INFECTIONS DES PATHOLOGIES PULMONAIRES CHRONIQUES

LES NOUVEAUTES DE L'ANNEE

Antoine GUERDER

27 novembre 2015

Hôpitaux Universitaires
Pitié Salpêtrière - Charles Foix

CONFLITS D'INTERET

- Néant

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BPCO

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The relationship between Helicobacter pylori seropositivity and COPD.

Sze MA[1], Chen YW[1], Tam S[1], Tashkin D[2], Wise RA[3], Connett JE[4], Man SP[1], Sin DD[1].

- Près de 5000 fumeurs
  - BPCO Gold I et II
- 2 groupes :
  - HP+ : 18%
  - HP-
- HP + :
  - Conditions socioéconomiques plus précaires
  - Plus petits : -1,2cm

Table 1 Patient characteristics of the *Helicobacter pylori* positive and negative groups

	H. pylori negative	*H. pylori* positive
N	3928	837
Age	53.2±6.8	55.1±6.4*
Sex (% male)	63.4	61.5
Smoking start (years)	17.5±3.8	17.6±4.0
Pack years	40.2±18.6	40.1±19.1
BMI	25.6±3.9	25.4±3.8
Race (% Caucasian)	97.6	89.7
Height (m)	1.721±0.097	1.709±0.091**
Sustained quitters (at 5 years, % of total)	53.6	56.0
Education (years)	13.8±2.8	12.8±2.9‡
Median income (US$)	34 678±11 345	31 470 ±10 659‡
Ln (natural logarithm), CRP (mg/L)	0.995±0.689	1.063±0.714†

Continuous data are shown as mean±SD.
*p Value=2.4×10^{-15}.
**p value=0.0015.
†p value=0.012.
‡p value <0.00001.
BMI, body mass index; CRP, C reactive protein.

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- Dans le groupe HP :
  - VEMS (valeur absolue) initial plus bas
  - Risque de décès par pathologie cardiovasculaire augmenté : RR : 1.61
  - CRP augmentée : 1.063 (vs 0.995)
- Absence de différence significative :
  - Déclin du VEMS
  - Nombre de sujets HP+ entre Gold 1 et Gold 2
  - Mortalité par trouble respiratoire
  - Mortalité en général

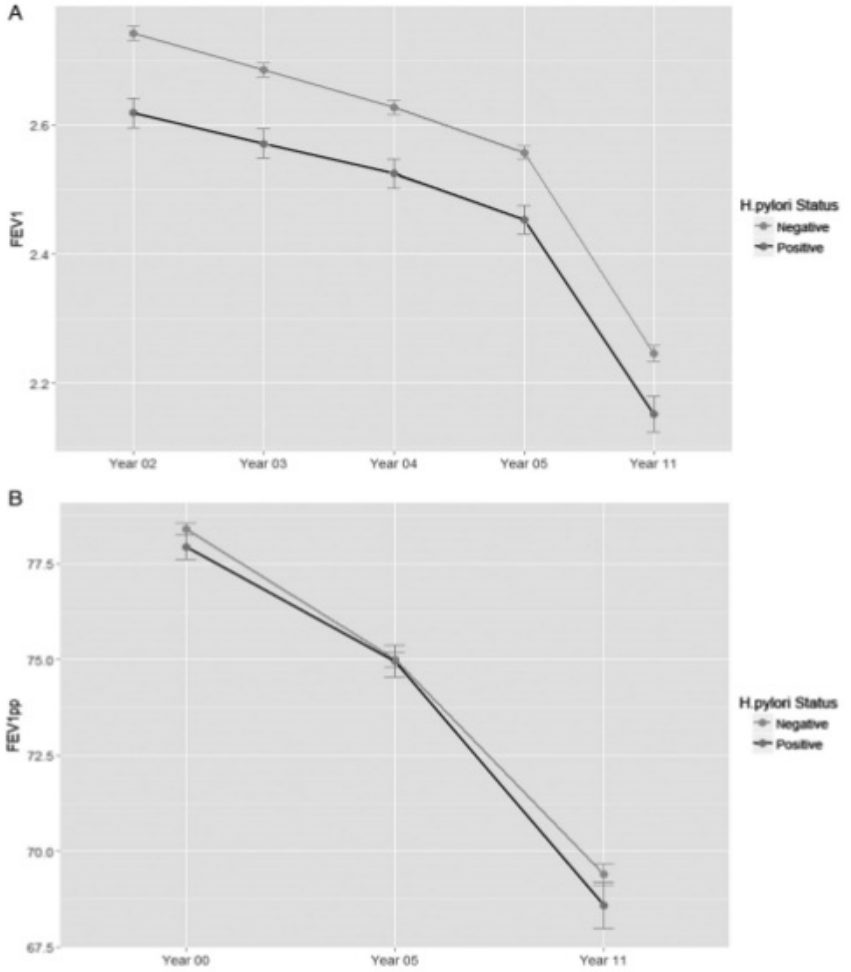

Figure 1 (A) Mean FEV_1 (L) over 11 years according to *Helicobacter pylori* status. There was no significant difference in the slope of the two lines ($p>0.05$). However, at every measured time point, those with *H. pylori* had significantly lower FEV_1 after Bonferroni correction (p value <0.009). (B) Mean FEV_1 per cent predicted (FEV_1pp) over 11 years according to *H. pylori* status. There was no significant difference in both the slope and mean FEV_1pp measured between the two groups ($p>0.05$).

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- *Helicobacter pylori* :
  - Génère une inflammation systémique
  - Augmente le risque cardiovasculaire
  - Est lié à des troubles de la croissance (donc diminution du VEMS)
  - Serait un facteur favorisant le développement d'une BPCO ?

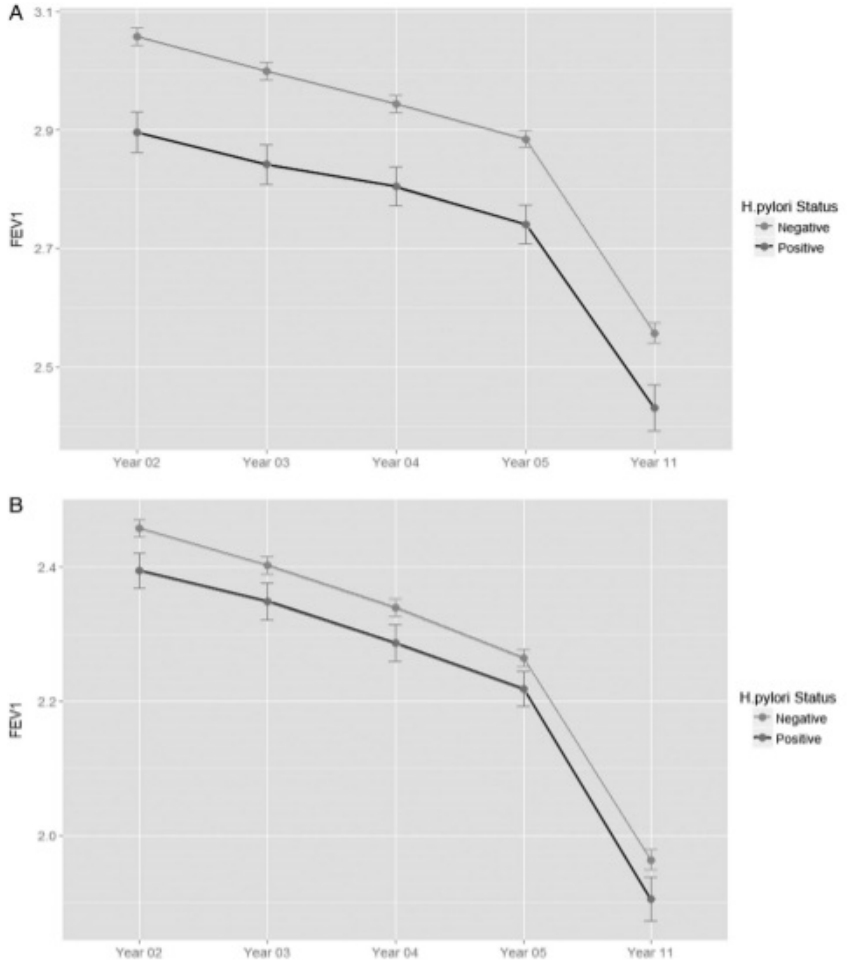

Figure 3 (A) Mean FEV_1 (L) over 11 years in GOLD 1 for *Helicobacter pylori* positive and negative groups. No difference in slope was observed ($p>0.05$); however, at every year, except year 11, the mean FEV_1 (L) was lower in the *H. pylori* positive group versus the negative group ($p<0.005$). (B) Mean FEV_1 (L) over 11 years in GOLD 2 for *H. pylori* positive and negative groups. No difference was observed between slope and mean FEV_1 between the two groups ($p>0.05$).

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J Infect Dis. 2015 Nov 12. pii: jiv527. [Epub ahead of print]

Pneumococcal Infection Aggravates Elastase-Induced Emphysema via MMP-12 Overexpression.

Takahashi S[1], Ishii M[1], Namkoong H[1], Hegab AE[1], Asami T[1], Yagi K[1], Sasaki M[1], Haraguchi M[1], Sato M[1], Kameyama N[1], Asakura T[1], Suzuki S[1], Tasaka S[1], Iwata S[2], Hasegawa N[3], Betsuyaku T[1].

