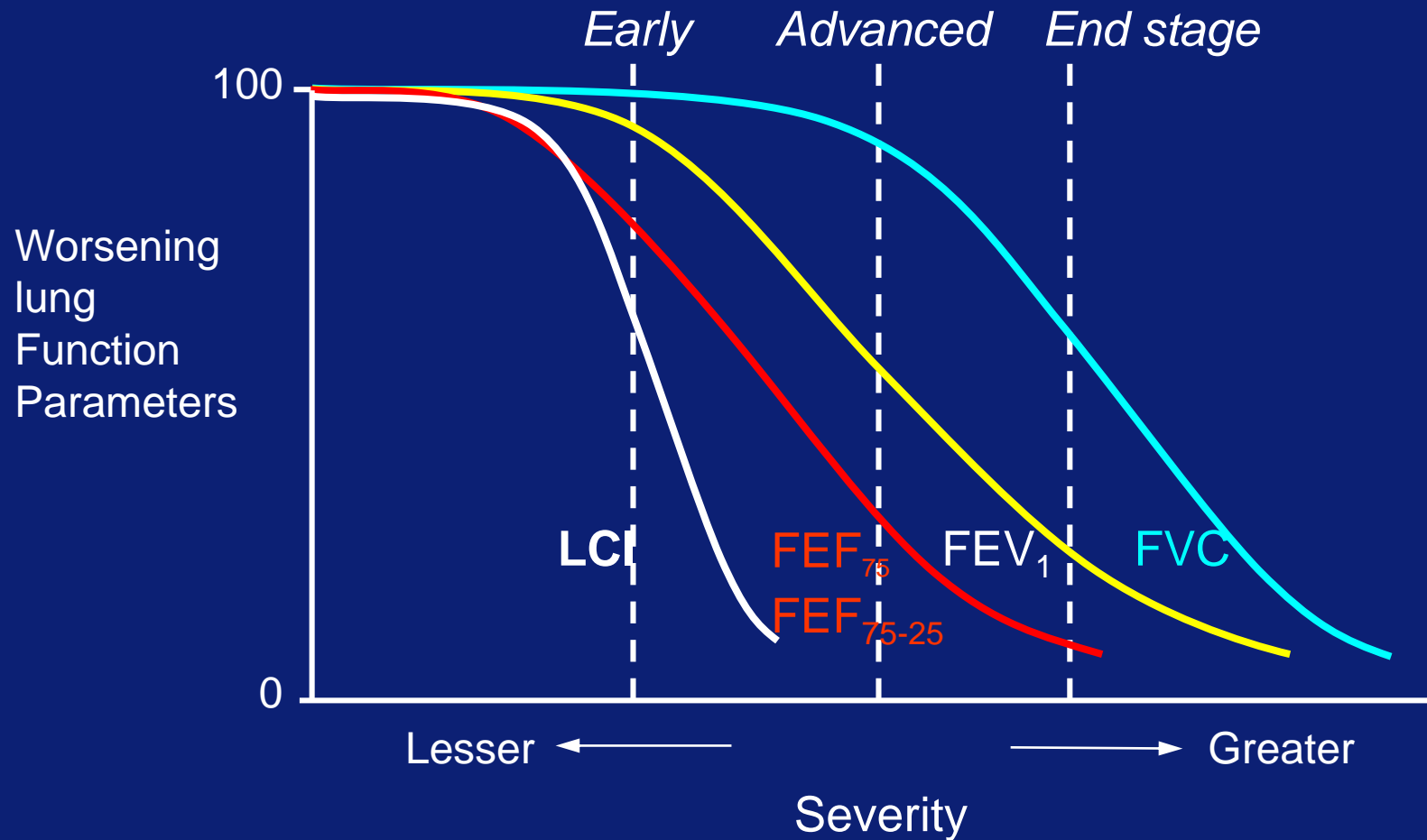
FEV₁



FEF₇₅



Sensitivity of lung function parameters varies with severity of disease

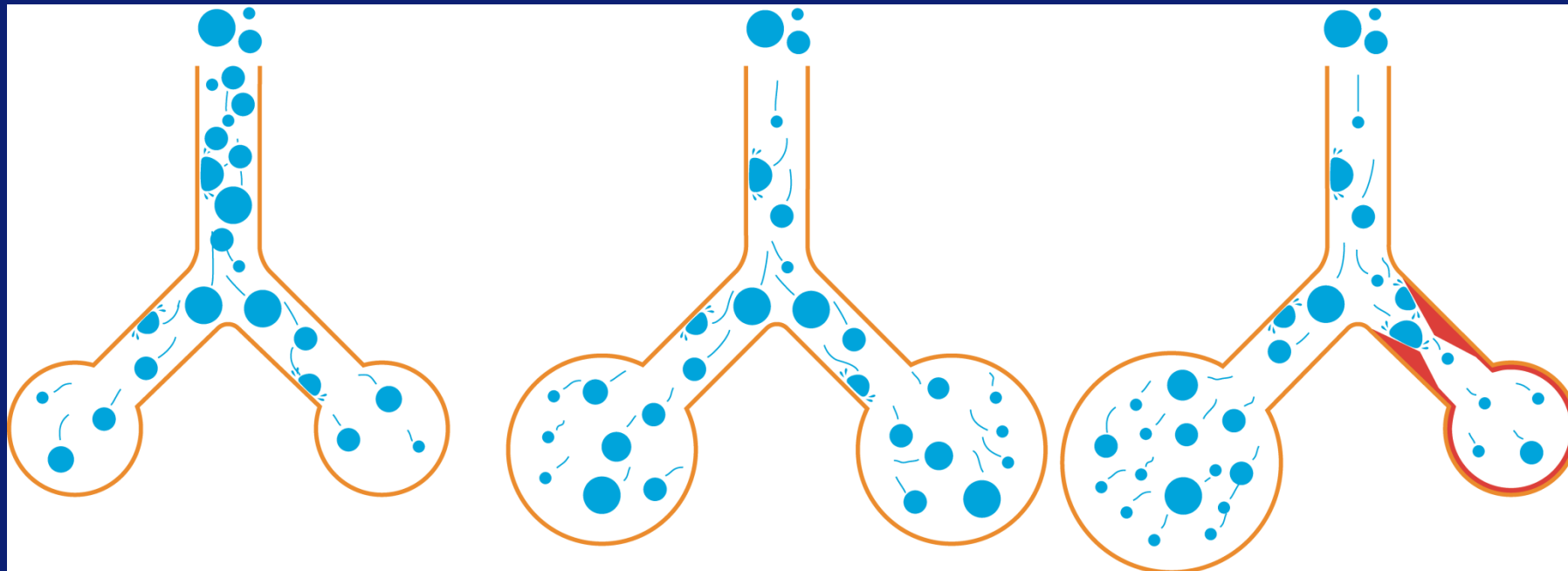


Aerosol deposition in health and disease

Healthy

Healthy

Lung disease
obstruction



Tidal volume breathing

Deep inhalation

Deep inhalation

Dornase alfa targeting of small airways using a smart nebulizer (Akita®)



Smart Card technology:

