

Universität
Rostock



Traditio et Innovatio



Universitätsmedizin
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Non-Cystic Fibrosis Bronchiectasis - Indication for Long-term Antibiotics?

Hilte Geerdes-Fenge, Abteilung für Infektionskrankheiten/Tropenmedizin

Conflicts of Interest

Memberships

Deutsche Gesellschaft für Pneumologie und Beatmungsmedizin (DGP)

Deutsche Gesellschaft für Infektiologie (DGI)

Paul-Ehrlich-Gesellschaft für Chemotherapie (PEG)

Lecture fees

Pfizer

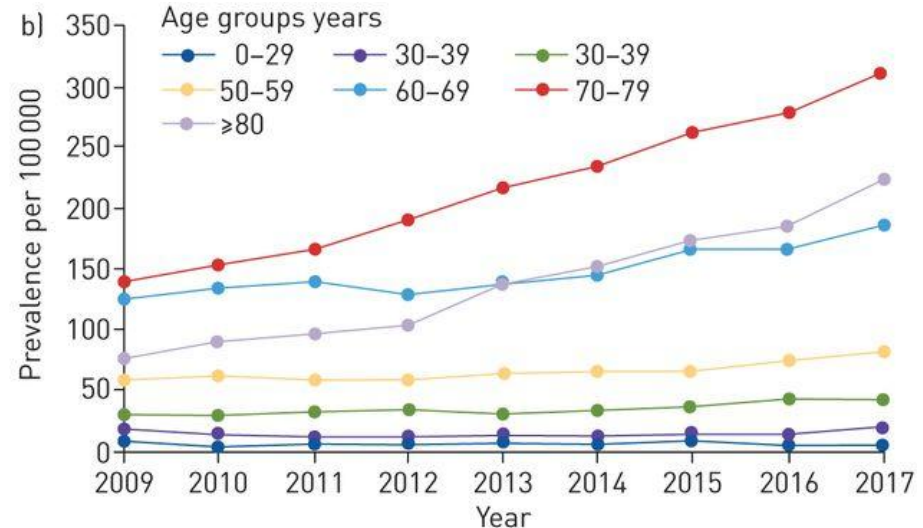
insmed

BDI

DGIM

Non-CF Bronchiectasis – globally increasing Prevalence

- Prevalence in Germany 100 per 100.000 population
- Mean age 68 yrs
- Sex ratio balanced

