CFC CENTRO FIBROSI CISTICA VERONA

# Levofloxacina inalatoria

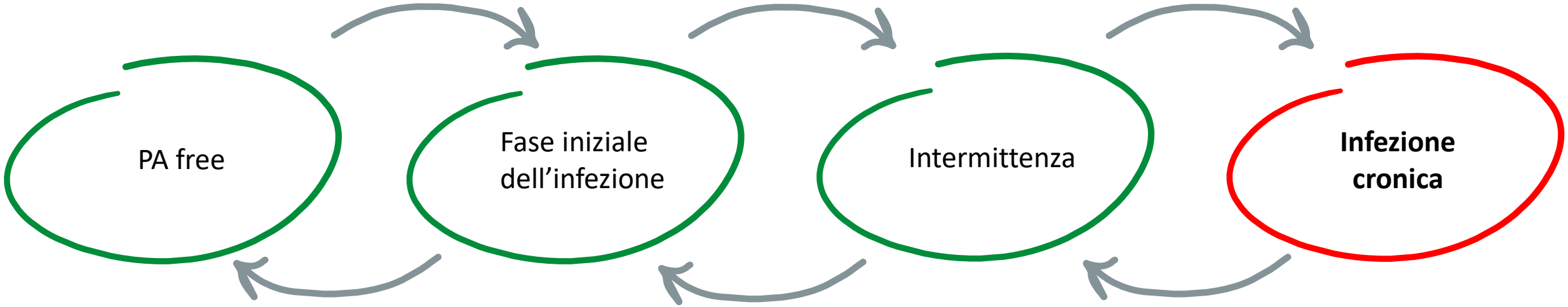
## *Esperienza clinica del Centro di Verona*

**Francesca Lucca**

**Napoli, 22 ottobre 2021**

SIFC
SOCIETÀ ITALIANA
PER LO STUDIO DELLA FIBROSI CISTICA

# La marcia ..di Pseudomonas aeruginosa




- Declino clinico e funzionale più rapido
- Maggior morbidità e mortalità
- Danno parenchimale
- Disregolazione infiammatoria

Kosorok MR. Pediatr Pulmonol 2001
Lund-Palau H et al. Expert Rev Respir Med 2016
Emerson J et al. Pediatr Pulmonol 2002

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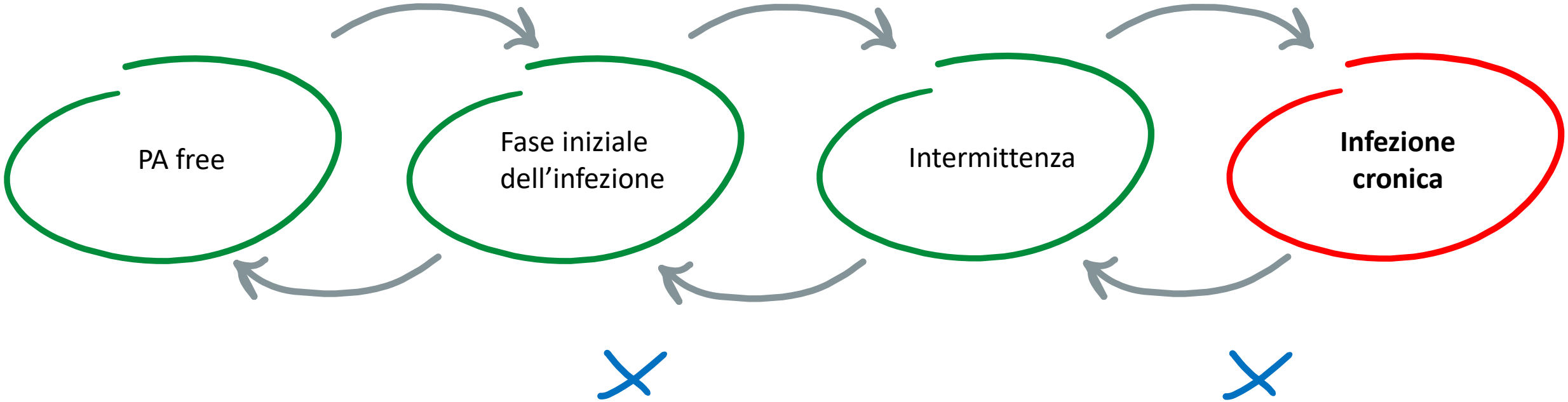


Castellani C et al. ECFS Best practice guidelines. Journal of Cystic Fibrosis 17 (2018) 153–178

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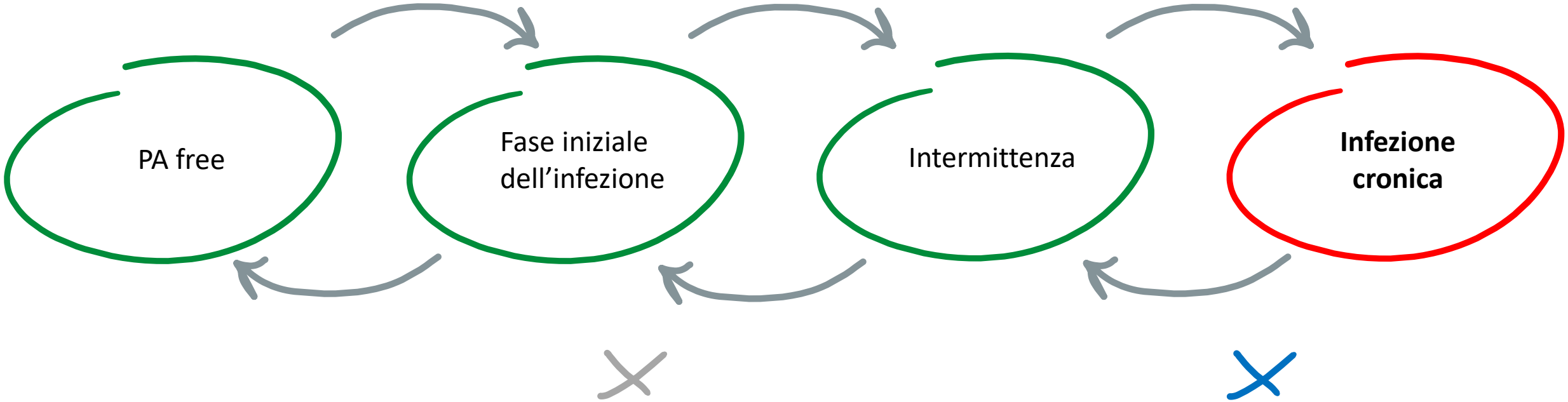
# La marcia ..di Pseudomonas aeruginosa




Alte concentrazioni nelle vie respiratorie con basse concentrazioni sistemiche

**Terapia antibiotica inalatoria**

Castellani C et al. ECFS Best practice guidelines. Journal of Cystic Fibrosis 17 (2018) 153–178

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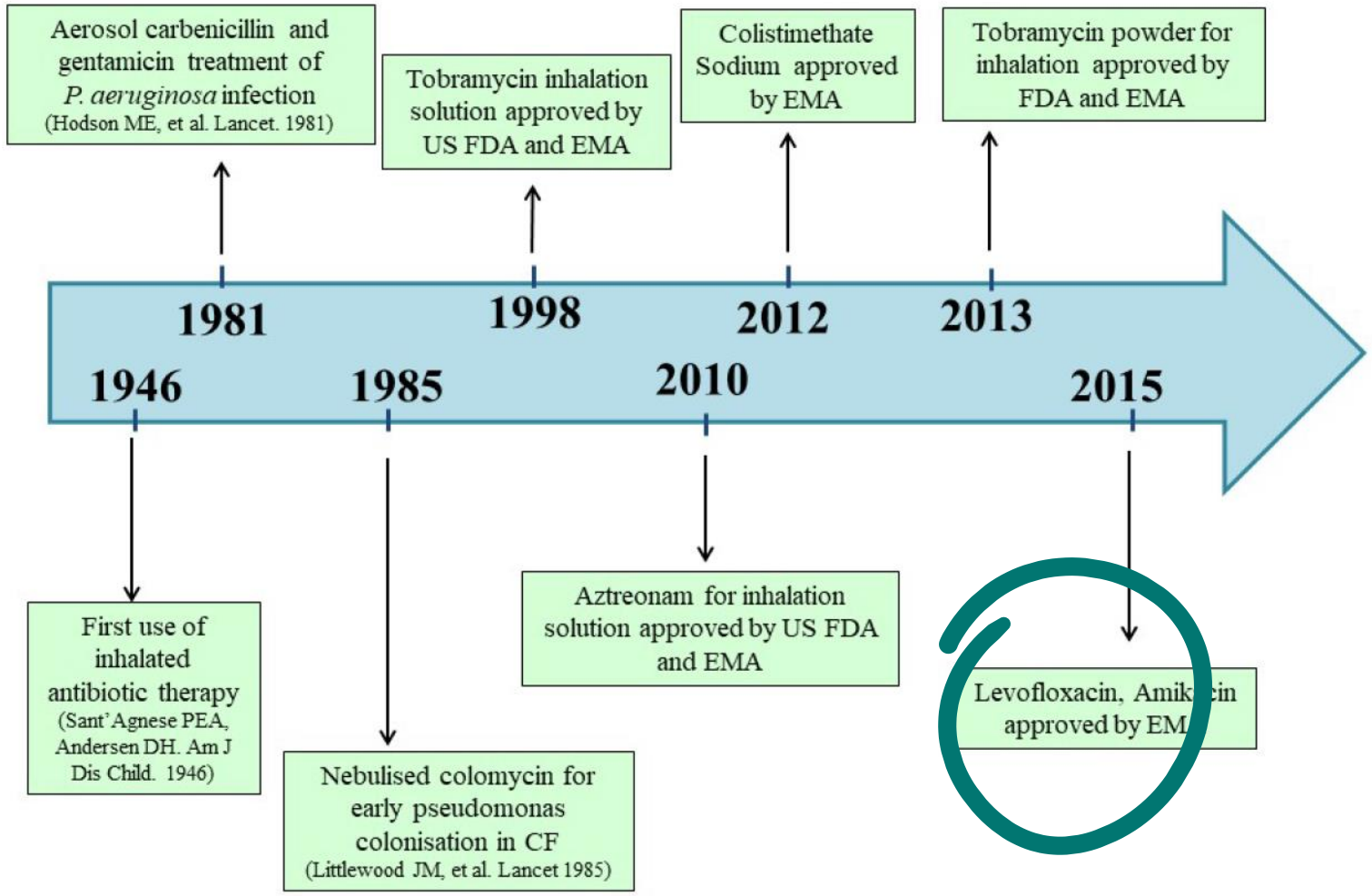
# Levofloxacina inalatoria (LIS): timeline




