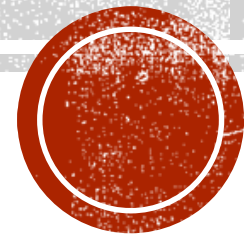


EXACERBATION BPCO

PRISE EN CHARGE AMBULATOIRE

Dr Grégoire Humair

24.03.2022



PLAN

- Définition
- Diagnostic différentiel
- Risques et conséquences des exacerbations
- Prise en charge :
 - Bronchodilatateurs de courte durée d'action
 - Corticostéroïdes
 - Antibiotique
 - Autres mesures
- Take home message



EXACERBATION BPCO

- GOLD 2022 :
 - Aggravation aiguë des symptômes respiratoires
 - Résultant en une majoration de la thérapie habituelle



EXACERBATION BPCO

- Critères d'Anthonisen
 - Majoration de la dyspnée
 - Majoration de la quantité des expectorations
 - Majoration de la purulence des expectorations
- Autres symptômes :
 - Toux
 - Wheezing
 - Fatigue



additional therapy. In everyday practice, exacerbation is a clinical diagnosis of exclusion suggested by changes in symptoms, but only made when the clinician has considered and, where appropriate, excluded other causes of symptom changes in a patient with known COPD.

Lancet Respir Med 2018

Published Online

February 9, 2018

[http://dx.doi.org/10.1016/](http://dx.doi.org/10.1016/S2213-2600(18)30049-3)

[S2213-2600\(18\)30049-3](http://dx.doi.org/10.1016/S2213-2600(18)30049-3)



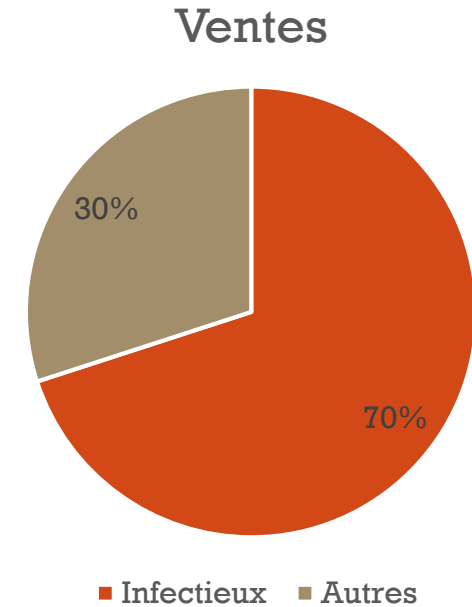
DIAGNOSTIC DIFFÉRENTIEL

- Pneumonie
- Pneumothorax
- Épanchement pleural
- Embolie pulmonaire
- Décompensation cardiaque
- Arythmie



TRIGGERS

- Infectieux
 - Viral : Rhinovirus, RSV, Influenza, Parainfluenza, Adenovirus
 - Bactérien : H. influenza, M. catarrhalis, S. pneumoniae, P. aeruginosa
- Non infectieux
 - Tabac
 - Pollution de l'air (outdoor et indoor)
 - Changements météorologiques (température, humidité)
 - Arrêt des traitements inhalés
 - Embolie pulmonaire
 - Décompensation cardiaque
- Idiopathique (10 à 30%)



EXACERBATION BPCO : DEGRÉ DE SÉVÉRITÉ

- Selon les critères d'Anthonisen
 - 1/3 : léger
 - 2/3 : modéré
 - 3/3 : sévère
- Selon le traitement
 - Léger : bronchodilatateurs de courte durée d'action (SABD) uniquement
 - Modéré : SABD + corticoïdes systémiques et/ou antibiotiques
 - Sévère : patients nécessitant une visite aux Urgences ou hospitalisation



PULMONARY PERSPECTIVE

An Updated Definition and Severity Classification of Chronic Obstructive Pulmonary Disease Exacerbations

The Rome Proposal

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Am J Respir Crit Care Med Vol 204, Iss 11, pp 1251–1258, Dec 1, 2021

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Originally Published in Press as DOI: 10.1164/rccm.202108-1819PP on September 27, 2021



EXACERBATION BPCO : PHYSIOPATHOLOGIE

PULMONARY PERSPECTIVE

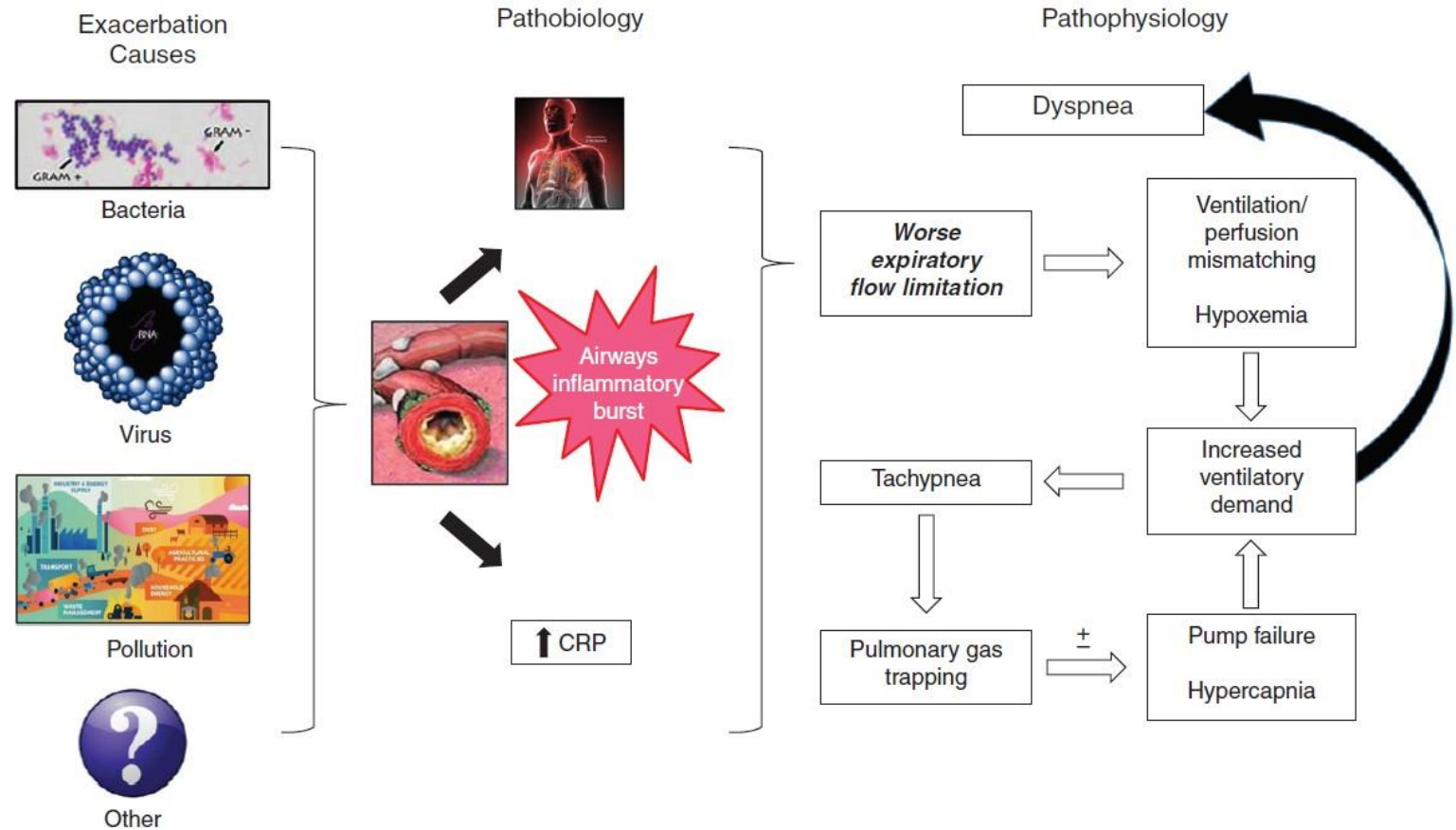


Figure 1. Causes, pathobiological mechanisms, and pathophysiological consequences in an exacerbation of chronic obstructive pulmonary disease (7, 35). CRP = C-reactive protein.



Table 1. The Rome Proposal for an Updated Definition and Severity Classification of COPD Exacerbations

Definition	In a patient with COPD, an exacerbation is an event characterized by dyspnea and/or cough and sputum that worsen over ≤ 14 d, which may be accompanied by tachypnea and/or tachycardia and is often associated with increased local and systemic inflammation caused by airway infection, pollution, or other insult to the airways.
Diagnostic approach	<ol style="list-style-type: none">1. These events can be life-threatening and require adequate evaluation and treatment.2. Complete a thorough clinical assessment for evidence of COPD and potential respiratory and nonrespiratory concomitant diseases, including consideration of alternative causes for the patient's symptoms and signs: primarily pneumonia, heart failure, and pulmonary embolism.3. Assess:<ol style="list-style-type: none">a. Symptoms, severity of dyspnea as determined by using a VAS, and documentation of the presence of cough.b. Signs (tachypnea, tachycardia), sputum volume and color, and respiratory distress (accessory muscle use).4. Evaluate severity by using appropriate additional investigations such as pulse oximetry, laboratory assessment, and CRP and/or arterial blood gases.5. Establish the cause of the event (viral, bacterial, environmental, other).

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; CRP = C-reactive protein; VAS = visual analog scale.