- EABPCO :
  - Aggravent l'emphysème
  - Protéases : élastase du PNN, cathépsine, metalloprotéinases (MP) MMP2, MMP9, MMP12
- Méthode :
  - 300 souris
  - Induction d'un emphysème : comparaison avec placebo
  - Infection : pneumocoque : S10
  - Surveillance :
    - Clinique
    - Scannographique
    - Biologique : marqueurs de l'inflammation et cytokines
    - LBA

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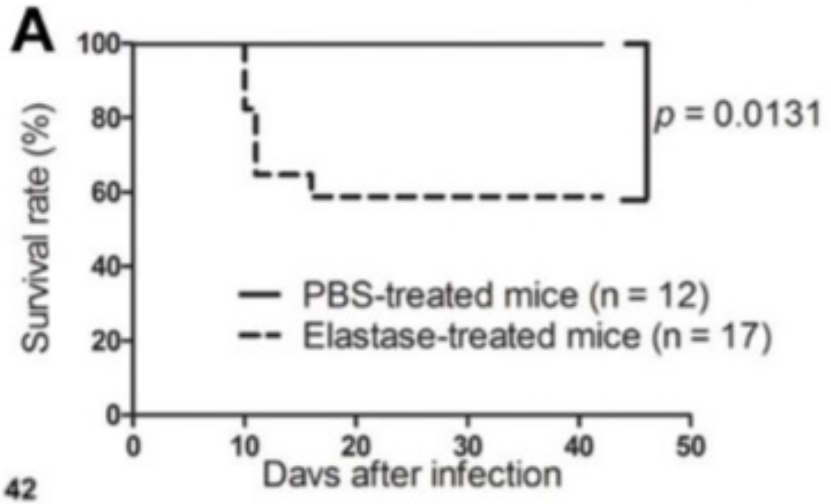
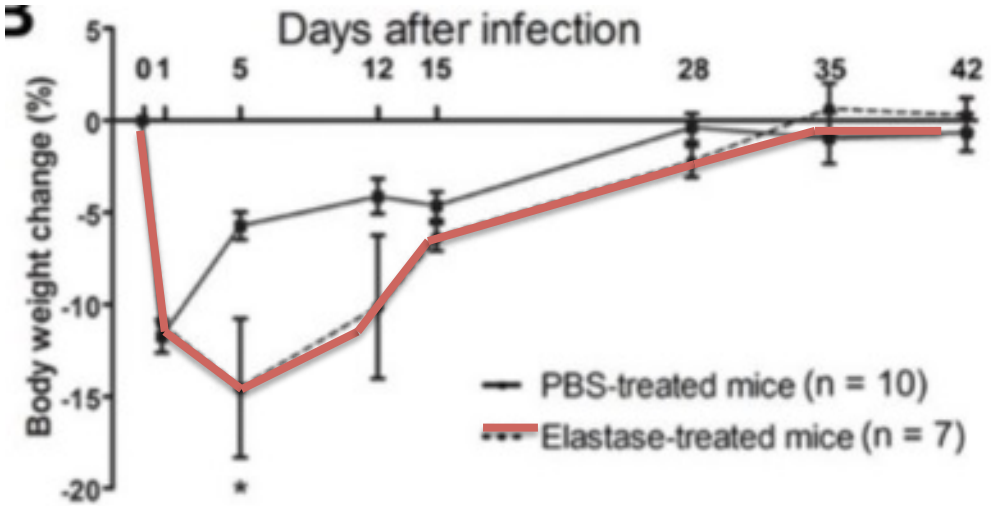
- Dans le groupe emphysème induit vs placebo :
  - Mortalité plus élevée
  - Amaigrissement plus marqué





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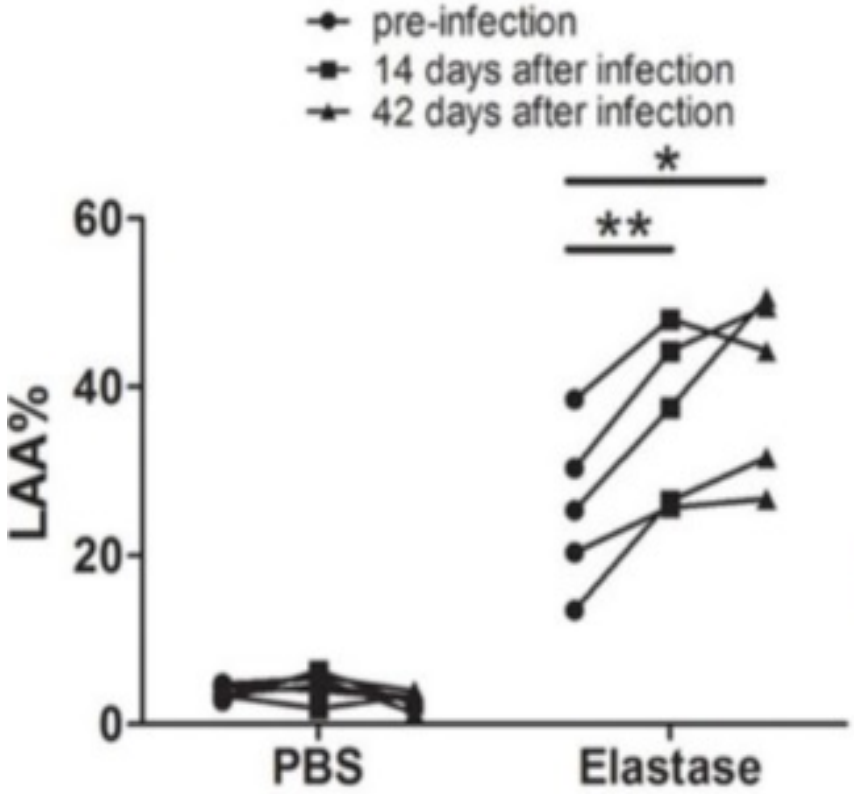

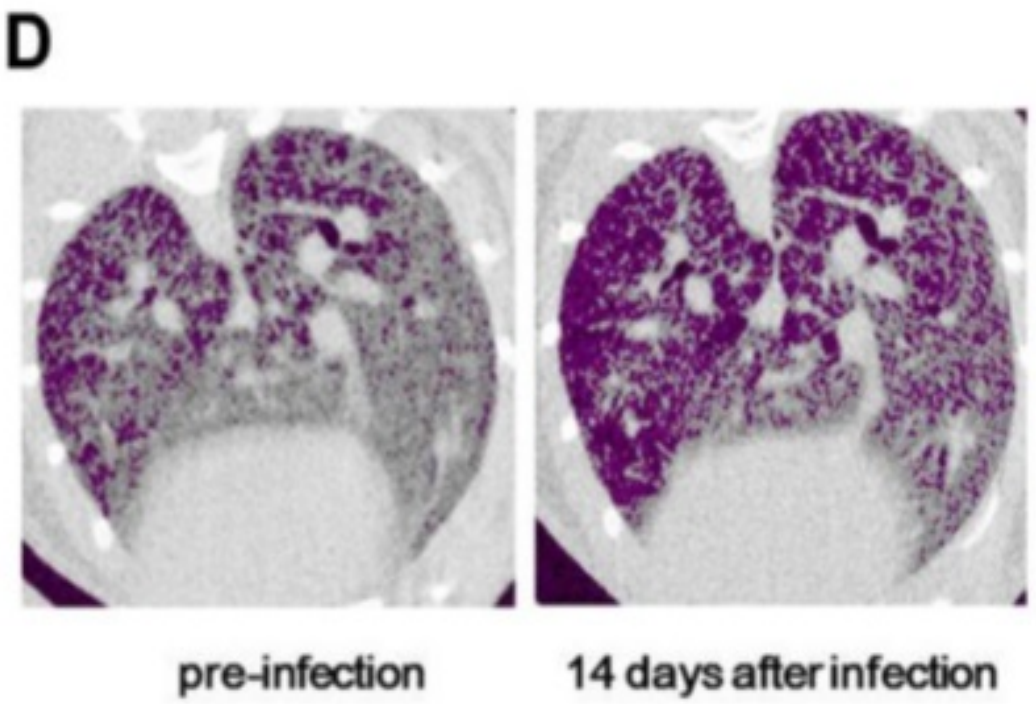

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Pneumococcal Infection Aggravates Elas

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Iwata S[2], Hasegawa N[3], Betsuyaku T[1].

- Augmentation :
  - Recrutement des cellules de l'immunités
- Modulation des cytokines dans le LBA :
  - Augmentation : CCL2, CXCL1, CXCL2, IL6
  - Diminution TNFα
  - Taux identiques pour les autres marqueurs
- Pas de différence dans l'élimination bactérienne

