Aérosols d’antibiotiques et maladies bronchiques suppuratives

Patrice Diot, Tours

Problématiques de l’antibiothérapie inhalée

- Les molécules/dispositifs
- Les indications

Les molécules ayant l'AMM

DCI / spécialité	Volume unitaire	Classe thérapeutique
terbutaline (BRICANYL®)	2 ml	bronchodilatateur
salbutamol (VENTOLINE®)	2,5 ml	bronchodilatateur
ipratropium (ATROVENT®)	1 ou 2 ml	bronchodilatateur
budésonide (PULMICORT®)	2 ml	corticoïde
beclometasone (BECLOSPIN®)	1 ou 2 ml	corticoïde
cromoglycate de sodium (LOMUDAL®)	2 ml	anti-allergique
pentamidine (PENTACARINAT®)	6 ml	antibiotique
tobramycine (TOBI®)	5 ml et poudre	antibiotique
colistine (COLIMYCINE®)	3 ml et poudre	antibiotique
aztreonam lysine (CAYSTON®)	1 ml	antibiotique
dornase alfa (PULMOZYME®)	2,5 ml	mucolytique
iloprost (VENTAVIS®)	2 ml	traitement HTAP
melaleuca viridiflora (GOMENOL®)	5 ml	décongestionnant ORL

Les molécules/dispositifs en développement

- Amikacine ± liposomale (Transave)
- Ciprofloxacine liposomale (Aradigm) ou poudre (Bayer)
- Levofloxacine (MP-376) (MPEX)
- Azithromycine (Int J Pharmaceutics 2010; 395: 205-214)
- Telithromycine (Drug Dev Indust Pharmacy 2010; 36: 861-6)
- Tobramycine/Fosfomycine (Gilead)
- Gentamycine, Ceftazidime, Cefotaxime, Carbenicilline, Amoxicilline, Vancomycine
- …

Aérosols d'antibiotiques

Domaines d'application en pratique clinique

- Mucoviscidose
- Bronchectasies hors mucoviscidose
- Pneumonies et ventilation assistée
- Pneumonies nosocomiales

Inhaled medication and inhalation devices for lung disease in patients with cystic fibrosis: A European consensus ☆

Harry Heijerman *, Elsbeth Westerman, Steven Conway, Daan Touw
Gerd Döring for the consensus working group [1]

Journal of Cystic Fibrosis 8 (2009) 295–315

Journal of Cystic Fibrosis

Inhaled medication and inhalation devices for lung disease in patients with cystic fibrosis: A European consensus ☆

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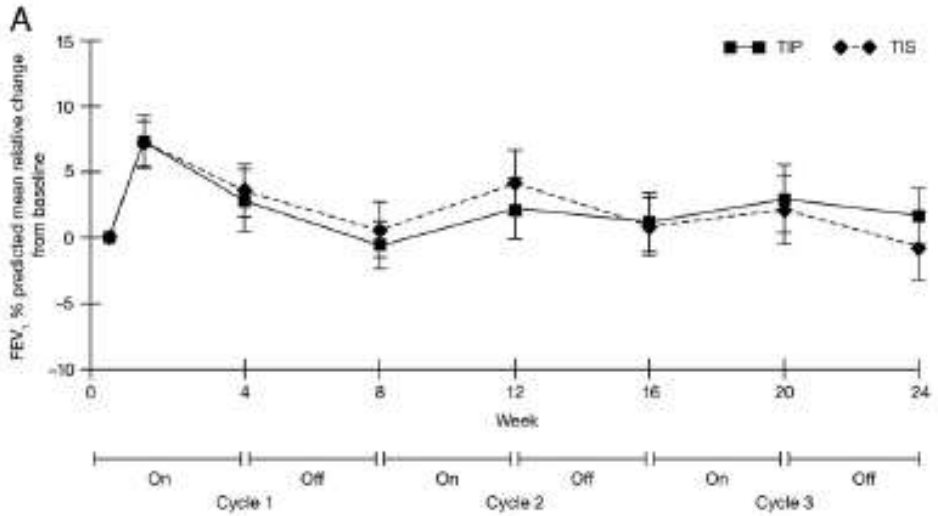
Q7 Which inhaled antibiotics can be recommended?

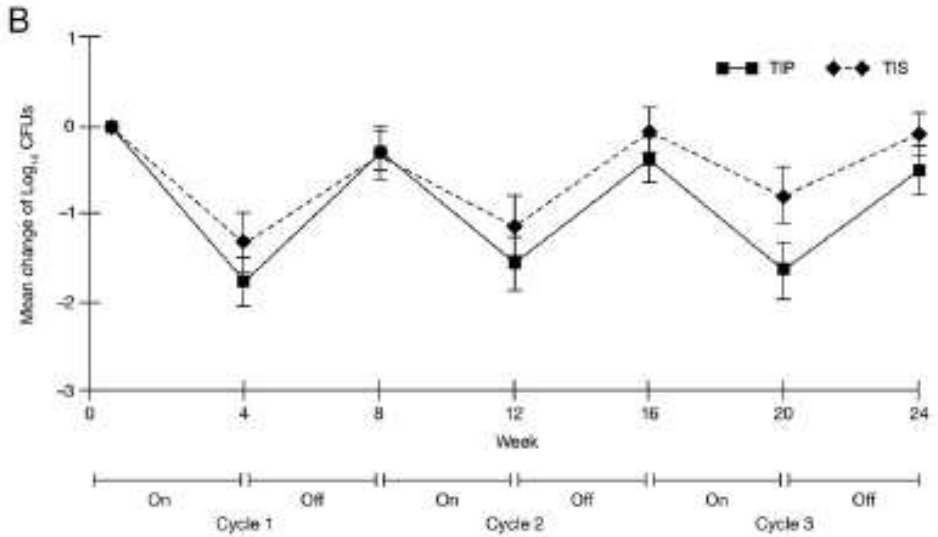
Tobramycin [A] and colistimethate sodium [B] preparations for inhalation are recommended. Microbiological breakpoints for systemic infections (susceptible, intermediate, resistant) do not predict the clinical efficacy of inhaled antibiotics [B].

Journal of Cystic Fibrosis 8 (2009) 295–315

Journal of Cystic Fibrosis

Safety, efficacy and convenience of tobramycin inhalation powder in cystic fibrosis patients: The EAGER trial





TIP: poudre, 112 mg X 2

TIS: solution pour nébulisation, 300 mg X 2

Journal of Cystic Fibrosis

Journal of Cystic Fibrosis xx (2010) xxx – xxx

Safety, efficacy and convenience of colistimethate sodium dry powder for inhalation (Colobreathe DPI) in patients with cystic fibrosis: a randomised study

Antje Schuster,[1] Cynthia Haliburn,[2] Gerd Döring,[3] Martin Harris Goldman,[4] for the Freedom Study Group

Schuster A, *et al*. *Thorax* 2013;**68**:344–350.

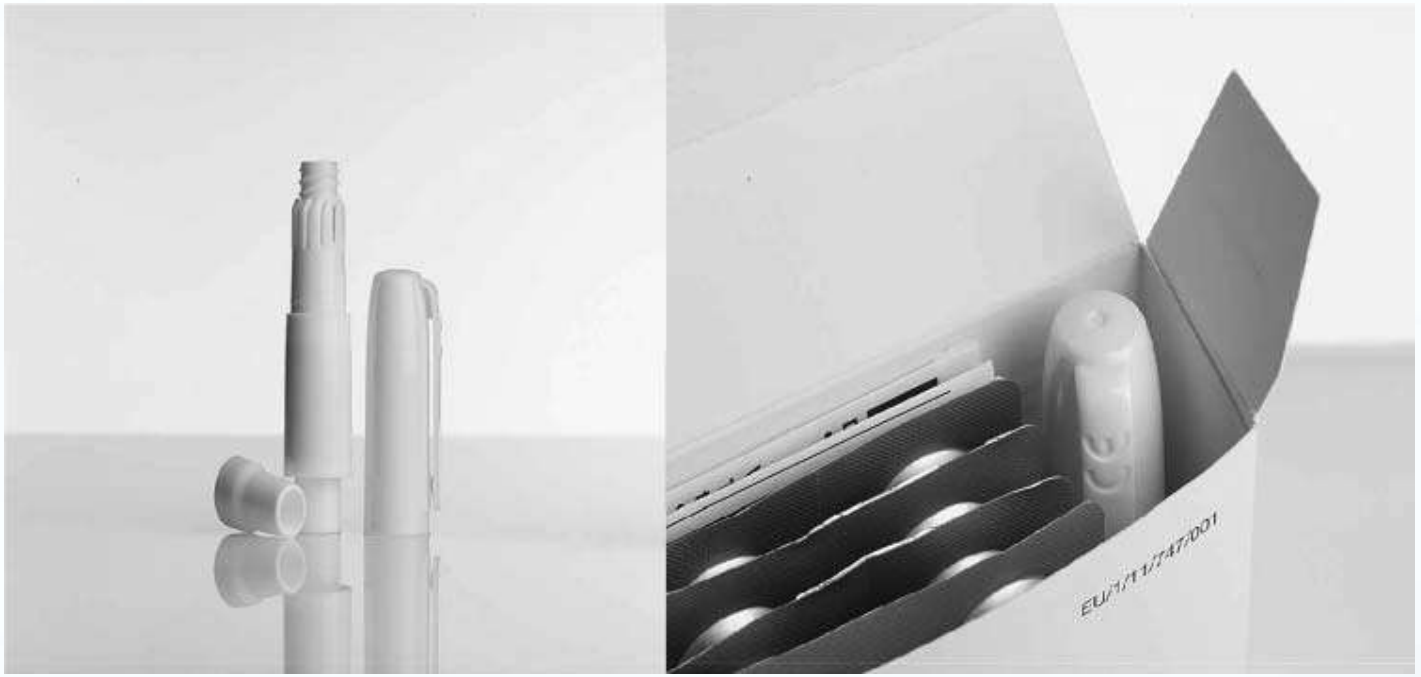


Figure 1 Turbospin® inhaler and appearance of Colobreathe packaging.