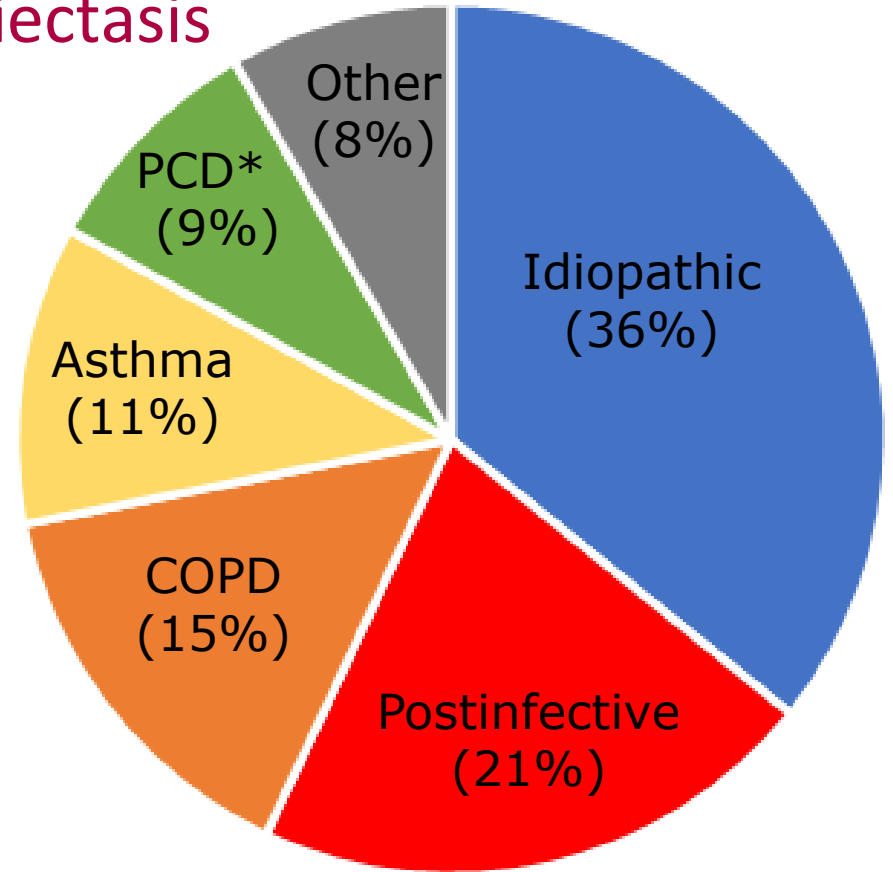


Increase in prevalence of bronchiectasis in women in Germany, 2009-2017

Etiology of Non-CF Bronchiectasis

German Bronchiectasis
Registry PROGNOSIS

1000 patients with
bronchiectasis German
hospitals and practices,
2015-2018



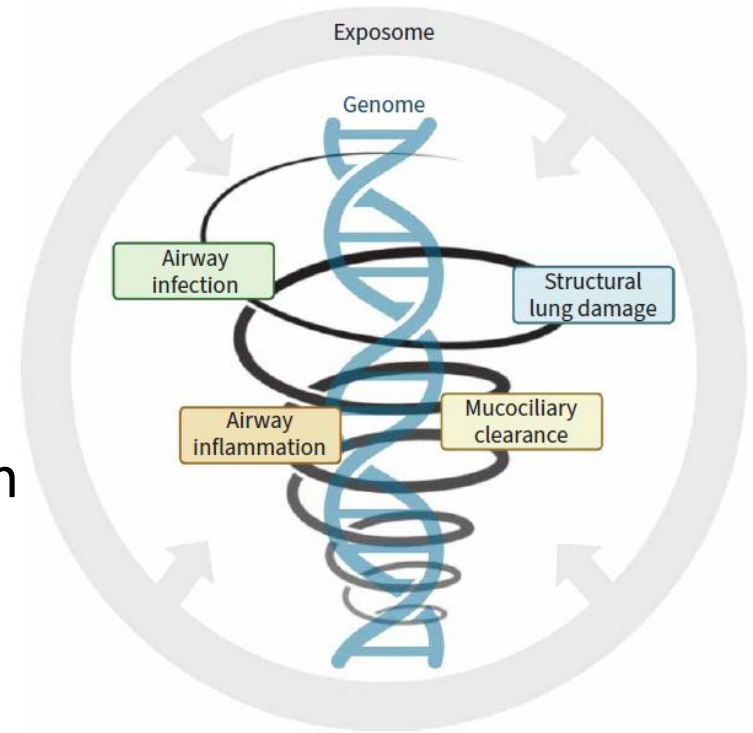
* PCD: primary ciliary dyskinesia

Bronchiectasis – a heterogeneous clinical syndrome

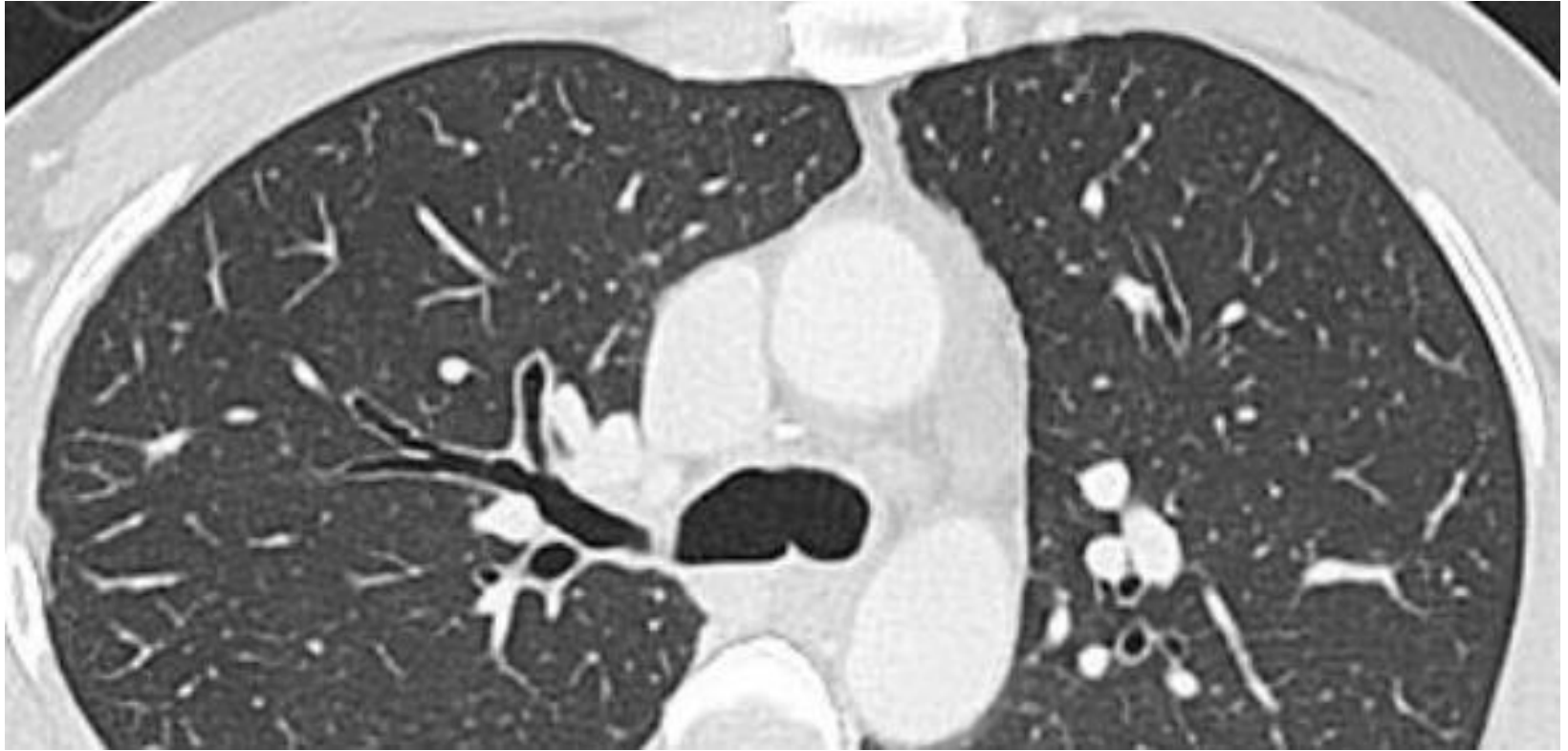
Vicious vortex of bronchiectasis:

Consequences:

- permanent bronchial dilatation
- chronic cough, sputum production
- pulmonary exacerbations
- reduced quality of life



Cylindrical Bronchiectasis, Post-Tuberculosis



42 yrs old female patient from The Philippines, TB in childhood

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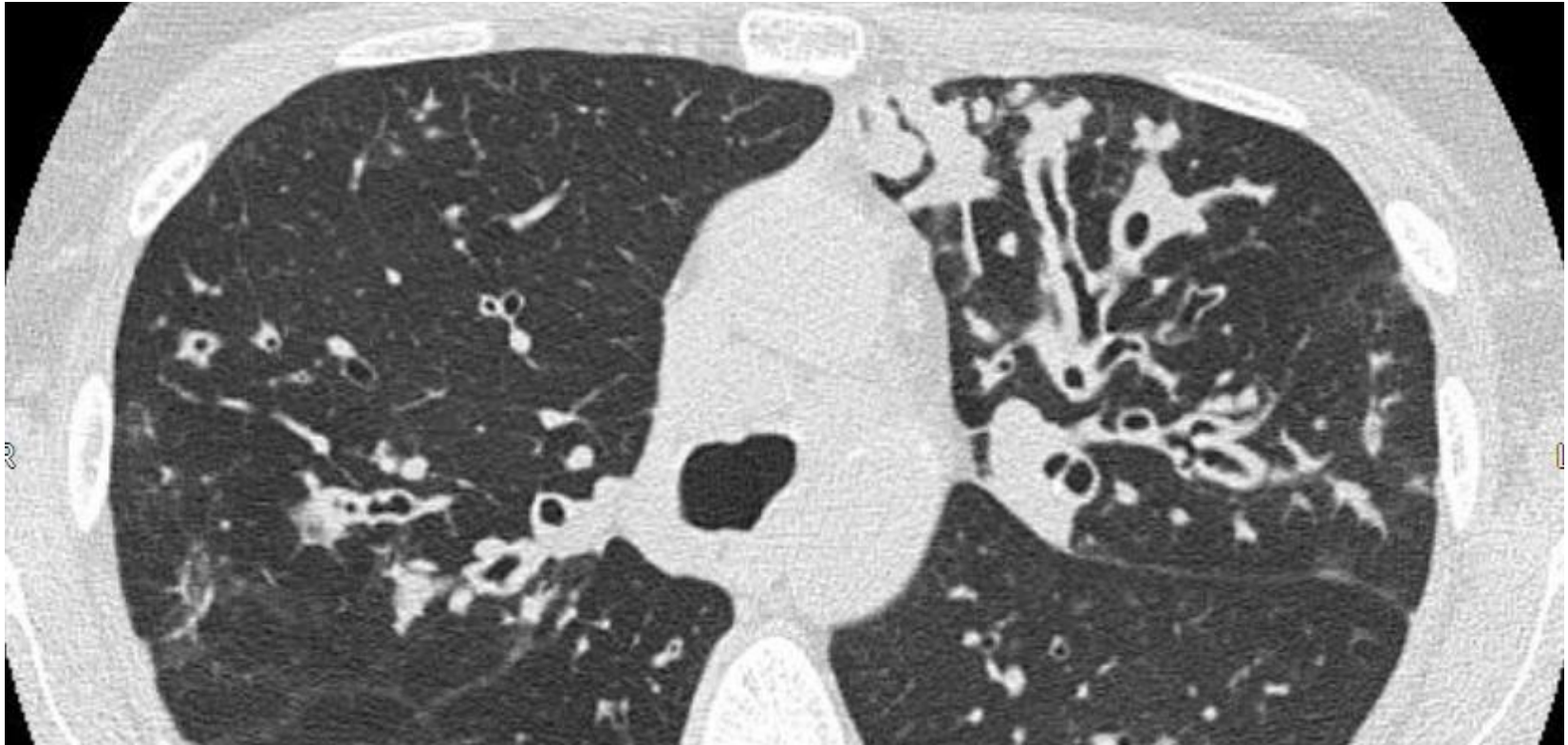
Cylindrical Bronchiectasis, Lady Windermere Syndrome



