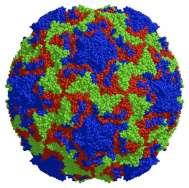
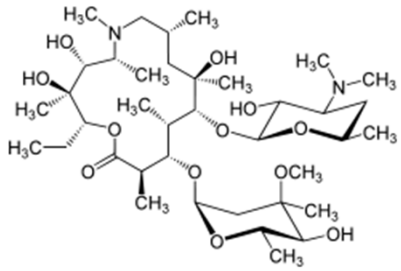
Actualités mucoviscidose 2015

Hors modulateurs du CFTR

Marie MITTAINE
CRCM pédiatrique Toulouse
31 Mars 2016

Fondamental





Virus - Azithromycine

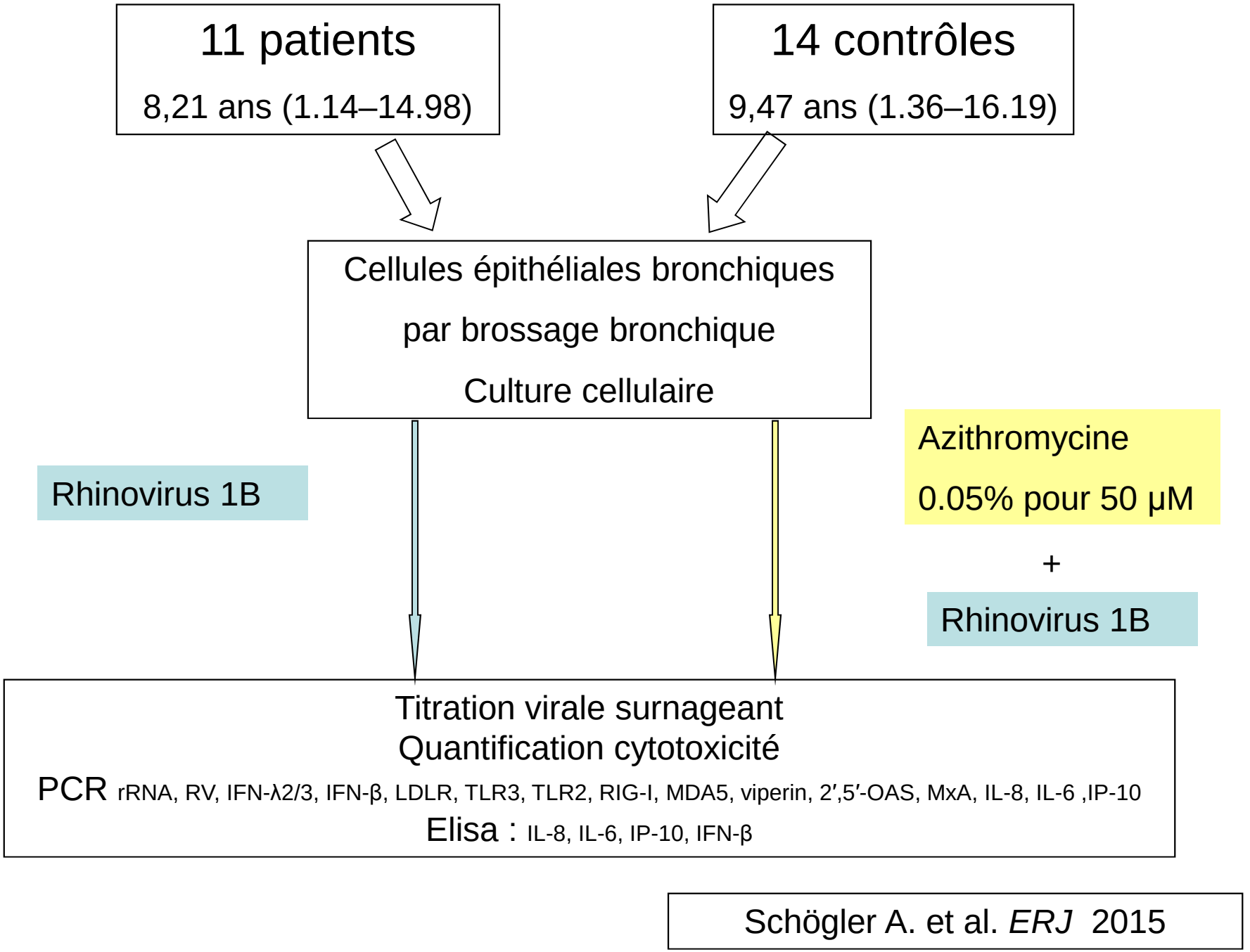
Novel antiviral properties of azithromycin in cystic fibrosis airway epithelial cells

Aline Schögler[1,2,3], Brigitte S. Kopf[1,2], Michael R. Edwards[4], Sebastian L. Johnston[4], Carmen Casaulta[1], Elisabeth Kieninger[1], Andreas Jung[5], Alexander Moeller[5], Thomas Geiser[2,6], Nicolas Regamey[1,2,7] and Marco P. Alves[1,2,7]

EUROPEAN RESPIRATORY *journal*

OFFICIAL SCIENTIFIC JOURNAL OF THE ERS

2015; 45: 428–439

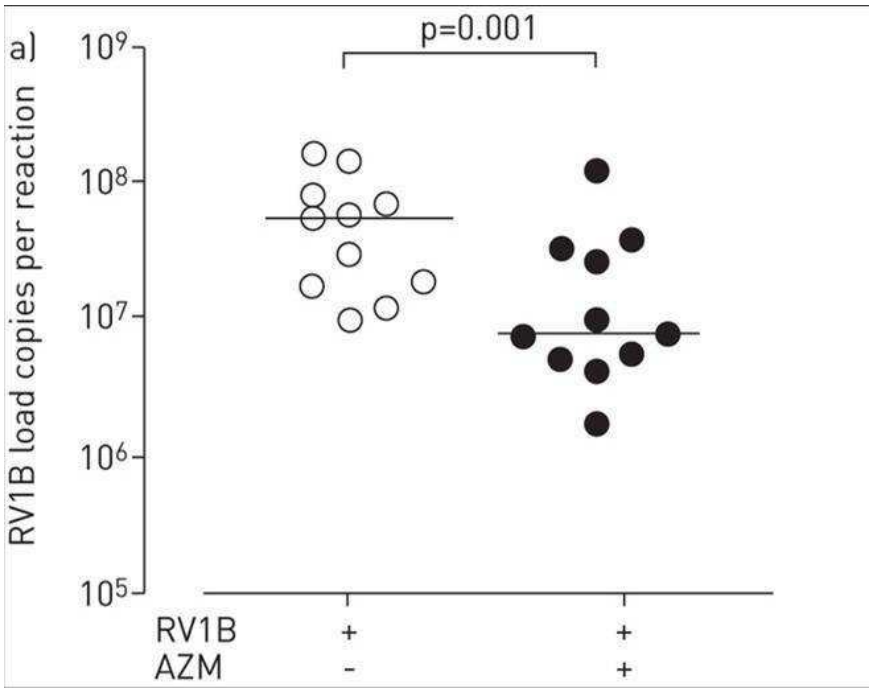


Schögler A. et al. *ERJ* 2015

Cellules épithéliales CF ont une susceptibilité accrue au RV1B :

Virus dans surnageant CF = 2,7 x cellules contrôles

AZM réduit la réplication virale x 9 des cellules épithéliales contrôles infectées par RV1B



Cellules épithéliales CF :

