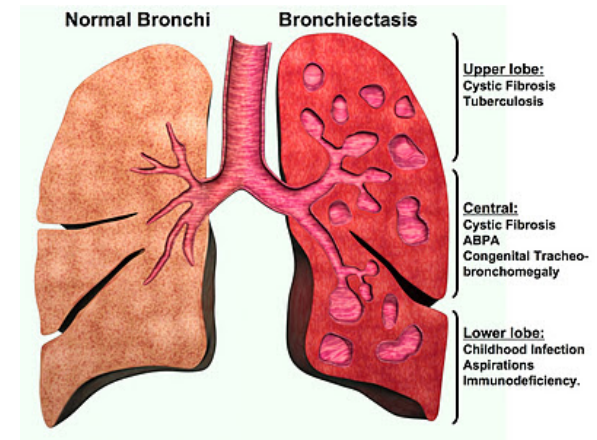


Intérêt et limite des thérapeutiques inhalées dans les dilatations des bronches en dehors de la mucoviscidose

Pr. Ag Chaouch Nawel
Pavillon 2, Hôpital A. Mami Ariana, Tunisie
AFMP, Izmir, avril 2016

Introduction



DDB hors mucoviscidose



DDB liées à une mucoviscidose

Appliquer les recommandations de la mucoviscidose ?

▶ déoxyribonucléase 1



recombinante humaine (rhDNase):

- Efficacité démontrée au cours des DDB en rapport avec une mucoviscidose

(Milla CE. *Thorax* 1998)

- Aggravation de la fonction respiratoire des DDB hors mucoviscidose

(O'Donnell AE et al. *Chest* 1998)

Pathogénie des DDB

Vicious cycle hypothesis

Anti
Inflammatoires

Neutrophil
Inflammation
(Proteases)

Airway
Destruction and
Distortion
(Bronchiectasis)

BD

Vaccination

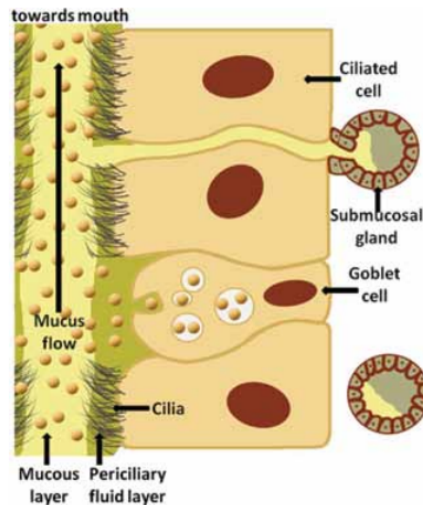
Antibiothérapie

Agents facilitant le
drainage
bronchique

Drainage
bronchique

Bacterial
Colonization

Abnormal
Mucus
Clearance





Quel traitement
inhalé ?

Traitements inhalés des DDB

Anti
Inflammatoires

Neutrophil
Inflammation
(Proteases)

Airway
Destruction and
Distortion
(Bronchiectasis)

BD

Vaccination

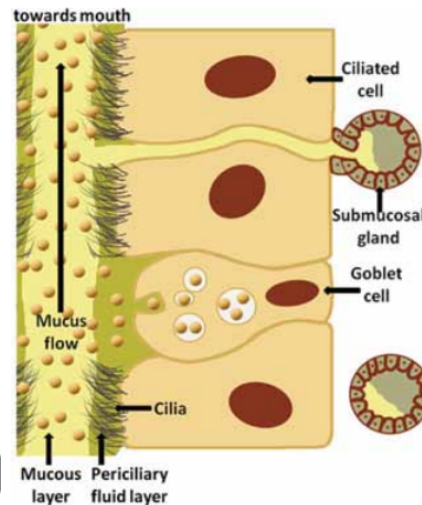
Antibiothérapie

Agents facilitant le
drainage
bronchique

Drainage
bronchique

Bacterial
Colonization

Abnormal
Mucus
Clearance



Inhalation de substances facilitant le drainage bronchique

- ▶ Nébulisation d'eau: étude sur 8 patients montre une amélioration de la quantité des expectorations recueillies pendant une séance de drainage bronchique

Conway JH et al. Respir Med 1992

- ▶ Nébulisation de sérum physiologique: amélioration du drainage bronchique

Sutton PP et al . Thorax 1988

Kellett F et al. Respir Med 2005

- ▶ Nébulisation de terbutaline: amélioration du drainage bronchique

Inhalation de substances hyperosmolaires

Table 1 Comparison between mannitol and hypertonic saline.

Hyperosmolar agent	Mannitol	Hypertonic saline
Dose	400 mg bid	6 or 7% bid
Delivery	By an inhaler	By nebulizer
Duration of effect	Sustained (up to 24 h)	Short



Nebulised 7% hypertonic saline improves lung function and quality of life in bronchiectasis

- ▶ Étude randomisée contrôlée croisée en aveugle sur 3 mois (28 patients)

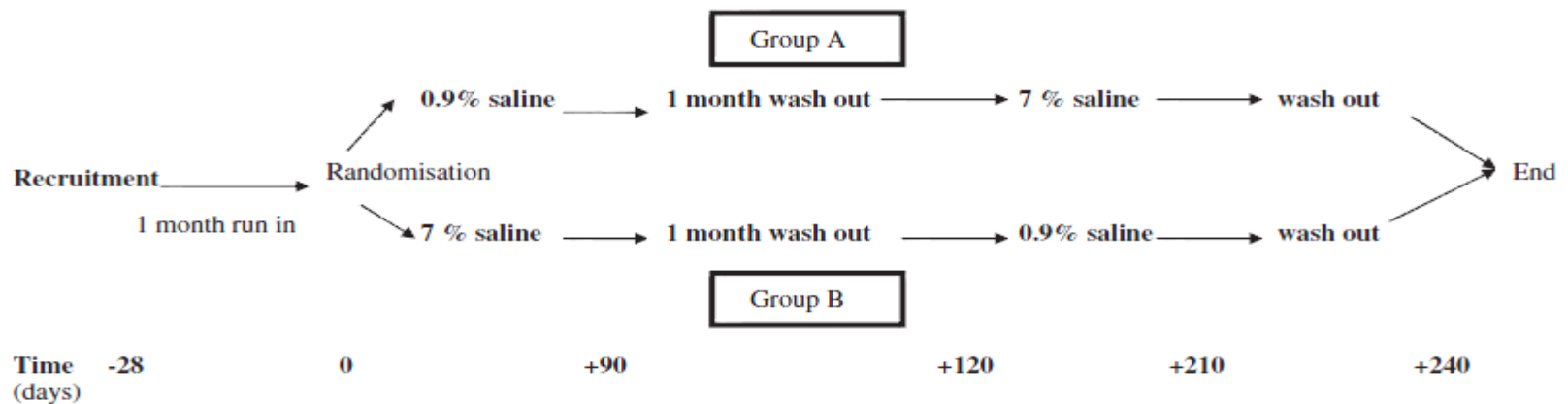
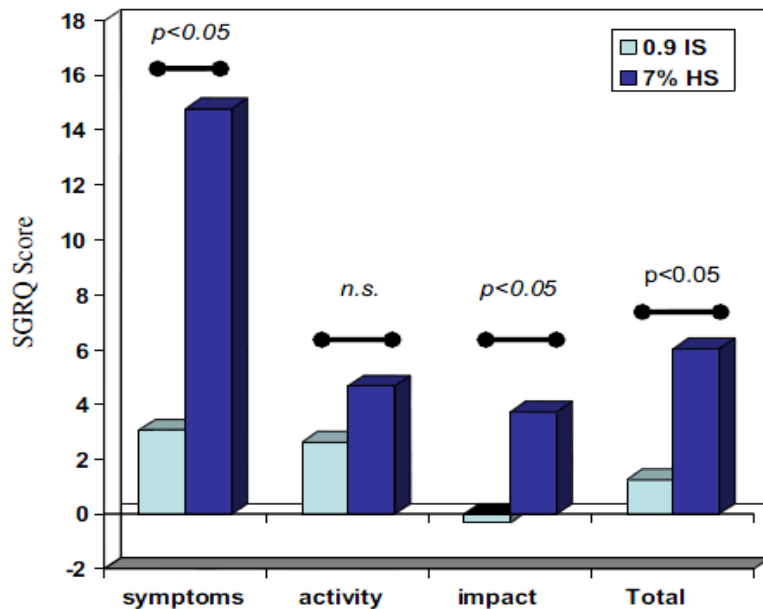


Table 2 Changes in lung function over treatment periods (% change from pre-treatment baseline).

Phase	Active (HS)	Placebo (NS)	P value
FEV ₁ % change (95% C.I.)	15.1 (8.2;22.0)	1.8 (-8.9;10.7)	<0.01
FVC % change (95% C.I.)	11.23 (8.6;13.9)	0.72 (-7.4;8.9)	<0.01

Nebulised 7% hypertonic saline improves lung function and quality of life in bronchiectasis



Amélioration significative de la qualité de vie, des exacerbations et de la fonction respiratoire

Table 3 Outcome of exacerbations/health care utilization.

