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New or old kids on the block:

the role and management of non-tuberculous mycobacteria in CF.

South Eastern European CF congres, 16-17 november, 2018, Ljubljana, Slovenia

H.G.M. Arets, Pediatric Pulmonologist, MD, PhD, Associate professor Medical education, UMC Utrecht, Utrecht, The Netherlands

Atypical Mycobacteria (AMB)

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- = non-tuberculous mycobacteria (NTM)
- = other than M. tuberculosis (complex) and M. leprae

New kids on the block……..?

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- MRSA
- Stenotrophomonas maltophilia
- Achromobacter xylosoxidans
- Non-tuberculous mycobacteria

…… or old ones??

New beautiful emerging pathogens……..

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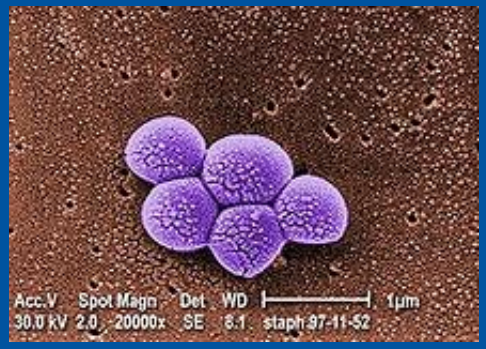
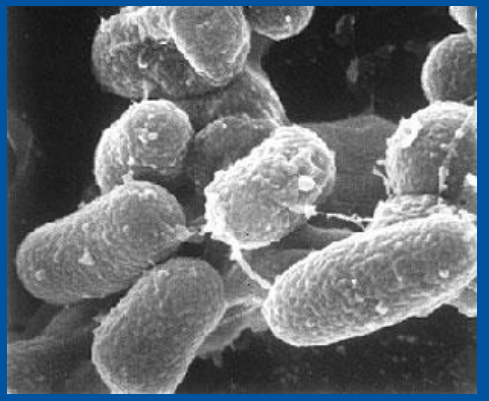
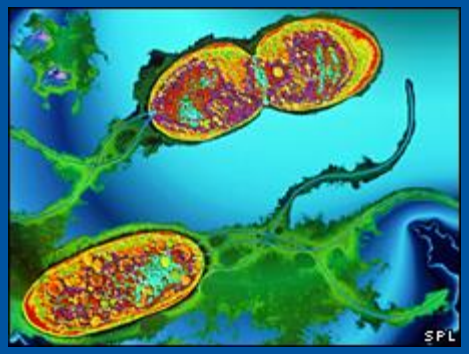


MRSA



Atypical mycobacteria



Stenotrophomonas maltophilia

Achromobacter xylosoxidans

Today… what about AMB.

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- Epidemiology/prevalence
- Transmission and prevention
- Clinical significance
- Eradication/maintenance treatment
- Conclusion

Dutch CF registry 2017

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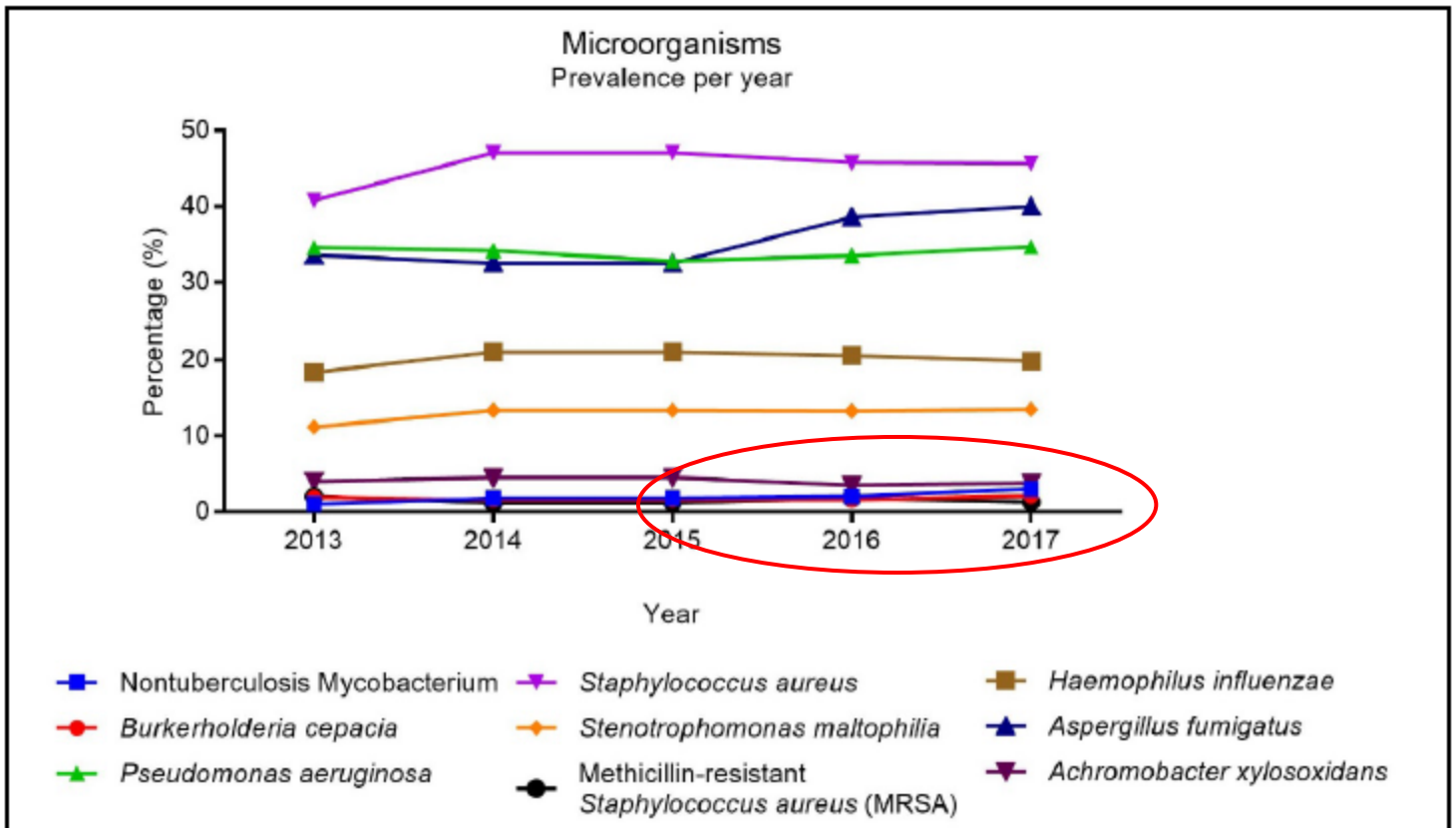


