Exacerbation de BPCO - Approche EBM

Pierre-Olivier Bridevaux

« The greater our knowledge increases, the greater our ignorance unfolds » John F. Kennedy



Plan

BPCO:

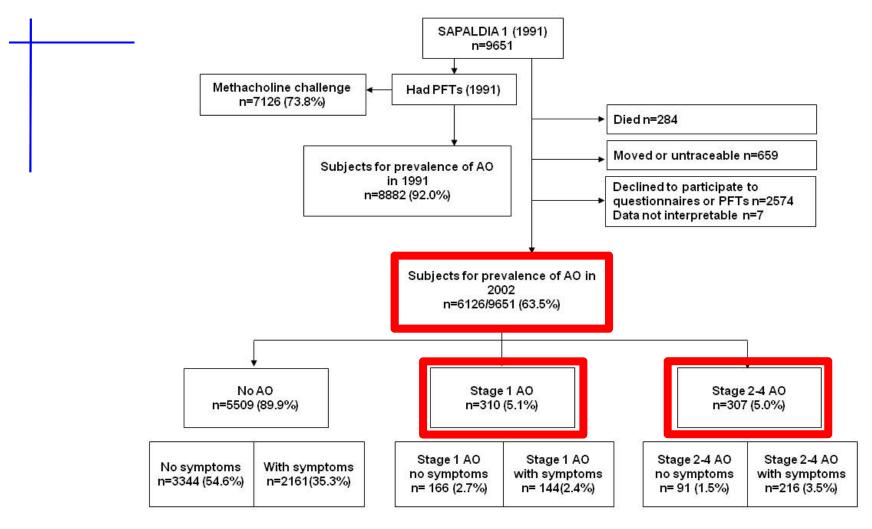
- Epidémiologie générale de la BPCO
- Fréquence des exacerbations

Exacerbation de de BPCO (articles publiés de 2005 à juin 2010)

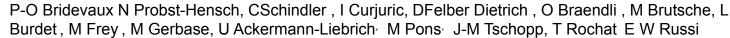
- Interventions pharmacologiques
- Interventions non pharmacologiques (patient)
- Interventions non pharmacologiques (système de soins)



Results from the SAPALDIA cohort study (European Resp J 2010 april 22)

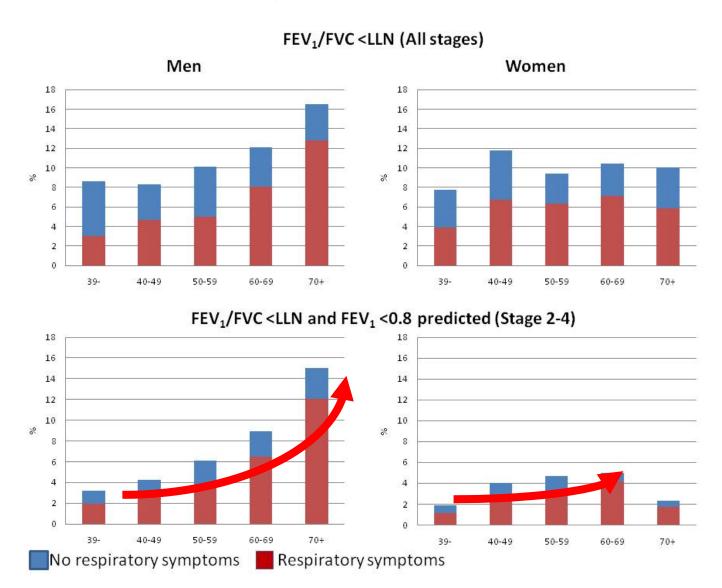


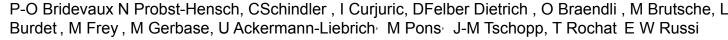
AO: airflow obstruction; PFTs : Pulmonary functions tests; Obstruction: $FEV_1/FVC < LLN$; Stage 1: $FEV_1 \ge 0.8$ predicted; Stage2-4: $FEV_1 < 0.8$ predicted





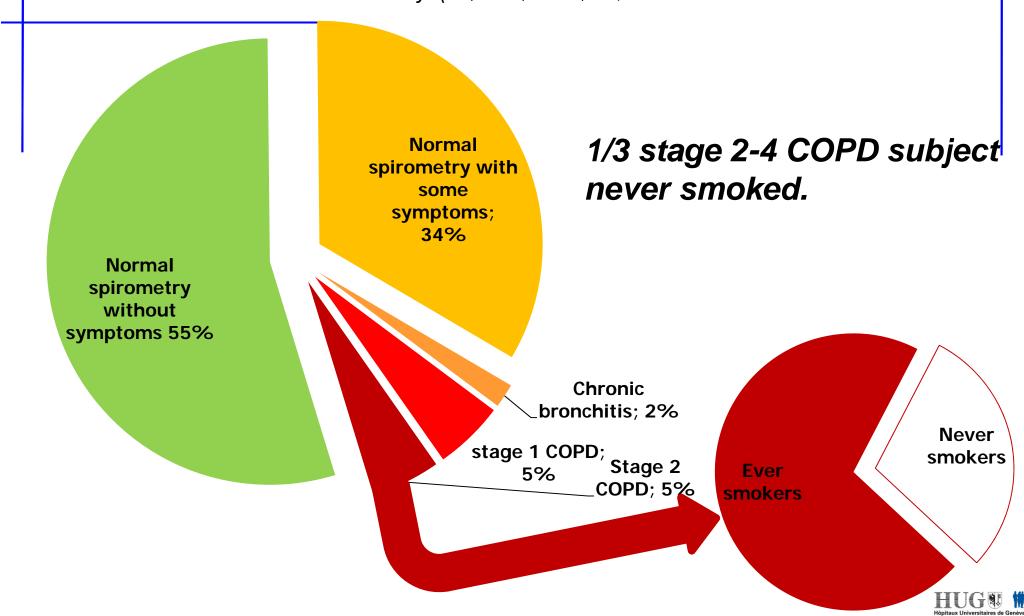
Results from the SAPALDIA cohort study (European Resp J 2010 april 22)