	Baseline retrospective recall	Active prospective	Placebo prospective	P value active: placebo
Annualised antibiotic use n/year	2.11	2.43	5.43	<0.05
Annualised exacerbations n/year	2.60	2.14	4.85	<0.05

The long term effect of inhaled hypertonic saline 6% in non-cystic fibrosis bronchiectasis

- ▶ Étude randomisée contrôlée double aveugle, 40 patients (inhalation de SP 6% vs inhalation SP 0.9%) 2 fois /j pendant 12 mois.

Bonne tolérance du traitement

Table 2 Number of exacerbations over 12 months.

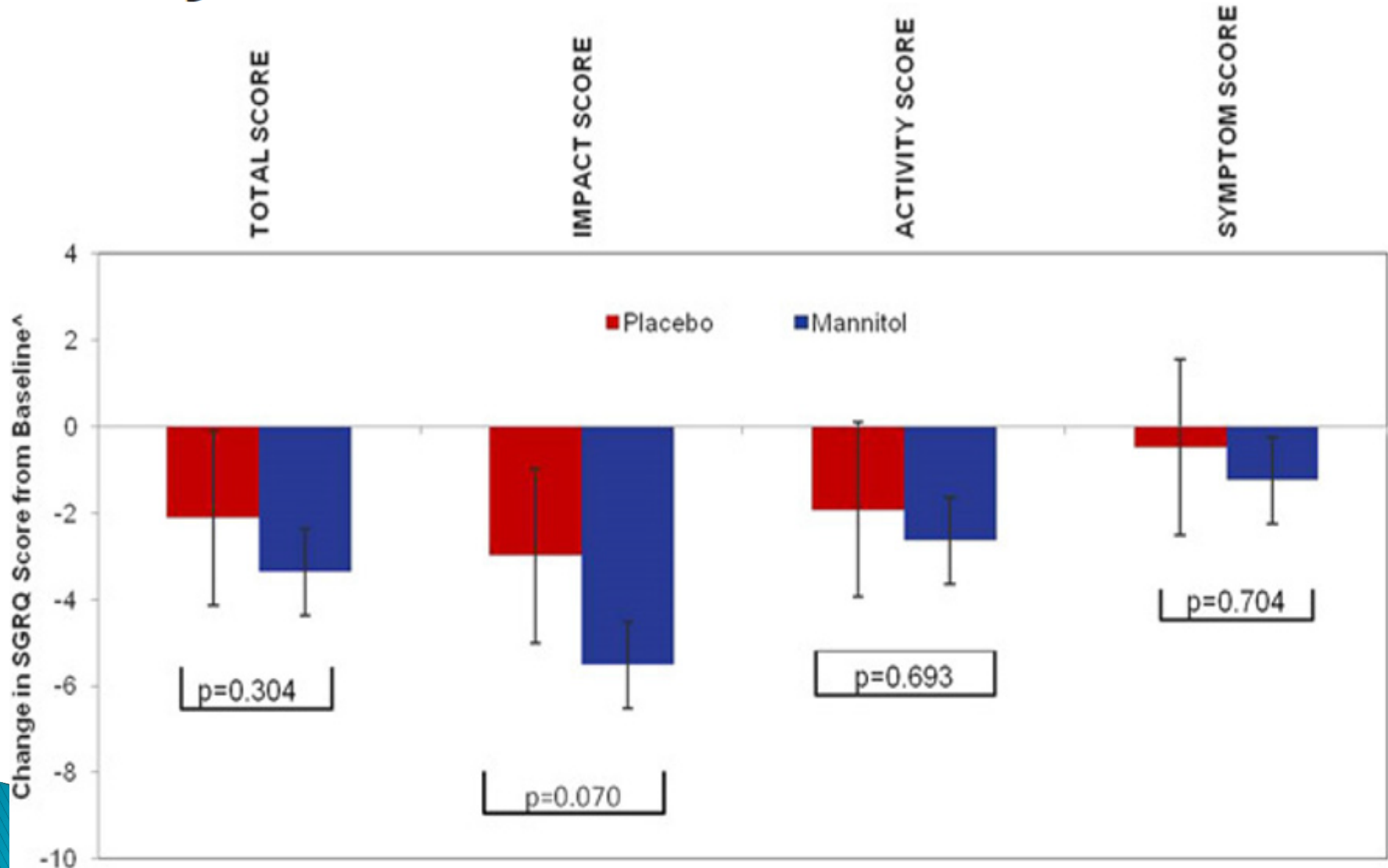
	IS (0.9%)	HTS (6%)	p value
Exacerbations	1.0 (0–4)	3.0 (0–6)	0.24
Exacerbations requiring antibiotics	0.5 (0–3)	1.0 (0–2.5)	0.99
Exacerbation days	2.0 (0–26)	12.0 (1–26)	0.57
Exacerbation days requiring antibiotics	1.0 (0–19.5)	2.0 (0–7)	0.77

Réduction de la colonisation des expectorations dans les deux groupes (50% vs 15%; $p=0.046$)

Table 5 Lung function.

	Baseline	3 months	6 months	12 months	p value
FEV₁					0.70
IS	2.16 (0.75)	2.23 (0.89)	2.24 (0.95)	2.18 (0.92)	
HTS	2.28 (0.87)	2.36 (0.91)	2.41 (0.88)	2.37 (0.90)	
FVC					0.62
IS	3.23 (0.95)	3.26 (1.07)	3.22 (1.1)	3.14 (1.12)	
HTS	3.27 (1.00)	3.31 (1.11)	3.32 (1.07)	3.25 (1.06)	
FEF_{25–75%}					0.41
IS	1.39 (0.85)	1.61 (1.07)	1.71 (1.20)	1.57 (0.98)	
HTS	1.62 (1.02)	1.73 (0.98)	1.87 (1.14)	1.86 (1.08)	

Phase 3 Randomized Study of the Efficacy and Safety of Inhaled Dry Powder Mannitol for the Symptomatic Treatment of Non-Cystic Fibrosis Bronchiectasis



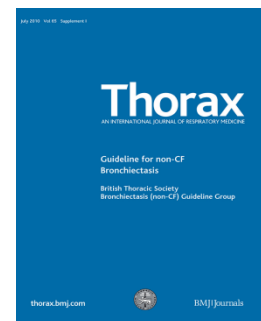
Inhaled mannitol for non-cystic fibrosis bronchiectasis: a randomised, controlled trial.

- ▶ Étude randomisée contrôlée double aveugle
- ▶ Mannitol (400mgx2 /j) vs mannitol faible dose
- ▶ 461 patients
- ▶ Traitement pd 52 semaines
- ▶ Résultats :
 - Pas de différence pour les exacerbations (RR=0,92; p=0,31)
 - Augmentation du temps jusqu'à la première exacerbation (RR=0,78; p=0,02)
 - Amélioration de la qualité de vie (-2,4; p=0,046)
 - Effets secondaires minimales et similaires dans les deux groupes

Recommendations BTS 2010

Recommendations for adjunctive treatments (1—, ^{390 391 3}385 389 392—395)

- ▶ Sterile water inhalation may be used before airway clearance to facilitate clearance. [B]
- ▶ The use of nebulised normal saline prior to airway clearance could be considered to increase sputum yield, reduce sputum viscosity and improve ease of expectoration. [B]
- ▶ The use of nebulised hypertonic saline prior to airway clearance could be considered to increase sputum yield, reduce sputum viscosity and improve ease of expectoration. [B]
- ▶ When nebulised hypertonic saline is first administered, FEV₁ or PEF readings should be done before and 5 min after treatment to assess for possible bronchoconstriction. [D]
- ▶ When nebulising hypertonic saline, pretreat with a bronchodilator in those with bronchial hyper-reactivity. [D]
- ▶ Consider using nebulised β_2 agonists prior to treatment to enhance sputum clearance. [B]





Effet des ATB inhalés?