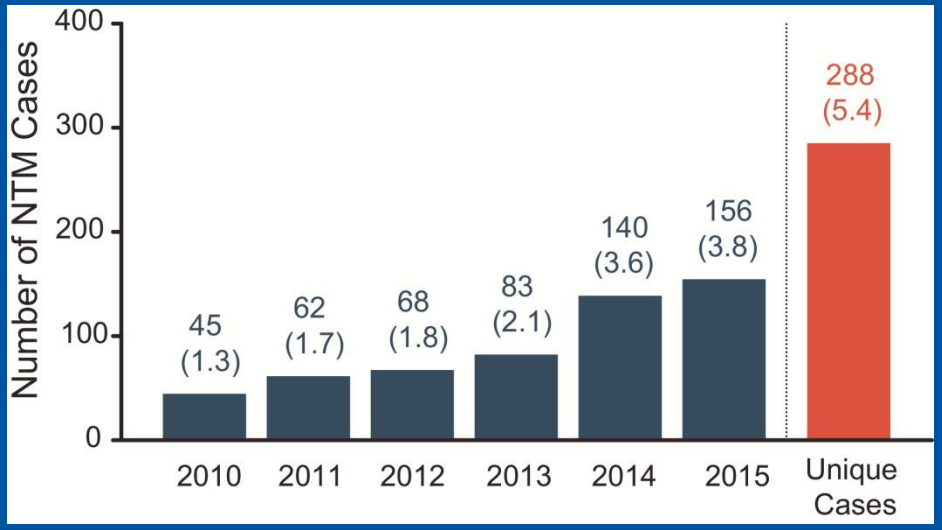
Figure 18. Prevalence of microorganisms in 2013-2017.

Epidemiology of Nontuberculous Mycobacteria Infection in Children and Young People With Cystic Fibrosis: Analysis of UK Cystic Fibrosis Registry

University Medical Center Utrecht

Aaron I. Gardner,[1] Elliot McClenaghan,[1] Gemma Saint,[2,3] Paul S. McNamara,[2,3] Malcolm Brodlie,[1,4,a] and Matthew F. Thomas[1,4,a]

[1]Institute of Cellular Medicine, Faculty of Medical Sciences, Newcastle University, Newcastle upon Tyne, [2]Department of Child Health, University of Liverpool, and [3]Alder Hey Children's National Health Service Foundation Trust, and [4]Department of Paediatric Respiratory Medicine, Great North Children's Hospital, Newcastle upon Tyne Hospitals National Health Service Foundation Trust, United Kingdom



Up to 5%

……. USA prevalence is 13%

…… no data from SE Europe?

50% carry over
(=from earlier yrs)

Table 3. Nontuberculous Mycobacteria Origin

Year	New Cases (%)	Carryover (%)	Reinfection (%)	Total
2010	45 (100)	0 (0)	0 (0)	45
2011	26 (41.9)	36 (58.1)	0 (0)	62
2012	26 (38.2)	41 (60.3)	1 (1.5)	68
2013	27 (32.5)	54 (65.1)	2 (2.4)	83
2014	88 (62.9)	45 (32.1)	7 (5.0)	140
2015	76 (48.7)	76 (48.7)	4 (2.6)	156
Total (%)	288 (52.0)	252 (45.5)	14 (2.5)	554

Origin of nontuberculous mycobacteria cases per year, data visualized in Figure 3A.

What species?

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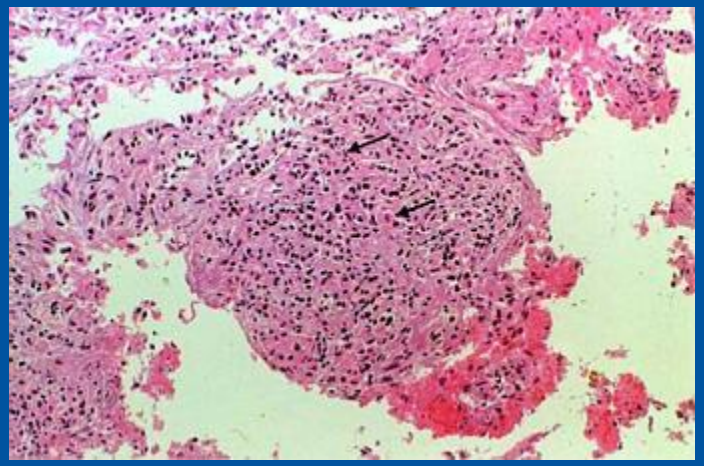
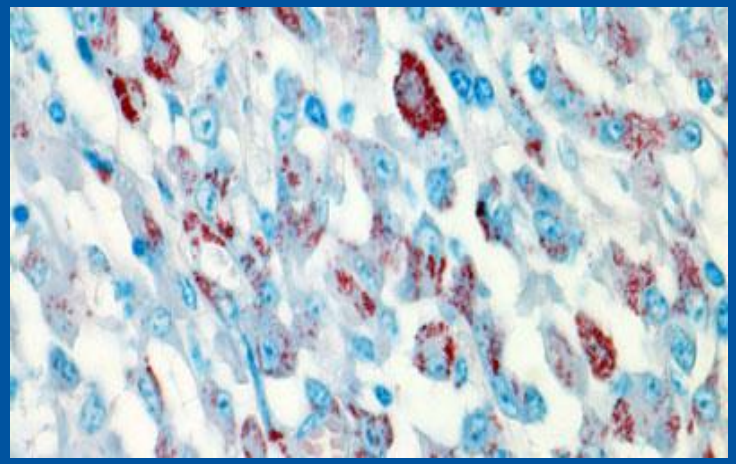
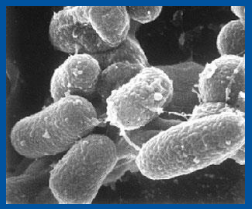
- Mycobacterium avium (complex) USA>Europe (F>M)
- Mycobacterium abcessus Europe > USA (M>F)
  - *More fulminant course and less favourable outcome*
  - *More difficult to treat*



M abscessus



M avium complex



Why increasing prevalence?