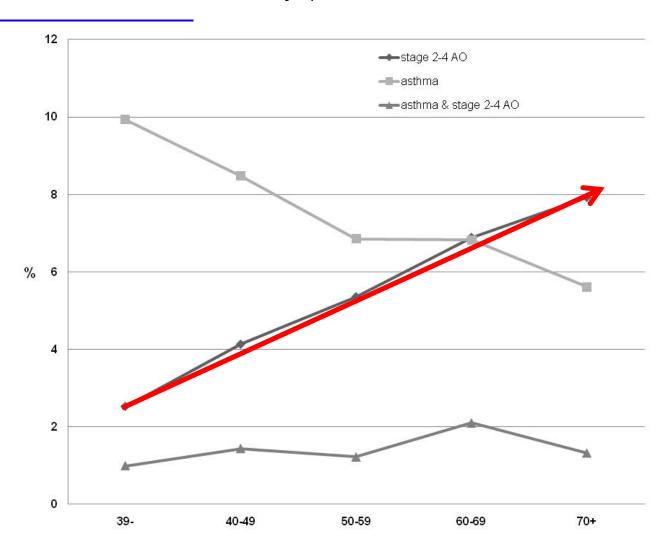




Results from the SAPALDIA cohort study (European Resp. J 2010 april 22)



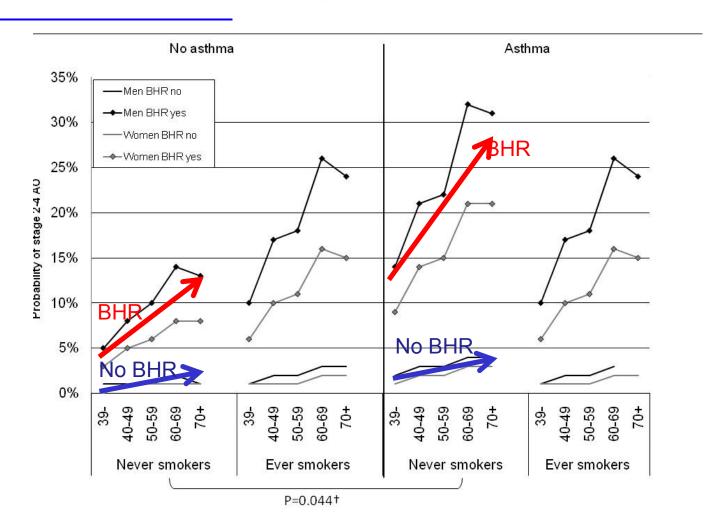
Results from the SAPALDIA cohort study (European Resp. J 2010 april 22)



P-O Bridevaux N Probst-Hensch, CSchindler, I Curjuric, DFelber Dietrich, O Braendli, M Brutsche, L Burdet, M Frey, M Gerbase, U Ackermann-Liebrich, M Pons, J-M Tschopp, T Rochat E W Russi



Results from the SAPALDIA cohort study (European Resp J 2010 april 22)





Results from the SAPALDIA cohort study (European Resp J 2010 april 22)

Risk factors for airflow obstruction (2002) in never smokers

	OR AO in 2002 (95% CI)
Positive Metacholine challenge (1991)	8.2 (4.2 - 16.2)
Asthma (1991)	3.3 (1.5 – 7.3)
Passive smoking (1991)	1.5 (0.4 – 5.3)



Epidémiologie des exacerbations de BPCO

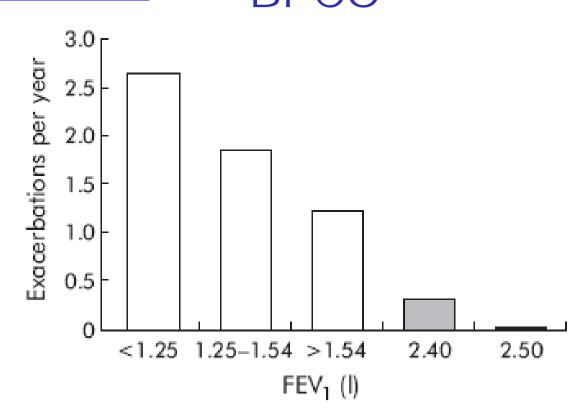
- USA (310 mio habitants)
- CH (7.7 mio habitants)
- GE (453 241 habitants)
- ~600'000 admissions ¹
- ~ 15'000 admissions
- ~ 870 admissions

- Exacerbation de BPCO = 2.4 % des admissions en urgence 2
- La plupart des exacerbations sont traitée en ambulatoire ³
- 50 % des exacerbations ne sont pas rapportée 3 4