Taccetti, G.; Francalanci, M.; Pizzamiglio, G.; Messore, B.; Carnovale, V.; Cimino, G.; Cipolli, M. Cystic Fibrosis: Recent Insights into Inhaled Antibiotic Treatment and Future Perspectives. Antibiotics **2021**, 10, 338

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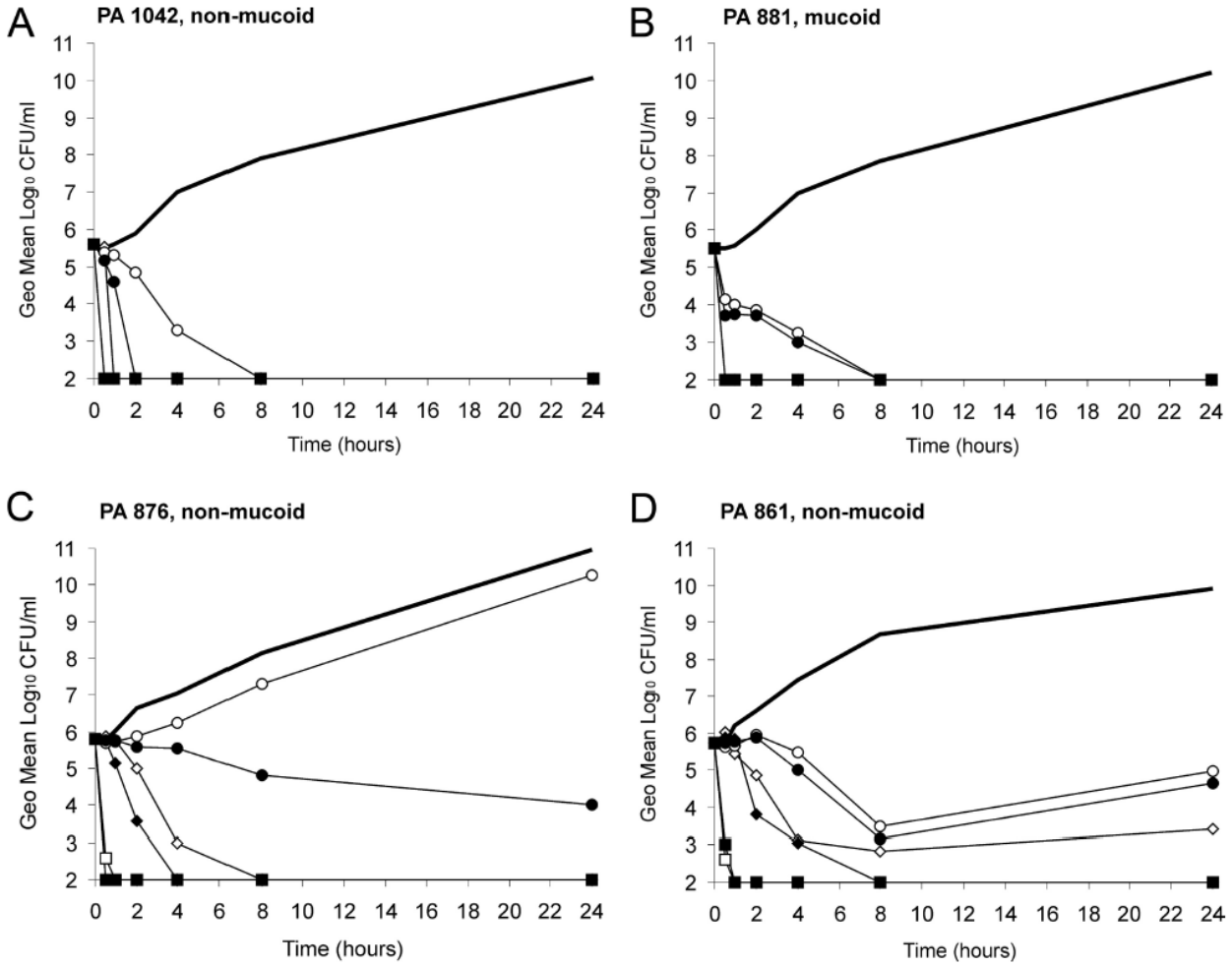
# Levofloxacina inalatoria (LIS): timeline

- Target: DNA girasi, topoisomerase IV → inibisce la replicazione batterica
- Attività battericida rapida
- Attività anti biofilm più espressa rispetto agli aminoglicosidi e all'aztreonam




King P et al. Antimicrob. Agents Chemother. 2010, 54, 143–148

# Levofloxacina inalatoria (LIS): timeline

Pharmacokinetics and Safety of MP-376 (Levofloxacin Inhalation Solution) in Cystic Fibrosis Subjects▽

Geller DE et al. Antimicrobial agents and chemotherapy. 2011;55(6):2636-40

Fase 1

- Ben tollerato
- In pz FC stabili, alte concentrazioni nell'espettorato, basse concentrazioni sieriche

**Levofloxacin Inhalation Solution (MP-376) in Patients with Cystic Fibrosis with *Pseudomonas aeruginosa***

Geller DE et al. Am J Respir Crit Care Med Vol 183. pp 1510–1516, 2011

Placebo RCT

- Riduzione della densità di PA all'espettorato a 28 gg
- Miglioramento della funzione respiratoria (ppFEV$_1$)
- Riduzione della necessità di altri anti-PA

A phase 3, multi-center, multinational, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of levofloxacin inhalation solution (APT-1026) in stable cystic fibrosis patients

Flume PA et al. Journal of Cystic Fibrosis 15 (2016) 495–502

Placebo RCT

- Non superiore al placebo nel time to a PEX
- Miglioramento della funzione respiratoria (ppFEV$_1$)
- Riduzione della densità di PA all'espettorato a 28 gg
- Ben tollerato (disgeusia, tosse, emottisi)

A phase 3, open-label, randomized trial to evaluate the safety and efficacy of levofloxacin inhalation solution (APT-1026) versus tobramycin inhalation solution in stable cystic fibrosis patients☆

Stuart Elborn J et al. Journal of Cystic Fibrosis 14 (2015) 507–514

Randomised, open-label non inferiority

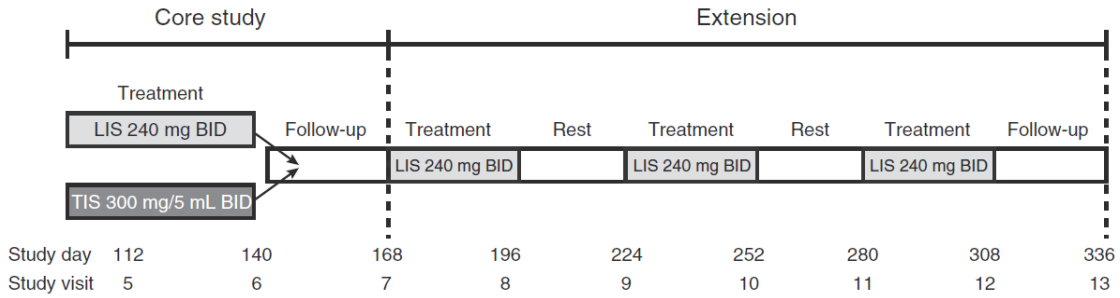
- Non inferiore nell'effetto su ppFEV$_1$, evento PEX, riduzione della densità di PA all'espettorato
- Profilo di sicurezza simile (ecc alterazione gusto)
- Nessuna variazione della MIC durante lo studio

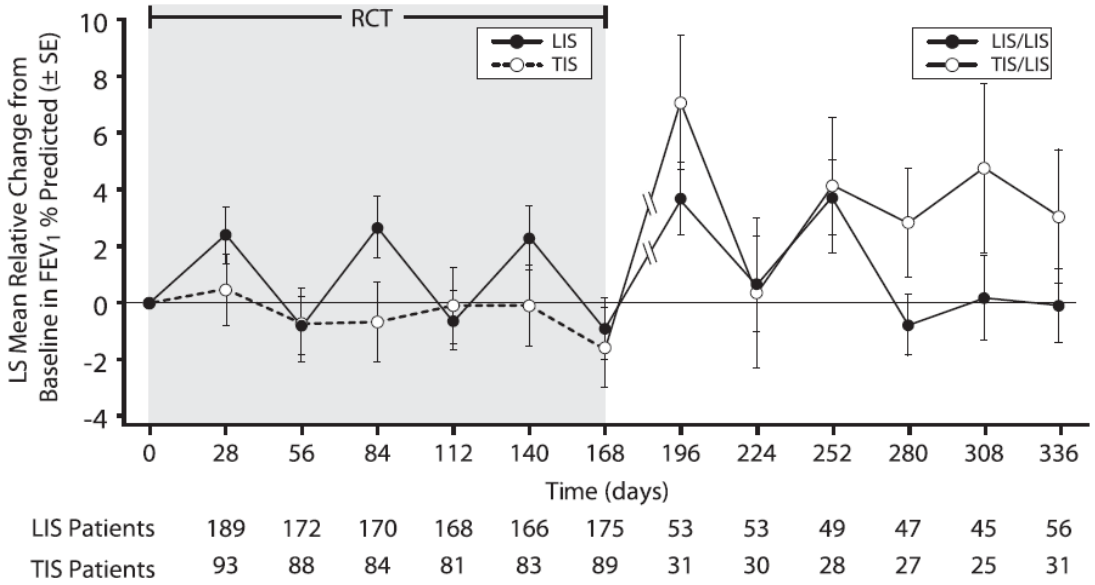
# Levofloxacina inalatoria (LIS): timeline

Safety and efficacy of prolonged levofloxacin inhalation solution (APT-1026) treatment for cystic fibrosis and chronic *Pseudomonas aeruginosa* airway infection☆

Stuart Elborn J et al. Journal of Cystic Fibrosis 15 (2016) 634–640

open-label extension




- Nessun evento avverso significativo di nuova insorgenza
- Nessun cambiamento della suscettibilità in vitro di PA a FQ
- $ppFEV_1$ in LIS/LIS alla fine di 6 cicli di tp non differiva dal dato all'inizio dell'estensione

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# Levofloxacina inalatoria (LIS): timeline

## Clinical impact of levofloxacin inhalation solution in cystic fibrosis patients in a real-world setting

Schwartz C et al. Journal of Cystic Fibrosis 2021 Jun 4;S1569-1993(21)