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- Better detection methods (molecular techniques, PCR, new culture techniques)
- Increased surveillance
- Increased use of antibiotics
- Prognosis older age
- More severe disease

Today… what about AMB.

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- Epidemiology/prevalence
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- Clinical significance
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Atypical Mycobacteria: where do they come from?

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- environmental organisms
- relatively low virulence and slow growth
- soil and water
- You only find what you look for……AMB not in regular cultures

What patients are at risk??

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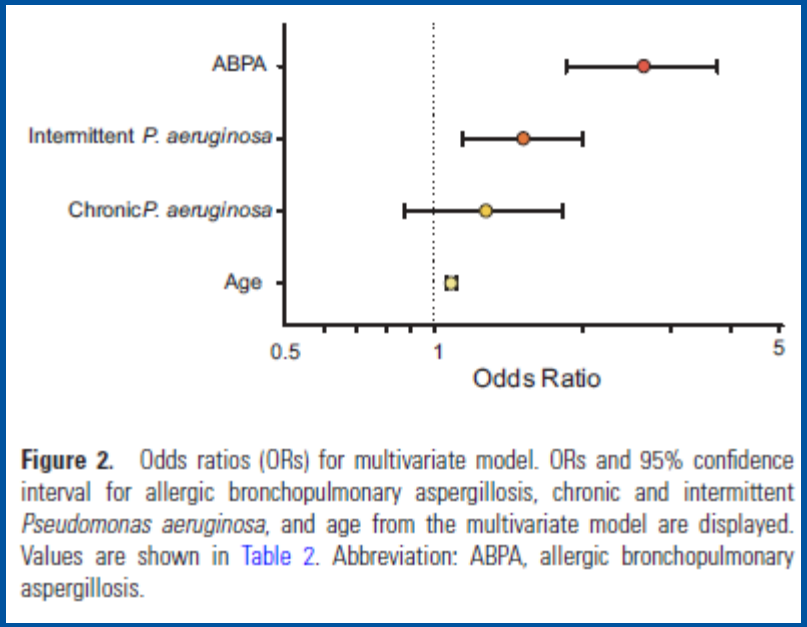

Figure 2. Odds ratios (ORs) for multivariate model. ORs and 95% confidence interval for allergic bronchopulmonary aspergillosis, chronic and intermittent *Pseudomonas aeruginosa*, and age from the multivariate model are displayed. Values are shown in Table 2. Abbreviation: ABPA, allergic bronchopulmonary aspergillosis.

TABLE 3. MULTIVARIABLE LOGISTIC MODEL OF CHARACTERISTICS ASSOCIATED WITH NONTUBERCULOUS MYCOBACTERIA

Characteristics	OR Association with Culture Positivity*	95% CI for Odds Ratio
FEV_1, % predicted		
Severe, < 40	1.0†	
Moderate, 40 to < 70	1.8	1.1, 3.0
Mild, 70 to < 90	2.0	1.1, 3.8
Normal, ⩾ 90	3.3	1.6, 7.0
Age at enrollment, yr		
Pediatric, 10 to < 18	1.0†	
Adult, 18 to < 30	1.8	1.1, 3.0
Adult, ⩾ 30	4.1	2.3, 7.5
Pseudomonas aeruginosa	0.7	0.4, 1.1
Staphylococcus aureus	1.6	1.1, 2.4
BMI, kg/m^2		
Normal–obese, ⩾ 18.5	1.0†	
Malnourished, < 18.5	1.9‡	1.2, 3.0

Definition of abbreviations: BMI = body mass index; CI = confidence interval; OR = odds ratio.

* OR of an association of a given characteristic with subject having positive cultures, relative to subject with negative cultures for nontuberculous mycobacteria, controlling for all other characteristics in model.

† Reference group for odds ratio comparisons.

‡ In univariable stratified analysis, this association was only seen in the pediatric population: OR (95% CI) for age 10 to < 18 years = 3.62 (1.31, 10.83); for age ⩾ 18 years = 0.87 (0.49, 1.53). Interaction term for age × BMI, however, was not significant in model building process.

Gardner et al. CID 2018
Olivier et al. AJRCCM 2003

Risk factors/associations?

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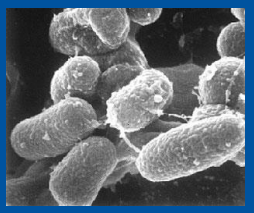
- older age
- poor nutrition
- increased frequency of intravenous antibiotic administration
- Diabetes
- treatment with corticosteroids or NSAIDS
- ABPA
- Pseudomonas??
- Staphylococcus
- Aspergillus chronic infection
- Declining lungfunction??

- more severe disease

Royal Brompton/ ATS



Prevention?

British Thoracic Society guidelines for the management of non-tuberculous mycobacterial pulmonary disease (NTM-PD)

Charles S Haworth,[1] John Banks,[2] Toby Capstick,[3] Andrew J Fisher,[4] Thomas Gorsuch,[5] Ian F Laurenson,[6] Andrew Leitch,[7] Michael R Loebinger,[8] Heather J Milburn,[9] Mark Nightingale,[10] Peter Ormerod,[11] Delane Shingadia,[12] David Smith,[13] Nuala Whitehead,[14] Robert Wilson,[8] R Andres Floto[1,15]

- Source of infection is environmental
- Even CF patients living together have different strains of AMB when infected
- However……sporadic human to human of M abscessus in CF??????
  - *prevention is hardly possible en infection comes form live long exposure to soils and aerosols*
  - *adequate infection control policies, both inpatient and outpatient to minimise risk of person-to-person transmission (as for many bacteria).*

Today… what about AMB.

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- Epidemiology/prevalence
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Clinical significance?