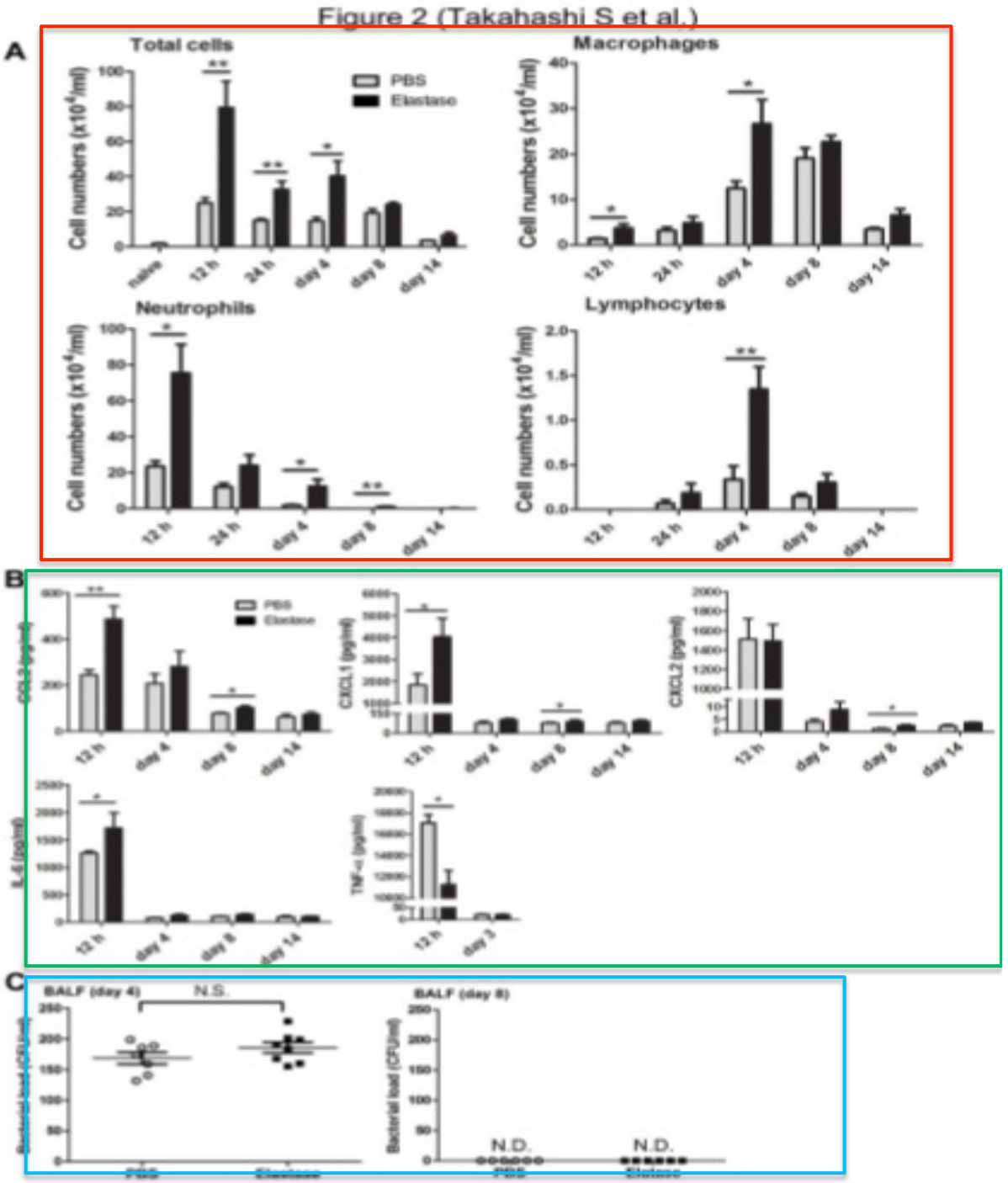

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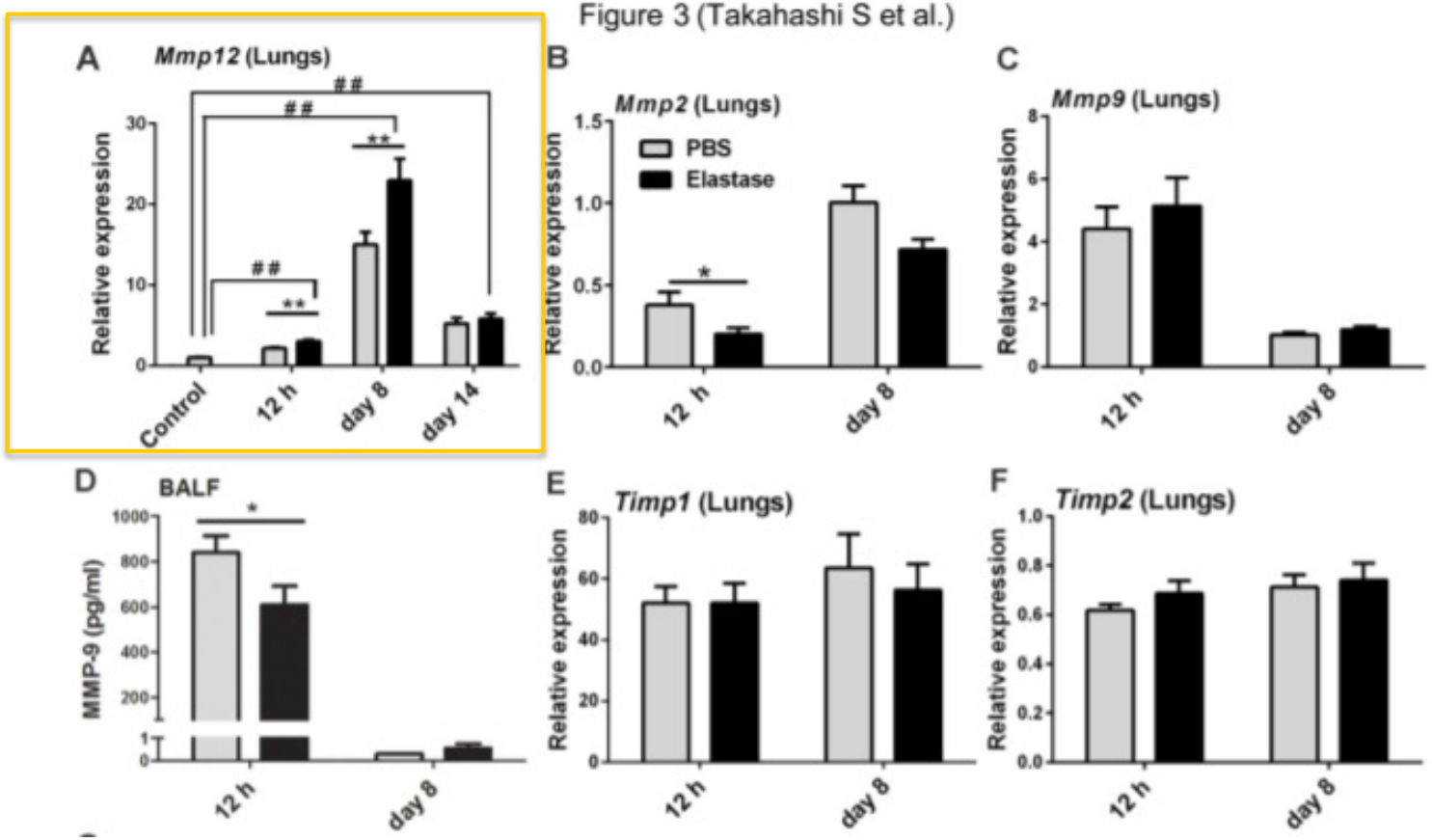
Figure 3 (Takahashi S et al.)



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Pneumococcal Infection Aggravates Elastase-In

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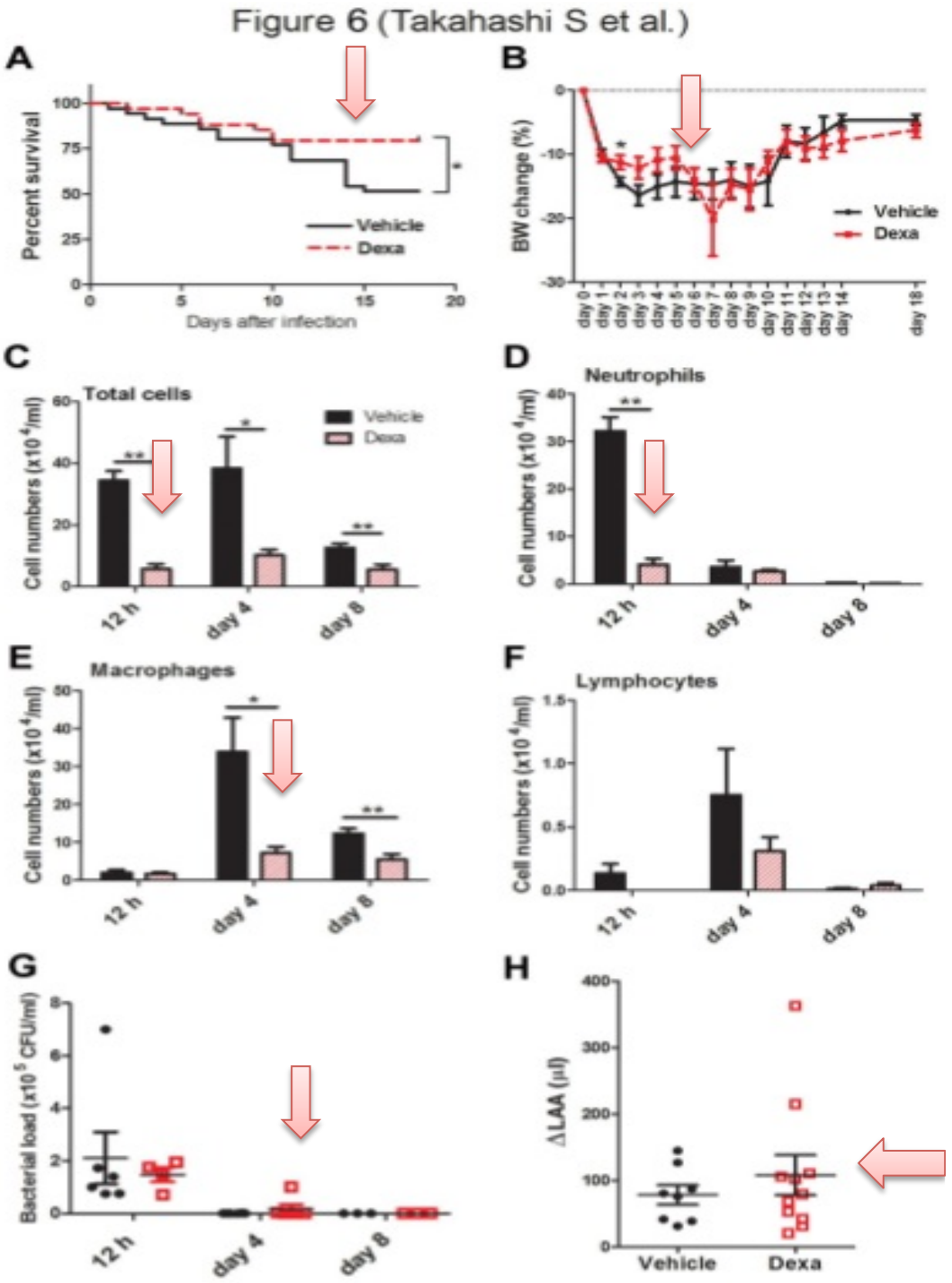
Iwata S[2], Hasegawa N[3], Betsuyaku T[1].

- Une corticothérapie à J2 améliore :
  - Survie
  - Réduit la perte de poids
  - Diminue le recrutement des macrophages et des polynucléaires
  - Diminue les taux de TNFα, IL6 et CXCL1
  - En diminuant MMP9 et l'activité de l'élastase des PNN
  - Sans diminution de MMP12
- Sans aggravation de l'infection
- Sans ralentir la progression de l'emphysème



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Thorax. 2015 Oct;70(10):930-8. doi: 10.1136/thoraxjnl-2015-207194. Epub 2015 Jul 15.

Effects of different antibiotic classes on airway bacteria in stable COPD using culture and molecular techniques: a randomised controlled trial.

Brill SE[1], Law M[2], El-Emir E[1], Allinson JP[1], James P[1], Maddox V[3], Donaldson GC[1], McHugh TD[3], Cookson WO[1], Moffatt MF[1], Nazareth I[4], Hurst JR[5], Calverley PM[6], Sweeting MJ[7], Wedzicha JA[1].

- Antibiothérapie de longue durée (9 semaines) vs placebo :
  - 99 sujets randomisés
  - VEMS moyen : 50.5%
- Pas de modification VEMS :
  - Moxifloxacine : +40mL
  - Doxycycline : +30mL
  - Azithromycine : 0mL
- Non significatifs :
  - Qualité de vie
  - Exacerbations

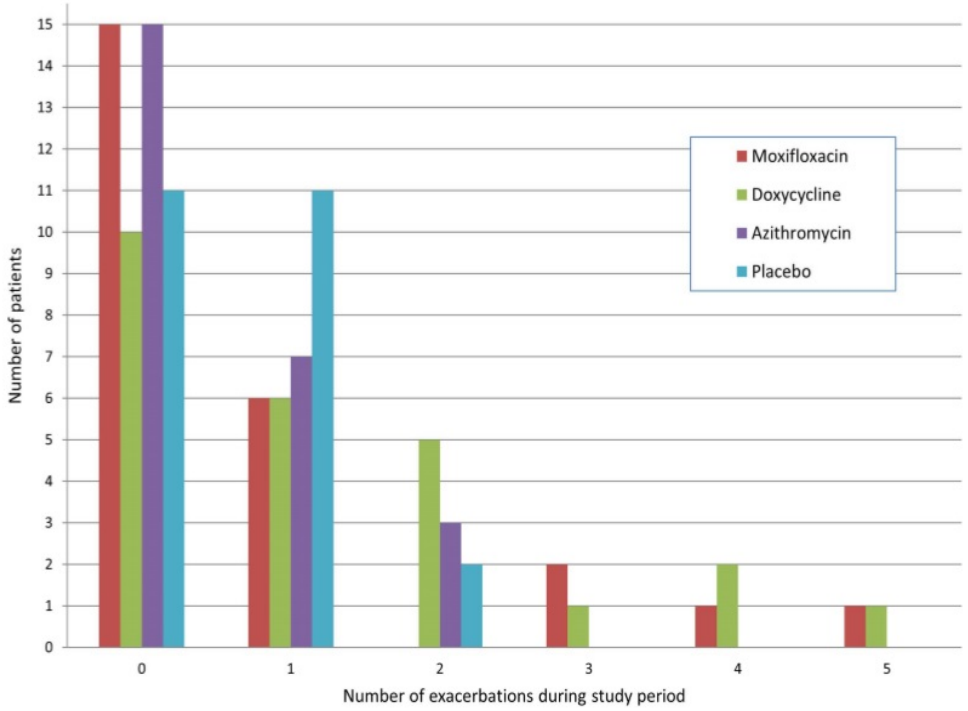

Figure 4 Frequency of exacerbations experienced by patients during the study period, by treatment group.