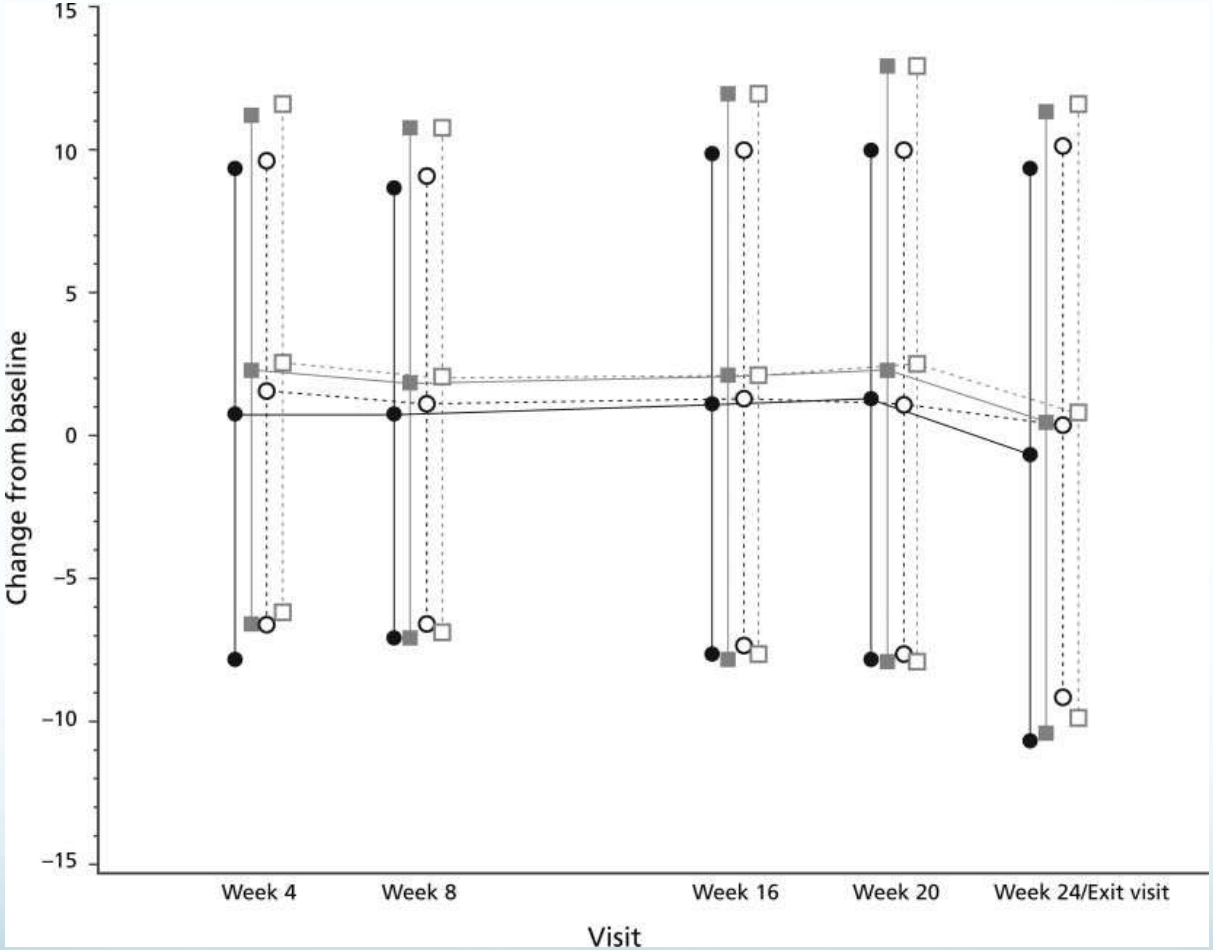


Figure 3 Forced expiratory volume in 1 s % predicted change from baseline (intention-to-treat population). ●—●—●= Colobreathe dry powder for inhalation (CDPI) group; ■—■—■= tobramycin inhaler solution (TIS) group; ○- -○- -○= CDPI completed patients; □- -□- -□= TIS completed patients.

Inhaled medication and inhalation devices for lung disease in patients with cystic fibrosis: A European consensus ☆

Harry Heijerman *, Elsbeth Westerman, Steven Conway, Daan Touw
Gerd Döring for the consensus working group [1]

Q12 Are novel inhaled antibiotics for the treatment of *P. aeruginosa* and other CF-related bacterial pathogens needed?

For the treatment of *P. aeruginosa* and other CF-related bacterial pathogens new developments of inhaled antibiotics are urgently needed, since tobramycin and colistimethate sodium are not sufficiently effective and are not tolerated by all CF patients.

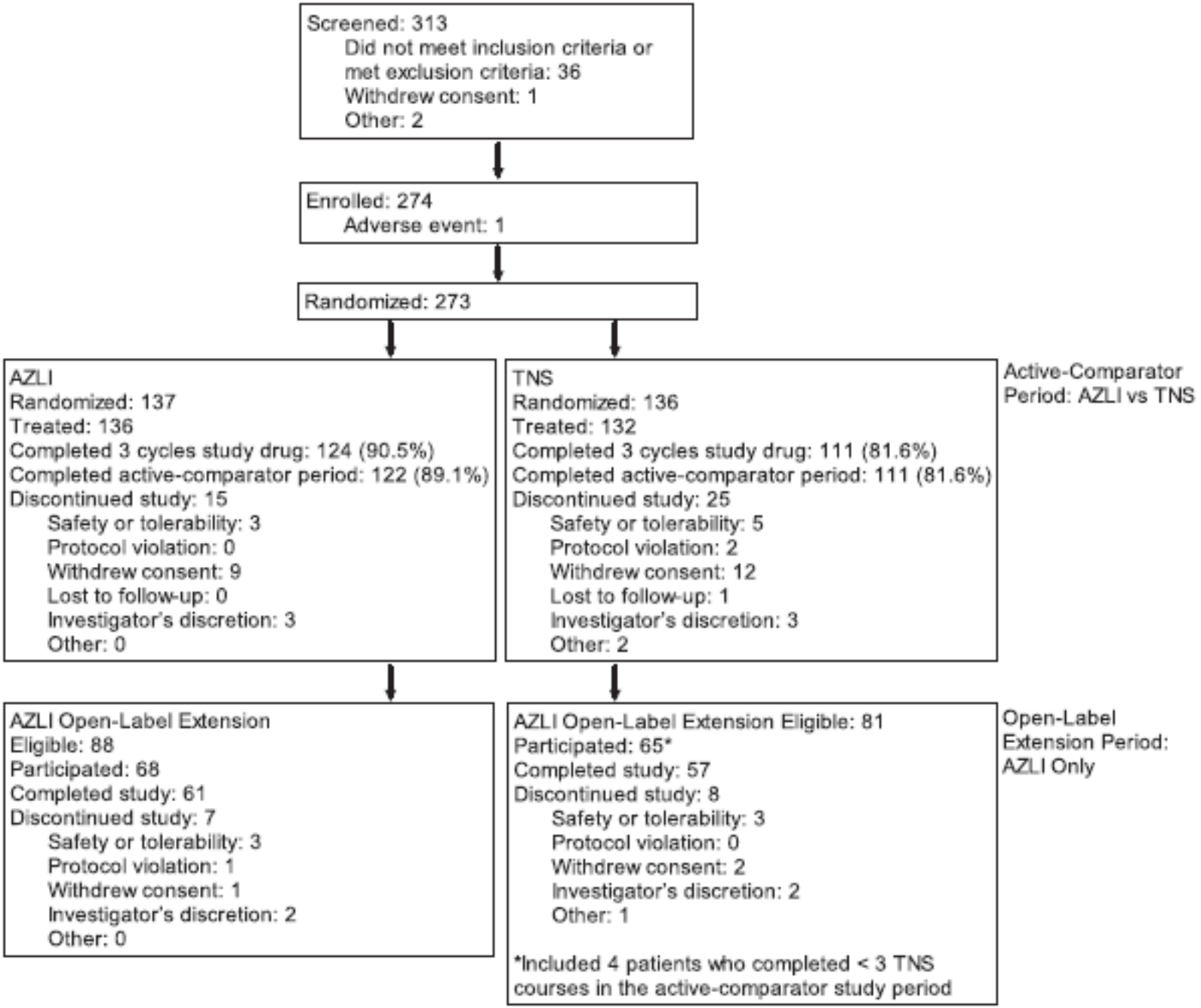
Journal of Cystic Fibrosis 8 (2009) 295–315

