VIII Curso de Antimicrobianos

Actualización en Fibrosis Quística

Guión

- Introducción
  - Recuerdo Histórico
  - Definición de FQ
  - Clínica y diagnóstico
  - Pronóstico
  - Microbiología. P. aeruginosa.
  - Antibióticos inhalados.
- Nuevos tratamientos: dónde estamos?
- ATB inhalada en FQ: del presente al futuro

"… que se reconoce a la gente embrujada si, al rascarles la frente, uno después nota un sabor salado en los dedos"

1606

Dr. Don Juan Alonso de los Ruyzes de Fontecha

(Universidad de Alcalá)

Introducción. Recuerdo Histórico

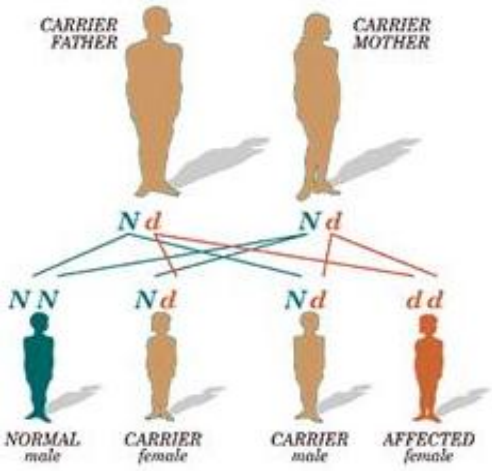
- 1595 – Primera descripción Apa macroscópica (Peter Paaw, Leiden)
- 1938 – Primera descripción clínica e histopatológica (Dorothy Andersen, NY)
- 1943 – Mucoviscidosis (Farber)
- 1945 – Herencia AR (Andersen & Hodges)
- 1952 – Teoría patogénica de las lesiones en la FQ

Introducción. Recuerdo Histórico

- 1952 – Eliminación anormal de cloro en el sudor (Di'Sant Agnese, NY)
- 1959 – Test de iontoforesis con pilocarpina (Gibson & Cook)
- 1983 – Detección de la reabsorción defectuosa de cloro de las células epiteliales
- Identificación del gen CFTR (Riordan, Rommers & Kerem, 1989, *Science*)

Fibrosis Quística. Definición.

- Enfermedad hereditaria AR grave más frecuente en población blanca.
- Incidencia 1/4500 recién nacidos vivos.
- Frecuencia de portadores: 1/25.



Fibrosis Quística. Definición.

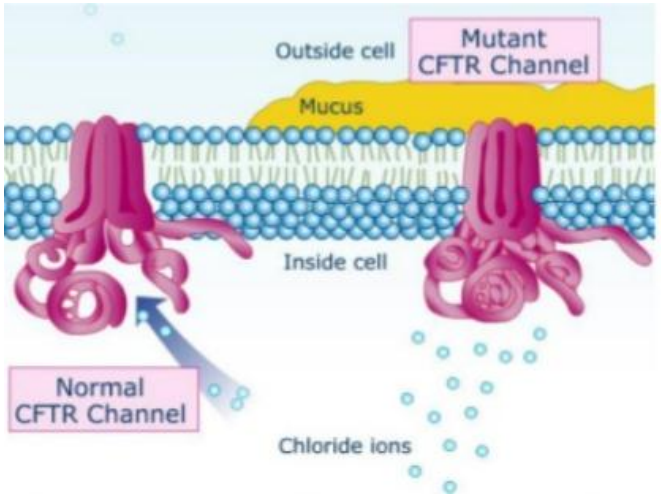
- Producida por mutaciones en el gen CFTR (cystic fibrosis transmembrane regulator), localizado en el brazo largo del cromosoma 7, codifica para una glicoproteína transmembrana, canal de cloro regulado por AMPc.
- Se han descrito > 1800 mutaciones diferentes.
- Mutación más frecuente: FΔ508 (pérdida de fenilalanina)

Fibrosis Quística. Definición.

- Tipos de mutaciones
  - I: iniciación anómala de la transcripción
  - II: problemas durante el procesamiento/maduración de la proteína (se termina degradando)
  - III: alteraciones en la regulación del canal CFTR
  - IV: conducción anómala del flujo de cloro
  - V: síntesis reducida o procesado defectuoso de una CFTR normal.
  - VI: mutaciones que condicionan la pérdida de un extremo terminal COOH- (disminución de la estabilidad de la molécula).

Fibrosis Quística. Definición.

- Funcionamiento defectuoso de la CFRT: alteración del transporte de Cloro y Sodio en las glándulas epiteliales exocrinas que se hallan principalmente en el aparato respiratorio, digestivo, páncreas y glándulas sudoríparas.
- Resultado: producción de moco espeso y viscoso que obstruye los conductos del órgano afectado.



Fibrosis Quística. Manifestaciones Clínicas

TABLA I. Características clínicas de la fibrosis quística en la infancia.

Enfermedad sino-pulmonar crónica manifestada por

- Colonización/infección bronquial persistente por gérmenes típicos: *Staphylococcus aureus*, *Haemophilus influenzae*, *Pseudomonas aeruginosa* o *Burkholderia cepacia*
- Tos y expectoración crónica
- Anormalidades persistentes en la radiografía de tórax: bronquiectasias, infiltrados, atelectasias, hiperinsuflación
- Obstrucción de las vías aéreas con sibilancias y atrapamiento aéreo
- Pólipos nasales y anormalidades radiológicas de los senos paranasales
- Acropaquias

Alteraciones gastrointestinales y nutricionales

- Intestinales: íleo meconial, prolapso rectal, síndrome de obstrucción intestinal distal
- Pancreáticas: insuficiencia pancreática exocrina, pancreatitis recurrente
- Hepáticas: enfermedad hepática crónica con alteraciones clínico-analíticas o evidencia histológica de cirrosis biliar focal o cirrosis multilobular
- Nutricionales: malnutrición, hipoproteinemia y edema, complicaciones secundarias a deficiencias vitamínicas

Síndromes por pérdida de sal

- Alcalosis metabólica crónica
- Pérdida aguda de sal

TABLA II. Presentación clínica de la fibrosis quística en el adulto.

Síntomas y signos gastrointestinales y hepáticos

- Pancreatitis aguda recurrente
- Cirrosis
- Litiasis biliar
- Hipertensión portal con varices esofágicas
- Ictericia

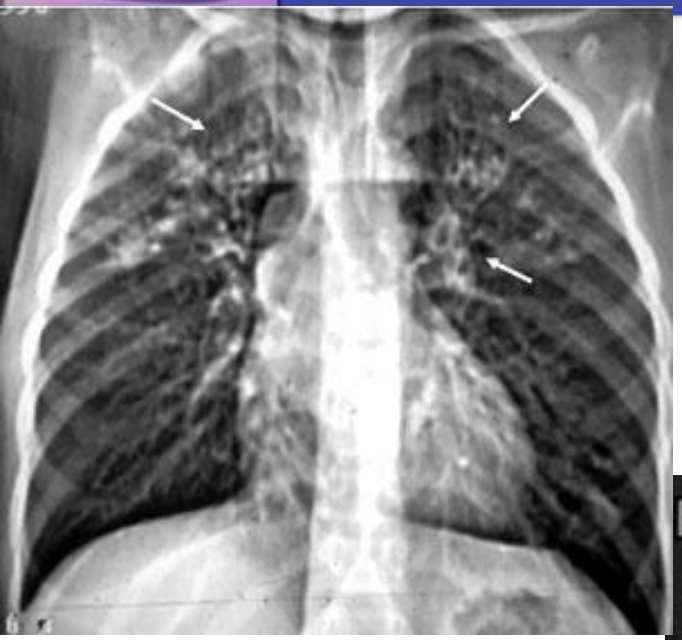
Síntomas y signos respiratorios

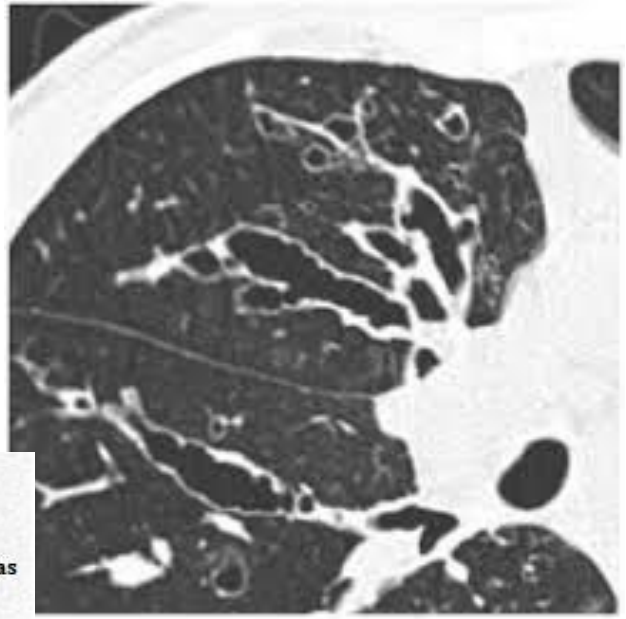
- Infecciones pulmonares recurrentes
- Tos crónica
- Sinusitis
- Poliposis nasal