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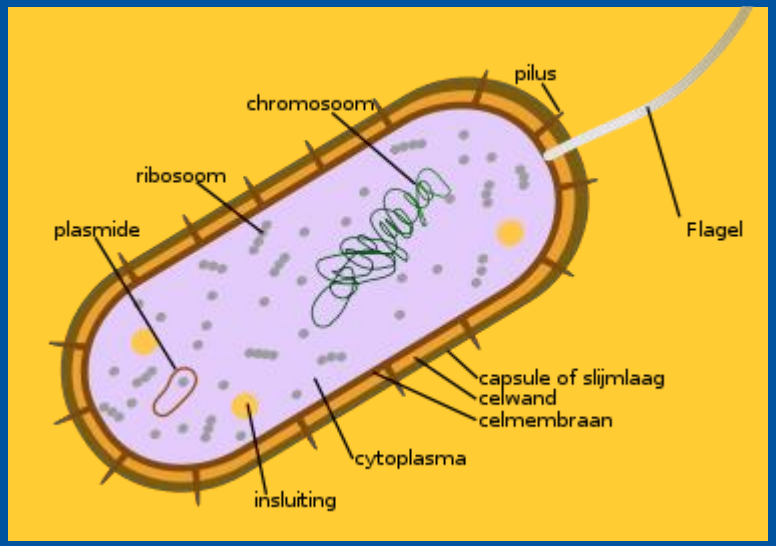

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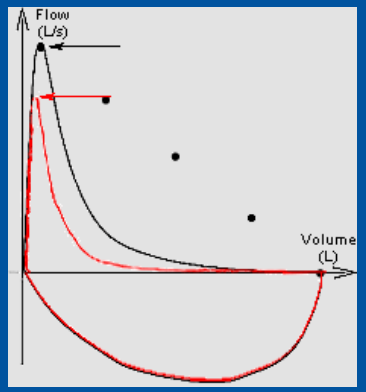

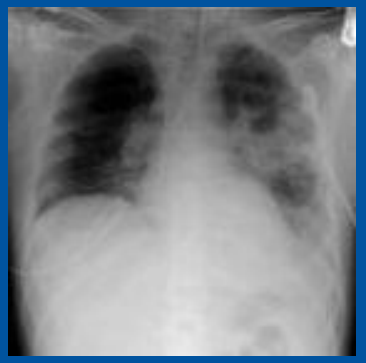

How relevant is this bug?

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- From transient, intermittent to chronic colonisation
  - *Asymptomatic infection*

- From harmless to severe infection
  - *progressive inflammatory lung damage,*
  - *a condition termed ‘NTM pulmonary disease’ (NTM-PD)*

 This creates considerable difficulties in deciding who and when to treat…….

 Not all patients will benefit from treatment for NTM

Atypical mycobacteria-clinical significance

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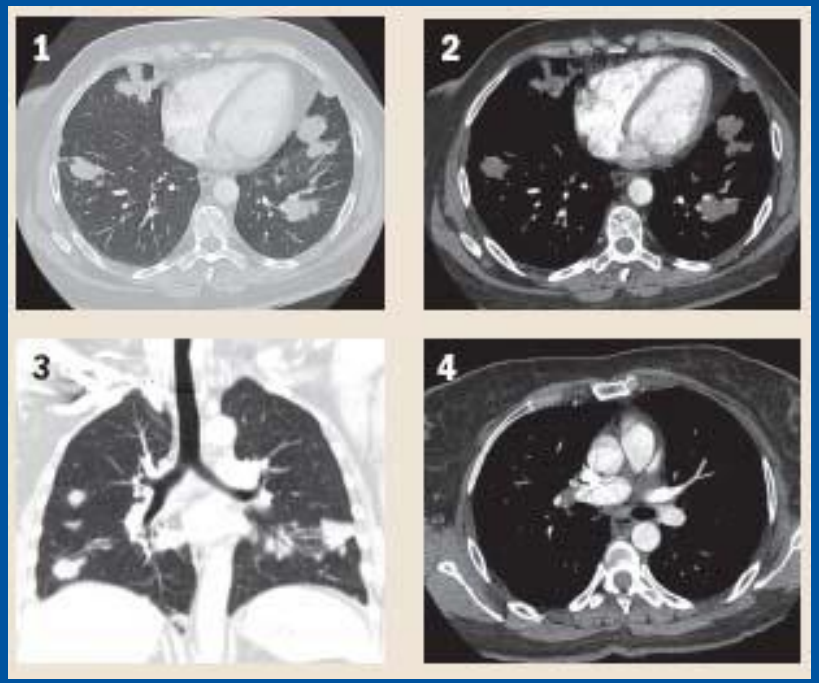
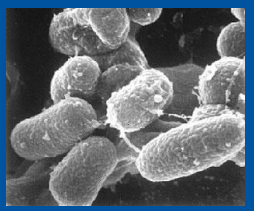
- considerable overlap between the clinical and radiological presentation of NTM and CF

- ATS criteria for disease
  - *Acid fast bacilli*
    - Biopsy or Bal ≥1,
    - sputum ≥2,
  - *CT scan:*
    - Patchy infiltrates
    - (new) bronchiectasis





Clinical impact?

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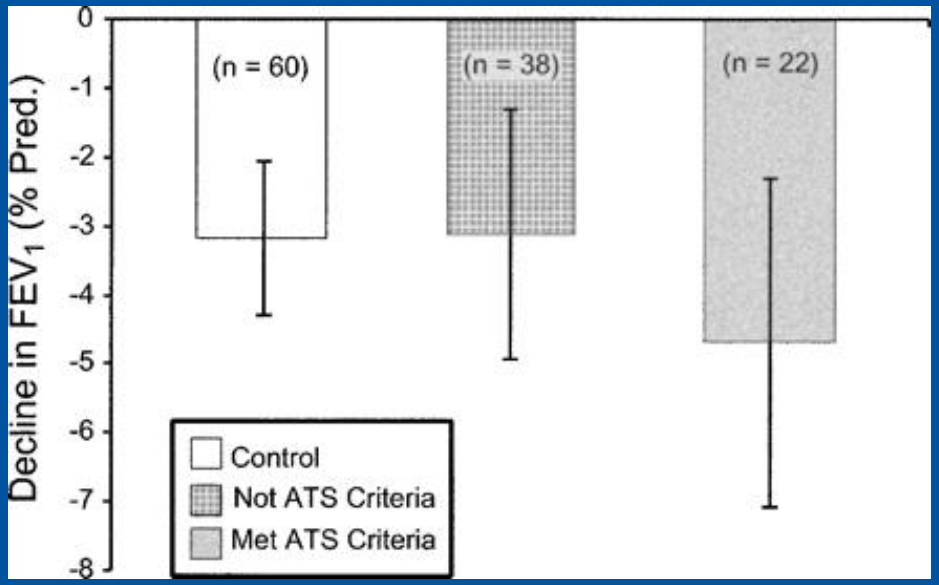
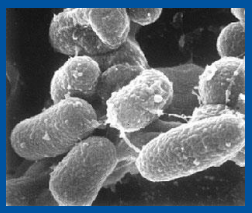
- No consistent effect on FEV1 demonstrated
- CF patients meeting ATS criteria show a non-significant FEV1 decrease
- CT score impaired in AMB positive patients during follow up:
  - *ATS criteria group 6/6 (100%)*
  - *Non ATS criteria group 4/18 (22%)* $p < 0.0006$
  - *Controls 3/8 (38%).*



