

***Burkholderia Cepecia* in CF**

CF conference

19.10.2017

Outline

- Patients presentation
- *Burkholderia* species epidemiology
- Clinical presentation
- Epidemic strains & Bcc outbreaks
- Treatment
- Discussion

Case presentation A.A

- 17 years old boy
- Diagnosis with meconium ileus after birth
- Heterozygote: $\Delta F508/W1282X$
- Pancreatic insufficient
- Impaired Glucose Tolerance (IGT) from 2015
- Mal nutrition BMI 15-17
- **Compliance** is good with routine CF medications, but refusal to IV therapy or gastrostomy installation
- **Psychosocially**: clever boy, very desperate in the last few years.

Case presentation 1: A.A

Sputum Cultures:

- *Staph aureus* ,*Pseudomonas* mucoid type
- *Burkholderia cepacia* since 01/2012
- PCR 16S typing: *Burkholderia stabilis*

In the past: sensitive to Meropenem, Ceftazidime, Levofloxacin, Minocycline

Now: fully resistant

Sputum culture A.A

חיידיק	אנטיביוטיקה	רגישות	תשובה
Burkholderia cepacia		[...]	.
Burkholderia cepacia	Levofloxacin	[..R]	32
Burkholderia cepacia	Minocycline	[..R]	48
Burkholderia cepacia	Sulfamethoxa/Trimeth	[..R]	32
Burkholderia cepacia	Meropenem	[..R]	32
Burkholderia cepacia	Ceftazidime	[..R]	256
Burkholderia cepacia	Chloramphenicol	[..R]	256

Case presentation 1: A.A

Regular care:

Routine CF medications **plus:**

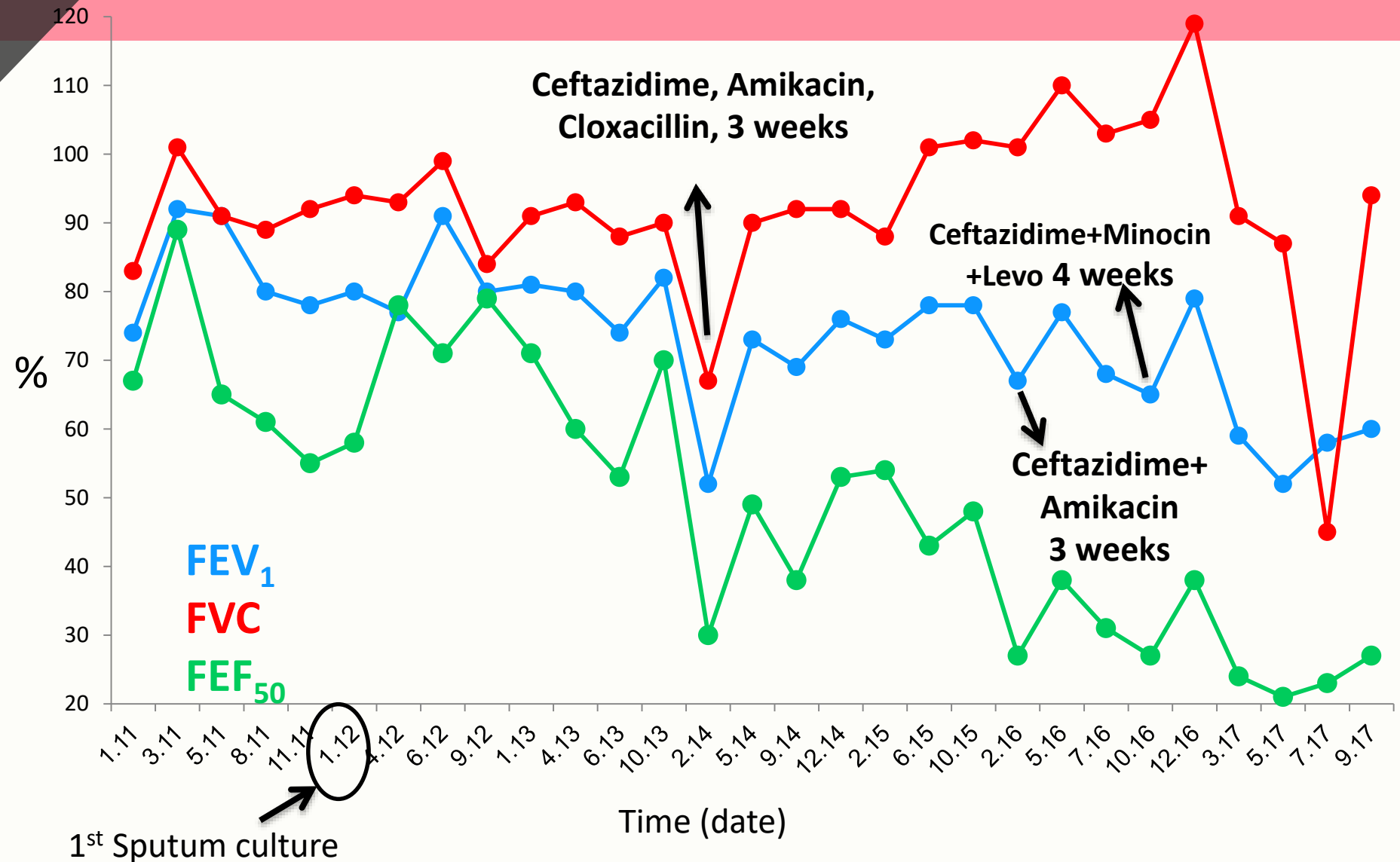
Azetronam/Gentamycin inhalation

Meropenem inhalations 500 mg (twice daily)