- Breathing pattern adjusted to FVC of patient

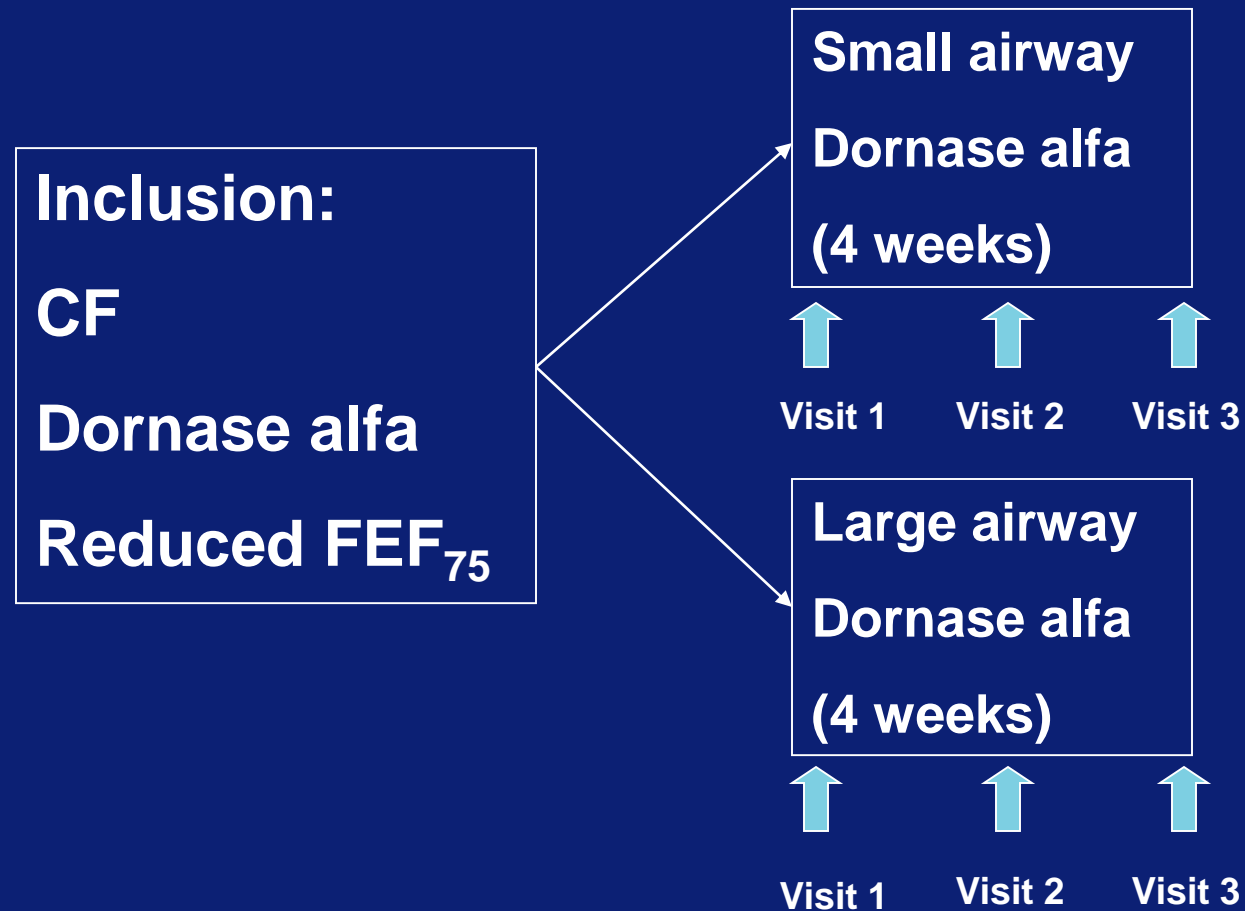
Central deposition:

- 6 μm mesh
- controlled, slow and normal depth inspiration
- Aerosol bolus in middle of breath

Peripheral deposition:

- 4 μm mesh
- controlled, slow and deep inspiration
- Aerosol bolus at start of breath

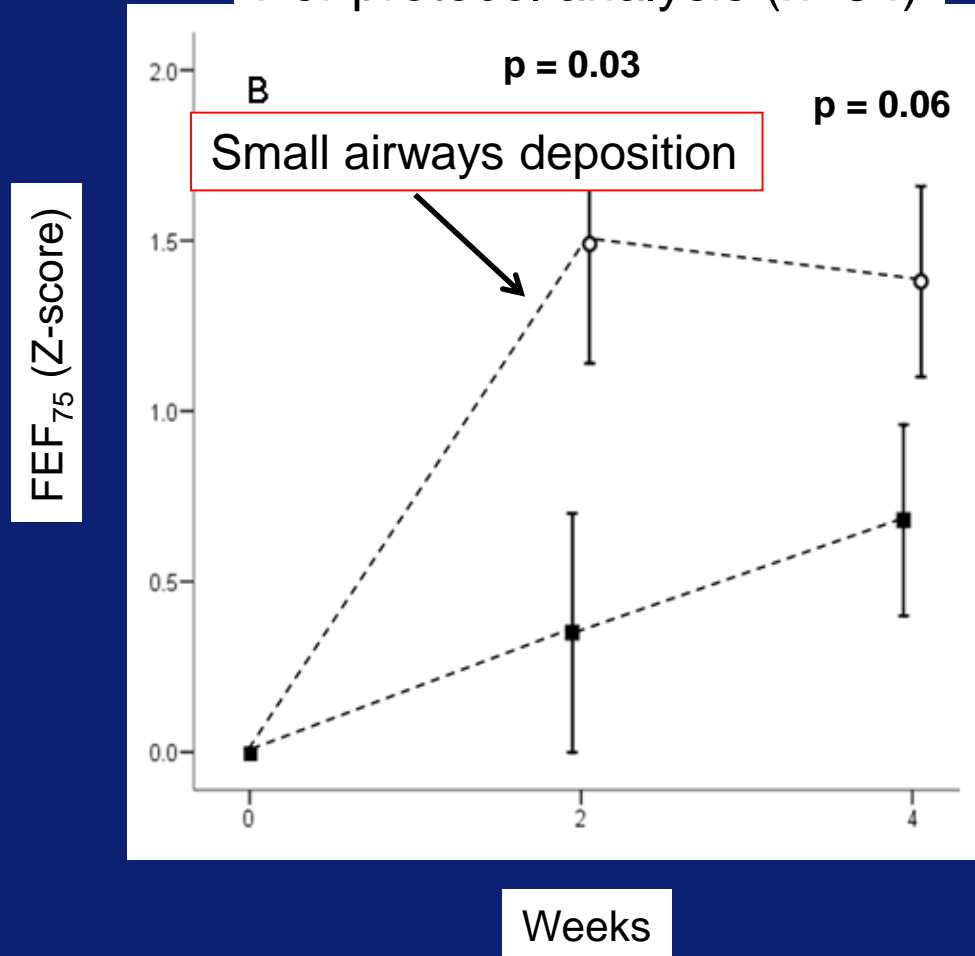
Dornase alfa targetting of small airways: study design