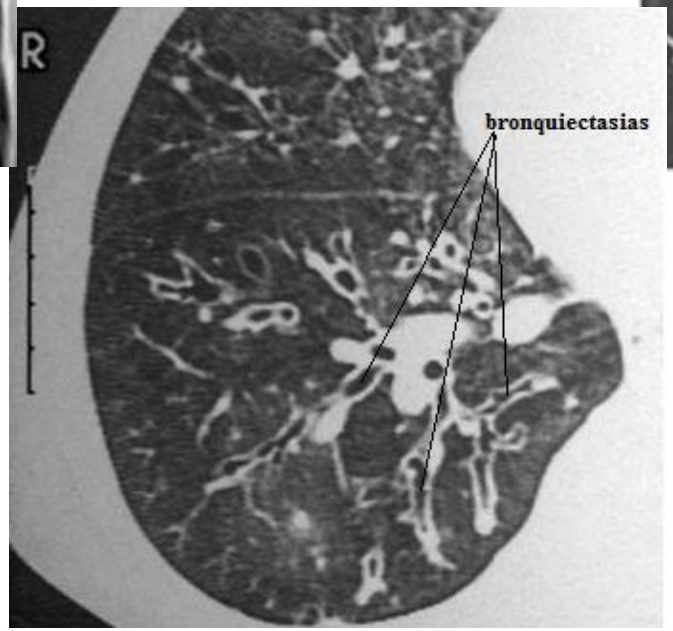
Otros síntomas y signos

- Infertilidad
- Golpe de calor
- Despistaje genético de familiares

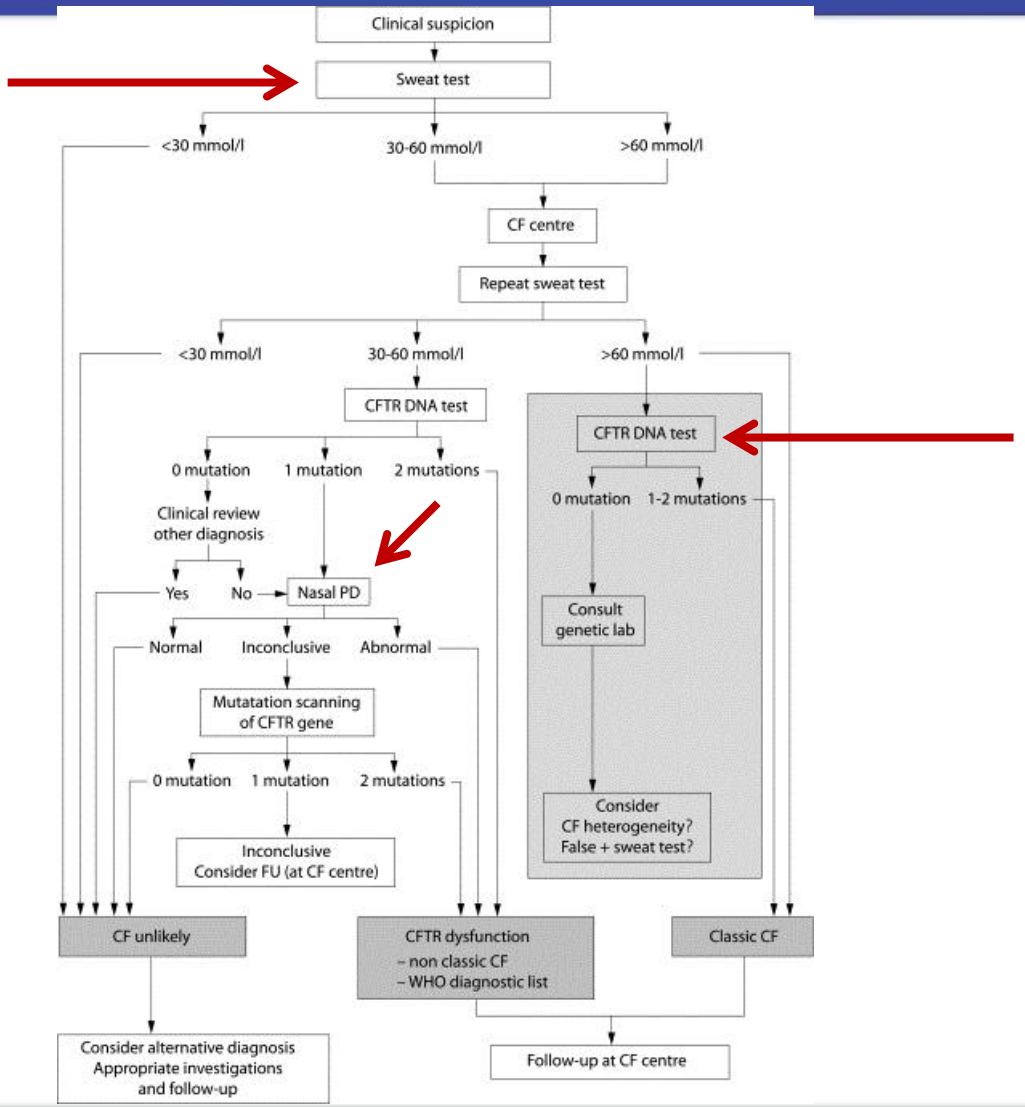
Fibrosis Quística. Manifestaciones Clínicas