Journal of Cystic Fibrosis

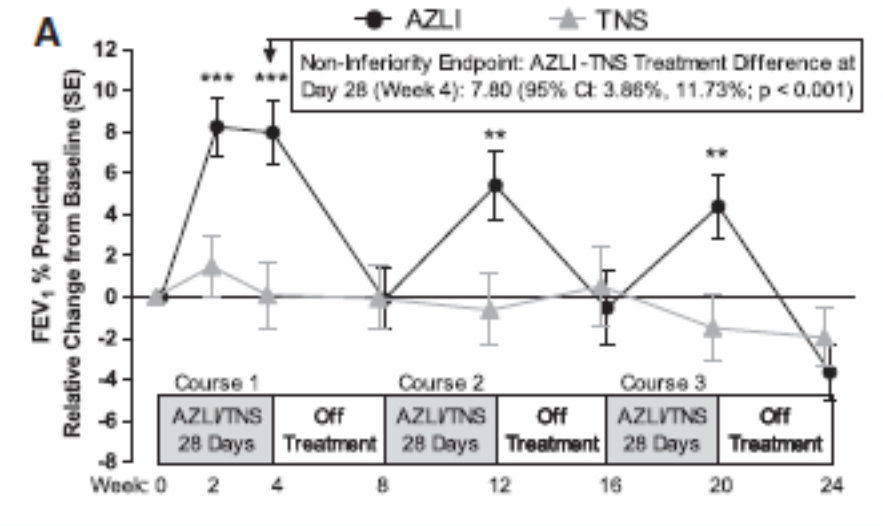
Inhaled aztreonam lysine vs. inhaled tobramycin in cystic fibrosis: A comparative efficacy trial☆

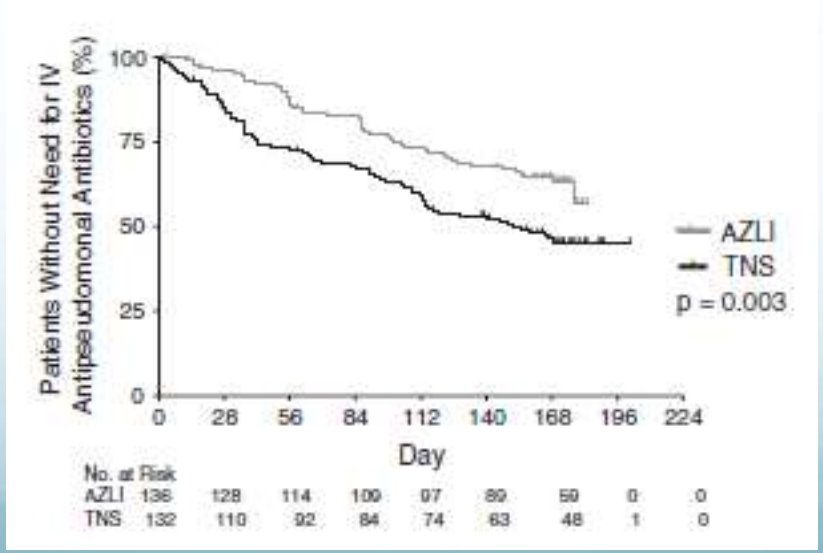
Baroukh M. Assael [a,*], Tacjana Pressler [b], Diana Bilton [c], Michael Fayon [d], Rainald Fischer [e], Raphael Chiron [f], Mario LaRosa [g], Christiane Knoop [h], Noel McElvaney [i], Sandra A. Lewis [j], Mark Bresnik [k], A. Bruce Montgomery [j], Christopher M. Oermann [l]
For the AZLI Active Comparator Study Group [l]

Journal of Cystic Fibrosis 12 (2013) 130–140


Screened: 313
Did not meet inclusion criteria or met exclusion criteria: 36
Withdrew consent: 1
Other: 2
Enrolled: 274
Adverse event: 1
Randomized: 273
AZLI
Randomized: 137
Treated: 136
Completed 3 cycles study drug: 124 (90.5%)
Completed active-comparator period: 122 (89.1%)
Discontinued study: 15
Safety or tolerability: 3
Protocol violation: 0
Withdrew consent: 9
Lost to follow-up: 0
Investigator's discretion: 3
Other: 0
TNS
Randomized: 136
Treated: 132
Completed 3 cycles study drug: 111 (81.6%)
Completed active-comparator period: 111 (81.6%)
Discontinued study: 25
Safety or tolerability: 5
Protocol violation: 2
Withdrew consent: 12
Lost to follow-up: 1
Investigator's discretion: 3
Other: 2
Active-Comparator Period: AZLI vs TNS
AZLI Open-Label Extension
Eligible: 88
Participated: 68
Completed study: 61
Discontinued study: 7
Safety or tolerability: 3
Protocol violation: 1
Withdrew consent: 1
Investigator's discretion: 2
Other: 0
AZLI Open-Label Extension Eligible: 81
Participated: 65*
Completed study: 57
Discontinued study: 8
Safety or tolerability: 3
Protocol violation: 0
Withdrew consent: 2
Investigator's discretion: 2
Other: 1
*Included 4 patients who completed < 3 TNS courses in the active-comparator study period
Open-Label Extension Period: AZLI Only

Inhaled aztreonam lysine vs. inhaled tobramycin in cystic fibrosis: A comparative efficacy trial☆



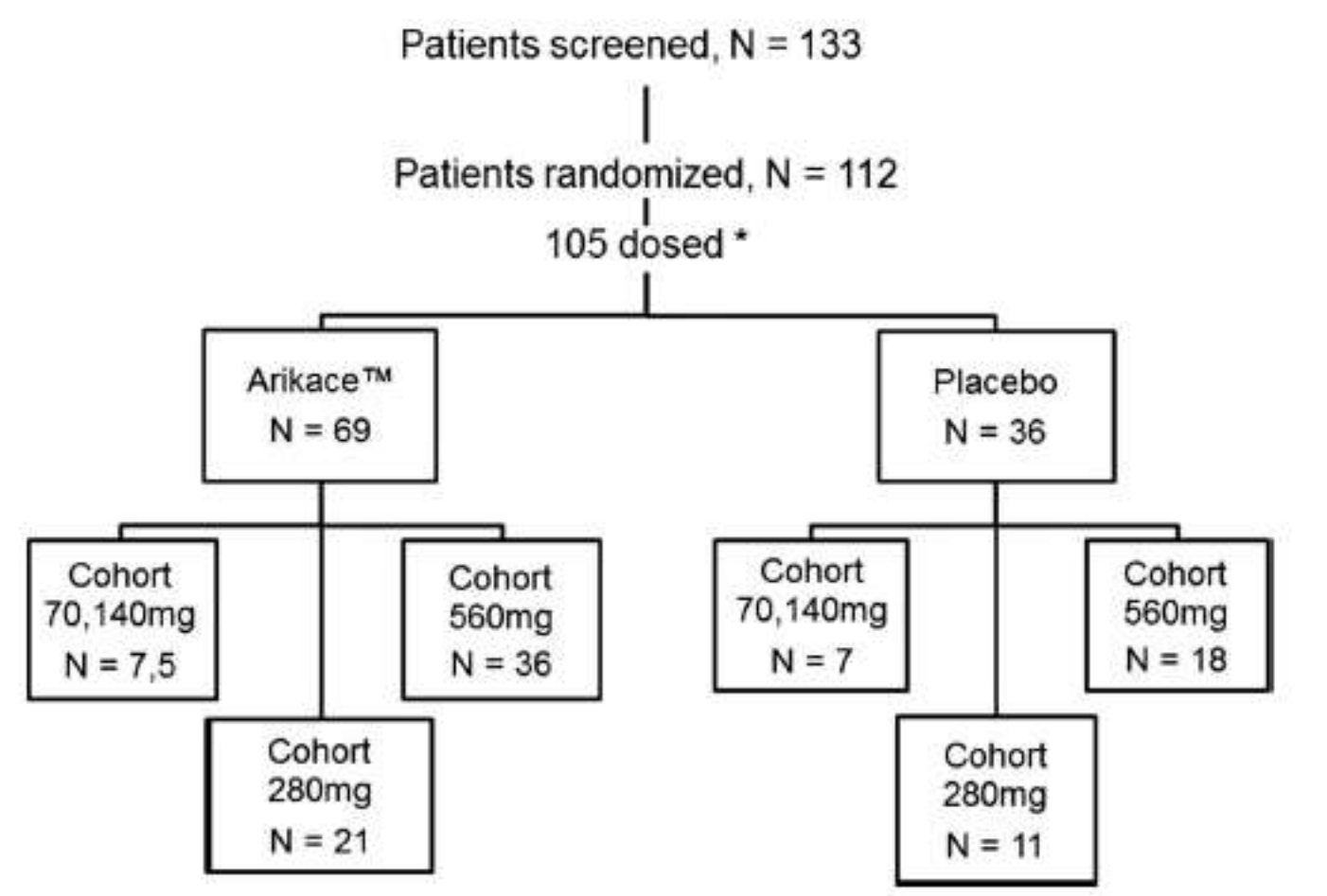


Phase II studies of nebulised Arikace in CF patients with *Pseudomonas aeruginosa* infection