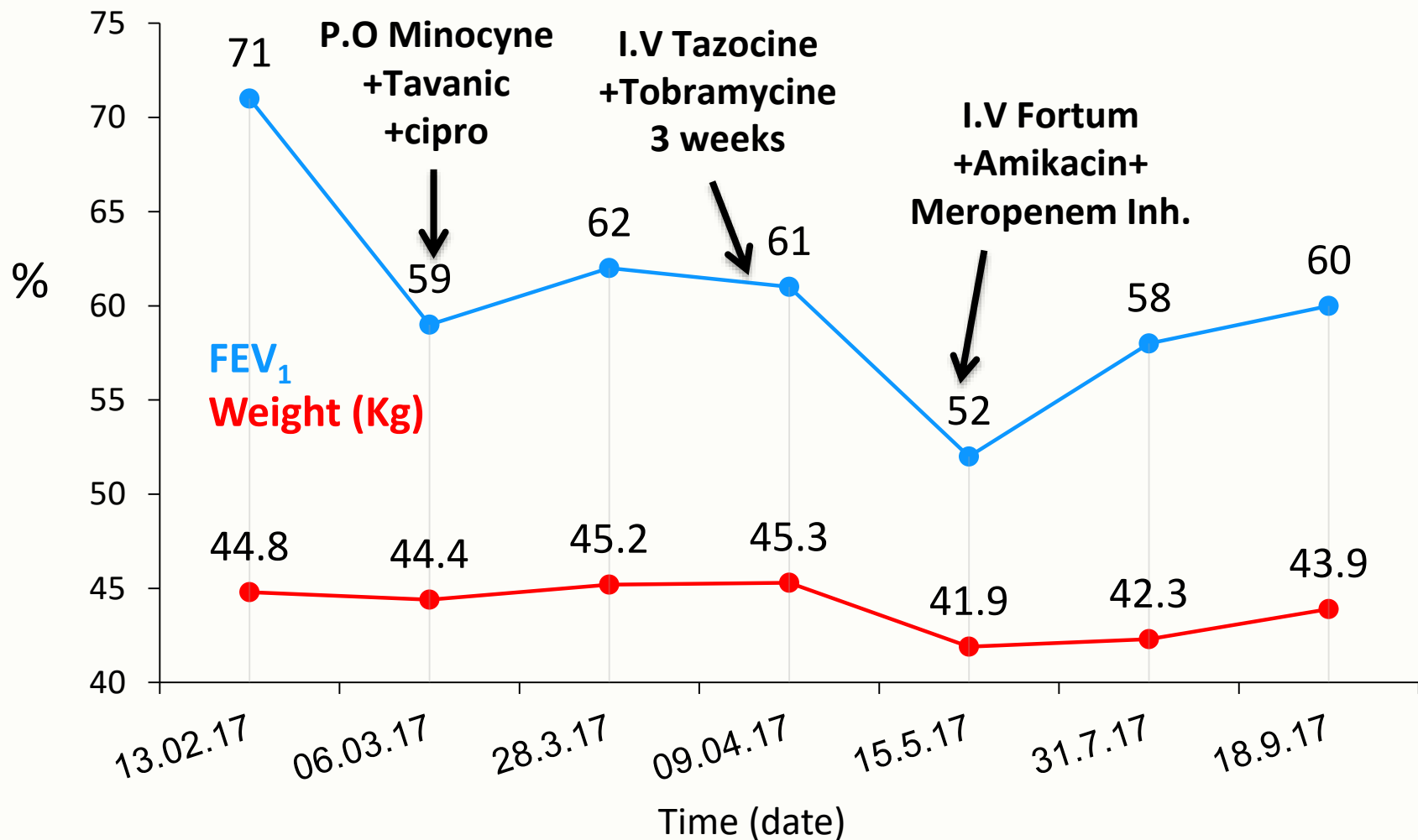
P.O Resprim twice daily

P.O Levofloxacin/Minocycline (recurrent courses with mild exacerbations)