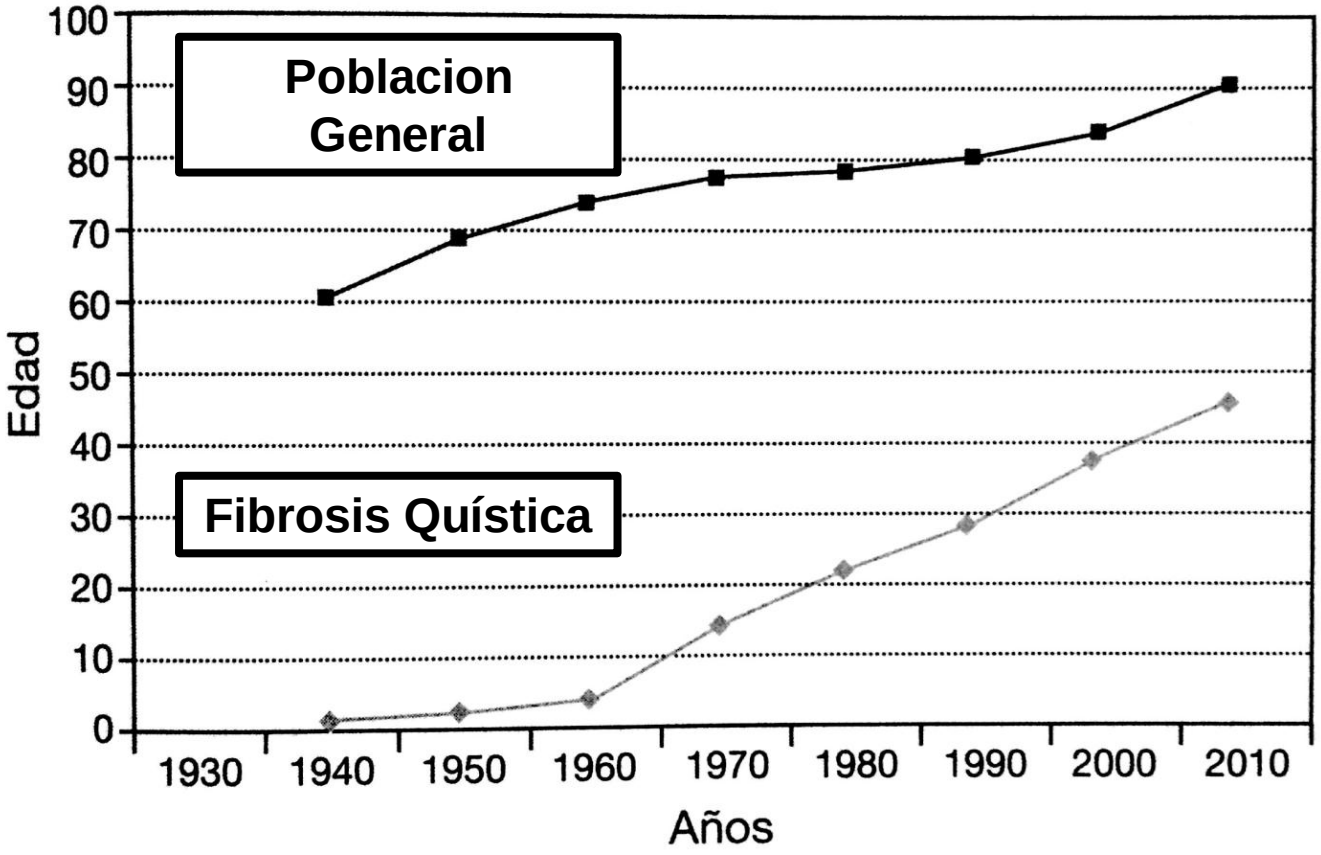




Fibrosis Quística. Diagnóstico

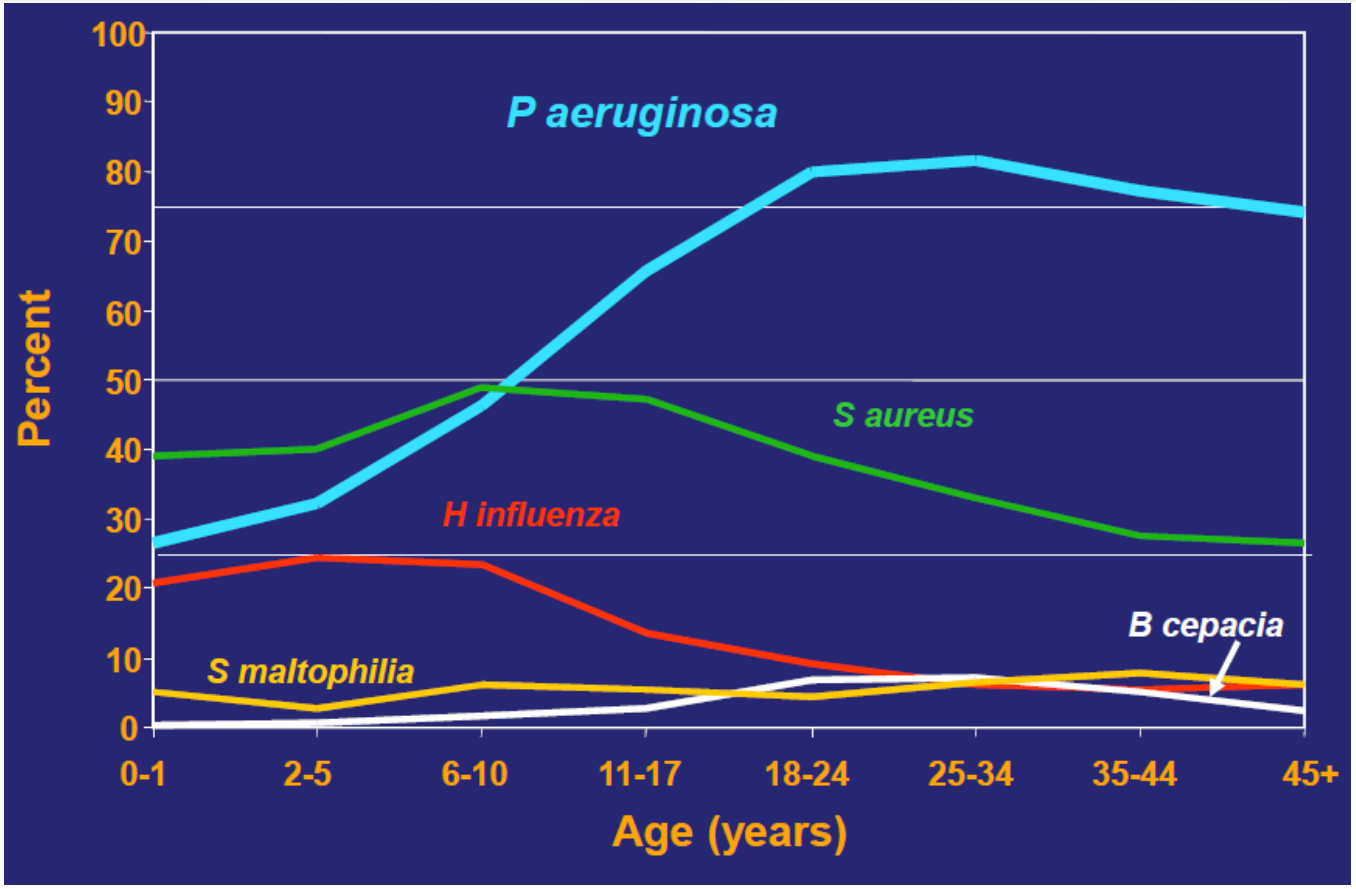


Fibrosis Quística. Pronóstico



Mediana de la supervivencia de FQ y las población general

Fibrosis Quística. Microbiología



Saiman L et al. Infect Control Hosp Epidemiol. 2003
Saiman L et al. Clin Microbiol Rev. 2004
Cystic Fibrosis Foundation. Patient Registry Annual Data Report

Fibrosis Quística. P. aeruginosa

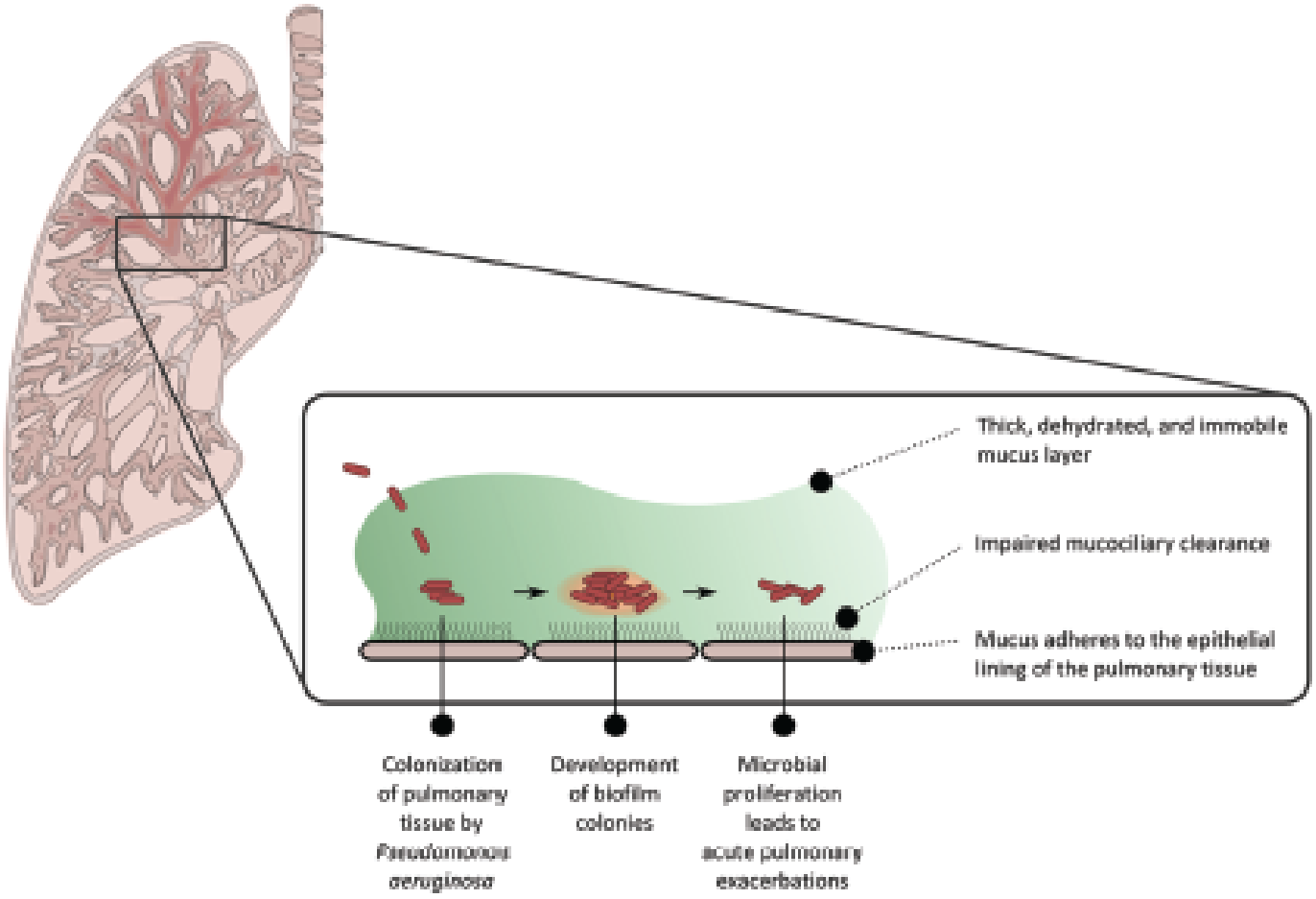


Figure 1. *Pseudomonas aeruginosa* biofilm formation and growth in the lungs of patients with cystic fibrosis.

