ACUTE EXACERBATIONS OF COPD
ROLE OF INFECTION AND ANTIMICROBIAL THERAPY

W. Vincken, MD, PhD
Head Respiratory Division
UZ Brussel – VUB
On behalf of the IDAB workgroup

ACUTE EXACERBATIONS OF COPD : Overview of topics

1. DEFINITIONS : COPD & AECOPD

2. IMPORTANCE / IMPACT OF AECOPD

3. ETIOLOGY OF AECOPD : non-infectious
   infectious

4. DIAGNOSIS OF AECOPD

5. TREATMENT OF AECOPD

6. PREVENTION OF AECOPD

Definition of COPD : GOLD

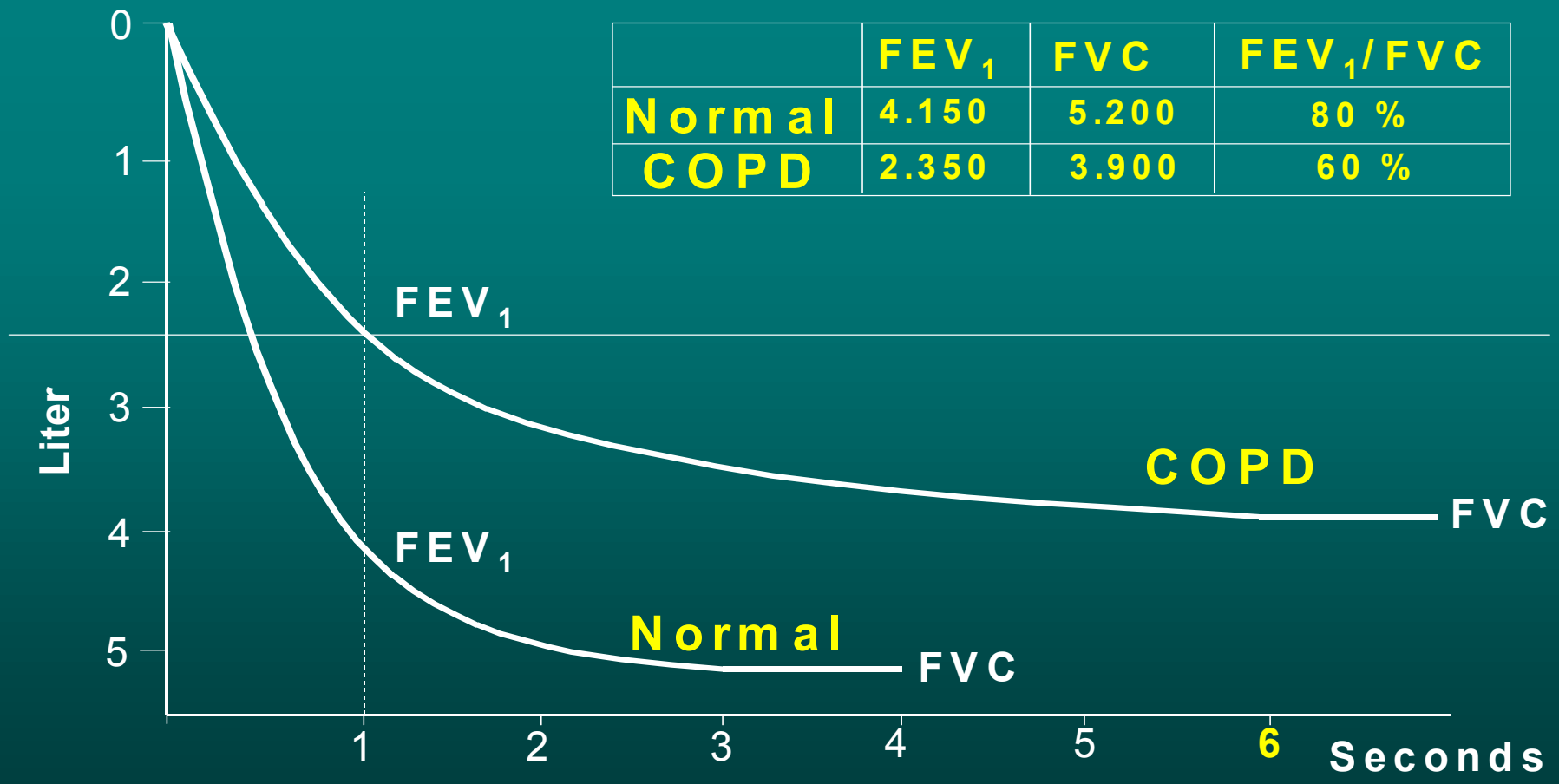
"Chronic obstructive pulmonary disease (COPD)
is a disease state characterized by the progressive development of airflow limitation that is not fully reversible.

The airflow limitation *(defined as an FEV_1/FVC ratio < 70%)* is usually both progressive and the result of an abnormal inflammatory response of the lungs to noxious particles and/or gases *(usually from tobacco smoke)* ".

Systemic inflammatory component.

Spirometry: Normal and COPD

	FEV_1	FVC	FEV_1/FVC
Normal	4.150	5.200	80 %
COPD	2.350	3.900	60 %



GOLD classification of COPD severity

Stage 1 - 4 : obstructive defect : **FEV_1 / FVC < 70 %**

- Stage 1 : $FEV_1 \geq 80\%$ P +/- symptoms
- Stage 2 : $FEV_1 \geq 50\%$ P +/- symptoms
- Stage 3 : $FEV_1 \geq 30\%$ P +/- symptoms
- Stage 4 : $FEV_1 < 30\%$ P or
  $FEV_1 < 50\%$ P *plus* CRIS or RHF

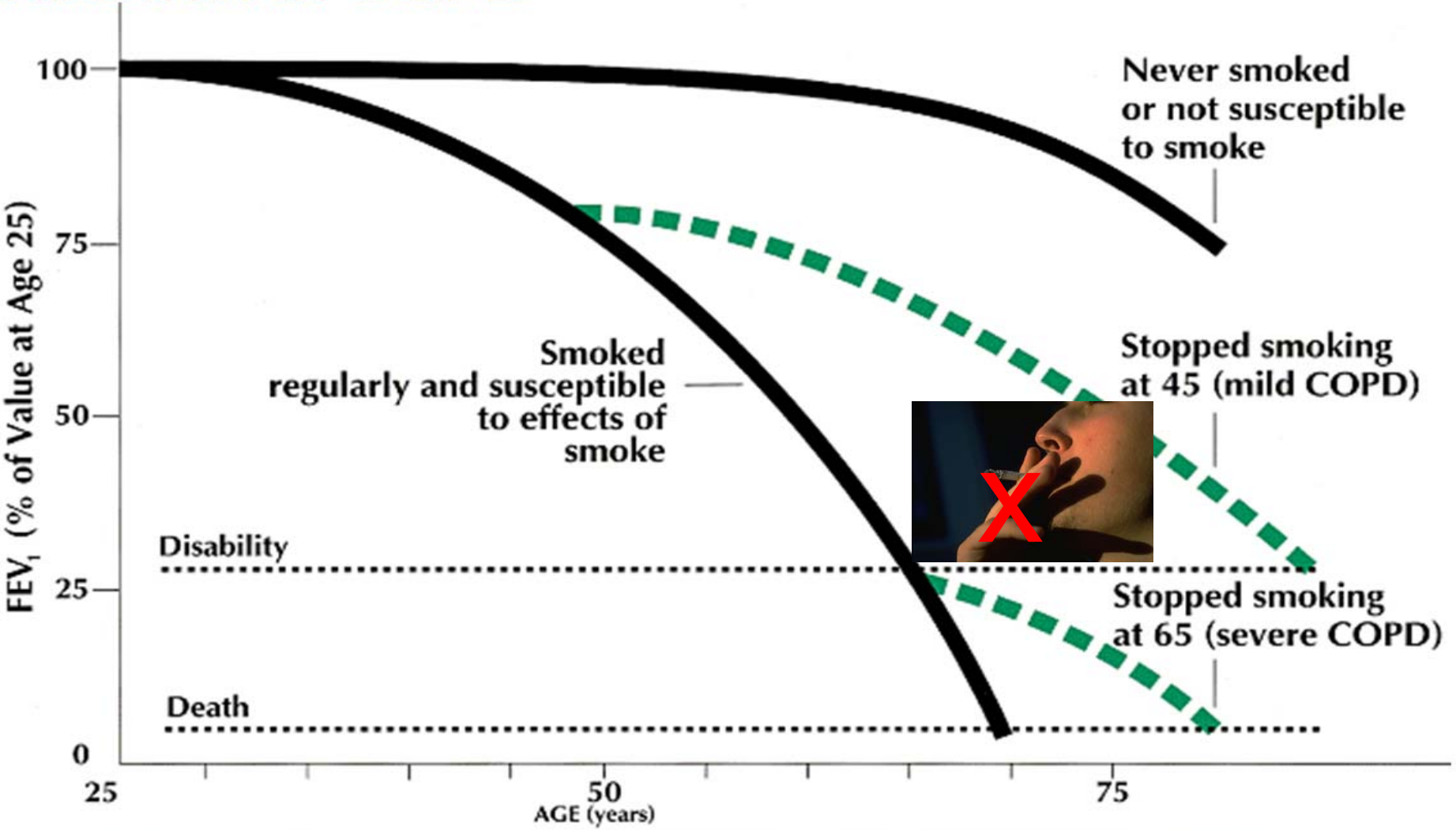
COPD differs from simple CB

- Simple (smoker's) CB: "chronic cough and sputum production for > 3 mo/yr for > 2 yrs" without airflow limitation

= / =

- COPD: smoker's lung disease (CB, bronchiolitis, emphysema) leading to airflow obstruction, hence, reduced pulmonary functional reserve

Smoking cessation is the only intervention shown to slow the rate of decline in lung function in COPD



Fletcher C, Peto R. *BMJ.* 1977;1:1645-1648.