- 1 Snow et al Evidence based guideline for management of COPD acute exacerbation, Ann Intern Med 2001
- 2 Donaldson & Wedzicha, COPD exacerbations: Epidemiology Thorax 2006,
- 3 Seemungal et al, Time course and recovery of exacerbation in patients with COPD AJRCCM 2000
- 4 Miravitles et al, Effect of exacerbation on QoL Thorax 2004



Epidémiologie des exacerbations de BPCO

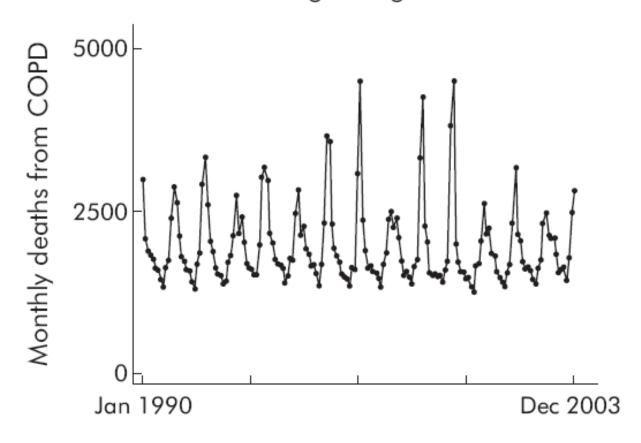


GOLD III: 3.4 exacerbations / an GOLD II: 2.7 exacerbations / an



COPD Monthly mortality

Men and women living in England and Wales



ICD9 490-492 and 496 (ad 2001) ICD10 J40-J44 (2001-2003)



Sélections des articles

Flow chart



Sélections des articles

Flow chart





Ram FSF, Rodriguez-Roisin R, Granados-Navarrete A, Garcia-Aymerich J, Barnes NC

Systematic review and meta-analysis of 11 RCT (917 patients with COPD exacerbations)

Outcomes: mortality, treatment failure





Ram FSF, Rodriguez-Roisin R, Granados-Navarrete A, Garcia-Aymerich J, Barnes NC

Mortality (short term)

Review: *Antibiotics for exacerbations of chronic obstructive pulmonary disease

Comparison: 01 Antibiotics versus Placebo

Outcome: 01 Mortality

Study or sub-category	Antibiotic Group n/N	Placebo Group n/N	RR (fixed) 95% Cl	VVeight %	RR (fixed) 95% Cl		
Nouira 2001	4/47	18/46	<u> </u>	80.08	0.22 [0.08, 0.59]		
Pines 1968	1/15	3/15	900 00 00 00 00 00 00 00 00 00 00 00 00	13.20	0.33 [0.04, 2.85]		
Pines 1972	0/89	1/86	36 32	6.71	0.32 [0.01, 7.80]		
Total (95% CI)	151	147	•	100.00	0.24 [0.10, 0.57]		
Total events: 5 (Antibiotic (Group), 22 (Placebo Group)						
Test for heterogeneity: Chi	$l^2 = 0.16$, df = 2 (P = 0.92), $l^2 = 0\%$						
Test for overall effect: Z =	3.21 (P = 0.001)		320 035 546				
	ar va		0.001 0.01 0.1 1	10 100 1000			
			Favours antibiotic Favo	ours placebo			

RR 0.23 (CI95% 0.10 - 0.52) NNT: 8 (6 to 17) in favor of antibiotics.

Comment: All 3 studies included only hospitalized patients





Ram FSF, Rodriguez-Roisin R, Granados-Navarrete A, Garcia-Aymerich J, Barnes NC

Treatment failure (No resolution of symptoms or deterioration)

Review. *Antibiotics for exacerbations of chronic obstructive pulmonary disease.

Comparison: 01 Antibiotics versus Placebo

02 Treatment Failure (no resolution or deterioration of symptoms after trial medication or death)

Study or sub-category	Antibiotic Group ruN	Placebo Group n/N	RR (tixed) 95% CI	Weight %	RR (fixed) 95% CI
Alonso 1992	2/29	6/29		6.39	0.33 [0.07, 1.52]
Bmcs 1965	6/29	19/29		20.23	0.32 [0.15, 0.68]
Pines 1968	6/15	15/15	() () () () () () () () () ()	15.97	0.40 [0.22, 0.74]
Pines 1972	31/89	53/86	X0-50-20-20-20-20-20-20-20-20-20-20-20-20-20	57.41	0.57 [0.41, 0.79]
Total (95% CI)	162	159	•	100.00	0.47 [0.36, 0.62]
Total events: 45 (Antibiotic	Group), 93 (Placebo Group)				annumber of the state of the st
Test for heterogeneity: Ch	2 = 2.69, off = 3 (P = 0.44), l^{2} = 09	6			
Test for overall effect: Z =	5.41 (P < 0.00001)				
		D	1 0.2 0.5 1 2	5 10	
			Favours antibiotic Favour	rs placebo	

RR 0.47 (CI95% 0.26 - 0.62) NNT: 3 (3 to 5) in favor of antibiotics.