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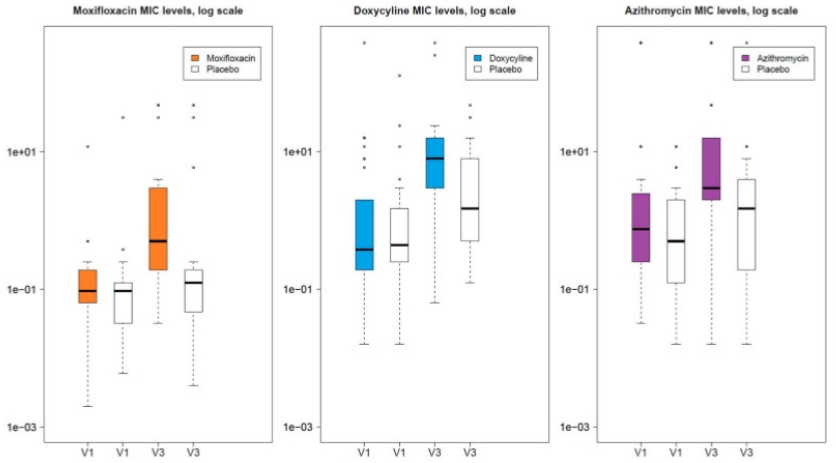
- Majoration des facteurs de résistance (p=0.01) :
  - Moxifloxacine : 4.82 [1.4-16.2]
  - Doxycycline : 3.74 [1.5-9.6]
  - Azithromycine : 6.23 [1.7-23.5]



e 3 Boxplots for each treatment arm showing mean inhibitory concentrations (MICs) against that antibiotic compared with placebo before fter 3 months of treatment. Note that MICs for all detected isolates are shown, and the number of isolates before and after treatment is not sarily comparable.

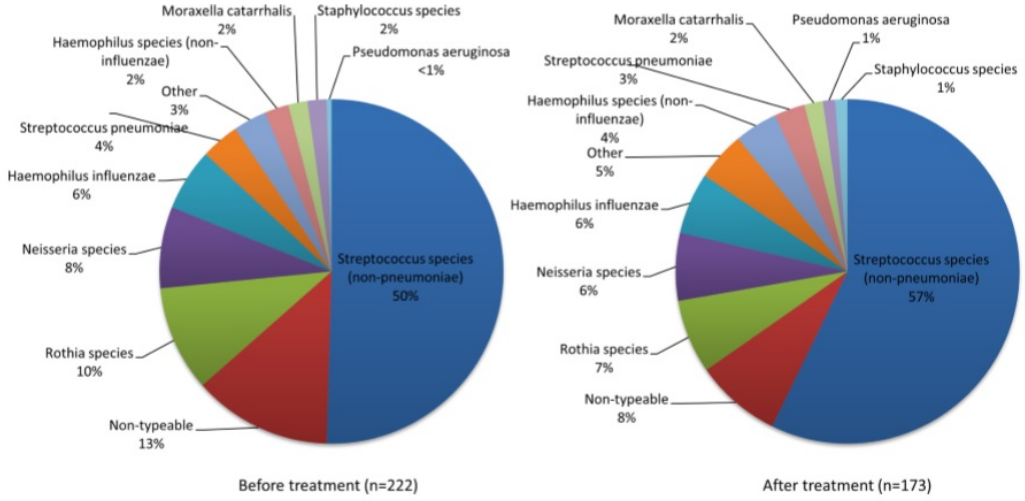


Figure 2 Species breakdown of all cultured isolates (n=395) before and after treatment.

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ASTHME

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Cochrane Database Syst Rev. 2015 Sep 15;9:CD002997. doi: 10.1002/14651858.CD002997.pub4.

Macrolides for chronic asthma.

Kew KM[1], Undela K, Kotortsi I, Ferrara G.

- 23 études - n=1512
- Qualité : plutôt pauvre
- Absence de supériorité par rapport au placebo pour :
  - Les hospitalisations
  - La prise de corticoïdes systémiques
  - Les symptômes :
    - Echelles de symptômes
    - Contrôle de l'asthme
    - Qualité de vie
  - L'utilisation des traitements de secours
- Tendance à améliorer :
  - La fonction respiratoire : VEMS : MD : 0.08 [0.02-0.14]
  - Les biomarqueurs d'activité de l'asthme :
    - Taux d'éosinophiles dans les expectorations et dans le sang
    - Protéine cationique de l'éosinophile
  - Sans conséquence clinique

Analysis 1.9. Comparison 1 Macrolide versus placebo, Outcome 9 FEV1 (L).

Review: Macrolides for chronic asthma

Comparison: 1 Macrolide versus placebo

Outcome: 9 FEV_1 (L)

Study or subgroup	Macrolide N	Placebo N	Mean Difference (SE)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Amayasu 2000 (1)	17	17	-0.01 (0.9)		0.1 %	-0.01 [-1.77, 1.75]
Cameron 2012	39	38	0.03 (0.0561)		28.7 %	0.03 [-0.08, 0.14]
He 2009	20	20	0.09 (0.0459)		42.9 %	0.09 [0.00, 0.18]
Kraft 2002	26	26	-0.05 (0.2126)		2.0 %	-0.05 [-0.47, 0.37]
Shoji 1999 (2)	14	14	0.12 (0.3137)		0.9 %	0.12 [-0.49, 0.73]
Sutherland 2010 (3)	47	45	0 (0.1)		9.0 %	0.0 [-0.20, 0.20]
Wang 2014	29	29	0.15 (0.1225)		6.0 %	0.15 [-0.09, 0.39]
Xiao 2013	106	104	0.15 (0.1071)		7.9 %	0.15 [-0.06, 0.36]
Yan 2008	20	20	0.4 (0.1939)		2.4 %	0.40 [0.02, 0.78]
Total (95% CI)	**318**	**313**			**100.0 %**	**0.08 [0.02, 0.14]**

Heterogeneity: $Chi^2 = 5.35$, df = 8 (P = 0.72); $I^2 = 0.0\%$

Test for overall effect: Z = 2.59 (P = 0.0097)

Test for subgroup differences: Not applicable

-1 -0.5 0 0.5 1

Favours placebo Favours macrolide

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Thorax. 2015 May;70(5):458-67. doi: 10.1136/thoraxjnl-2014-206067. Epub 2015 Mar 6.

Macrolide therapy suppresses key features of experimental steroid-sensitive and steroid-insensitive asthma.

Essilfie AT[1], Horvat JC[1], Kim RY[1], Mayall JR[1], Pinkerton JW[1], Beckett EL[1], Starkey MR[1], Simpson JL[1], Foster PS[1], Gibson PG[1], Hansbro PM[1].

- Corticorésistance :
  - Asthme plus sévère
  - Inflammation non-éosinophilique ou neutrophilique
  - Associée à une augmentation de l'expression des voies Th1, Th11 (phénotype plus sévère)
  - Lien avec les infections à *Chlamydia pneumoniae* et *Haemophilus influenzae* (60%) (réponse inflammatoire neutrophilique intense)
  - Doses de corticoïdes plus élevées

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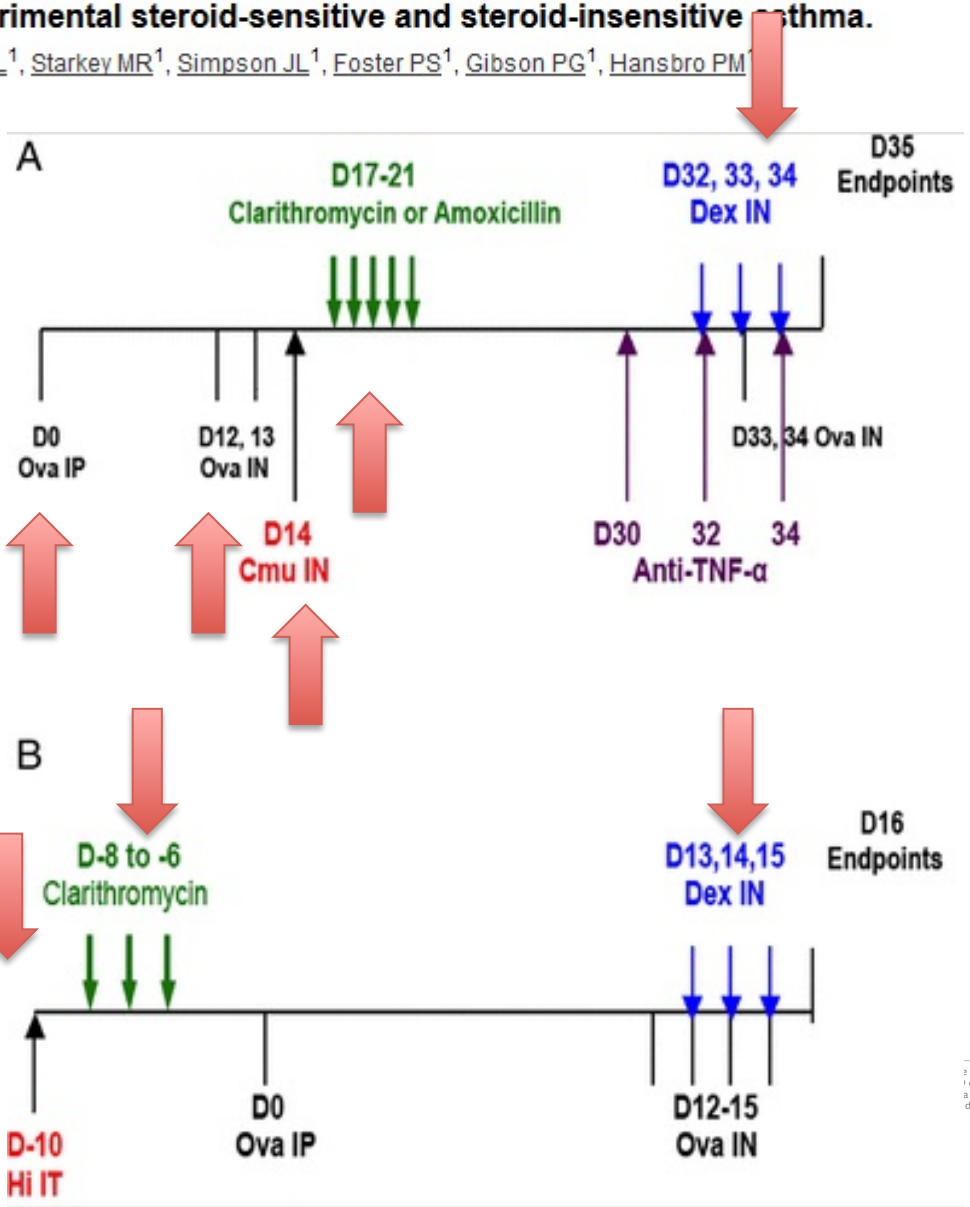
- Création modèle de souris « asthmatiques »
- Bras : résistance aux corticoïdes, induite par une infection à *Chlamydia* ou *Haemophilus*