J P Clancy,[1] L Dupont,[2] M W Konstan,[3] J Billings,[4] S Fustik,[5] C H Goss,[6] J Lymp,[7] P Minic,[8] A L Quittner,[9] R C Rubenstein,[10] K R Young,[11] L Saiman,[12] J L Burns,[6] J R W Govan,[13] B Ramsey,[6] R Gupta,[14] for the Arikace Study Group

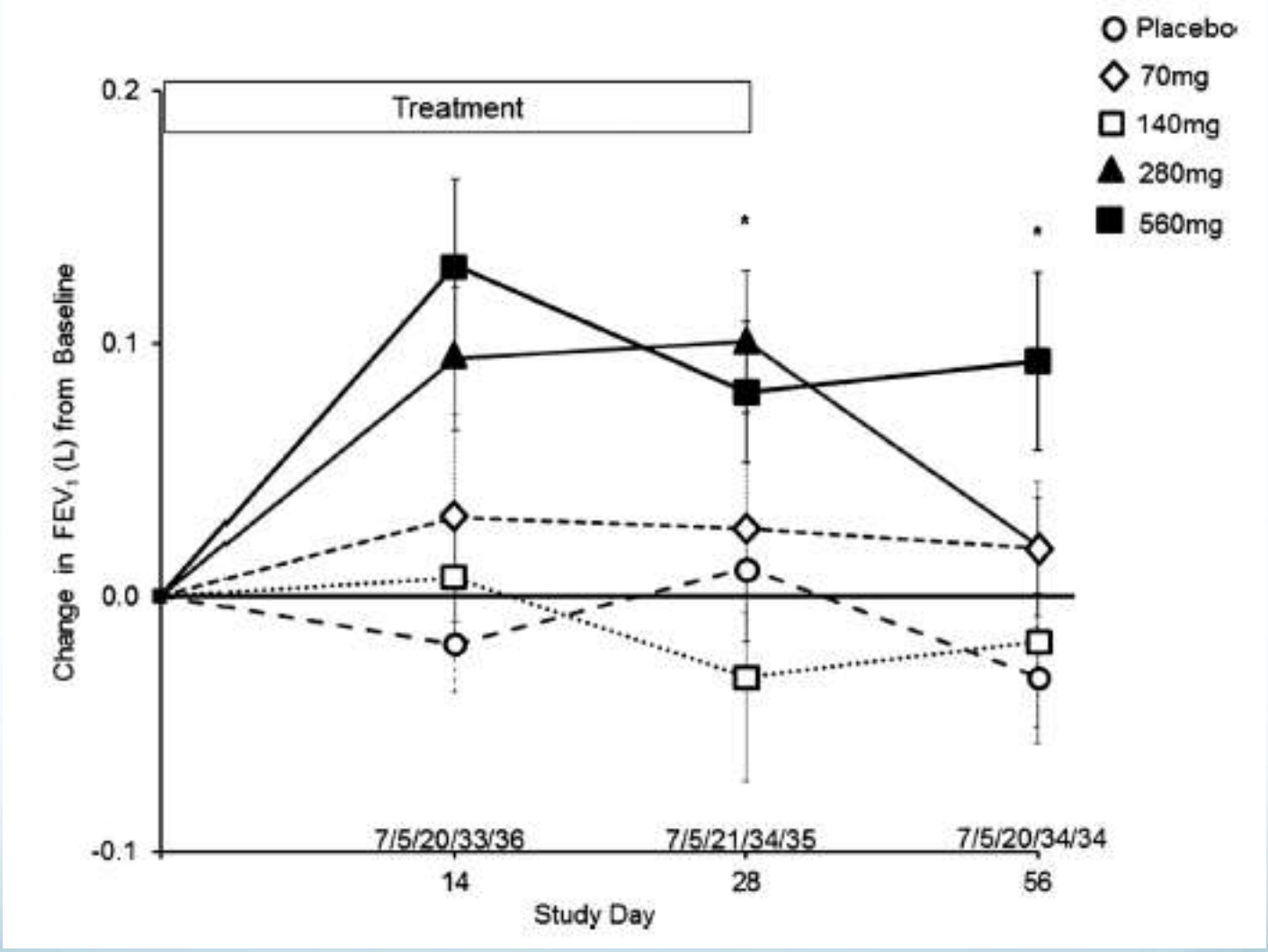
Clancy JP, *et al*. *Thorax* 2013;**68**:818–825.

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



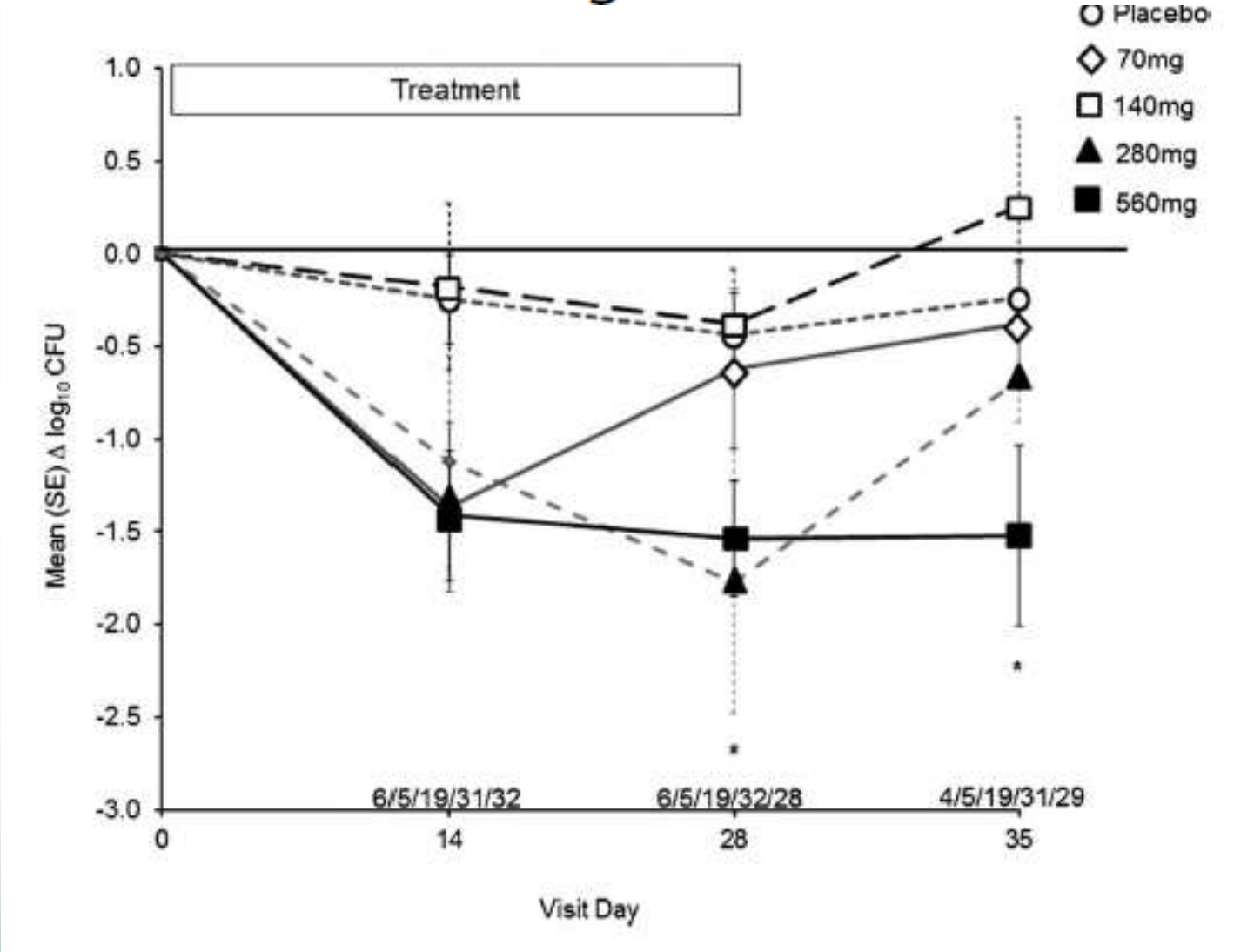
Clancy JP, *et al*. *Thorax* 2013;**68**:818–825.