Open-label single-center
Real-world setting

Criteri di inclusione
- Età uguale o superior a 18 anni
- Consenso infomato

Esclusione
- Trapianto di organo solido
- ABPA
- Già in LIS
- Terapia con modulatori CFTR da meno di 12 mesi

| | FEV1d0Mean ± SD | FEV1d28Mean ± SD | FEV1d365Mean ± SD | FEV1 d0 vs d28P value | FEV1 d0 vs d365P value |
|---|---|---|---|---|---|
| ALL (n=86) | 48,44 ± 18,61 | 50,71 ± 18,63 | 50,79 ± 19,59 | 0.0027 | 0.0443 |
| Change from Col to Levo (n=37) | 43,54 ± 15,53 | 46,51 ±15,79 | 46,27 ± 15,69 | 0.0213 | 0.0221 |
| Change from Tobi to Levo (n=20) | 53,85 ± 18,00 | 56,60 ± 19,70 | 56,35 ± 20,54 | 0.0266 | 0.2192 |
| Change from Azli to Levo (n=29) | 50,97 ± 21,50 | 52,00 ± 20,48 | 52,72 ± 22,57 | 0.8378 | 0.4164 |

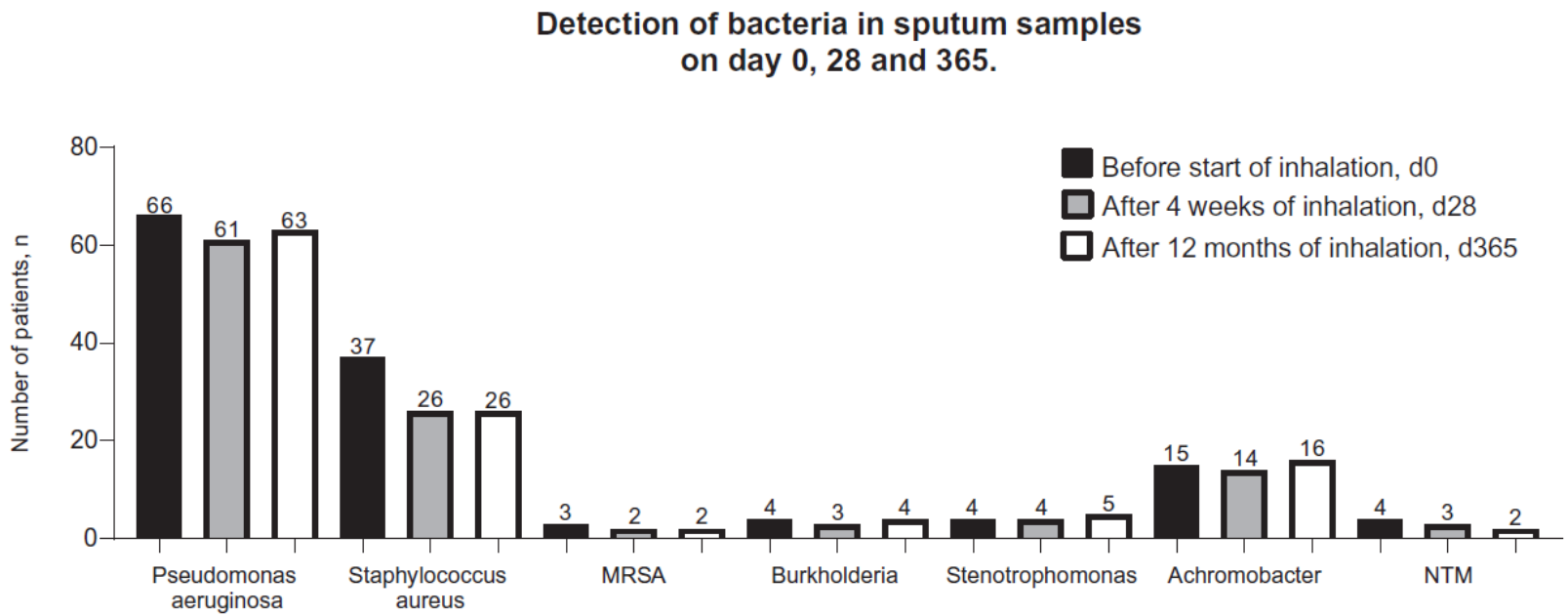
| | Exacerbations per yearYear 1 (-12 months prior to levofloxacin)Mean ± SD | Exacerbations per yearYear 2 (+12 months after initiation of levofloxacin)Mean± SD | Exacerbations per year P value |
|---|---|---|---|
| ALL (n=86) | 3,23 ± 1,39 | 2,71 ± 1,58 | 0,0024 |
| Change from Col to Levo (n=37) | 3,00 ± 1,35 | 2,73 ± 1,58 | 0,2747 |
| Change from Tobi to Levo (n=20) | 3,40 ± 1,35 | 2,10 ± 1,52 | 0,0001 |
| Change from Azli to Levo (n=29) | 3,41 ± 1,45 | 3,10 ± 1,54 | 0,2578 |

# Levofloxacina inalatoria (LIS): timeline

Clinical impact of levofloxacin inhalation solution in cystic fibrosis patients in a real-world setting

Schwartz C et al. Journal of Cystic Fibrosis 2021 Jun 4;S1569-1993(21)

Open-label single-center
Real-world setting




0/86 broncostruzione - chiusura
49/86 disgeusia (57%)
5/86 tendinite (5,8%)

# Levofloxacina inalatoria (LIS): indicazioni

Trattamento delle infezioni polmonari CRONICHE dovute a *Pseudomonas aeruginosa* in pazienti ADULTI affetti da FIBROSI CISTICA

Cicli di 28 giorni on/off

USO SCONSIGLIATO

- Insufficienza renale severa (Cl creat < 20 ml/min)
- Ipersensibilità ai FQ
- Gravidanza, allattamento
- Storia di tendinopatia o epilessia

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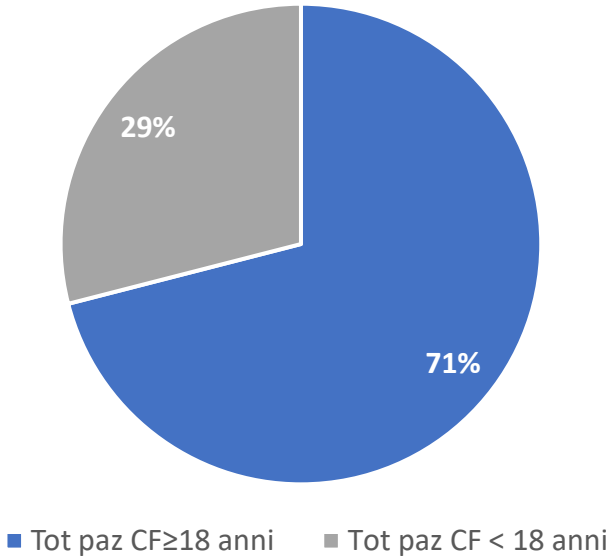
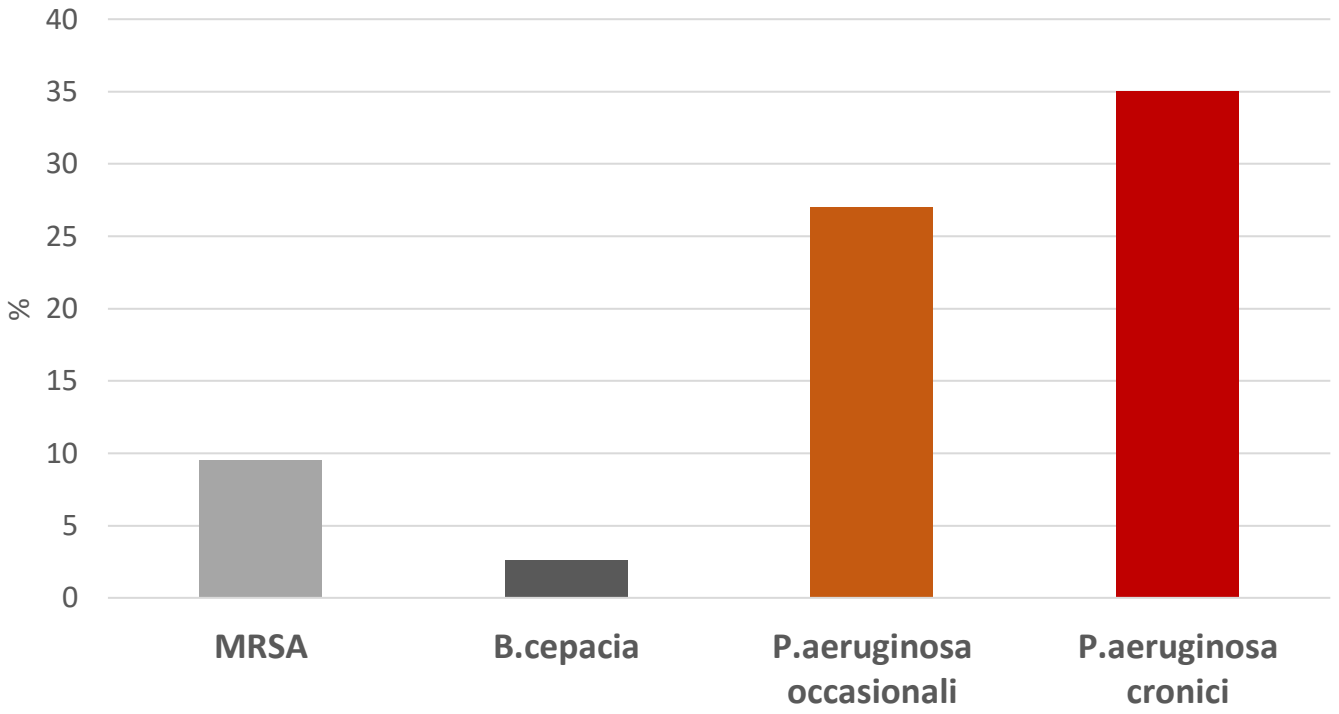
# Esperienza clinica del Centro di Verona