Comment: All 4 studies included only hospitalized patients



Outcome



Ram FSF, Rodriguez-Roisin R, Granados-Navarrete A, Garcia-Aymerich J, Barnes NC

Treatment failure (No resolution of symptoms or deterioration)

*Antibiotics for exacerbations of chronic abstructive pulmonary disease (Wiley incorporated)

Comparison: D1 Antibiotics versus placebo

Outcome: D2 Treatment failure (no resolution or deterioration of symptoms after trial medication of any duration or dea

Study or sub-category	Antibiotic Group n/N	Placebo Group n/N	RR (fixed) 95% CI	Weight %	RR (fixed) 95% CI
Arthonisen 1987	19/57	28/59		36.31	0.70 [0.45, 1.11]
Jørgensen 1992	49/132	49/136		63.69	1.03 [0.75, 1.41]
Total (95% CI)	189	195		100.00	0.91 [0.70, 1.18]
Total events: 68 (Antibiotic	Graup), 77 (Placebo Graup)		***		
Teat for heterageneity: Chi	2 = 1.84, df = 1 (P = 0.17), l^{2} = 45	.7%			
Test for overall effect: Z =	0.71 (P = 0.48)				
			0.1 0.2 0.5 1 2	5 10	
			Favours antibiotic Fevours pla	acebo	

RR 0.91 (CI95% 0.70 – 1.18)

Comment: No benefit of antibiotics for ambulatory patients



Review:



Ram FSF, Rodriguez-Roisin R, Granados-Navarrete A, Garcia-Aymerich J, Barnes NC

Conclusions:

- 1) Antibiotics decrease mortality, treatment failure and sputum purulence
- 2) In agreement with S. Saint (1995)
- 3) No effect of specific antibiotics





Ram FSF, Rodriguez-Roisin R, Granados-Navarrete A, Garcia-Aymerich J, Barnes NC

Systematic review and meta-analysis of 11 RCT (917 patients with COPD exacerbations)

Outcomes: mortality (3 studies), treatment failure





Ram FSF, Rodriguez-Roisin R, Granados-Navarrete A, Garcia-Aymerich J, Barnes NC

Systematic review and meta-analysis of 11 RCT (917 patients with COPD exacerbations)

Outcomes: mortality (3 studies), treatment failure



Antibiotics in Addition to Systemic Corticosteroids for Acute Exacerbations of Chronic Obstructive Pulmonary Disease AJRCCM 2010

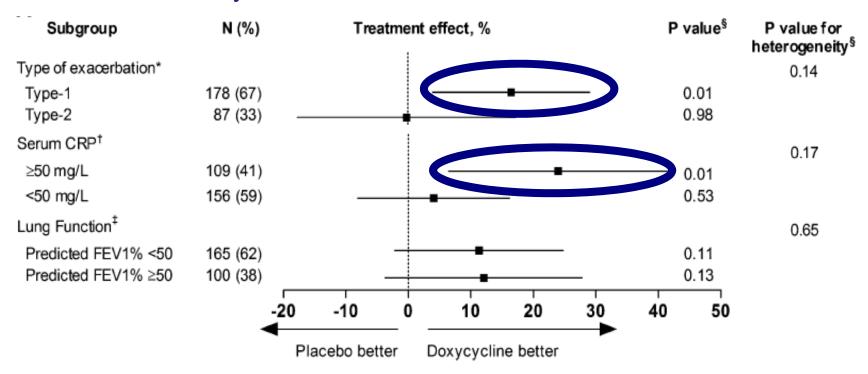
Patients: 265 severe exacerbations (inpatients)

Intervention: Placebo vs doxycycline

Outcomes: time to failure, symptom score, CRP

Results: day 10, clinical success (OR 1.9 Cl95% 1.1 3.2)

day 30, similar



Levofloxacin 500 mg once daily vs cefuroxime 250 mg twice daily in patients with acute exacerbations of COPD. (Int J of antimicrobial agents 2007)

Background: 50% AECOPD are positive for bacteria. Do antibiotics increase

time to relapse?

Patients: 689 outpatients FEV1 52%,

Intervention: multicentric (F, B, D, A, Tunisia & Turkey, Sanofi-Aventis sponsored

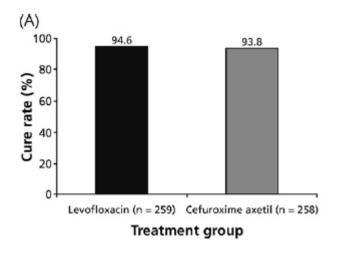
levofloxacine 500 mg od vs cefuroxime 250 bid (10 days)

Outcomes: microbiological cure at 17-21 days. Time to relapse

Results: ...



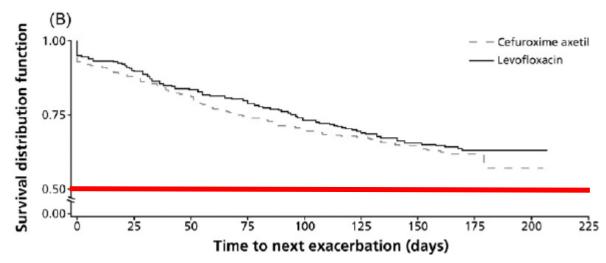
Levofloxacin 500 mg once daily vs cefuroxime 250 mg twice daily in patients with acute exacerbations of COPD. (Int J of antimicrobial agents 2007)



Conclusions:

No difference between levofloxacine and Cefuroxime

Comments: Industry driven



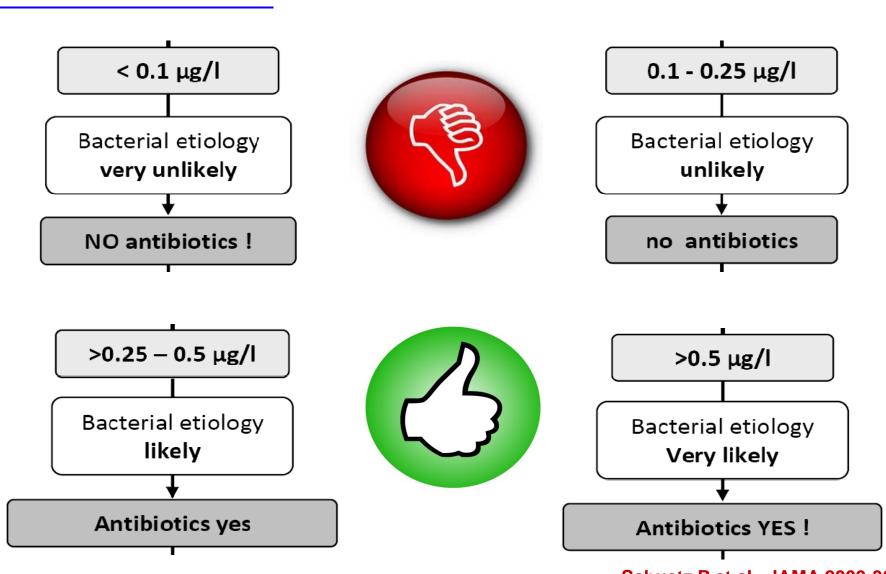


Usefulness of Procalcitonin for targeting the use of antibiotics?

- Pragmatic study comparing two strategies
 - Treatment recommandations based on pro-CT values
 - Standard care
- 228 patients with acute exacerbation of COPD



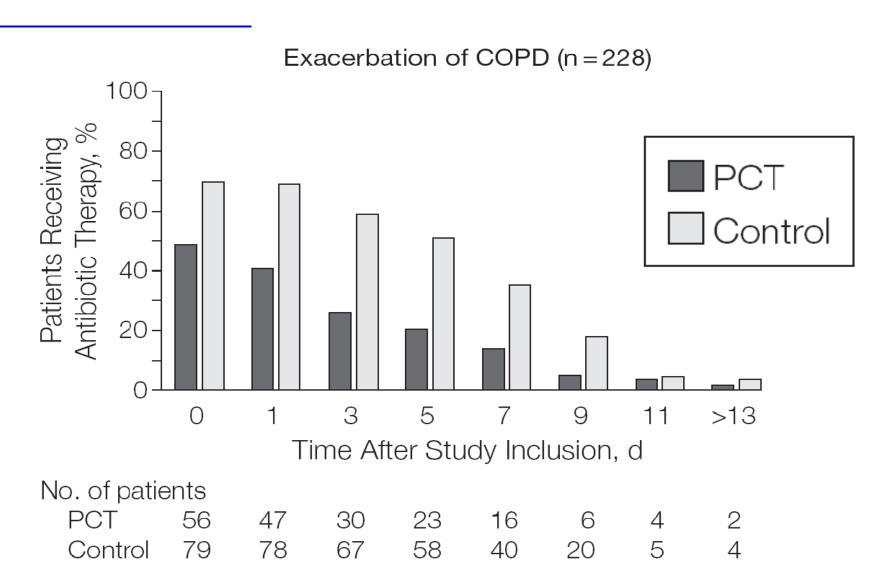
ProCT guided antibiotherapy



Schuetz P et al., JAMA 2009;302:1059



ProCT guided antibiotherapy



Schuetz P et al., JAMA 2009;302:1059

ProCT guided antibiotherapy: limitations

Prob [bact inf_] = [COPD stage] + [acute symptoms] + [chest Xray] + [CRP] + [ProCT]

In outpatient setting...

- 1. ATB is delayed while waiting for test result
- 2. False negative result (too early?)
- 3. No outpatient studies Lower specificity to be expected in outpatient setting

Systemic corticosteroids for acute exacerbations of chronic obstructive pulmonary disease (Review)



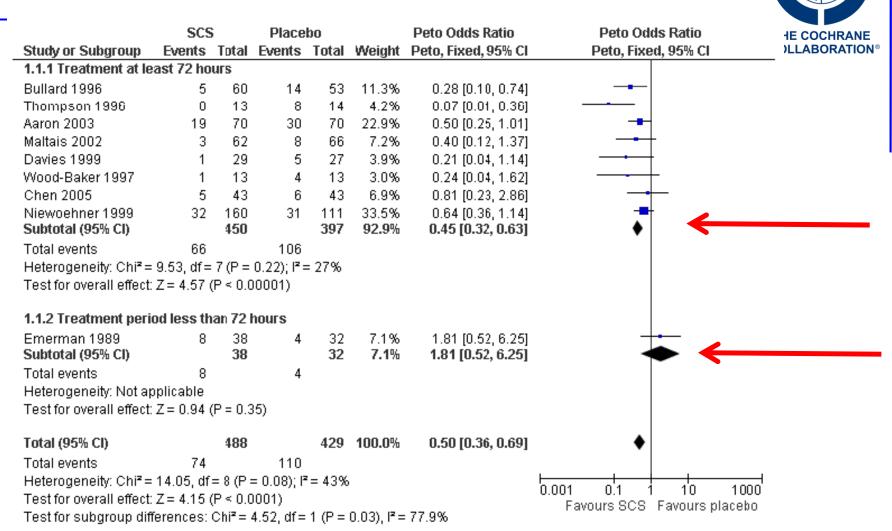
Walters JAE, Gibson PG, Wood-Baker R, Hannay M, Walters EH

Systematic review and meta-analysis of 10 RCT (1051 patients with COPD exacerbations)