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

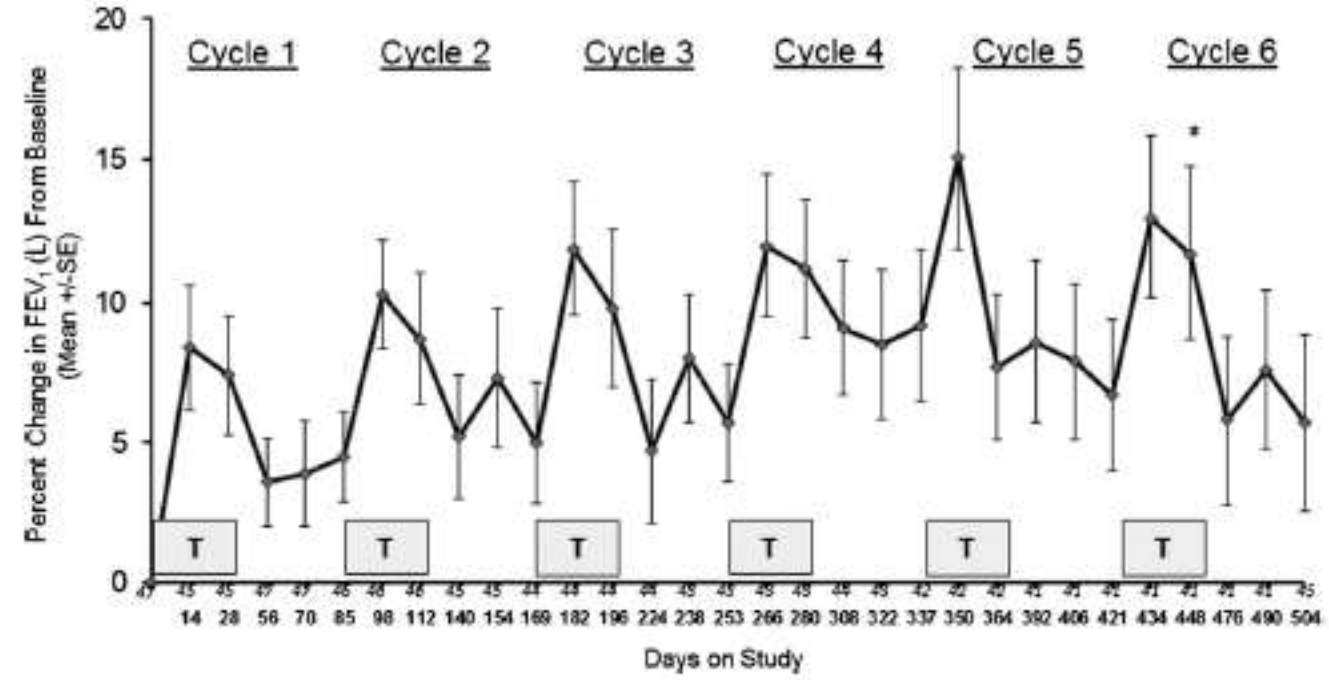


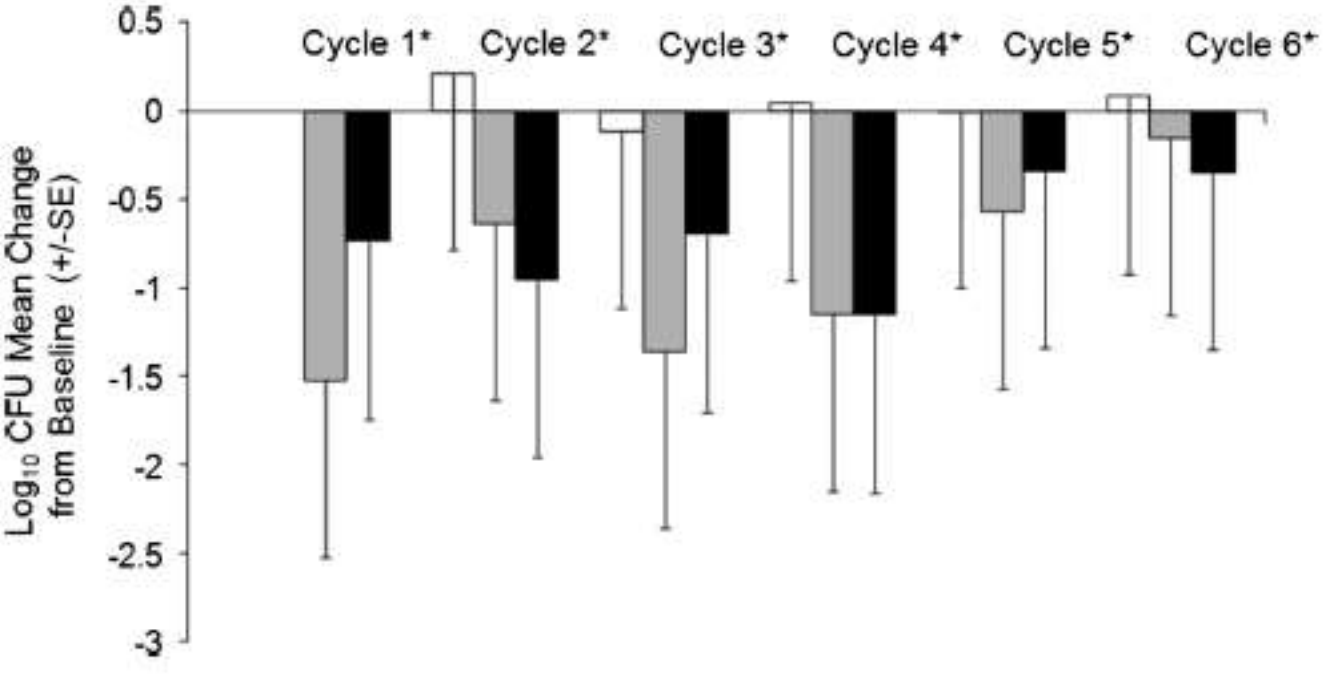
Clancy JP, *et al*. *Thorax* 2013;**68**:818–825.

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



Clancy JP, *et al*. *Thorax* 2013;**68**:818–825.


Cycle 1
Cycle 2
Cycle 3
Cycle 4
Cycle 5
Cycle 6
Percent Change in FEV1 (L) From Baseline (Mean +/-SE)
20
15
10
5
0
T
*
14 28 56 70 85 98 112 140 154 169 182 196 224 238 253 266 280 308 322 337 350 364 392 406 421 434 448 476 490 504
Days on Study


Cycle 1*
Cycle 2*
Cycle 3*
Cycle 4*
Cycle 5*
Cycle 6*
Log10 CFU Mean Change from Baseline (+/-SE)
0.5
0
-0.5
-1
-1.5
-2
-2.5
-3

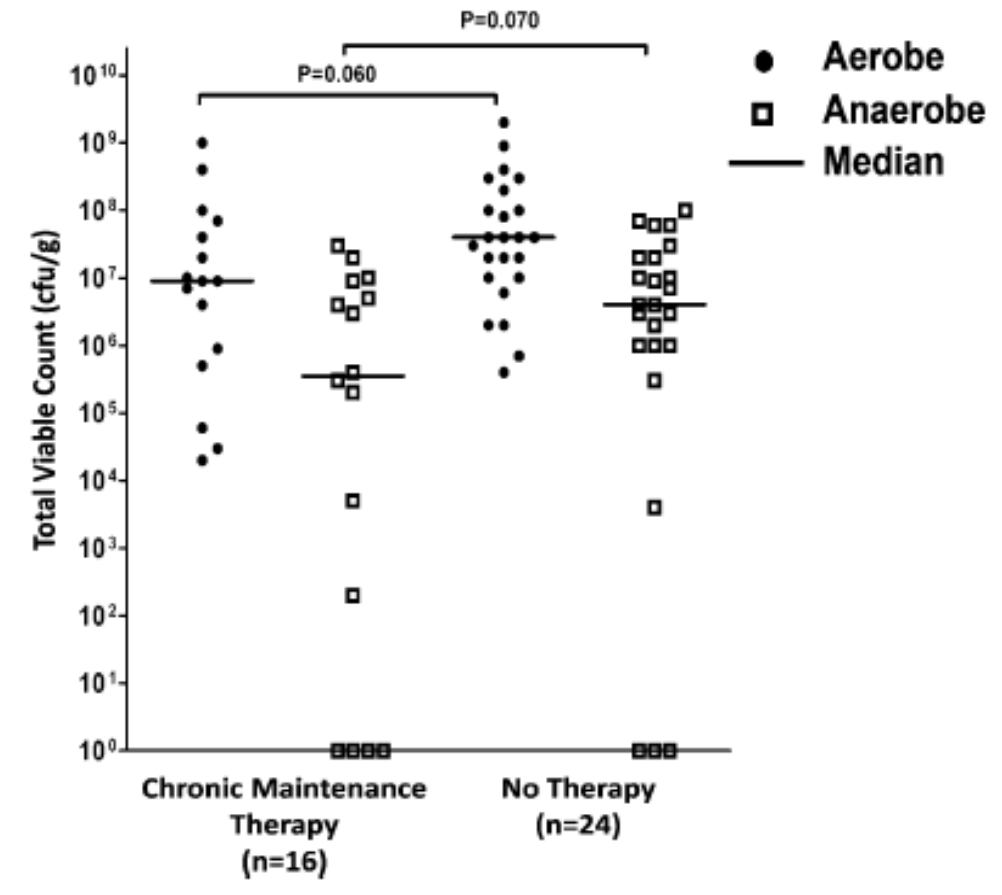
L' antibiothérapie inhalée dans les DDB hors mucoviscodose: rationnel 1