Definition of AECOPD

- There is no widely agreed and consistently used definition [Pauwels 2004]
- Considerable heterogeneity in presentation (mild to life threatening)
- Differentiate AE from temporary, more progressive worsening of symptoms [Burge 03/21] [Rodriguez-Roisin 00/16]

Definition of AECOPD

ERS/ATS 2004 COPD guideline :

- **An AE of COPD is an (*acute*) event in the natural course of the disease characterised by a change in the patient's baseline symptoms (dyspnea, cough and/or sputum) beyond day-to-day variability and sufficiently severe to warrant a change in management**

- **Operational classification of severity :**
  - » **Level I : treated at home**
  - » **Level II : requires hospitalisation**
  - » **Level III : leads to respiratory failure**

Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. Celli B. ERJ 2004

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Importance / Impact of AECOPD

- Common and frequent event in many patients

  (median frequency 2.7/y in moderately severe COPD) [Seemungal 98/05]

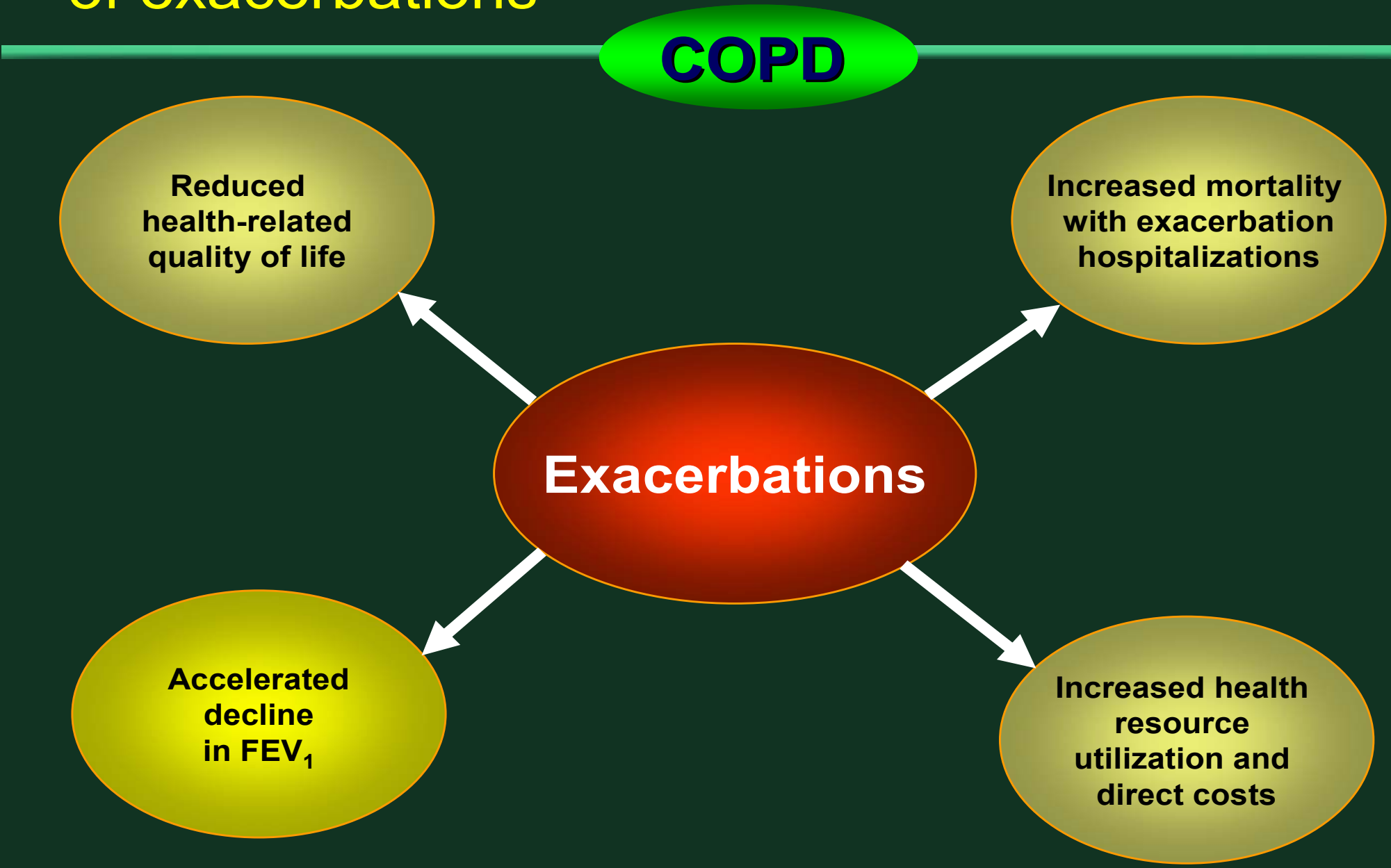
- Frequency and severity of AE increase with increasing severity of COPD

  [Donaldson 03/19] [Vestbo 89/02] , age and bronchial hypersecretion

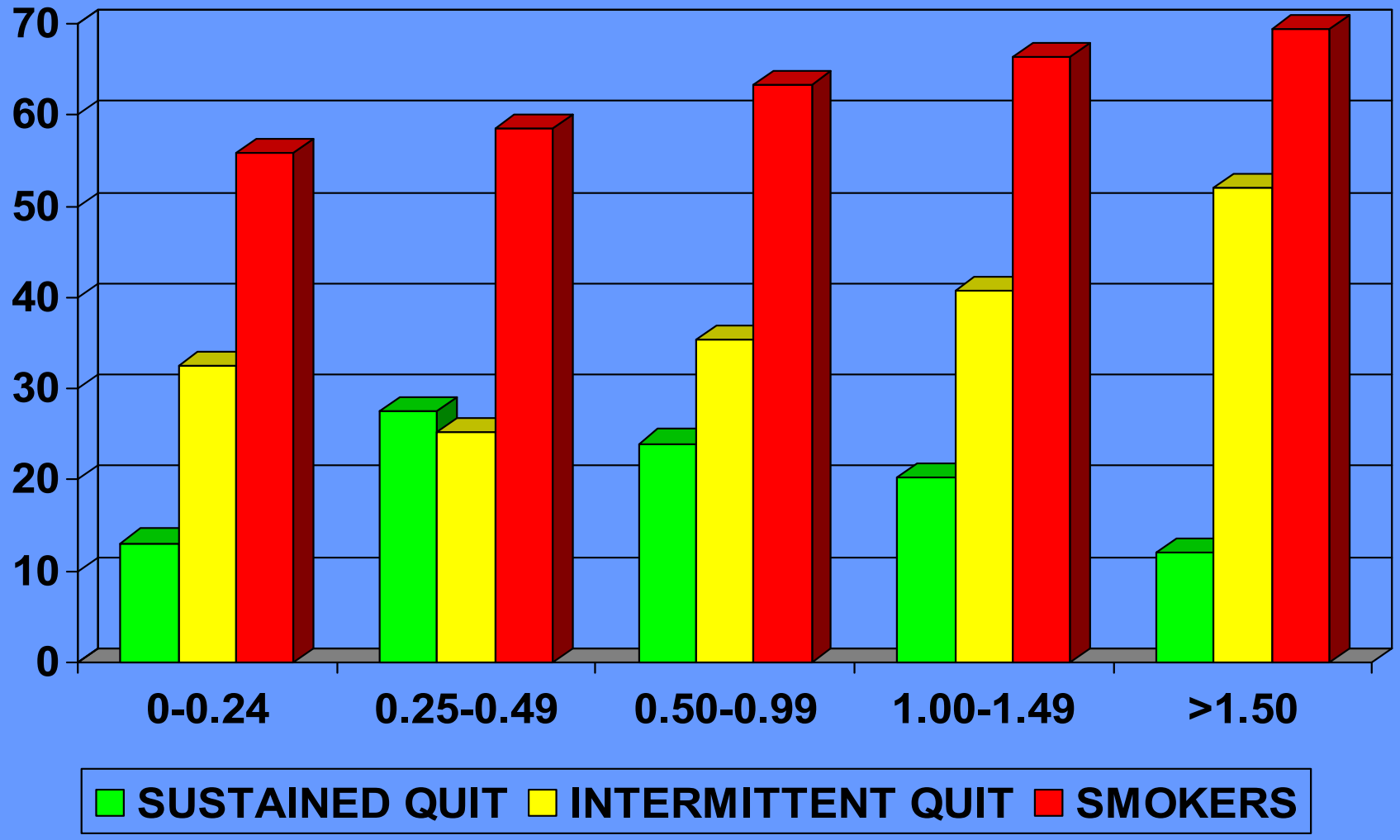
- Recovery is prolonged and often incomplete in a significant proportion of patients [Seemungal 00/11]