80 yrs old female patient from Germany, M avium and M marseillense

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Varicose and Cystic Bronchiectasis in Cystic Fibrosis (CF)



42 yrs old female patient, CF, ABPA, Pseudomonas aeruginosa

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Long-term Antibiotic Therapy of CF-Bronchiectasis

- Approved therapy with antibiotics:
- Inhaled therapy with Tobramycin, Colistin, Aztreonam and Levofloxacin
- Oral therapy with Azithromycin

Game-changer in CF-Bronchiectasis Therapy

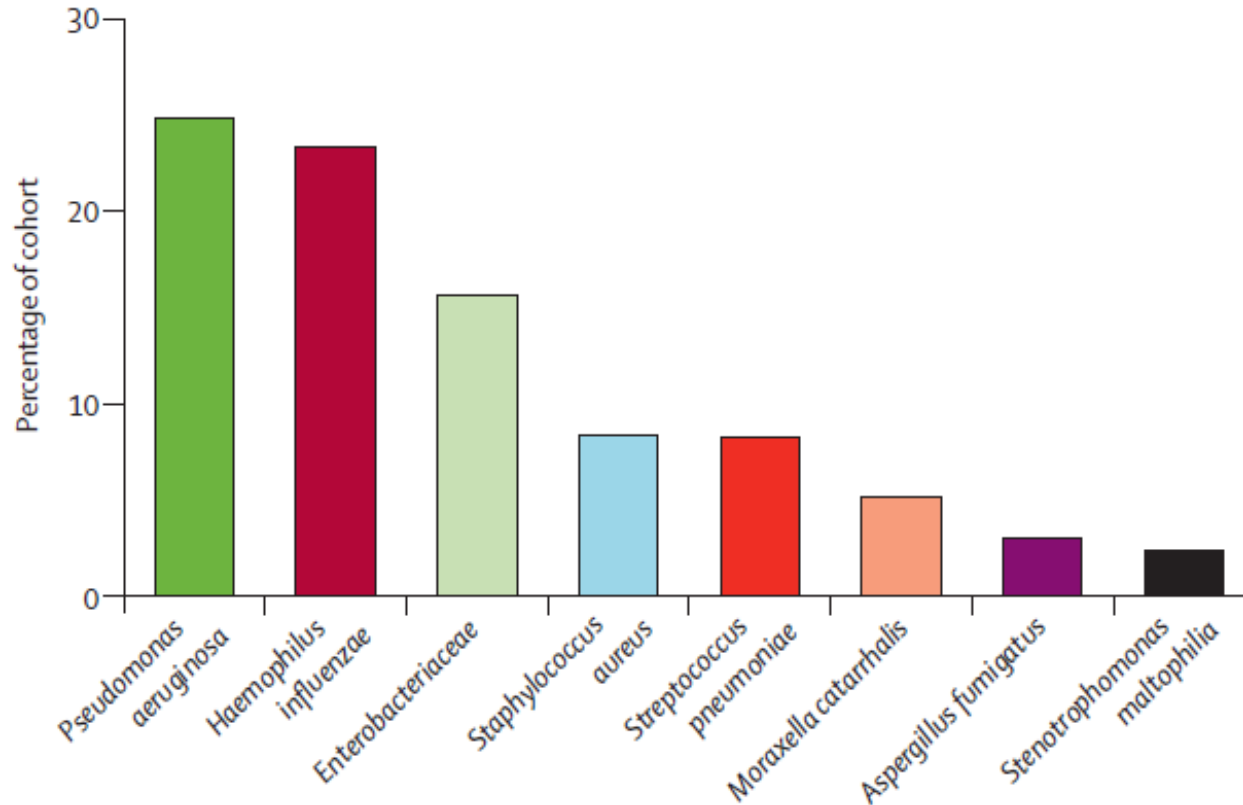
- Cause of CF: Mutations of CFTR (Cystic Fibrosis Transmembrane Conductance Regulator) - gene
- CFTR-Modulators can correct or enhance deficient proteins
- Increased mucus clearance -> reduced infections

„Game-changer“ in Non-CF Bronchiectasis Therapy ??