Lung Microbiota and Bacterial Abundance in Patients with Bronchiectasis when Clinically Stable and during Exacerbation

Michael M. Tunney[1,2*], Gisli G. Einarsson[1,2*], Lan Wei[1,2], Maire Drain[3], Erich R. Klem[4], Chris Cardwell[5], Madeleine Ennis[3], Richard C. Boucher[4], Matthew C. Wolfgang[4,6], and J. Stuart Elborn[1,3*]

Am J Respir Crit Care Med Vol 187, Iss. 10, pp 1118–1126, May 15, 2013

Lung Microbiota and Bacterial Abundance in Patients with Bronchiectasis when Clinically Stable and during Exacerbation



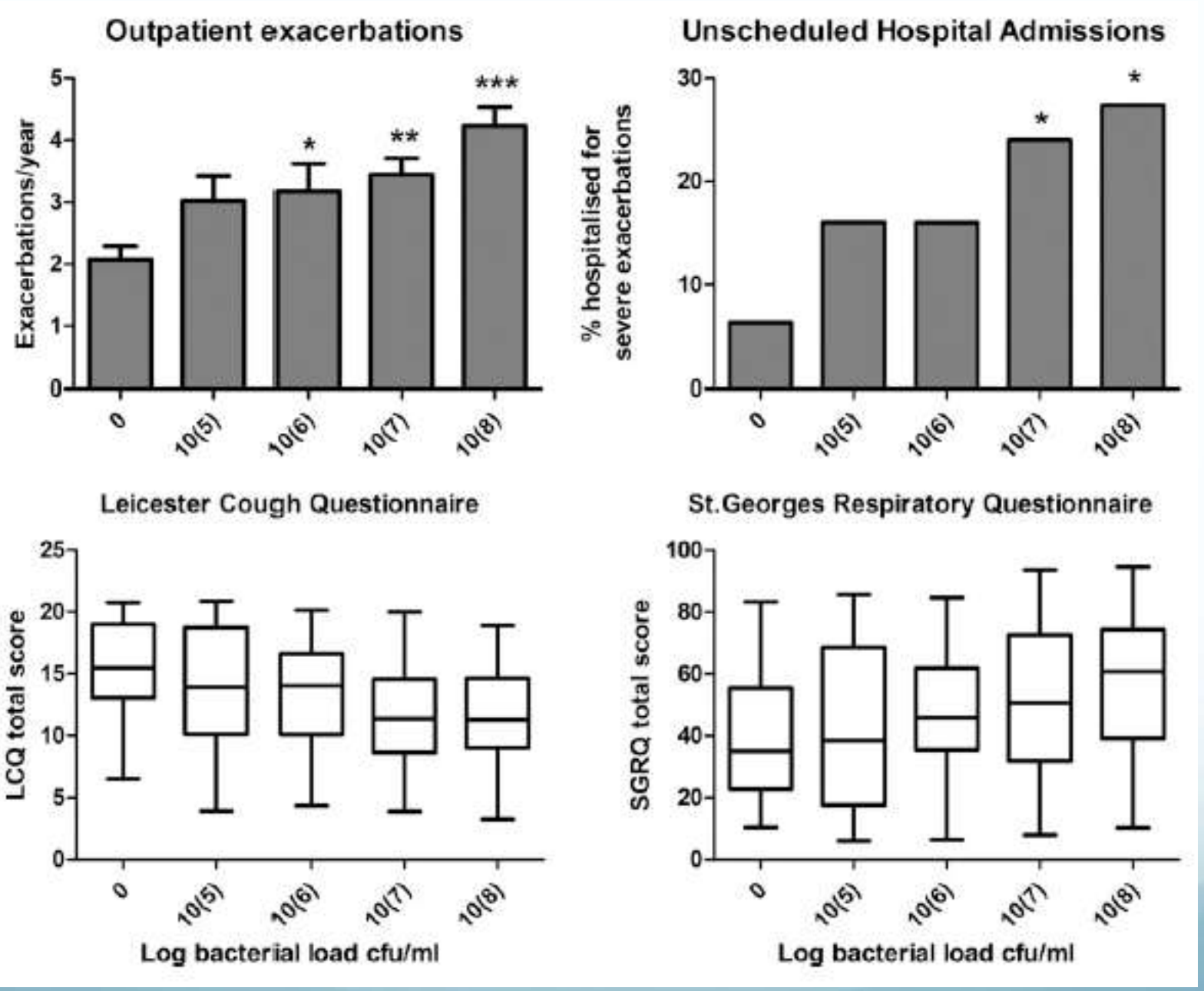
Am J Respir Crit Care Med Vol 187, Iss. 10, pp 1118–1126,

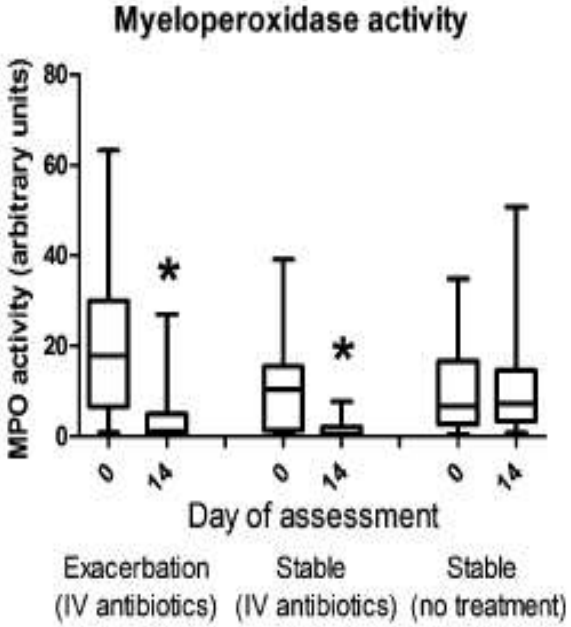
L’antibiothérapie inhalée dans les DDB hors mucoviscodose: rationnel 2

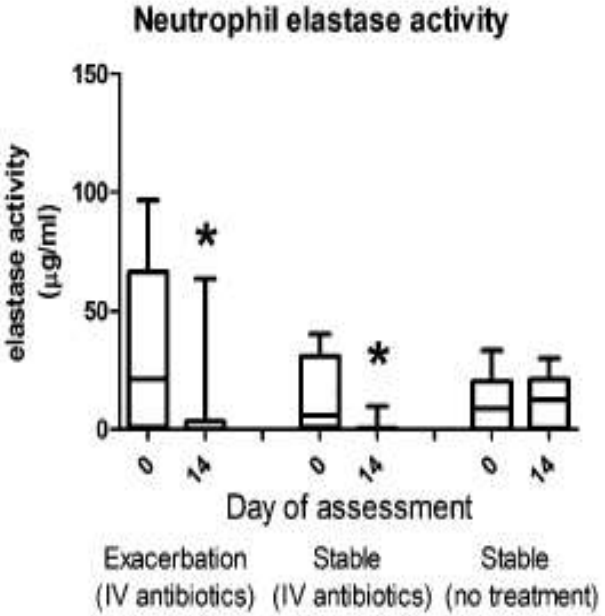
Short- and Long-Term Antibiotic Treatment Reduces Airway and Systemic Inflammation in Non–Cystic Fibrosis Bronchiectasis

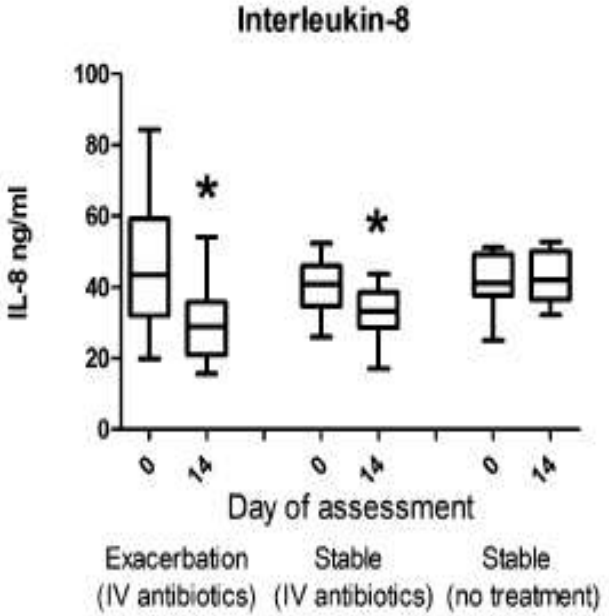
James D. Chalmers[1], Maeve P. Smith[2], Brian J. McHugh[1], Cathy Doherty[3], John R. Govan[3], and Adam T. Hill[1,2]