AZM diminue réplication virale x 7

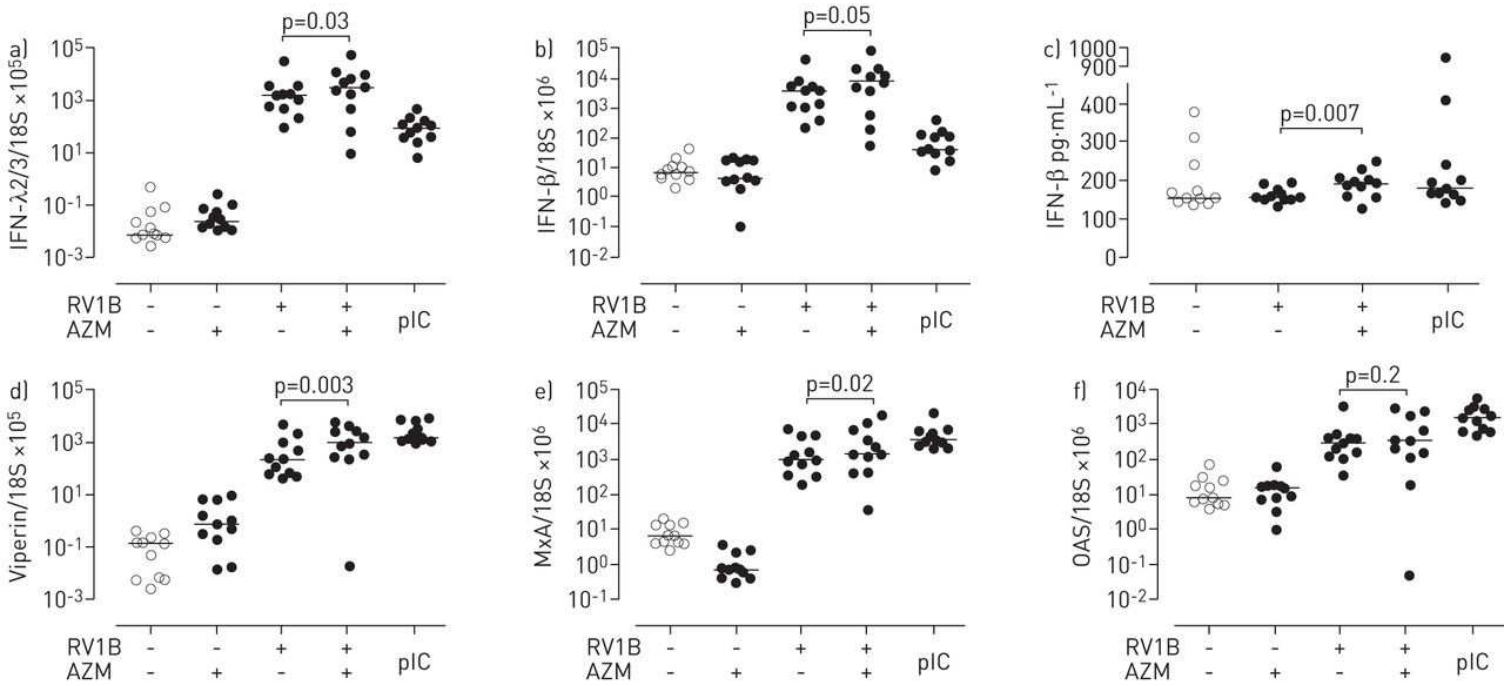
Schögler A. et al. *ERJ* 2015

Amplification réponse antivirale par **la voie de l'Interféron :**

PRRs (pattern recognition receptors), IFN, et ISGs (IFN-stimulated genes)

Pas par cytotoxicité induite par AZM

Pas par action anti-inflammatoire de l'AZM



Schögler A. et al. *ERJ* 2015

Effet antiviral azithromycine sur cellules épithéliales CF *in vitro*

Schögler A. et al. *ERJ* 2015

➔Nécessité études cliniques :

Prevention of Bronchiectasis in Infants With Cystic Fibrosis (COMBATCF)

Clinicaltrials NCT01270074

➔Consensus français prescription AZM

National consensus regarding azithromycin use in cystic fibrosis

Abely M. et al. *Rev Mal Respir* 2015 Jun;32(6):557-65

➔Si prescription : contrôle ECG (QTc)

Lenehan PJ et al. *JCF* 2015 Dec 11[Epub ahead of print]

Explorations

Diabète

Acta Diabetol
DOI 10.1007/s00592-015-0791-3

ORIGINAL ARTICLE

The 1-h oral glucose tolerance test glucose and insulin values are associated with markers of clinical deterioration in cystic fibrosis

Adèle Coriati[1,2] · Sophie Ziai[1,2] · Annick Lavoie[3] · Yves Berthiaume[1,3,4] · Rémi Rabasa-Lhoret[1,2,3,4]

Acta Diabetologica 2015 Jul 29

240 patients

adultes (25,8 ± 7,9 ans)

BMI 21,7 ±3 kg/m2

VEMS 73,2 ± 21,4%

80,3% enzymes pancréatiques

Profil de tolérance glucidique :
56,3% : Normal
28,3 % : Intolérance glucidique
15,4 % : Diabète

HGPO :
1.75 g de glucose/kg, maximum 75 g
Prélèvement glycémie et insulinémie :
T0, 30, 60, 90 et 120 minutes
Spirométrie
BMI

Analyse à **T60** :

Comparaison VEMS et BMI groupes :

- glycémie > ou < **11 mmol/L**
- insulinémie < ou > **43,4µU/ml**

Corrélations :

- valeurs glycémies et insulinémies
- avec VEMS et BMI

Coriati A. et al. *Acta Diabetol.* 2015

Glycémie haute à T60 corrélée à un VEMS bas

(r = −0.225, P = 0.001)

Insulinémie haute à T60 corrélée à un BMI haut

(r = 0.184, P = 0.004)

	Low I < 43.4 µU/mL (N = 119)			High $I \geq$ 43.4 µU/mL (N = 121)		
	Low G < 11.0 mmol/L (N = 59)	High $G \geq$ 11.0 mmol/L (N = 60)	P value	Low G < 11.0 mmol/L (N = 60)	High $G \geq$ 11.0 mmol/L (N = 61)	P value
Sex (% women)	42.4	33.3	0.311	55.0	54.1	0.921
Age (years)	25.6 ± 6.2	26.4 ± 7.1	0.744	25.1 ± 7.5	26.3 ± 10.3	0.835
Weight (kg)	56.9 ± 9.5	59.3 ± 10.8	0.217	62.4 ± 11.3	61.4 ± 11.5	0.631
BMI (kg/m^2)	20.8 ± 2.4	21.3 ± 3.1	0.350	22.6 ± 3.2	22.2 ± 2.9	0.532
% FEV_1	71.9 ± 22.5	67.5 ± 20.2	0.280	80.8 ± 17.0	72.5 ± 23.4	0.05

Coriati A. et al. *Acta Diabetol.* 2015

- Chez l'adulte, données à 1h de l'HGPO corrélées à fonction respiratoire / BMI

- Chez l'enfant
  - Corrélation VEMS et glycémie à T60

  Brodsky J. et al. *Diabetes Care* 2011 Feb; 34(2) : 292-5
  - Pas d'effet significatif objectivé de la glycémieT60 sur déclin VEMS (manque de puissance)

  Sheikh S. et al. *Ped. Pulmonol*. 2015 Oct; 50(10): 963-9

➔ Prendre en compte le T60 !

Coriati A. et al. *Acta Diabetol.* 2015

Audition

ELSEVIER

Journal of Cystic Fibrosis 14 (2015) 248 – 254

Journal of Cystic Fibrosis
www.elsevier.com/locate/jcf

Original Article

High-frequency audiometry reveals high prevalence of aminoglycoside ototoxicity in children with cystic fibrosis

Ghada Al-Malky [a,*], Sally J. Dawson [a], Tony Sirimanna [b], Emmanouil Bagkeris [c], Ranjan Suri [d]

[a] University College London Ear Institute, 332 Gray's Inn Road, London WC1X 8EE, UK
[b] Department of Audiology & Audiological Medicine, Great Ormond Street Hospital, London WC1N 3JH, UK
[c] MRC Centre of Epidemiology for Child Health, UCL Institute of Child Health, University College London, London WC1N 1EH, UK
[d] Department of Paediatric Respiratory Medicine, Great Ormond Street Hospital, London WC1N 3JH, UK

70 patients . 10 (4-16) ans. Sans anomalie de l'oreille moyenne

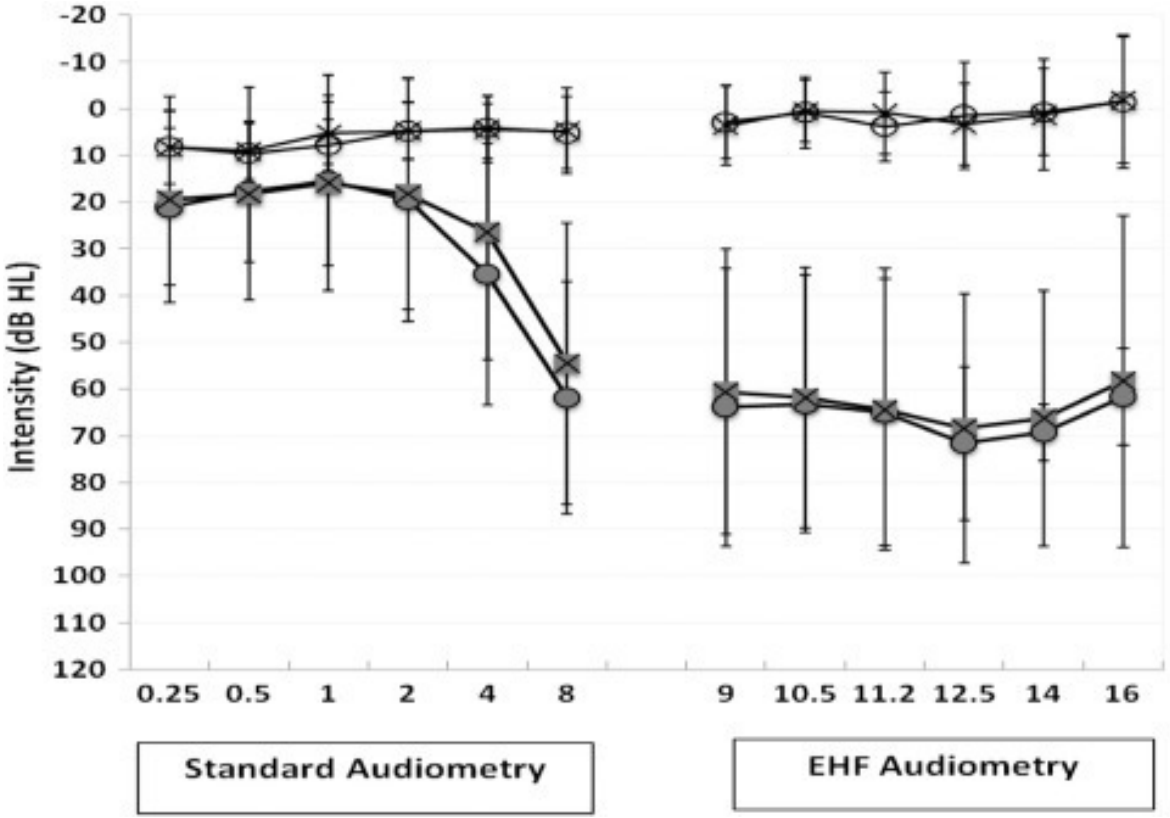
Nombre de cures d'aminosides et taux sériques :

- « non-exposés » : n = 7
- « faiblement exposés » <10 cures : n = 38
- « fortement exposés » ≥10 cures (10 à 40, moyenne 20) n = 25

Evaluation :

Audiométrie tonale standard (PTA) : fréquence 0,25 à 8 kHz
Audiométrie haute fréquence (EHF) : fréquence 9 à 16 kHz
Oto-émissions acoustiques

Al-Malky G. et al. *JCF* 2015



Facteurs associés ototoxicité :

- Nombre **cures aminosides IV** : 11/25 (44%) des enfants fortement exposés
- Vancomycine IV
- Tobramycine nébulisée

Ototoxicité **non corrélée au taux sérique d'aminosides**

13/63 (21%) des patients exposés aux aminosides

0/7 des patients non exposés

5 enfants : seulement à 8kHz

15/63 (25%) des patients exposés aux aminosides

0/7 des patients non exposés

2 ototoxicités non détectées par PTA

Al-Malky G. et al. *JCF* 2015

Quel examen ?