- Important cause of the considerable morbidity and mortality associated with COPD

The clinical course of COPD: consequences of exacerbations

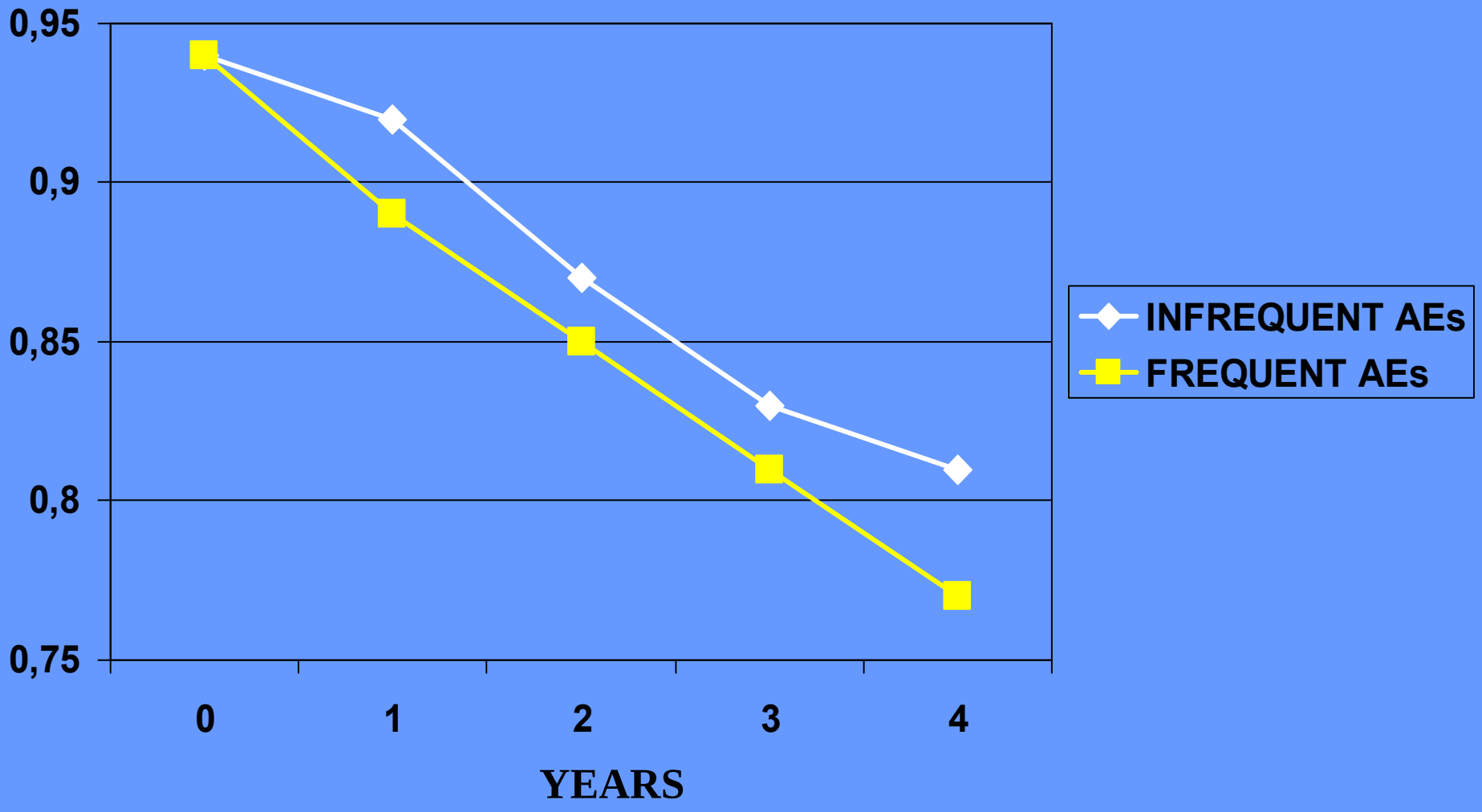


Effect of LRTI on annual rate of decline of FEV_1 (ml/yr)



Kanner RE et al. AJRCCM 2001

Percentage change in FEV_1 over 4 y



Donaldson GC et al. Thorax 2002; 57: 847-852

Impact of AECOPD on COPD's course

- As yet unaccomplished goals of COPD treatment
  - Slow down decline in PF
  - Prolong survival
- AEsCOPD
  - boost COPD's already accelerated decline in PF
  - shorten life expectancy
- Reduction in frequency of AECOPD may have a major impact on COPD's natural course and is a primary goal in the treatment of COPD

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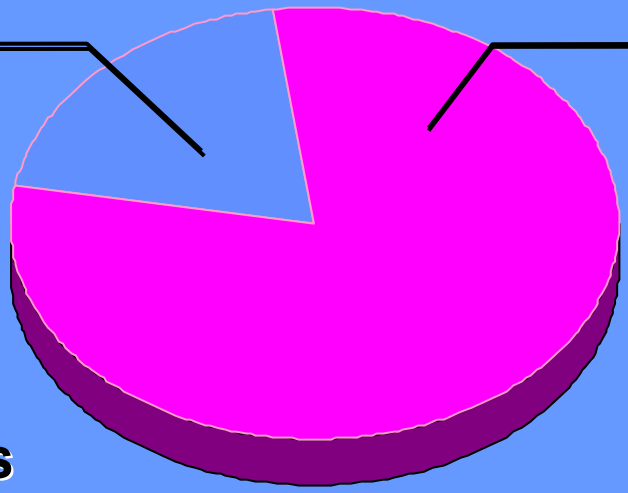
Etiology of acute exacerbations of COPD

Primary	• Bronchial infection (viral, bacterial) in ~ 50-80 %? • Non-infectious (air pollution, …) • Unidentified (1/3)
Secondary (mimics of AECOPD)	• Pneumonia • Pulmonary embolism • Pneumothorax • Rib fractures/chest trauma • Inappropriate use of sedatives, narcotics, ß-blocking agents • R- and/or L-heart failure or arrhythmias

Etiology of primary AECOPD

20 %
non-infectious

- Environmental factors
- Non-compliance with medications



80 %
infectious

- Bacterial pathogens
  40 - 50 %
- Viral infection
  30 - 40 %
- Atypical Bacteria
  5 - 10 %