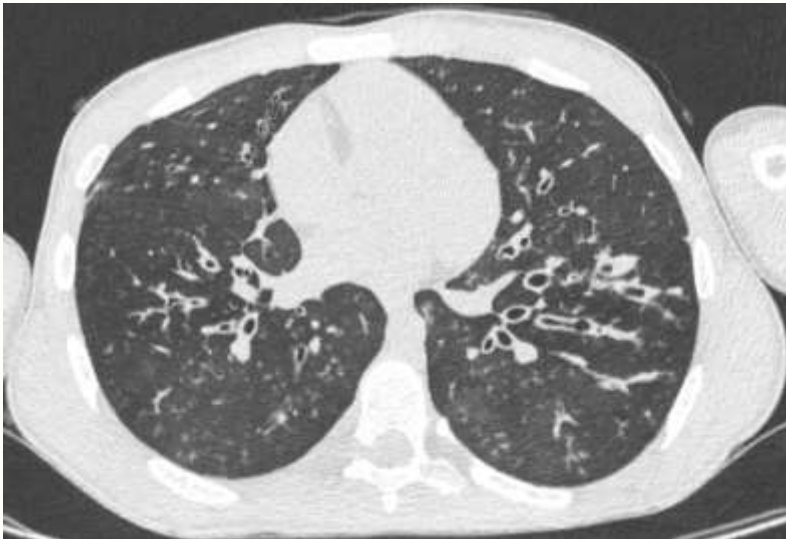
Lung function test 2011-2017



Lung function test 2017



CT January 2016



Case presentation 2: M.M

- 38 year old women
- Presented after birth
- Homozygous W1282X mutation
- The older of 3 siblings with CF
- CFRD since age of 13 years
- Good compliance
- Stable over the years

Sputum cultures:

- *Staph aureus* , *Pseudomonas*, *Candida*
- ***Burkholderia stabilis*** since Feb. 2015

Case presentation 2: M.M

Regular care :