Age (yrs)	Gender	Symptoms	No. of IV AGs	Assessment of ototoxicity[a]			
				Standard PTA	Brock[b]	EHF PTA	DPOAE
15.9	M	HL	3	+	0	++	++
14.6	F	HL, T	3	++	3	++	++
15.1	F	None	4	−ve	0	++	−ve
12.0	F	None	8	++	0	++	−ve
5.5	F	None	14	+	0	++	−ve
10.8	F	HL, T	14	++	2	++	++
14.0	M	None	15	−ve	0	++	++
16.4	F	None	17	++	1	++	−ve
12.5	M	HL	18	+	1	++	NT
13.8	F	HL, T	24	++	4	++	NT
16.2	F	None	26	+	1	++	−ve
12.9	F	None	30	++	1	++	++
14.4	M	HL, T	32	++	2	++	NT
11.8	F	T	37	+	1	++	++
10.6	F	None	40	++	1	++	++

HL: hearing loss, T: tinnitus, RT: right ear, NT: not tested.

[a] '−ve': normal non-ototoxic responses, '+': ototoxicity recorded at one frequency only (8 kHz at standard PTA), '++': ototoxicity recorded at ≥2 consecutive frequencies.

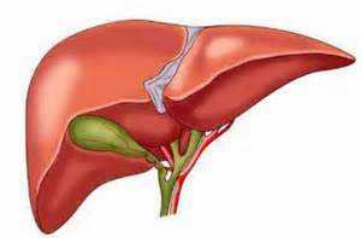
[b] Brock's hearing loss grading (0 to 4): 0 = no ototoxicity, 4 = severe ototoxicity.

8/15 enfants n'ont pas de symptômes

Al-Malky G. et al. *JCF* 2015

- Ototoxicité chez 25 % des enfants exposés aux aminosides !
  - Surtout si plus de 10 cures
  - Pas de différence des taux sériques entre patients avec ou sans ototoxicité
- Les auteurs conseillent **une audiométrie haute fréquence annuelle**

Al-Malky G. et al. *JCF* 2015



Atteinte hépatique

HEPATOLOGY
Official Journal of the American Association for the Study of Liver Diseases
AASLD

Aspartate Aminotransferase to Platelet Ratio and Fibrosis-4 as Biomarkers in Biopsy-Validated Pediatric Cystic Fibrosis Liver Disease

Daniel H. Leung,[1,2] Mahjabeen Khan,[2] Charles G. Minard,[3] Danielle Guffey,[3] Louise E. Ramm,[4] Andrew D. Clouston,[5] Gregory Miller,[5] Peter J. Lewindon,[4,6] Ross W. Shepherd,[1,2,4] and Grant A. Ramm[4,7]

Hepatology 2015 Nov ; 62(5) :1576-83

67 enfants (8,7 ans) CFLD si ≥ 2 critères

- Hépatomégalie +/- splénomégalie
- Elévation ALT > 6 mois
- Echographie hépatique anormale

104 enfants CFnLD

10,9 ans

Biopsie hépatique (n= 51) :

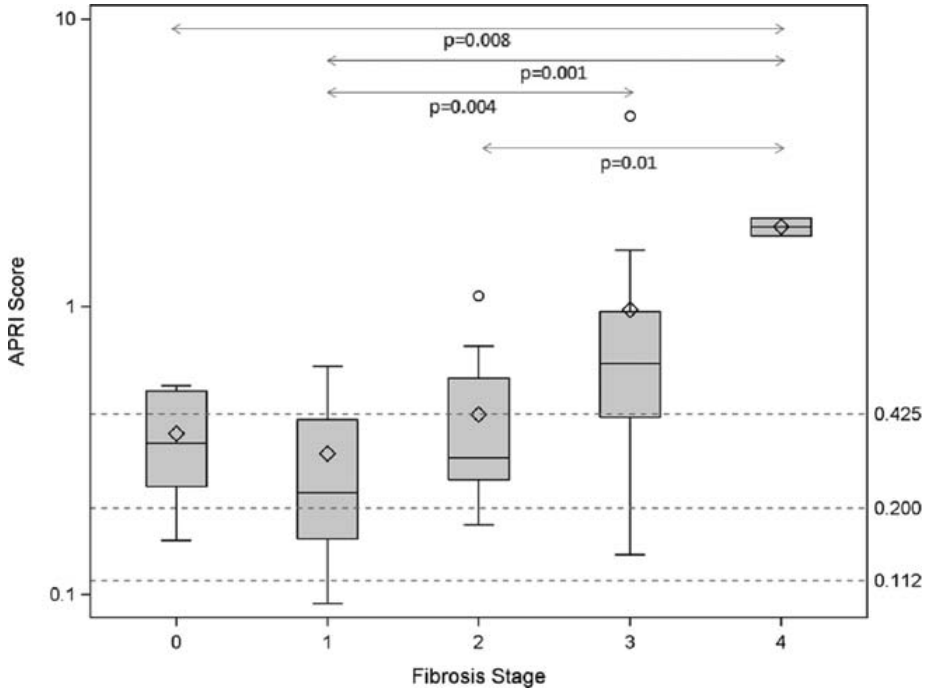
classification Metavir fibrose stade 0 à 4

$$\text{APRI} = \frac{\text{AST/upper limit of normal AST} \times 100}{\text{Platelet Count } (10^9/\text{L})}$$

$$\text{FIB-4} = \frac{\text{Age (years)} \times \text{AST [U/L]}}{\text{Platelets } [10^9/\text{L}] \times (\sqrt{\text{ALT [U/L]}})}$$

Leung DH. et al. *Hepatology* 2015

- Index APRI et FIB-4
  - prédictifs de **CFLD**
  - Corrélés à la **gravité histologique**
  - APRI meilleur que FIB4

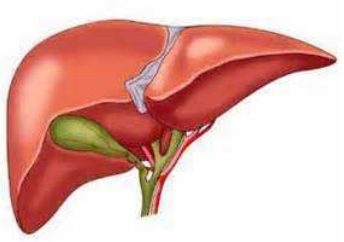


- FIB-4 prédit mieux l'**hypertension portale** qu'APRI
- Ne détectent pas les patients porteurs de **varices oesophagiennes**

Table 3. Proposed APRI Cutoffs for Fibrosis Stage

APRI Score	Predicted Fibrosis Stage
<0.112	0
(0.112, 0.200)	1
(0.200, 0.425)	2
≥0.425	3/4

Leung DH. et al. *Hepatology* 2015



$$\text{APRI} = \frac{\text{AST/upper limit of normal AST} \times 100}{\text{Platelet Count } (10^9/\text{L})}$$

- APRI = outils de dépistage non invasif de l'atteinte hépatique de la mucoviscidose
- A combiner avec données cliniques, biologiques et échographiques
- Indication évolutivité ?

Leung DH. et al. *Hepatology* 2015

Prise en charge

Nutrition - Psychologie

Behavioral and Nutritional Treatment for Preschool-Aged Children With Cystic Fibrosis: A Randomized Clinical Trial

Powers, Scott; Stark, Lori; Chamberlin, Leigh; Filigno, Stephanie; Sullivan, Stephanie; Lemanek, Kathleen; Butcher, Jennifer; Driscoll, Kimberly; Daines, Cori; Brody, Alan; Schindler, Teresa; Konstan, Michael; McCoy, Karen; Nasr, Samya; Castile, Robert; Acton, James; Wooldridge, Jamie; Ksenich, Roberta; Szczesniak, Rhonda; Rausch, Joseph; Stallings, Virginia; Zemel, Babette; Clancy, John

JAMA Pediatrics
Formerly *Archives of Pediatrics & Adolescent Medicine*

169(5):e150636, May 2015

Patients 2 à 6 ans. 7 centres USA. Randomisée contrôlée

Intervention comportementale et nutritionnelle n = 36	Education et attention (contrôle) n = 42

7 sessions hebdomadaires puis 4 sessions mensuelles :

Entretien ou téléphone

- Habitudes alimentaires
- Gestion pratique snacks/repas
- **Comportement** à table (social learning theory)
- **Evaluation** repas et prise d'enzymes
- **Objectifs** à chaque repas

- Informations nutritionnelles théoriques
- Informations générales sur mucoviscidose et pédiatrie

Pas d'auto-évaluation, pas d'objectifs à chaque repas, pas d'évaluation graphique, pas d'aide comportementale

Powers S. et al. *JAMA Ped.* 2015

Table 3. Changes in Energy Intake, Weight *Z* Score, and Height *Z* Score[a]