Fibrosis quística. ATB inhalados

Con el tratamiento ATB inhalado conseguimos…

- Depósito pulmonar elevado
- Acción rápida y directa. No se inactiva
- Toxicidad sistémica escasa
- Permite tratamiento domiciliario
- Erradicar la primoinfección por PA
- Mantenimiento en la colonización por PA

Fibrosis quística. ATB inhalados

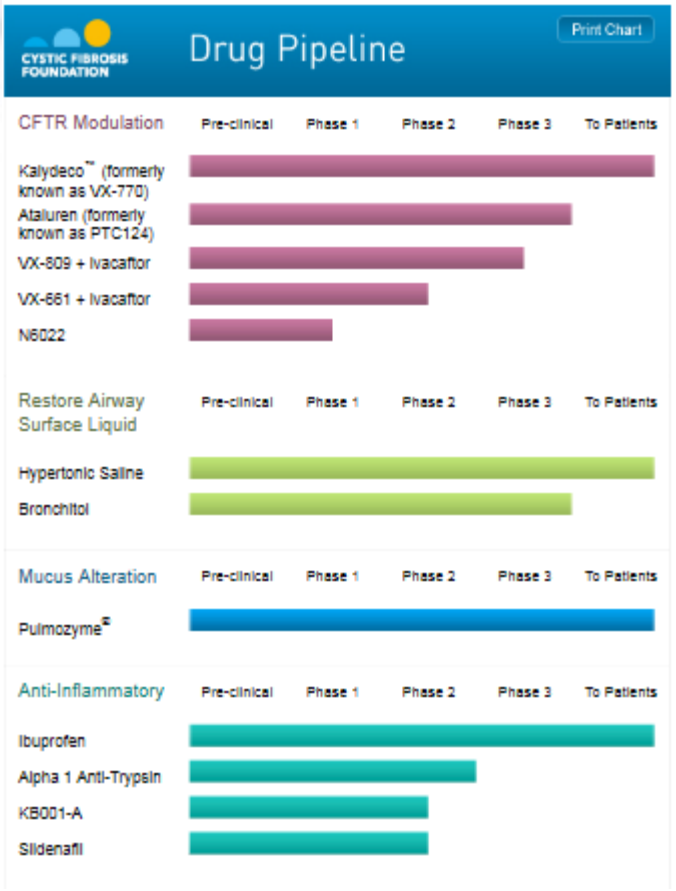
Inconvenientes

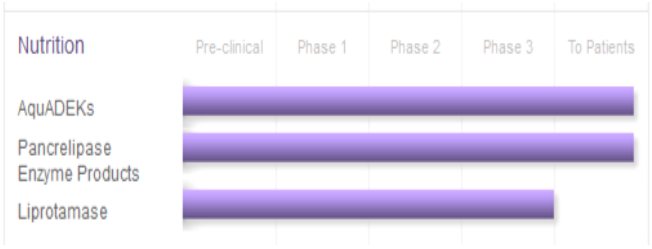
- Dosis incierta.
- Zonas ciegas.
- Técnico-dependencia
- Efectos adversos locales (tos, disgeusia…)
- Absorción sistémica variable
- Consumo de tiempo
- Aprendizaje
- Compatibilidad fármaco/equipo
- Pobre adherencia
- Contaminación
- Control de higiene

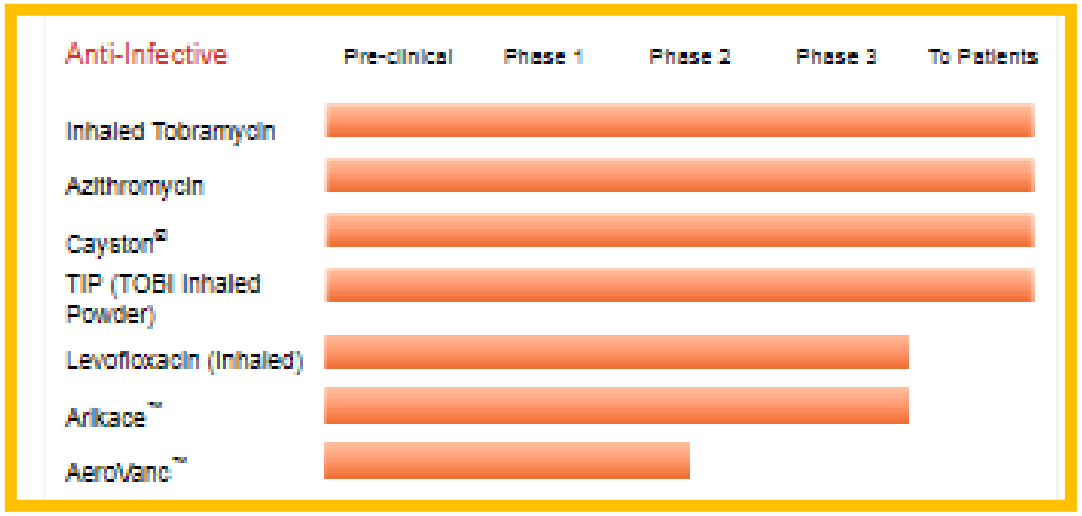
Guión

- Introducción
  - Recuerdo Histórico
  - Definición de FQ
  - Clínica y diagnóstico
  - Pronóstico
  - Microbiología. P. aeruginosa
  - Antibióticos inhalados
- Nuevos tratamientos: dónde estamos?
- ATB inhalada en FQ: del presente al futuro

Tratamiento de la FQ. Situación actual







http://www.cff.org
DrugDevelopment Pipeline

Guión

- Introducción
  - Recuerdo Histórico
  - Definición de FQ
  - Clínica y diagnóstico
  - Pronóstico
  - Microbiología. P. aeruginosa
  - Antibióticos inhalados
- Nuevos tratamientos: dónde estamos?
- ATB inhalada en FQ: del presente al futuro

AMINOGLUCÓSIDOS

Tobramicina nebulizada

- Bactericida Gram (-). Inhibe la síntesis de proteínas.
- 2 formulaciones de tobramicina inhalada
  - TOBI (Novartis) 300 mg en 5 ml
  - Bramitob (Chiesi) 300 mg en 4 ml.
- Administración cada 12 horas.
- Ciclos ON-OFF (28 días).

Tobramicina nebulizada

- Sistemas de nebulización
  - Pari LC Plus
  - Pari eFlow rapid
  - Optineb-ir

Table 1
In vitro nebulisation parameters of Bramitob® and Tobi®, administered using a Pari LC Plus® nebuliser and Pari Turbo Boy™ air compressor, measured using a breathing simulator or multistage liquid impinger [12].

Parameter (mean[a])	Bramitob®	Tobi®
Nebulisation time (min)	15	22
Respirable dose (mg)	98.25	113.05
Fine particle fraction (% of total dose)	33.15	35.92
Mass median aerodynamic diameter (μm)	4.18	4.18

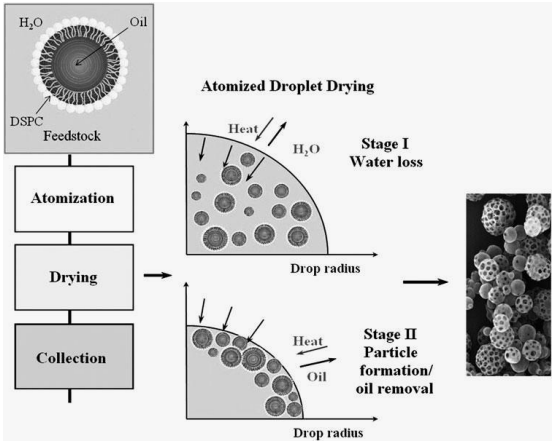
[a] Values shown are the mean of two determinations.

Tobramicina inhalada. Eficacia clínica

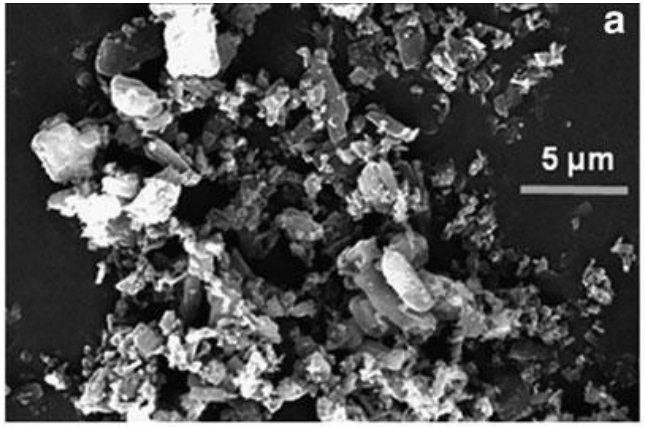
- No presenta ototoxicidad ni nefrotoxicidad.
- Mejora el FEV1 y FVC. ***(Ramsey. 1993, Ramsey, 1999. Lenoir, 2007)***
- Disminuye la densidad bacteriana. ***(Moss, 2002)***
- Reduce la frecuencia de exacerbaciones y hospitalizaciones. ***(Ramsey, 1993. Ramsey 1999, Chuchalin, 1992)***
- Posible baja adherencia al tratamiento
  - Necesidad de numerosos tratamientos diarios
  - Mal sabor
  - Tiempo de nebulización
  - Tratamientos caros

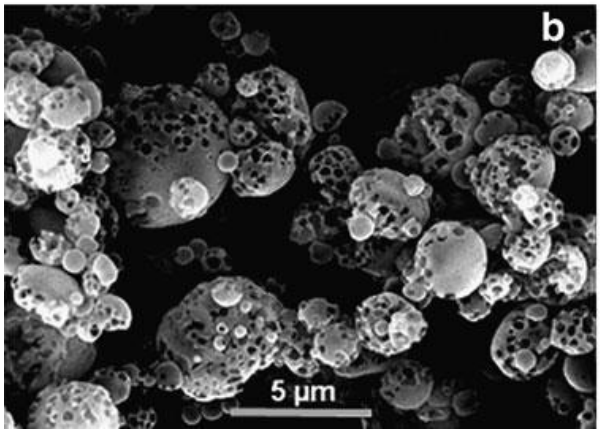
Tobramicina inhalada en polvo seco

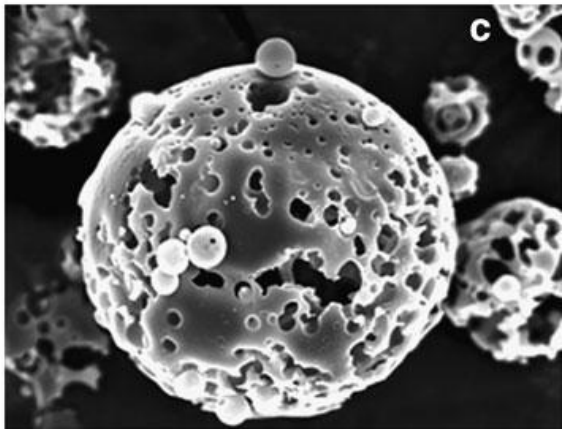
- TOBI Podhaler 28 mg (Novartis) polvo seco para inhalación (cápsula dura).
- Tecnología Pulmosphere™.
- Dosis: 112 mg (4 cápsulas x 28 mg de tobramicina en polvo seco) 2 veces al día.