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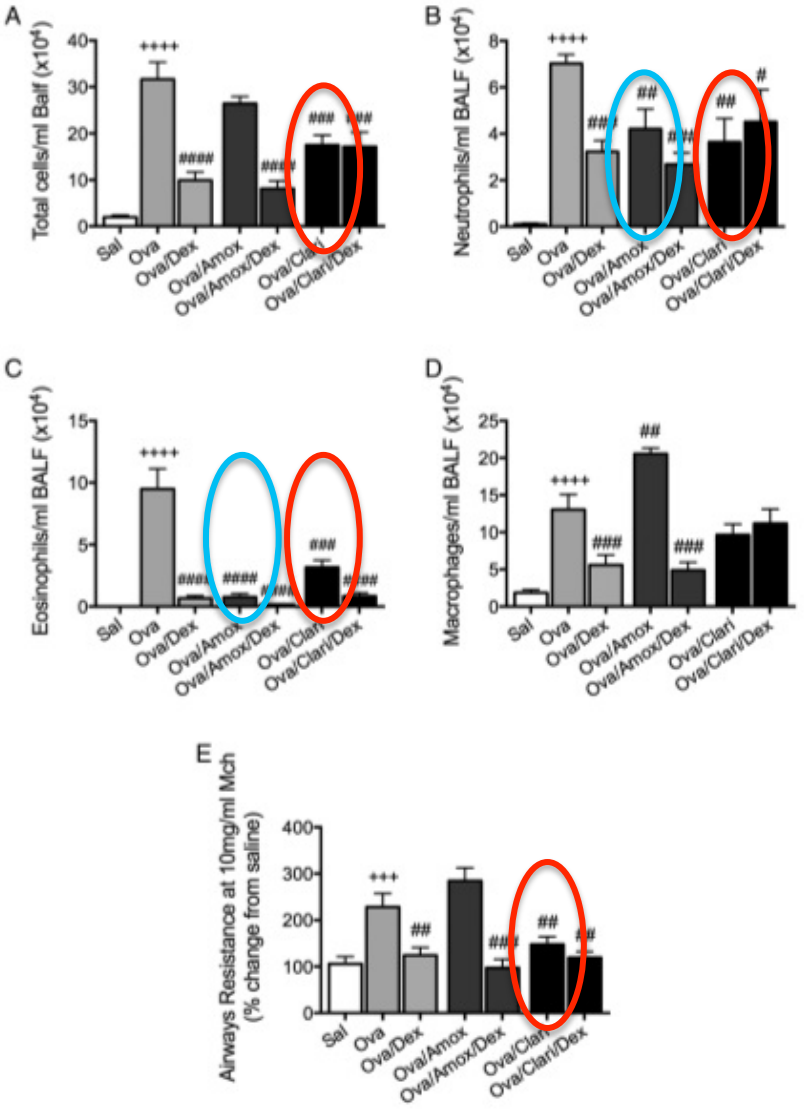
- Modèle “asthme corticosensible” :
  - Amoxicilline réduit quelques effets
  - Clarithromycine diminue tous les effets



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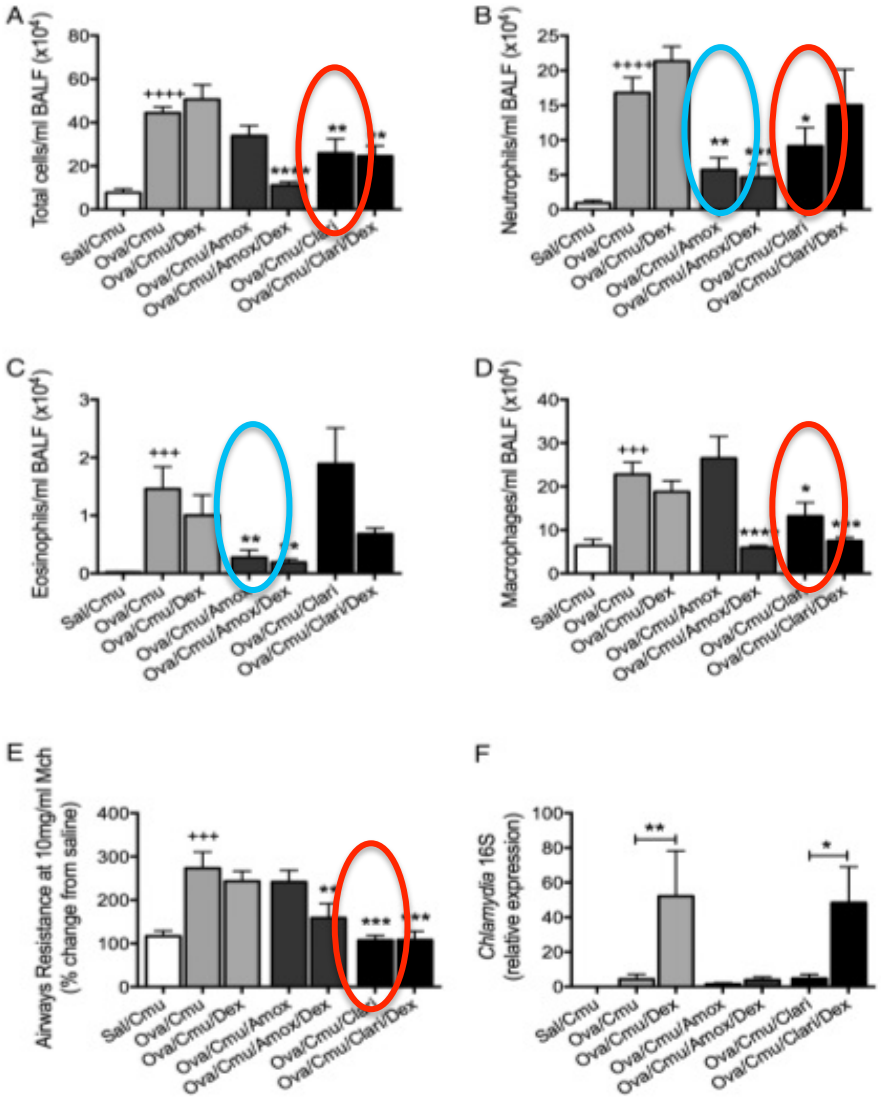
- Modèle « asthme corticorésistant » induit par *Chlamydia* :
  - La clarithromycine diminue les principaux effets
    - Cellules totales LBA
    - Macrophages LBA
    - Résistances des VA



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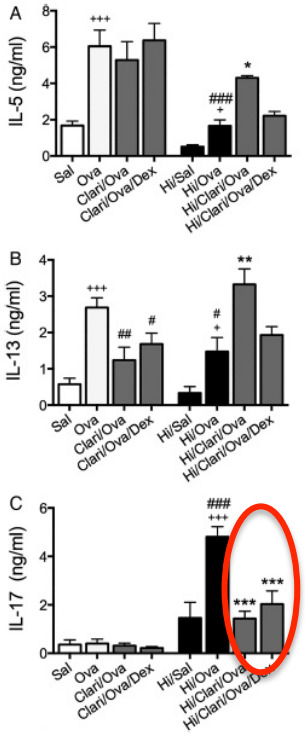
- Modèle « asthme corticorésistant » induit par *Haemophilus* :
  - Clarithromycine
    - diminue : PNN et IL17
    - Diminue les résistances des VA



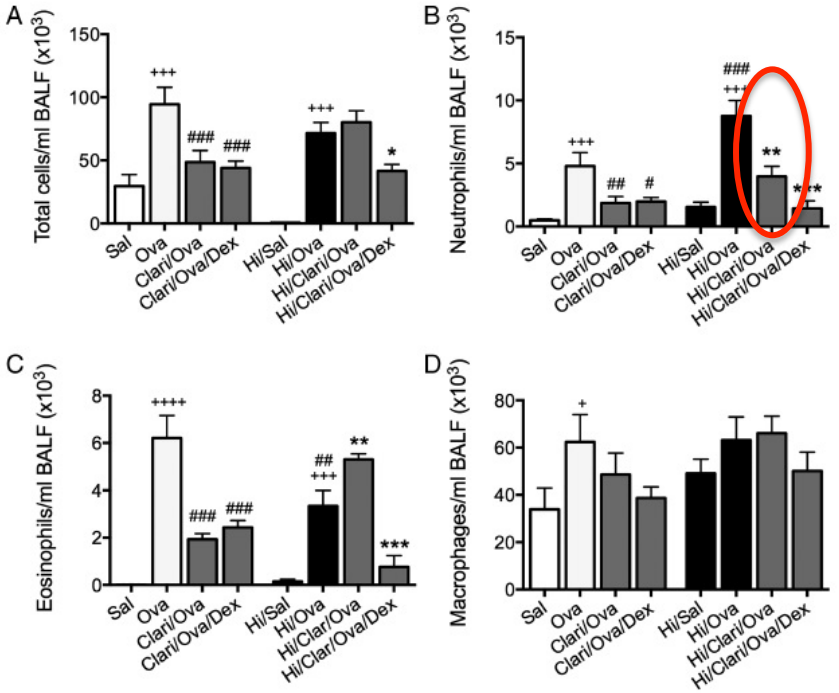
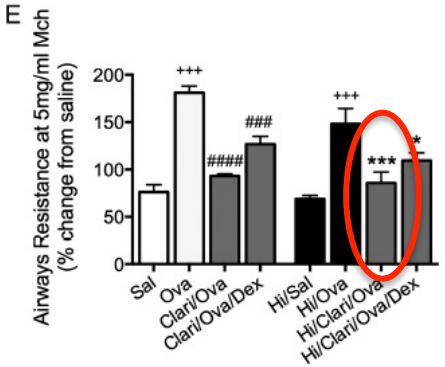


Figure 7 Clarithromycin suppresses interleukin (IL)-17 responses in *Haemophilus influenzae* (*Hi*)-induced, severe, steroid-insensitive, neutrophilic allergic airways disease. Effects of clarithromycin treatment on IL-5 (A), IL-13 (B), and IL-17 (C) release from mediastinal lymph nodes. Results are representative of two independent experiments, with a total of six mice/group, and all data are presented as means±SEM. $^{+++}p<0.001$, $^{+}p<0.05$ compared with non-allergic (Sal, or Hi/Sal) controls, $^{###}p<0.001$, $^{##}p<0.01$, $^{#}p<0.05$ compared with allergic (Ova) controls, $^{***}p<0.001$, $^{**}p<0.01$, $^{*}p<0.05$ compared with infected, allergic (Hi/Ova) groups.