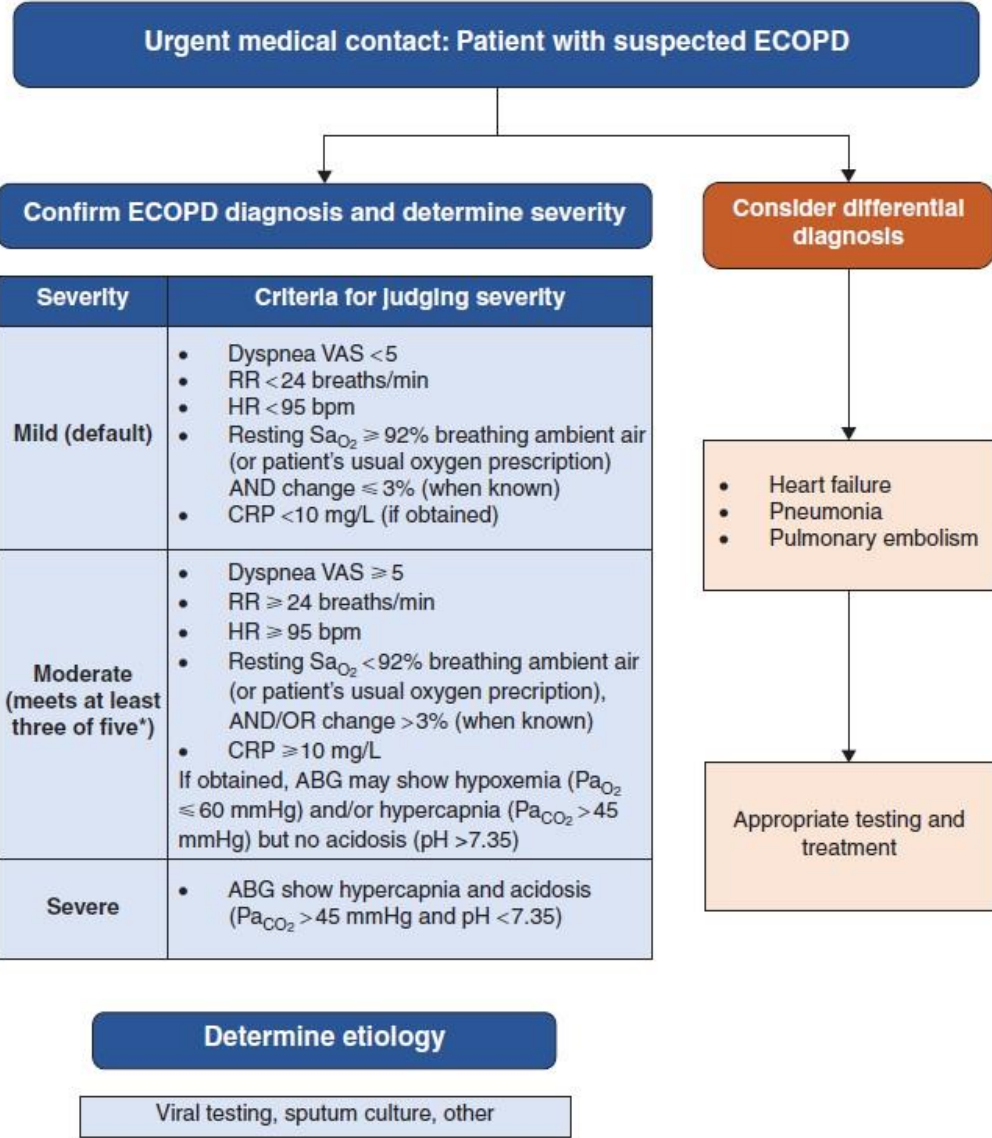


Figure 2. Diagnostic approach to a patient suspected of an ECOPD. *Dyspnea (as determined by using a VAS), RR, HR, oxygen saturation (absolute and/or change), and CRP. ABG = arterial blood gas; CRP = C-reactive protein; ECOPD = exacerbation of chronic obstructive pulmonary disease; HR = heart rate; RR = respiratory rate; VAS = visual analog scale.



TABLE 3

RECOVERY FROM EXACERBATION IN PEFR AND TOTAL SYMPTOM SCORE IN 91 PATIENTS WITH 504 EXACERBATIONS

	PEFR (IQR)	Symptoms (IQR)
Median time to recovery, d*	6 (1 to 14)	7 (4 to 14)
% Exacerbations recovering within 35 d	75.2	86.1
% Exacerbations recovering within 91 d	80.2	90.9
% Exacerbations in which the next exacerbation occurs before complete recovery in PEFR	3.4	1.4
% Exacerbations with indeterminate recovery [†]	9.3	3.1
% Exacerbations that do not recover at 91 d	7.1	4.6

Definition of abbreviation: IQR = interquartile range.

* Results are presented as median (IQR).

[†] Recovery could not be determined for these exacerbations because of missing data.



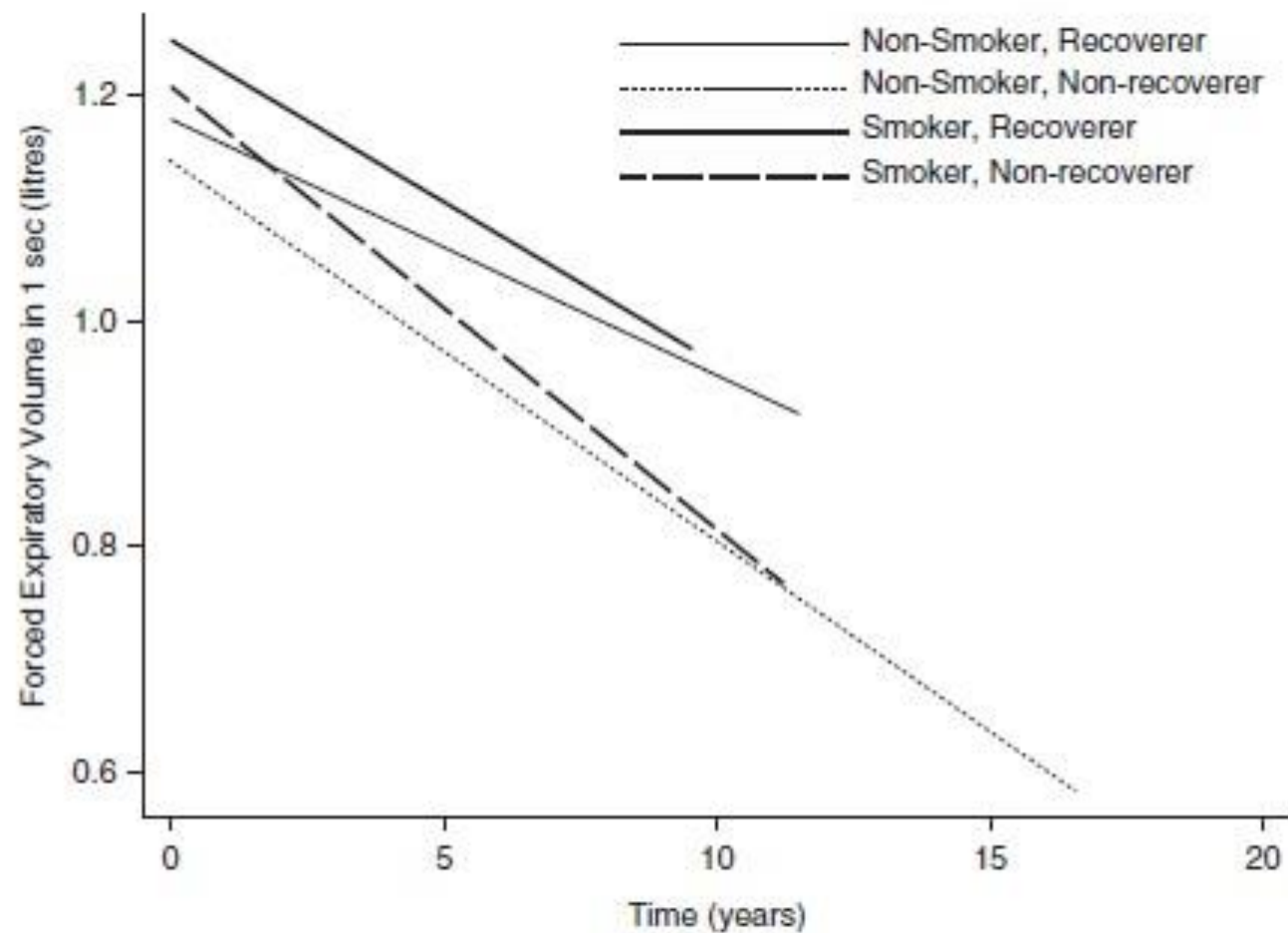


Figure 5. FEV₁ decline in four groups of patients with chronic obstructive pulmonary disease (smokers and nonsmokers) and those with and without exacerbations where peak expiratory flow never returned to preexacerbation levels.



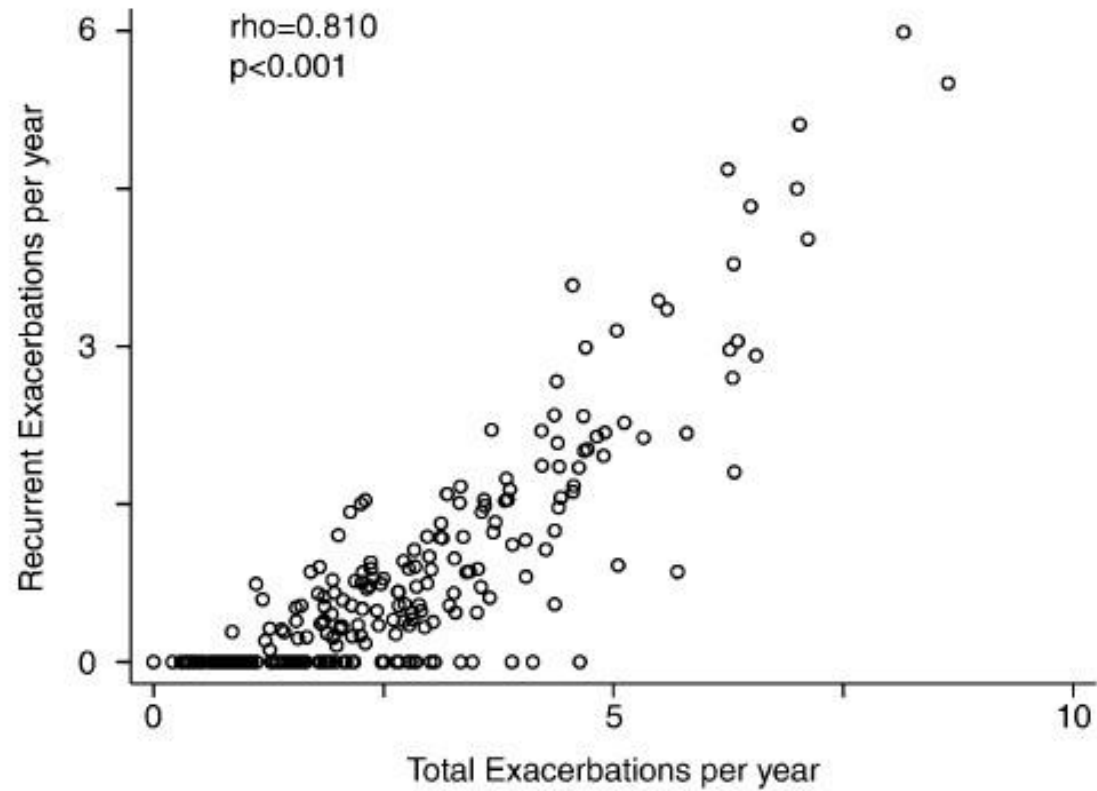


Figure 5. Relationship between the total annual number of exacerbations and the number of recurrent exacerbations in individual patients ($n = 297$; $\rho = 0.81$; $P < 0.001$).