Routine CF medications **plus**

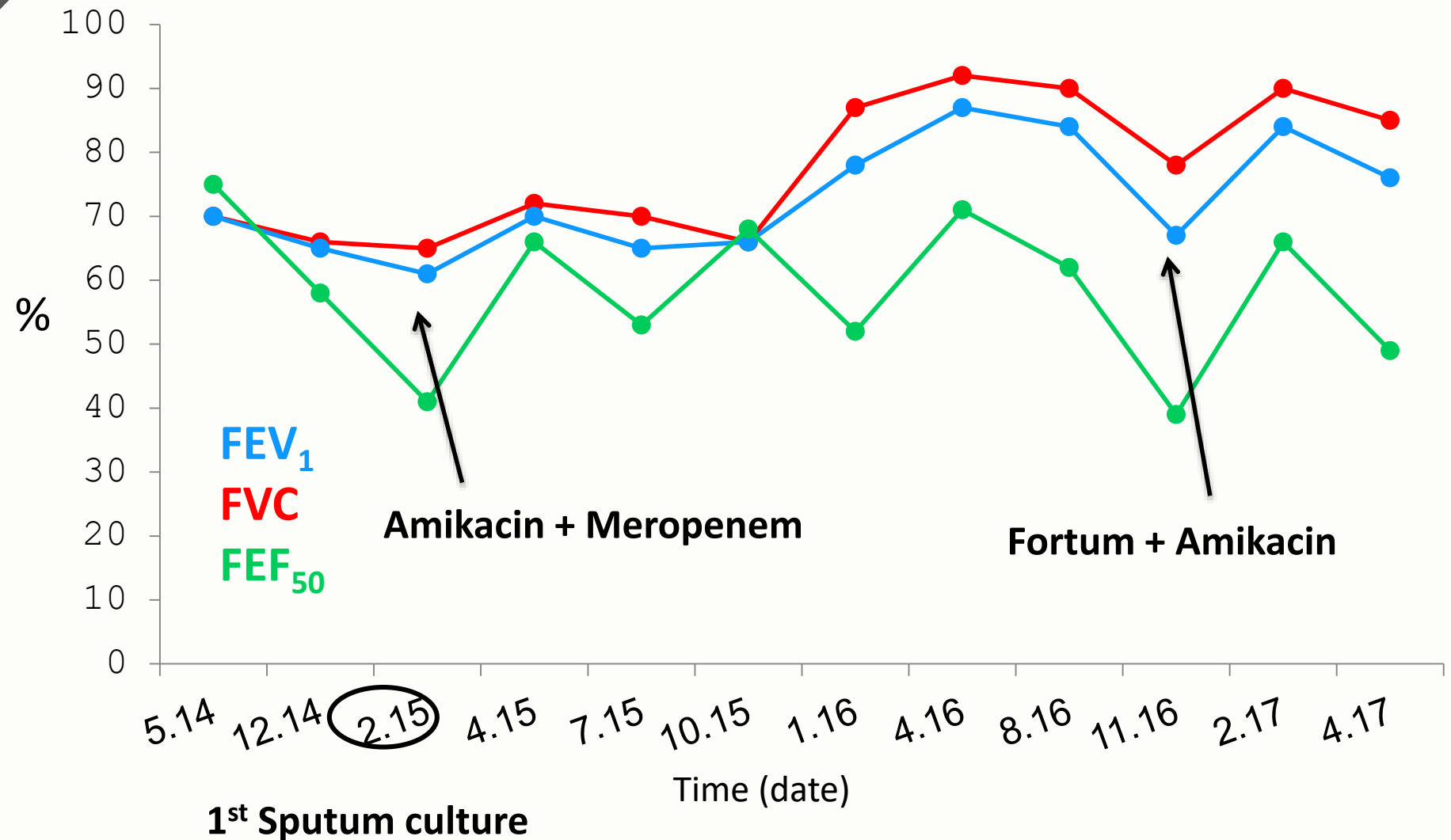
Coliracin inhalation

PTC study until few months ago

Sputum culture

תשובה	רגישות	אנטיביוטיקה	חיידיק
.	[...]		Candida tropicalis
≤ 0.25	[S..]	Amphotericine B	Candida tropicalis
≤ 1	[S..]	Fluconazole	Candida tropicalis
≤ 0.12	[S..]	Voriconazol	Candida tropicalis
≤ 0.25	[S..]	Caspofungin	Candida tropicalis
stabilis	[...]	'Quantity'	Burkholderia sp.
32	[..R]	Levofloxacin	Burkholderia sp.
2	[S..]	Minocycline	Burkholderia sp.
32	[..R]	Sulfamethoxa/Trimeth	Burkholderia sp.
32	[..R]	Meropenem	Burkholderia sp.
4	[S..]	Ceftazidime	Burkholderia sp.
32	[..R]	Chloramphenicol	Burkholderia sp.

Lung function test 2014-2017



Case presentation 3: M.S

- 34 years old woman
- Presented after birth
- Homozygous W1282X mutation
- One of three siblings diagnosed with CF
- CFRD from age of 16 years, insulin pump, unbalanced, (HBA₁C -10)
- Chronic renal failure with gross proteinuria (Creatinin-2.2/BUN-28)
- **2006 liver transplantation** due to cirrhosis with varices bleeding and liver failure
- Recurrent parotitis

Case presentation 3: M.S

- Sputum cultures:
- *Staph aureus*
- *Pseudomonas*
- ***Burkholderia stabilis*** since 2011
- Stable for many years
- In the past two years numerous exacerbations treated with IV medication

Sputum culture

חייזק	אנטיביוטיקה	רגישות	תשובה
Burkholderia cepacia		[...]	.
Burkholderia cepacia	Levofloxacin	[..R]	32
Burkholderia cepacia	Minocin	[..R]	16
Burkholderia cepacia	Sulfamethoxa/Trimeth	[..R]	32
Burkholderia cepacia	Ceftazidime	[..R]	256
Burkholderia cepacia	Meropenem	[..R]	32
Burkholderia cepacia	Chloramphenicol	[..R]	32