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BRONCHECTASIES

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Thorax. 2014 Dec;69(12):1073-9. doi: 10.1136/thoraxjnl-2014-205587. Epub 2014 Sep 21.

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

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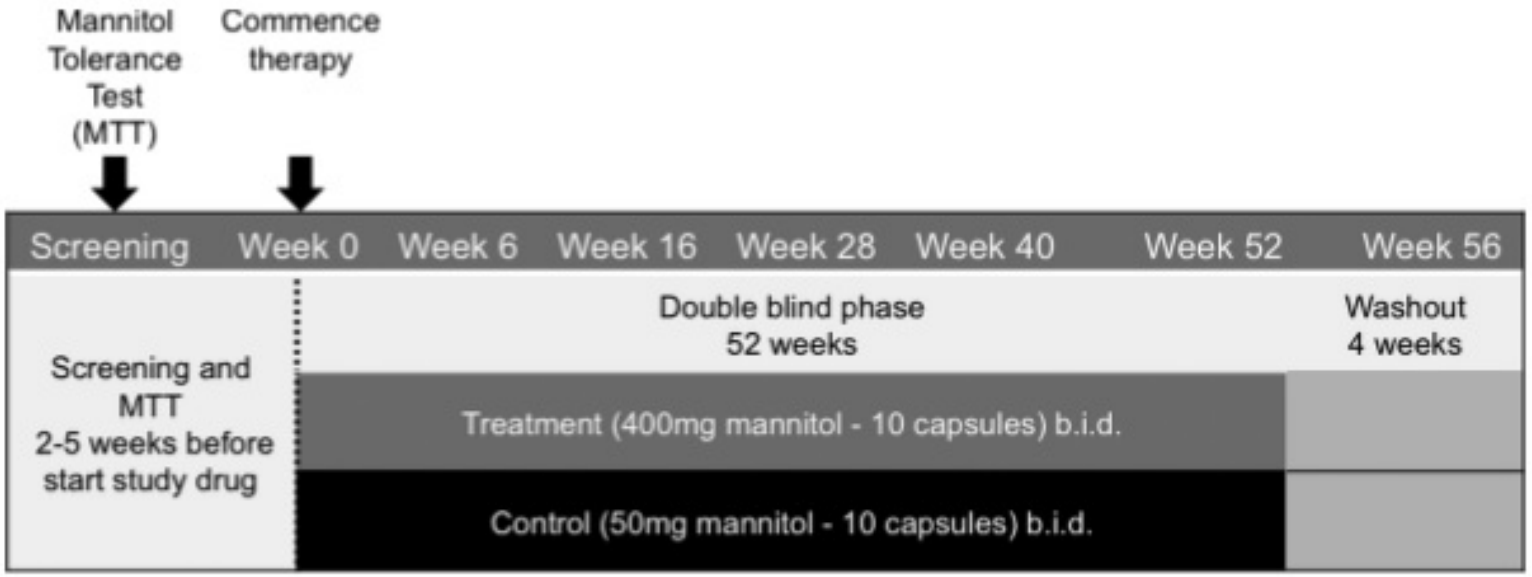

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BRONCHECTASIES

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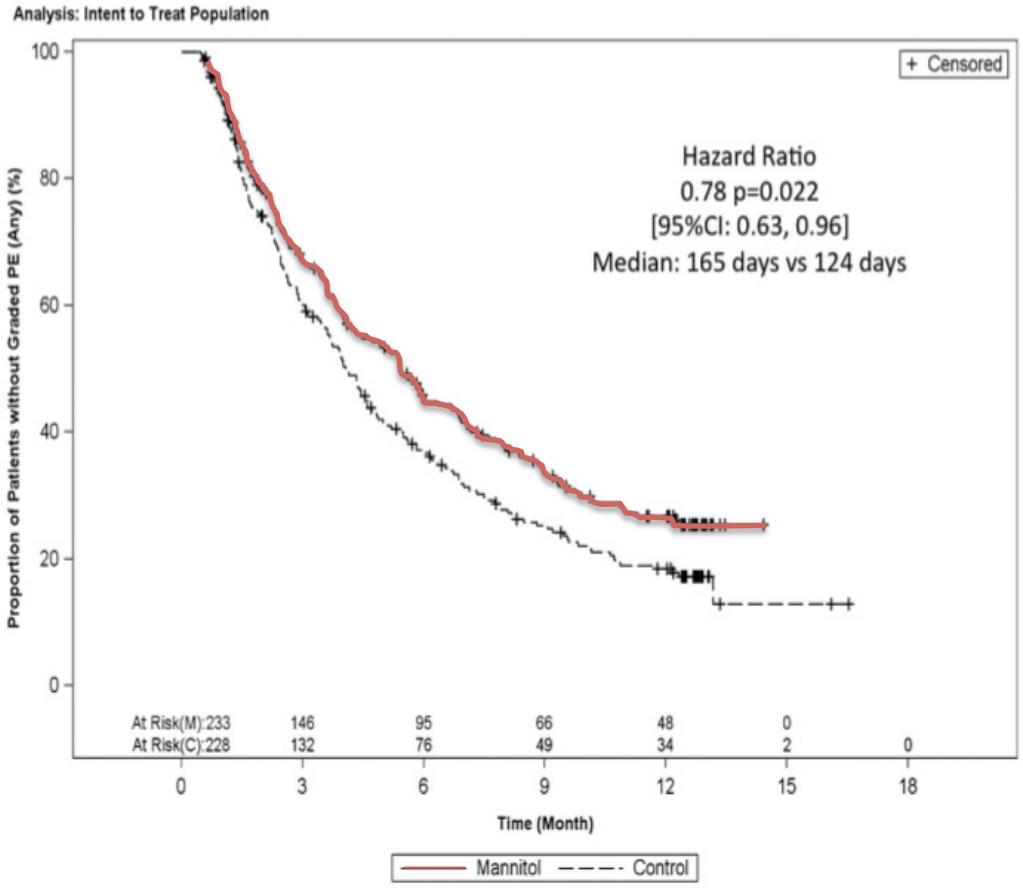
- Mannitol :
  - Retarde le délai de survenue d'exacerbation de 39 jours
  - Diminue le nombre de jours d'antibiotiques : -24% (p=0.049)
  - Améliore la qualité de vie
- Pas de modification :
  - Nombre total d'exacerbations
  - Fonction respiratoire



BRONCHECTASIES

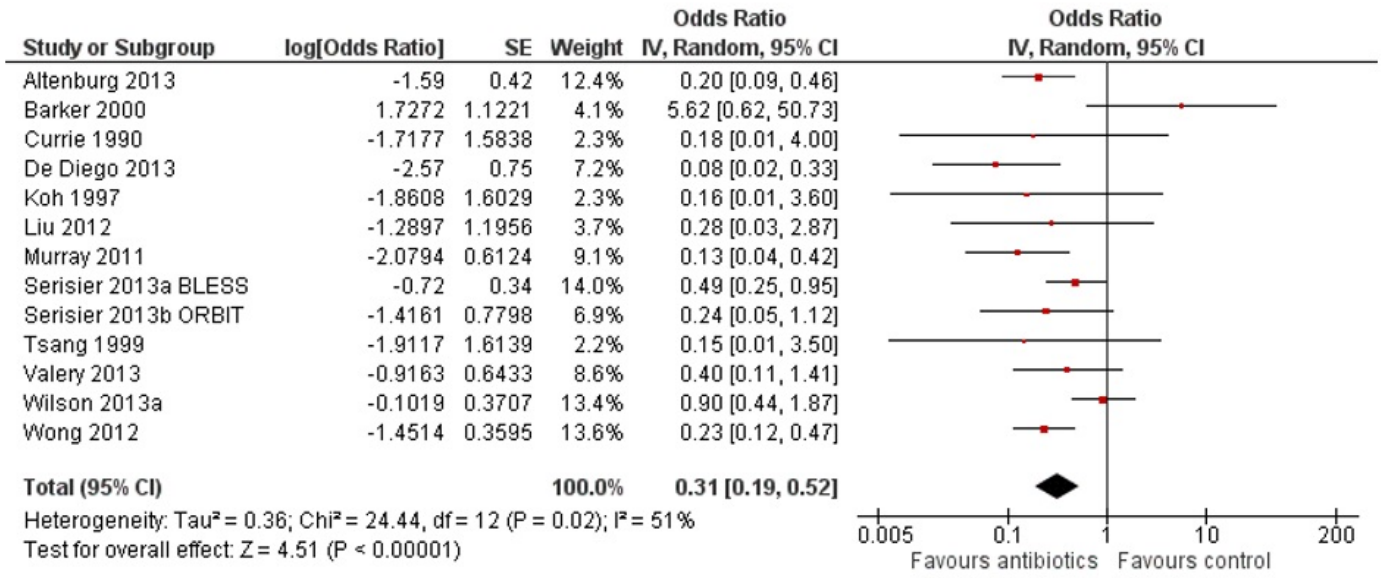
Cochrane Database Syst Rev. 2015 Aug 13;8:CD001392. doi: 10.1002/14651858.CD001392.pub3.

Prolonged antibiotics for non-cystic fibrosis bronchiectasis in children and adults.

Hnin K[1], Nguyen C, Carson KV, Evans DJ, Greenstone M, Smith BJ.

- 18 études, 1157 patients
- Antibiothérapie prolongée per os (n=12) ou inhalée (n=6)
- 4 à 83 semaines
- Résultats :
  - Diminution du risque d'exacerbations (OR : 0.31 [0.19-0.52] p<0.00001) et d'hospitalisations (MD : 0.6 – p=0.03)

Figure 3. Forest plot of comparison: 1 Continuous antibiotics versus standard treatment with or without added placebo (parallel groups), outcome: 1.1 Exacerbations.



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Hnin K[1], Nguyen C, Carson KV, Evans DJ, Greenstone M, Smith BJ.

- Résultats :
  - Majoration du risque de résistances (OR : 3.48 [1.20-10.07] p=0.02)

Analysis 1.9. Comparison 1 Continuous antibiotics versus standard treatment with or without added placebo (parallel groups), Outcome 9 Emergence of resistance.