Journal of Aerosol Medicine and Pulmonary Drug Delivery 2011; 24, Number 4: 175–182

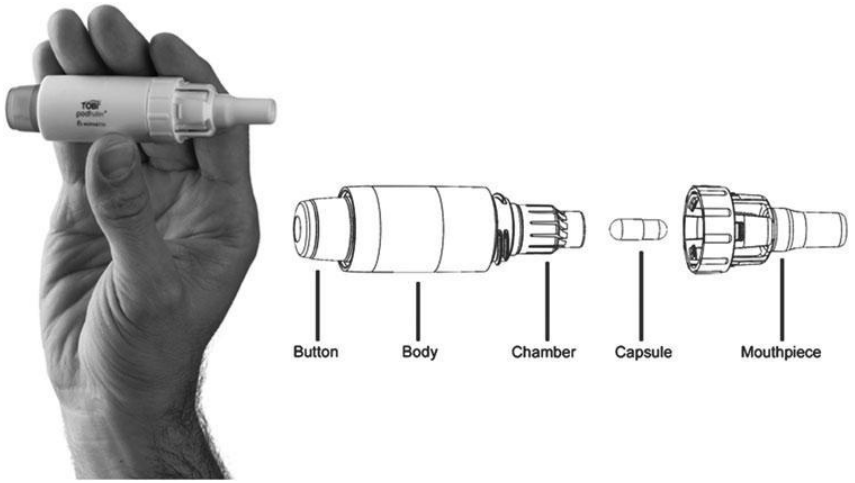






DE Geller. Journal of Aerosol Medicine and Pulmonary Drug Delivery 2011; 24, 4: 175–182

TOBI Podhaler + T-326 Inhalador



- Esferas porosas de MMAD > 4 micras
- Disminuye el área de contacto y reduce la aglomeración
- El 90% de la superficie es DSPC lo que reduce la cohesión
- Requiere menores flujos inspiratorios
- La fracción depositada es 3 veces la de TIS con Pari LC Plus
- Relación deposito vía periferia / vía central: 1.6 (66%)

DE Geller. Journal of Aerosol Medicine and Pulmonary Drug Delivery 2011; 24, 4: 175–182

TOBI Podhaler. Estudios Clínicos

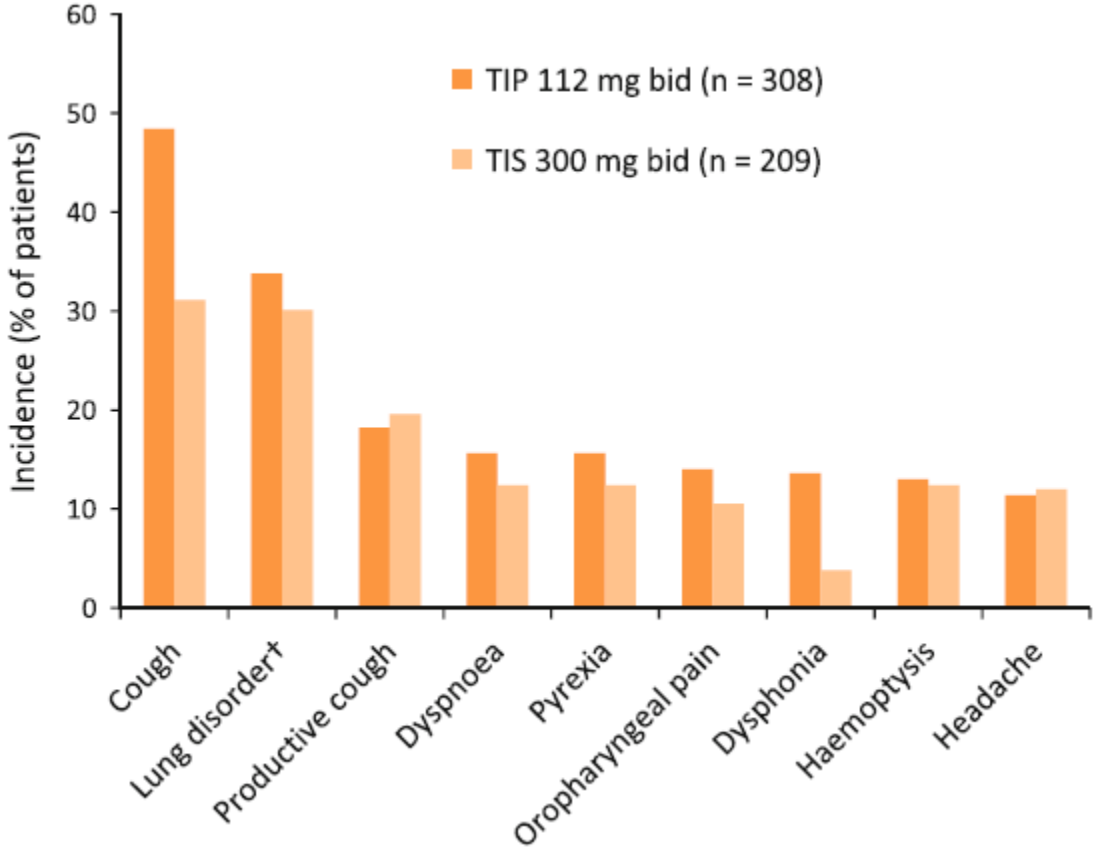
Tobramycin inhalation powder for P. aeruginosa infection in cystic fibrosis: The **EVOLVE trial**. Konstan MW, Geller DE, Miníc P, Brockhaus F, Angyalosi G. *Pediatric Pulmonol 2010*

- **Dosis de 112 mg (4 cap de 28 mg) / 12 horas "versus"placebo**
- **46 TIP/ 49 Placebo (6 – 21 años)**
- **Efectivo: FEV1, Densidad bacteriana**
- **Bien tolerado: Tos. No ototoxicidad ni nefrotoxicidad**
- **Tiempo de administración: 4 – 6 min**

Safety, efficacy and convenience of tobramycin inhalation powder in CF patients: The **EAGER trial**. Konstan MW, Flume PA, Chiron R, Higgins M, Brockhaus F, Zhang J, Angyalosi G, He E, Geller DE. *J Cyst Fibrosis 2011;10(1):54-61*

- **Dosis de 112 mg (4 caps de 28 mg)/ 12 horas "versus" TOBI**
- **553 pacientes, randomizados 3:2 TIP/TIS**
- **Similar eficacia, tolerancia y efectos adversos**
- **Tiempo administración: 5.5 min / 19.7 min.**
- **Superior satisfacción / conveniencia**

TOBI Podhaler. Estudios Clínicos

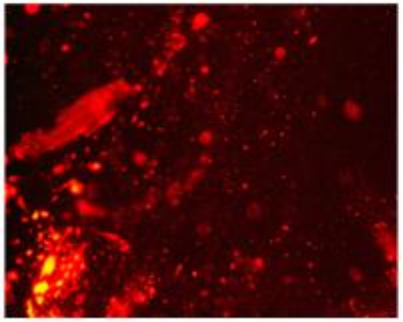


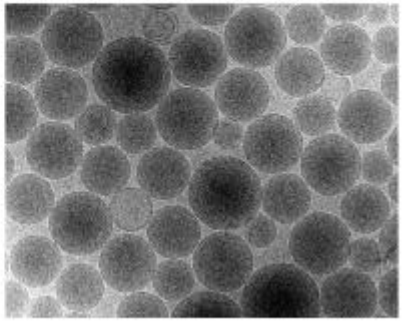
Konstan MW. J Cyst Fibrosis 2011;10(1):54-61

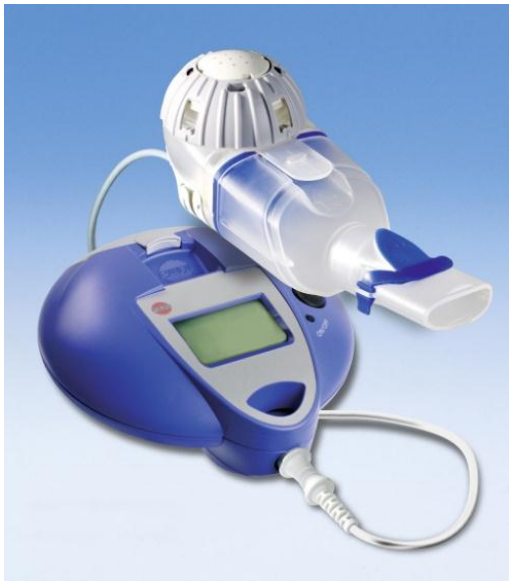
Amikacina liposomal inhalada. Arikace®

- Bactericida Gram (-) y (+).
- Aricace® (Insmed). Administración 1 vez al día
- Nebulizador: PARI e-Flow

Microscopic Images of ARIKAYCE Liposomes







Amikacina liposomal inhalada. Arikace®

Thorax. 2013 Sep;68(9):818-25. doi: 10.1136/thoraxjnl-2012-202230. Epub 2013 Jun 8.