## CFC Verona distribuzione per età




549 pazienti con età ≥ 18 anni

## Prevalenza colonizzazioni croniche adulti CFC VR

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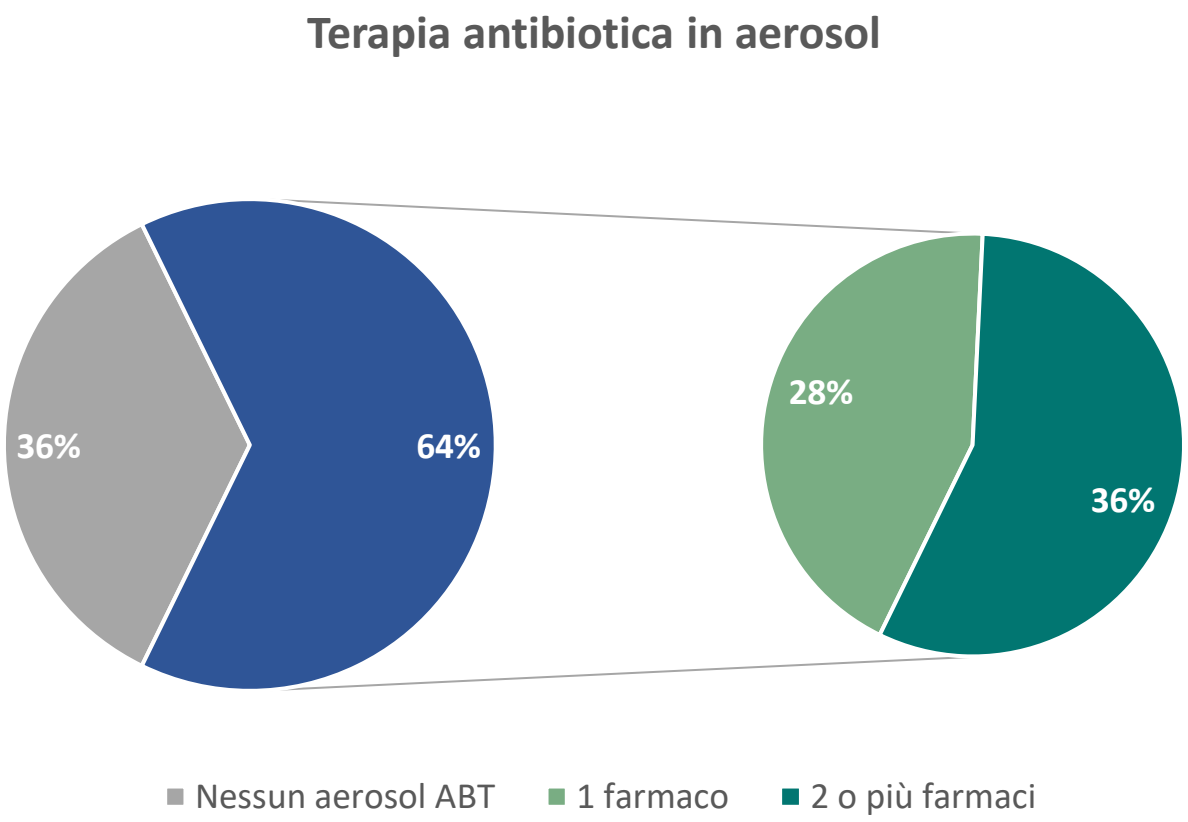
# Esperienza clinica del Centro di Verona

354 pazienti (64,5%) eseguono almeno un antibiotico in aerosol

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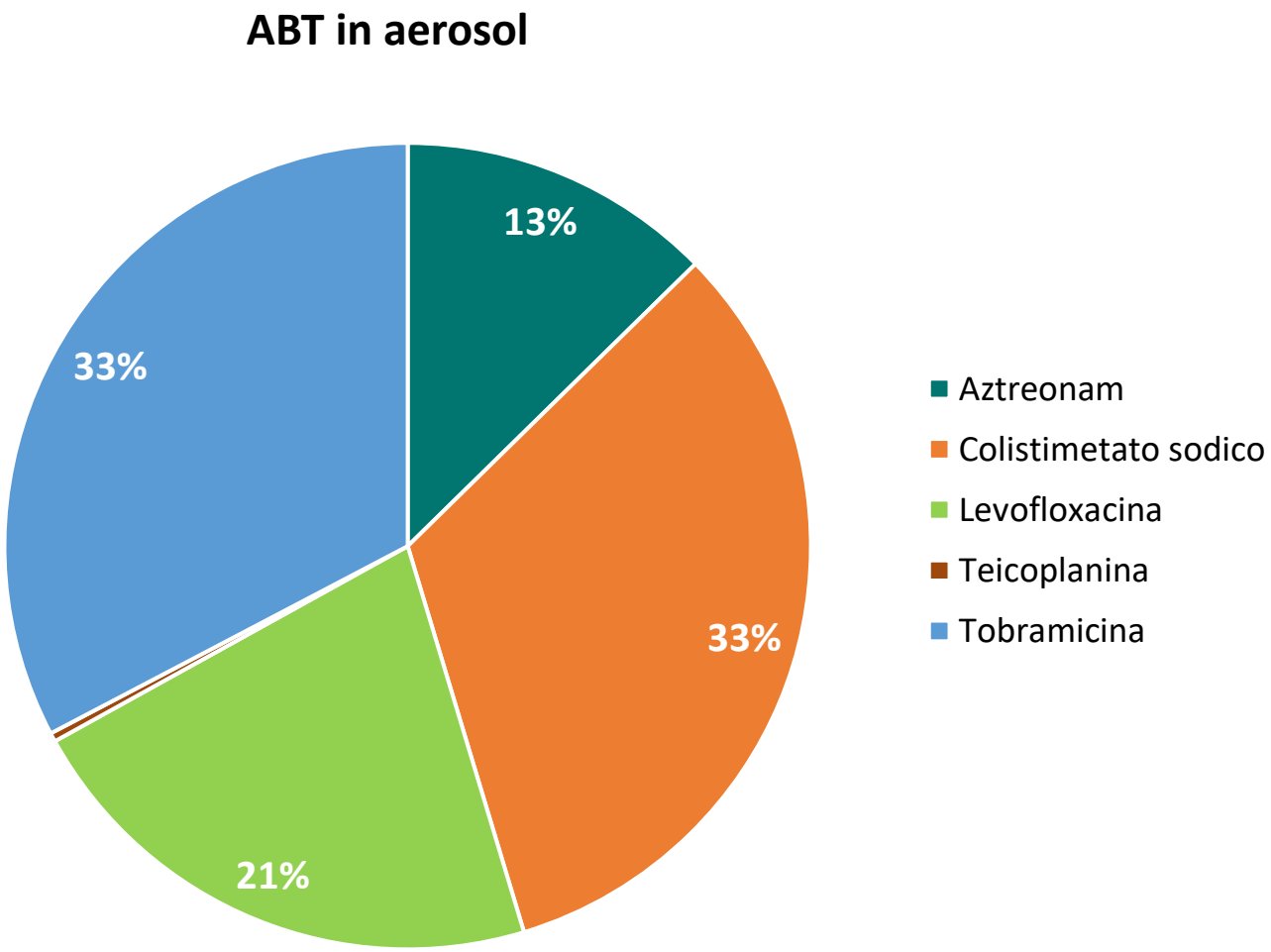
# Esperienza clinica del Centro di Verona

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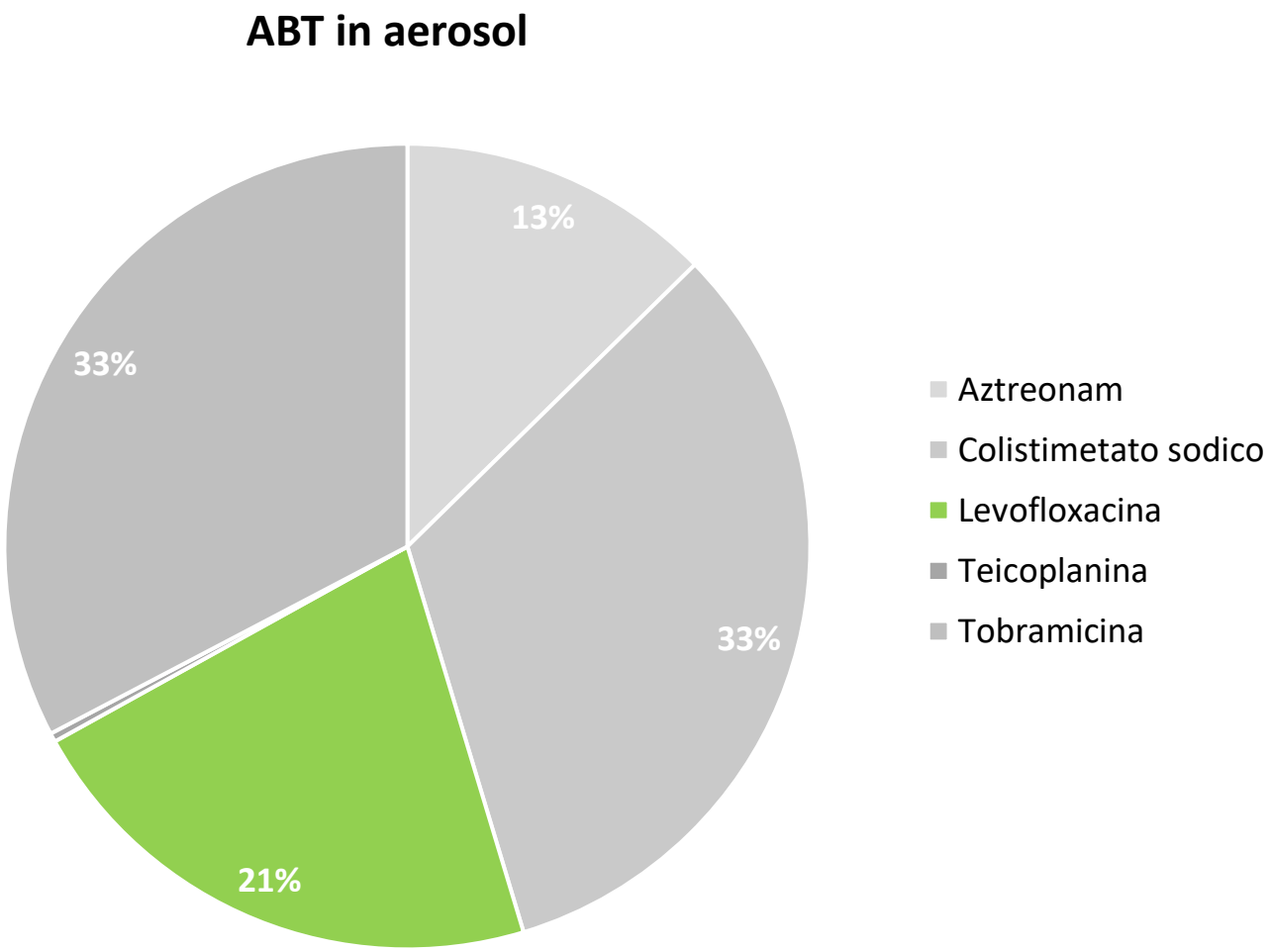
# Esperienza clinica del Centro di Verona