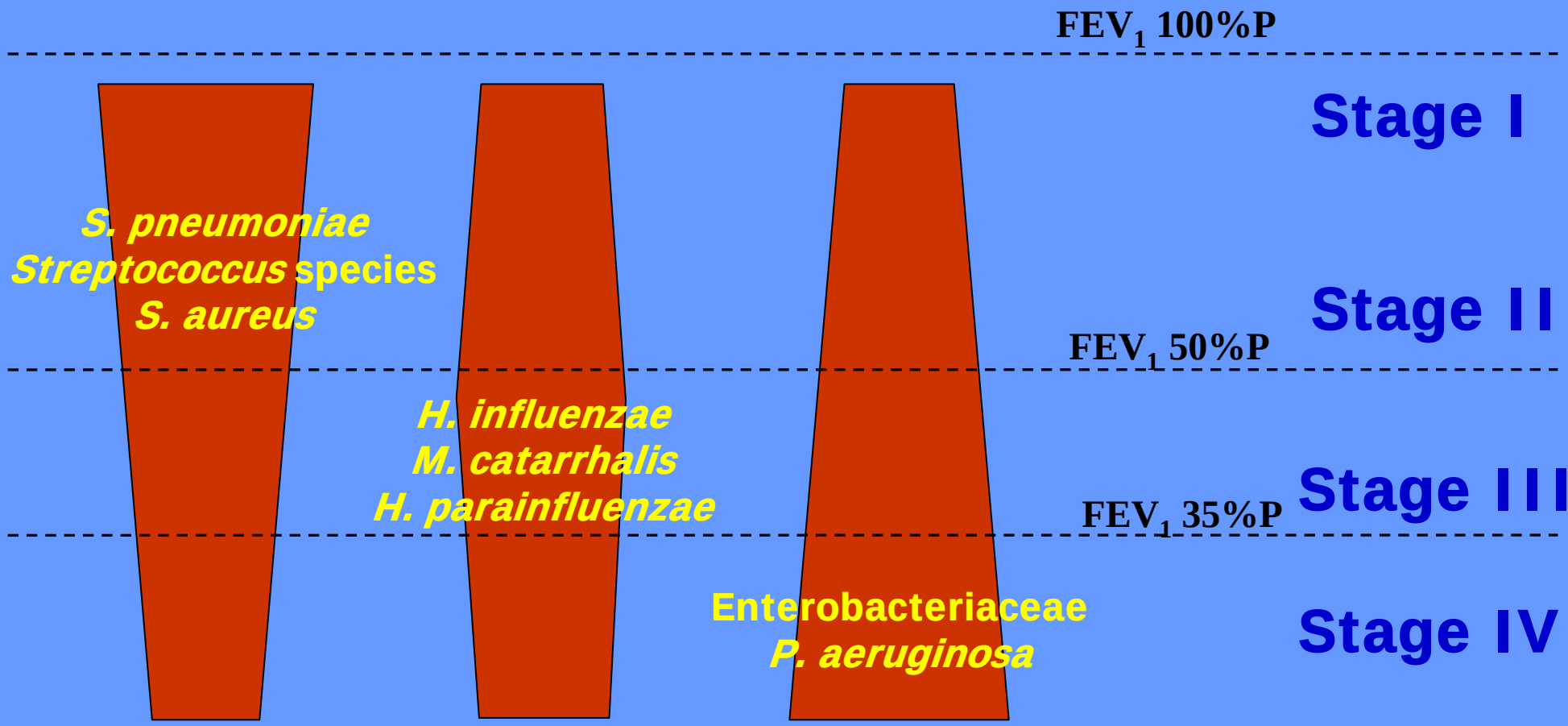
Sethi et al. Chest 2000; 117: 380s-5s

Major Bacterial Pathogens in AECOPD

	No. of patients	% Culture +	Percentage of total isolates		
			H. influenzae	*M. catarrhalis*	*S. pneumoniae*
Total	9614	48.6			
Mean	687	53.7	31.2	14	14.2
Range	140–2180	28.1–88.6	13–50	4–21	7–26
Comments	14 studies meta-analysis	Sputum specimens	Non-typeable		

Obaji & Sethi. Drugs and Aging 2001; 18: 1-11

Bacterial Pathogens According to Severity of Underlying COPD



Eller J et al. Chest 1998; 113:1542-8

ACUTE EXACERBATIONS OF COPD : Overview of topics

1. **DEFINITIONS : COPD & AECOPD**

2. **IMPORTANCE / IMPACT OF AECOPD**

3. **ETIOLOGY OF AECOPD :** **non-infectious**
   infectious

4. **DIAGNOSIS OF AECOPD** : AECOPD is a clinical diagnosis :
   based on signs & symptoms. There is no confirmatory diagnostic test.

5. **TREATMENT OF AECOPD**

6. **PREVENTION OF AECOPD**

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5. TREATMENT OF AECOPD : general therapy
   antibiotic therapy

6. PREVENTION OF AECOPD

GENERAL TREATMENT OF AECOPD [Buhl 04/30]

Earlier recognition and treatment of AE improves recovery [Wilkinson 2004]

1. BRONCHODILATORS (inhaled, via spacer or nebulised)

increase dose and / or frequency

combination of a fast-acting β_2-agonist + anticholinergic

2. SYSTEMIC STEROIDS (PO or IV → PO)

methylprednisolone 0.5 mg/kg/d

short (10-14 days) course (cave side effects)

3. SUPPORTIVE MEASURES

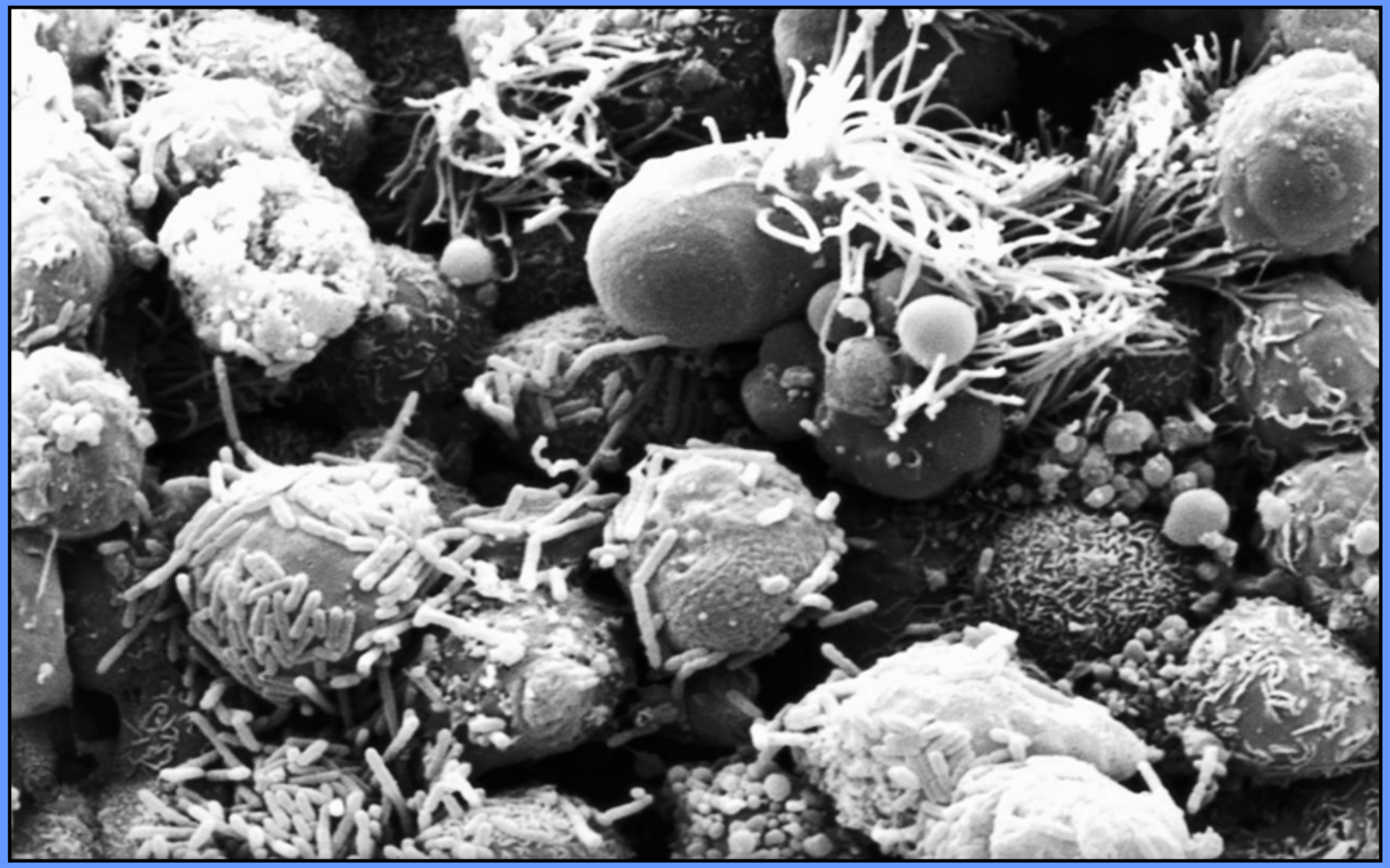
* Controlled oxygen therapy (to obtain an S_aO_2 > 90%)
* NIPPV (if Acute Ventilatory Failure)
* No proven effect of physiotherapy, mucolytics (anti-oxidants), theophylline

4. ANTIBIOTICS : controversial

Antibiotics in AECOPD: PROBLEMS :

- In principle, antibiotic treatment is only indicated in bacterial AECOPD
  - Not all AEs are of bacterial origin, hence require antibiotic treatment
  - However, in clinical practice it is difficult / impossible to differentiate a bacterial AE from a non-bacterial (viral or non-infectious) AE : there is no clinical / paraclinical diagnostic marker of a bacterial AE
- Even if a bacterial pathogen is found, there is always the issue of chronic (upper / lower) airway colonisation and / or innocent bystander