Phase II studies of nebulised Arikace in CF patients with Pseudomonas aeruginosa infection.

Clancy JP[1], Dupont L, Konstan MW, Billings J, Fustik S, Goss CH, Lymp J, Minic P, Quittner AL, Rubenstein RC, Young KR, Saiman L, Burns JL, Govan JR, Ramsey B, Gupta R; Arikace Study Group.

Collaborators (33)

Author information

Abstract

RATIONALE: Arikace is a liposomal amikacin preparation for aerosol delivery with potent Pseudomonas aeruginosa killing and prolonged lung deposition.

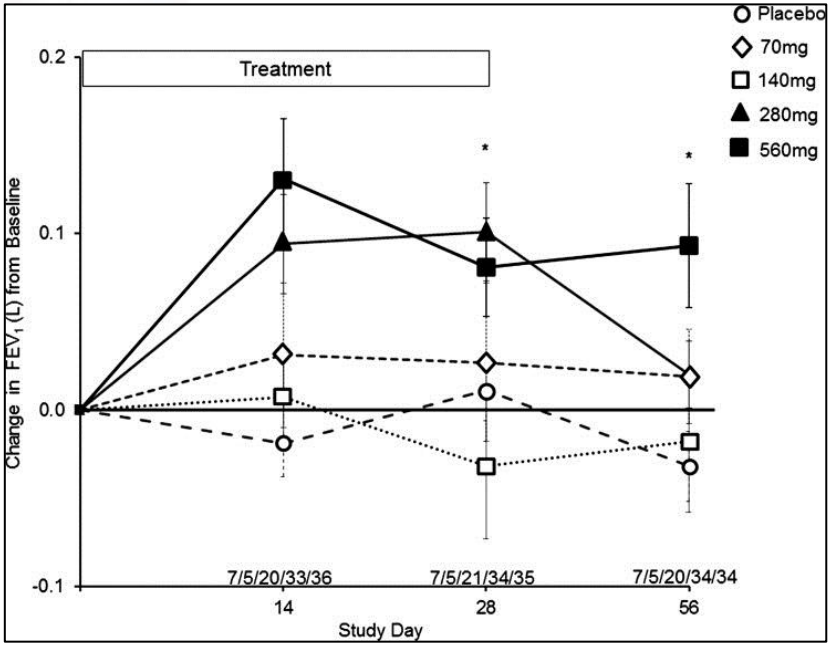
OBJECTIVES: To examine the safety and efficacy of 28 days of once-daily Arikace in cystic fibrosis (CF) patients chronically infected with P aeruginosa.

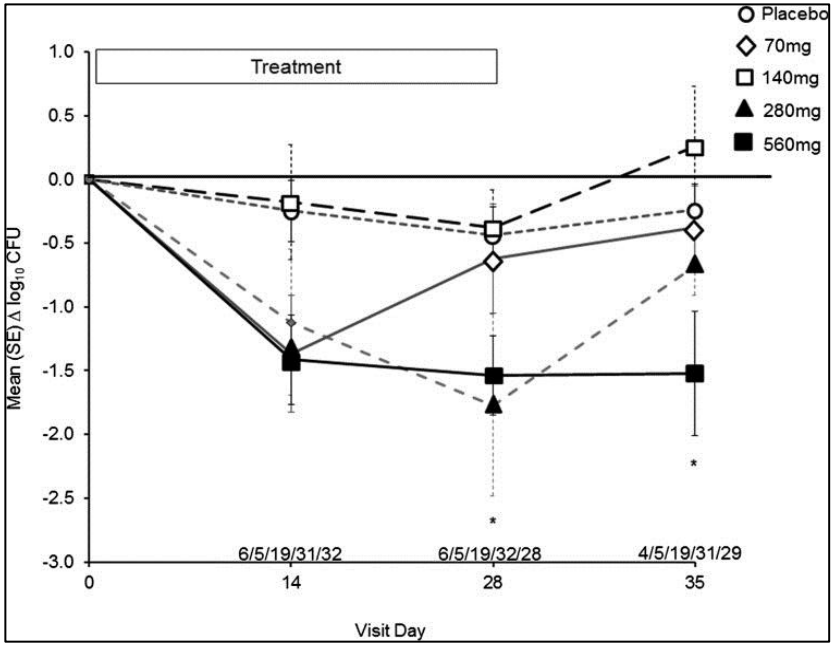
METHODS: 105 subjects were evaluated in double-blind, placebo-controlled studies. Subjects were randomised to once-daily Arikace (70, 140, 280 and 560 mg; n=7, 5, 21 and 36 subjects) or placebo (n=36) for 28 days. Primary outcomes included safety and tolerability. Secondary outcomes included lung function (forced expiratory volume at one second (FEV1)), P aeruginosa density in sputum, and the Cystic Fibrosis Quality of Life Questionnaire-Revised (CFQ-R).

RESULTS: The adverse event profile was similar among Arikace and placebo subjects. The relative change in FEV1 was higher in the 560 mg dose group at day 28 (p=0.033) and at day 56 (28 days post-treatment, 0.093L±0.203 vs -0.032L±0.119; p=0.003) versus placebo. Sputum P aeruginosa density decreased >1 log in the 560 mg group versus placebo (days 14, 28 and 35; p=0.021). The Respiratory Domain of the CFQ-R increased by the Minimal Clinically Important Difference (MCID) in 67% of Arikace subjects (560 mg) versus 36% of placebo (p=0.006), and correlated with FEV1 improvements at days 14, 28 and 42 (p<0.05). An open-label extension (560 mg Arikace) for 28 days followed by 56 days off over six cycles confirmed durable improvements in lung function and sputum P aeruginosa density (n=49).

CONCLUSIONS: Once-daily Arikace demonstrated acute tolerability, safety, biologic activity and efficacy in patients with CF with P aeruginosa infection.

Amikacina liposomal inhalada. Arikace®





Clancy JP et al. Thorax. 2013 Sep;68(9):818-25

Amikacina liposomal inhalada. Arikace®

- Ensayos clínicos en Fase con Arikace®

Arikace™

Overview | Clinical Trials | News

Arikace Compared to TOBI in People with CF with Chronic Pseudomonas Aeruginosa Infections
This trial will look at whether Arikace is effective in treating chronic lung infections caused by Pseudomonas aeruginosa in people with Cystic Fibrosis. The effectiveness, safety and tolerability of Arikace will be compared to TOBI, an inhalation antibiotic already available for use.
Phase: 3
Recruitment Status: Not Yet Recruiting

Study of Arikace in People with CF with Chronic Lung Infection Due to Pseudomonas Aeruginosa
Liposomal amikacin for inhalation (Arikace) was developed as a possible treatment for chronic infection due to Pseudomonas aeruginosa in people with CF. The purpose of this double-blind, placebo controlled study is to determine whether Arikace is effective in treating chronic lung infections caused by Pseudomonas aeruginosa in people with CF.
Phase: 3
Recruitment Status: Not Yet Recruiting

Long term study of Arikace in people with CF with Chronic Pseudomonas Aeruginosa Lung Infection
This study will look at the long term safety and tolerability of Arikace in people with Cystic Fibrosis for up to approximately 2 years.
Phase: 3
Recruitment Status: Not Yet Recruiting

Arikace for Nontuberculous Mycobacteria (NTM)
The purpose of this study is to determine whether Arikace is effective in treating recalcitrant nontuberculous mycobacterial lung disease. The safety and tolerability of Arikace in this patient population will also be assessed.
Phase: 3
Recruitment Status: Recruiting Completed

POLIMIXINAS

Colimicina nebulizada

- Bactericida Gram (-). Daña la membrana
- Presentaciones disponibles
  - Colimicina GES 2 millones/12 horas.
  - Promixin (1M/ml) + I-Neb 1 millón/12 horas
  - No aparecen resistencias (no mes OFF)
  - Menor efecto sobre el FEV1 que TOBI
  - Disminuye la densidad bacteriana
  - Útil en erradicación y mantenimiento