Outcomes: treatment failure, duration of hospitalisation, mortality, adverse events



Systemic steroids: Treatment failure (Therapy intensification or change or ICU admission or NIV)



Comment: Heterogeneity related to therapy duration

NNT: 10(7-16)



Systemic steroids: Mortality



	SCS		Place			Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup			Events	Total	Weight	Peto, Fixed, 95% Cl	Peto, Fixed, 95% Cl
1.4.1 Treatment at least 72 hours							
Albert 1980	2	22	3	22	12.4%	0.64 [0.10, 4.05]	
Bullard 1996	3	60	2	53	13.2%	1.33 [0.22, 7.97]	
Thompson 1996	0	13	0	14		Not estimable	
Maltais 2002	1	62	0	66	2.7%	7.88 [0.16, 397.96]	-
Aaron 2003	1	74	1	73	5.4%	0.99 [0.06, 15.92]	
Davies 1999	1	29	1	27	5.4%	0.93 [0.06, 15.28]	
Wood-Baker 1997	0	14	1	17	2.7%	0.16 [0.00, 8.29]	
Niewoehner 1999	13	160	11	111	58.2%	0.80 [0.34, 1.88]	-
Subtotal (95% CI)		434		383	100.0%	0.87 [0.45, 1.66]	•
Total events	21		19				
Heterogeneity: Chi² = 2.28, df = 6 (P = 0.89); l² = 0%							
Test for overall effect:	Z = 0.43 (P = 0.8	67)				
1.4.2 Treatment less	than 72 h	OUTS					
Emerman 1989	0	52	0	44		Not estimable	
Subtotal (95% CI)	-	52	_	44		Not estimable	
Total events	0		0				
Heterogeneity: Not ap	plicable		-				
Test for overall effect: Not applicable							
Total (95% CI)		486		427	100.0%	0.87 [0.45, 1.66]	•
Total events	21		19				٦
Hatergraph it Chiz = 2.20 df = 6/D = 0.00\ /Z = 000							
T-45							
	7 = 0.437	P = 0.6	(7)				Favours SCS Favours Placebo

Comment: No change in mortality



Systemic corticosteroids for acute exacerbations of chronic obstructive pulmonary disease (Review)



Walters JAE, Gibson PG, Wood-Baker R, Hannay M, Walters EH

Hospitalization duration

2 studies (n=295 patients)

-1.22 days (Cl95% -2.26 -0.18)

Adverse events (hyperglycemia, insomnia)

7 studies

OR 2.33 (CI95% 1.60-3.40) 1/6 patients



Systemic corticosteroids for acute exacerbations of chronic obstructive pulmonary disease (Review)



Walters JAE, Gibson PG, Wood-Baker R, Hannay M, Walters EH

Conclusions

- 1) Lower risk of treatment failure (NNT 10)
- 2) Shorter LoS
- 3) No effect on mortality
- 4) Higher risk of minor adverse event (NNH 6)
- 5) Cannot conclude about dosage (recommended 30 to 40 mg) and duration (recommended <10 days)





Ram FSF, Picot J, Lightowler J, Wedzicha JA

Systematic review and meta-analysis of 14 RCT (758 patients with COPD exacerbations)

Outcomes: Mortality, Intubation rate, treatment failure, pH improvement, treatment failure, duration of hospitalisation, adverse events





Ram FSF, Picot J, Lightowler J, Wedzicha JA

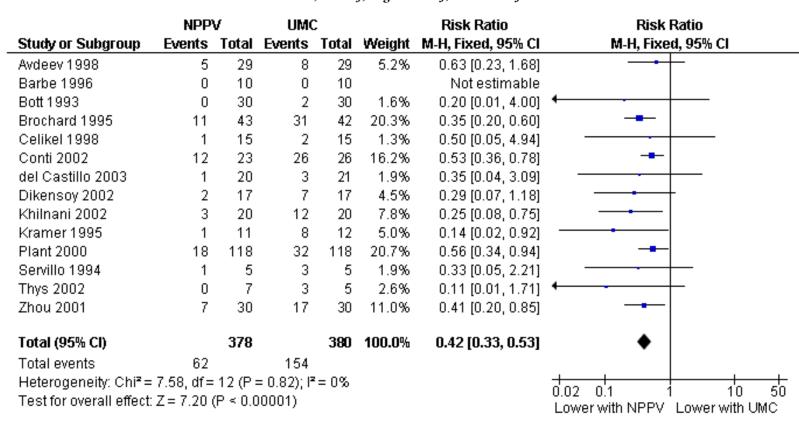
	NPP	٧	UMC	;		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Avdeev 1998	3	29	9	29	13.8%	0.33 [0.10, 1.11]	
Barbe 1996	0	10	0	10		Not estimable	
Bott 1993	3	30	9	30	13.8%	0.33 [0.10, 1.11]	
Brochard 1995	4	43	12	42	18.6%	0.33 [0.11, 0.93]	
Celikel 1998	0	15	1	15	2.3%	0.33 [0.01, 7.58]	
Conti 2002	6	23	5	26	7.2%	1.36 [0.48, 3.86]	
Dikensoy 2002	1	17	2	17	3.1%	0.50 [0.05, 5.01]	
Khilnani 2002	3	20	2	20	3.1%	1.50 [0.28, 8.04]	- -
Plant 2000	12	118	24	118	36.7%	0.50 [0.26, 0.95]	
Servillo 1994	1	5	1	5	1.5%	1.00 [0.08, 11.93]	
Total (95% CI)		310		312	100.0%	0.52 [0.35, 0.76]	•
Total events	33		65				
Heterogeneity: Chi ² = 6.94, df = 8 (P = 0.54); I^2 = 0%							
Test for overall effect: Z = 3.37 (P = 0.0008) 0.02 0.1 1 10 50 Lower with NPPV Lower with UMC							