Olivier et al. AJRCCM 2003



Atypical mycobacteria-flow diagram

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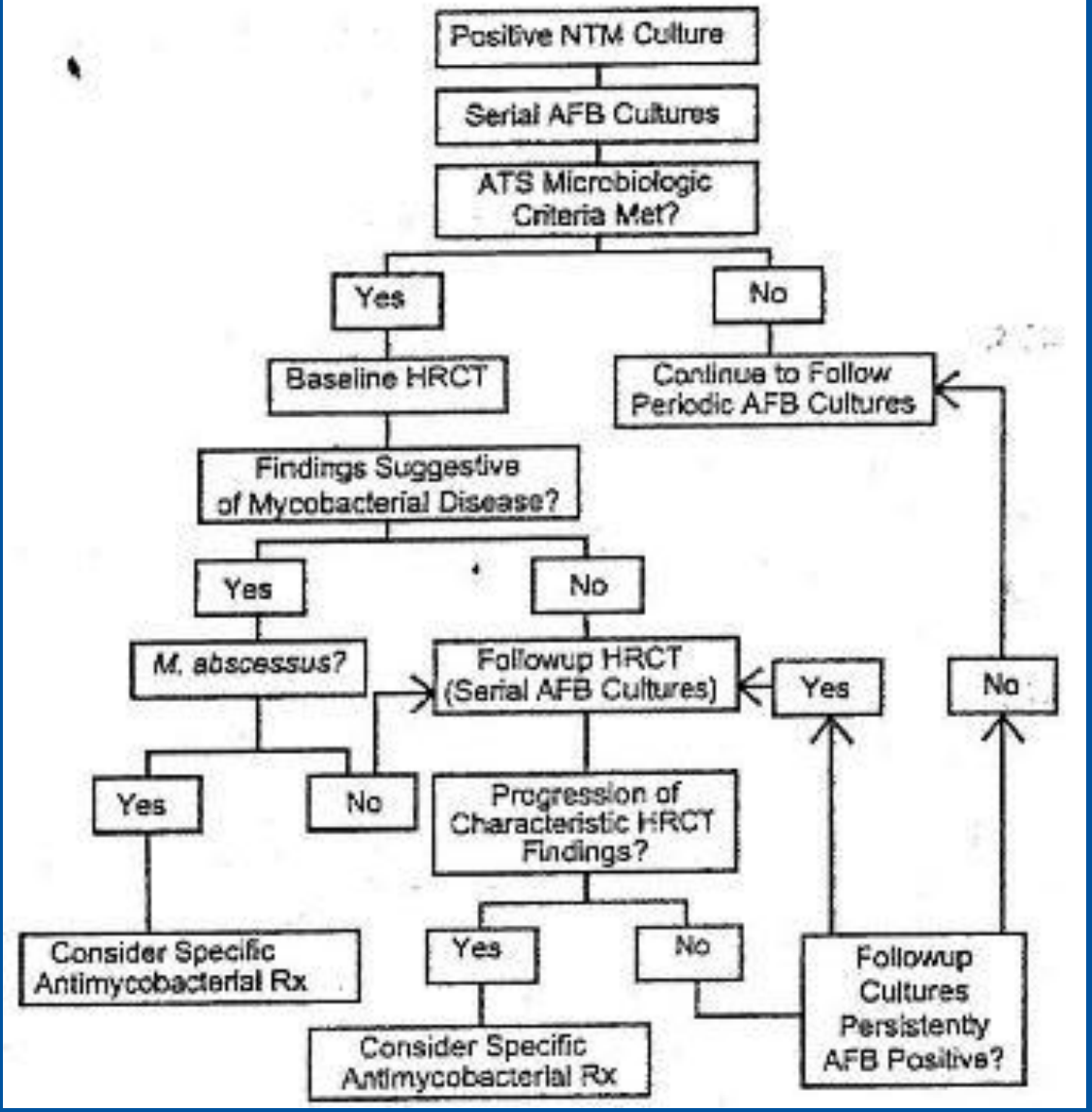
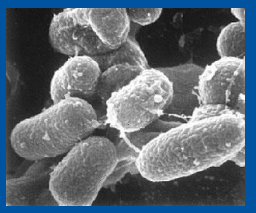