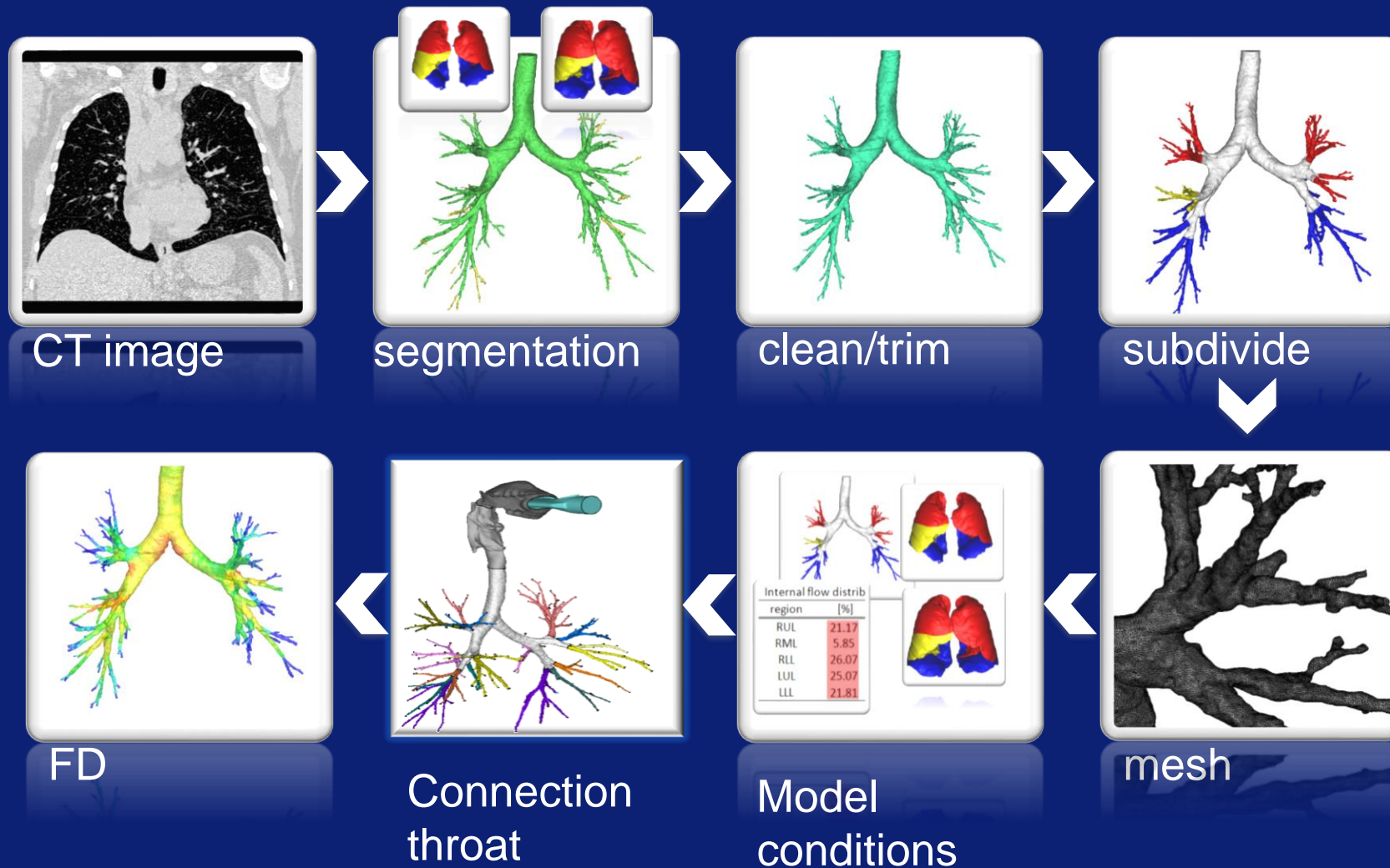
↑ : pulmonary function tests: Spirometry
during study: symptom diaries

Primary endpoint: FEF₇₅

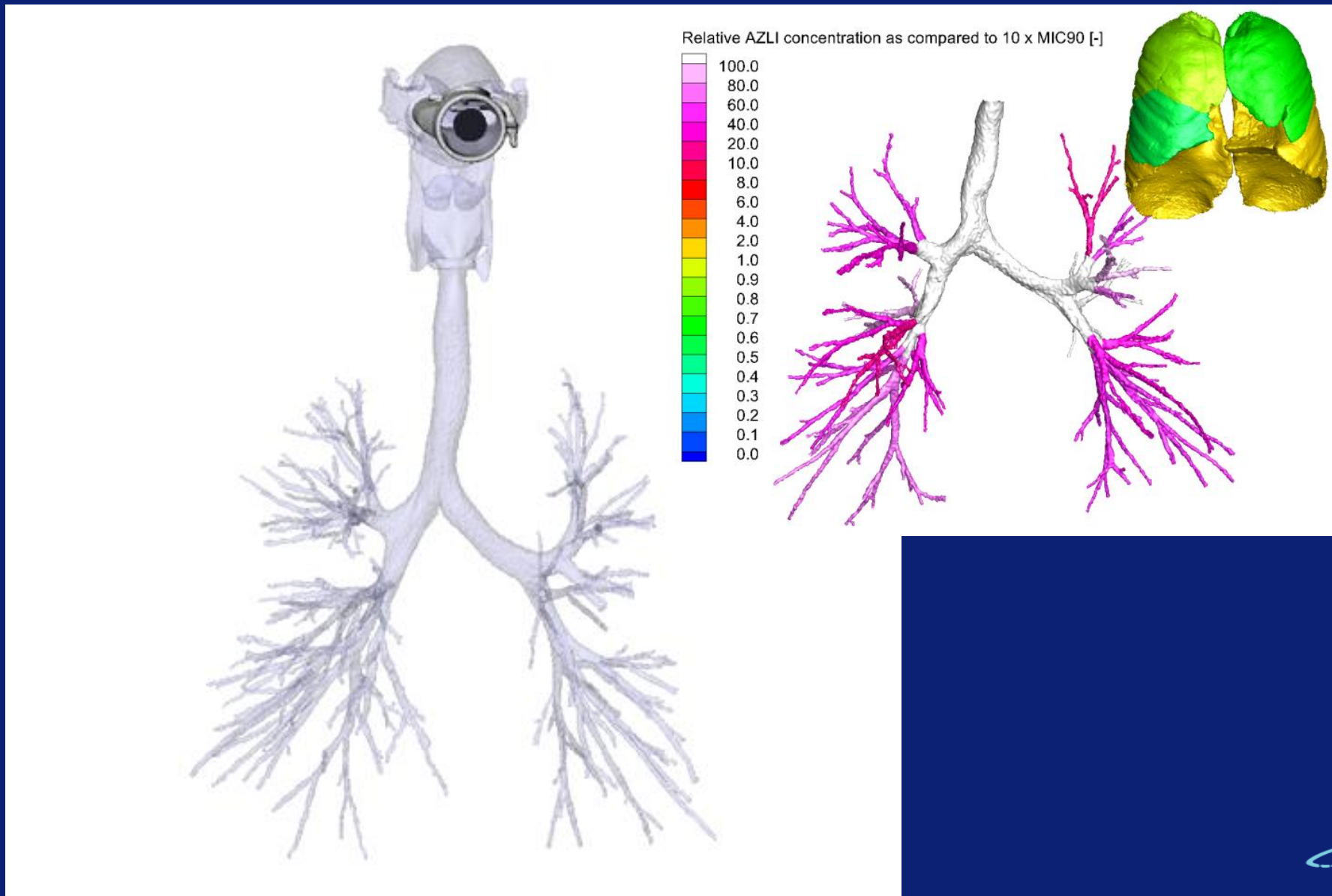
Per protocol analysis (n=34)