Review: Prolonged antibiotics for non-cystic fibrosis bronchiectasis in children and adults

Comparison: 1 Continuous antibiotics versus standard treatment with or without added placebo (parallel groups)

Outcome: 9 Emergence of resistance

Study or subgroup	Antibiotics n/N	Control n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Barker 2000	4/37	1/37		16.2 %	4.36 [0.46, 41.06]
Orriols 1999	1/7	4/8		13.5 %	0.17 [0.01, 2.09]
Serisier 2013b ORBIT	4/19	1/20		15.7 %	5.07 [0.51, 50.21]
Valery 2013	19/51	4/37		33.8 %	4.90 [1.50, 15.99]
Wilson 2013a	6/60	0/64		10.9 %	15.39 [0.85, 279.32]
Wong 2012	2/46	0/45		10.0 %	5.11 [0.24, 109.51]
Total (95% CI)	**220**	**211**		**100.0 %**	**3.48 [1.20, 10.07]**

Total events: 36 (Antibiotics), 10 (Control)

Heterogeneity: $Tau^2 = 0.50$; $Chi^2 = 7.05$, df = 5 (P = 0.22); $I^2 = 29\%$

Test for overall effect: Z = 2.30 (P = 0.021)

Test for subgroup differences: Not applicable

0.005 0.1 1 10 200

Favours antibiotics Favours control

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INFECTIONS DES PATHOLOGIES PULMONAIRES CHRONIQUES

LES NOUVEAUTES DE L'ANNEE

MUCOVISCIDOSE

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Chest. 2015 Jul 23. doi: 10.1378/chest.15-0676. [Epub ahead of print]

Changing Epidemiology of the Respiratory Bacteriology of Patients with Cystic Fibrosis.

Salsgiver EL, Fink AK, Knapp EA, LiPuma JJ, Olivier KN, Marshall BC, Saiman L.

- Etude observationnelle rétrospective (Registre de la fondation contre la mucoviscidose) : flore des ECBC sur 6 ans
- 31915 patients
- Germes les plus prévalents :
  - SAMS (52%)
  - *P. aeruginosa* (50%)
  - SAMR (26.5%)
  - *H. influenzae* (15.6%)
  - *S. maltophilia* (13.4%)

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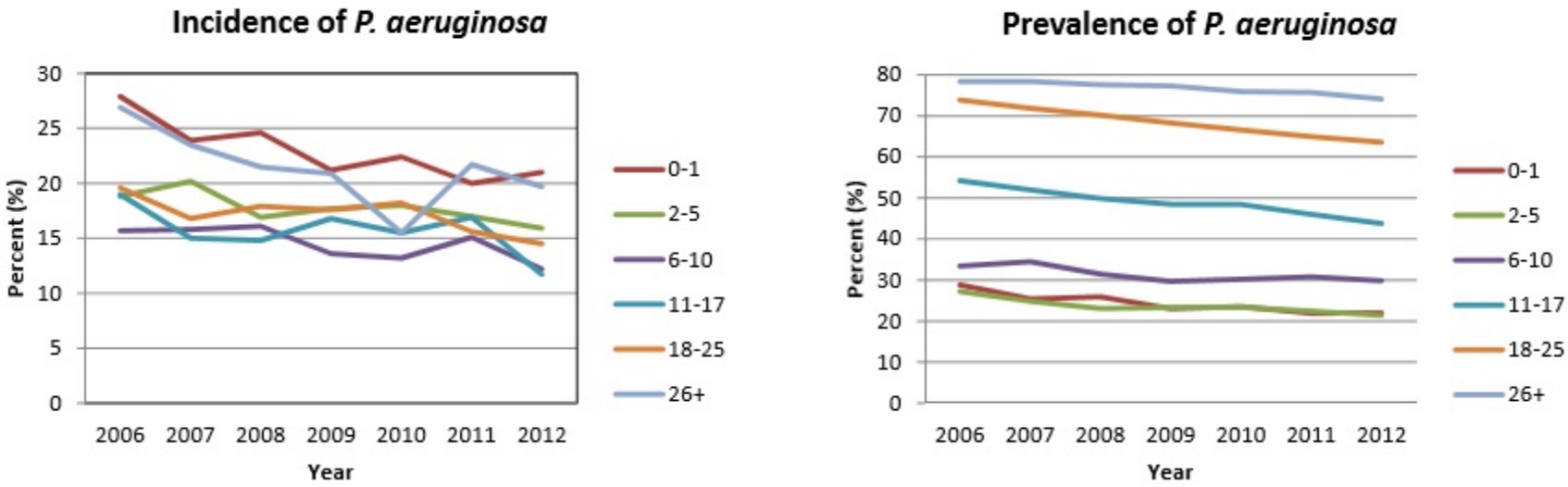
- Tendance à la diminution de :
  - *P. aeruginosa*
  - *H. influenzae*
  - *B. cepacia complex*

Figure 2.

A. Overall Incidence and Prevalence of *Pseudomonas aeruginosa* in patients with CF from 2006 to 2012. The overall incidence and prevalence of *Pseudomonas aeruginosa* among patients with CF is shown by age strata.



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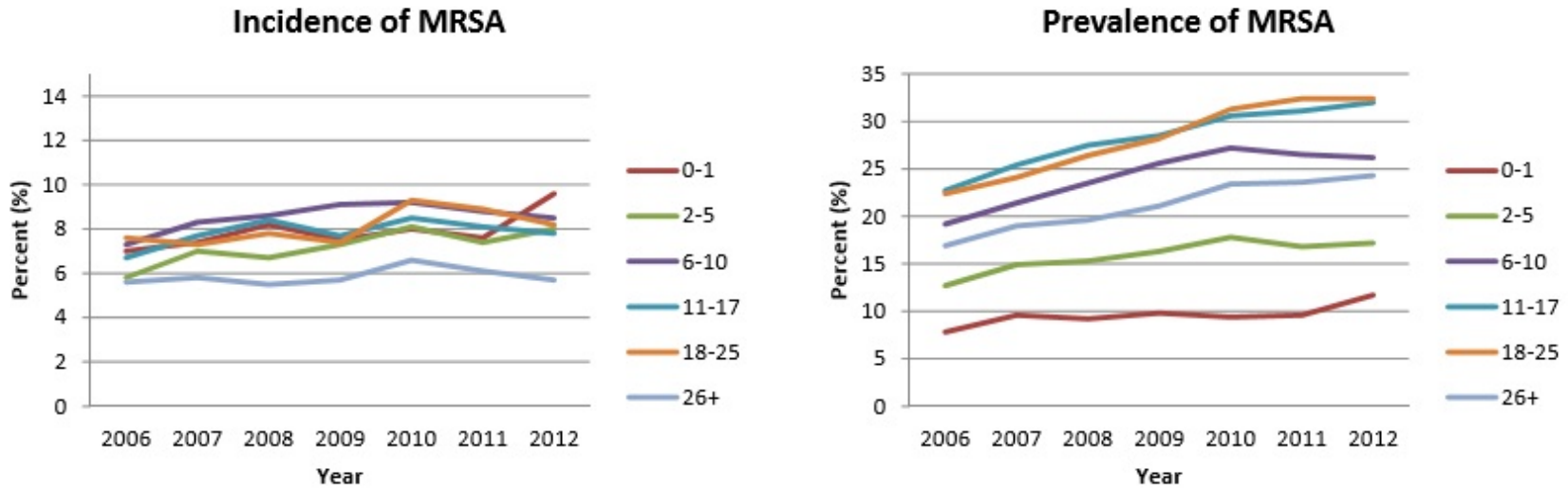
- Tendance à la majoration :
  - SAMR
  - *S. maltophilia*
  - Mycobactéries non tuberculeuses (45 à 54%, p<0.01)

B. Overall Incidence and Prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) in patients with CF from 2006 to 2012. The overall incidence and prevalence of MRSA among patients with CF is shown by age strata. These data reflect an analysis of the United States Cystic Fibrosis Foundation Patient Registry.



MUCOVISCIDOSE

J Cyst Fibros. 2015 Aug 21. pii: S1569-1993(15)00176-9. doi: 10.1016/j.jcf.2015.08.002. [Epub ahead of print]

Anti-Pseudomonas aeruginosa IgY antibodies augment bacterial clearance in a murine pneumonia model.

Thomsen K[1], Christophersen L[2], Bjarnsholt T[3], Jensen PØ[2], Moser C[2], Høiby N[3].

- 3 groupes de 8 souris :
  - Contrôles
  - IgY contrôles
  - IgY anti-pyocyanique
- Injection prophylactique
- Injection d'une solution de *P. aeruginosa*

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- Traitement prophylactique diminue :
  - Les signes cliniques d'infection