Royal Brompton



Steffi

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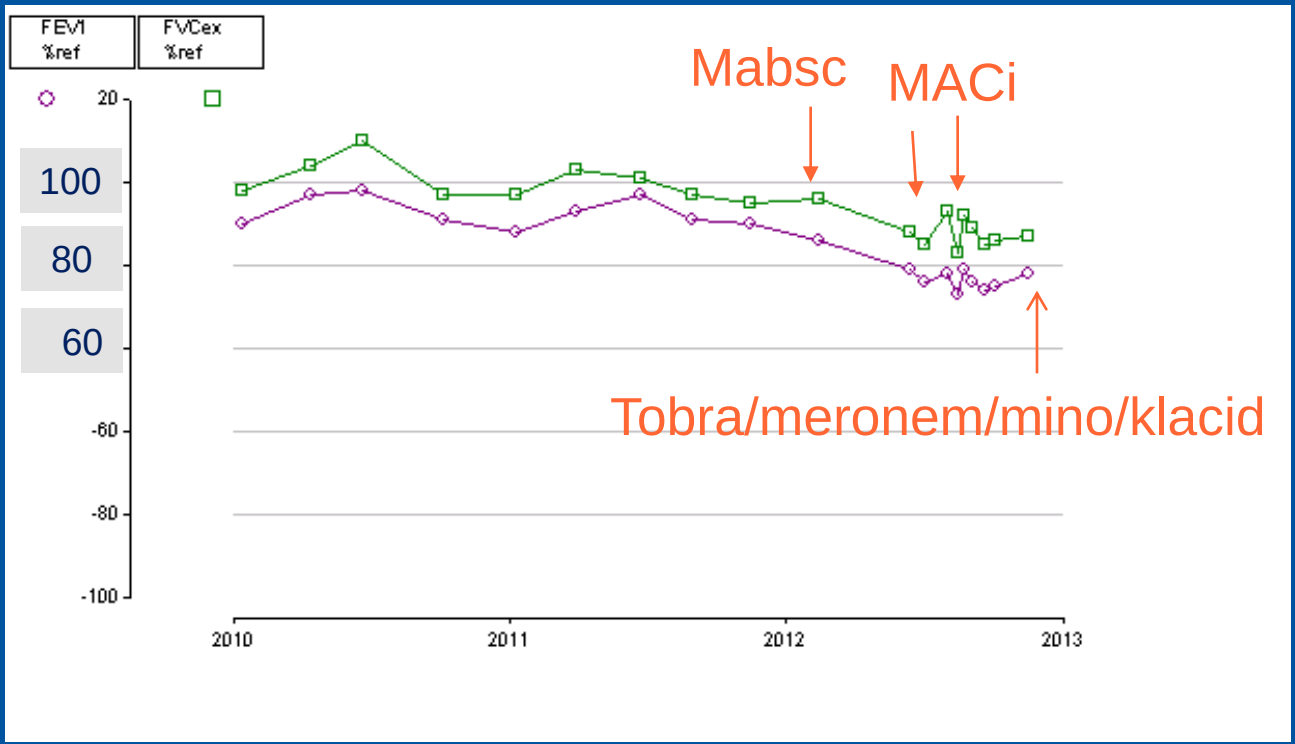
- CF, 2xdF508, S aureus (candida), Cotrimoxazol maintenance
- Mycobacterium abcessus in feb, april, juni 2012
- Increased symptoms, no effect “normal Abs”, finally meronem en tobra
- Redefinition M absc as MAC…...



Steffi: risk factors??

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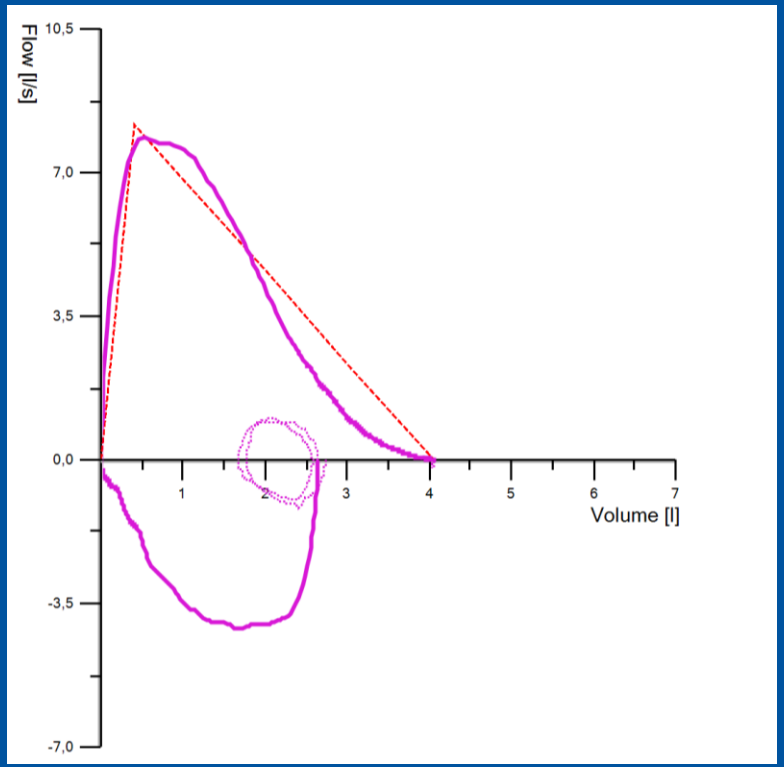
- 12 years
- Intermittent Pseudomonas positive
- No ABPA
- Well preserved lungfunction



Mycobacterium treatment

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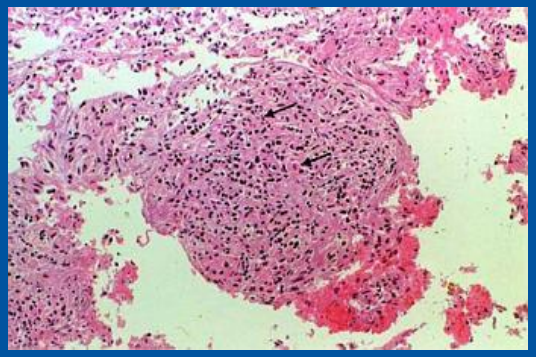
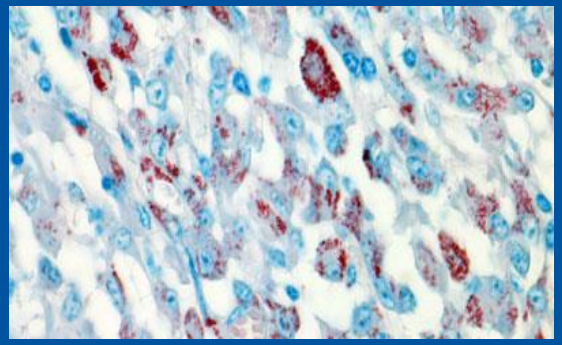
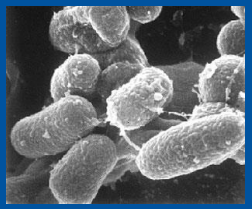
- ***M. abcessus***



- ***M. avium complex***



- ***Treat when***
  - *1. positive cultures*
  - *2. symptoms/CT abnormalities*
  - *3. Exclusion of an alternative diagnosis: consider and treat all non mycobacterial organisms/causes*



We decided to treat, because…….