Antibiothérapie inhalée

- ▶ Traiter une infection bactérienne (eradication antibiotherapy)
 - ▶ Diminuer la charge bactérienne chez des patients colonisés (suppressive antibiotherapy)
 - ▶ Traiter une exacerbation
 - ▶ ATB utilisés: tobramycin, gentamycin, colistin, cipro...
- 

State of the art review: management of bronchiectasis in adults



TABLE 2 Current state of development of inhaled antibiotic agents for non-cystic fibrosis bronchiectasis

Agent [ref.]	n	Current phase of development	Primary outcome	Duration	Patient population	Main results	Safety
Amoxicillin [78–80]	6 [78]; 3 [79]; 5 [80]	Three open label studies following failure of oral antibiotics	Sputum purulence	Continuous; 4 months/16 weeks	Bronchiectasis patients with purulent sputum that failed to clear following oral amoxicillin	Reduced sputum purulence; reduced neutrophil elastase activity; reduced sputum volume; improved PEFR.	No issues identified.
Tobramycin [81]	A: 37; P: 37	Phase II study	<i>P. aeruginosa</i> bacterial load	28 days treatment (total duration 8 weeks)	<i>P. aeruginosa</i> -colonised patients; mean age 66 versus 63 years; FEV1 mean 56 versus 53%	Significant reduction in <i>P. aeruginosa</i> load (mean difference $4.56 \log_{10} \text{ cfu} \cdot \text{mL}^{-1}$, $p < 0.01$); 13/37 cleared <i>P. aeruginosa</i> from sputum; no significant change in FEV1, $p = 0.41$.	Increased dyspnoea, chest pain and wheezing; new resistance to tobramycin in 4/36.
Gentamicin [82]	A: 27; P: 30	Single-blind randomised controlled trial	Bacterial load	12 months	Patients colonised with any pathogens in at least three sputum samples in the preceding 12 months; two exacerbations in the previous year; able to tolerate test dose of gentamicin; FEV1 >30% predicted; exsmokers of >1 year; not on long-term antibiotics.	Significant difference in bacterial load at 12 months ($2.96 \log_{10} \text{ cfu} \cdot \text{mL}^{-1}$ versus $7.67 \log_{10} \text{ cfu} \cdot \text{mL}^{-1}$, $p < 0.0001$); reduction in exacerbations (median 0 in the gentamicin group, 1.5 in the saline group, $p < 0.0001$); improved SGRQ and LQCQ scores; reduced airway inflammation.	Bronchospasm in 21.9%, two withdrawals; elevated serum gentamicin levels required dose reduction in one patient; no resistant isolates detected.
Colistin [83]	A: 73; P: 71	Phase III double-blind randomised controlled trial	Time to first exacerbation	6 months (patients withdrawn following exacerbation)	<i>P. aeruginosa</i> -colonised patients (two or more positive cultures in 12 months) and within 21 days of completing antipseudomonal antibiotics for an exacerbation.	Missed primary end-point (colistin 165 days, placebo 111 days, $p = 0.11$); improved SGRQ (mean difference -10.5 points, $p = 0.006$); improved time to first exacerbation in patients taking >80% of doses.	Five patients (7%) developed bronchoconstriction leading to discontinuation; no resistant strains at follow-up.



State of the art review: management of bronchiectasis in adults

Agent [ref.]	n	Current phase of development	Primary outcome	Duration	Patient population	Main results	Safety
Ciprofloxacin DPI [86]	A: 60; P: 64	Phase II double blind randomised controlled trial	Bacterial load	28 days treatment with follow-up to 84 days	Idiopathic or post-infective bronchiectasis; two or more exacerbations in the previous 12 months (one hospitalisation); able to produce sputum; culture positive for target microorganisms.	Mean difference in bacterial load $-3.62 \log_{10} \text{cfu}\cdot\text{mL}^{-1}$ versus $-0.27 \log_{10} \text{cfu}\cdot\text{mL}^{-1}$, $p<0.001$; no significant differences in proportion of patients with exacerbations (36.7 versus 39.1%, $p=0.6$); no significant difference in SGRQ (mean difference -3.56 , $p=0.059$).	10% of patients developed resistance (MIC $>4 \text{mg}\cdot\text{L}^{-1}$) in the ciprofloxacin group; no difference in adverse events between groups.
Liposomal ciprofloxacin [87]	A: 20; P: 22	Phase II study double blind randomised controlled trial	Bacterial load after first 28-day treatment cycle with intervening 28-day off periods	24 weeks (three 28 day treatment cycles)	<i>P. aeruginosa</i> -colonised patients; ≥ 2 exacerbations in previous 12 months.	Reduction in <i>P. aeruginosa</i> bacterial load -4.2 versus $-0.08 \log_{10} \text{cfu}\cdot\text{mL}^{-1}$, $p=0.002$; reduced number of exacerbations in the active treatment group (OR 0.2 95% CI 0.04–0.89, $p=0.027$); median time to pulmonary exacerbations reduced in the per protocol population ($p=0.046$).	No significant difference in minimal inhibitory concentrations to ciprofloxacin at day 28; no increase in adverse events.

Antibiothérapie inhalée

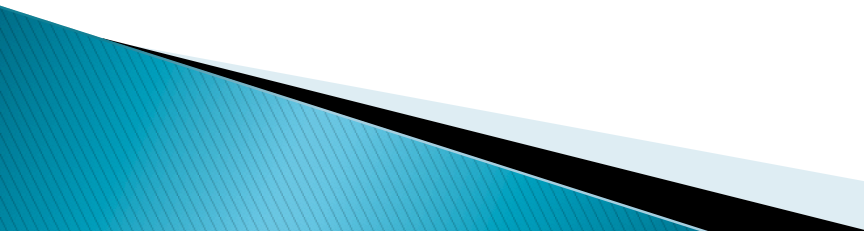
- ▶ 1^{ère} infection à *P. Aeruginosa*: antibiothérapie inhalée et antibiothérapie systémique

Bilton D. Chest 2006

Barker AF. N Engl Med 2002

- ▶ Colonisation bactérienne: antibiothérapie inhalée si exacerbations fréquentes ou déclin rapide de la fonction respiratoire

BTS 2010



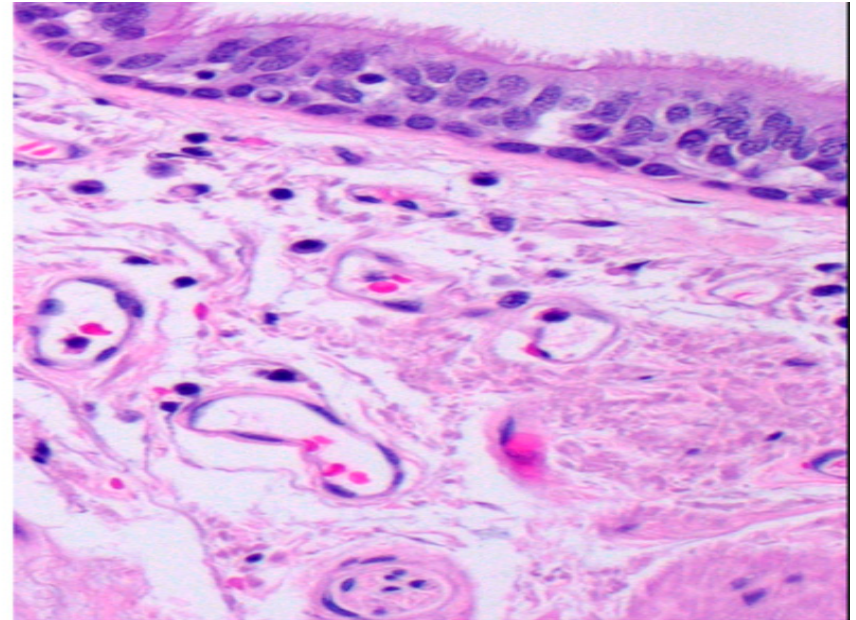
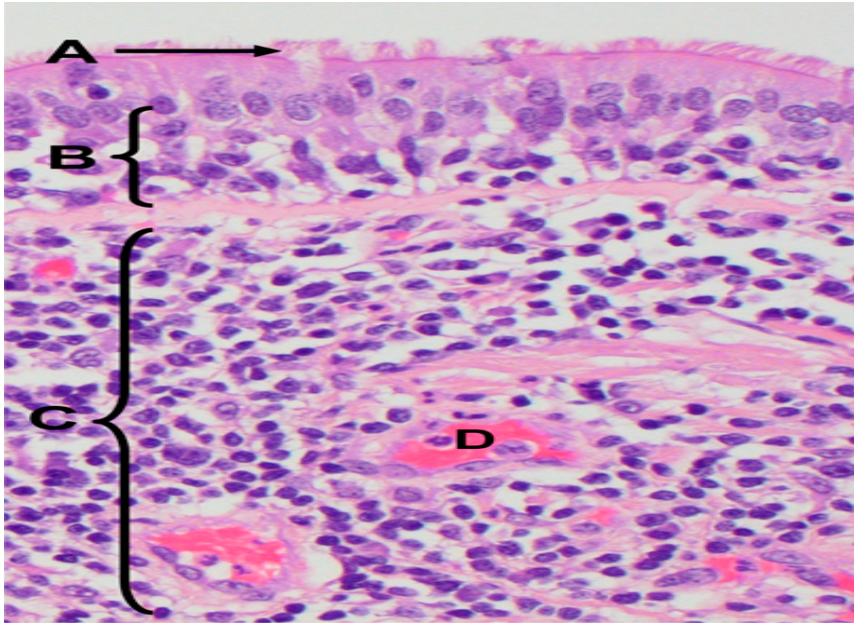


Effet des anti-
inflammatoires?

Effets des AINS

- ▶ Inflammation des VAS: PNN

(Pamela. AJRCCM 2013)



- ▶ Les AINS préviennent la détérioration de la fonction respiratoire au cours de la mucoviscidose (ibuprofène).