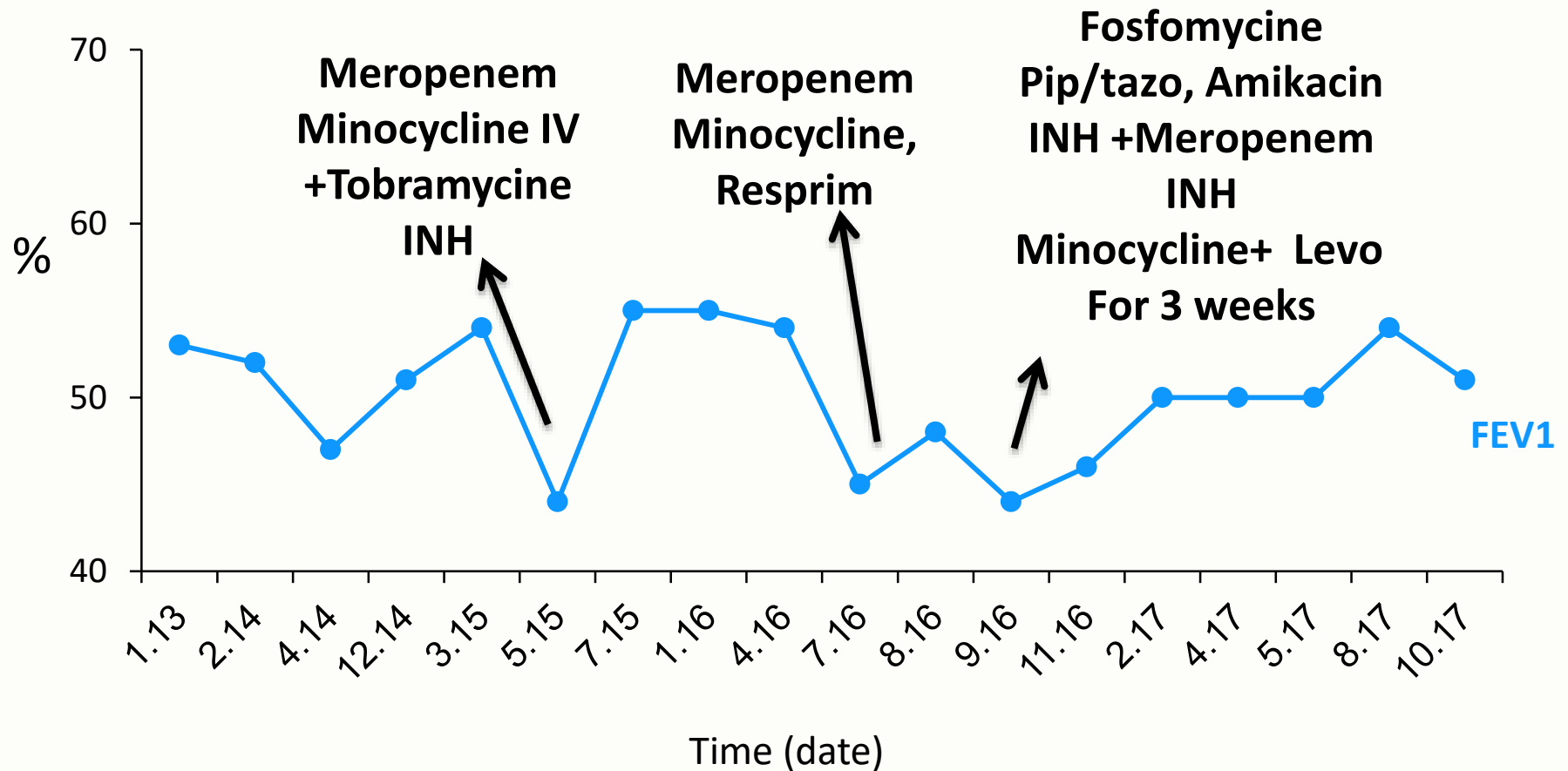
Case presentation 3: M.S

Routine CF medications

plus

- Prograph (2 mg*2/d)
- Prednisone (5 mg*1/d)
- Tobramycin and Meropenem inhalations
- Minocycline, Levofloxacin recurrent with exacerbation

Lung Function Test



Sub typing of *B.stabilis*

MALDI TOF analysis results:

2 sub-types of *B.stabilis*:

- One identical type for the two sisters
- Different sub-type for patient 1

***Burkholderia* Species**

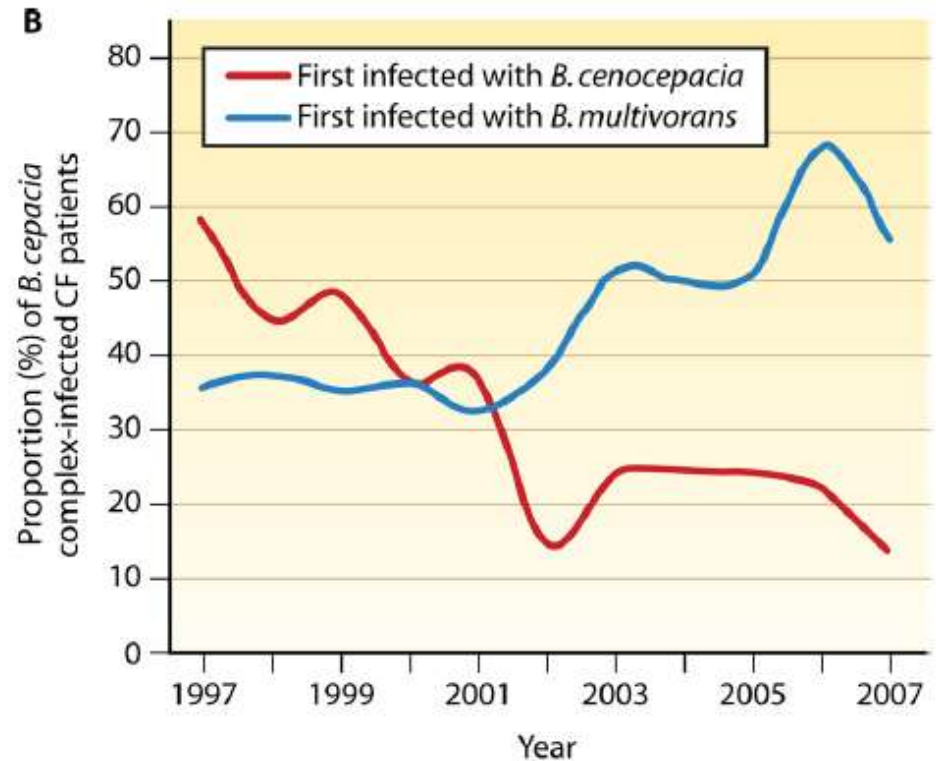
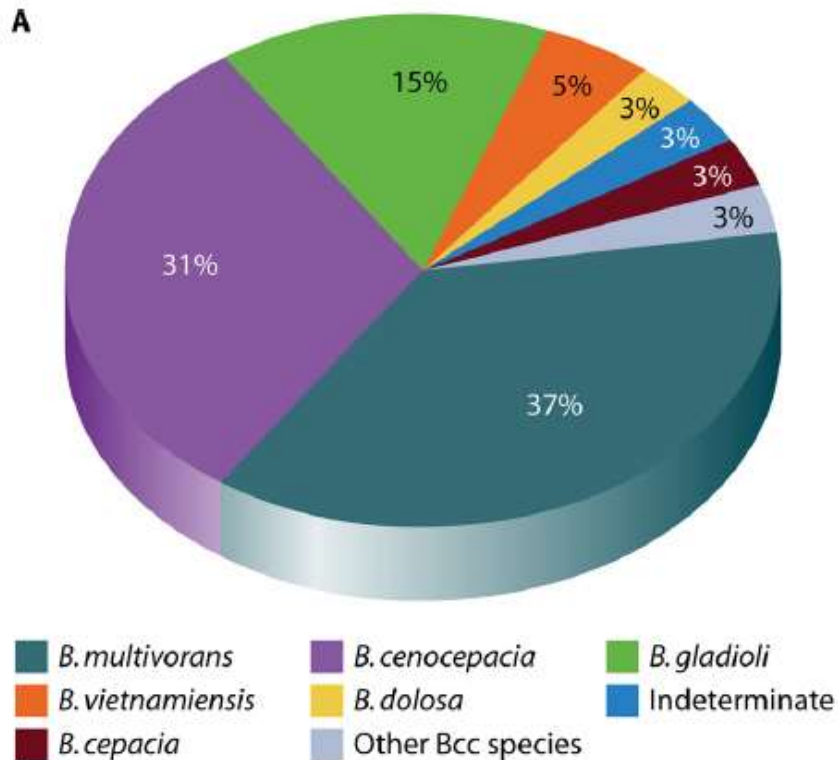
- Gram-negative, aerobic, rod-shaped bacteria
- More than 60 species in the natural environment
- ***B.cepacia complex*** (Bcc): 18 closely related species (genomovars)
- Not pathogenic for healthy humans
- First reports of Bcc infection in CF patient in the late 1970s-early 1980s
- Chronic severe respiratory tract infections in CF patients (3-4% USA/GB)