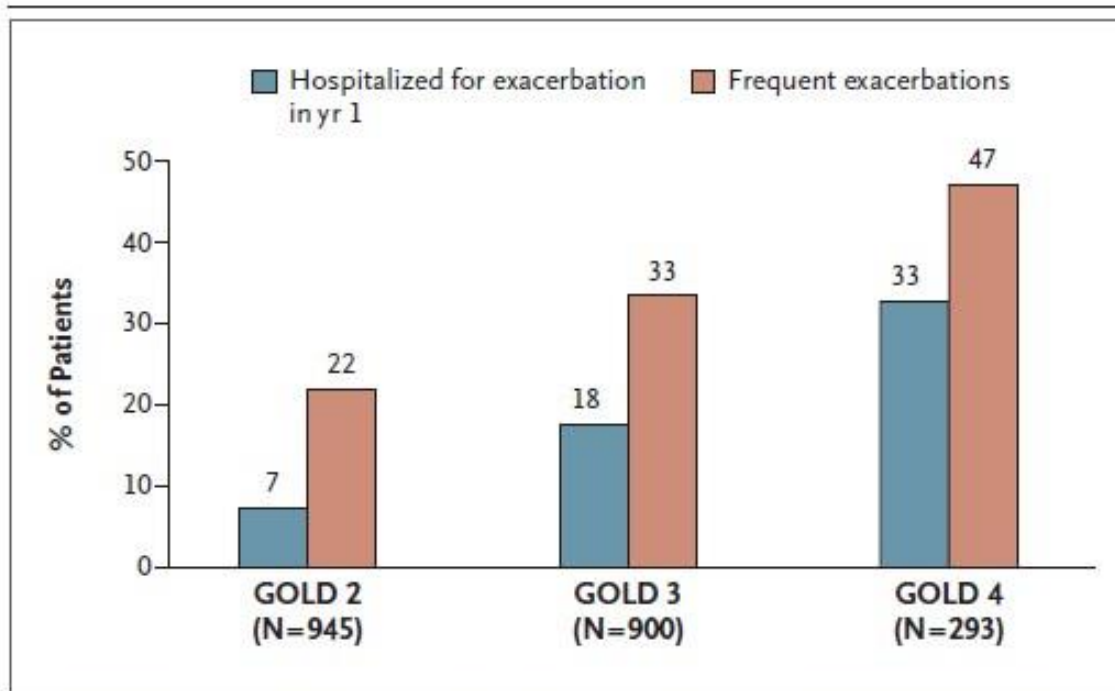


Figure 1. Association of Disease Severity with the Frequency and Severity of Exacerbations during the First Year of Follow-up in Patients with Chronic Obstructive Pulmonary Disease.

Patients with two or more exacerbations during the year were considered to have frequent exacerbations. An exacerbation requiring hospitalization was classified as severe. Disease severity was classified according to the stages of disease defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD). $P < 0.001$ for both comparisons.



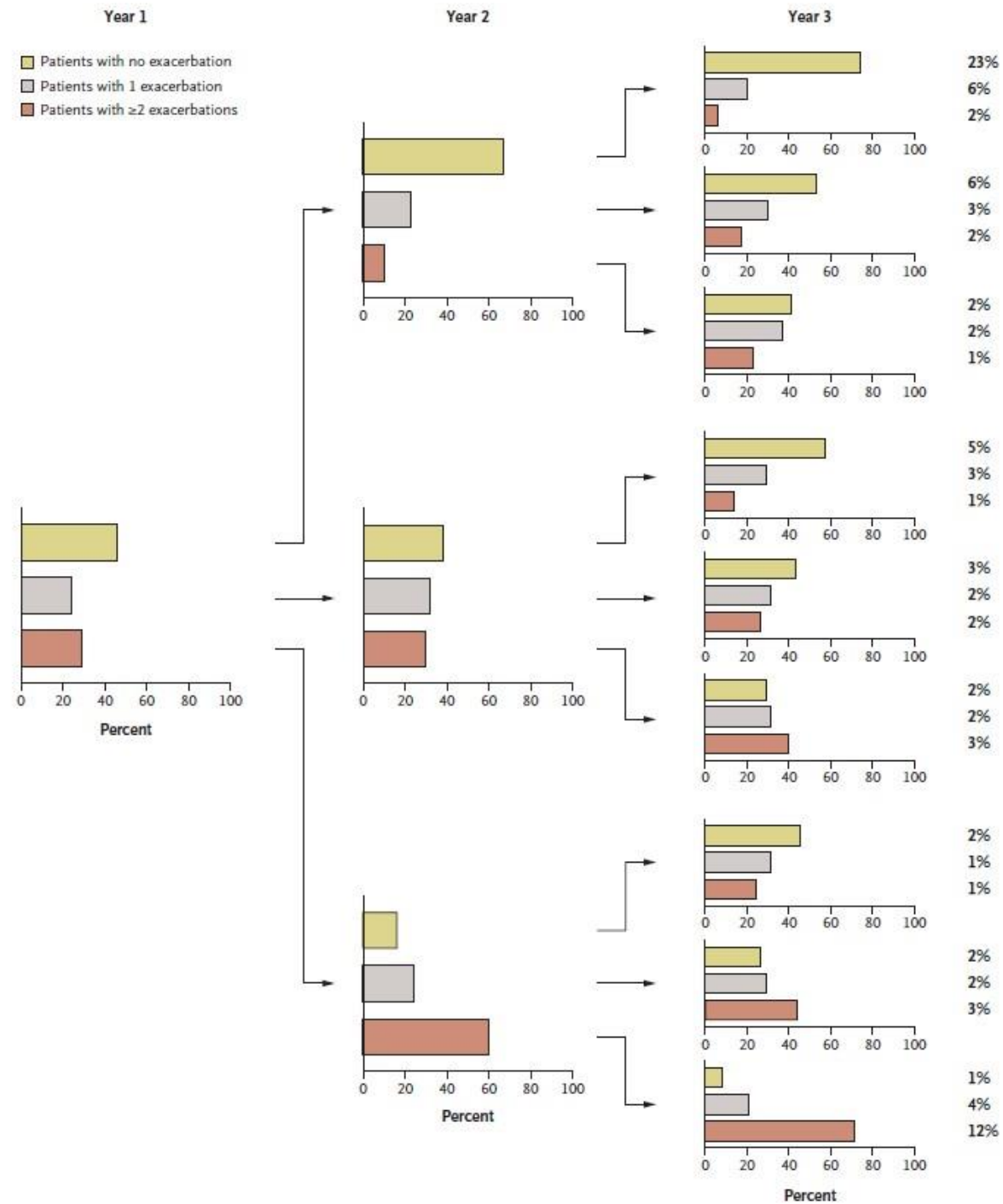


Figure 2. Stability of the Frequent-Exacerbation Phenotype in the 1679 Patients with Chronic Obstructive Pulmonary Disease Who Completed the Study.

The bars at the left show the proportions of patients with no exacerbations, one exacerbation, or two or more exacerbations in year 1. The bars in the middle show the respective incidence of exacerbations for these patients in year 2; the bars at the right show the respective incidence in year 3. The percentages at right denote the proportions of all patients with no exacerbations, one exacerbation, or two or more exacerbations. Numbers do not sum to 100 because of rounding.



TABLE 4 Mortality rates after hospitalisation for a chronic obstructive pulmonary disease exacerbation at different time-points for the six studies included and the 10 studies excluded from the meta-analysis fulfilling all inclusion criteria except follow-up >1.5 yrs

	Patients n	Mortality rate %					
		In-hospital	3 months	6 months	1 yr	2 yrs	5 yrs
Studies included in the meta-analysis							
CONNORS [15]	1016	11	NR	33	43	49	NR
VESTBO [16]	487	NR	NR	NR	NR	NR	44
GROENEWEGEN [17]	171	8	16	18	23	NR	NR
GUNEN [18]	205	8.3	NR	24	33	39	NR
McGHAN [19]	54269	3.6	NR	NR	24	NR	57
Brekke [20]	996	9.9	22	27	32	41	NR
Studies excluded from the meta-analysis[#]							
FUSO [10]	590	14	NR	NR	NR	NR	NR
CYDULKA [21] [†]	131974	6	NR	NR	NR	NR	NR
ERIKSEN [22]	300	8.6	19	NR	36	NR	NR
PATIL [9]	71130	2.5	NR	NR	NR	NR	NR
YOHANNES [23]	104	3.8	NR	NR	38	NR	NR
WANG [24]	282	9.9	NR	NR	NR	NR	NR
PRICE [25]	7529	7.4	15	NR	NR	NR	NR
BUSTAMENTE [26]	763	6.4	NR	NR	NR	NR	NR
KINNUNEN [27]	72896 [‡]	3.2	NR	NR	NR	NR	NR
DRANSFIELD [28]	825	5.2	NR	NR	NR	NR	NR
Overall estimate based on all 16 studies % (95% CI)[†]		6.7 (5.7–7.7)	18 (14–22)	26 (20–32)	33 (25–40)	43 (37–50)	51 (38–63)

NR: not reported. [#]: follow-up <1.5 yrs; [†]: results year 1991; [‡]: overall weighted average mortality rates based on random effects analysis; [§]: number of admissions instead of number of patients.