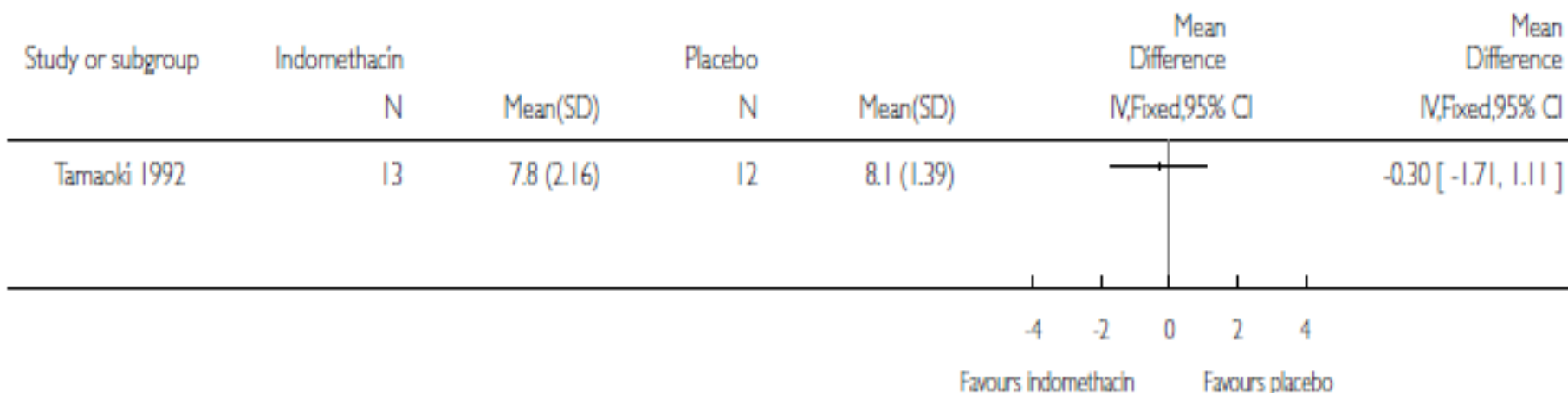
Inhaled non-steroid anti-inflammatories for children and adults with bronchiectasis (Review)

Analysis 1.5. Comparison 1 NSAID versus placebo, Outcome 5 Bacterial load of sputum at end of study (Log10 cfu/g).

Review: Inhaled non-steroid anti-inflammatories for children and adults with bronchiectasis

Comparison: 1 NSAID versus placebo

Outcome: 5 Bacterial load of sputum at end of study (Log10 cfu/g)



Effet des CI?

- ▶ Inflammation des VAS

(Pamela. AJRCCM 2013)

- ▶ DDB augmente le risque d'HRB: 45% des DDB ont une HRB

(Müsellim et al. JCAM 2013)

(Ip M et al. Lung 1991)

- ▶ 20% des patients DDB ont une réversibilité aux B2 mimétiques

(Jain NK et al. Indian J Chest Dis Allied Sci 1992)

- ▶ Association DDB–asthme fréquente

Inhaled steroids for bronchiectasis (Review)



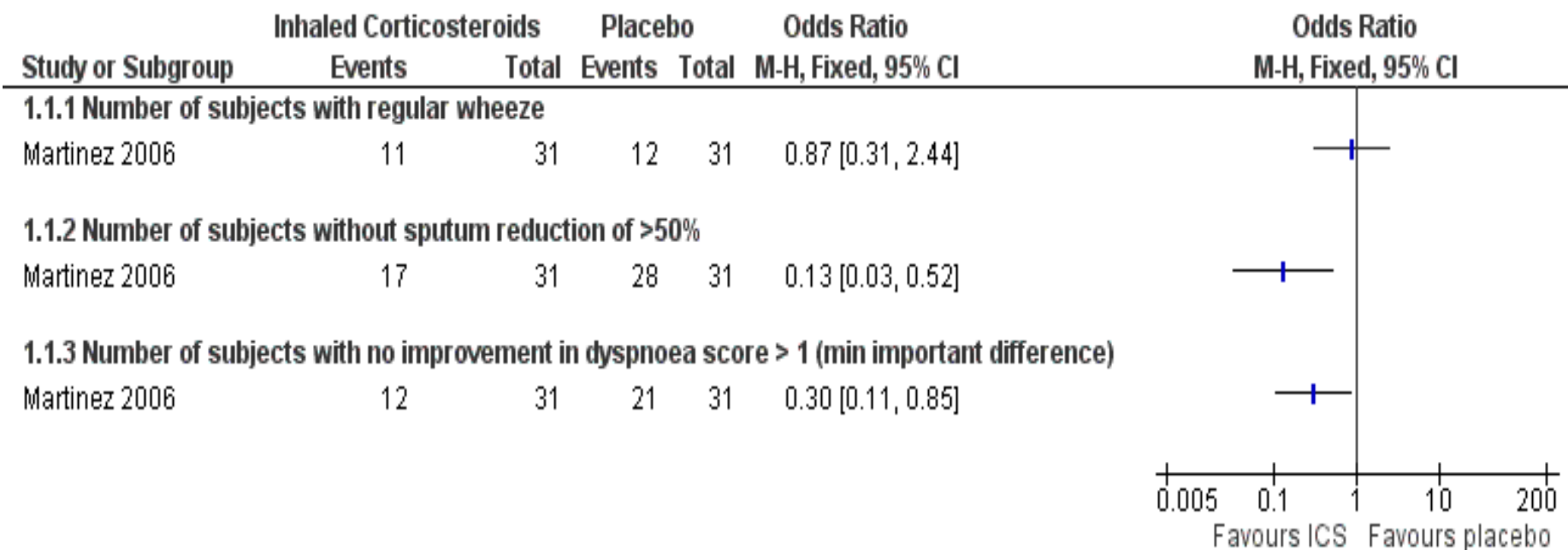
**Cochrane
Library**

Cochrane Database of Systematic Reviews

- ▶ Pas d'étude sur l'enfant
- ▶ 6 études de l'adulte: 278 patients
 - 5 sur 6 n'ont pas exclues l'asthme
 - ABPA exclue dans 2 études
 - 5 études contre placebo
 - 1 étude vs pas de traitement
 - DDB à l'état stable
 - CI à doses modérées à élevées
 - Durée de suivi: 4 à 52 sem

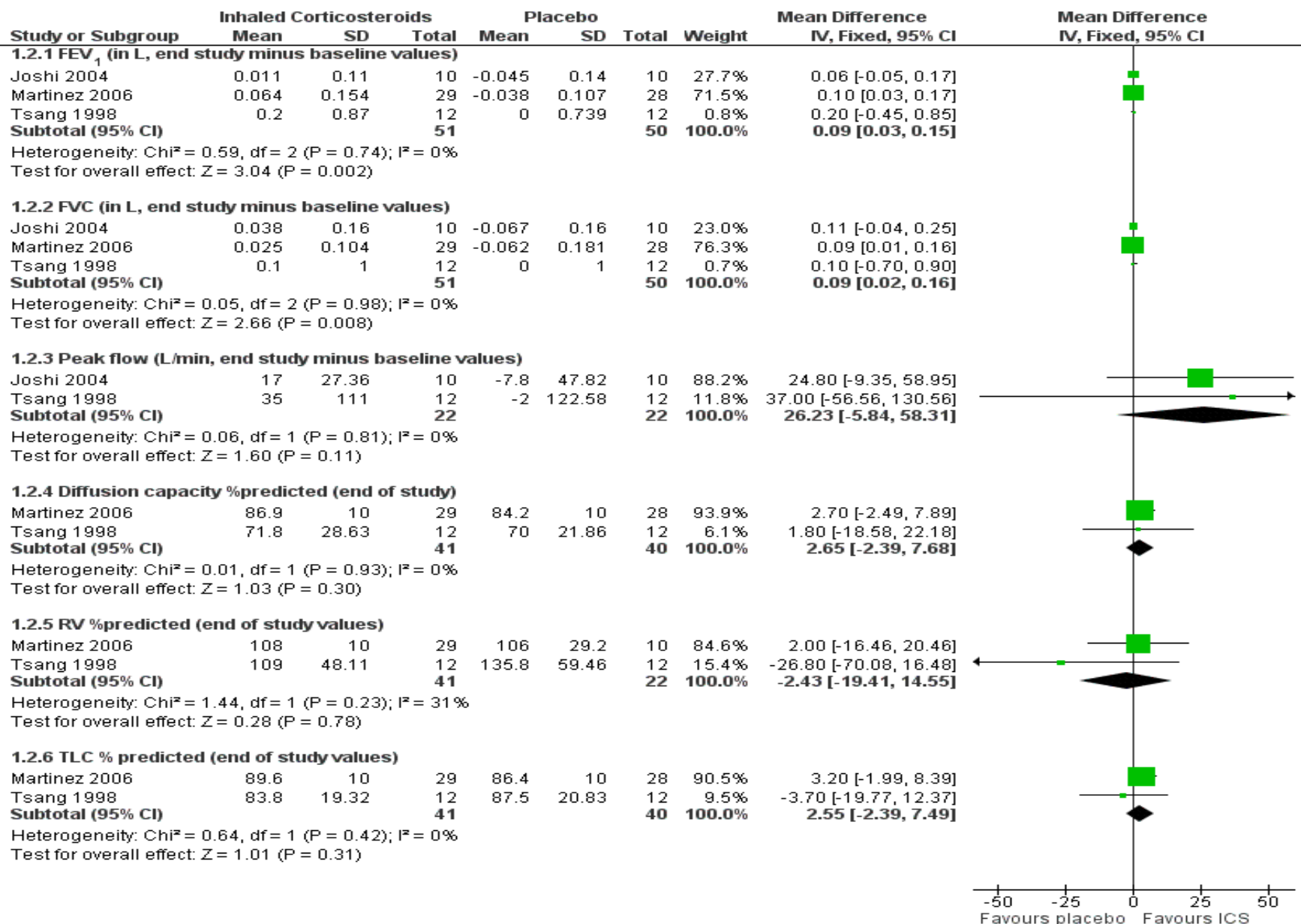
Inhaled steroids for bronchiectasis

Forest plot of comparison: 1 Stable State Bronchiectasis (6 months or less), outcome: 1.1 Clinical severity indices.