Variable	Mean (SD)						Group Mean Difference in Change (95% CI)	*P* Value
	Behavioral and Nutrition Treatment (n = 36)			Education and Attention Control Treatment (n = 42)				
	Baseline	Posttreatment	Change	Baseline	Posttreatment	Change		
Energy intake, kcal/d[b]	1462 (330)	1947 (459)	485 (355)	1461 (332)	1529 (387)	58 (248)	431 (282 to 581)	<.001
Weight *z* score	−0.36 (0.75)	−0.24 (0.76)	0.12 (0.40)	0.51 (0.85)	−0.45 (0.77)	0.06 (0.32)	0.09 (−0.06 to 0.24)	.25
	Baseline	Follow-up	Change	Baseline	Follow-up	Change		
Height *z* score	−0.39 (0.85)	−0.30 (0.88)	0.09 (0.26)	−0.69 (0.82)	−0.71 (0.86)	−0.02 (0.32)	0.14 (0.001 to 0.27)	.049
Energy intake, kcal/d[b,c]	1462 (330)	1960 (440)	545 (504)	1461 (332)	1739 (416)	277 (429)	239 (33 to 444)	.02
Weight *z* score[c]	−0.36 (0.75)	−0.22 (0.83)	0.15 (0.48)	−0.51 (0.85)	−0.40 (0.96)	0.11 (0.62)	0.07 (−0.19 to 0.32)	.61

Amélioration apports caloriques et taille par une intervention comportementale et nutritionnelle

Powers S. et al. *JAMA Ped.* 2015

Conforte données cochrane 2014

Goldbeck L. et al. **Psychological interventions for individuals with cystic fibrosis and their families**. *Cochrane Database of Systematic Reviews* 2014

via the Internet (in English and French language). After failure of nutrition counselling alone to improve calorie intake, behavioral interventions aiming at improving intake should be considered, in the short-term, as an alternative to tube-feeding with its medical and psychosocial side effects (e.g. Oliver 2004; Van Biervliet

Intervention comportementale = **outil supplémentaire** pour l'enfant préscolaire

Powers S. et al. *JAMA Ped.* 2015

Posture – Activité Physique

The Journal of Pediatrics

Volume 166, Issue 3, March 2015, Pages 710–716.e2

Original Article

Physical Exercise Recommendations Improve Postural Changes Found in Children and Adolescents with Cystic Fibrosis: A Randomized Controlled Trial

Cláudia S. Schindel, MsC[1], Patrícia X. Hommerding, PhD[2], Denizar A.S. Melo, PhD[3], Rafael R. Baptista, PhD[4], Paulo J.C. Marostica, PhD[5], Márcio V.F. Donadio, PhD[1, 3,]

Phase I

34 patients

7 à 20 ans

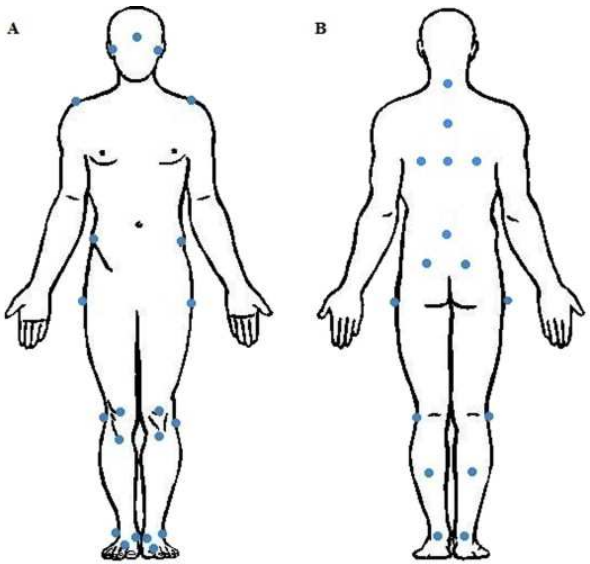
VEMS 99%

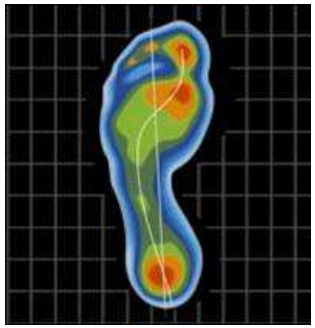
34 sujets sains

appariés

Evaluation Posturale

Baropodométrie statique et dynamique





Phase II

17 patients

« contrôles »

17 patients

« activité physique »

3 mois

Livret illustré. Tel 1x / 2 semaines

3 fois / semaine

Exercice aérobie au choix
>20 minutes
Exercices d'étirement
2 x20 secondes

Evaluation par questionnaire

Schindel C. et al. *J. Ped.* 2015

Phase I

Anomalies de posture patients versus contrôles :

Inclinaison tête, ceinture scapulaire et pelvis, lordose cervicale, distance latérale thoracique

Pas de différence significative baropodométrique

Phase II

Activité physique améliore la posture

Activité physique modifie baropodométrie

Schindel C. et al. *J. Ped.* 2015

Table V. Comparison of the variation between the control and intervention groups after 3 months of follow-up

Variables	Control (n = 17)	Intervention (n = 17)	*P*	ES
Lung function (Δ)				
FEV_1 (%)	2.7 ± 12.8	−1.8 ± 8.6	.24	0.41
FVC (%)	1.8 ± 12.2	−0.41 ± 6.8	.52	0.22
$FEF_{25\%-75\%}$ (%)	7.3 ± 24.2	−3.8 ± 13.9	.11	0.56
Postural evaluation (Δ)				
Head tilt (°)	0.56 ± 2.4	−0.7 ± 1.8	.59	0.07
Scapular girdle tilt (°)	0.26 ± 1.7	−0.38 ± 1.2	.21	0.43
Pelvic tilt (°)	1.74 ± 3.6	−0.05 ± 4.8	.23	0.42
A-P trunk tilt (°)	−0.34 ± 1.4	−0.09 ± 2.2	.70	0.14
Cervical lordosis (°)	1.8 ± 2.5	−1.8 ± 2.6	.0003	1.41
Thoracic kyphosis (°)	1.2 ± 2.8	−1.2 ± 2.6	.01	0.89
Lumbar lordosis (°)	3.2 ± 6.7	−0.94 ± 4.9	.05	0.71
Lateral chest distance (cm)	0.93 ± 1.0	−0.07 ± 1.2	.01	0.91
Anteroposterior chest distance (cm)	0.45 ± 1.4	0.34 ± 1.1	.08	0.63
Abdominal protrusion (cm)	0.56 ± 1.3	−0.34 ± 1.1	.04	0.75
Static baropodometry (Δ)				
Mean pressure (kgf/cm^2)	7.5 ± 8.5	0.0 ± 0.0	.001	1.25
Area of contact (cm^2)	4.3 ± 5.6	−3.2 ± 8.8	.01	1.02
Anterior displacement (%)	1.3 ± 11.4	−2.8 ± 8.1	.24	0.41
Dynamic baropodometry (Δ)				
Duration of the step (ms)	28.4 ± 166.8	48.9 ± 117	.68	0.14
Maximal pressure (kgf/cm^2)	0.23 ± 0.9	−0.04 ± 0.2	.24	0.41
Area of contact (cm)	56.4 ± 22.1	50.81 ± 13.1	.38	0.31

- Activité physique améliore la posture
- Exercices d'assouplissement associés à exercice aérobie

Schindel C. et al. *J. Ped.* 2015

➔ Recommandations exercice physique : ECFS 2014

Swisher A et al. Exercise and Habitual physical activity for people with cystic fibrosis: a clinical practice guideline for prescription.
Cardiopulmonary Physical Therapy J. Dec 2015: 26 (4) p85-98

Nébulisations

Editor's choice
Scan to access more free content

ORIGINAL ARTICLE

A randomised trial of hypertonic saline during hospitalisation for exacerbation of cystic fibrosis

Ruth L Dentice,[1,2] Mark R Elkins,[1,2] Peter G Middleton,[3] Jennifer R Bishop,[3] Peter A B Wark,[4] Douglas J Dorahy,[4] Christopher J Harmer,[2] Honghua Hu,[2,5] Peter T P Bye[1,2]

THORAX

Thorax 2016 ; 71 :141-147

Patients adultes hospitalisés pour exacerbation

67 patients traités

sérum salé hypertonique (HS) x3/j

28±9 ans VEMS = 49±22

65 patients contrôles

sérum salé isotonique x 3 / j

27±9 ans VEMS = 47±19

Bonne tolérance

Bonne adhérence aux nébulisations

Pas de réduction du temps d'hospitalisation :

12 jours groupe HS versus 13 jours groupe contrôle (ns)