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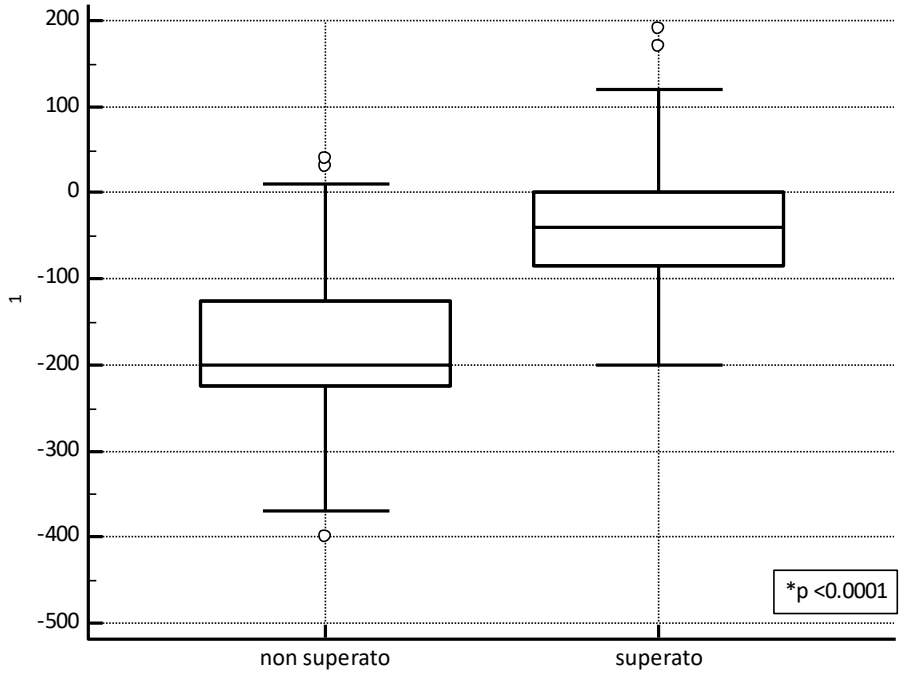
# LIS: esperienza clinica del CFC di Verona

Dal 2016 sono stati eseguiti **165** challenge nei pazienti adulti con colonizzazione cronica da P.aeruginosa


| Dati anamnestici | Challenge superato | Challenge non superato |
|---|---|---|
| **età** | 30,2 [24,1-38,3] | 32,8 [25,8-42,2] |
| **Cicli ABT/anno** | 3 [2-4] | 3 [2-5] |
| **ppFEV$_1$** | 60 [43-76] | 54 [46-78,5] |
| **BMI (kg/m$^2$)** | 20,8 [18,9-22,6] | 20,7 [19,3-22,2] |

mediana [IQR]

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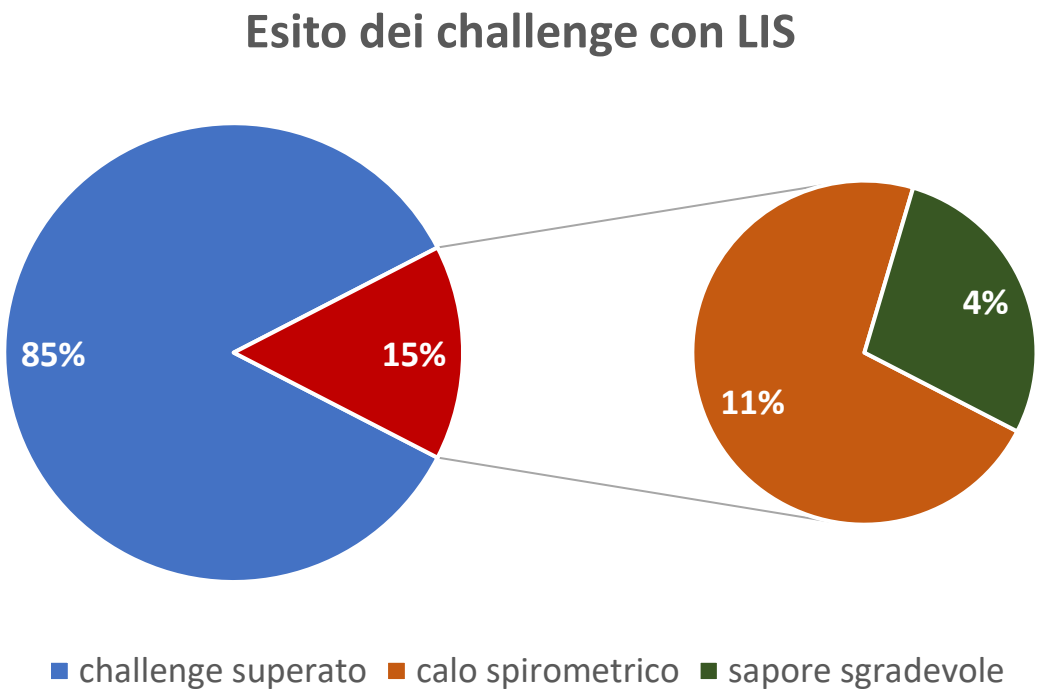


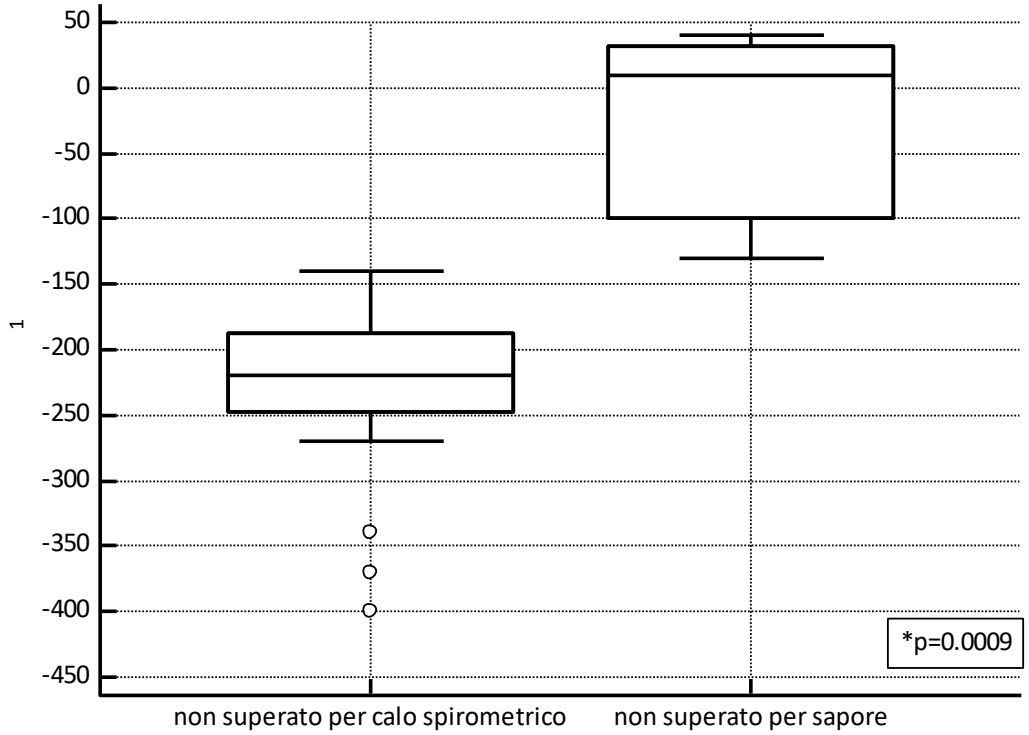


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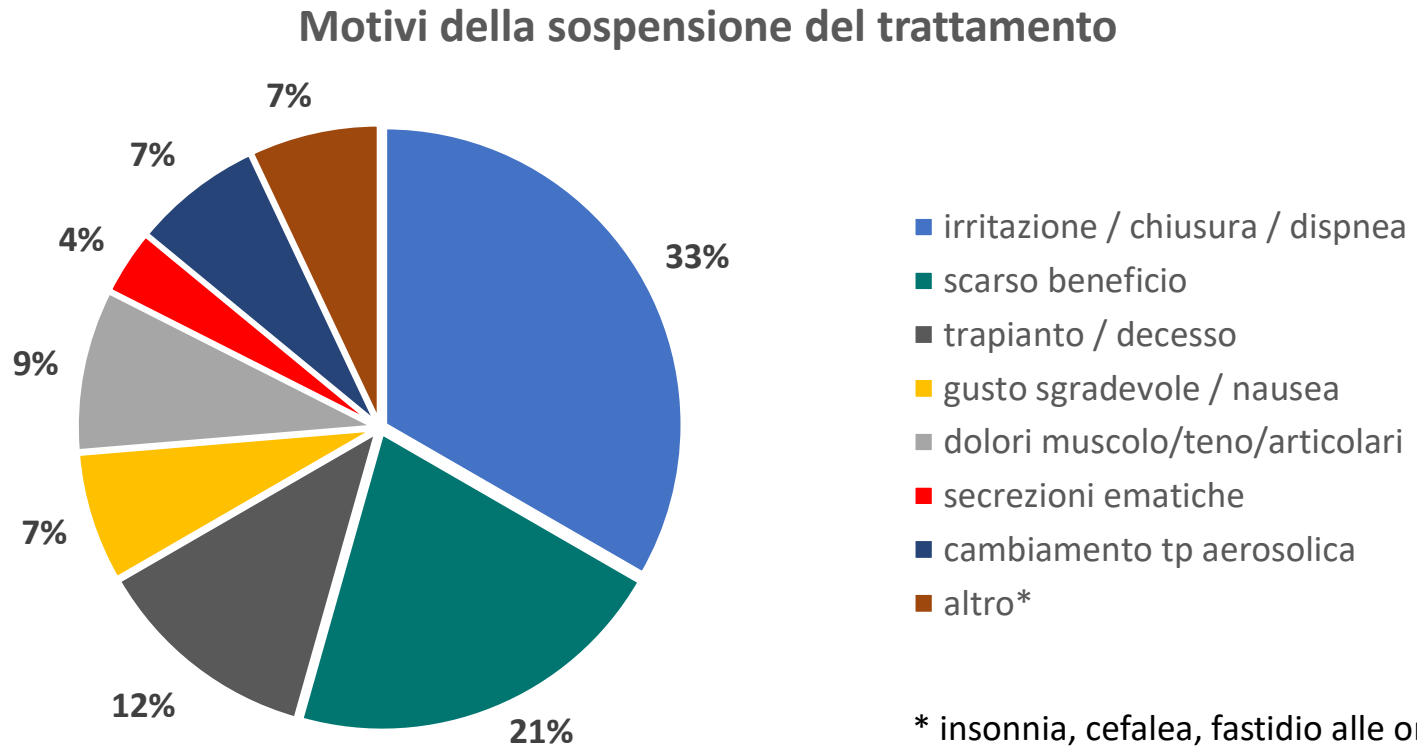
# LIS: esperienza clinica del CFC di Verona