Etude sur 6 mois

Forest plot of comparison: 1 Stable State Bronchiectasis (6 months or less), outcome: 1.2 Lung function indices.

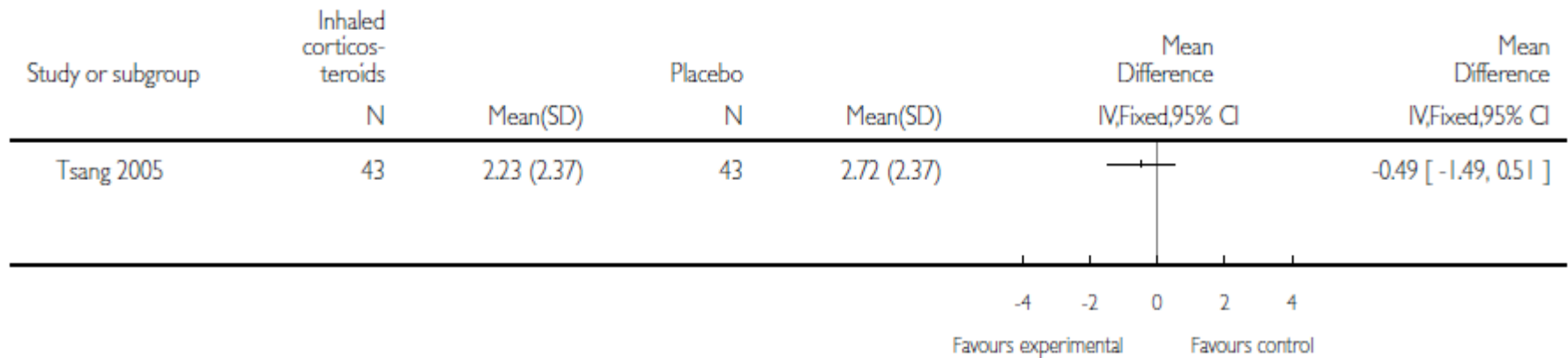


Analysis 2.2. Comparison 2 Stable State (>6 months), Outcome 2 Average exacerbation per subject.

Review: Inhaled steroids for bronchiectasis

Comparison: 2 Stable State (>6 months)

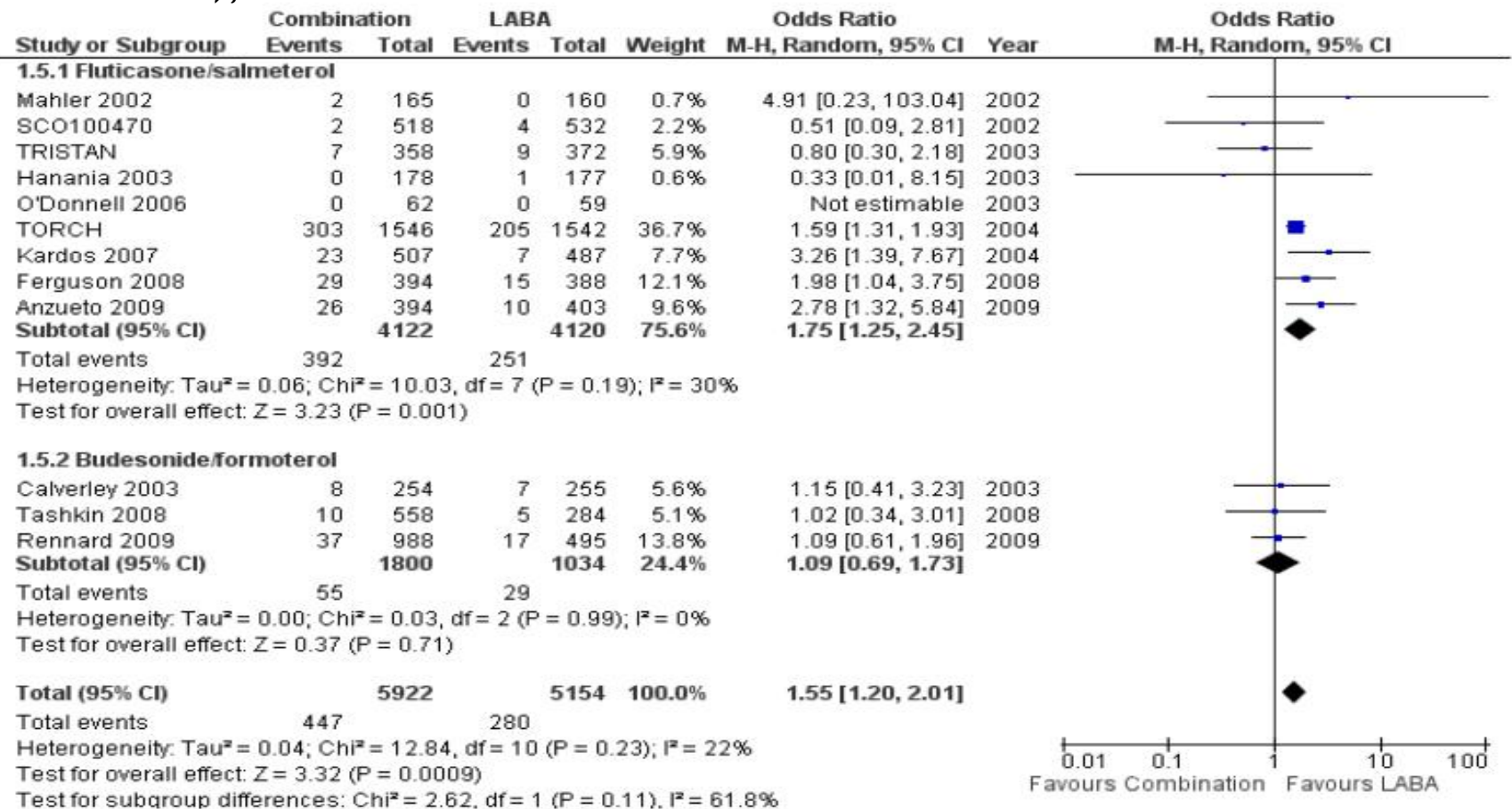
Outcome: 2 Average exacerbation per subject



Augmentation de la concentration des germes dans les expectorations

Combined corticosteroid and long-acting beta₂-agonist in one inhaler versus long-acting beta₂-agonists for COPD