Dentice RL et al. *Thorax* 2016

Evolution VEMS

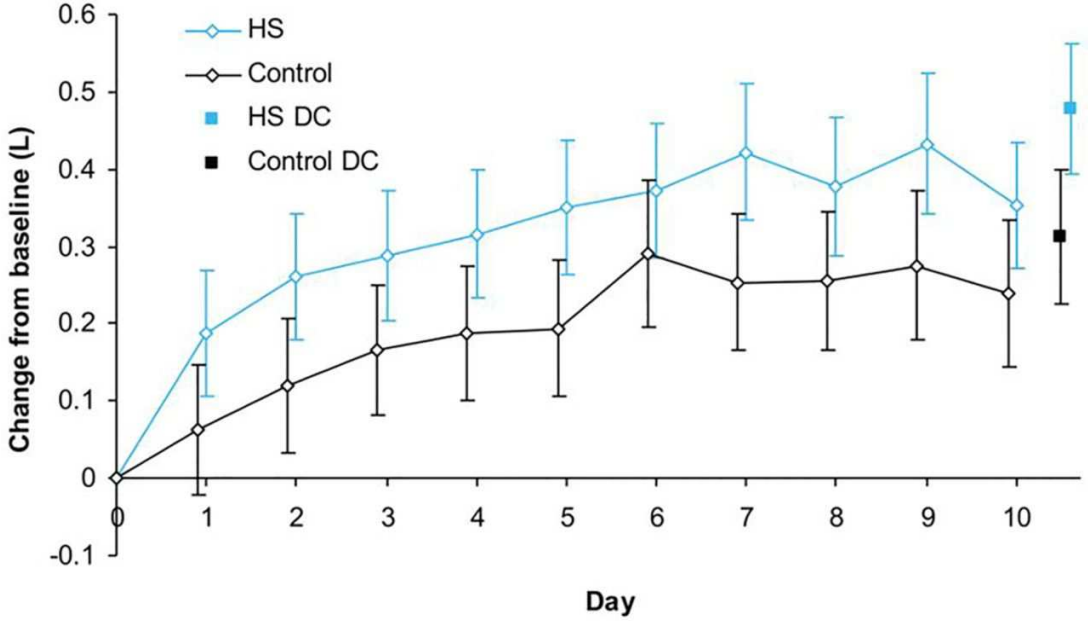
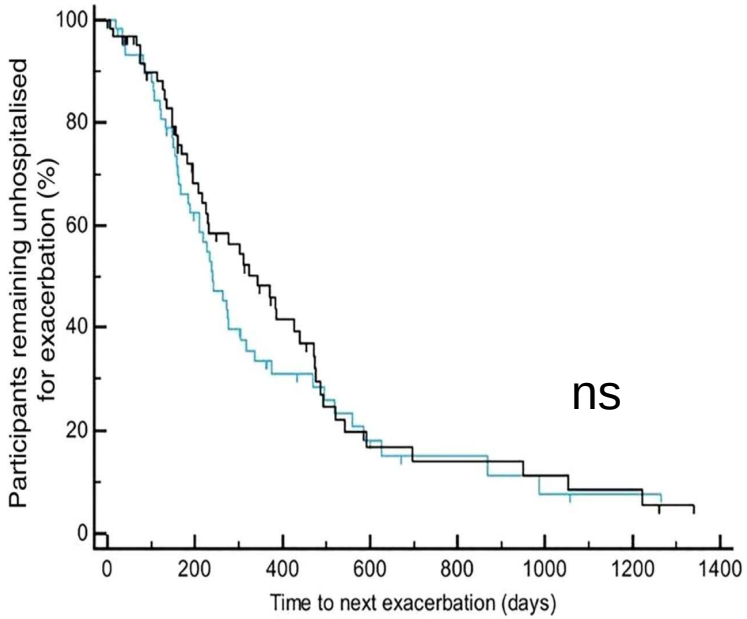


Table 2 Number and proportion of trial participants in each group who failed to regain their pre-exacerbation FEV_1, with relative risk (95% CI) due to hypertonic saline use

Characteristic	Hypertonic saline (n=67)	Control (n=65)	Relative risk (95% CI)
Failed to regain pre-exacerbation FEV_1 by discharge, n (%)	17 (25)	28 (43)	0.59 (0.36 to 0.96)

Pre-exacerbation FEV_1 is defined as the best forced expiratory volume in 1 s recorded as an outpatient in the 6 months before the exacerbation.



Symptômes :

Groupe HS : diminution **troubles du sommeil, encombrement bronchique, dyspnée**, fatigue et toux (EVA)

Pas de différence sur score de qualité de vie

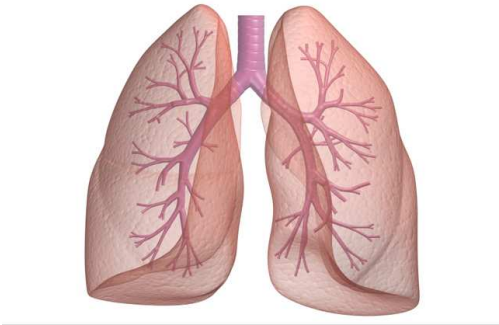
Dentice RL et al. *Thorax* 2016

- HS lors des exacerbations bien toléré, bonne adhérence
- Pas d'effet sur durée d'hospitalisation
- Mais amélioration :
  - plus rapide de la fonction respiratoire
  - symptômes subjectifs
  - taux de récupération du VEMS pré-exacerbation

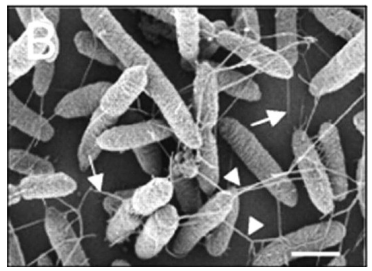
➔ Pas d'argument pour interrompre HS lors d'une exacerbation

➔ CAT lors des cures à domicile ?

Dentice RL et al. *Thorax* 2016



Transplantation



Pan-Resistant *Achromobacter xylosoxidans* and *Stenotrophomonas maltophilia* Infection in Cystic Fibrosis Does Not Reduce Survival After Lung Transplantation

Leonard Jason Lobo, MD,[1] Zeynep Tulu, MS, MEMP,[2] Robert M. Aris, MD,[1] and Peadar G. Noone, MD[1]

Transplantation. 2015 October ; 99 (10) : 2196-202

Etude rétrospective : 1990 – 2013. Transplantations > 16 ans (n = 186)

Analyse *S. Maltophilia* (n=31) et *A. xylosoxidans* (n=24) résistants

Devenir post greffe : survie, mortalité attribuable au germe

	Pan-resistant *S. maltophilia* (n = 5)	MDR *S. maltophilia* (n = 26)	Pan-resistant *A. xylosoxidans* (n = 9)	MDR *A. xylosoxidans* (n = 15)
Recurrence of primary pathogen within first year of transplantation	1 (20%)	12 (46%)	9 (100%)	5 (33%)
P values	0.34		0.002	

Décès	4 (80%)	13 (50%)	8 (89%)	10 (67%)
Décès < 1 an	0	7 (27%)	0	2 (13%)
Décès par infection par germe initial	**0**	**2 (8%)**	**0**	**2 (13 %)**

Lobo L. et al. *Transplantation* 2015

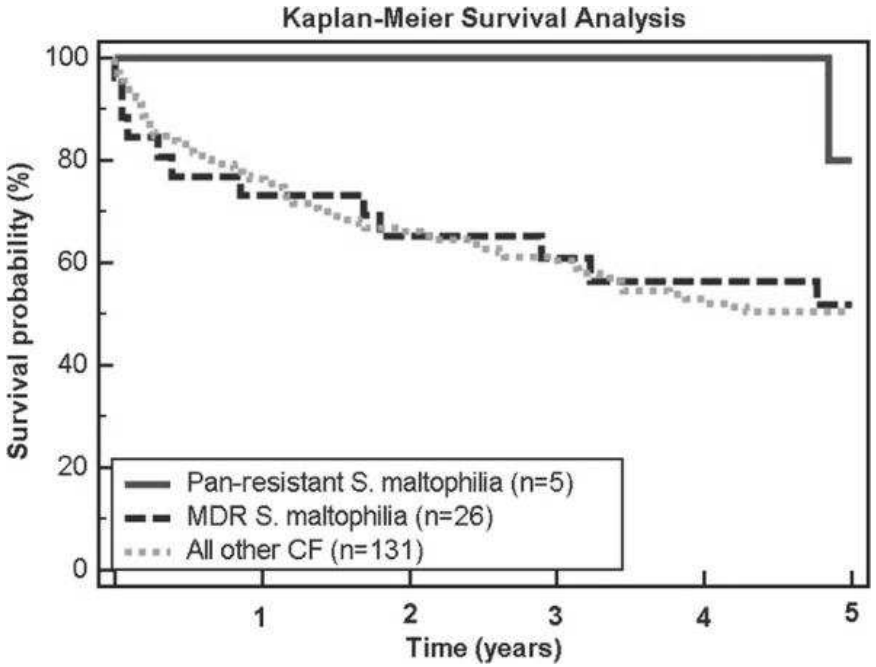


FIGURE 1 . The 5-year survival, following lung transplantation, comparison of pan-resistant S maltophilia (n = 5), MDR S maltophilia (n = 26), and CF patients without A xylosoxidans, S maltophilia or B cenocepacia (n = 131). **P value of 0.43.**