- Antiinflammatory therapy against neutrophil action
- Inhibition of Cathepsin C / dipeptidyl peptidase 1 (DDP-1)

- decreases the activation of neutrophil-derived serine proteases

EMBARC : European Bronchiectasis Register (Non-CF)

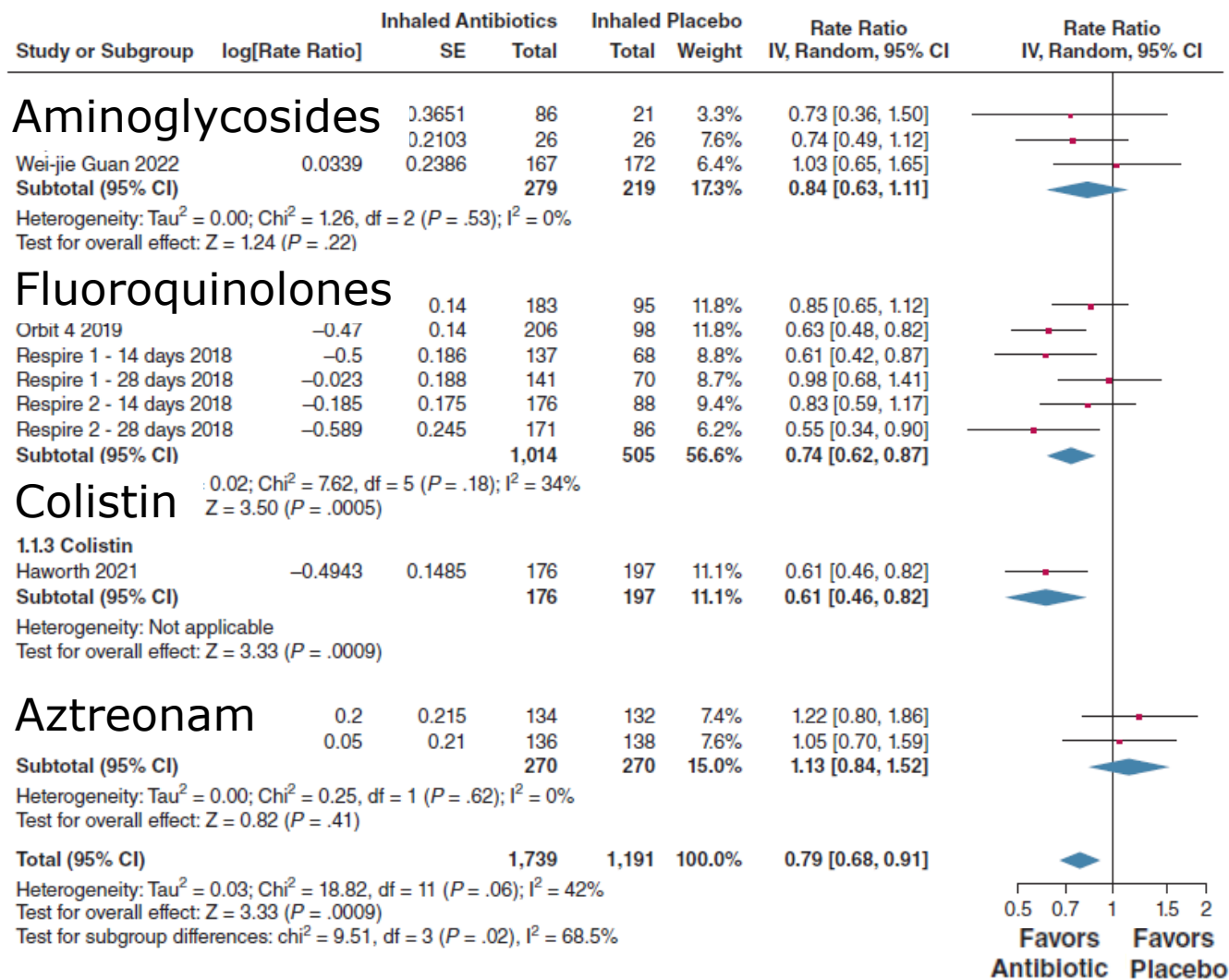


Inhaled Antibiotics in Non-CF Bronchiectasis

Metaanalysis of 20 RCTs including 3468 patients

- slight reduction in exacerbations (-21%)
- reduction in severe exacerbations (-52%)
- small but significant improvements in quality of life
- eradication of chronic infection (33% vs 16%)