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- Symptoms: more coughing, sputum and LF decline
- No effect “other” treatment effective
- M absc and M avium
- “Confusion at a higher level”
  - *Increasing awareness of the importance of AMB and advise to treat with a low threshhold*

Today… what about AMB.

University Medical Center Utrecht

- Epidemiology/prevalence
- Transmission and prevention
- Clinical significance
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- Conclusion

Mycobacterium abscessus-treatment

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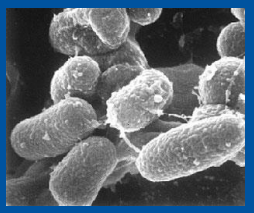
- *M. abcessus* is universally resistant to standard anti-tuberculous agents
- No antibiotic regimen based on *in vitro* susceptibilities has led to long-term sputum conversion

- First line therapy (3 weeks): 4 drugs
  - *(American Thoracic Society (ATS): minimal 2 drugs)*

- First line maintenance therapy

Royal Brompton



Mycobacterium Abcessus-treatment First choice

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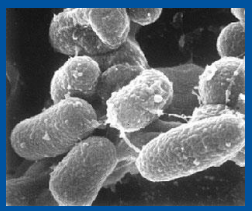
- **Intensive phase therapy (4-12/52)**
  - *Amikacin i.v.*
  - *Meropenem i.v.*
  - *Cefoxitin i.v.*
  - *Clarithromycin p.o.*
  - *(tigecyclin (+anti-emetic) when intolerant to one of the i.v. drugs)*
  - *(alternative is linezolid (50% sensitivity)) combined with clarithro*
- **Continuation therapy (>/= 18/12 depending on response)**
  - *Amikacin neb*
  - *Ciprofloxacin neb*
  - *Minocycline po*
  - *Clarithromycin po*

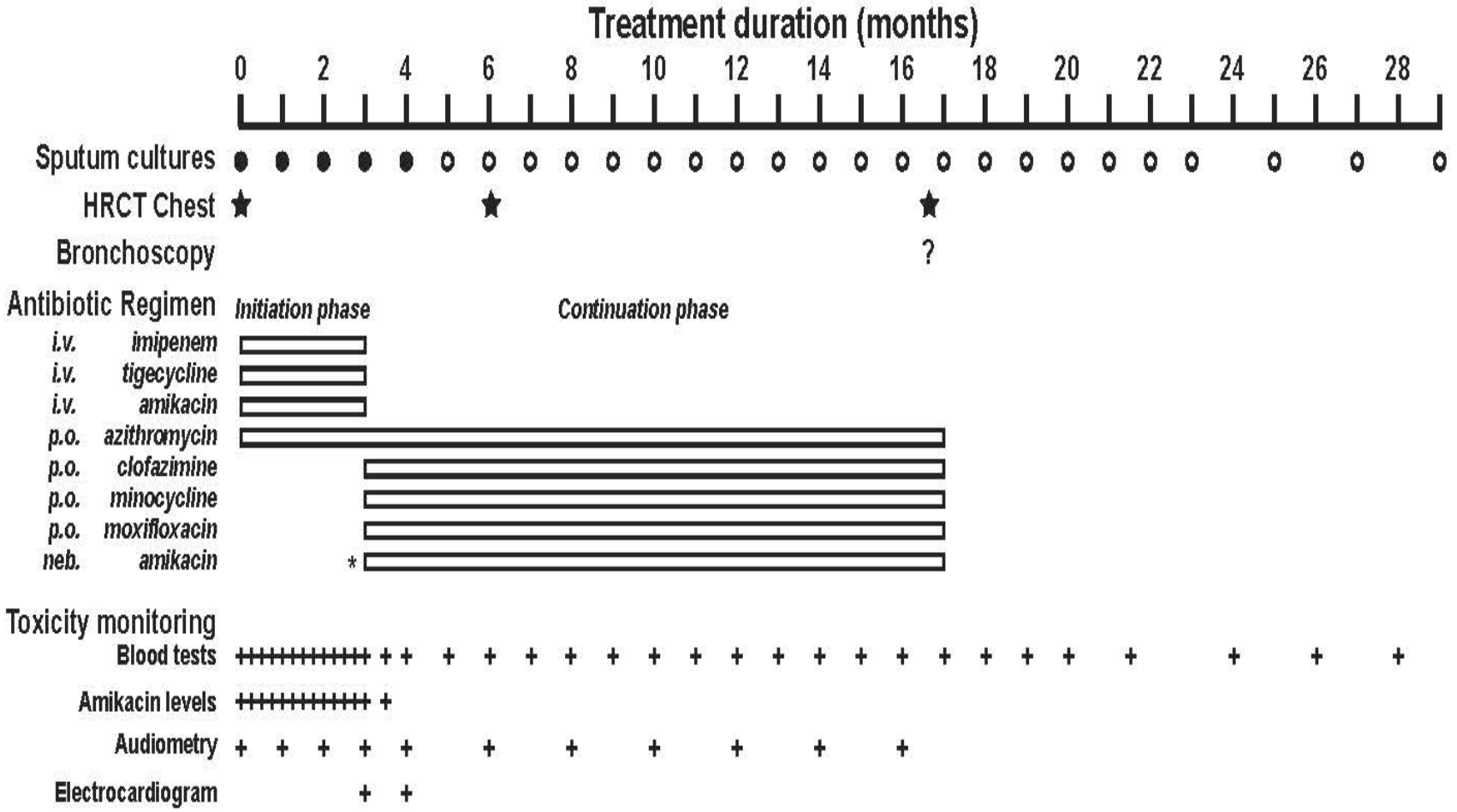
Royal Brompton/ ATS



Cystic Fibrosis Foundation and European Cystic Fibrosis Society Guidelines for the Management of Nontuberculous Mycobacteria in Individuals with Cystic Fibrosis

Floto et al. Thorax 2017

A. Typical *M. abscessus* treatment schedule



Effectivity?

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- **Failure =**
  - *Increasing sputum and breathlessness*
  - *Fevers*
  - *Sweats*
  - *Rising CRP*
  - *No response to treatment with non-mycobacterial antibiotics*
  - *Persistent positivity on sputum AAFB smear*
- second line R/

- **Succes =**
  - *sputum culture negative on serial samples collected over a period of one year.*
- At this point the organism will be regarded as eradicated and maintenance therapy may be stopped.

Follow up: inform your patient!