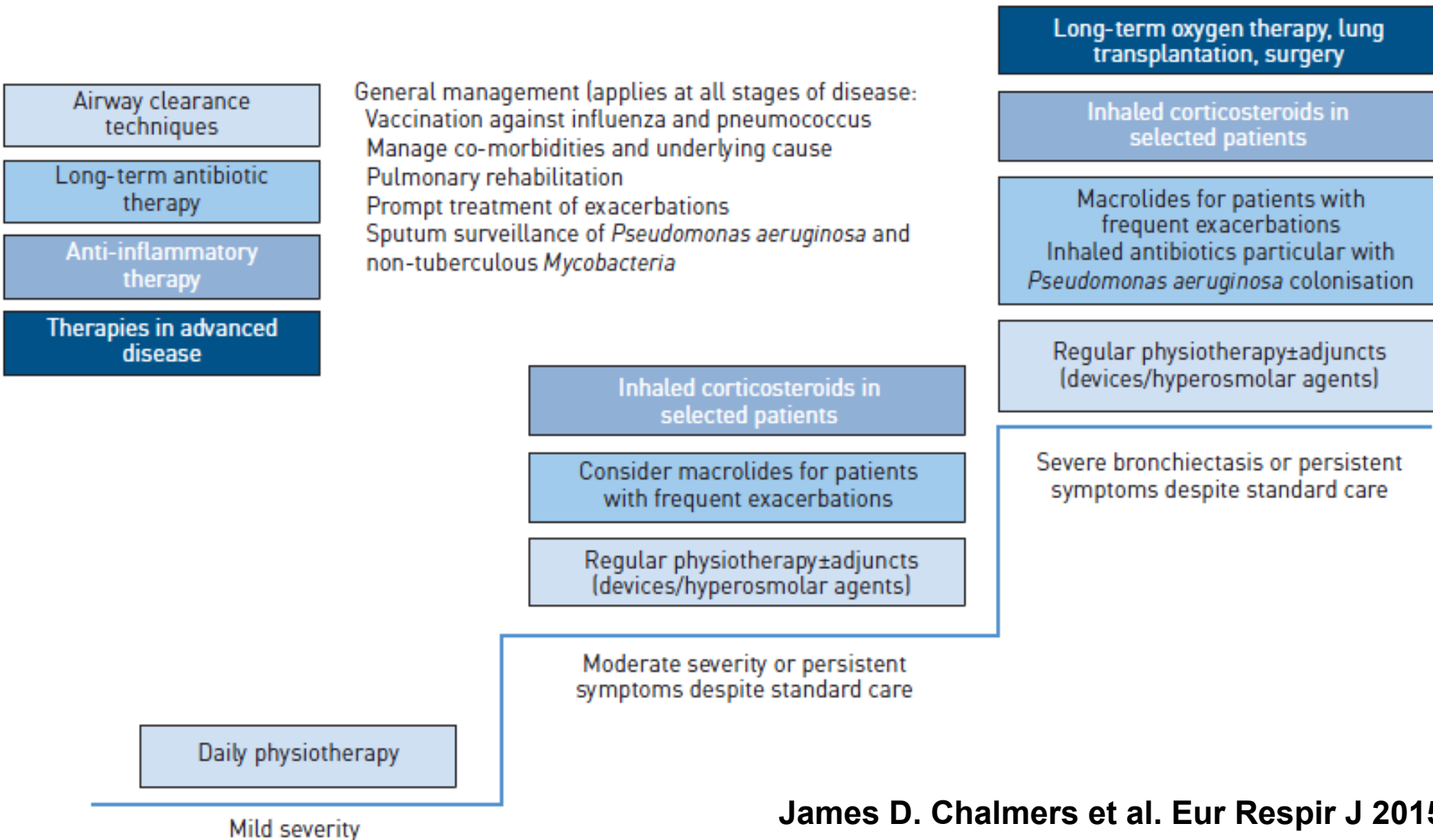
Combined inhalers versus long-acting beta₂-agonists (primary outcomes), outcome: 1.3 Pneumonia.



State of the art review: management of bronchiectasis in adults



The stepwise management of non-CF bronchiectasis.





Effet des
bronchodilatateurs
longue action (BDLA)?

Pourquoi les BDLA inhalés

- ▶ Association fréquente des DDB avec l'asthme et la BPCO

- 29 à 50% des patients BPCO ont des DDB

O'Brian et al. Thorax. 2000

Patel IS et al. AJRCCM 2004

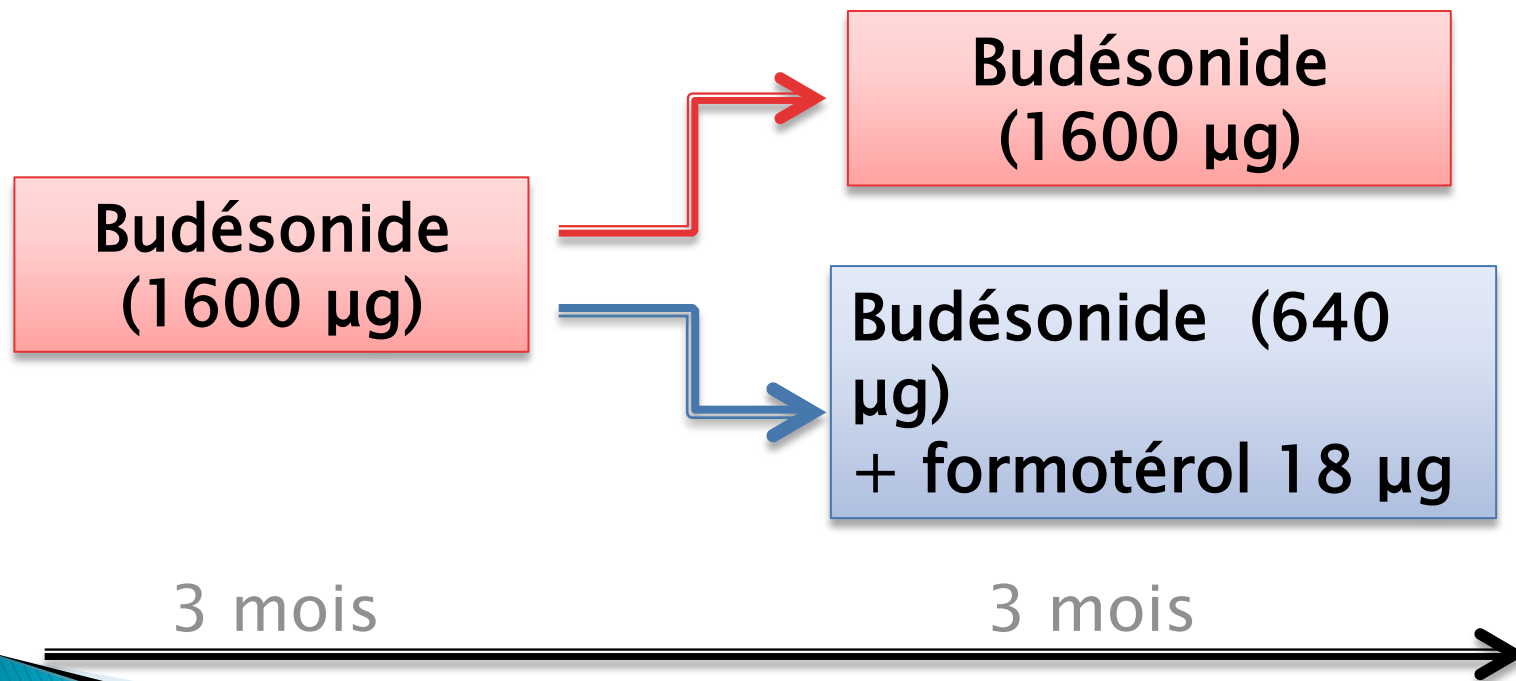
- ▶ « Asthma-like symptoms » et « COPD-like symptoms » chez les patients DDB: fréquents et aggravent le pronostic

Keinstinen T et al. ERJ 1997

Field CE et al. Archives of disease in childhood 1969

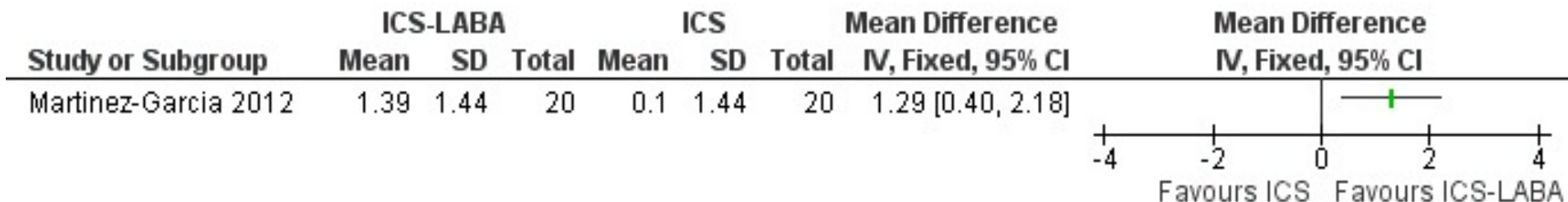
Combination inhaled corticosteroids and long-acting beta₂-agonists for children and adults with bronchiectasis (Review)

- ▶ 1 étude retenue (Martinez–Garcia 2012)
- ▶ Étude randomisée contrôlée croisée (40 patients)

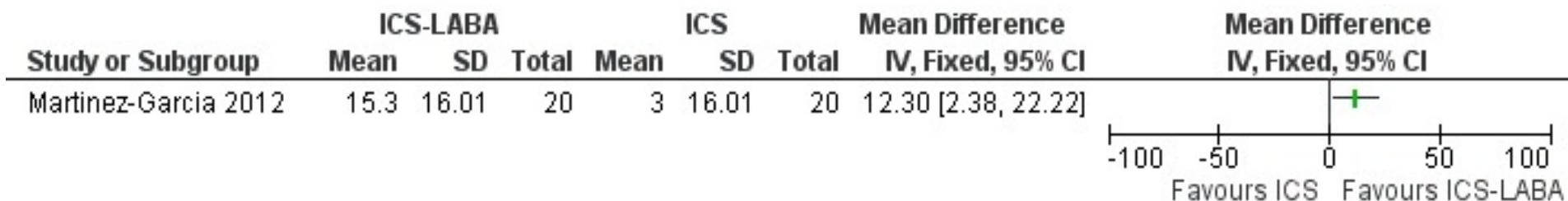


Combination inhaled corticosteroids and long-acting beta₂-agonists for children and adults with bronchiectasis (Review)

Forest plot of comparison: transient dyspnea index.