Dal 2016 LIS è stata prescritta a **134** pazienti (11 in monoterapia, 123 on/off con altro ABT inalatorio)

- 77 ONGOING in media da 37,7 mesi (14-58)
- 57 SOSPESI in media dopo 16,6 mesi (1-57)

Nessuna differenza al baseline tra ongoing e sospesi ($FEV_1$, età, BMI, cicli ABT sistemici/annui, altri ABT in aerosol concomitanti)




* insonnia, cefalea, fastidio alle orecchie, febbricola

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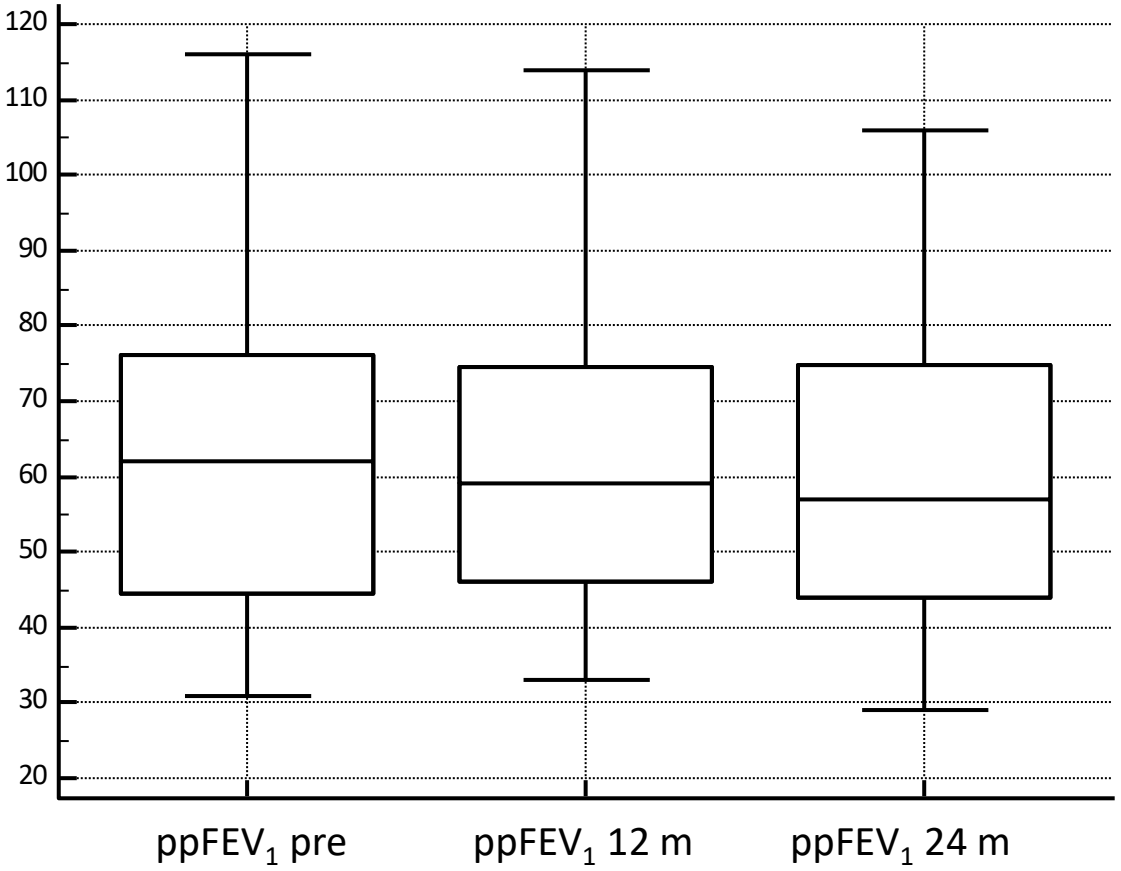
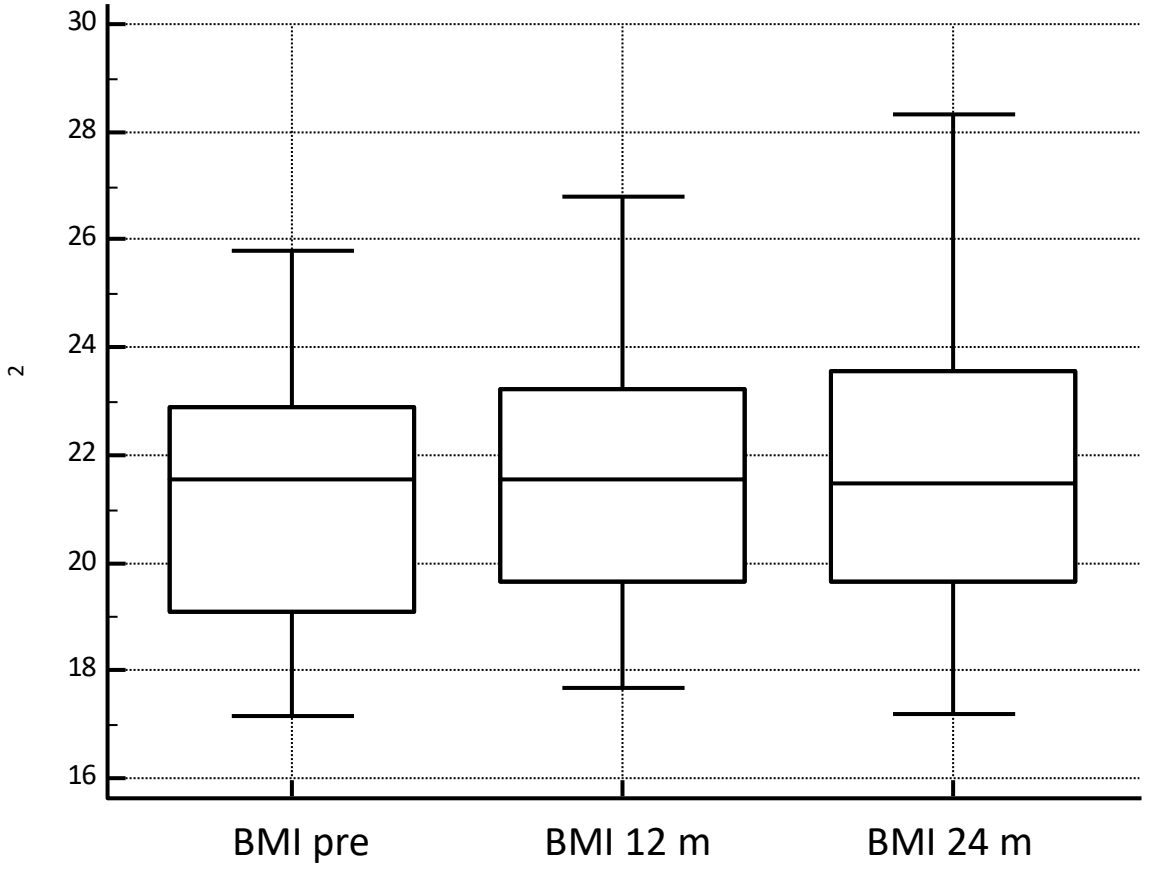
# LIS: esperienza clinica del CFC di Verona