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- potential benefits and adverse effects
- Treatment for up to 18 months and effect is unclear.
- regular monitoring
  - *Full blood count, renal and hepatic function*
  - *If hepatics >5x ULN stop all drugs and reintroduce one by one after normalisation*
  - *Side effects might be reason for introducing 2 nebulised treatments.*
  - *audiometry*
- Adequate contraception
- Report of side effects a.s.a.p.

Mycobacterium avium complex (MAC)

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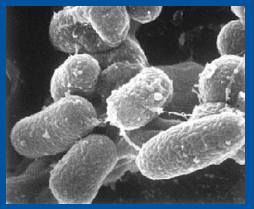
- Better correspondence in vitro and in vivo susceptibility
- Initial therapy should be triple oral therapy
- Severely ill patients: start with 2 weeks i.v. amikacin and a second anti-pseudomonal antibiotic.



Mycobacterium avium complex-treatment

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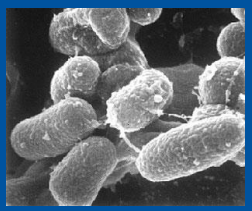
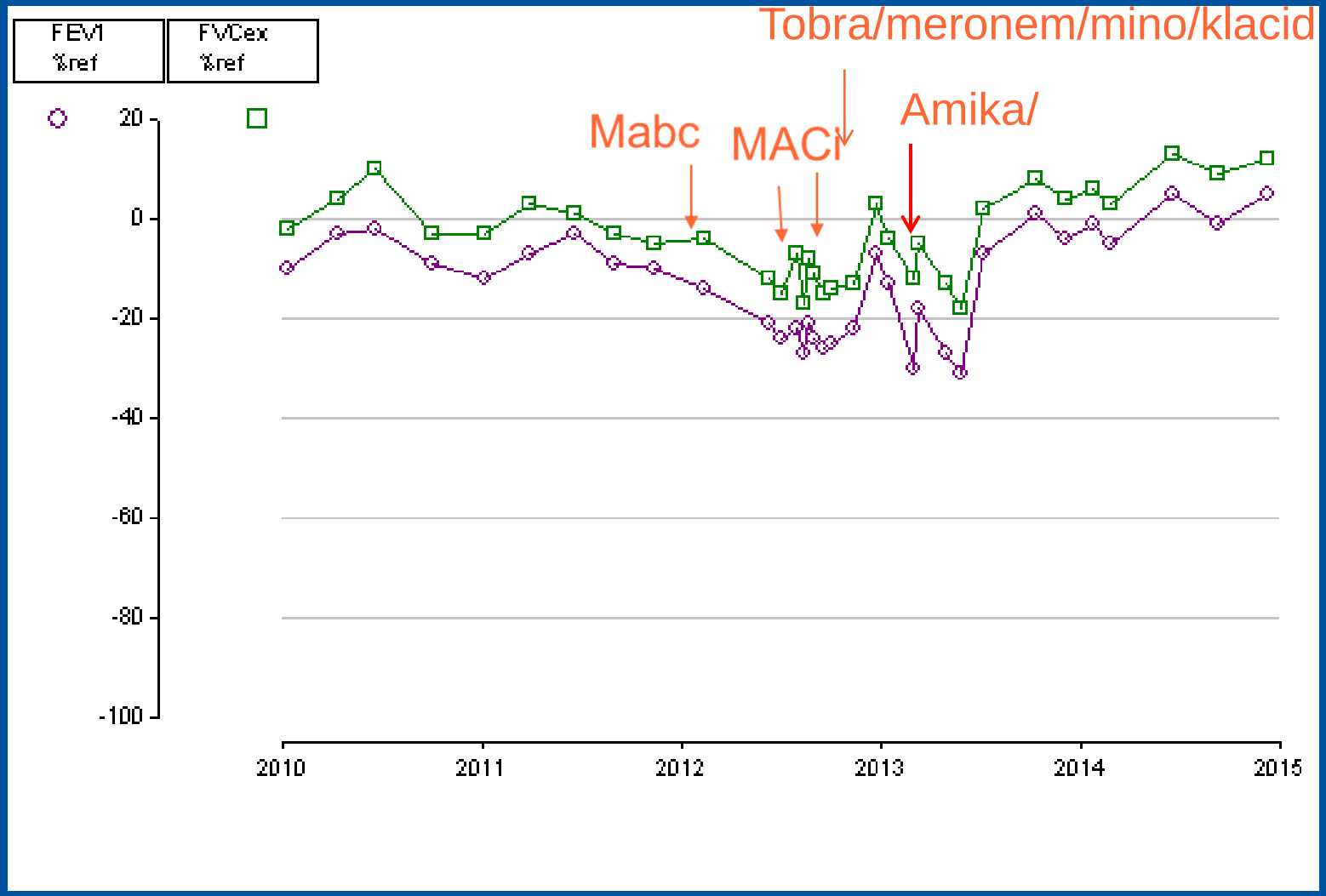
- **12-18 months treatment (**until culture negative for 12 months).
  - ***Rifampicin***
  - ***Clarithromycin or Azithromycin***
  - ***Ethambutol***

- **Cave potential benefits and adverse effects**
  - *regular monitoring throughout the duration of trea*
    - Full blood count, renal and hepatic function
    - If hepatics >5x ULN stop all drugs and reintroduce one by one after normalisation
  - *adequate contraception*
  - *Check visual acuity (ethambutol)*



Steffi

University Medical Center Utrecht



General comments

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- Duration of therapy not evidence based
- Treatment recommendation not specific for CF
- Treatment effects:
  - *<< 100% eradication*
  - *Eradication =/= clinical improvement*
  - *Clinical improvement =/= eradication*

- Treatment hampered by side effects

Today… what about AMB.

University Medical Center Utrecht

- Epidemiology/prevalence
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Atypical Mycobacteria: conclusions

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- They are everywhere
- Prevention is hard
- Often unclear clinical significance (M. absc > M. avium??)
- Treat on an individual basis, when all other reasons for deterioration are understood/treated
  - *Treatment of other pathogens*
  - *Consider CFRD, ABPA, resistance development, unknown pathogens*
- Try to objectivate role of “new pathogen”
  - *E.g. CT for AMB*
- Often intensive treatments (and side effects)
  - *Educate and inform your patients.*

Questions??

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