PRISE EN CHARGE EN AMBULATOIRE



TRAITEMENT

- BUT :
 - Minimiser l'impact négatif de l'exacerbation
 - Prévenir le risque d'exacerbation future



TRIAGE

▶ POTENTIAL INDICATIONS FOR HOSPITALIZATION ASSESSMENT*

- Severe symptoms such as sudden worsening of resting dyspnea, high respiratory rate, decreased oxygen saturation, confusion, drowsiness.
- Acute respiratory failure.
- Onset of new physical signs (e.g., cyanosis, peripheral edema).
- Failure of an exacerbation to respond to initial medical management.
- Presence of serious comorbidities (e.g., heart failure, newly occurring arrhythmias, etc.).
- Insufficient home support.

*Local resources need to be considered.

TABLE 5.2

Environ 80% → prise en charge ambulatoire



TRAITEMENT

Bronchodilatateurs

Corticostéroïdes

Antibiotiques



BRONCHODILATEURS

- B2-agonistes de courte durée d'action (SABA) +/- anticholinergique de courte durée d'action (SAMA)
- Route d'admission
 - MDI (metered dose inhaler) avec ou sans chambre d'inhalation
 - Nébuliseurs



Pas de différence



BRONCHODILATEURS

- **SABA**

- Ventolin aérosol doseur 100 mcg → 1 à 2 puffs 1x/h pendant 2-3 doses puis 1x/2-4h selon réponse
- Ventolin sol inhal 0.5% → 0.25 à 0.5 ml dans 3 ml NaCl 0.9% 1x/h pendant 2 à 3 doses puis 1x/2-4h selon réponse

- **SAMA**

- Atrovent N aérosol doseur (ipratropium 20 mcg) → 2 bouffées 1x/4-6h
- Atrovent sol inhal 250 mcg/2ml → 1 dose 1x/4-6h

- **Combinaisons SABA/SAMA**

- Berodual N aérosol doseur (fénotérol 50 mcg et ipratropium 21 mcg)
- Dospir sol inhal (salbutamol 2.5 mg et ipratropium 500 mcg)
- Ipramol sol inhal (salbutamol 2.5 mg et ipratropium 500 mcg)



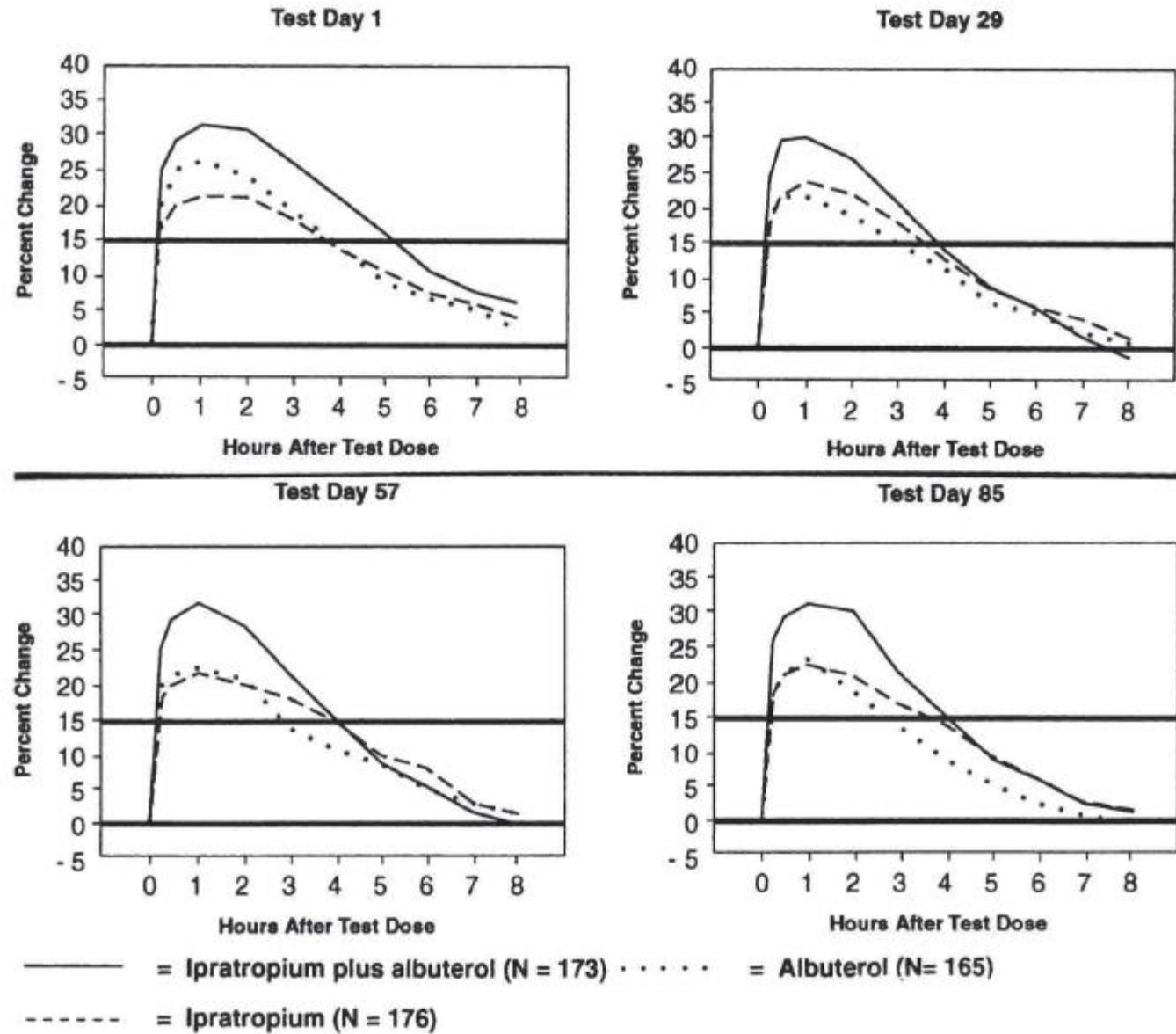


FIGURE 1. Percent changes in mean FEV₁ from test day baselines.

In chronic obstructive pulmonary disease, a combination of ipratropium and albuterol is more effective than either agent alone. An 85-day multicenter trial. COMBIVENT Inhalation Aerosol Study Group. Chest 1994; 105:1411.



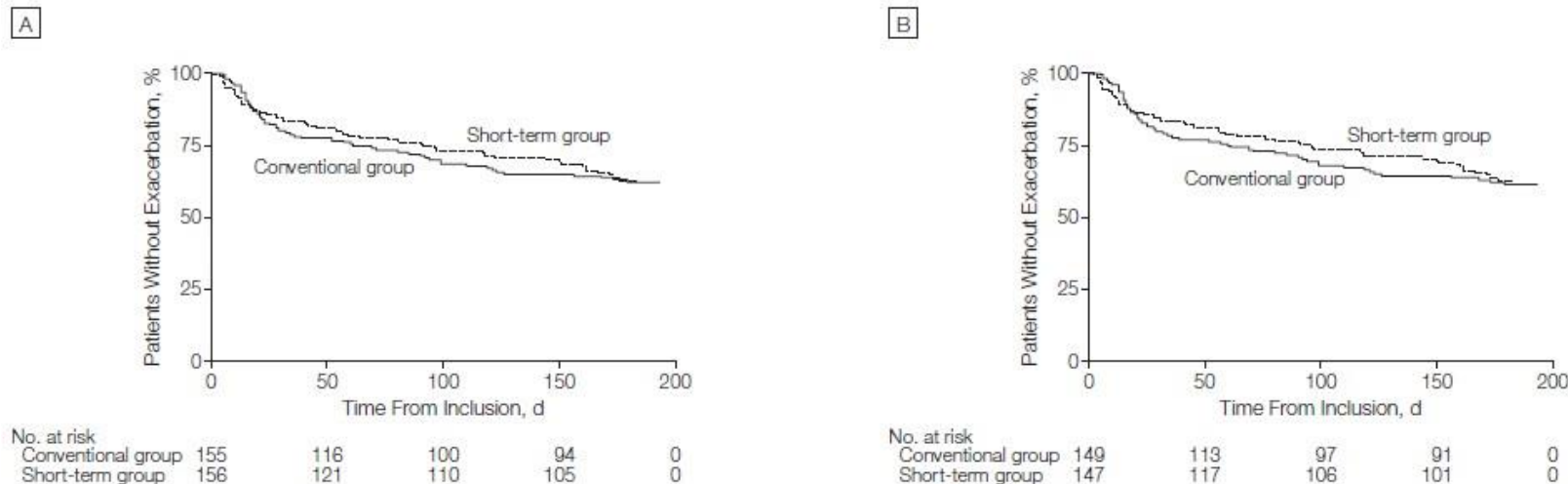
CORTICOSTÉROÏDES

- Améliorent
 - fonctions pulmonaires
 - oxygénation
- Diminuent
 - temps de récupération
 - risque de rechute précoce
 - risque d'échec thérapeutique
 - durée d'hospitalisation