**Funzione respiratoria**




**Stato nutrizionale**

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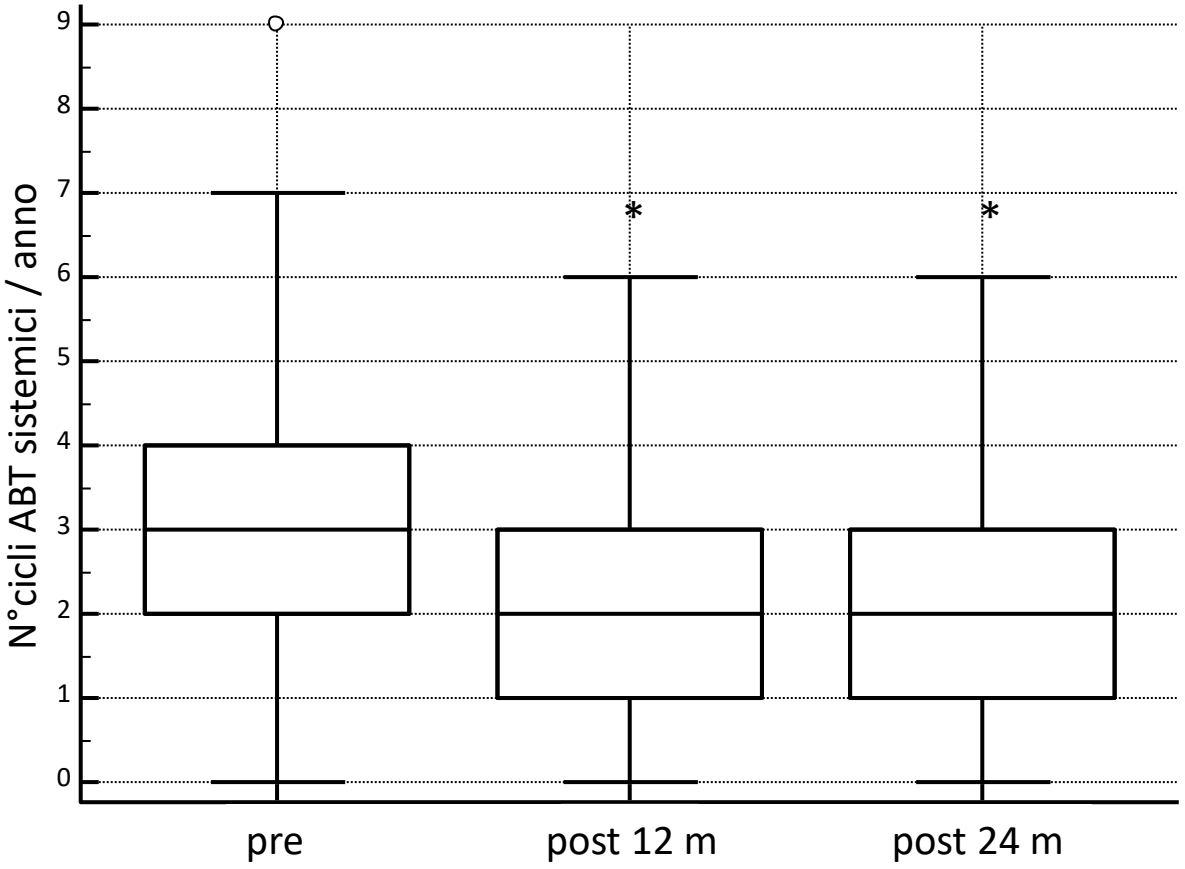
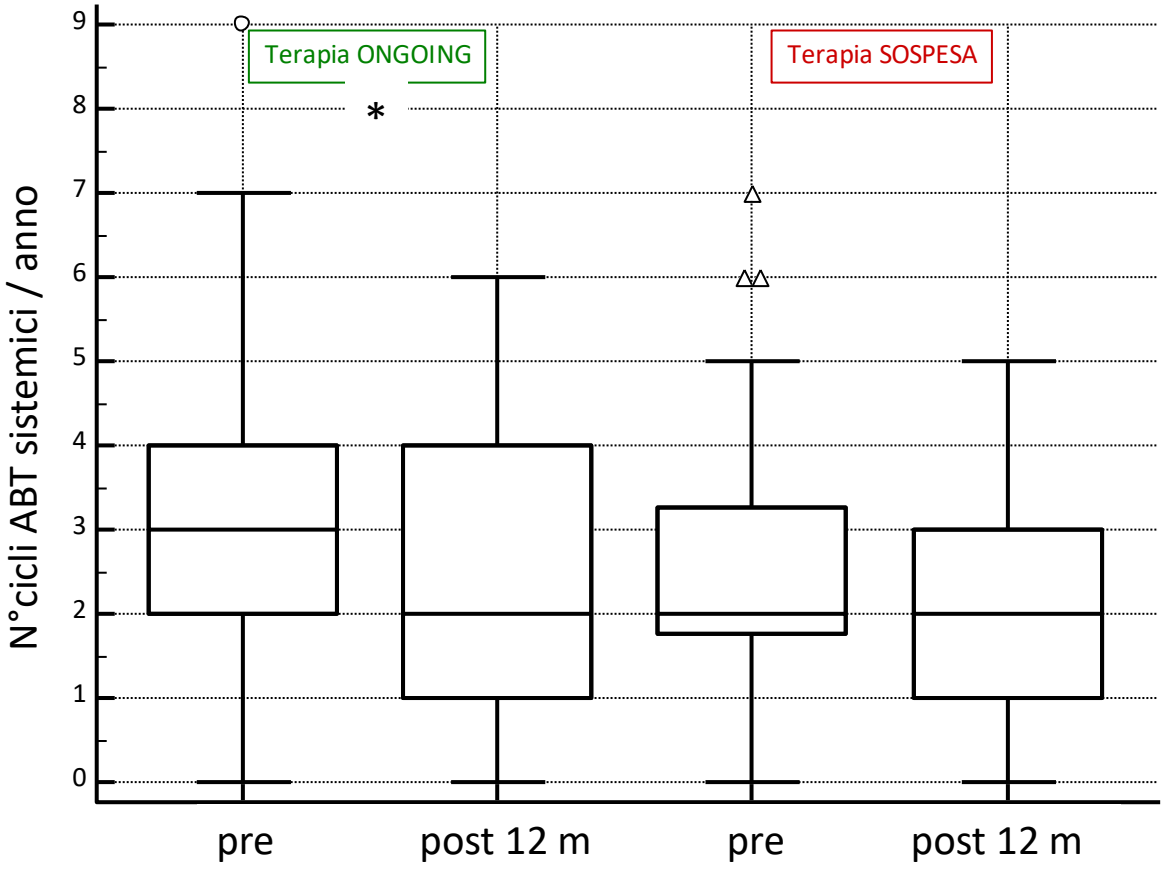
# LIS: esperienza clinica del CFC di Verona

**Cicli ABT sistemici annui**




*p<0.005




*p=0.0048

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# LIS: esperienza clinica del CFC di Verona

Osservazione condotta sui pazienti adulti, con colonizzazione cronica da P. aeruginosa

**CONSIDERAZIONI CONCLUSIVE**

- Superamento del challenge nel 85% (vera broncostruzione nel 11%)
- Irritazione delle vie aeree, disgeusia e dolori mio/teno/articolari segnalati nel 33%, 7% e 9% rispettivamente
- Funzione respiratoria e stato nutrizionale mantenuti nel corso dell'osservazione
- Riduzione del n° di cicli antibiotici sistemici necessari

**LIMITI**

estrazione retrospettiva, disparità di condizioni tra pazienti, terapie concomitanti non tracciate, assenza di un pool di controllo

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# Levofloxacina inalatoria: panoramica

Review

ECFS best practice guidelines: the 2018 revision

*5.2. How should chronic bacterial infection with P. aeruginosa be treated?*

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 on alternate months for patients over 6 years with chronic *P. aeruginosa*, irrespective of the severity of lung disease and continued indefinitely [32]. Whilst studies are lacking for children younger than 6 years, treatment at equivalent doses is also recommended in this age group. The licensed regimen is 300 mg twice daily for 28 days, alternating with 28 days off treatment. A dry powder inhalation of tobramycin (TOBI Podhaler™) has been shown to be of equivalent efficacy [33]. Inhaled aztreonam lysine [34] is recommended as an alternative by both European and US guidelines. Colistimethate (2 MU twice daily) is used widely in Europe and is now also available as a dry powder preparation [35]. A specialist physiotherapist should advise on the timing of inhalational drugs and on appropriate inhalation techniques.

C. Castellani et al. / Journal of Cystic Fibrosis 17 (2018) 153–178

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# Levofloxacina inalatoria: panoramica

[Intervention Review]

**Inhaled anti-pseudomonal antibiotics for long-term therapy in cystic fibrosis**

Cochrane Library
Trusted evidence.
Informed decisions.
Better health.

**Selection criteria**

We selected trials if inhaled anti-pseudomonal antibiotic treatment was used for at least three months in people with cystic fibrosis, treatment allocation was randomised or quasi-randomised, and there was a control group (either placebo, no placebo or another inhaled antibiotic).

18 trials (3042 participants aged between 5 and 56 years)

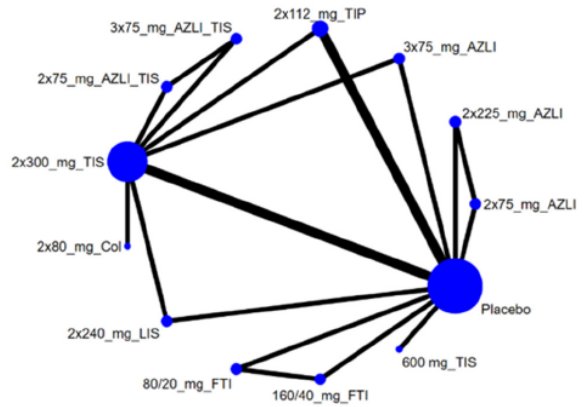
We found limited evidence that inhaled antibiotics improved lung function (four of the 11 placebo-controlled trials, n = 814). Compared to placebo, inhaled antibiotics also reduced the frequency of exacerbations (three trials, n = 946), risk ratio 0.66 (95% confidence interval (CI) 0.47 to 0.93). There were insufficient data for us to be able to report an effect on nutritional outcomes or survival and there were insufficient data for us to ascertain the effect on quality of life. There was no significant effect on antibiotic resistance seen in the two trials that were included in meta-analyses. Tinnitus and voice alteration were the only adverse events significantly more common in the inhaled antibiotics group. The overall quality of evidence was deemed to be low for most outcomes due to risk of bias within the trials and imprecision due to low event rates.

Of the eight trials that compared different inhaled antibiotics or different antibiotic regimens, there was only one trial in each comparison. Forced expiratory volume at one second ($FEV_1$) % predicted was only found to be significantly improved with aztreonam lysine for inhalation compared to tobramycin (n = 273), mean difference -3.40% (95% CI -6.63 to -0.17). However, the method of defining the endpoint was different to the remaining trials and the participants were exposed to tobramycin for a long period making interpretation of the results problematic. No significant differences were found in the remaining comparisons with regard to lung function. Pulmonary exacerbations were measured in different ways, but one trial (n = 273) found that the number of people treated with antibiotics was lower in those receiving aztreonam than tobramycin, risk ratio 0.66 (95% CI 0.51 to 0.86). We found the quality of evidence for these comparisons to be directly related to the risk of bias within the individual trials and varied from low to high.

SmithS et al. *Cochrane Database of Systematic Reviews* 2018, Issue 3. Art. No.: CD001021

# Levofloxacina inalatoria: panoramica

| | Littlewood et al. 2012 [11] | | Elborn et al. 2016 [12] | | Current NMA "Varannai et al. 2021" | |
|---|---|---|---|---|---|---|
| Duration | 4 weeks | 20 weeks | 4 weeks | 24 weeks | 4 weeks | 24 weeks |
| No. of RCTs | 7 trials | Insufficient data | 7 trials | 9 trials | FEV1: 14 trials, CFQ: 7 trials Pa.: 14 trials | 9 trials |
| Antibiotics involved | TIS (300 mg/4 mL), TIS (300 mg/5 mL), TIP, colistin, AZLI | | TIS, TIP, colistin, AZLI, LIS | TIS, TIP, AZLI, LIS | TIS, TIP, colistin, AZLI, LIS, amikacin, FTI | TIS, TIP, AZLI, LIS |
| Outcome | FEV1, Pa. sputum density, acute exacerbations | | FEV1 relative and absolute change, Pa. sputum density, CFQR-RSS change, hospitalization, use of additional antibiotics, study withdrawal rates. | | Relative change in FEV1%, change in *Pseudomonas* sputum density, change in CFQR-RSS, hospitalization, time to acute exacerbation. | |
| Results | All treatments led to an improvement compared to a placebo; tobramycin formulations led to an improvement over AZLI or colistin (although these were not significant differences). | | The relative change in FEV1% was numerically the highest with AZLI, LIS reduced *Pseudomonas* sputum density significantly better than a placebo, although TIP, TIS, and AZLI were numerically more effective. As regards hospitalization, an indirect comparison was conducted due to a lack of trials. Additional antibiotics were required for TIS- and placebo-treated patients compared to LIS. | Changes in FEV1 and sputum density were numerically more effective with LIS compared with TIP and TIS, and they were significantly better than with a placebo. Significantly fewer patients were hospitalized with LIS than with TIP, TIS, and a placebo. Additional antibiotics were required for TIS-, TIP-, and placebo-treated patients compared to LIS. | Aztreonam combined with 28 days of tobramycin were the best treatments as regards changes in FEV1% and sputum density. | The NMA was not conducted for 24 weeks to avoid reproduction of the result from the previous NMA. |