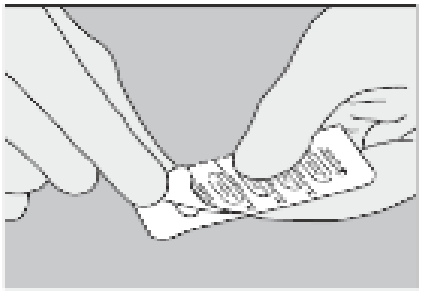
Malla / Malla + AAD

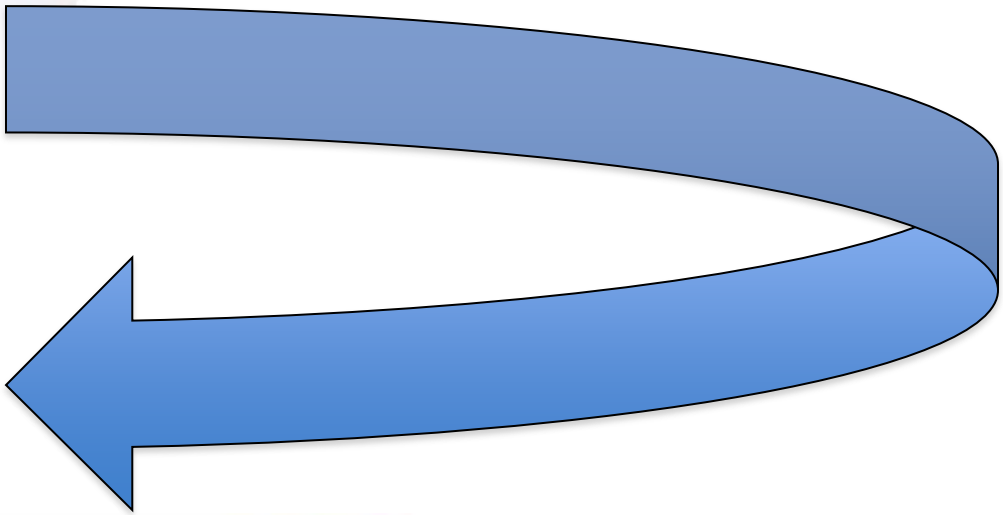
Colimicina de GES

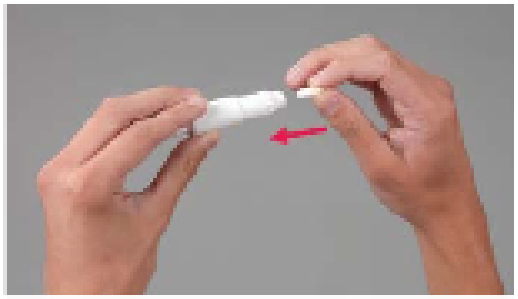
Promixin + I-neb AAD

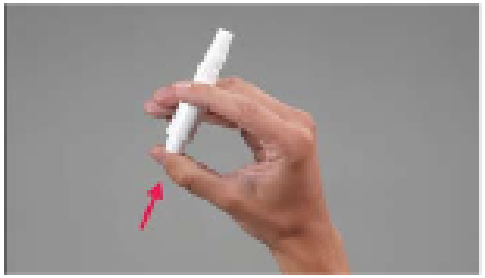
Colimicina en polvo seco. Colobreathe®

- Forest Laboratories receives European Marketing Authorisation for Colobreathe® Dry Powder Inhaler. Forest Laboratories UK (24/02/2012).
- Formulación en polvo seco.
- Capsulas de 125 mg (1.662.500 IU) 1 inh/12 horas.
- Inhalador turbospin desechable.
- Misma eficacia que TOBI.
- Mejor aceptabilidad (T. admin. < 60 seg).
- Buena tolerancia.









Colobreathe + Turbospin inhaler

β-LACTÁMICOS

Aztreonam Lisina. Cayston®

- Monobactámico. Bactericida Gram (-). Inhibe la síntesis de pared bacteriana.
- Gilead Sciences
- Formulación: Vial liofilizado de 75 mg
- Frecuencia: 1 vial cada 8 horas
- Ciclos de 28 días (ON-OFF)
- Sistema de administración: Pari Altera
- Tiempo de administración: 2 minutos.
- No alergia cruzada con los β-lactámicos

Aztreonam Lisina. Cayston®

- Mejora los síntomas, la función pulmonar, la densidad bacteriana, retrasa el tiempo hasta la agudización y reduce los días de estancia hospitalaria. ***(McCoy, 2008. Retsch-Bogart, 2009)***
- Seguro y eficaz a largo plazo. No se ha asociado a aumento de resistencias. **(Oermann, 2010 y 2011)**
- Eficacia no inferior a TOBI. Buena tolerancia.
- Alternativa para ciclos ON-OFF

Aztreonam Lisina. Cayston®

TABLE 4. NEW AND MODIFIED RECOMMENDATIONS

Treatment	Recommendation	Certainty of Net Benefit	Estimate of Net Benefit	Recommendation
Ivacaftor*	For individuals with CF, 6 years of age and older, with at least one G551D *CFTR* mutation, the Pulmonary Clinical Practice Guidelines Committee strongly recommends the chronic use of ivacaftor to improve lung function and quality of life and reduce exacerbations.	High	Substantial	A
Inhaled aztreonam—moderate to severe disease†	For individuals with CF, 6 years of age and older, with moderate to severe lung disease and *Pseudomonas aeruginosa* persistently present in cultures of the airways, the CF Foundation strongly recommends the chronic use of inhaled aztreonam to improve lung function and quality of life.	High	Substantial	A
Inhaled aztreonam—mild disease†	For individuals with CF, 6 years of age and older, with mild lung disease and *P. aeruginosa* persistently present in cultures of the airways, the CF Foundation recommends the chronic use of inhaled aztreonam to improve lung function and quality of life.	Moderate	Moderate	B
Chronic use of ibuprofen (age < 18 yr)	For individuals with CF, between 6 and 17 years of age, with an $FEV_1 \geq 60\%$ predicted, the CF Foundation recommends the chronic use of oral ibuprofen, at a peak plasma concentration of 50–100 μg/ml, to slow the loss of lung function.	Moderate	Moderate	B
Chronic use of ibuprofen (age ≥ 18 yr)	For individuals with CF, 18 years of age and older, the CF Foundation concludes that the evidence is insufficient to recommend for or against the chronic use of oral ibuprofen to slow the loss of lung function or reduce exacerbations.	Low	—	I
Azithromycin without *P. aeruginosa*	For individuals with CF, 6 years of age and older, without *P. aeruginosa* persistently present in cultures of the airways, the CF Foundation recommends the chronic use of azithromycin should be considered to reduce exacerbations.	Moderate	Small	C
Chronic inhaled β_2-adrenergic receptor agonists	For individuals with CF, 6 years of age and older, the CF Foundation concludes that the evidence is insufficient to recommend for or against chronic use of inhaled β_2-adrenergic receptor agonists to improve lung function and quality of life or reduce exacerbations.	Low	—	I
Oral antistaphylococcal antibiotics, chronic use	For individuals with CF, 6 years of age and older, with *Staphylococcus aureus* persistently present in cultures of the airways, the CF Foundation concludes that the evidence is insufficient to recommend for or against the chronic use of oral antistaphylococcal antibiotics to improve lung function and quality of life or reduce exacerbations.	Low	—	I

Cystic Fbrosis Pulmonary Guidelines. Chronic medications for maintenance of lung health. 2013

QUINOLONAS

Levofloxacino inhalado

- L-isómero de la forma racémica del ofloxacino.
- Fluoroquinolona de 3ª generación.
- Amplio espectro de acción frente a Gram (+) y (-) incluyendo actividad bactericida contra P. aeruginosa.
- Alteración en la replicación del DNA.

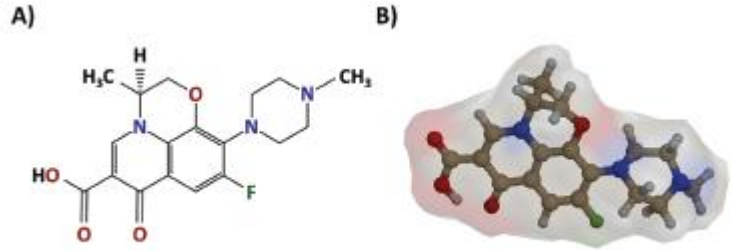


Figure 2. Chemical and molecular structure of levofloxacin.

Levofloxacino inhalado

- Dosis de 240 mg (100 mg/ml) cada 24 horas parecen las más adecuadas (pacientes ≥ 6 años y ≥30 Kg peso).
- Buena seguridad y tolerancia.

Geller D et al. Pediatric Pulmonol (2011)

- Potente ATB reducción de UFC en esputo (PA, Burkholderia cepacia, Achromobacter xylosoxidans y S aureus) y más potente que aztreonam y aminoglucósidos frente a PA.

King et al. Antimicrob Agents Chemoter, 2010

Levofloxacino inhalado

Development of levofloxacin inhalation solution to treat *Pseudomonas aeruginosa* in patients with cystic fibrosis

Chris Stockmann, Catherine M.T. Sherwin, Krow Ampofo and Michael G. Spigarelli

Abstract: Inhaled therapies allow for the targeted delivery of antimicrobials directly into the lungs and have been widely used in the treatment of cystic fibrosis (CF) acute pulmonary exacerbations. Nebulized levofloxacin solution (MP-376) is a novel therapy that is currently being evaluated in phase I, II, and III clinical trials among patients with stable CF and recent isolation of *Pseudomonas aeruginosa* from sputum. Phase I studies have investigated the single and multiple-dose pharmacokinetics of MP-376 and shown that it is rapidly absorbed from the lungs and results in low systemic concentrations. A subsequent phase IB study found that MP-376 pharmacokinetics were comparable among adults and children 6–16 years of age. Further phase II studies reported that sputum *P. aeruginosa* density decreased in a dose-dependent manner among patients who were randomized to MP-376 when compared with patients who received placebo. Improvements in pulmonary function and a decrease in the need for other antipseudomonal antibiotics were also reported for patients who received inhaled levofloxacin. The most common adverse event was dysgeusia (abnormal taste sensation), which was reported by nearly half of the participants who received MP-376. No serious drug-related adverse events were reported. These findings are encouraging; however, data from the two ongoing phase III trials are needed to determine whether MP-376 demonstrates substantial evidence of safety and efficacy as a chronic CF maintenance therapy and therefore may be useful in routine clinical practice.