→ Prednisone 40 mg 1x/j pendant 5 jours, pas plus de 14 jours



Figure 2. Time to Reexacerbation of Chronic Obstructive Pulmonary Disease

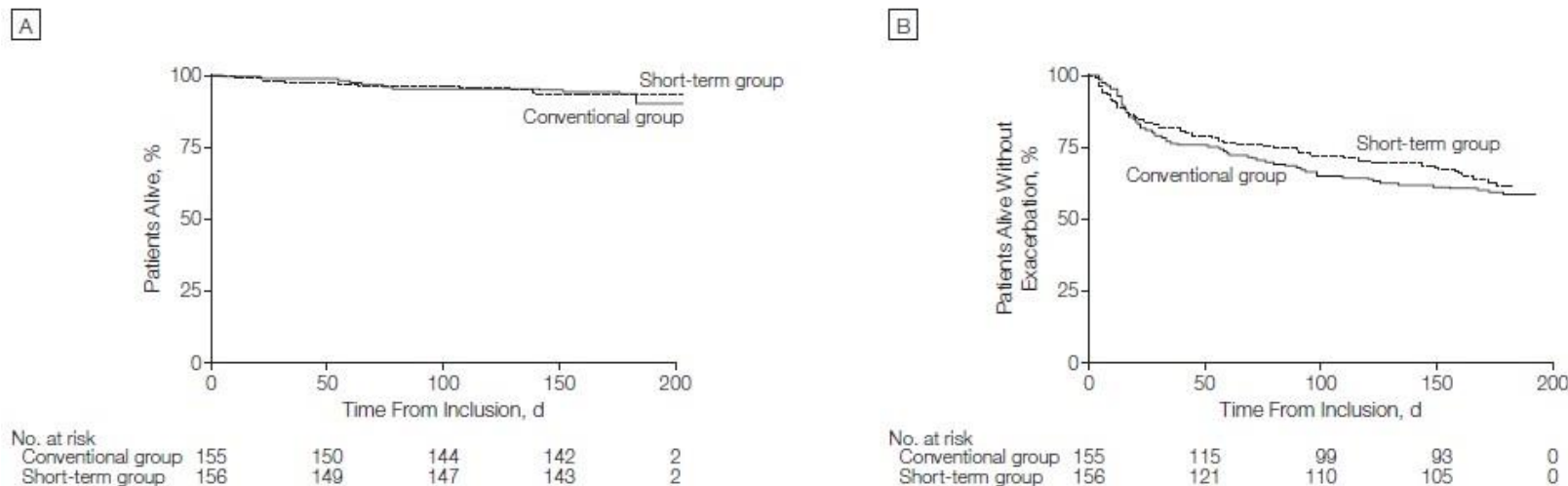


A, Proportions of patients without reexacerbation in the intention-to-treat analysis. B, Proportions of patients without reexacerbation in the per-protocol analysis. Survival curves did not differ significantly when compared by the log-rank test. Hazard ratios for the short-term vs conventional treatment group were 0.95 (90% CI, 0.70-1.29; P for noninferiority = .006) in the intention-to-treat analysis and 0.93 (90% CI, 0.68-1.26; P for noninferiority = .005) in the per-protocol analysis. P values were obtained using the Wald test.

Etude REDUCE

- Randomisée non-infériorité
- 311 patients
- Prednisone 40 mg/j
- 5 jours vs 14 jours

Figure 3. Overall Survival of Patients With Chronic Obstructive Pulmonary Disease



A, Proportion of patients alive (intention-to-treat analysis). B, The survival curve for the combined outcome death, reexacerbation, or both. Survival curves did not differ significantly when compared by the log-rank test ($P = .87$ for time to death, $P = .57$ for time to reexacerbation or death).

Leuppi JD, et al. Short-term vs conventional glucocorticoid therapy in acute exacerbations of chronic obstructive pulmonary disease: the REDUCE randomized clinical trial. *JAMA* 2013; 309:2223.



ANTIBIOTIQUES

- Utilisation restent controversée
- Oui si évidences d'infection bactérienne
- Réduisent
 - mortalité à court terme
 - échec de traitement
 - récurrence précoce
 - temps de récupération
 - purulence des expectorations
 - Si soins intensifs, réduction durée séjour

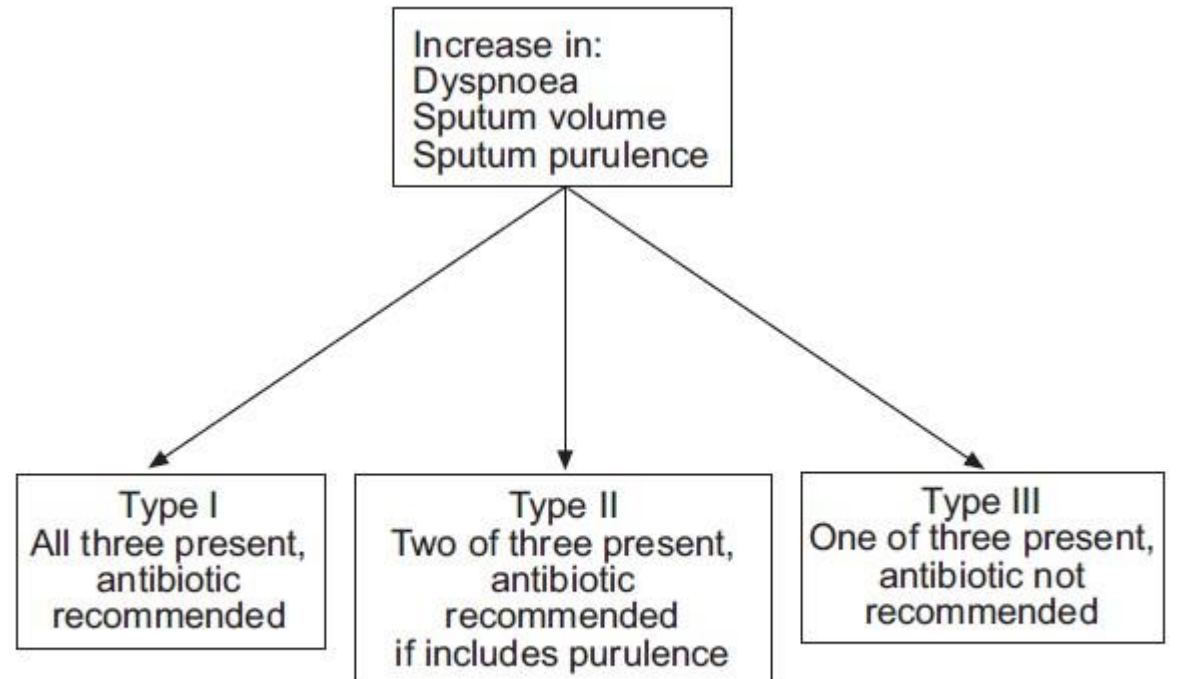


FIGURE 1. Patient stratification by characteristics of exacerbation.



ANTIBIOTIQUES

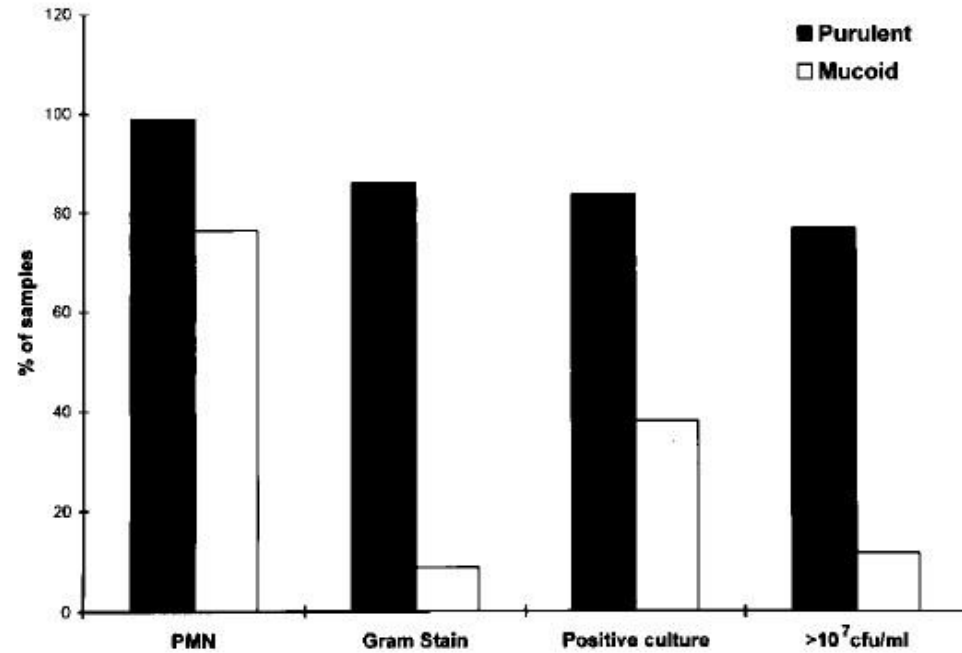


FIGURE 1. Sputum characteristics are shown for samples classified as purulent and mucoid exacerbations at presentation. Histograms are the proportion of samples showing > 25 neutrophils/low-power field (PMN), bacterial type seen on Gram's stain, positive bacterial culture, and samples with > 10⁷ cfu/mL of a putative pathogen.

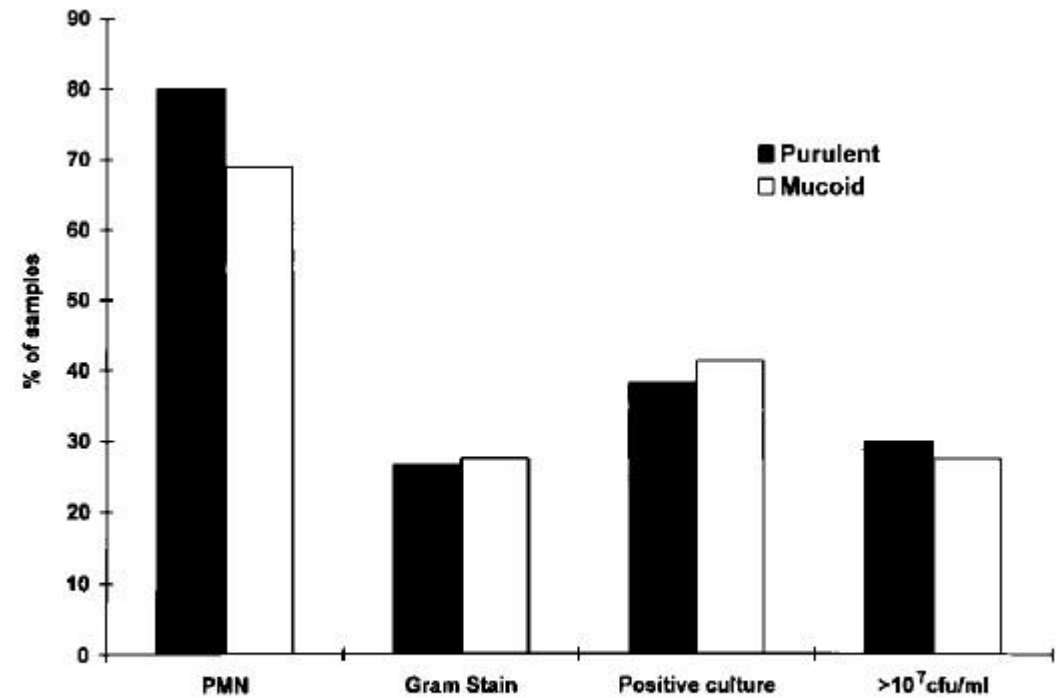


FIGURE 3. Sputum characteristics for both groups seen in the stable clinical state.