Epidemic strains

Acquisition and transmission

- Epidemic strains: well adapted to human infection, widely distributed in the natural environment (*B. gladioli* & *B. cepacia* - plant pathogens)
- Inter patient transmission: strains common to CF patients in wider geographic regions.
- New *Burkholderia* infection in CF patients: acquisition of strains from the natural environment.

Species distribution in CF



***Burkholderia* outbreaks**

- Outbreaks due to contaminated medical devices and products (mouthwashes, ultrasound gels, skin antiseptics, and medications – hospitalized, non-CF patients)
- Interpatient spread: Genotyping studies identified strains common to multiple patients receiving care in the same CF centers.

Bcc in CF: clinical manifestations

- Accelerated loss of lung function, lower BMI, more hospital admissions and increased mortality
- Wide spectrum: asymptomatic chronic infection → life threatening necrotizing pneumonia
- Individual patient outcomes are unpredictable and influenced by host-pathogen interactions as well as microbial virulence factors

Cepacia syndrome

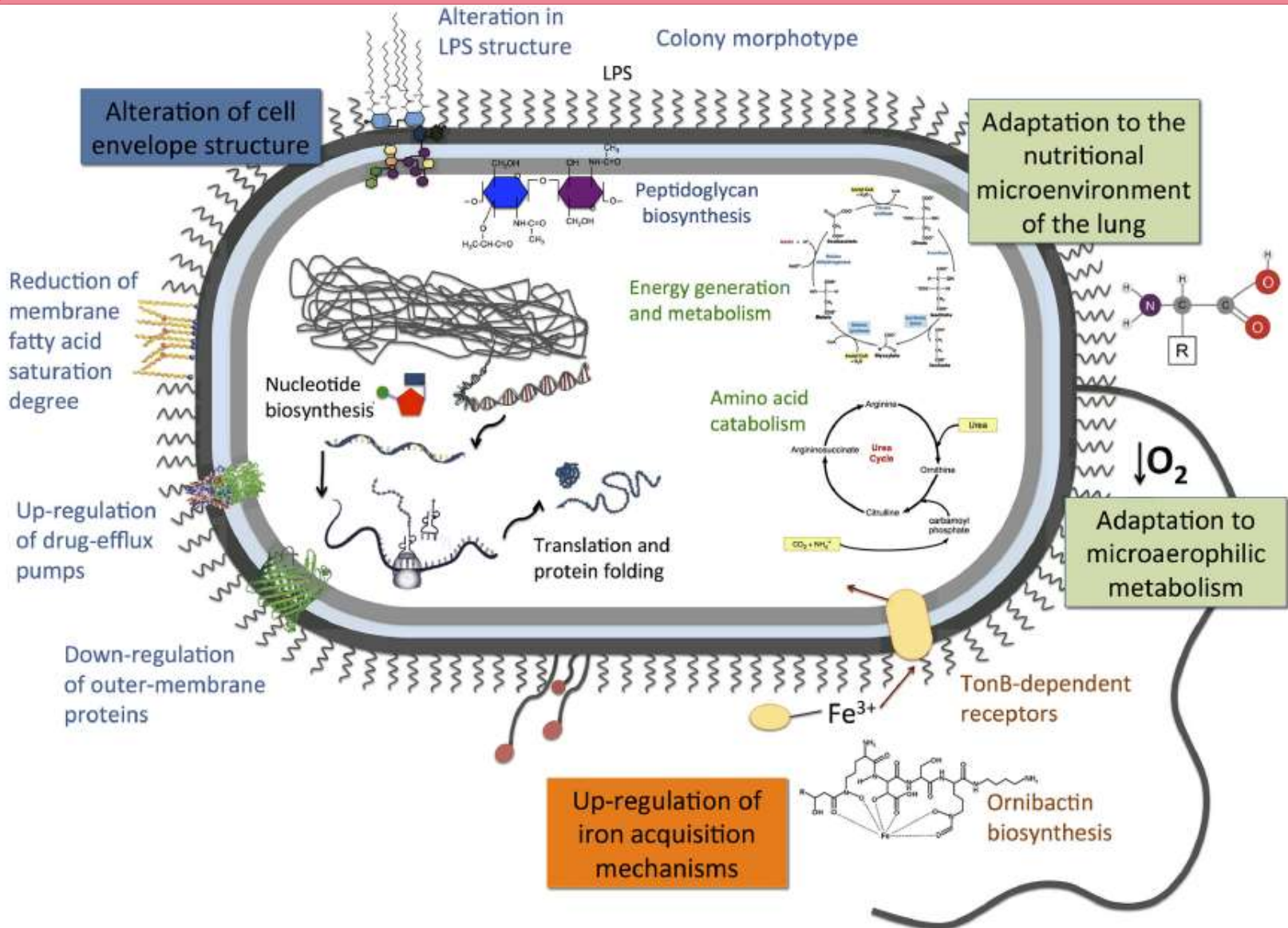
- Necrotizing pneumonia, pyrexia, almost universally fatal outcome