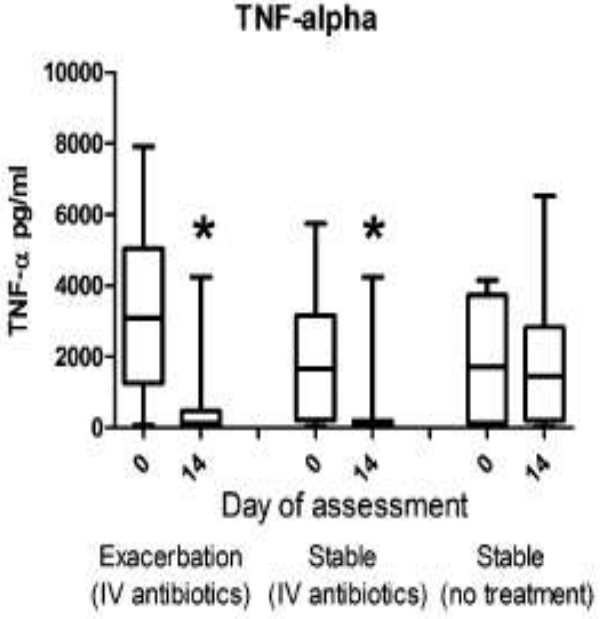
Am J Respir Crit Care Med Vol 186, Iss. 7, pp 657–665, Oct 1, 2012

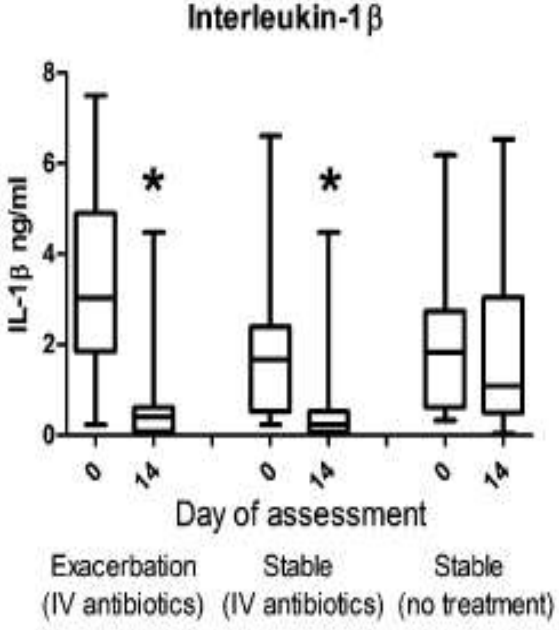

Outpatient exacerbations
Exacerbations/year
0
1
2
3
4
5
*
**
***
0
10(5)
10(6)
10(7)
10(8)
Unscheduled Hospital Admissions
% hospitalised for severe exacerbations
0
10
20
30
*
*
0
10(5)
10(6)
10(7)
10(8)
Leicester Cough Questionnaire
LCQ total score
0
5
10
15
20
25
0
10(5)
10(6)
10(7)
10(8)
Log bacterial load cfu/ml
St.Georges Respiratory Questionnaire
SGRQ total score
0
20
40
60
80
100
0
10(5)
10(6)
10(7)
10(8)
Log bacterial load cfu/ml

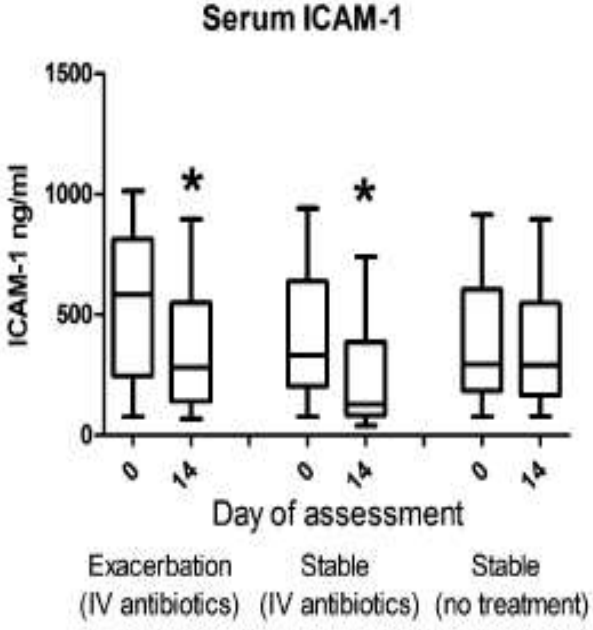

Myeloperoxidase activity
MPO activity (arbitrary units)
80
60
40
20
0
0
14
0
14
0
14
Day of assessment
Exacerbation (IV antibiotics)
Stable (IV antibiotics)
Stable (no treatment)


Neutrophil elastase activity
elastase activity (μg/ml)
150
100
50
0
0
14
0
14
0
14
Day of assessment
Exacerbation (IV antibiotics)
Stable (IV antibiotics)
Stable (no treatment)


Interleukin-8
IL-8 ng/ml
100
80
60
40
20
0
0
14
0
14
0
14
Day of assessment
Exacerbation (IV antibiotics)
Stable (IV antibiotics)
Stable (no treatment)


TNF-alpha
TNF-α pg/ml
10000
8000
6000
4000
2000
0
0
14
0
14
0
14
Day of assessment
Exacerbation (IV antibiotics)
Stable (IV antibiotics)
Stable (no treatment)


Interleukin-1β
IL-1β ng/ml
8
6
4
2
0
0
14
0
14
0
14
Day of assessment
Exacerbation (IV antibiotics)
Stable (IV antibiotics)
Stable (no treatment)

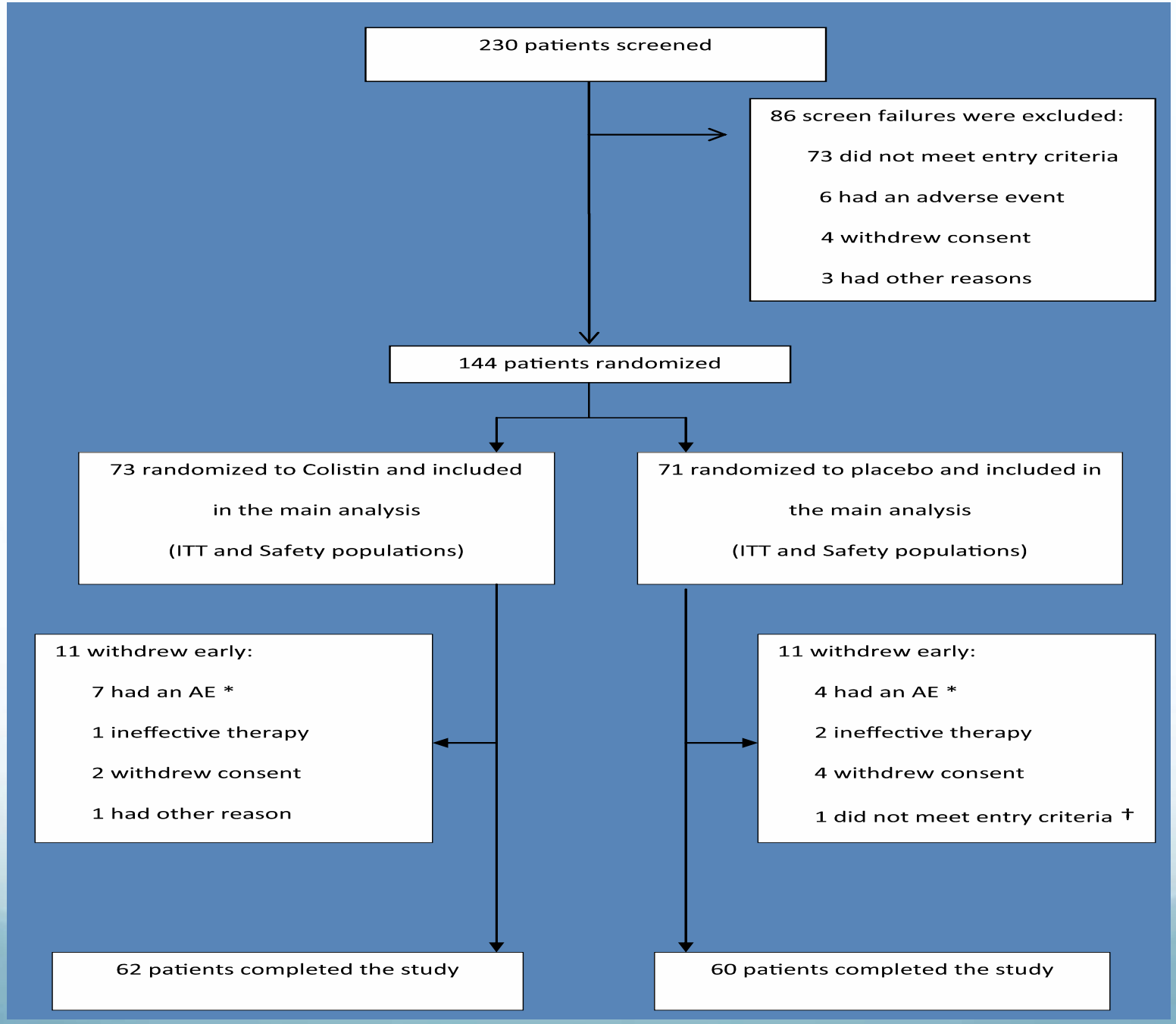

Serum ICAM-1
ICAM-1 ng/ml
1500
1000
500
0
0
14
0
14
0
14
Day of assessment
Exacerbation (IV antibiotics)
Stable (IV antibiotics)
Stable (no treatment)