Inhaled Antibiotics Effect on exacerbation

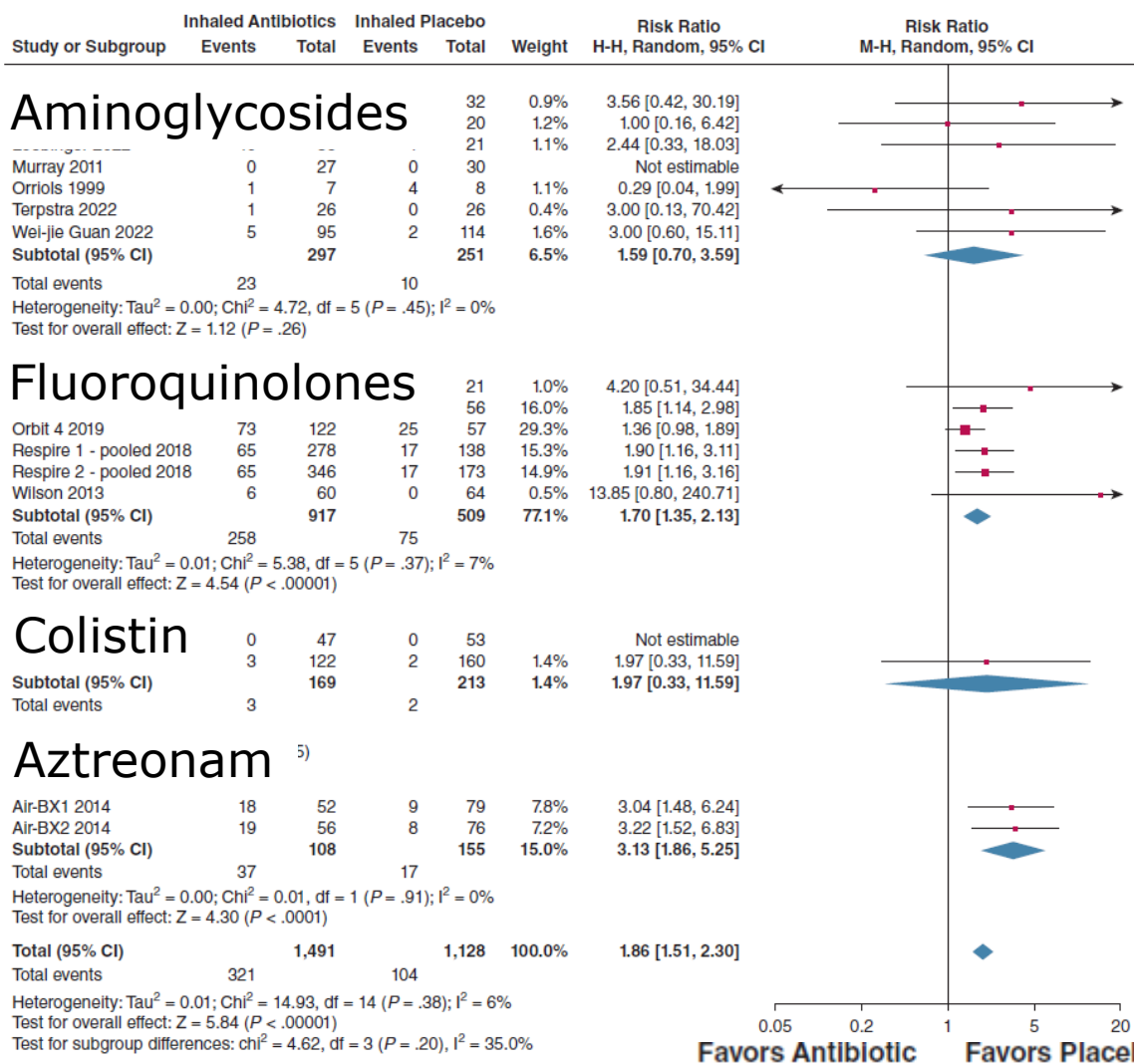


Inhalative Antibiotics in Non-CF Bronchiectasis

- no effects on lung function (FEV1)
- no differences in mortality
- no differences in side effects (4% vs. 3%), but more bronchospasm with aminoglycosides
- Increase in antibiotic resistance (22% vs. 9%)

Inhaled Antibiotics

Effect on Antibiotic Resistance



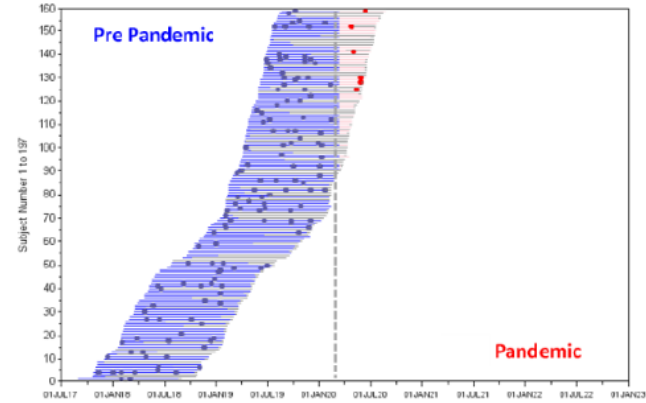
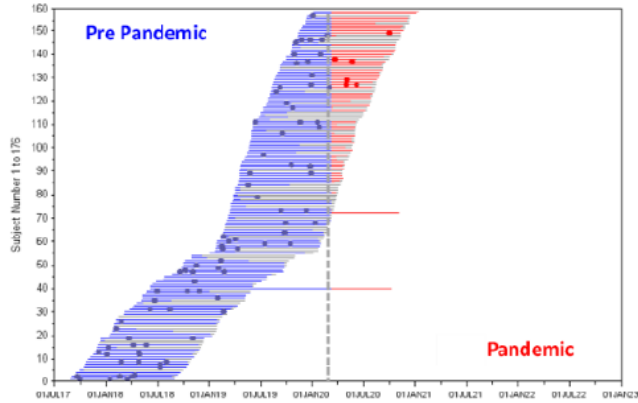
Inhaled Colistin: Promis-I and Promis-II