- Blood cultures are positive for BCC (pre terminal phase)
- ***B. cenocepacia* (genomovar III)**, especially the ET12 epidemic strain. also reports with *B. cepacia* (I) and *B. multivorans* (II)
- Bcc sepsis : mortality in CF patients after lung transplantation (especially pre-transplant *B. cenocepacia* - contraindication)
- Successful treatment : case reports, combination of IV antibiotics +/- immunomodulation

***Burkholderia cepacia* Complex Regulation of Virulence Gene Expression**

Mechanisms used by Bcc bacteria to adapt the CF lung:

- Antibiotic resistance
- Adherence to the respiratory epithelia
- Adaptation to low oxygen
- Iron acquisition
- Transport and efflux systems
- Biofilm formation
- Quorum sensing

Long term colonization of Bcc



Treatment

No consensus exists regarding early eradication treatment and chronic maintenance therapy for Bcc in CF

Eradication therapy for Bcc in CF patients. Cochrane 2016

- **Main results:** No studies looking at the eradication of Bcc were identified



Antibiotic treatment for *B.cepacia* complex in CF patients experiencing a pulmonary exacerbation

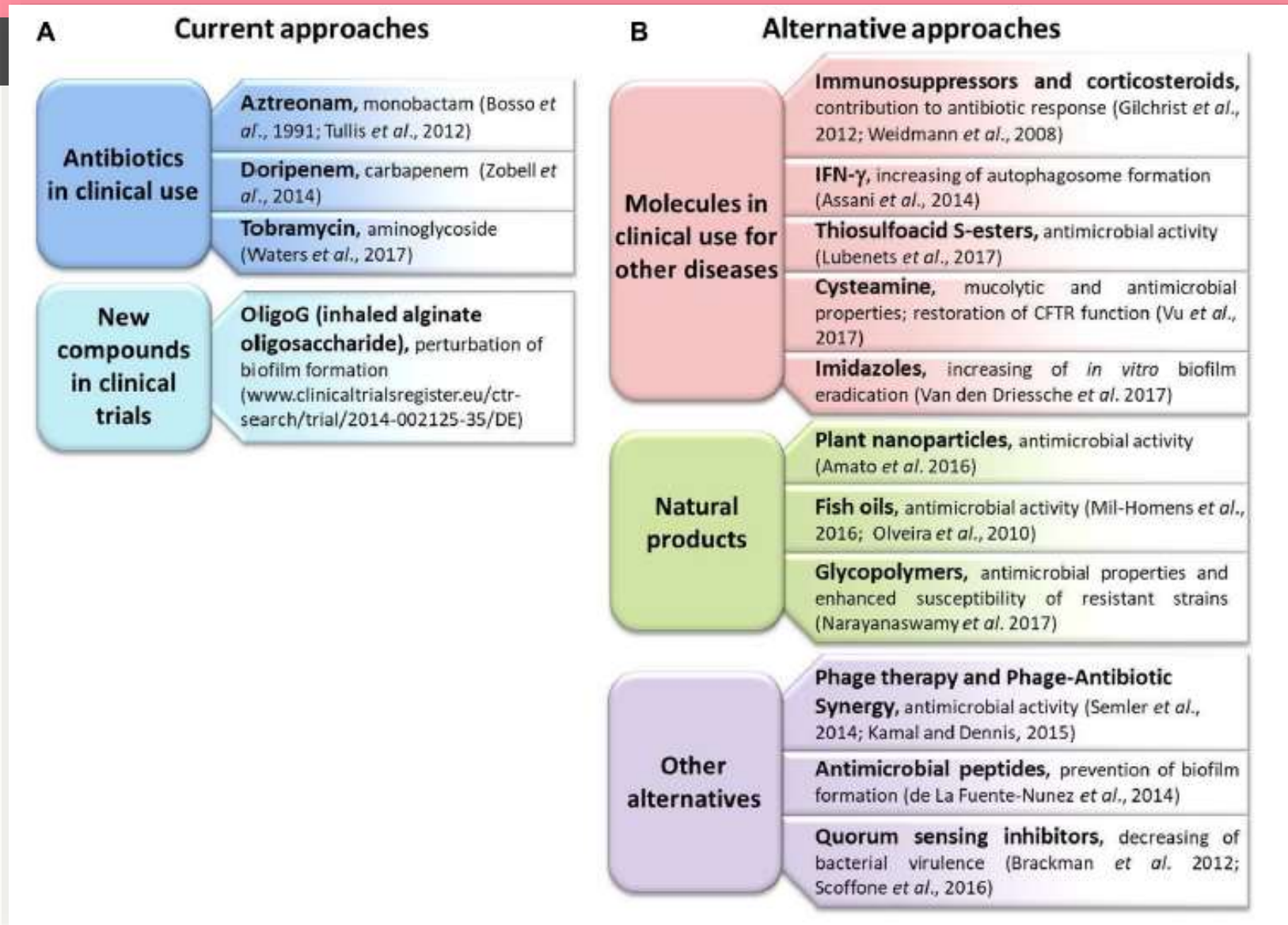
Main results: No trials were included in this review.