ANTIBIOTIQUES

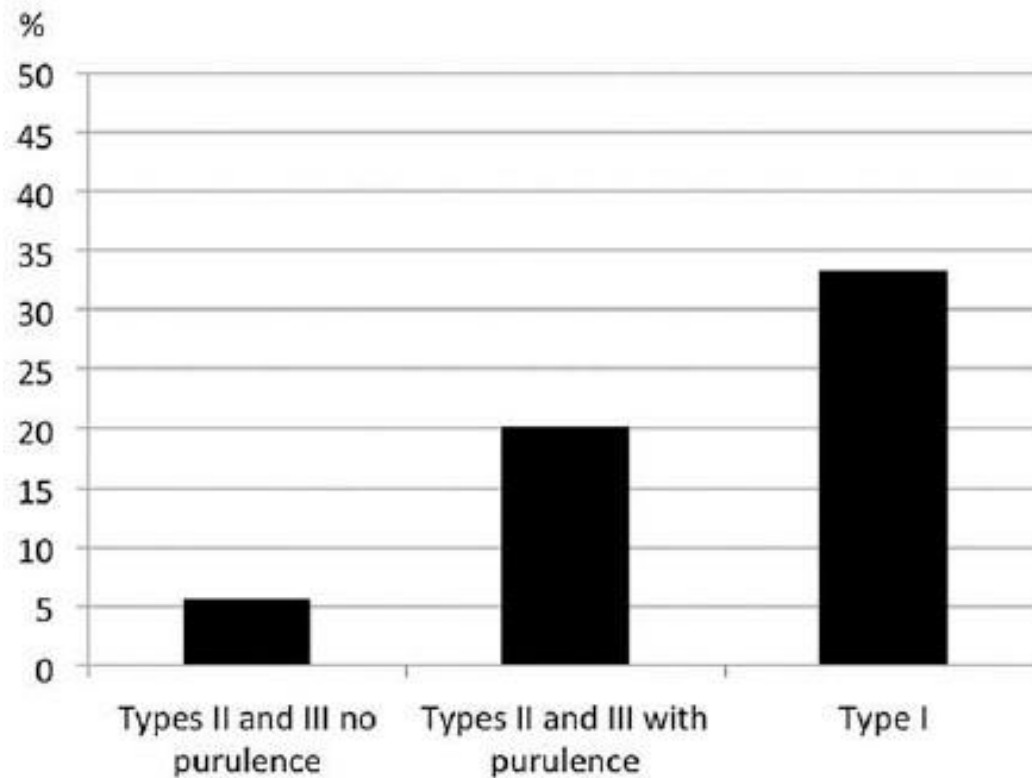


FIGURE 1. Percentage of failure rates in exacerbations of mild to moderate COPD not treated with antibiotics according to Anthonisen criteria.

- 310 patients > 40 ans
- BPCO avec VEMS > 50%
- Amoxicilline-clavulanate 2x/j pdt 8 jours vs placebo



ANTIBIOTIQUES

Table 2—Univariate and Multivariate Logistic Regression Analysis of Exacerbation Factors That Predict Clinical Failure of Exacerbations of Mild to Moderate COPD Not Treated With Antibiotics

Variable	Univariate		Multivariate		Multivariate With CRP	
	OR (95% CI)	P Value	OR (95% CI)	P Value	OR (95% CI)	P Value
Increased dyspnea	1.6 (0.6-3.8)	.32	2.3 (0.9-5.9)	.078	1.3 (0.4-3.9)	.32
Increased sputum volume	2.1 (0.7-6.5)	.20	1.8 (0.6-6.1)	.32	0.6 (0.2-2.4)	.20
Increased sputum purulence	5.9 (1.7-20.7)	.005	6.3 (1.8-22.5)	.005	6.1 (1.5-25.0)	.005
CRP level \geq 40 mg/L	13.4 (5.3-34.3)	<.001	NA	...	13.4 (4.6-38.8)	<.001

NA = not assessed. See Table 1 legend for expansion of other abbreviation.



ANTIBIOTIQUES

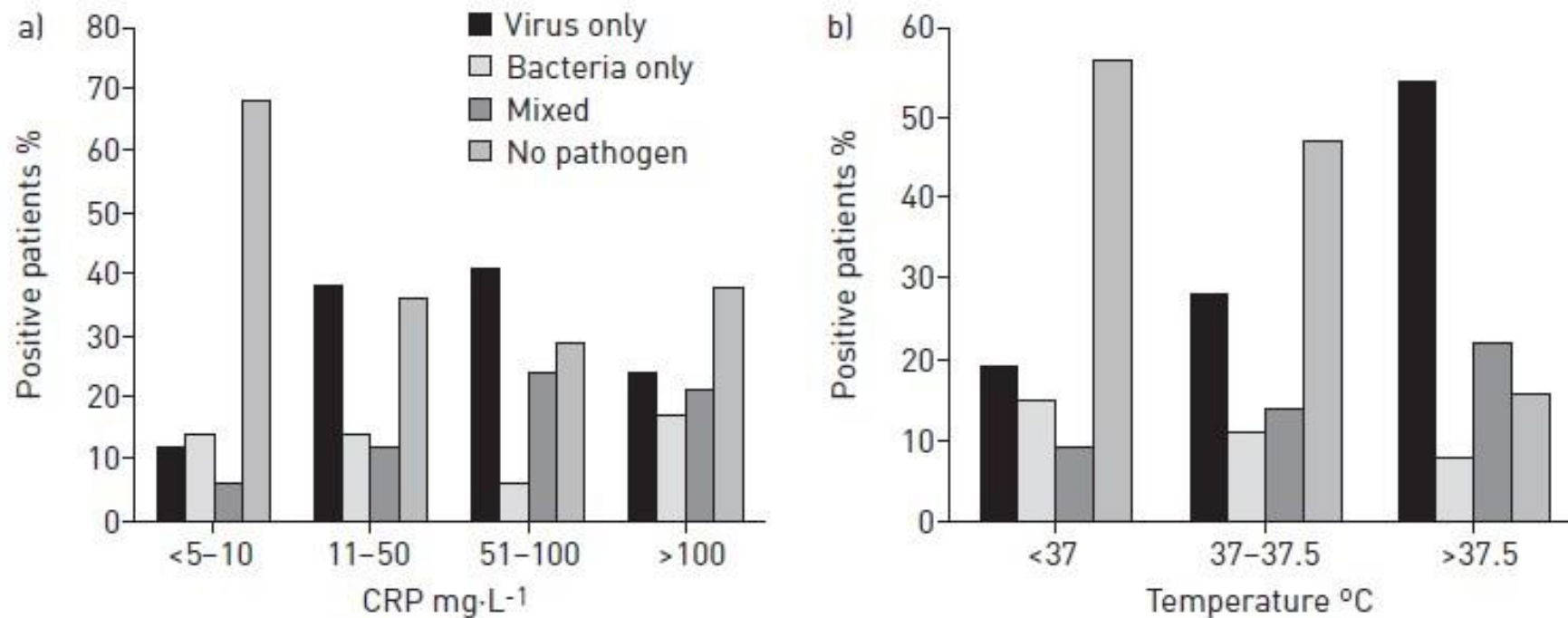
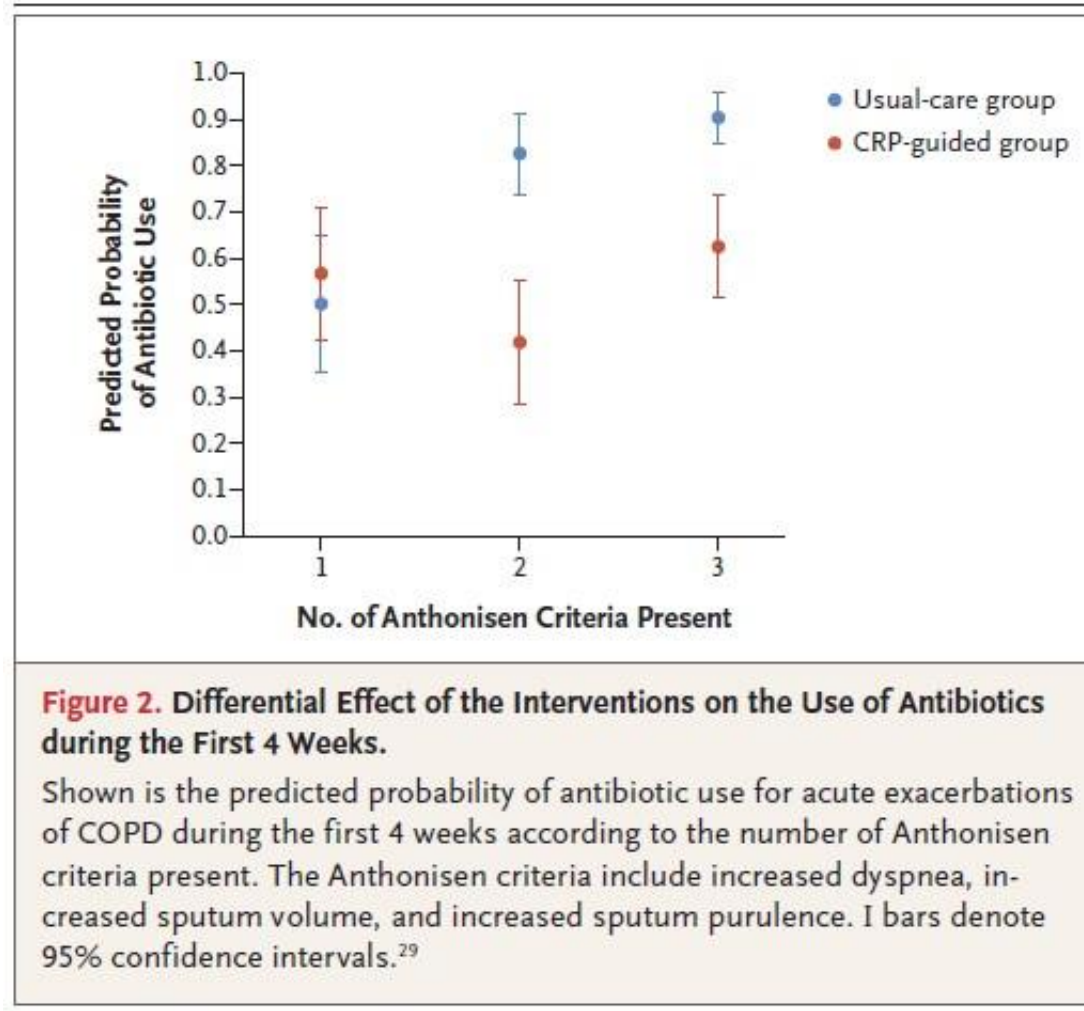


FIGURE 3 The proportion of patients with viruses only detected, bacteria only detected, mixed viral and bacterial detection, and no pathogens detected by a) serum C-reactive protein (CRP) and b) temperature.