Patient specific modeling of regional deposition of inhaled dornase alfa

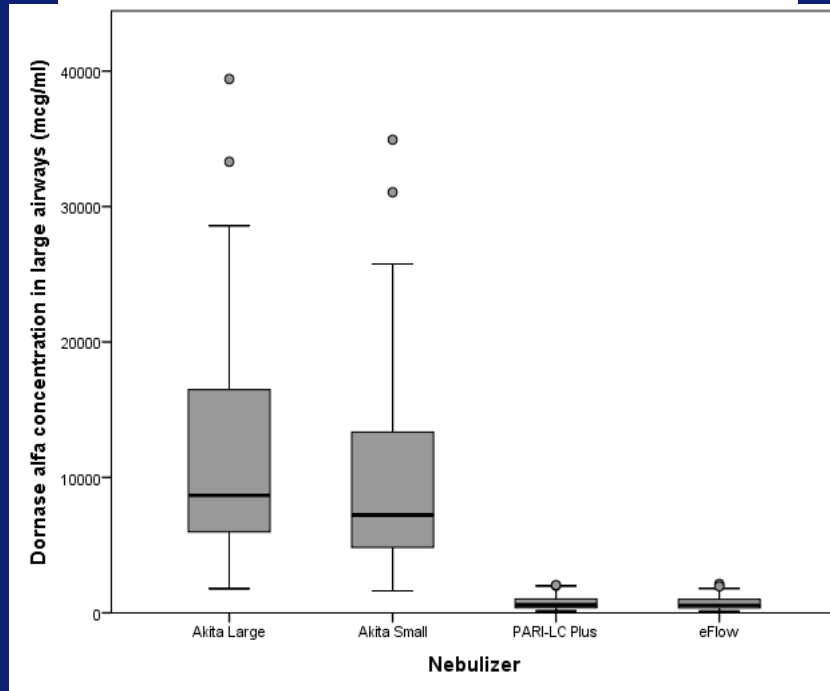


Fluid dynamic modelling

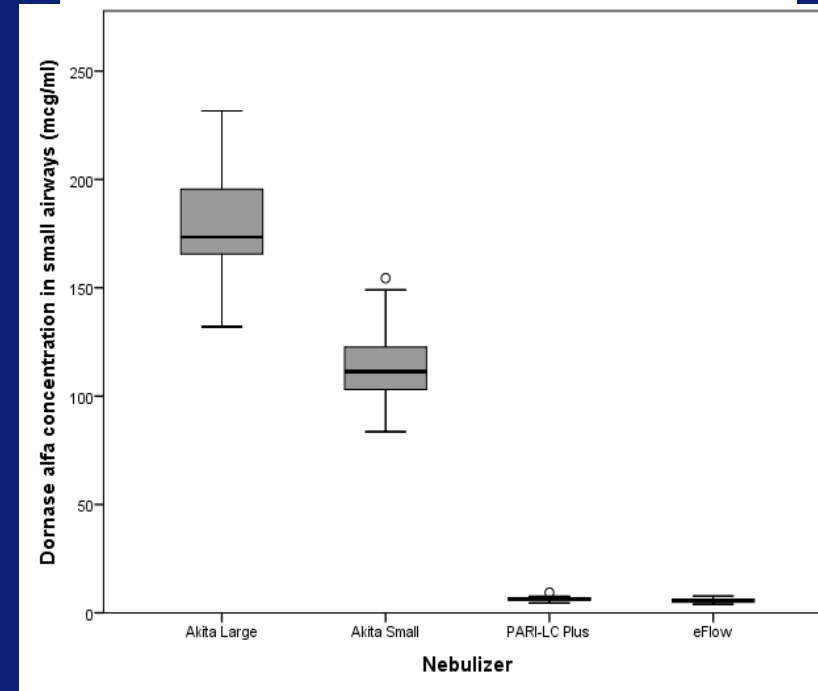


Smart nebulizer: substantial improvement of deposition dornase alfa in small airways deposition

Large airways concentrations



Small airways concentrations



Should initial or new bacterial infection with *Pseudomonas aeruginosa* be treated?

2014

positive culture result). There is robust evidence that eradication treatment for *P. aeruginosa* is effective but no one regimen has yet been shown to be preferred because of superior efficacy [29]. Options include 28 days of tobramycin solution for inhalation (TIS) and up to 3 months of a combination of nebulised colistimethate and oral ciprofloxacin [30]. Follow-up cultures to document eradication after treatment are crucial.

Where is Aztreonam (AZLI)?
Where is the evidence for colistin cipro combination?

2018

culture result). There is robust evidence that eradication treatment for *P. aeruginosa* is effective but no one regimen has yet been shown to be preferred because of superior efficacy [29]. Options include 28 days of tobramycin solution for inhalation (TIS) and up to 3 months of a combination of nebulised colistimethate and oral ciprofloxacin [30]. Follow-up cultures to document eradication after treatment are crucial.

How should chronic infection with *P.Aeruginosa* be treated?

2014

When eradication therapy has failed, the diagnosis of chronic infection is made and long term inhaled antibiotic therapy should be commenced [18]. USA guidelines recommend TIS

Over 70 papers on eradication
Why does eradication fails in some patients?

2018

When eradication therapy has failed, the diagnosis of chronic infection is made and long term inhaled antibiotic therapy should be commenced [31]. USA guidelines recommend TIS

Why eradication fails in some subjects?