Mortality: favors NIV 0.52 (CI95% 0.35 - 0.76) NNT 10 (7 - 20) Comments: No difference between pH subgroup (<7.30 and >=7.30)





Ram FSF, Picot J, Lightowler J, Wedzicha JA



Intubation: favors NIV 0.42 (CI95% 0.33 - 0.53), NNT 4 (4 - 5)





Ram FSF, Picot J, Lightowler J, Wedzicha JA

Studies	Outcome	Change (CI95%)
7	pH (within first hour)	0.03 (0.02 - 0.04)
7	PaCO2 (kPa)	-0.40 (-0.78 -0.03)
8	LoS (days)	-3.2 (-4.4 -2.1)



Non-invasive positive pressure ventilation for treatment of respiratory failure due to exacerbations of chronic obstructive pulmonary disease (Review)



Ram FSF, Picot J, Lightowler J, Wedzicha JA

Conclusions

- 1) NIV reduces mortality, need for intubation, and LoS, improves pH and PaCO2
- 2) No differences between pH subgroup
- 3) No differences in studies conducted in ICU or outside



Iron Lung vs Mask Ventilation in acute exacerbation of COPD: A Randomized crossover study (Intensive care med 2009)

Background: NIPPV vs medical therapy: less intubation & mortality

Patients: 141 patients (PaCO2 90 mm Hg!; pH 7.25)

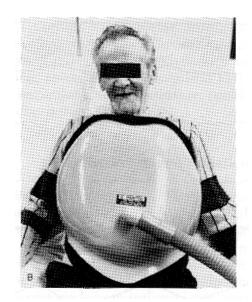
Intervention: Intermediate respiratory ICU

IRON LUNG (inspiration -30 to -40 cm & exp. 10 to 15 cm H2O)

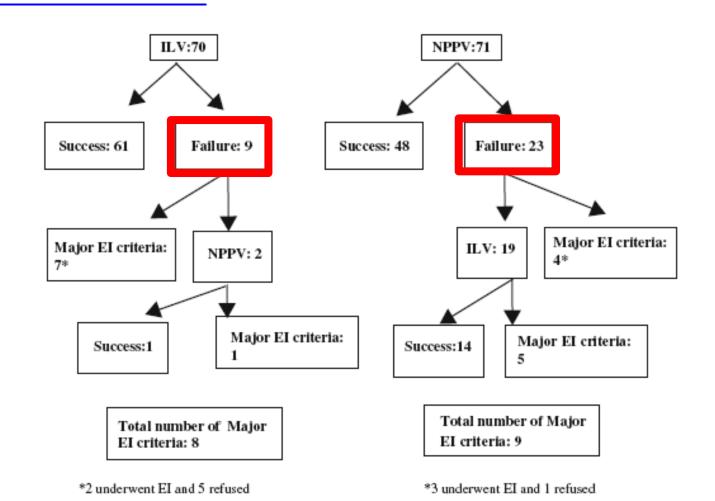
vs NIPPV (BiPAP EPAP 4-5 IPAP 12 to 20, goal VT 6 ml/min/kg)

Outcomes: Intubation rate, treatment failure on first treatment, LoS

Results: ...



Iron Lung vs Mask Ventilation in acute exacerbation of COPD: A Randomized crossover study (Intensive care med 2009)



Iron Lung vs Mask Ventilation in acute exacerbation of COPD: A Randomized crossover study (Intensive care med 2009)

Table 3 Complications in patients treated as first line with ILV and NPPV

	ILV	NPPV	P
Back pain	1	0	0.994
Treatment intolerance	5	7	0.782
Vomiting	1	1	0.843
Conjunctivitis	0	1	0.994
VAP	2	0	0.470
Abdominal hyperdistension	2	1	0.99
Skin necrosis	0	6	0.039
Gastrointestinal bleeding	3	2	0.987
Total complications	14	18	0.577



Iron Lung vs Mask Ventilation in acute exacerbation of COPD: A Randomized crossover study (Intensive care med 2009)

Conclusions:

- 1) No difference on intubation rate
- IRON LUNG better on minor criteria (Respiratory rate >35, pH below 7.3 or deteriorating, decreasing Glascow)
- 3) No skin necrosis on IRON LUNG

Comments:

Very experienced team; Failure of treatment not blinded (Bias?)



A multicenter RCT of NIV with Helium-oxygen mixture in exacerbations of COPD (Critical Care med 2010)

Background: Heliox (He 65%, O₂ 35%) density lower than air oxygen. Work of breathing reduced. However no proven clinical efficacy.

Patients: 204 patients (PaCO₂ 73 mm Hg)

Intervention: ICU

NIV (EPAP 5 IPAP 17 to 20, FIO₂ 35%, >6h/day)

vs NIV + heliox (idem + heliox)

Outcomes: Intubation rate, treatment failure, LoS, mortality

Results: ...