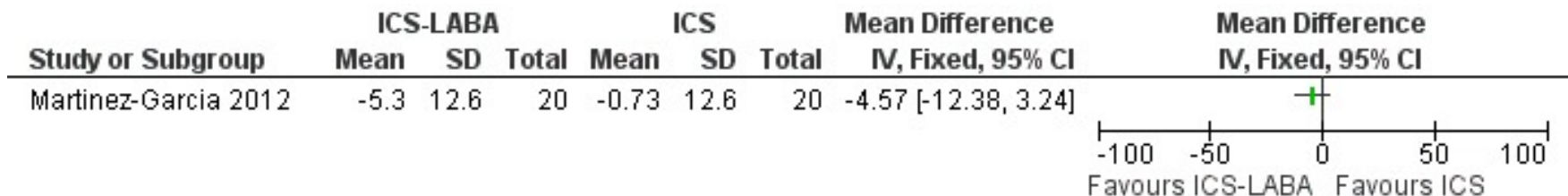


Forest plot of comparison: cough-free days.

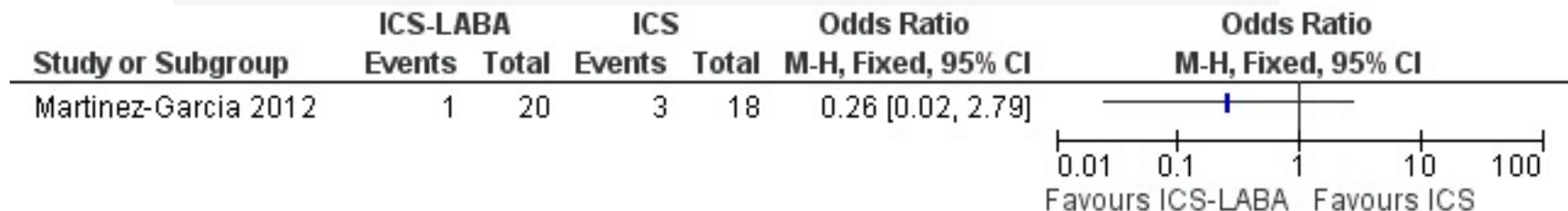


Combination inhaled corticosteroids and long-acting beta₂-agonists for children and adults with bronchiectasis (Review)

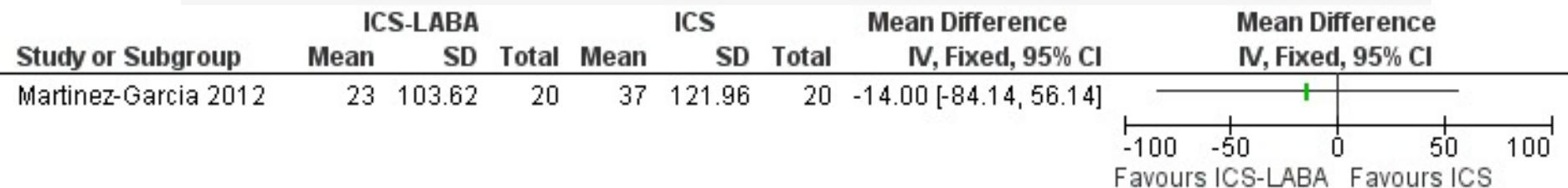
Forest plot of comparison: quality of life (total SGRQ score).



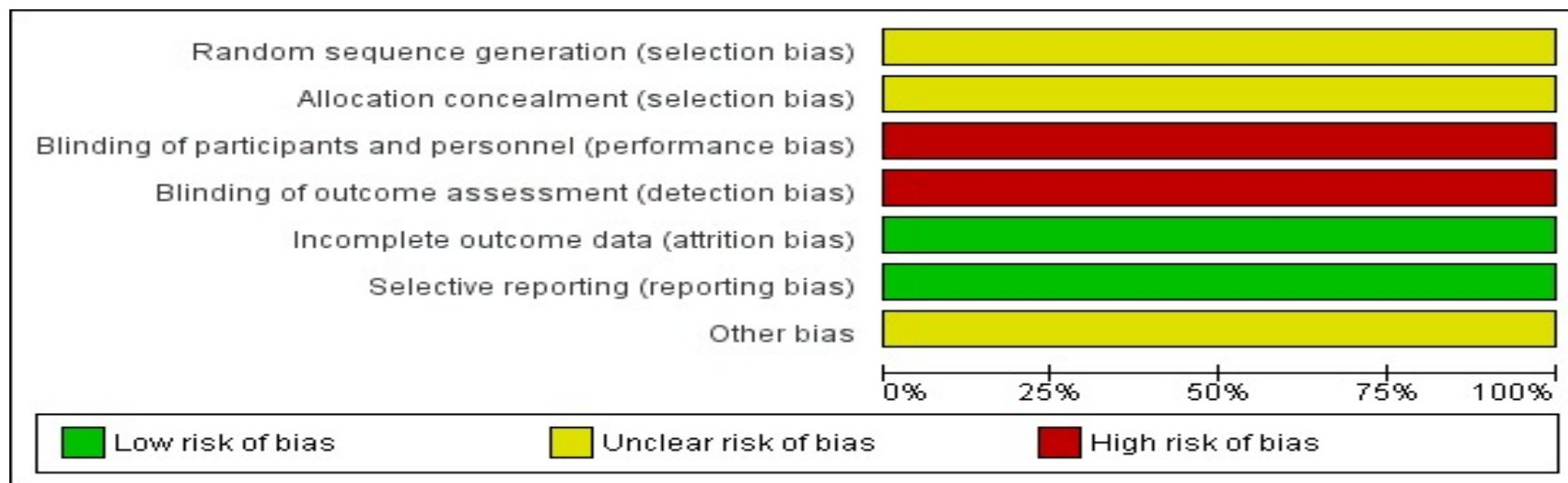
Forest plot of comparison: exacerbations.



Forest plot of comparison: FEV1 (change from baseline in mL).



Combination inhaled corticosteroids and long-acting beta₂-agonists for children and adults with bronchiectasis (Review)



GRADE Working Group grades of evidence.

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.



Effet des LAMA?

Anticholinergic therapy for bronchiectasis (Review)

OBJECTIVES: To determine the effect of anticholinergic therapy in acute exacerbations and stable bronchiectasis.

SEARCH STRATEGY: The Cochrane Airways Group clinical trials register was searched using the terms bronchiectasis AND anticholinergic OR ipratropium bromide OR tiotropium OR atropine.

SELECTION CRITERIA: Only randomised controlled trials were considered.

DATA COLLECTION AND ANALYSIS: Two reviewers assessed the retrieved studies working independently.

MAIN RESULTS: Twelve studies were identified, of which six were obtained for further scrutiny. One was translated from Italian. None met the inclusion criteria.

REVIEWER'S CONCLUSIONS: No formal recommendations can be made about the use of anticholinergic therapy in acute or stable bronchiectasis based on the literature currently available.

Lasserson T et al. Cochrane Database Syst Rev. 2001

Tiotropium Ameliorates Symptoms in Patients with Chronic Airway Mucus Hypersecretion which is Resistant to Macrolide Therapy

CONCLUSION: Tiotropium improved the symptoms of cough, sputum and breathlessness in the macrolide-resistant cases of DPB or similar disorders. These beneficial effects might be due to the suppression of airway secretion through the anticholinergic effect of tiotropium on the submucosal gland, however, the long-term efficiency of this treatment still needs to be further assessed.

Yoshinobu Saito et al. Inter Med 2008

[Therapeutic effect of tiotropium bromide powder inhalation in patients with stable bronchiectasis].

[Article in Chinese]

Li XL¹, Cai SX, Zhao HJ, Dong LM, Shen XB, Liu LY, Hu GD.