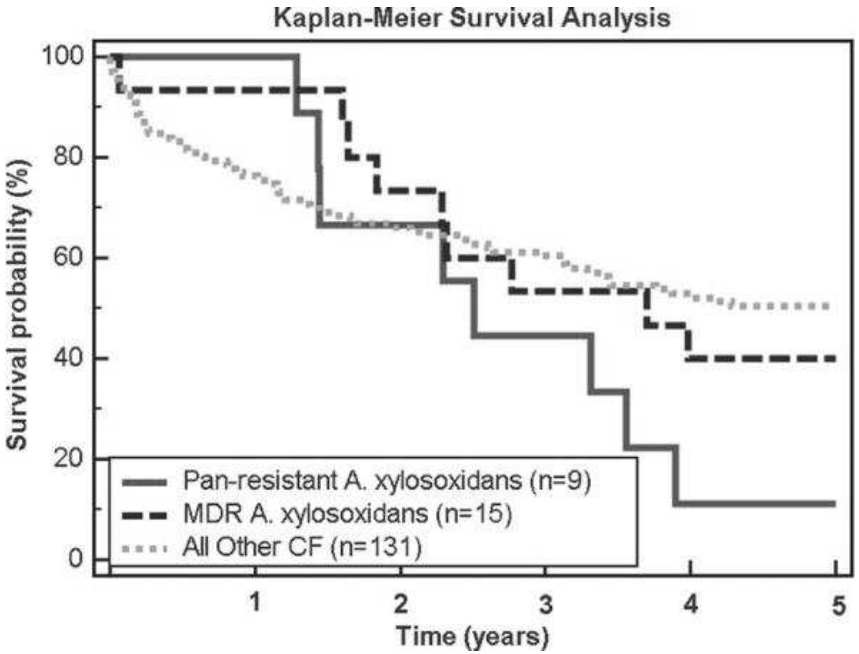
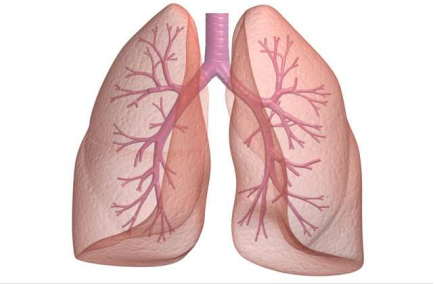
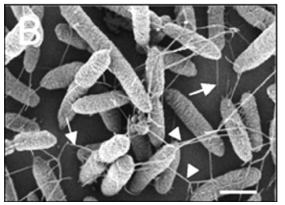


FIGURE 2 . The 5-year survival, following lung transplantation, comparison of pan-resistant A xylosoxidans (n = 9), MDR A xylosoxidans (n = 15), and CF patients without A xylosoxidans, S maltophilia or B cenocepacia (n = 131). **P value of 0.23.**

Lobo L. et al. *Transplantation* 2015





Brooke J Clin. Microbiol. Rev. 2012

• Récurrence fréquente en post greffe de *S. Maltophilia* et *A. xylosoxidans* résistants

• Pas de différence de survie post transplantation (mais petit effectif +++)

• Les auteurs préconisent que la présence de ces germes **n'écarte pas la possibilité d'une transplantation**

Lobo L. et al. *Transplantation* 2015

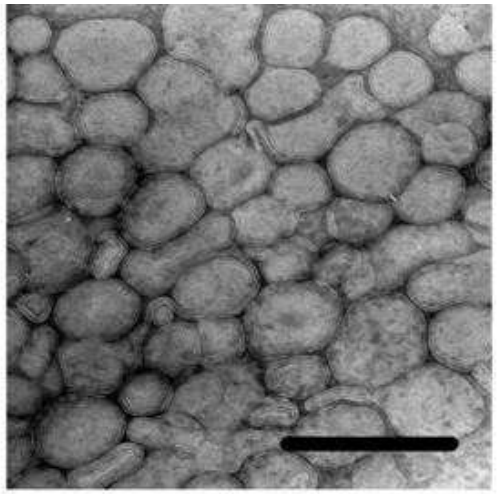
Thérapie génique

Repeated nebulisation of non-viral *CFTR* gene therapy in patients with cystic fibrosis: a randomised, double-blind, placebo-controlled, phase 2b trial

Eric W F W Alton, David K Armstrong, Deborah Ashby, Katie J Bayfield, Diana Bilton, Emily V Bloomfield, A Christopher Boyd*, June Brand, Ruaridh Buchan, Roberto Calcedo, Paula Carvelli, Mario Chan, Seng H Cheng, D David S Collie, Steve Cunningham*, Heather E Davidson, Gwyneth Davies, Jane C Davies*, Lee A Davies, Maria H Dewar, Ann Doherty, Jackie Donovan, Natalie S Dwyer, Hala I Elgmati, Rosanna F Featherstone, Jemyr Gavino, Sabrina Gea-Sorli, Duncan M Geddes, James S R Gibson, Deborah R Gill*, Andrew P Greening, Uta Griesenbach*, David M Hansell, Katharine Harman, Tracy E Higgins*, Samantha L Hodges, Stephen C Hyde*, Laura Hyndman, J Alastair Innes*, Joseph Jacob, Nancy Jones, Brian F Keogh, Maria P Limberis, Paul Lloyd-Evans, Alan W Maclean, Michelle C Manvell, Dominique McCormick, Michael McGovern, Gerry McLachlan, Cuixiang Meng, M Angeles Montero, Hazel Milligan, Laura J Moyce, Gordon D Murray*, Andrew G Nicholson, Tina Osadolor, Javier Parra-Leiton, David J Porteous*, Ian A Pringle, Emma K Punch, Kamila M Pytel, Alexandra L Quittner, Gina Rivellini, Clare J Saunders, Ronald K Scheule, Sarah Sheard, Nicholas J Simmonds, Keith Smith, Stephen N Smith, Najwa Soussi, Samia Soussi, Emma J Spearing, Barbara J Stevenson, Stephanie G Sumner-Jones, Minna Turkkila, Rosa P Ureta, Michael D Waller, Marguerite Y Wasowicz, James M Wilson, Paul Wolstenholme-Hogg, on behalf of the UK Cystic Fibrosis Gene Therapy Consortium*

THE LANCET
Respiratory Medicine

Vol 3, September 2015: 684-691

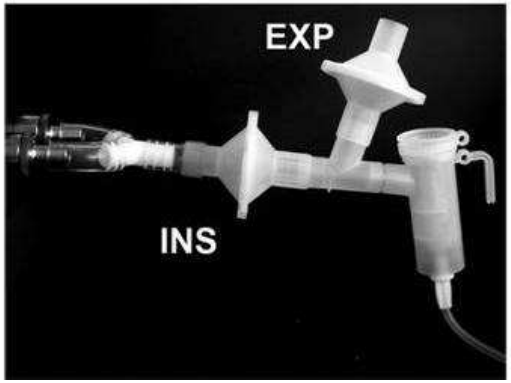


400 nm

gêne CFTR : 13,3 mg ADN plasmidique

+

liposome : 7,5 mg de mélange lipidique non viral



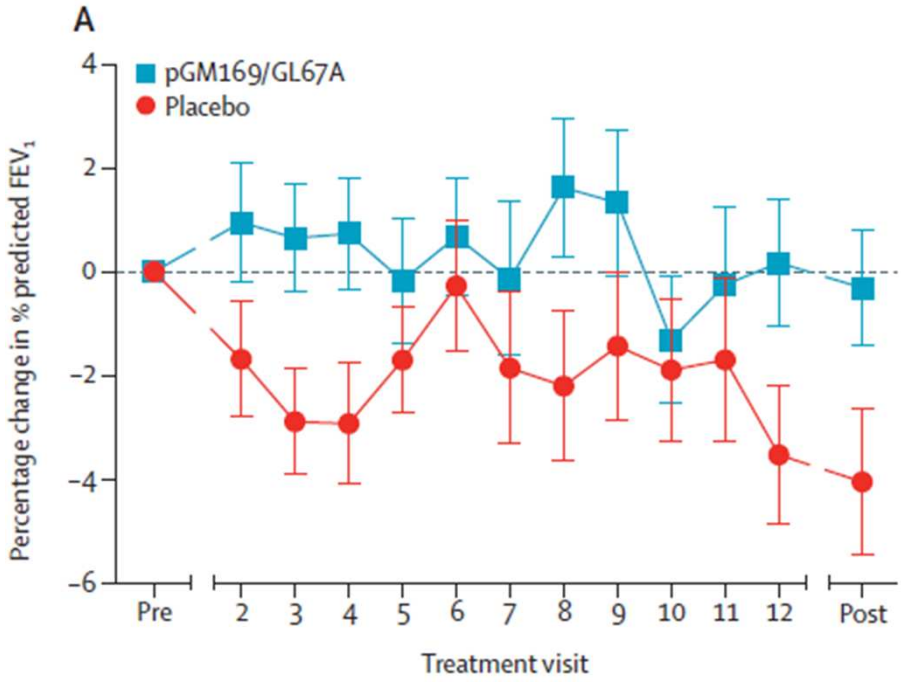
Images : Davies LA et al. *Hum Gene Ther Clin Dev* 2014