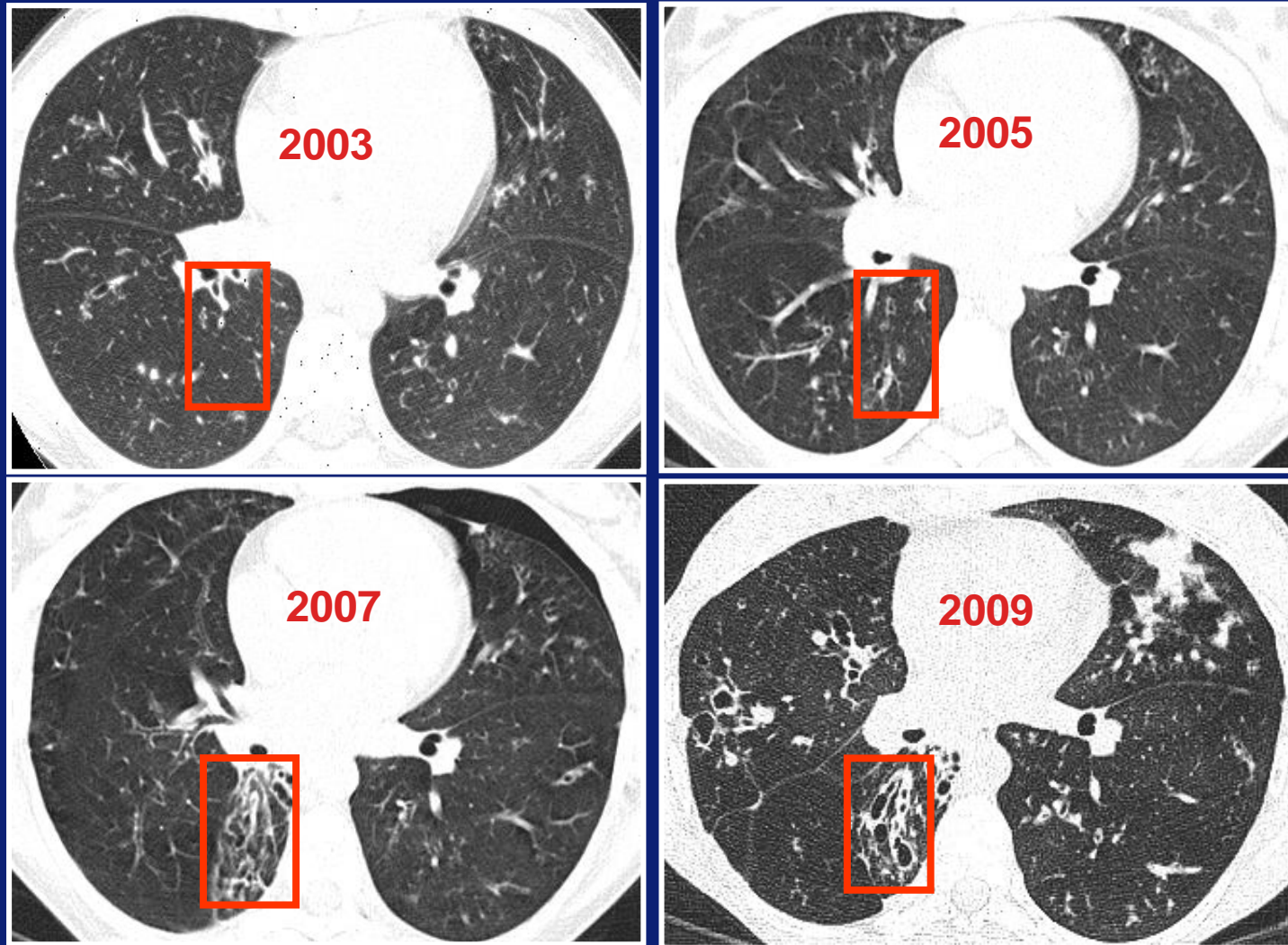
- Adherence to therapy
- Technical failure nebulizer
- Inhalation competence
- Age
- Sinus infection by *Pseudomonas aeruginosa*
- *Pseudomonas aeruginosa* related (Mucoid)
- Severity of structural lung abnormalities

Daily observations of Nebulizer use and Technique Competence can be an issue!

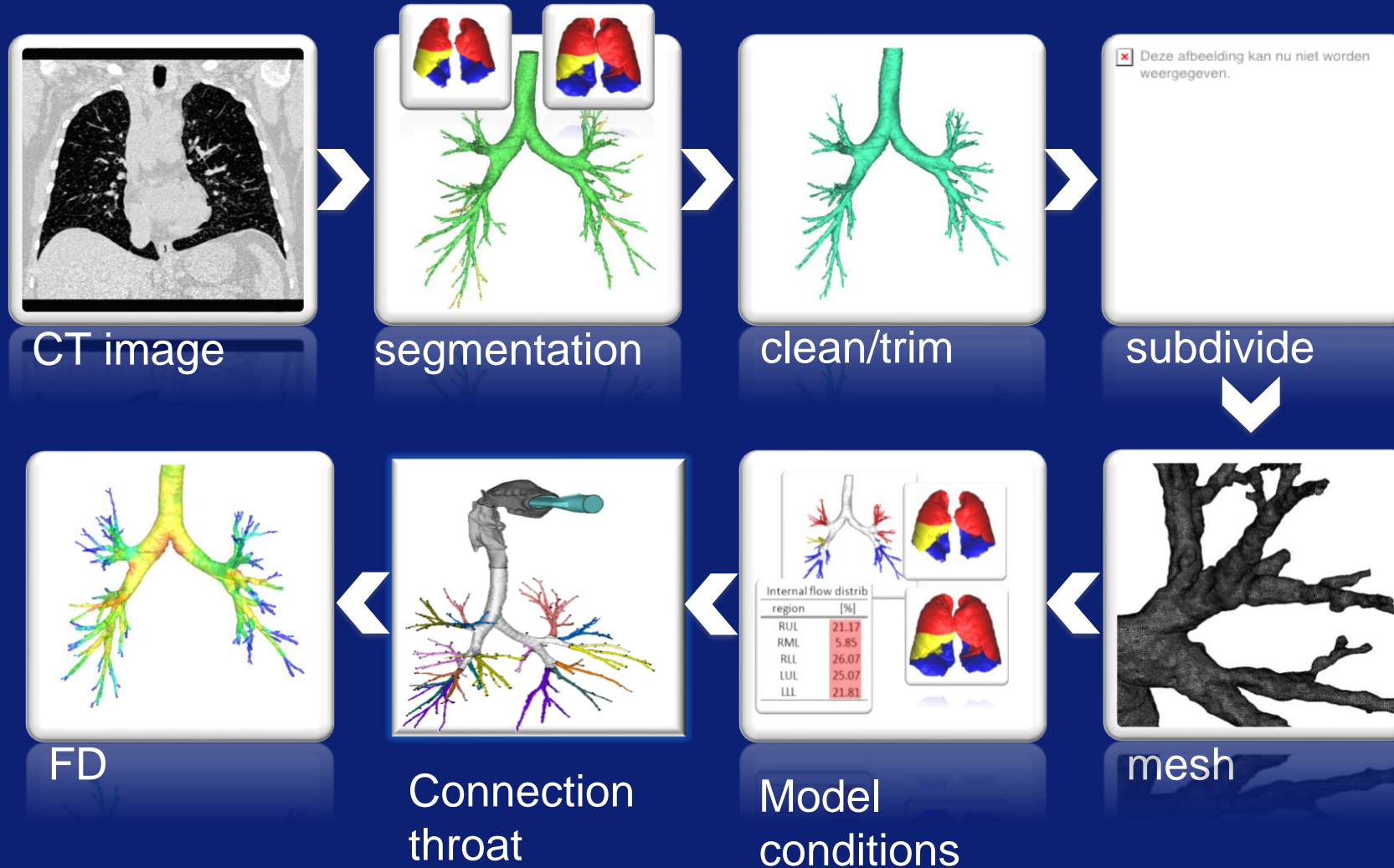


- N=32, age 6-18 years
- Major errors 13%

What about the impact of structural changes on the success rate of eradication?