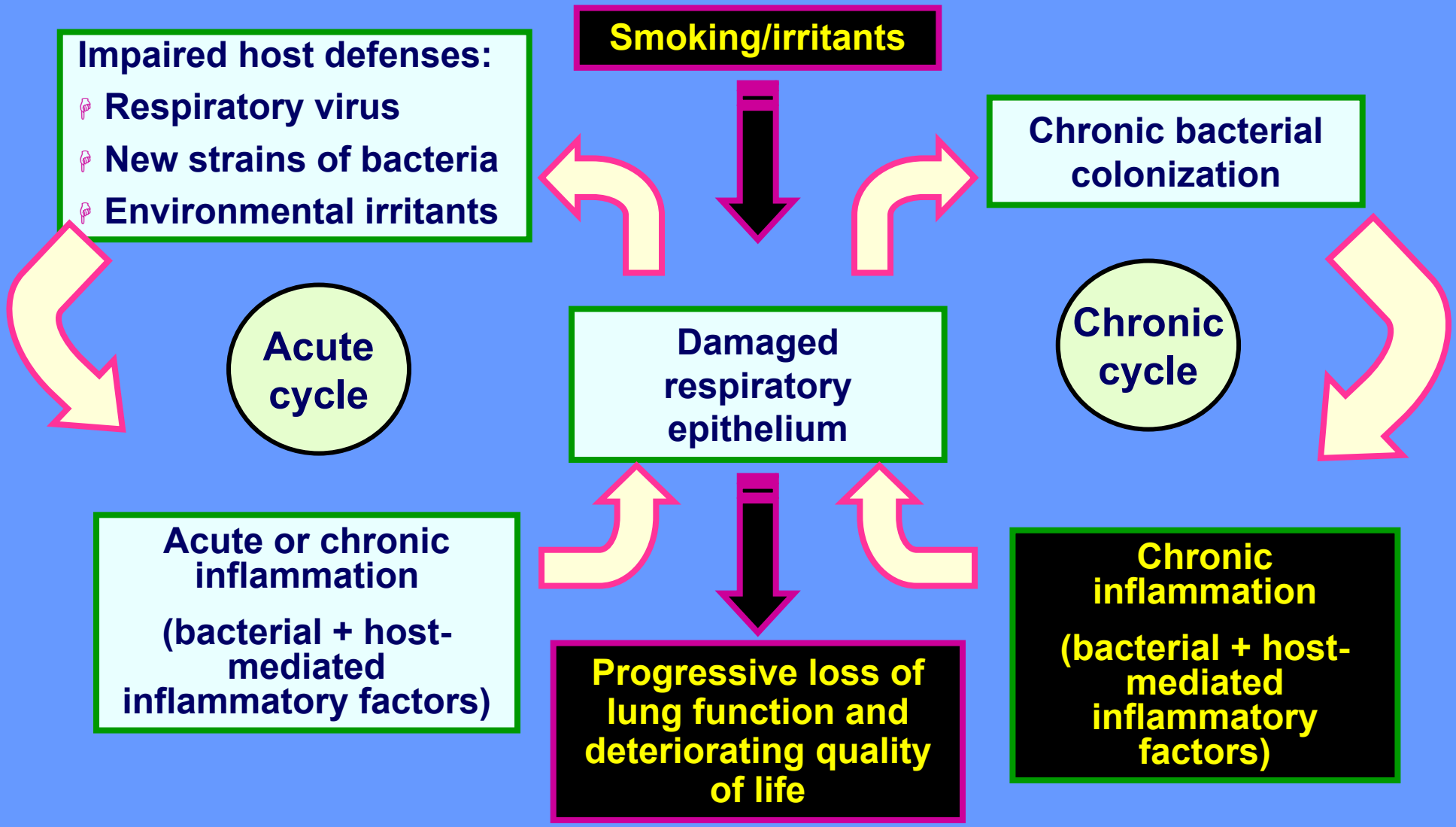
Damaged airway mucosa



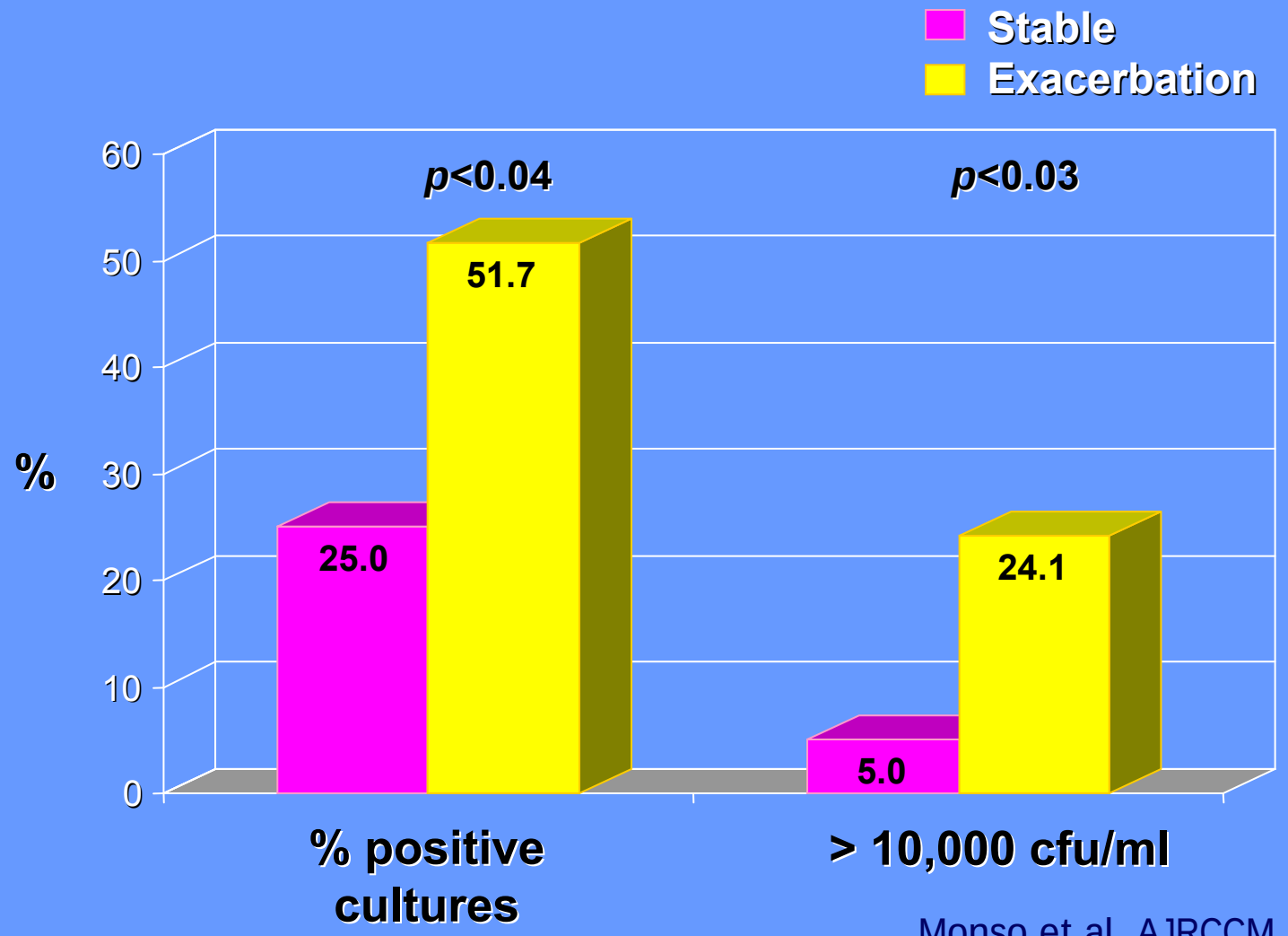
Scanning electron micrograph showing bacterial damage to the cilia and epithelium

P K Jeffery

Summary of Pathogenesis



Bronchoscopy in AECOPD



Monso et al. AJRCCM 1995:1316-20

Lower airway bacterial colonisation in the stable state modulates airway inflammation in COPD