Stockmann C et al. Ther Adv Respir Dis 2014; 8(1):13-21

Ciprofloxacino inhalado en polvo seco

- Inhalado en polvo seco. Bayer
- Pulmosphere® + Inhalador T-326 (Novartis)
- Ensayo clínico en fase I en sujetos sanos
  - No eventos adversos significativos.
  - Depósito bronquial-alveolar: 40%.
  - Mínima absorción sistémica

Stass H. Clin Drug Investig 2013 Jun;33(6):419-27

Ciprofloxacino inhalado en polvo seco

Clinical Therapeutics/Volume 35, Number 10, 2013

Tolerability and Pharmacokinetic Properties of Ciprofloxacin Dry Powder for Inhalation in Patients With Cystic Fibrosis: A Phase I, Randomized, Dose-Escalation Study☆

Heino Stass, MD[1]; Boris Weimann[2]; Johannes Nagelschmitz, PhD, MD[1]; Claudia Rolinck-Werninghaus, MD[3]; and Doris Staab, MD[3]

[1]Bayer Pharma AG, Global Drug Discovery, Development Clinical Pharmacology, Cardiovascular/Primary Care, Wuppertal, Germany; [2]Chrestos Concept GmbH & Co. KG, Ratingen, Germany; and [3]Pediatric Pneumology and Immunology, Charité University Hospital, Berlin, Germany

- Paciente FQ 18-60 años. Colonización por PA. Estables.
- FEV1≥30%. BMI 16-30 Kg/m^2
- Aleatorizado, simple ciego, control (placebo), dosis múltiples.

Ciprofloxacino inhalado en polvo seco

- Resultados: Efectos adversos

Table II. Summary of treatment-emergent adverse events (TEAEs) in this study of the tolerability and pharmacokinetic properties of ciprofloxacin dry powder for inhalation (DPI) 32.5 mg qd, 65 mg qd, and 32.5 mg bid in patients with cystic fibrosis (safety population, n = 25).*

	Ciprofloxacin DPI			
Parameter, no. (%)	32.5 mg qd (n = 6)	65 mg qd (n = 6)	32.5 mg bid (n = 6)	Placebo (n = 7)
Any TEAE	6 (100)	6 (100)	5 (83)	7 (100)
Dysgeusia†	6 (100)	6 (100)	5 (83)	3 (43)
Bronchospasm	4 (67)‡	3 (50)	2 (33)§	3 (43)§
Cough	2 (33)	0	0	1 (14)
Upper respiratory tract infection	1 (17)	1 (17)	1 (17)	0
Lung infection	1 (17)	0	1 (17)	0
Blood creatine phosphokinase increased	1 (17)	0	0	2 (29)
Throat irritation	1 (17)	0	0	1 (14)
Headache	0	1 (17)	2 (33)§	3 (43)

Ciprofloxacino inhalado en polvo seco

Eur Respir J. 2013 May;41(5):1107-15. doi: 10.1183/09031936.00071312. Epub 2012 Sep 27.

Ciprofloxacin dry powder for inhalation in non-cystic fibrosis bronchiectasis: a phase II randomised study.

Wilson R[1], Welte T, Polverino E, De Soyza A, Greville H, O'Donnell A, Alder J, Reimnitz P, Hampel B.

⊕ Author information

Abstract

This phase II, randomised, double-blind, multicentre study (NCT00930982) investigated the safety and efficacy of ciprofloxacin dry powder for inhalation (DPI) in patients with non-cystic fibrosis bronchiectasis. Adults who were culture positive for pre-defined potential respiratory pathogens (including Pseudomonas aeruginosa and Haemophilus influenzae) were randomised to ciprofloxacin DPI 32.5 mg or placebo administered twice daily for 28 days (with 56 days of follow-up). Bacterial density in sputum (primary end-point), pulmonary function tests, health-related quality of life and safety were monitored throughout the study. 60 subjects received ciprofloxacin DPI 32.5 mg and 64 received placebo. Subjects on ciprofloxacin DPI had a significant reduction ($p<0.001$) in total sputum bacterial load at the end of treatment (-3.62 log10 CFU·g(-1) (range -9.78-5.02 log10 CFU·g(-1))) compared with placebo (-0.27 log10 CFU·g(-1) (range -7.96-5.25 log10 CFU·g(-1))); the counts increased thereafter. In the ciprofloxacin DPI group, 14 (35%) out of 40 subjects reported pathogen eradication at end of treatment versus four (8%) out of 49 in the placebo group ($p=0.001$). No abnormal safety results were reported and rates of bronchospasm were low. Ciprofloxacin DPI 32.5 mg twice daily for 28 days was well tolerated and achieved significant reductions in total bacterial load compared with placebo in subjects with non-cystic fibrosis bronchiectasis.

Glucopéptidos

Vancomicina inhalada

Aerosolized Vancomycin for the Treatment of Methicillin-Resistant *Staphylococcus aureus* Infection in Cystic Fibrosis

Luis Máiz, MD, PhD,[1*] **Rafael Cantón**, PD, PhD,[2] **Nuria Mir**, PD,[2] **Fernando Baquero**, MD, PhD,[2] and **Héctor Escobar**, MD, PhD[1]

Pediatric Pulmonology 26:287–289 (1998)

- 250 g Vancomicina en 4 ml agua destilada cada 12 horas (Venstream jet nebulizer + CR-60)
- Mejoría clínica, de la función pulmonar y redujo en nº de colonias (No consiguió erradicación).
- No resistencias.

Vancomicina inhalada en polvo seco. Aerovanc™

- Vancomicina en polvo seco (cápsula)
- AeroVanc™ (Savara Pharmaceuticals)
- Podría aportar buena eficacia clínica y reducir los efectos adversos de la adminsitración ev
- No aprovada por la FDA

Vancomicina inhalada en polvo seco. Aerovanc™

- EC fase I
- Múltiples dosis
- Voluntarios sanos y pacientes con FQ
- Resultados no publicados

Enrollment:	25
Study Start Date:	November 2011
Study Completion Date:	March 2012
Primary Completion Date:	March 2012 (Final data collection date for primary outcome measure)

Arms
Experimental: Aerovanc 16 mg in healthy volunteers
Experimental: AeroVanc 32 mg in healthy volunteers
Experimental: AeroVanc 80 mg in healthy volunteers
Active Comparator: IV vancomycin in healthy volunteers
Experimental: AeroVanc 32 mg in CF patients
Experimental: AeroVanc 80 mg in CF patients

http://www.clinicaltrials.gov/ct2/show/results/NCT01537666?sect=X0125

Vancomicina inhalada en polvo seco. Aerovanc™

- Actualmente ensayo clínico en Fase II, randomizado, doble ciego y control con placebo en pacientes con FQ colonizados por MRSA.

Vancomicina inhalada en polvo seco. Aerovanc™

Primary Outcome Measures:

- Change from Baseline at Day 29 of the dosing period (start of AeroVanc/Placebo administration is considered Day 1 of the dosing period) in the number of MRSA colony forming units (CFU) in sputum culture. [Time Frame: Day 29 of treatment period] [Designated as safety issue: No]

Secondary Outcome Measures:

- Change from Baseline in each pulmonary function test (PFT) [Time Frame: Days 8, 15 and 29 of treatment period] [Designated as safety issue: Yes]
- Change from Baseline in Cystic Fibrosis Respiratory Symptom Diary (CF-RSD) scores. [Time Frame: Days 8, 15 and 29 of treatment period] [Designated as safety issue: No]
- Change from Baseline in MRSA sputum density. [Time Frame: Days 8 and 15 of treatment period] [Designated as safety issue: No]
- Time from start of dosing to first administration of other antimicrobial medications (oral, intravenous and/or inhaled) due to respiratory symptoms. [Time Frame: Entire study: Day 1 of treatment period through 8 week post-treamtent follow up visit] [Designated as safety issue: No]
- Time from start of dosing to exacerbation of signs/symptoms (Fuchs criteria). [Time Frame: Entire study: Day 1 of treatment period through 8 week post-treamtent follow up visit] [Designated as safety issue: No]
- Change from Baseline in high sensitivity CRP and blood neutrophils [Time Frame: Day 29 of the dosing period] [Designated as safety issue: Yes]

Estimated Enrollment:	80
Study Start Date:	March 2013
Estimated Study Completion Date:	September 2014
Estimated Primary Completion Date:	September 2014 (Final data collection date for primary outcome measure)

Conclusiones

- Tratamiento actual FQ → Pronóstico
- La fisioterapia respiratoria y el tratamiento antibiótico siguen siendo cruciales.
- Terapia ATB inhalada: Presente
  - Más formulaciones para inhalación
  - Formulaciones en polvo seco
- Futuro más esperanzador: fármacos moduladores CFRT – Terapia génica?