- phase 3, multicentre, randomised, double-blind, placebo-controlled, parallel group interventional trials over 12 mo
- adult patients with Non-CF bronchiectasis chronically infected with *P aeruginosa*
- at least two exacerbations requiring oral antibiotics or one requiring intravenous antibiotics in the previous year
- PROMIS-I : randomisation of 177 patients to inhaled colistimethate sodium, 200 patients to placebo
- PROMIS-II: 152 pt colistimethate sodium, 135 pt placebo

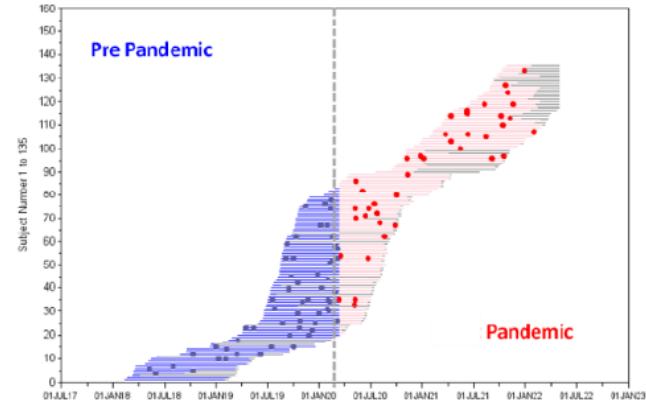
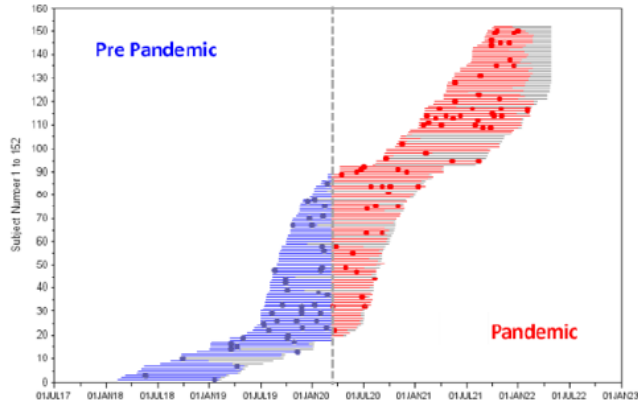
CMS

placebo

PROMIS-I



PROMIS-II



Calendar Time

Calendar Time

Inhaled Colistin: Promis-I and Promis-II

- annual exacerbation rate 0.58 in the colistimethate sodium group versus 0.95 in the placebo group (rate ratio 0.61; 95% CI 0.46–0.82; $p=0.0010$).
- No effect in PROMIS-II due to effect of COVID-19 pandemic (0.89 vs 0.89; rate ratio 1.00; 95% CI 0.75–1.35; $p=0.98$)

Who benefits from inhalative AB Therapy?