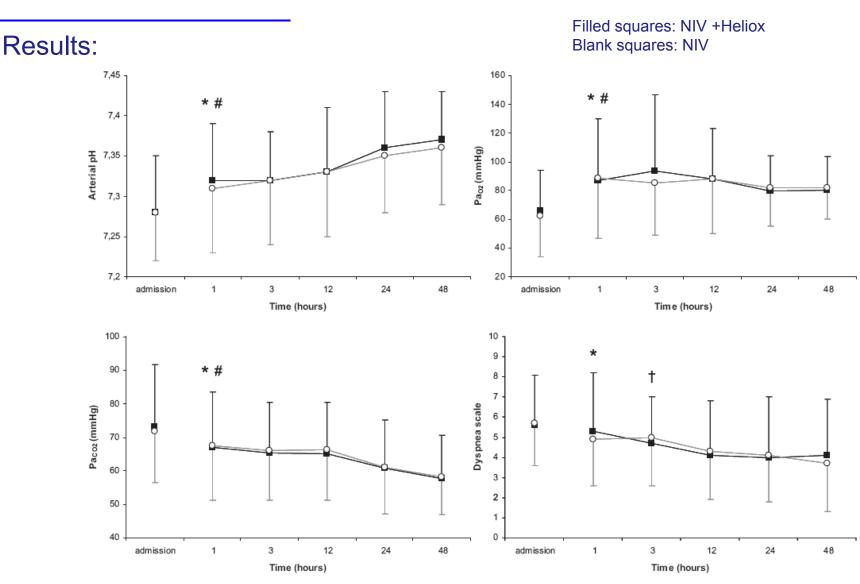
A multicenter RCT of NIV with Helium-oxygen mixture in exacerbations of COPD (Critical Care med 2010)

Results:

Table 2. Comparison of outcomes in the two study groups

	Noninvasive Ventilation, ${ m HeO}_2$ Group (n = 102)	Noninvasive Ventilation, Air-Oxygen Group (n = 102)	р
Duration of noninvasive ventilation, days	3.8 ± 2.9	4.2 ± 3.0	.3
Intubated patients, n; % Time to intubation, days	25; 24.5 2.4 ± 1.8	31; 30.4 4.6 ± 6.9	.35 .09

A multicenter RCT of NIV with Helium-oxygen mixture in exacerbations of COPD (Critical Care med 2010)



A multicenter RCT of NIV with Helium-oxygen mixture in exacerbations of COPD (Critical Care med 2010)

Conclusions:

- 1) Similar intubation rate
- 2) Similar LoS and mortality

Comments:

The largest clinical study on heliox, however negative.

« Physiologically sound, clinically useless »



Substitutive « hospital at Home » vs inpatient care for elderly patients with exacerbations of COPD: A randomized controlled trial (A multicenter RCT of NIV with Helium-oxygen mixture in exacerbations of COPD (Journal of the Am Geriatric Soc 2008)

Background: Hospital admission are costly, impacts QoL and maybe dangerous. Effect of Hospital at home on mortality, re-admission rate unknown.

Patients: 104 patients in Emergency Dep., >75 year-old (FEV₁ 42% pred,

PaCO₂ 45, pH 7.40)

Intervention: hospital at home after ED evaluation (2 Geriatricians, 1 nurses)

vs General Ward

Outcomes: Mortality and readmission rate at 6 months, costs

Results: ...

Substitutive « hospital at Home » vs inpatient care for elderly patients with exacerbations of COPD: A randomized controlled trial (Journal of the Am Geriatric Soc 2008)

Table 3. Treatments Received by Study Participants

	Geriatric Home Hospitalization Service (n = 52)	General Medical Ward (n = 52)	
Treatment	n (%)		
Oxygen therapy	30 (58)	38 (73)	.55
Intravenous antibiotics	40 (77)	39 (75)	.95
Intravenous steroids	23 (44)	27 (52)	.77
Beta-agonist bronchodilators	20 (39)	25 (48)	.66
Anticholinergic bronchodilators	26 (50)	21 (40)	.67



Substitutive « hospital at Home » vs inpatient care for elderly patients with exacerbations of COPD: A randomized controlled trial (Journal of the Am Geriatric Soc 2008)

At 6 months	Hospital at home	General Medical Ward	P value
Readmitted (%)	42	87	.001
Mortality (%)	17	23	0.72
Days to readmission (mean, SD)	78 (55)	37 (29)	.005
Total Costs Costs per day	1176 \$ 101 \$	1391 \$ 152 \$	0.38
Length of « stay » (mean, SD)	15.5 (9.5)	11.0 (7.9)	0.01



Substitutive « hospital at Home » vs inpatient care for elderly patients with exacerbations of COPD: A randomized controlled trial (Journal of the Am Geriatric Soc 2008)

Conclusions:

- 1) For selected COPD exacerbations, Hospital at home is safe
- 2) At 6 months, lower readmission rate, better QoL
- 3) Lower health care costs
- 4) Similar mortality

Comments:

Effect of geriatric assessment may confound the results.

« Clinical unit » do not exist in CH.





Exacerbation de BPCO Conclusions 2010

- 1) BPCO dans la population CH de 40 à 70 ans: ~ 5% (lég. plus basse qu'ailleurs)
- 2) Antibiothérapie: à proposer. Pro-CT acceptable en milieu hospitalier.
- Corticothérapie: à proposer.
- 4) VNI: à proposer si pH <7.35 et PaCO2 > 6.
 - a) Heliox (pas de preuves d'efficacité)
 - b) Pression négative (possible avantage par des groupes expérimentés)
- 5) Soins intégrés: études prometteuses