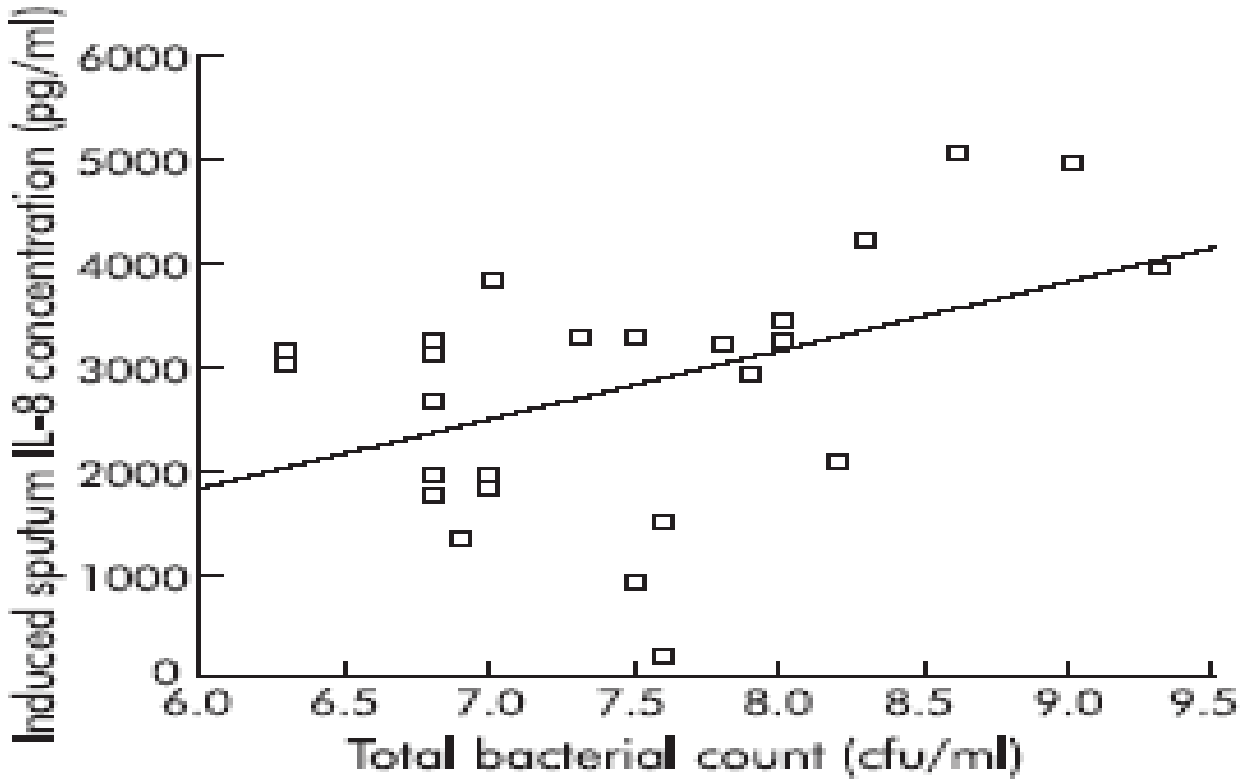
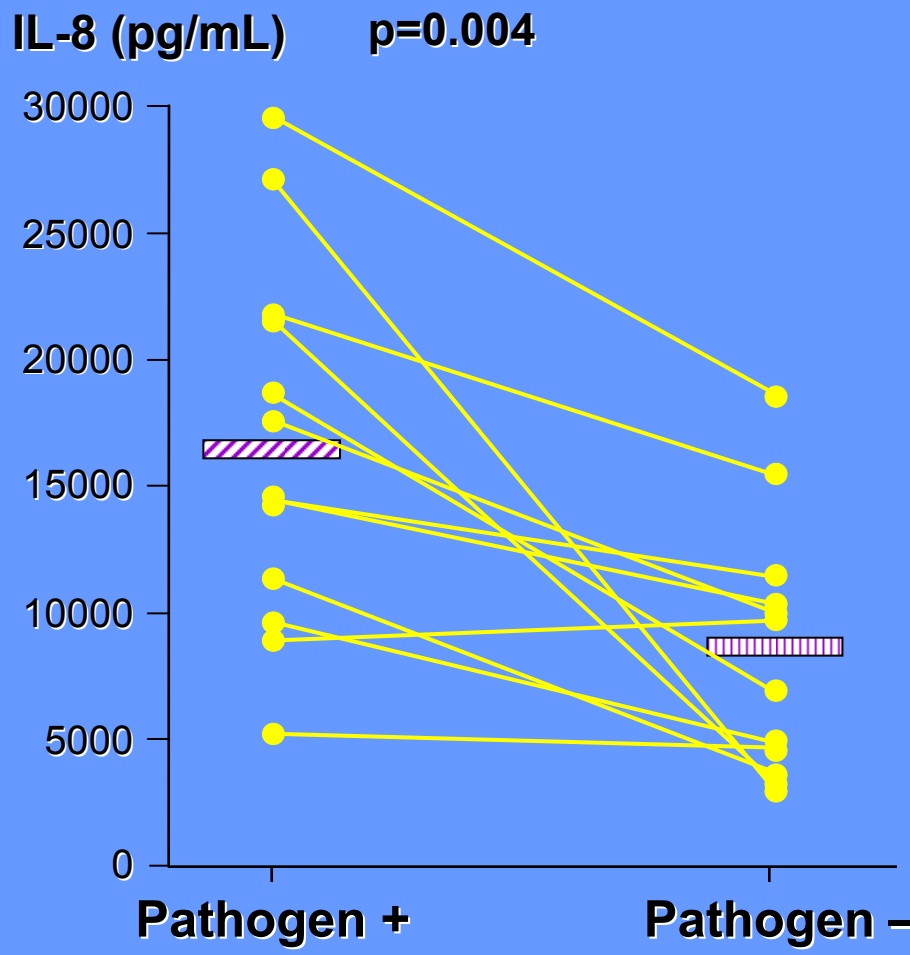


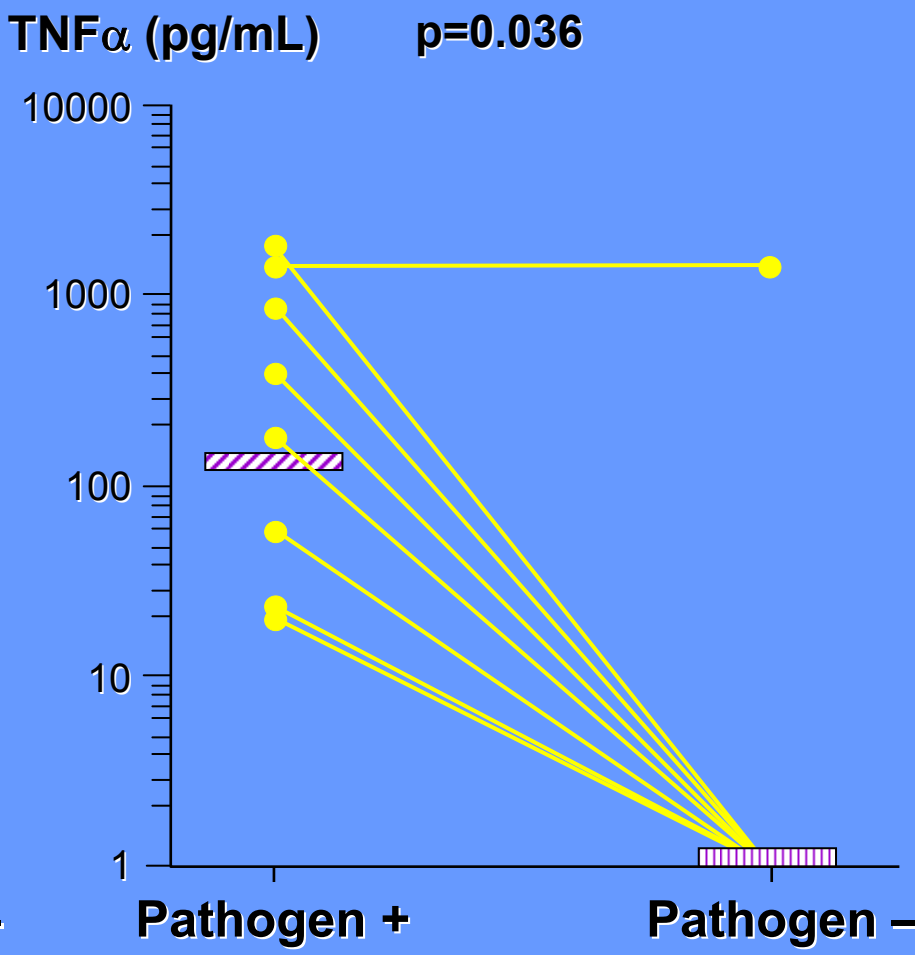
Figure 3 Relationship between total bacterial count (colony forming units/ml) and induced sputum IL-8 levels (Spearman's rho=0.459, p=0.02). The bacterial count data have been logarithmically transformed.

Patel, Seemungal, Wilks et al. Thorax 2002; 57: 759-64

Interleukin-8 and TNFα during AECOPD:

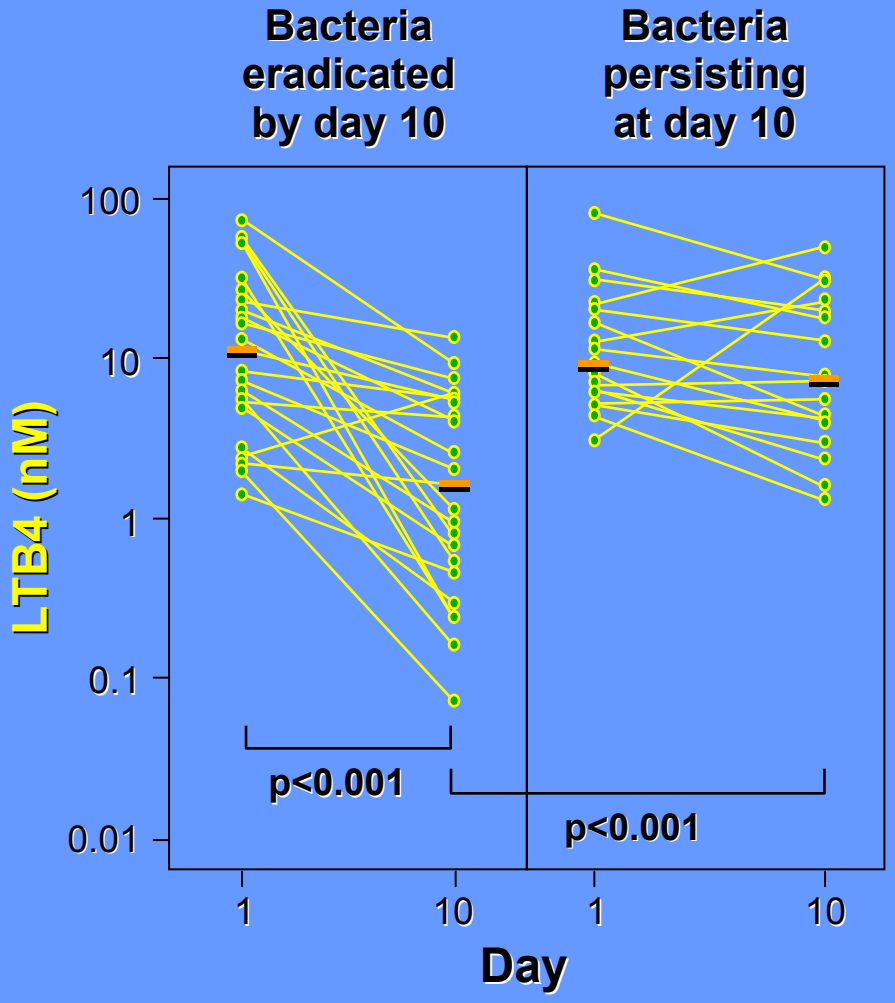
10-fold increased levels of inflammatory mediators, especially in the presence of bacterial pathogens