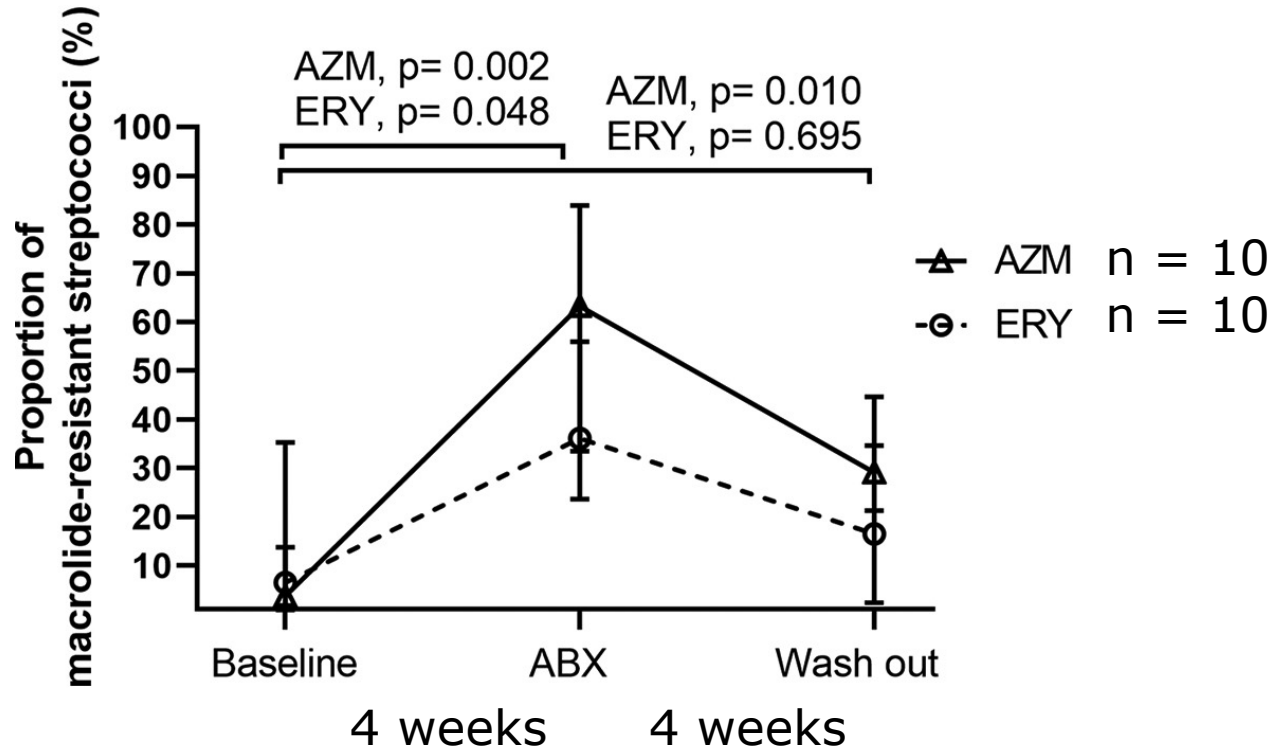
- chronic infection with *Pseudomonas aeruginosa*
- high bacterial burden in sputum
- (severe) exacerbation(s) in the last 12 months
- symptoms reducing quality of life

RCTs on Long-term Azithromycin Therapy in BX

RCT	EMBRACE n = 141, 2012		BAT n = 83, 2013	
Duration	26 weeks		52 weeks	
Azithromycin	500 mg 3 x / week	Placebo	250 mg OD	Placebo
Included patients	n = 71	n = 70	n = 43	n = 40
Exacerbations	0.59 / 6mo	1.57 / 6mo	0.90 / yr	1.95 / yr
Rate Ratio	0.39		0.46	
GI- Symptoms ^a	27%	13%	28%	20%
Tinnitus	0	0	12%	10%

^aGastrointestinal symptoms included nausea, vomiting, diarrhoea, epigastric discomfort and constipation.

ML Resistance in Oral Streptococci in LT AZM/ERY



Azithromycin Long-term Therapy and NTM

- Azithromycin is the main drug in NTM-therapy
- Recommended: exclusion of NTM-infection before azithromycin monotherapy to prevent resistance

Azithromycin Long-term Therapy and Risk of NTM

U.S.A. Bronchiectasis and NTM Research Registry:

Macrolide versus Non-ML at baseline, follow-up after 1 year

	Macrolide Group	Non-Macrolide Group
Mycobacterial Culture Results	(n = 91)	(n = 319)
Patients with any positive mycobacterial culture	3 (3.3%)	44 (13.8%)

Principles of Bronchiectasis Therapy: A³TTACK BX

A³

Assess (1) Diagnose + (2) Ätiologie + (3) Risiko

TT

Treatable Traits

Gezielte Therapie der Ätiologie, z.B.

- ABPA, Asthma,
- Alpha-1-Antitrypsinmangel, COPD,
- Autoimmunerkrankungen, CVID,
- CPA, NTM-Lungenerkrankung,
- CF und PCD etc.

B

Basic treatment

Optimale Bronchiektasen-Basistherapie, z.B.

- **Rauchstopp, Schutzimpfungen,**
- physiotherapeutische Atemtherapie,
- sekretolytische Therapie,
- Verneblerschulung,
- Rehabilitation,
- Optimierung des Selbstmanagements

ACK

Address Complications + Key comorbidities

Gezielte symptomorientierte Therapie der Komplikationen und wichtigsten Komorbiditäten, z.B.

- **Exazerbationen, chronische bakterielle o. fungale Infektion,**
- chronische Ventilationsstörung, muskuläre Dekonditionierung,
- obere Atemwege, kardiovaskulär, metabolisch, Psyche, etc.

X

Factor X

- Klinische Studien,
- "patient empowerment",
- zukünftig "disease modifying drugs" etc.

Shared decision on Long-term Antibiotics in Bronchiectasis