ANTIBIOTIQUES



Utilisation antibiotique réduite de 77.4% à 47.7% quand CRP basse (< 20 mg/l)



ANTIBIOTIQUES

- Pu C, Am J Respir Crit Care Med 2019
- Identification de symptômes et signes cliniques suggérant une infection bactérienne
 - Purulence expectoration (OR 2.3, $p < 0.01$)
 - Viscosité expectoration (OR 1.52, $p = 0.03$)
 - Majoration de la toux (OR 1.74, $p = 0.04$)
- **WHEEZING** → diminution de la probabilité d'infection bactérienne (OR 0.58, $p < 0.01$)



ANTIBIOTIQUES

- Selon GOLD 2022, antibiotiques si :
 - 3 symptômes cardinaux (sévère)
 - 2 symptômes cardinaux dont l'augmentation de la purulence des expectorations (modérée)
 - Ventilation mécanique (invasive ou non invasive)



ANTIBIOTIQUES

- Choix dépendant de :
 - Ambulatoire vs hospitalier
 - Risque de mauvaise évolution (> 65 ans, VEMS < 50%, exacerbations fréquentes, comorbidités)
 - Historique des germes antérieurs et susceptibilité
 - Épidémiologie et résistance locales
 - Risque d'infection à Pseudomonas
 - Colonisation connue ou isolation du Pseudomonas dans le passé (notamment 12 derniers mois)
 - VEMS < 30%
 - Bronchiectasies
 - Antibiotiques large spectre dans les 3 derniers mois
 - Corticothérapie systémique au long cours
 - Allergies, intolérances, interactions, effets secondaires



ANTIBIOTIQUES

- Si pas de FR de mauvaise évolution ou Pseudomonas
 - Macrolide (azithromycine, clarithromycine)
 - Céphalosporine de 2 ou 3^{ème} génération (cefuroxime, cefpodoxime)
 - Co-amoxicilline
- Si FR de mauvaise évolution, sans FR de Pseudomonas
 - Co-amoxicilline
 - Fluoroquinolone (levofloxacin, moxifloxacin)
- Si FR de Pseudomonas
 - Ciprofloxacine (levofloxacine) + culture d'expectoration
- Durée : 5 à 7 jours, evt 3 jours si azithromycine



AUTRES MESURES

- Arrêt du tabac
- Adhérence thérapeutique et technique d'inhalation
- Prise en charge diététique, support nutritionnel
- Vaccination (grippe, pneumocoque, SARS-CoV-2)
- Azithromycine
- Roflumilast
- Prise en charge des comorbidités

- Oxygénothérapie (nouvelle ou augmentation des besoins), nécessité ventilation
→ prise en charge aux Urgences +/- hospitalisation

- **Réhabilitation respiratoire**



The NEW ENGLAND JOURNAL *of* MEDICINE

ESTABLISHED IN 1812

AUGUST 25, 2011

VOL. 365 NO. 8

Azithromycin for Prevention of Exacerbations of COPD

Richard K. Albert, M.D., John Connett, Ph.D., William C. Bailey, M.D., Richard Casaburi, M.D., Ph.D., J. Allen D. Cooper, Jr., M.D., Gerard J. Criner, M.D., Jeffrey L. Curtis, M.D., Mark T. Dransfield, M.D., MeiLan K. Han, M.D., Stephen C. Lazarus, M.D., Barry Make, M.D., Nathaniel Marchetti, M.D., Fernando J. Martinez, M.D., Nancy E. Madinger, M.D., Charlene McEvoy, M.D., M.P.H., Dennis E. Niewoehner, M.D., Janos Porsasz, M.D., Ph.D., Connie S. Price, M.D., John Reilly, M.D., Paul D. Scanlon, M.D., Frank C. Sciurba, M.D., Steven M. Scharf, M.D., Ph.D., George R. Washko, M.D., Prescott G. Woodruff, M.D., M.P.H., and Nicholas R. Anthonisen, M.D., for the COPD Clinical Research Network



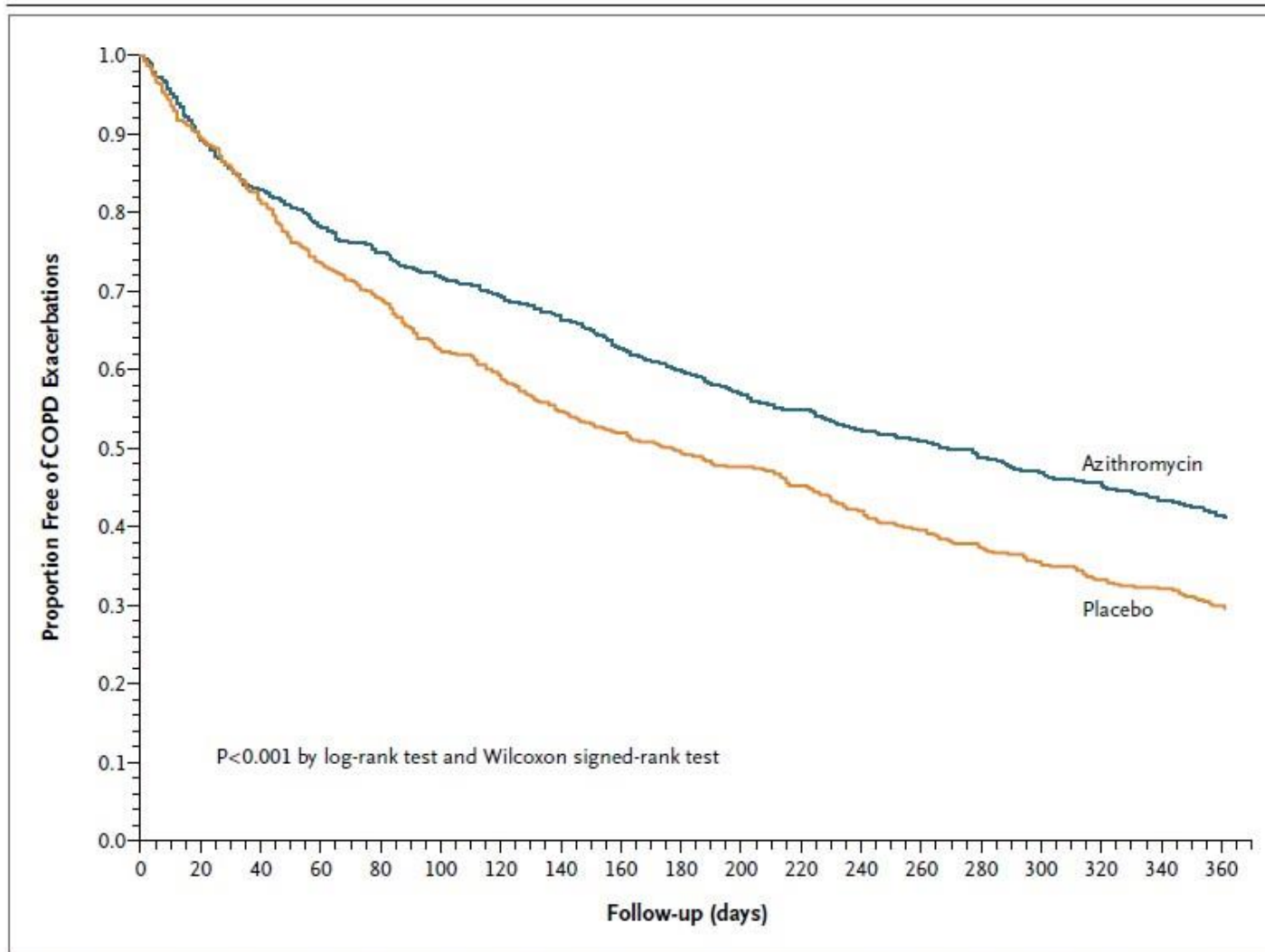
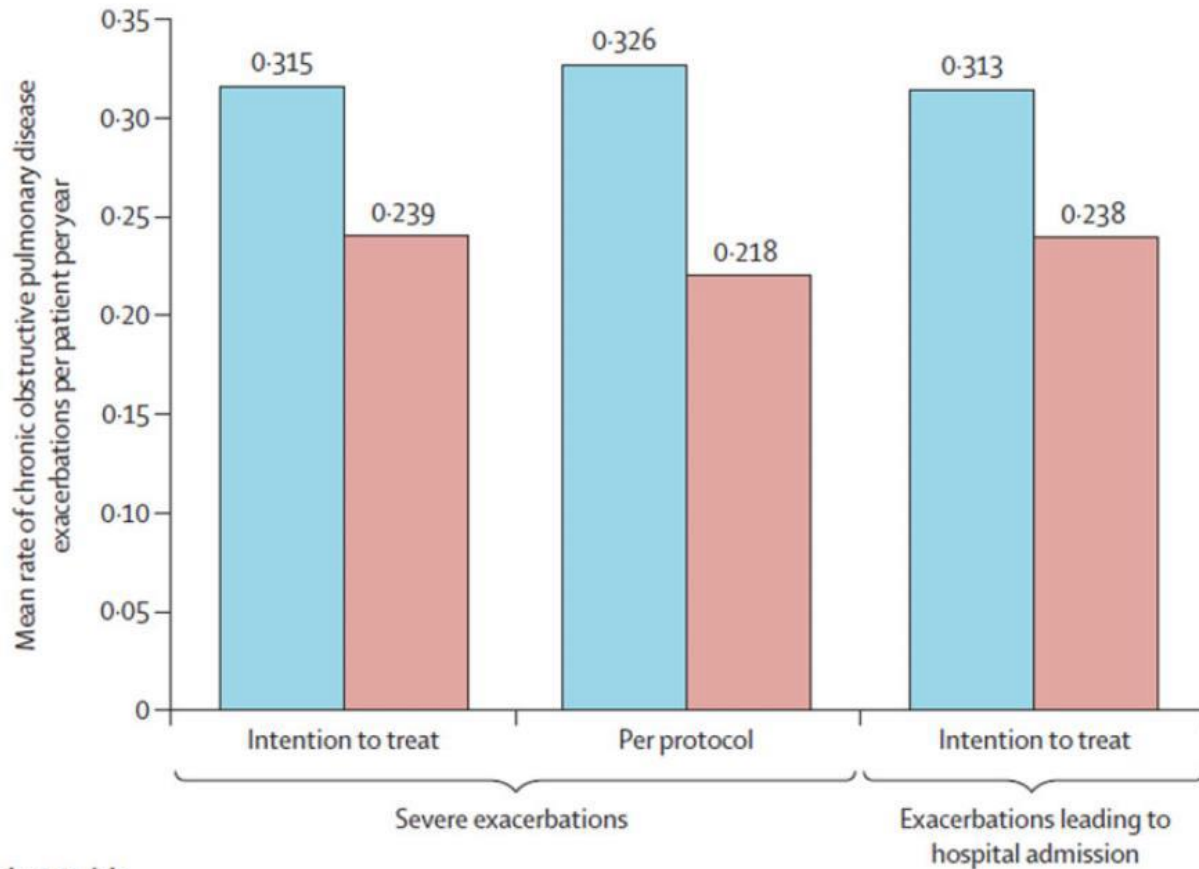


Figure 2. Proportion of Participants Free from Acute Exacerbations of Chronic Obstructive Pulmonary Disease (COPD) for 1 Year, According to Study Group.