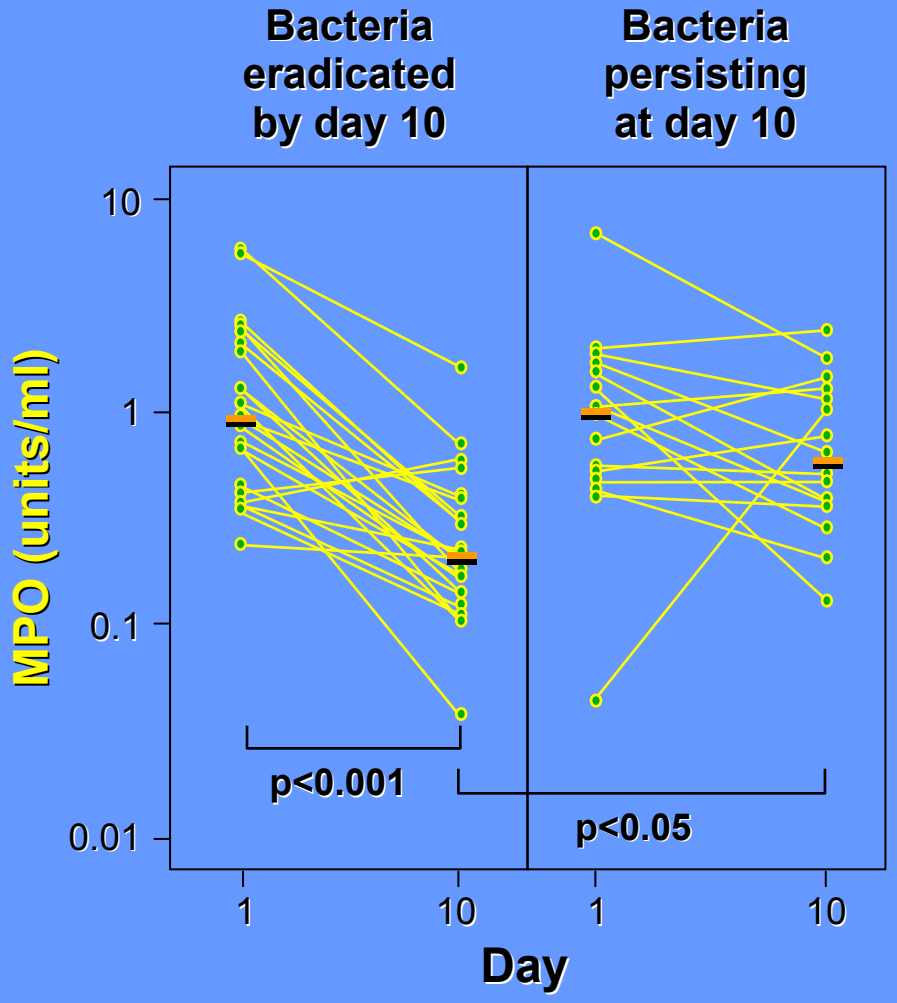




Sethi et al. Chest 2000; 118:1557-65

Bacterial eradication reduces and persistence favors airway inflammation following AECOPD

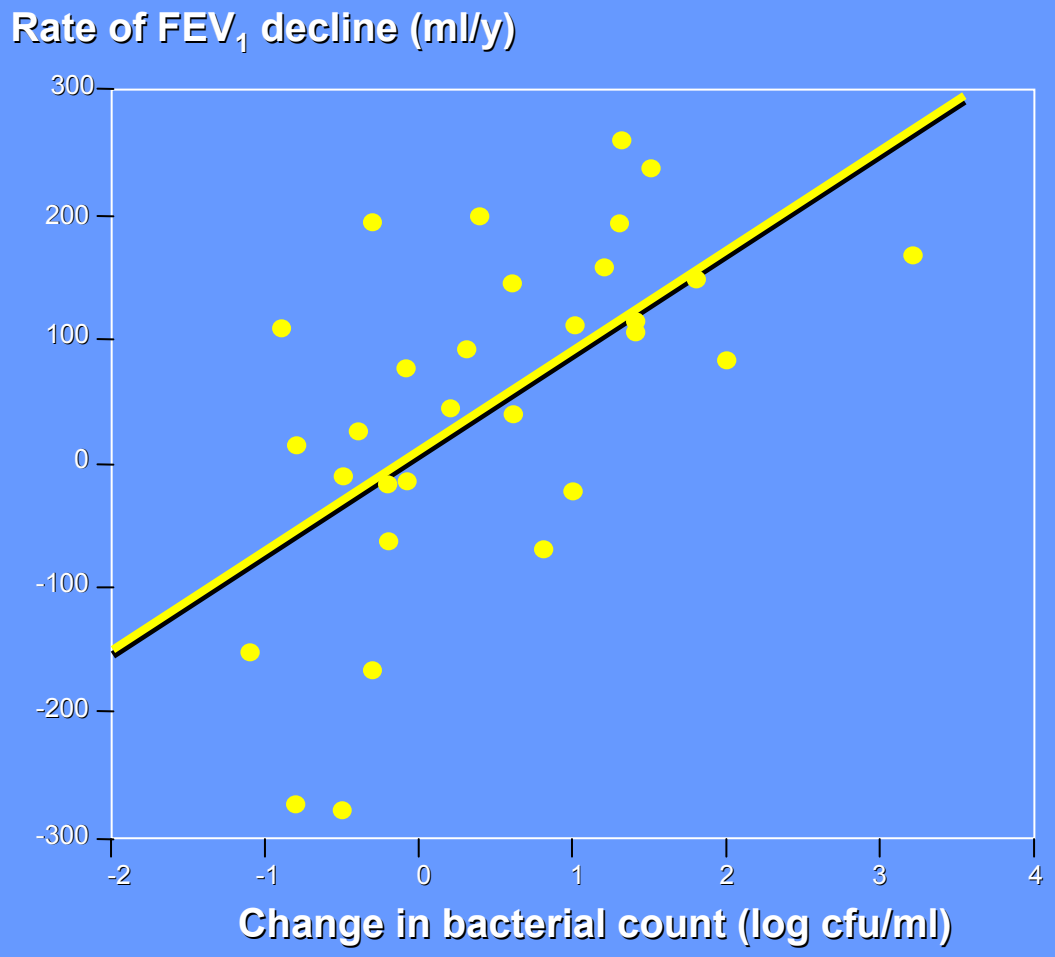




White et al. Thorax 2003; 58: 680-5

Rising airway bacterial load and species changes are associated with greater airway inflammation and accelerated decline in FEV_1

- Relationship between FEV_1 decline and change in bacterial load
- r = 0.593, p = 0.001
- Relationship true for absolute FEV_1 decline and decline expressed as % of baseline FEV_1



Wilkinson et al. AJRCCM 2003; 167: 1090

Antibiotic Treatment of AECOPD

A) WHEN ANTIBIOTICS ?