54 traités vs 64 placebo
(sérum salé 0,9 %)
>12 ans
50 à 90 % VEMS

Nébulisation **tous les 28 jours (+/- 5 jours) pendant 1 an**

Stop RhDnase la veille et le jour de la nébulisation

Alton E et al. *Lancet Respi Med* 2015



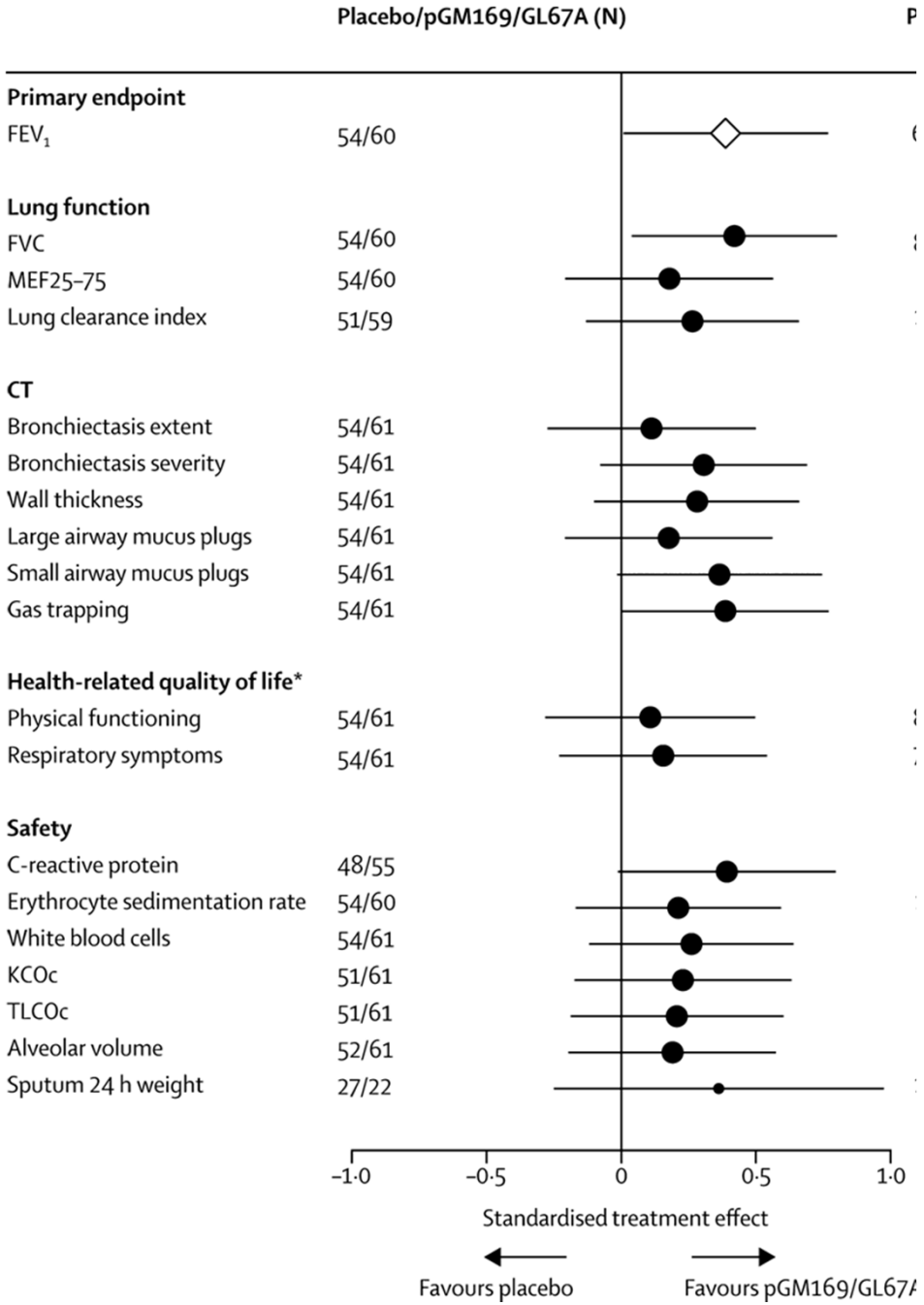
Stabilisation du VEMS (p =0,046)

Amélioration CVF et air piégé

Pas d'amélioration des autres paramètres

Tolérance OK

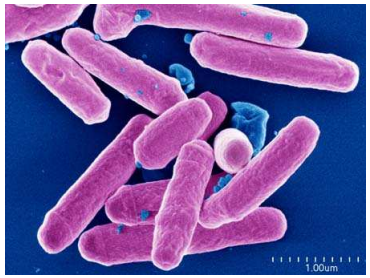
Alton E et al. *Lancet Respi Med* 2015



- Confirme **bonne tolérance** du traitement
- Originalité = vecteur non viral
- **Stabilisation** paramètre principal (VEMS)
- Sous-groupes répondeurs à identifier ?
- **Attente phase III** (en espérant meilleure efficacité …)

Alton E et al. Lancet Respi Med 2015

Mycobactéries



Supplement

OPEN ACCESS

US Cystic Fibrosis Foundation and European Cystic Fibrosis Society consensus recommendations for the management of non-tuberculous mycobacteria in individuals with cystic fibrosis

R Andres Floto,[1,2] Kenneth N Olivier,[3] Lisa Saiman,[4] Charles L Daley,[5] Jean-Louis Herrmann,[6,7] Jerry A Nick,[8] Peadar G Noone,[9] Diana Bilton,[10] Paul Corris,[11] Ronald L Gibson,[12] Sarah E Hempstead,[13] Karsten Koetz,[14] Kathryn A Sabadosa,[13] Isabelle Sermet-Gaudelus,[15] Alan R Smyth,[16] Jakko van Ingen,[17] Richard J Wallace,[18] Kevin L Winthrop,[19] Bruce C Marshall,[20] Charles S Haworth[2]

THORAX

Thorax 2016 ; 71 : i1–i22

Cystic Fibrosis Foundation and European Cystic Fibrosis Society recommendations on non-tuberculous mycobacteria (NTM) management in cystic fibrosis (CF).

Screening	**1.** The potential for cross-infection of NTM (particularly *M. abscessus* complex) between individuals with CF should be minimised by following national infection control guidelines.
	2. Cultures for NTM be performed annually in spontaneously expectorating individuals with a stable clinical course.
	3. In the absence of clinical features suggestive of NTM pulmonary disease, individuals who are not capable of spontaneously producing sputum do not require screening cultures for NTM.
	4. Culture and smears for acid fast bacilli from sputum should be used for NTM screening.
	5. Oro-pharyngeal swabs should not be used for NTM screening.
Microbiology	**6.** Cultures and smears for acid fast bacilli (AFB) from sputum, induced sputum, bronchial washings or broncho-alveolar lavage samples can be used to evaluate individuals with CF suspected to have NTM pulmonary disease.
	7. Transbronchial biopsies should not be routinely used to detect NTM in individuals with CF suspected to have NTM pulmonary disease.
	8. Oro-pharyngeal swabs should not be used to perform diagnostic smears and cultures in individuals with CF suspected to have NTM pulmonary disease.
	9. Respiratory tract samples should be cultured using both solid and liquid media.
	10. The incubation duration for NTM cultures should be for a minimum of 6 weeks.
	11. An NTM culture should be processed within 24 hours of collection to optimize the detection of NTM in respiratory samples. If a delay in processing is anticipated, refrigeration of samples is advised.
	12. Respiratory tract samples should be decontaminated using the standard N-Acetyl L-cysteine NALC (0.5%) – NaOH (2%) method.
	13. If a sample remains contaminated with gram-negative bacteria after standard NALC-NaOH decontamination, it should be further treated with either 5% oxalic acid or 1% chlorhexidine.
	14. Non-culture based methods should not be used for detecting NTM in respiratory tract samples.
	15. All NTM isolates from individuals with CF should undergo molecular identification.
	16. All NTM isolates from individuals with CF should be identified to the species level, except for *M. intracellulare*, *M. avium and M. chimaera*, where identification can be limited to *M. avium* complex (MAC), and *M. abscessus* complex, which should be sub-speciated.
	17. For *M. avium* complex, clarithromycin susceptibility testing should be performed on an isolate recovered prior to initiation of treatment. Clarithromycin susceptibility testing should also be performed on subsequent isolates if the patient a) fails to culture convert after six months of NTM treatment; b) recultures *M. avium* complex after initial culture conversion while on NTM treatment; or c) recultures *M. avium* complex after completion of NTM treatment.
	18. For *M. abscessus* complex, susceptibility testing should include at least clarithromycin, cefoxitin and amikacin (and preferably also tigecycline, imipenem, minocycline, moxifloxacin and linezolid).
	19. Drug susceptibility testing should be performed in accordance with CLSI guidelines.
Diagnosis	**20.** ATS/IDSA criteria for the diagnosis of NTM pulmonary disease should be used in individuals with CF
	21. Other CF pathogens and co-morbidities should be considered as potential contributors to a patient's symptoms and radiological features when determining the clinical significance of NTM positive cultures.
	22. NTM treatment should be considered for individuals with CF who have ATS/IDSA defined NTM pulmonary disease.
	23. Individuals receiving azithromycin as part of their CF medical regimen who have a positive NTM culture should not continue azithromycin treatment while evaluation for NTM disease is underway as azithromycin monotherapy may lead to resistance. A macrolide agent may be included in a multi-drug treatment regimen if criteria are met for NTM disease.
Treatment	**24.** Treatment of *M. abscessus* complex pulmonary disease should involve an intensive phase followed by a continuation phase.
	25. The intensive phase should include a daily oral macrolide (preferably azithromycin) in conjunction with 3-12 weeks of intravenous amikacin and one or more of the following: intravenous tigecycline, imipenem or cefoxitin, guided but not dictated by drug susceptibility testing. The duration of intensive phase therapy should be determined by the severity of infection, the response to treatment and the tolerability of the regimen.
	26. The continuation phase should include a daily oral macrolide (preferably azithromycin) and inhaled amikacin, in conjunction with 2-3 of the following additional oral antibiotics: minocycline, clofazimine, moxifloxacin and linezolid, guided but not dictated by drug susceptibility testing.
	27. Individuals with *M. abscessus* complex pulmonary disease should be managed in collaboration with experts in the treatment of NTM and CF as drug intolerance and drug-related toxicity occur frequently and changes in antibiotic therapy are often required.
	28. Monotherapy with a macrolide or other antimicrobial should never be used in the treatment of *M. abscessus* complex pulmonary disease.
	29. The same antibiotic regimen should be used for treatment of all species within the *M. avium* complex.
	30. Clarithromycin-sensitive *M. avium* complex pulmonary disease should be treated with a daily oral antibiotic regimen containing a macrolide (preferably azithromycin), rifampin and ethambutol.
	31. Intermittent (three-times-per week) oral antibiotic therapy should not be used to treat *M. avium* complex pulmonary disease.
	32. Monotherapy with a macrolide or other antimicrobial agent should never be used in the treatment of *M. avium* complex pulmonary disease.
	33. An initial course of intravenous amikacin should be considered for the treatment of *M. avium* complex pulmonary disease in the presence of one or more of the following: i)AFB smear positive respiratory tract samples; ii) Radiological evidence of lung cavitation or severe infection; iii) Systemic signs of illness.
	34. Clarithromycin-resistant *M. avium* complex pulmonary disease should be managed in collaboration with experts in the treatment of NTM and CF.
	35. Individuals with CF receiving NTM treatment should have expectorated or induced sputum samples sent for NTM culture every 4-8 weeks throughout the entire course of treatment to assess the microbiological response.
	36. A schedule for detecting drug toxicity (including hearing loss, visual loss, renal impairment and liver function test abnormalities) should be set in place at the time of NTM treatment initiation and implemented throughout treatment based on the specific drugs prescribed.
	37. An HRCT scan of the lungs should be performed shortly before starting NTM treatment and at the end of NTM treatment to assess the radiological response.
	38. NTM antibiotic therapy should be prescribed for 12 months beyond culture conversion (defined as three consecutive negative cultures, with the time of conversion being the date of the first of the three negative cultures) as long as no positive cultures are obtained during this 12 months.
	39. Individuals who fail to culture convert despite optimal NTM therapy may benefit from long term suppressive antibiotic treatment.
	40. When amikacin is given intravenously or when streptomycin is given intravenously or intramuscularly, serum levels should be monitored and dosing adjusted to minimize ototoxicity and nephrotoxicity.
	41. Serum levels of other anti-mycobacterial drugs should not be routinely obtained. However, absorption of oral medications is often reduced in CF. Therefore use of therapeutic drug monitoring should be considered for individuals failing to improve despite taking recommended drug regimens or for those on concomitant medications with significant interactions with NTM drugs.
	42. Interferon gamma should not be used as adjuvant therapy for NTM pulmonary disease in individuals with CF.
	43. Vitamin D should be supplemented according to national CF care guidelines.
	44. Lung resection should only be considered in extraordinary circumstances and in consultation with experts in the treatment of NTM and CF.
Transplantation	**45.** All individuals with CF being considered for lung transplantation should be evaluated for NTM pulmonary disease.
	46. The presence of current or previous respiratory tract samples positive for NTM should not preclude individuals being considered for lung transplantation.
	47. Individuals with CF who have NTM pulmonary disease and are being evaluated for transplantation should commence treatment prior to transplant listing.
	48. Individuals with CF receiving NTM treatment with sequential negative cultures may be eligible for transplant listing.
	49. Individuals with CF who have completed treatment for NTM pulmonary disease with apparent eradication of the organism may be eligible for transplant listing.
	50. The presence of persistent *M. abscessus* complex or *M. avium* complex infection despite optimal therapy is not an absolute contraindication to lung transplant referral.