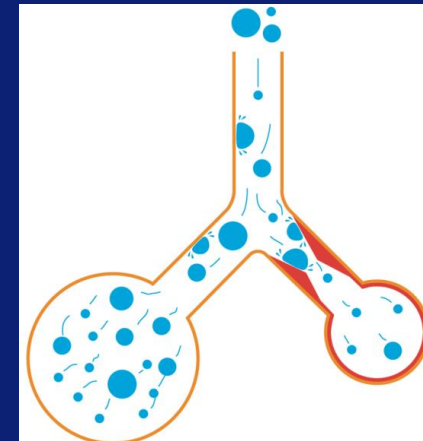
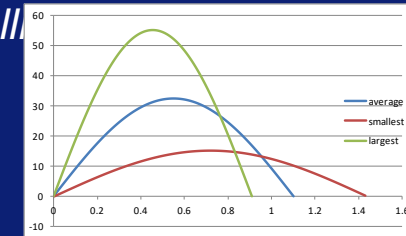


Patient specific modeling of regional deposition of inhaled antibiotics: AZLI



Patient specific modeling of regional deposition of inhaled antibiotics: Model conditions

- 40 CTs of CF patients
- CF-CT scoring of structural changes
- Median weight of an 11 [5-17] year old Dutch child: 38 kg
- Tidal volume of 10 [6-14] ml/kg: 380 [228-532] ml
- Respiration rate at 11 [5-17] years: 18 [22-14] breaths per minute *Wallace et al 2005*
- Inspiration/expiration ratio: $\frac{1}{2}$
- Sinusoidal breathing profile
- Particle size (μm): Large (4.4) / median (3.2) / small (2.8)
- Height lining fluid (μm): Thick (7) / median (5) / thin (3)

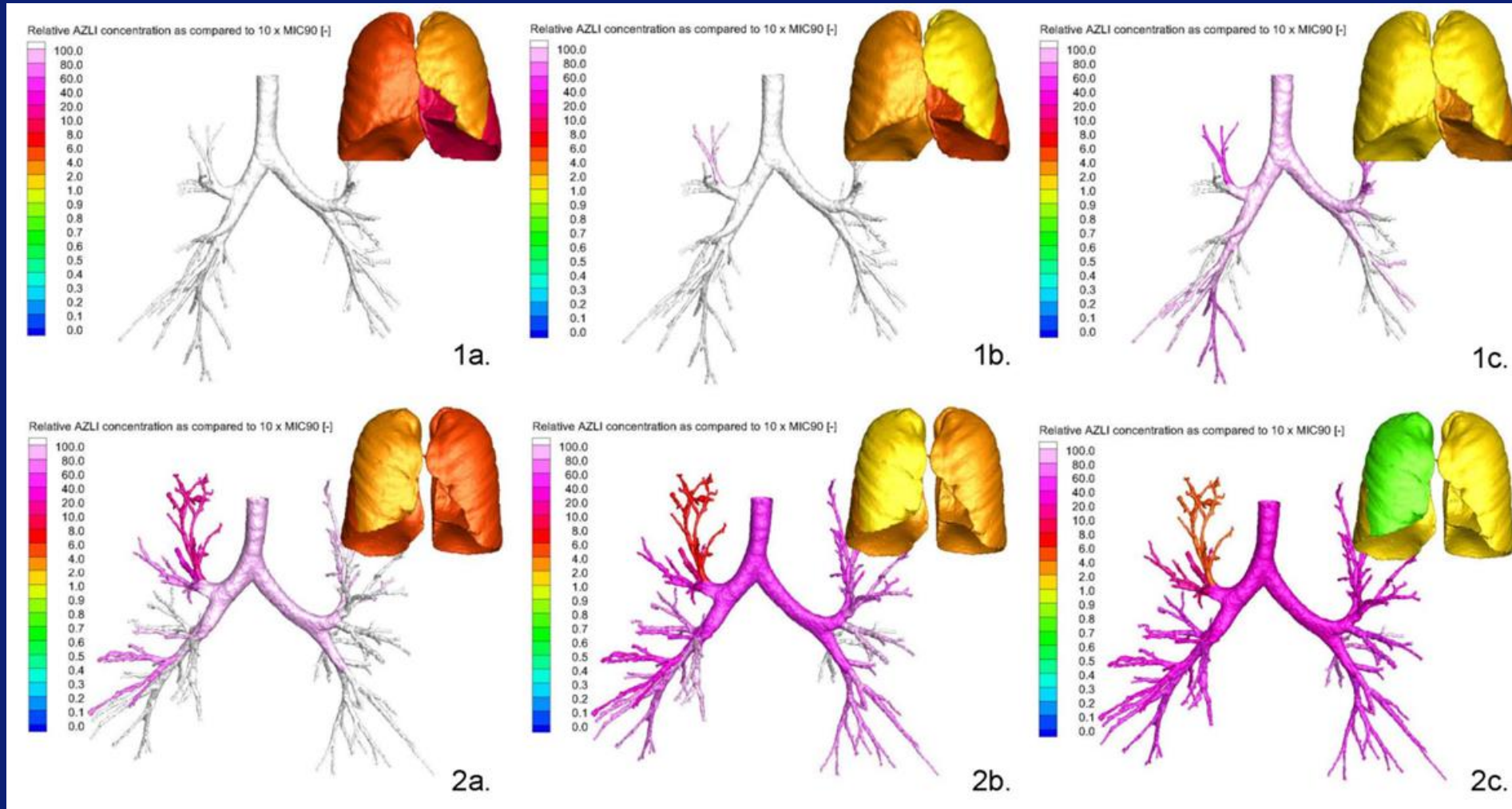


Patient specific modeling of regional deposition of inhaled antibiotics: AZLI concentrations