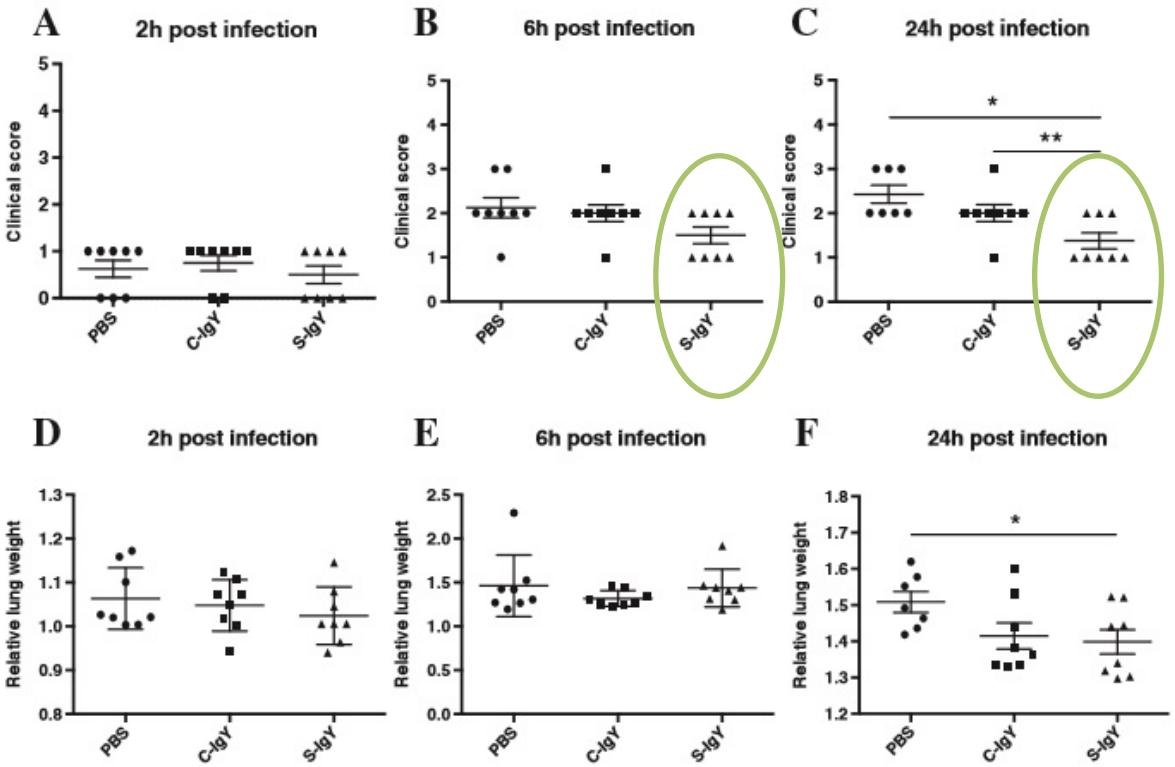

Fig. 1. Clinical symptom score was evaluated at specified time-points post-infection. Mice were treated with PBS (non-IgY control), C-IgY or S-IgY. (A) 2 h post-infection reveals no significant difference between groups. (B) The clinical symptom score was generally increased in all groups after 6 h of infection, however no significant difference between groups was observed. (C) 24 h post-infection the clinical symptom scores in the S-IgY treated group were significantly reduced compared to PBS and C-IgY controls. *$p < 0.002$, **$p < 0.04$. Lung weight relative to body weight determined at specified time-points post-infection. Mice were treated with PBS (non-IgY control), C-IgY or S-IgY. (D) 2 h post-infection the relative lung weights measured were similar in all groups. (E). After 6 h of infection there was an overall increase in relative lung weights, however there is no significant difference between groups. (F) Subsequently 24 h post-infection the relative lung weight in S-IgY group was significantly lower compared to PBS controls. *$p < 0.03$. Pooled data was obtained from two experiments. Error bars are means ± SD.

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- Traitement prophylactique diminue :
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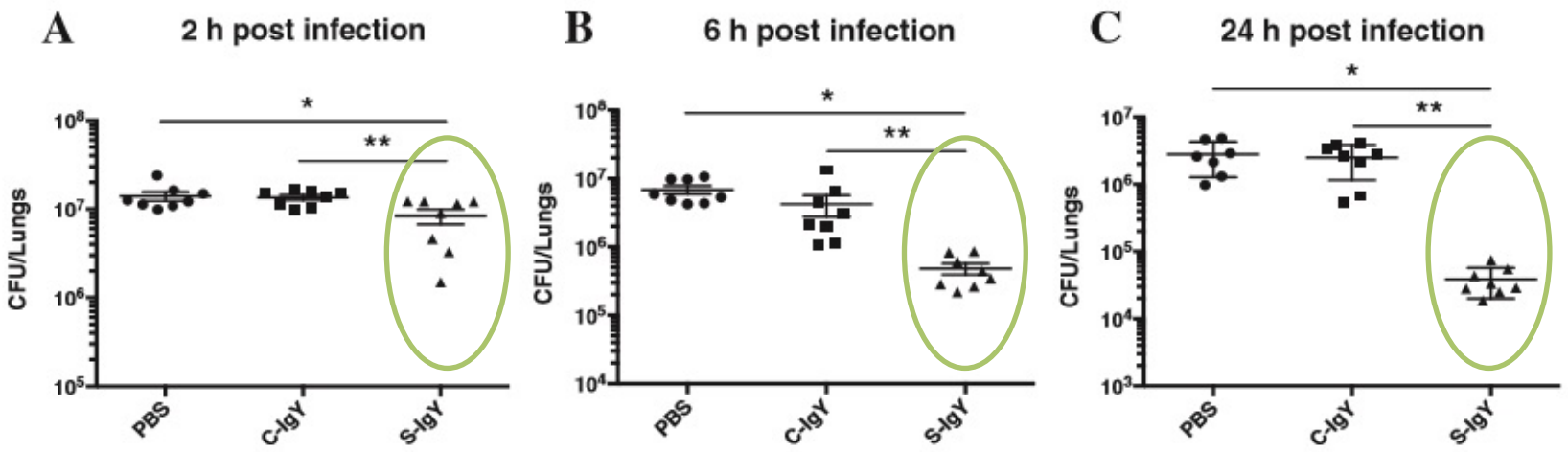

Fig. 2. Quantitative bacteriology of homogenized lungs at specified time-points post-infection. Mice were treated with PBS (non-IgY control), C-IgY or S-IgY. (A) The bacterial load after 2 h of infection was significantly reduced in the S-IgY treated group compared to PBS and C-IgY controls. *$p < 0.03$. **$p < 0.02$. (B) 6 h post-infection the bacterial burden in the S-IgY group was reduced by more than 1 log compared to PBS group and successively significantly lower than C-IgY treated group. *$p < 0.0001$ **$p < 0.03$. (C) The bacterial quantity in the S-IgY group was nearly diminished by 2 log compared to PBS controls after 24 h of infection and subsequently significantly reduced compared to C-IgY group. *$p < 0.0002$ **$p < 0.0001$. Pooled data was obtained from two experiments. Error bars are means ± SD.

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- Traitement prophylactique diminue :
  - Protège des bactériémies

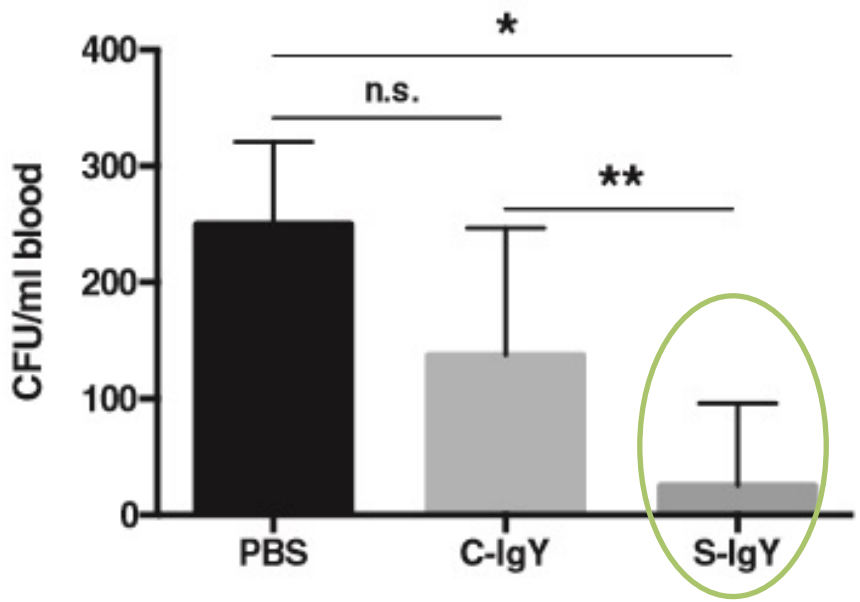

Fig. 3. Quantification of the bacterial load in blood 24 h post-infection. Mice were treated with PBS (non-IgY control), C-IgY or S-IgY. The bacterial burden in the S-IgY treated group was significantly lower compared to PBS and C-IgY controls. *$p < 0.001$ **$p < 0.03$. Pooled data was obtained from two experiments. Error bars are means ± SD.

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- Traitement prophylactique diminue :
  - Les marqueurs de l'inflammation

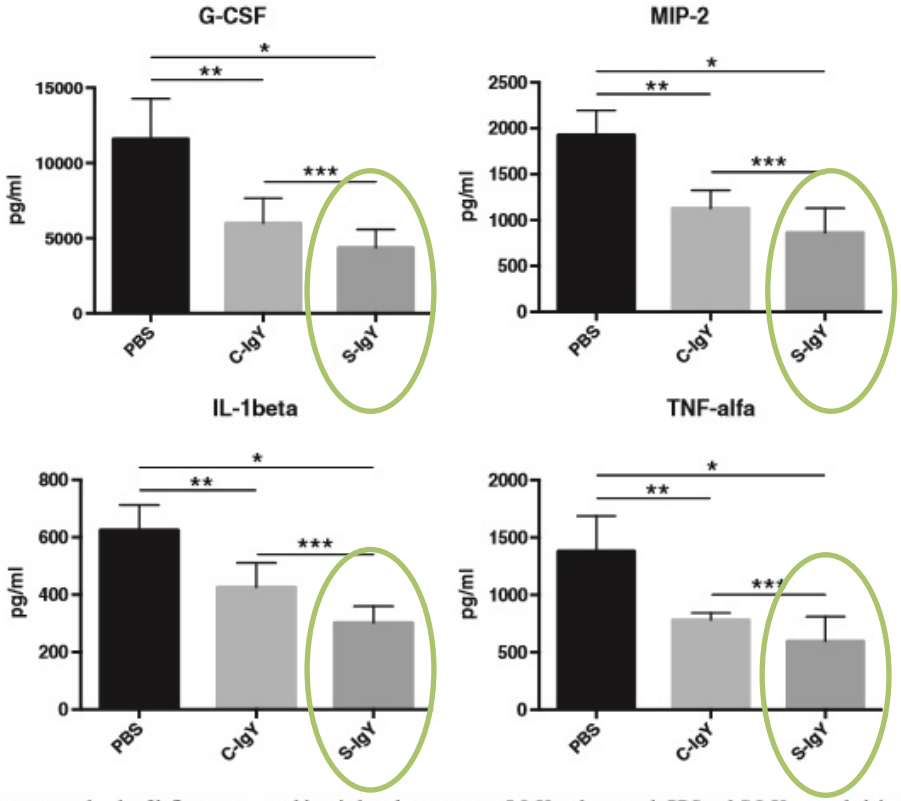

Fig. 5. Effects of IgY treatment on levels of inflammatory cytokines in lung homogenates. S-IgY or the controls PBS and C-IgY were administered prior to induction of pneumonia with *P. aeruginosa* PAO1. 24 h after inoculation mice were sacrificed and lung homogenates were used for assay. Pulmonary concentration of G-CSF was significantly reduced in S-IgY treated mice compared to controls (*$p < 0.0001$, ***$p < 0.05$) and the level of G-CSF in C-IgY mice was reduced compared to PBS (**$p = 0.0003$). The production of the chemokine MIP-2 was significantly reduced in mice treated with S-IgY compared to PBS (*$p < 0.0001$) and C-IgY (***$p < 0.05$) controls and similarly reduced in C-IgY group compared to PBS (**$p = 0.0003$). The inflammatory cytokine Il-1β was significantly reduced 24 h post-infection in S-IgY treated mice compared to controls (*$p < 0.0001$, ***$p < 0.005$). In mice receiving C-IgY the Il-1β production was significantly decreased compared to PBS controls (**$p < 0.0006$). IgY therapy also reduced TNF-α levels in lung homogenates, however S-IgY to lower levels than C-IgY (*$p < 0.0001$, **$p = 0.0001$, ***$p < 0.04$).

Merci de votre attention