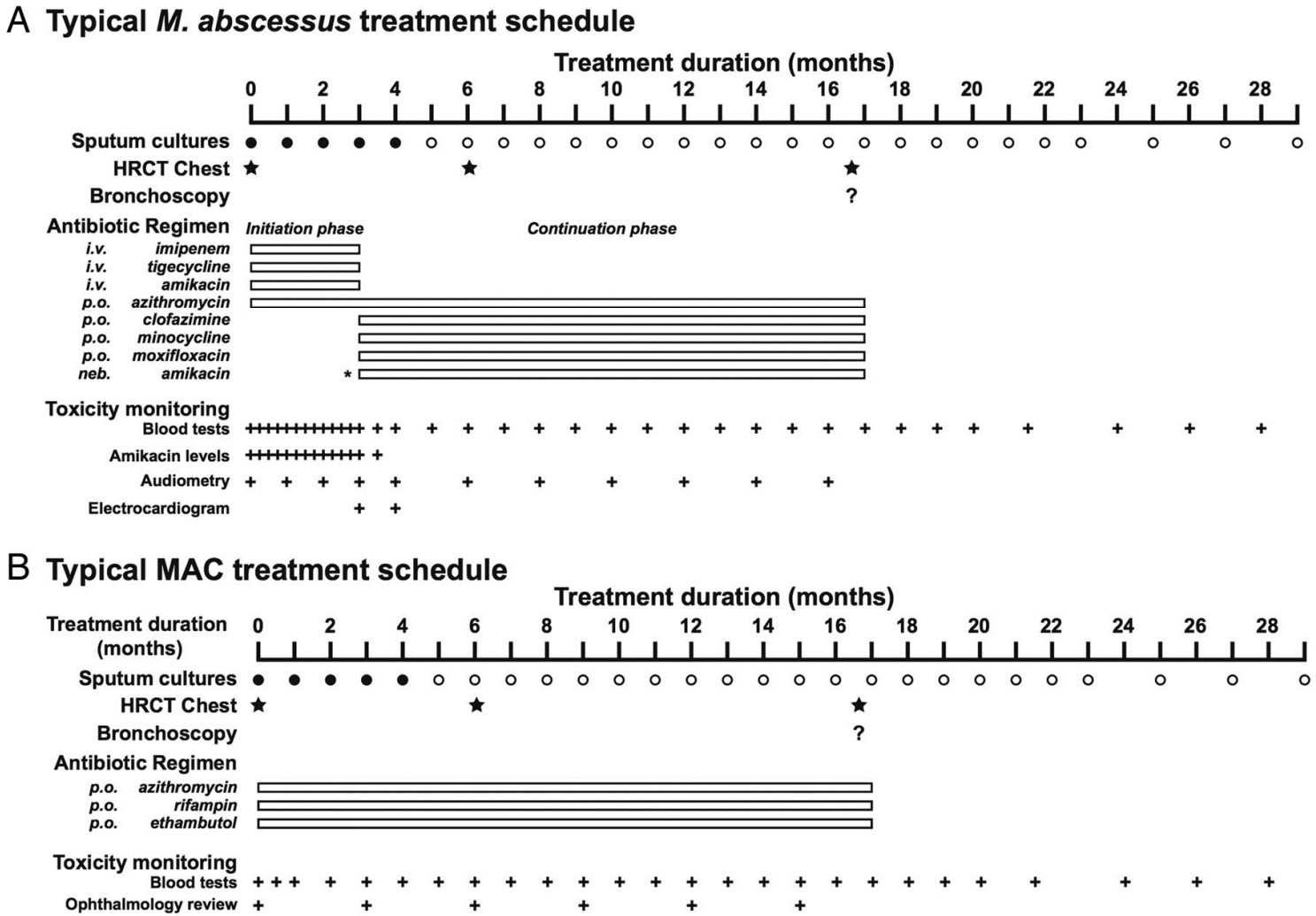
THORAX

Floto RA et al. *Thorax* 2016

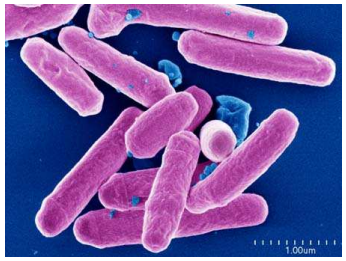
- Facteurs de risque
- Dépistage
- Microbiologie
- Diagnostic d’infection pulmonaire à NTM (consensus ATS-ERS 2007)
- Traitement
- Transplantation

Floto RA et al. *Thorax* 2016

Typical treatment schedules for individuals with CF with Mycobacterium abscessus or MAC pulmonary disease.



R Andres Floto et al. Thorax 2016;71:i1-i22



- Standardiser prélèvements et analyse microbiologique
- Si isolement Mycobactérie atypique

  ➔ Stop azithromycine

  ➔Lire le consensus !

- Si critères d'infection à NTM: « consider treatment»

Qvist T et al. *JCF.* 2015 Oct 5

Albrecht C. et al. *Eur Respir J*. 2016 Feb 4

Floto RA et al. *Thorax* 2016

Et aussi en 2015 …

LCI :

Ramsey K. et al. Lung Clearance Index and structural lung disease on computed tomography in early cystic fibrosis. *AJRCCM* 193 (1): 60, 2016

Stanojevic S. et al. Alternative outcomes for the multiple breath washout in children with CF. *JCF* 2015; 14 : 490-96

Anagnostopoulou P et al. False normal lung clearance index in infants with cystic fibrosis due to software algorithme. Ped pulmonol. 2015 Oct; 50(10) : 970-7

IRM :

Dournes G et al. Lung morphology assessment of cystic fibrosis using MRI with ultra-short echo time at submillimeter spatial resolution. *Eur radiol.* 2016 Feb2

Ciet P et al. Assessment of CF lung disease using motion corrected PROPELLER MRI: a comparison with CT. *Eur radiol.* 2016 Mar;26(3):780-7

Epreuve d'effort :

Quong B. et al. Cardiorespiratory and sensory responses to exercise in adults with mild cystic fibrosis. *J Appl Physiol* 119: 1289–1296, 2015

Fondamental :

Pankow S et al. ΔF508 CFTR interactome remodelling promotes rescue of cystic fibrosis *Nature* 2016

Merci !

François Brémont, Boubou Camara,
Laurence Frezefond, Christelle Garnier,
Hélène Guet-Revillet, Géraldine Labouret,
Emmanuel Mas, Laurent Têtu


Filière
MUCO | CFTR


SOCIETE
FRANCAISE
DE LA
MUCOVISCIDOSE
Fédération des C.R.C.M


VAINCRE LA
MUCOVISCIDOSE