The analyses were based on the participants who were randomly assigned to the group minus those who did not return for any follow-up assessment — 558 participants in the azithromycin group, of whom 317 (57%) had an acute exacerbation, and 559 in the placebo group, of whom 380 (68%) had an acute exacerbation.





Number at risk	Placebo 192; roflumilast 151	Placebo 167; roflumilast 120	Placebo 190; roflumilast 150
Patients with at least one exacerbation (n)			
Rate ratio (95% CI)	0.757 (0.601-0.952)	0.668 (0.518-0.861)	0.761 (0.604-0.960)
Two-sided p value	0.0175	0.0018	0.0209

Figure 4 The effect of roflumilast in reducing the rate of severe COPD exacerbations and exacerbations leading to hospital admission. (Reproduced from ref-

EFFET DU
DAXAS
(roflumilast)

Lancet 2015; 385: 857-66



RÉHABILITATION RESPIRATOIRE

- Stationnaire ou ambulatoire (au minimum 2x/semaine pendant 6 à 8 semaines)
- Améliore :
 - Dyspnée, tolérance à l'effort, capacité d'effort, qualité de vie et état de santé en général
- Réduit :
 - Le risque de réadmission à l'hôpital après une exacerbation récente (< 4 semaines)
 - Anxiété et dépression
 - Mortalité (pas clair)



Figure 4. Forest plot of comparison: 1 Rehabilitation versus control, outcome: 1.37 Hospital readmission (to end of follow-up) with separated new trial data.

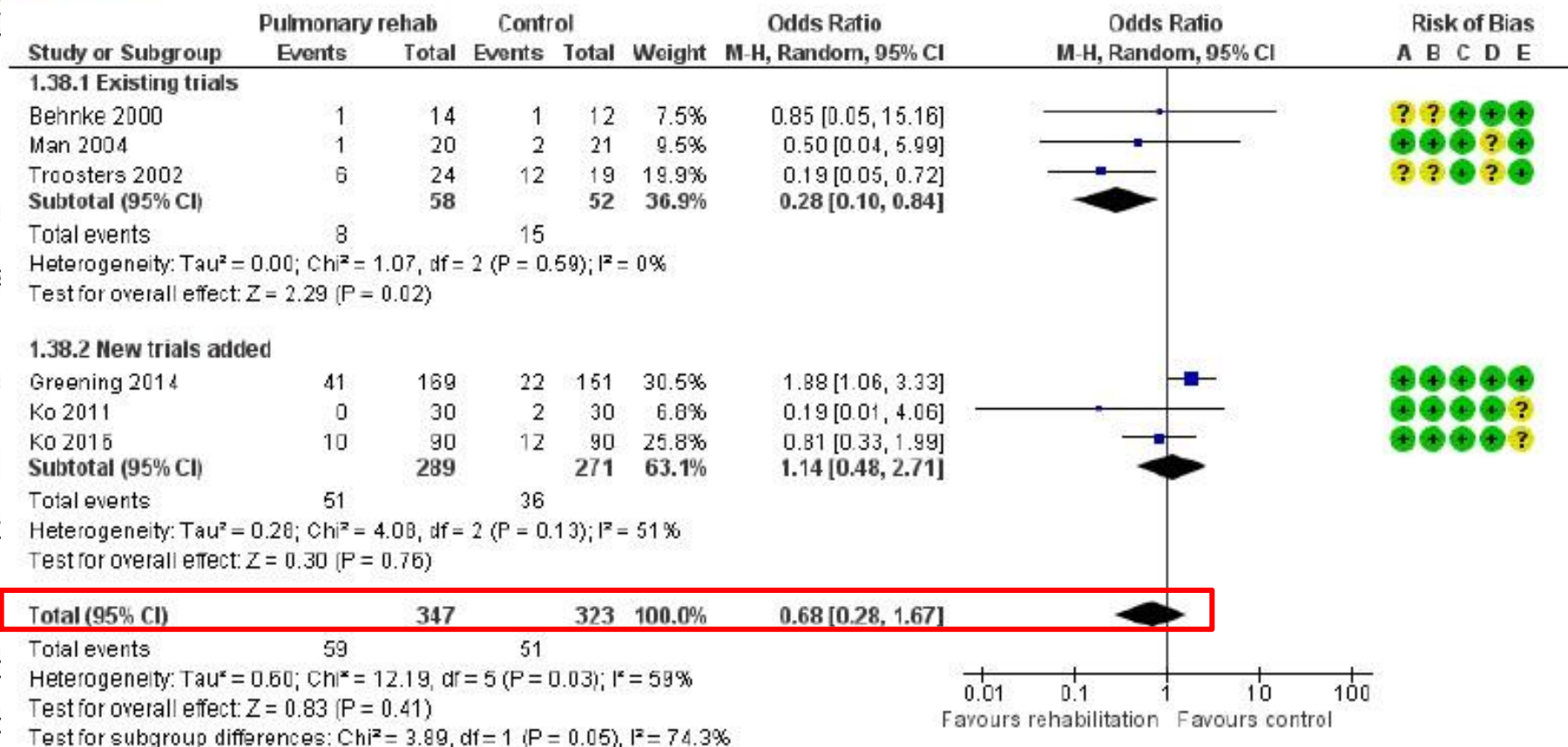
Study or Subgroup	Pulmonary rehab Events	Control Total	Events	Total
1.37.1 Existing trials				
Behnke 2000	3	14	9	14
Eaton 2009	11	47	15	47
Man 2004	2	20	12	20
Murphy 2005	2	13	5	13
Seymour 2010	2	30	10	30
Subtotal (95% CI)		124		
Total events	20		51	
Heterogeneity: Tau ² = 0.61; Chi ² = 8.15, df = 4 (P = 0.01); I ² = 74.3%				
Test for overall effect: Z = 3.06 (P = 0.002)				

1.37.2 New trials added				
Greening 2014	108	169	84	169
Ko 2011	16	30	13	30
Ko 2016	44	90	63	90
Subtotal (95% CI)		289		
Total events	168		160	
Heterogeneity: Tau ² = 0.49; Chi ² = 11.00, df = 2 (P = 0.003); I ² = 84.3%				
Test for overall effect: Z = 0.16 (P = 0.87)				

Total (95% CI)		413		
Total events	188		211	
Heterogeneity: Tau ² = 0.74; Chi ² = 29.80, df = 7 (P = 0.0001); I ² = 97.7%				
Test for overall effect: Z = 2.20 (P = 0.03)				
Test for subgroup differences: Chi ² = 4.65, df = 1 (P = 0.03); I ² = 78.3%				

- Risk of bias legend**
- (A) Random sequence generation (selection bias)
 - (B) Allocation concealment (selection bias)
 - (C) Incomplete outcome data (attrition bias)
 - (D) Selective reporting (reporting bias)
 - (E) Other bias

Figure 6. Forest plot of comparison: 1 Rehabilitation versus control, outcome: 1.38 Mortality with separated new trial data.



- Risk of bias legend**
- (A) Random sequence generation (selection bias)
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 - (E) Other bias



EXAMENS COMPLÉMENTAIRES

- **Culture d'expectoration : pas d'office en ambulatoire, sauf si :**
 - FR de Pseudomonas
 - absence d'amélioration sous traitement empirique initial
 - patient hospitalisé
- **Recherche virus respiratoire (Influenza) durant période endémique**
 - traiter si suspicion d'Influenza et si symptômes < 72h
- **Recherche COVID chez tous les patients durant la pandémie**
- **Radiographie du thorax**
 - Si patient aux Urgence ou hospitalisé
 - Si suspicion de pneumonie, pneumothorax, épanchement pleural ou décompensation cardiaque.



SUIVI MÉDICAL

- Suivi recommandé à 1-4 semaines
 - Contrôle de l'évolution
 - Documenter symptômes (CAT score, mMRC)
 - Revoir le traitement et technique d'inhalation
 - Evaluer si besoin d'oxygène au long cours
 - Considérer réhabilitation respiratoire
 - Evaluation des comorbidités
- Suivi recommandé à environ 3 mois
 - Contrôle de l'évolution
 - Revoir traitement inhalé et technique
 - Evaluer si besoin d'oxygène au long cours
 - Spirométrie



TAKE HOME MESSAGE

- Reconnaître une exacerbation et la traiter en conséquence
- Triage ambulatoire vs hospitalier
- B2-agoniste de courte durée d'action : traitement de première intention
 - Avec +/- anticholinergique de courte durée d'action
- Corticostéroïdes systémiques pour presque tous les patients, pas plus de 5-7 jours
- Antibiotiques : seulement si indication, pas plus de 5-7 jours
- Si besoin d'oxygénothérapie ou de majoration des débit ou si besoin de VNI → adresser le patient aux Urgences
- Prévention des nouvelles exacerbations



MERCI POUR VOTRE ATTENTION



MIX & REMIX