Thin lining fluid
Small diameter

Median lining fluid
Median diameter

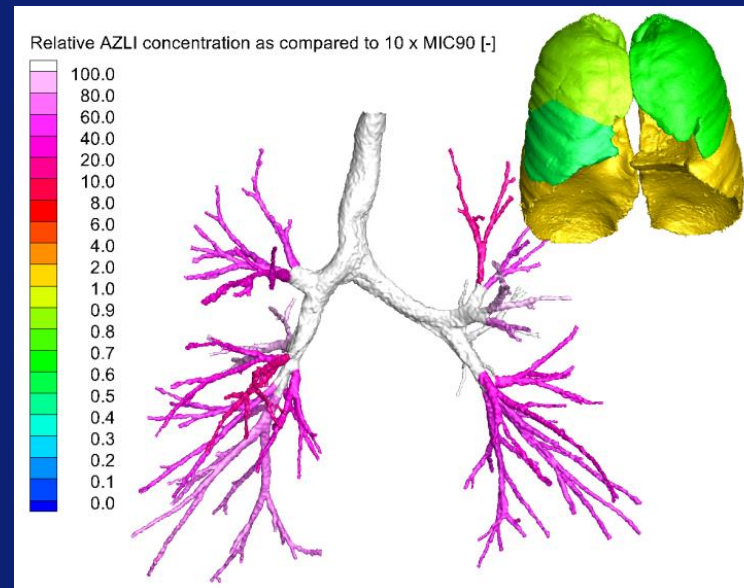
Thick lining fluid
Large diameter



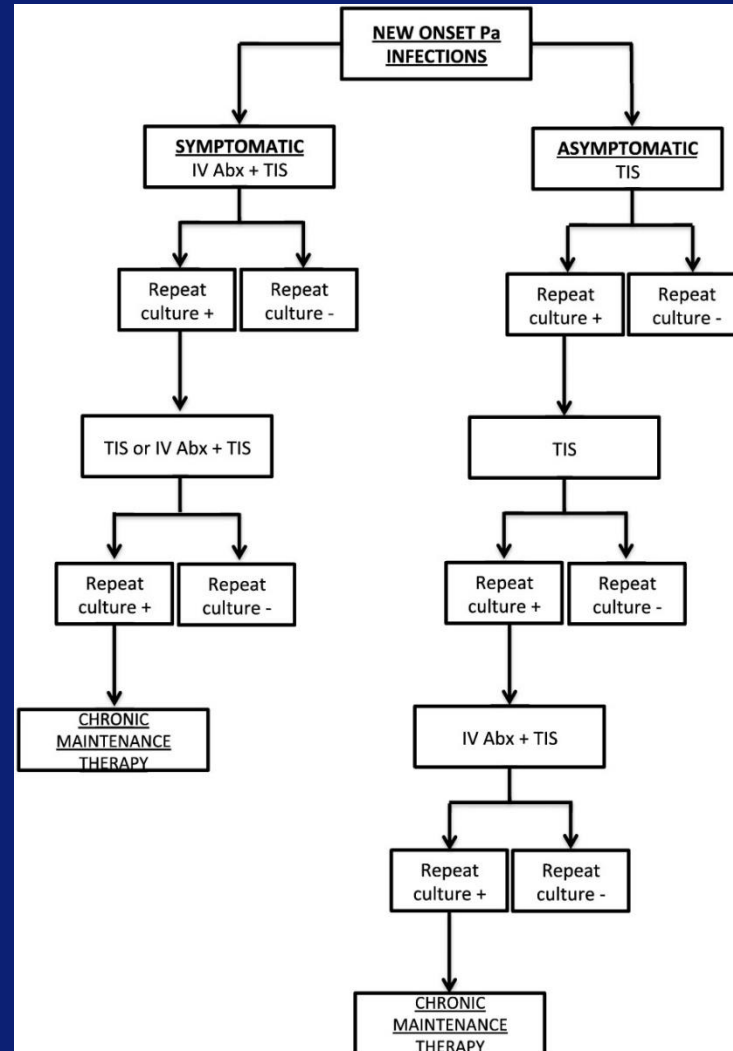
Patient specific modeling of regional deposition of inhaled antibiotics: Results

Inhaled antibiotics:

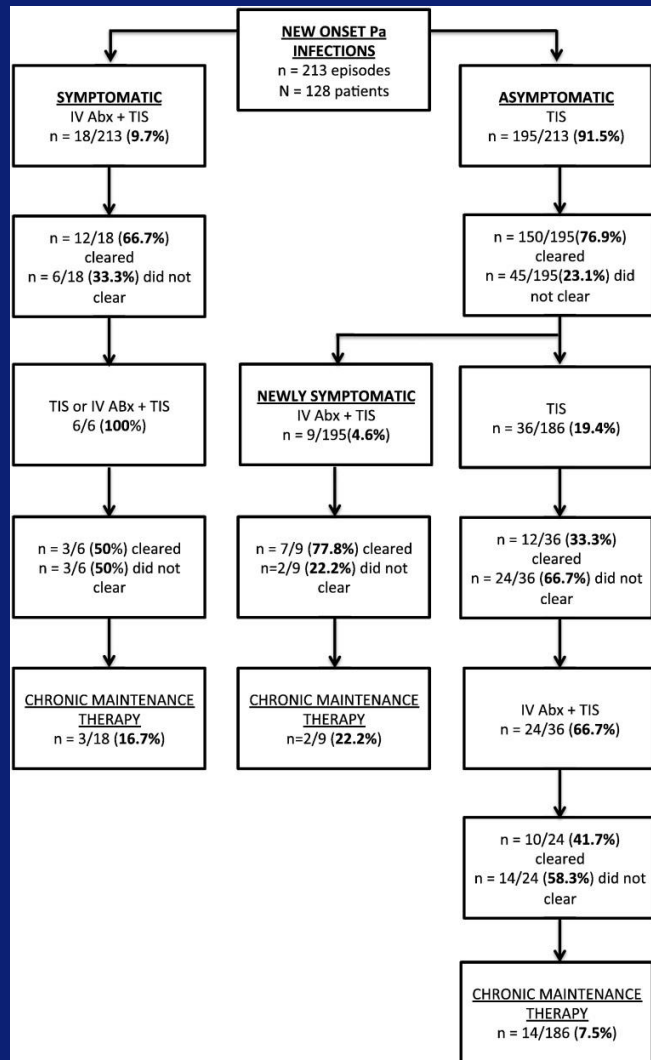
- Concentrations vary widely throughout the bronchial tree
- Inverse correlation [AZLI] in a lobe and CT-scores
- More diseased (upper) lobes received a lower [AZLI]
- [AZLI] can be, depending on the simulation settings, below the threshold of 10 x MIC90 or 1280 μ g/ml (for *P. Aeruginosa*)



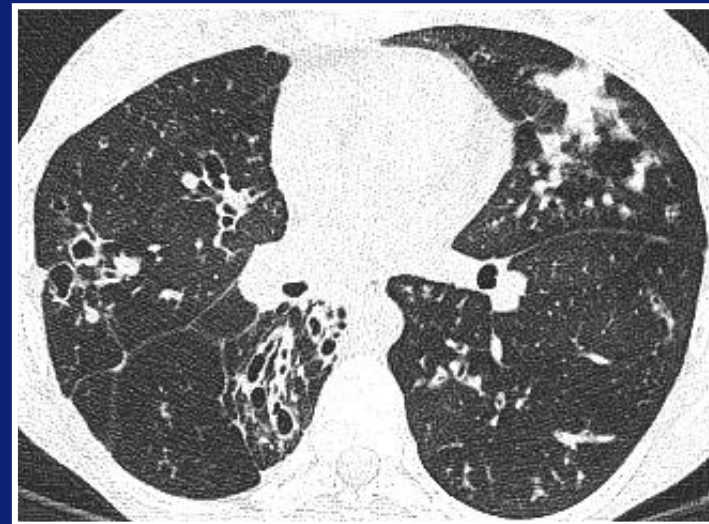
What to do when first eradication fails: Standardize, evaluate and publish



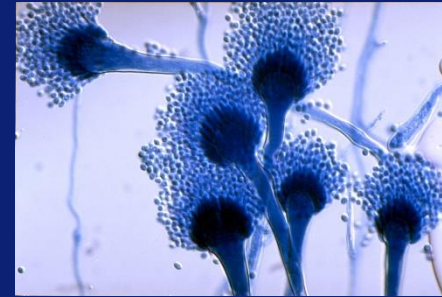
What to do when first eradication fails: Standardize, evaluate and publish



- Overall success in symptomatic 83.3%
- Overall success in asymptomatic 92%
- But only one week follow up after each step
- Definition of symptomatic?



How should fungal infections and severe/recurrent Allergic Bronchopulmonary Aspergillosis (ABPA) be treated?



2014

Aspergillus fumigatus as well as other fungi are commonly found in sputum of CF patients. Whilst their relevance is not entirely clear, more recent evidence suggests that *A. fumigatus* may act as a pathogen in at least in some CF patients [42].

Treatment is with oral prednisolone plus/minus antifungal therapy [17].

Over 250 papers on Aspergillus and CF since 2014?!

2018

Role of Aspergillus in sputum no longer discussed

need to be available to every CF care facility. Treatment is with oral prednisolone plus/minus antifungal therapy [30].