Inhaled Colistin in Patients with Bronchiectasis and Chronic Pseudomonas aeruginosa Infection

Charles S. Haworth[1], Juliet E. Foweraker[2], Peter Wilkinson[3], Robert F. Kenyon[4], and Diana Bilton[5]

[1]Cambridge Centre for Lung Infection and [2]Department of Microbiology, Papworth Hospital, Cambridge, United Kingdom; [3]Wilkinson Associates, Radnage, Bucks, United Kingdom; [4]Profile Pharma Ltd., Tangmere, Chichester, West Sussex, United Kingdom; and [5]Host Defence Unit, Royal Brompton Hospital, London, United Kingdom

American Journal of Respiratory and Critical Care Medicine Volume 189 Number 8 | April 15 2014


230 patients screened
86 screen failures were excluded:
73 did not meet entry criteria
6 had an adverse event
4 withdrew consent
3 had other reasons
144 patients randomized
73 randomized to Colistin and included in the main analysis (ITT and Safety populations)
71 randomized to placebo and included in the main analysis (ITT and Safety populations)
11 withdrew early:
7 had an AE *
1 ineffective therapy
2 withdrew consent
1 had other reason
11 withdrew early:
4 had an AE *
2 ineffective therapy
4 withdrew consent
1 did not meet entry criteria †
62 patients completed the study
60 patients completed the study

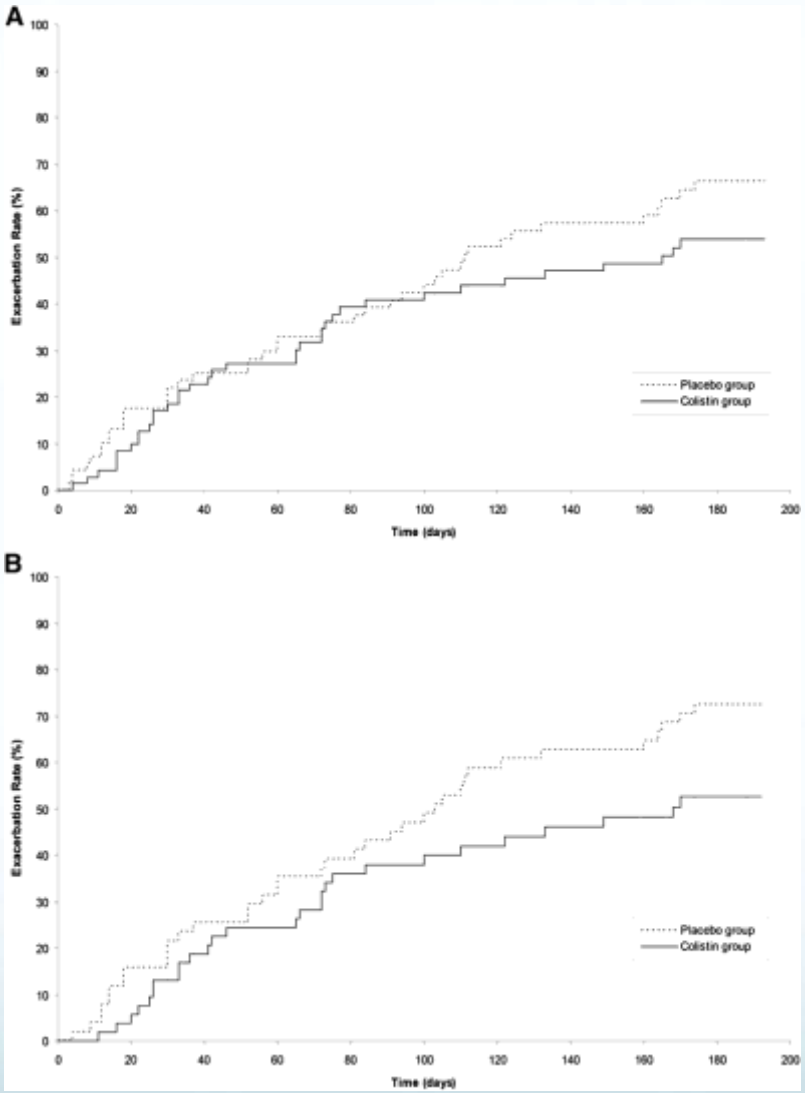


Figure 2. Kaplan-Meier plot of estimate of time to first exacerbation within (*A*) the whole intention-to-treat population, and (*B*) adherence quartiles 2–4 of the intention-to-treat population.

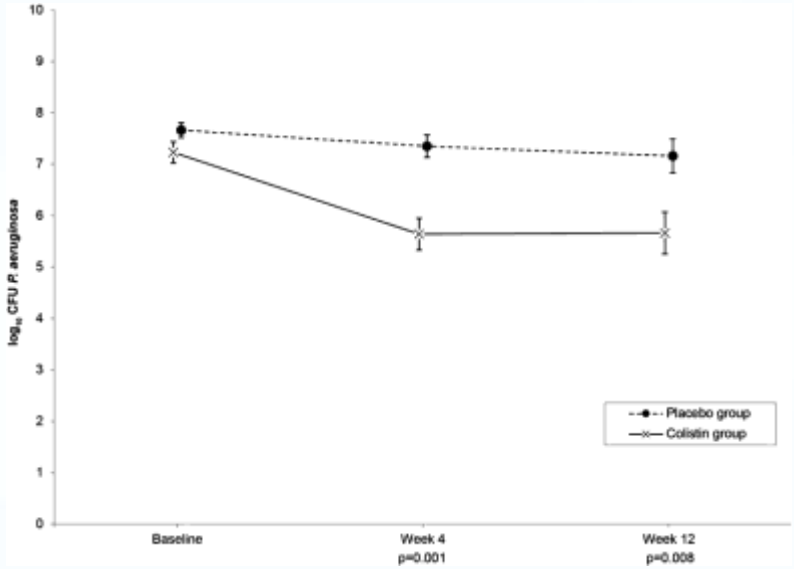


Figure 3. Change from baseline in $\log_{10}$ CFUs *Pseudomonas aeruginosa* within the whole intention-to-treat population. The treatment difference in change from baseline in *P. aeruginosa* CFUs was analyzed using the Wilcoxon rank sum test. Error bars denote SEM.

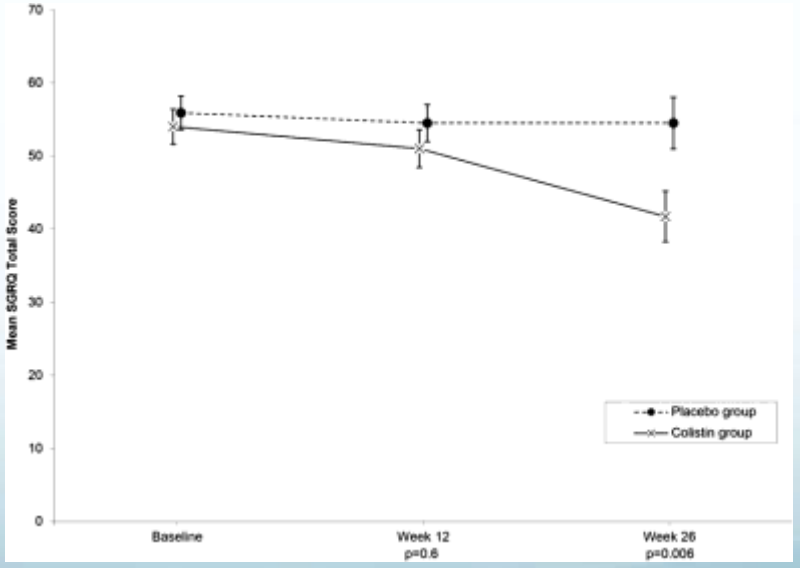


Figure 4. Change from baseline in St. George's Respiratory Questionnaire (SGRQ) total score within the whole intention-to-treat population. An analysis of covariance with treatment and center included in the model was used to examine treatment differences between groups for SGRQ total score. Error bars denote SEM.

Inhaled antibiotics for stable non-cystic fibrosis bronchiectasis: a systematic review

Alessandra Monteiro Brodt[1], Elizabeth Stovold[2] and Linjie Zhang[1]

Eur Respir J 2014; 44: 382–393

- 12 essais représentant 1264 patients adultes,
  dont 5 essais non publiés
- Molécules: amikacine, aztreonam, ciprofloxacine,
  gentamycine, colimycine, tobramycine
- Dispositifs: nébuliseur pneumatique 11
  inhalateur de poudre 1
- Endpoints: charge bactérienne, exacerbations (délai, nombre),
  qualité de vie, hospitalisations

Principaux résultats

- Réduction de la charge bactérienne
- Eradication bactérienne
- Réduction du risque d’exacerbation
- Bronchospasme 10%