Authors' conclusions:

- **Lack of evidence to guide decision making**
- **No conclusions about the optimal antibiotic regimens for people with CF who have chronic Bcc infections**
- **Clinicians must continue to assess each person individually, taking into account in vitro antibiotic susceptibility data, previous clinical responses and their own experience**



New therapies & approaches



Antibiotics in Clinical Use

Aztreonam:

- Monobactam against gram negative
- Inhibiting bacterial cell wall synthesis
- AZLI showed *in vitro* activity against Bcc.
- Double-blind, placebo-controlled, 24-weeks trial in 100, CF patients with chronic Bcc infection
- No significant differences were observed for any endpoints, including: FEV₁%, number of respiratory exacerbations, or hospitalizations

Antibiotics in Clinical Use

Tobramycin

- Aminoglycoside, prevents the formation of the 70S ribosomal complex
- *In vitro*: high-dose tobramycin reduced *Burkholderia* biofilm thickness
- Pilot, open-label trial of TOBI Podhaler for 28 days 10 adults and children with CF & chronic Bcc Results: decreased pulmonary bacterial burden (CFU/ml) and inflammation (IL8↓). However, lung function was not significantly improved ($\uparrow\text{FEV}_1=4.6\%$)

Molecules in clinical use for other diseases

Immunosuppressors and Corticosteroids

- The role in the management of Burkholderia infections is not completely understood.
- Worth considering for patients with poor prognosis (Cepacia syndrome)

IFN-g

- CF macrophages show a suboptimal IFN-g response during *B. cenocepacia* infection causing deficient autophagosome formation.
- Only in cell culture models and the efficacy *in vivo* has yet to be determined.

Gilchrist, et al. Successful treatment of cepacia syndrome with a combination of intravenous cyclosporin, antibiotics and oral corticosteroids. J. Cyst. Fibros. 2012

Assani, K, et al. IFN-g stimulates autophagy-mediated clearance of Burkholderia cenocepacia in human cystic fibrosis macrophages. PLoS ONE 2014

Molecules in clinical use for other diseases

Cysteamine

- Disrupt disulfide bonds
- Inhibition of bacterial biofilm & restore CFTR function in combination with potentiators and activators.
- Effect in combination with antimicrobial agents in vitro (Tobramycin, Ciprofloxacin, Trimethoprim-Sulfamethoxazole)

Phage Therapy and Phage-Antibiotic Synergy

- Bacterial viruses (bacteriophages) developed in the 1930s
- *B. cenocepacia* infections in a murine model: aerosolized phage treatments → decrease in bacterial loads within the lungs.
- Phage-antibiotic synergy (PAS): antibiotics + phages → form larger plaque (Ciprofloxacin, Meropenem, Tetracycline) (increased access to phage receptors)
- PAS effect was not altered when treating antibiotic resistant cells

Summary

- 3 patients - variable presentation
- *B. Stabilis* - acquisition from the natural environment, north of Israel?
- Epidemic Bcc adapt to the CF lung
- No guidelines regarding early eradication and chronic therapy for Bcc in CF
- Pipe line: to think out of the box



Thank you