- ▶ 22 patients DDB stables
- ▶ Tiotropium 18µg/j pendant 28jours
- ▶ Évaluation des symptômes, fonction respiratoire et BODE index

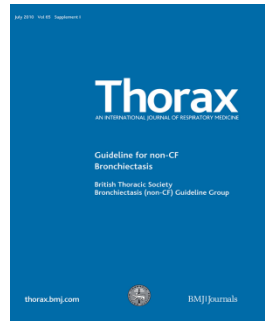
▶ Amélioration significative du score symptômes ($p<0.01$), de la tolérance à l'exercice et de l'index BODE ($p<0.05$)

▶ Pas d'amélioration de la fonction respiratoire

表 3 噻托溴铵治疗前后各种指标比较

疗效指标	平均值±标准差		<i>t</i>	<i>P</i>
	治疗前	治疗后		
FVC	2.29±1.00	2.32±1.01	-0.87	0.396
FEV1(%)	60.82±21.01	62.82±21.39	-1.86	0.077
FEV1/FVC	70.59±7.44	72.14±6.75	-1.48	0.153
MVV(%)	57.95±22.72	63.32±20.95	-3.14	0.005
6MVD	299.05±139.61	341.05±126.26	-5.30	0.000
BOED	3.91±3.54	3.36±3.14	2.98	0.007
症状评分	8.68±3.58	6.27±2.86	7.09	0.000

Recommendations BTS 2010

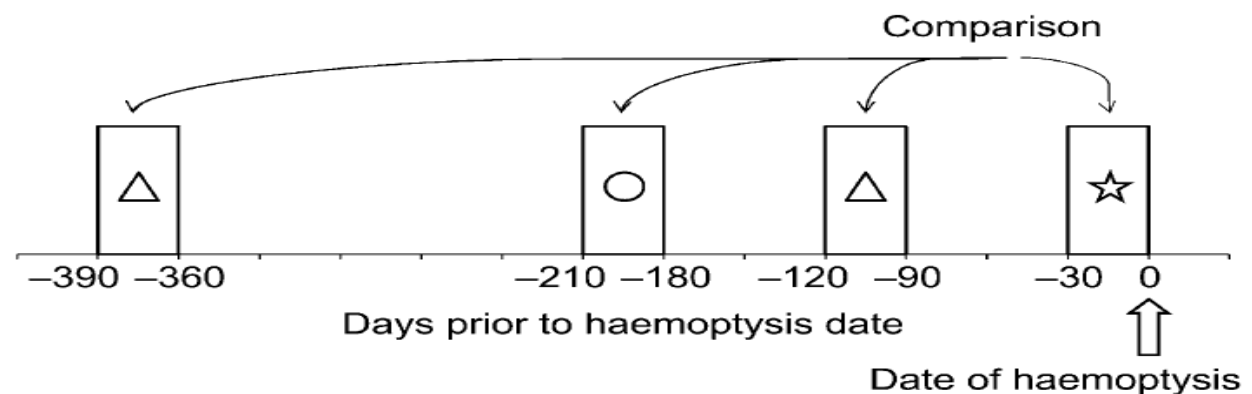


Recommendations (3³⁵⁶ 358 413–417)

- It seems appropriate to assess patients with airflow obstruction for reversibility to β_2 agonist and anticholinergic bronchodilators and to institute therapy where lung function or symptoms improve on therapy. [D]

Effect of inhalers on the development of haemoptysis in patients with non-cystic fibrosis bronchiectasis

- ▶ Étude cas croisés (chaque patient est son propre témoin) de 2007 à 2011 à Séoul (Corée)
- ▶ 192 Adultes, DDB confirmées par TDM, ttt inhalé > 390j avant l'hémoptysie (LABA, LABA-CI, LAMA, SABA)
- ▶ Comparaison de l'exposition aux thérapies inhalées 1 mois avant l'hémoptysie (risk period) et 6 à 7 mois avant l'hémoptysie (control period)



Effect of inhalers on the development of haemoptysis in patients with non-cystic fibrosis bronchiectasis

Table 1 Baseline characteristics of study subjects

	Total (N = 192) n (%) or mean $\pm$ SD		Total (N = 192) n (%) or mean $\pm$ SD
Male	115 (59.9)	History of inhaler use	
Age, years, median [Q1, Q3]	68 [59, 74]	Inhaler use (at least once)	
BMI, kg/m ²	21.2 $\pm$ 4.0	ICS/LABA	114 (59.4)
Follow-up duration, months, median [Q1, Q3]	84 [47, 132]	LAMA	98 (51.0)
Pulmonary function test (n = 167)		SABA	91 (47.4)
FEV ₁ (l)*	1.29 $\pm$ 0.56	Inhaler use pattern	
(% predicted)	56.9 $\pm$ 23.4	Single device	99 (51.6)
FVC (l)*	2.32 $\pm$ 0.84	Multiple devices	93 (48.4)
(% predicted)	74.7 $\pm$ 49.8	Inhaler type (at least once)	
FEV ₁ /FVC (%)	57.0 $\pm$ 18.0	Dry power inhaler	168 (87.5)
Bronchodilator response	18 (9.4)	Metered dose inhaler	91 (47.4)
History of smoking		Duration from last inhaler prescription to haemoptysis (days), median [Q1, Q3]	53 [22, 91]
Never	91 (47.4)	Haemoptysis events and other confounders	
Ex	53 (27.6)	Clinically significant events	89 (46.4)
Current	31 (16.1)	Emergency room visit	85 (44.3)
Unknown	17 (8.9)	Admission	64 (33.3)
Pack-year	38.2 $\pm$ 20.7	Embolotherapy	47 (24.5)
Charlson comorbidity index	2.1 $\pm$ 1.6	Anticoagulation	8 (4.2)
		Anti-platelet therapy	19 (9.9)

Effect of inhalers on the development of haemoptysis in patients with non-cystic fibrosis bronchiectasis

Table 2 Risk of haemoptysis according to inhaler use

	Control period <i>n</i> (%) [*]	Case period <i>n</i> (%) [†]	Univariate OR (95%CI)	Adjusted OR (95%CI) [‡]
Total events (<i>N</i> = 192)				
Any inhaler	118 (61.5)	156 (81.3)	3.53 (1.99–6.27)	<u>3.51 (1.96–6.28)</u>
ICS/LABA	68 (35.4)	89 (46.4)	2.91 (1.47–5.77)	2.62 (1.25–5.45)
LAMA	64 (33.3)	76 (39.6)	2.20 (1.04–4.65)	1.50 (0.68–3.32)
SABA	31 (16.1)	53 (27.6)	3.0 (1.52–5.94)	<u>2.51 (2.23–5.15)</u>
Clinically significant events (<i>n</i> = 89)				
Any inhaler	59 (66.3)	74 (83.1)	3.14 (1.34–7.36)	2.98 (1.26–7.01)
ICS/LABA	34 (38.2)	41 (46.1)	2.62 (1.38–4.96)	2.34 (1.19–4.63)
LAMA	31 (34.8)	38 (42.7)	3.40 (1.68–6.88)	2.80 (1.34–5.84)
SABA	17 (19.1)	23 (25.8)	2.73 (1.51–4.94)	2.46 (1.33–4.56)

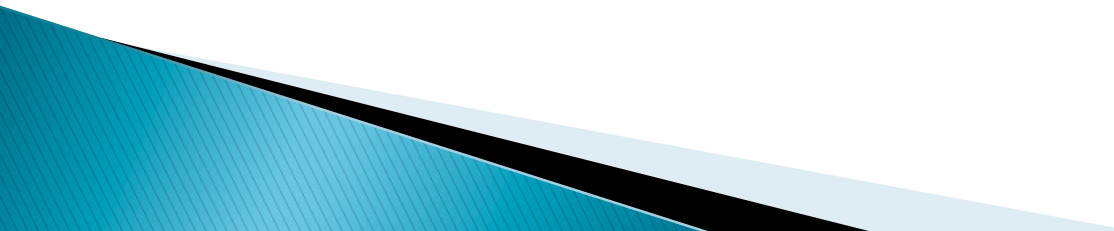
Table 4 Risk of haemoptysis according to inhaler combination

Type of inhaler combination (<i>N</i> = 192)	Control period <i>n</i> (%) [*]	Case period <i>n</i> (%) [†]	Univariate OR (95%CI)	Adjusted OR (95%CI) [‡]
SABA and ICS/LABA				
SABA single or ICS/LABA single	55 (28.6)	76 (39.6)	3.10 (1.52–6.32)	3.12 (1.46–6.68)
SABA with ICS/LABA	30 (15.6)	43 (22.4)	5.33 (1.55–18.30)	<u>5.52 (1.53–20.01)</u>
SABA and LAMA				
SABA single or LAMA single	59 (30.7)	75 (39.1)	1.94 (1.08–3.49)	1.92 (1.07–3.45)
SABA and LAMA	27 (14.1)	34 (17.7)	4.5 (0.97–20.83)	<u>3.61 (0.69–19.00)</u>
ICS/LABA and LAMA				
ICS/LABA single or LAMA single	73 (38.0)	95 (49.5)	3.0 (1.52–5.94)	3.07 (1.53–6.17)
ICS/LABA with LAMA	33 (17.2)	41 (21.4)	5.0 (1.10–22.82)	<u>4.76 (1.02–22.24)</u>

Perspectives d'avenir

- ▶ Thérapies inhalées sous forme de poudre sèche
- ▶ **Phagothérapie:**
 - Administration de virus dont l'hôte est la bactérie
 - Administration par voie inhalée (spray nasal, nébulisation, poudre sèche)
 - Études de phase I et II

Conclusion

- ▶ Données actuelles insuffisantes
 - ▶ Résultats controversés
 - ▶ Niveau de preuve faible
 - ▶ Amélioration des symptômes
 - ▶ Pas d'amélioration de la fonction respiratoire ? Qualité de vie ? exacerbations?
 - ▶ Autres études nécessaires + + +
- 

The background of the image is the flag of the Republic of Turkey, featuring a red field with a large white crescent and a five-pointed star. The flag is shown with a slight wavy texture, suggesting it is a close-up of a physical flag.

**Merci pour votre
attention**