Varannai O et al. Antibiotics 2021, 10, 936

Stuart Elborn J et al. Clinical Therapeutics/Volume 38, Number 10, 2016

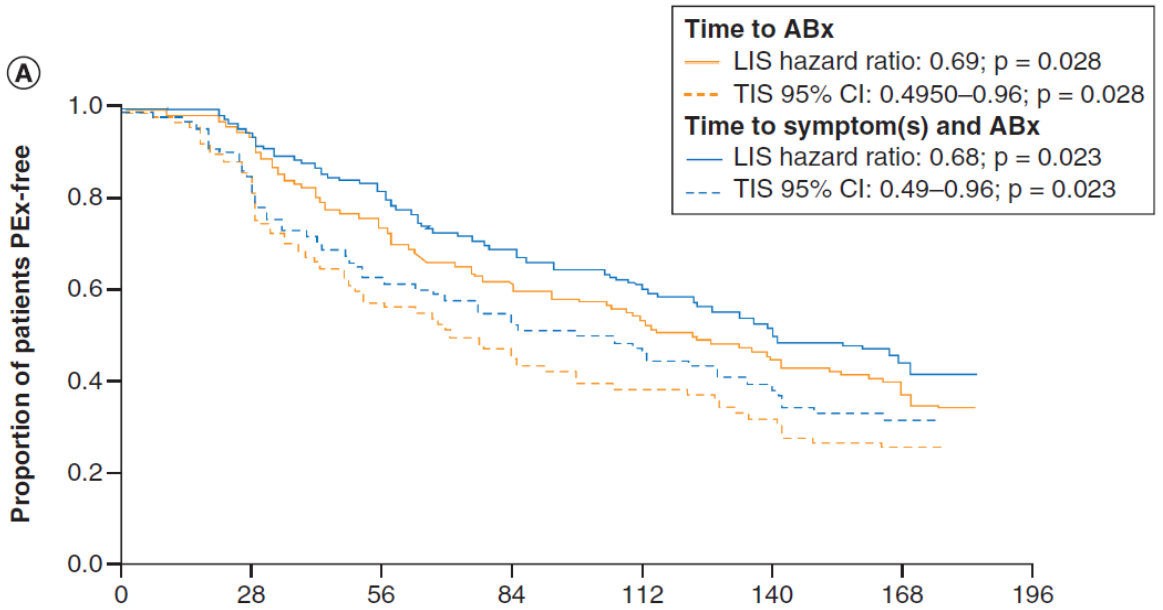
# Levofloxacina inalatoria: panoramica

| Elborn et al. 2016 [12] | | Current NMA "Varannai et al. 2021" | |
|---|---|---|---|
| 4 weeks | 24 weeks | 4 weeks | 24 weeks |
| 7 trials | 9 trials | FEV1: 14 trials,<br>CFQ: 7 trials<br>Pa.: 14 trials | 9 trials |
| TIS, TIP, colistin, AZLI, LIS | TIS, TIP, AZLI, LIS | TIS, TIP, colistin, AZLI, LIS, amikacin, FTI | TIS, TIP, AZLI, LIS |
| FEV1 relative and absolute change, Pa. sputum density, CFQR-RSS change, hospitalization, use of additional antibiotics, study withdrawal rates. | | Relative change in FEV1%, change in *Pseudomonas* sputum density, change in CFQR-RSS, hospitalization, time to acute exacerbation. | |
| The relative change in FEV1% was numerically the highest with AZLI. LIS reduced *Pseudomonas* sputum density significantly better than a placebo, although TIP, TIS, and AZLI were numerically more effective. As regards hospitalization, an indirect comparison was conducted due to a lack of trials. Additional antibiotics were required for TIS- and placebo-treated patients compared to LIS. | Changes in FEV1 and sputum density were numerically more effective with LIS compared with TIP and TIS, and they were significantly better than with a placebo. Significantly fewer patients were hospitalized with LIS than with TIP, TIS, and a placebo. Additional antibiotics were required for TIS-, TIP-, and placebo-treated patients compared to LIS. | Aztreonam combined with 28 days of tobramycin were the best treatments as regards changes in FEV1% and sputum density. | The NMA was not conducted for 24 weeks t avoid reproduction of th result from the previous NMA. |

Varannai O et al. Antibiotics 2021, 10, 936
Stuart Elborn J et al. Clinical Therapeutics/Volume 38, Number 10, 2016

# Levofloxacina inalatoria: future directions

Valutazione della prevenzione di PEX




Post hoc analisi degli studi di fase III


Fischer R et al. *Pediatr Pulmonol* 51(S45), S359 (2016)
Stuart Elborn J et al. FutureMicrobiol. (2021) 16(14), 1087–1104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Definizione e utilizzo in strategie di eradicazione

Definizione di strategie di terapia antibiotica continuativa (CAIT)

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Non solo P.aeruginosa

Table 1. Typical *in vitro* susceptibilities of bacteria that are frequently cultured from adults with cystic fibrosis to antimicrobials that are indicated for inhaled use with cystic fibrosis *P. aeruginosa* infections.

| Bacteria frequently cultured from people with CF | Antimicrobial (class) | | | |
|---|---|---|---|---|
| | Tobramycin (aminoglycoside) | Colistimethate (polymyxin) | Aztreonam (monobactam) | Levofloxacin (fluoroquinolone) |
| *Stenotrophomonas maltophilia* | – | +/- | – | + |
| *Achromobacter* spp. | – | + | – | +/- |
| *Burkholderia cepacia* complex | – | – | – | + |
| MSSA | + | – | – | + |
| MRSA | – | – | – | +/- or - |
| Streptococci | – | – | – | + |
| *Haemophilus influenzae* | + | – | + | + |
| *Pseudomonas aeruginosa* | + | + | + | + |
| Anaerobes | – | – | – | +/- |

LIS open-label (estensione)

- S. maltophilia 7.3% → 3.6%
- A. xylosoxidans 8.9% → 3.6%

≠

LIS open-label real-world

- No change

Chmiel JF et al. *Ann. Am. Thorac. Soc.* 11(7), 1120–1129 (2014)
Stuart Elborn J et al. Journal of Cystic Fibrosis 15 (2016) 634–640
Schwartz C et al. Journal of Cystic Fibrosis 2021 Jun 4;S1569-1993(21)

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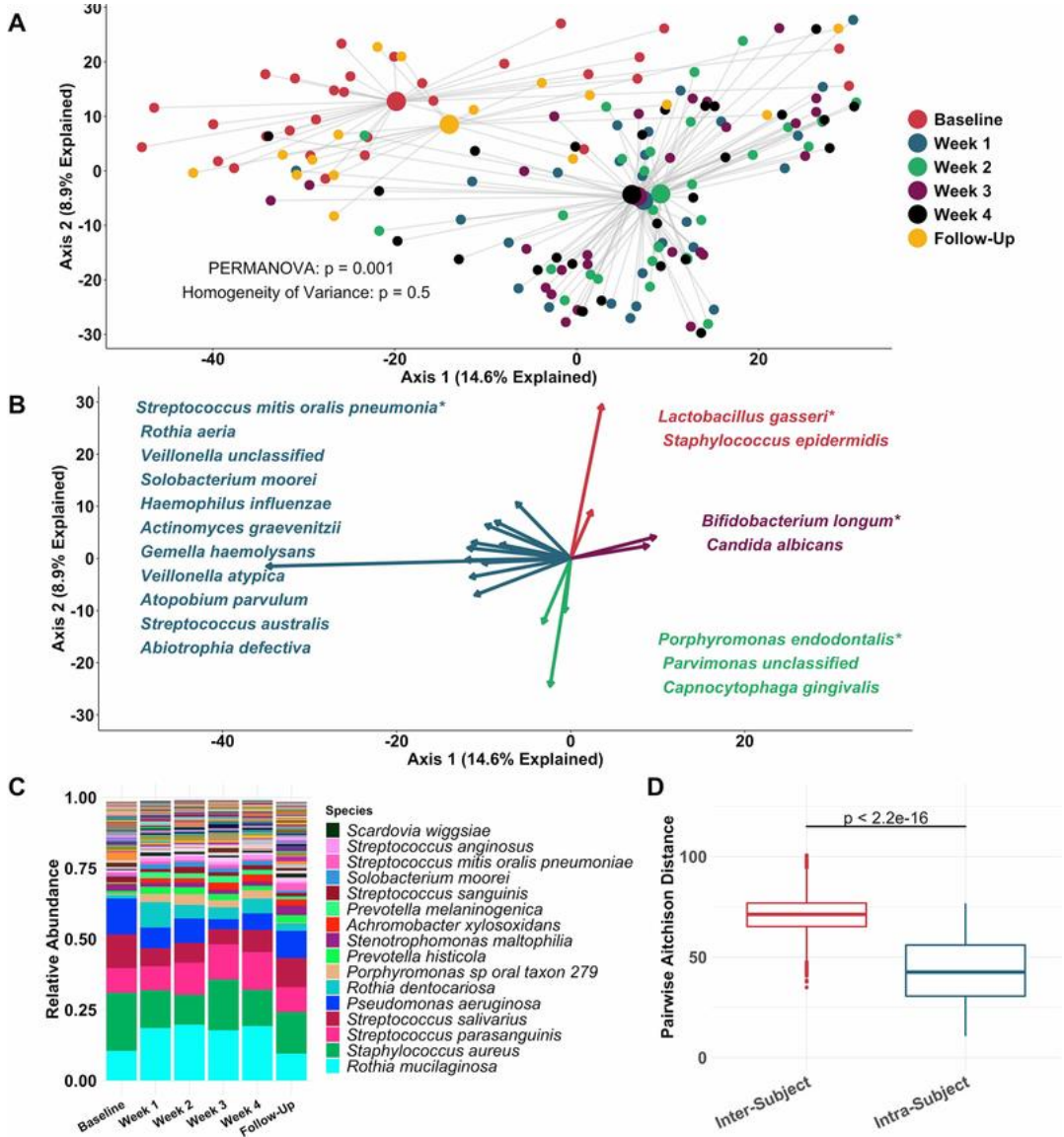
Non solo P.aeruginosa




Nelson MT et al. Thorax. 2020 Sep;75(9):780-790

# Levofloxacina inalatoria: future directions

Come cambia la terapia aerosolica inalatoria nell’era dei modulatori CFTR

Aderenza

Adeguamento della terapia cronica

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GRAZIE PER L’ATTENZIONE