How should we monitor lung disease?: Imaging

2014

Chest X-rays are routinely performed on an annual basis in most CF centres as well as at times of clinical deterioration. Other imaging modalities, such as high resolution CT scanning, should be available as well, and are used routinely in some CF centres.

Over 250 papers on CF and CT and Lung since 2014?!

2018

Chest X-rays are routinely performed on an annual basis in most CF centres as well as at times of clinical deterioration. Other imaging modalities, such as high resolution CT scanning, should be available as well, and are used routinely in some CF centres.

The impact of chest CT on clinical management of CF lung disease

- 36 case simulations (vignettes)
 - Web based
 - Cases randomly selected from 2 CF centers
 - Standard presentation: clinical history; microbiology; growth; lung function; present complains; physical examination; medications; physiotherapy routines
- Each clinician 8 case simulations (4 of each center)
 - Allocation through algorithm
- Each case presented 2 x to each clinician
 - Cross over design
 - 10 week interval between cases
 - With or without Chest CT
 - With or without CXR

Would you modify treatment or perform additional diagnostics?

| Overview | Growth and spirometry | Clinical findings at current annual check-up | Radiology | Current medication | Questions |
|--|--|--|-----------|--------------------|--|
| Would you modify the treatment regime? | | | | | |
| | Current therapy | | | Options | |
| Dornase alfa | 2 x dd 2.5 mg | <input type="radio"/> No <input type="radio"/> Yes | | Select an option ▼ | |
| Inhaled antibiotics | Tobramycin 2 x dd 300 mg 1-month-on/1-month-off | <input type="radio"/> No <input type="radio"/> Yes | | Select an option ▼ | |
| Oral antibiotics | - | <input type="radio"/> No <input type="radio"/> Yes | | Select an option ▼ | |
| Intravenous antibiotics | - | <input type="radio"/> No <input type="radio"/> Yes | | Select an option ▼ | |
| Macrolide antibiotics | 500 mg, 3 days /week | <input type="radio"/> No <input type="radio"/> Yes | | Select an option ▼ | |
| Inhaled hypertonic saline | - | <input type="radio"/> No <input type="radio"/> Yes | | Select an option ▼ | |
| Oral corticosteroids | - | <input type="radio"/> No <input type="radio"/> Yes | | Select an option ▼ | |
| Non steroidal anti inflammatory drugs | - | <input type="radio"/> No <input type="radio"/> Yes | | Select an option ▼ | |
| Anti-fungal therapy | Itraconazole 1 x dd 200 mg | <input type="radio"/> No <input type="radio"/> Yes | | Select an option ▼ | |
| Kind of nebulizer | Jet-nebulizer | <input type="radio"/> No <input type="radio"/> Yes | | Select an option ▼ | What is a smart nebulizer? |
| Physiotherapy | 1 x dd Positive Expiratory Pressure mask | <input type="radio"/> No <input type="radio"/> Yes | | Select an option ▼ | |
| Timing of clinical evaluation | 3 months | <input type="radio"/> No <input type="radio"/> Yes | | Select an option ▼ | |
| Timing of sputum culture analysis | 3 months | <input type="radio"/> No <input type="radio"/> Yes | | Select an option ▼ | |
| Would you perform any additional diagnostics? (More than 1 answer is possible) | | | | | |
| <input type="checkbox"/> Chest radiography | | | | | |
| <input type="checkbox"/> Oral glucose tolerance test | | | | | |
| <input type="checkbox"/> Bronchoscopy | | | | | |
| <input type="checkbox"/> Allergic bronchopulmonary aspergillosis test | | | | | |
| <input type="checkbox"/> Atypical mycobacteria | | | | | |
| <input type="checkbox"/> Consult other specialists | | | | | |
| <input type="checkbox"/> Other diagnostics | | | | | |

The impact of chest CT on clinical management of CF lung disease

- 44 EU and Australian clinicians
- Vignette pairs; CT = 143: CR = 167
- CT associated with:
 - increase in antifungal treatment RR 2.8 (1.3-6.0), p=0.02
 - bronchoscopies RR 1.6 (1.1-2.5), p=0.04
 - mycobacterial cultures RR 1.3 (1.0-1.5), p=0.02
 - need for hospitalization RR 1.4 (1.0-1.9), p=0.03
- CXR associated with:
 - increase in inhaled antibiotics RR 1.3 (1.0-1.6), p=0.04

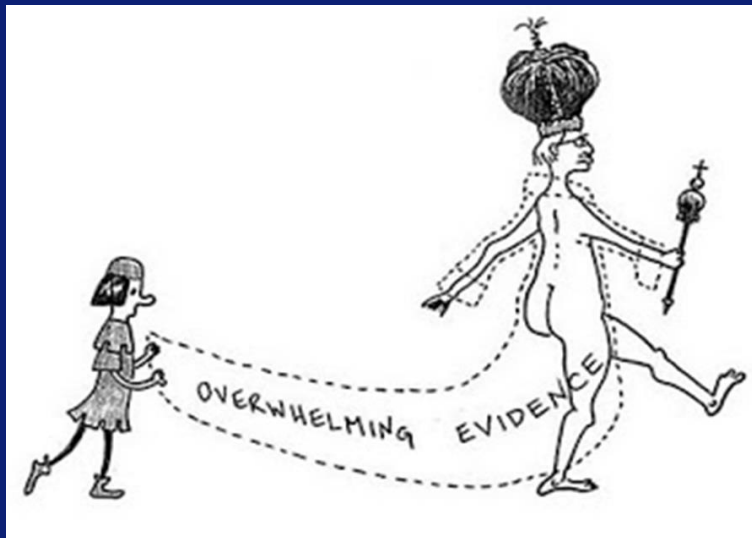
Conclusion:

CT but not CXR, at routine biennial follow-up associated with changes in treatment and/or diagnostics, including the need for hospitalization.

Pulmonary guidelines & current practice updates in treatments of CF lung disease

- 'The pirates codes are more guidelines than actually rules, welcome aboard the black pearl miss Turner' *Captain Barbossa: Pirates of the Carribian 2003*
- Guidelines are needed so you know where to deviate from
- No guideline can take into account all the unique clinical circumstances leading to therapy decisions for individual patients. Ren et al *Ann Am Thorac Soc 2018*
- Guidelines are tools that inform health professionals decisions rather than foster patient involvement in decision making
- Guidelines are mostly not up to date
- Quality guidelines for guidelines are needed
- Lets move to Medicine Based Evidence

Guidelines, beware: pick your choice



Searching evidence

"My students are dismayed when I say to them, half of what you are taught as medical students today, will have been shown to be wrong in 10 years, and the trouble is, none of us knows which half!"

≈ Dr. Sydney Burwell



INFORMATION RETRIEVAL

Pulmonary guidelines & current practice updates in treatments of CF lung disease

- Dornase alfa administration can be further optimized
 - The small airways are an important treatment target
- FEF₇₅% is a sensitive indicator of small airways involvement
- *Pseudomonas aeruginosa* eradication therapy
 - Optimize adherence and nebulizer competence
 - Take the severity of structural changes into account
 - Failed eradication: Follow the Sick Kids algorithm
- Treatment of Aspergillus is an important gap in our knowledge
- Monitoring of structural lung disease
 - CT is gold standard
 - Limited role for CXR

Erasmus MC