Criteria usually employed :

- Symptoms/severity of the AE :
  - presence of **3/3 Anthonisen criteria** (i.e. more severe AE, encompassing 40% of all patients with AECOPD) increases the chance that antibiotics are helpful [Anthonisen 87/01]
  - presence of **2/3 Anthonisen criteria if sputum purulence** is one of them
    i.e., purulence likely indicates the presence of bacteria [Stockley 2000]
  - Saint's meta-analysis confirms small but significant benefit from antibiotics [Saint 95/01]
- Presence of fever, increased CRP

Indication for Empiric Antibiotic Therapy in AECOPD

Severity of AECOPD

→ judged by 3 *Anthonisen criteria*:

- **Worsening of dyspnea**
- **Increased sputum volume**
- **Increased sputum purulence**

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- **Increased sputum purulence**

3/3	→	Type 1 or severe AE
2/3	→	Type 2 or moderate AE
1/3	→	Type 3 or mild AE

Indication for Empiric Antibiotic Therapy in AECOPD

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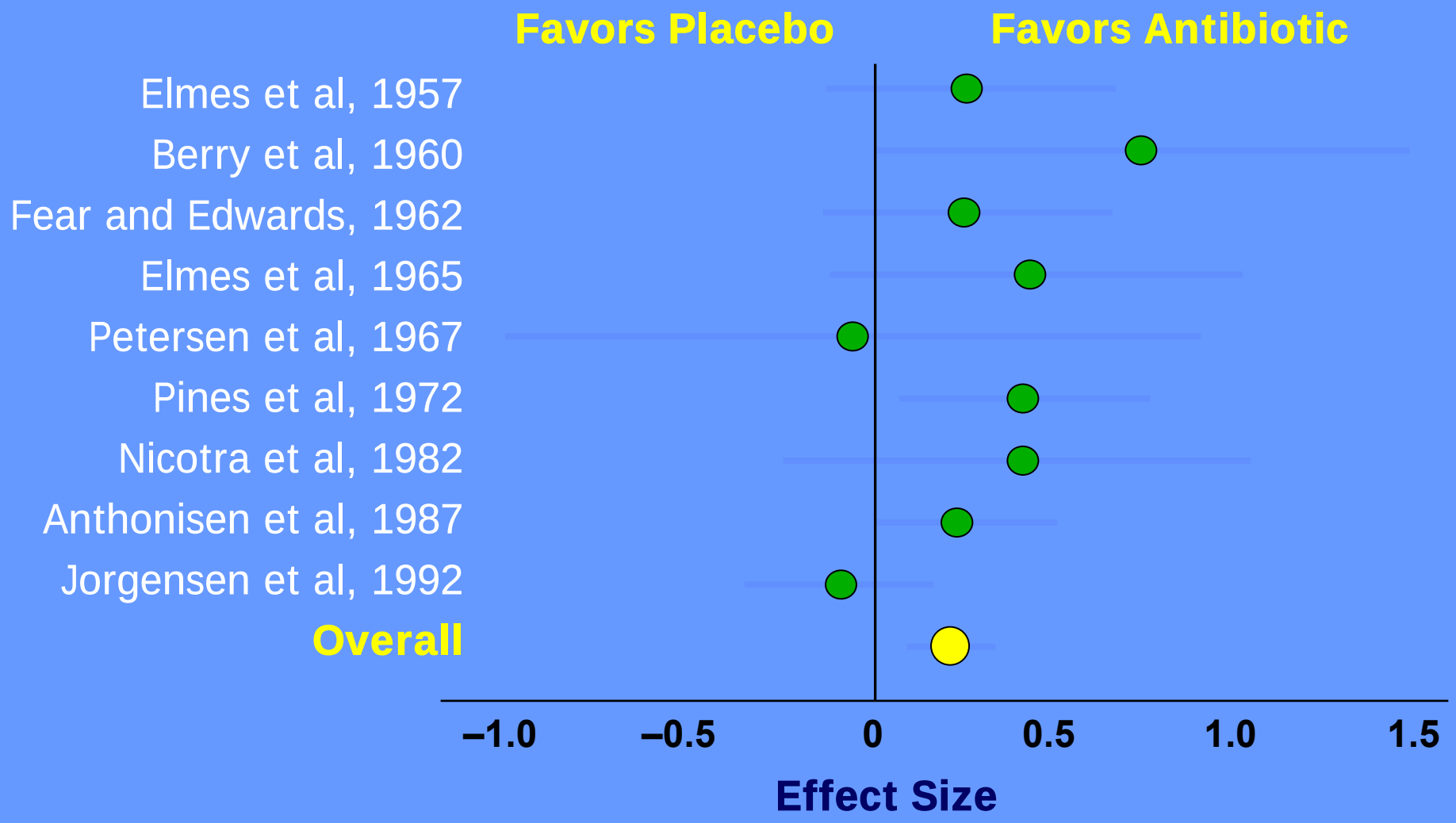
- **Increased sputum volume**
- **Increased sputum purulence**

3/3	→	Type 1 or severe AE
2/3	→	Type 2 or moderate AE
1/3	→	Type 3 or mild AE

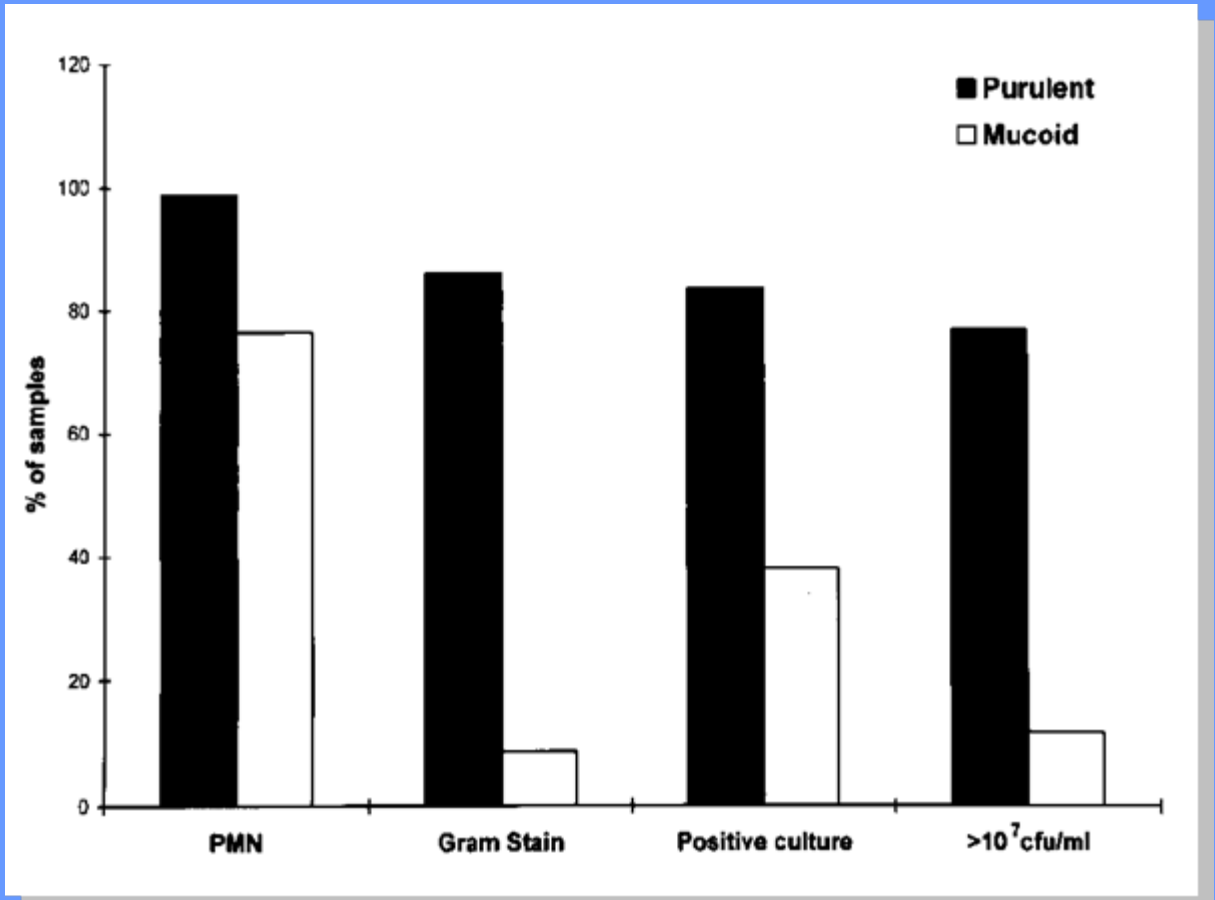
AB indicated/useful in Type 1 or severe AE, and Type 2 or moderate AE if sputum is purulent

Antibiotics Are Beneficial in AECB: a meta-analysis of placebo-controlled trials



Saint S et al. JAMA 1995; 273(12): 957-60

Antibiotics and AECB: when?



ECB
33
19
11
4

Purulence is an indicator of bacterial infection

Stockley RA, O'Brien C, Pye A, Hill SL. Chest 2000; 117(6):1638-45

A) WHEN ANTIBIOTICS (cont)?

Other criteria to take into account ?

- Severity of the AE according to other criteria than Anthonisen's: symptoms/signs of respiratory failure + ABG/S_aO_2 (+ PFT ?) [Nouria 01]

Evidence in favor: Nouira

Prospective, randomized, double-blind, placebo-controlled study
93 mechanically ventilated COPD patients
10 days antimicrobial treatment improves outcome of AECOPD

	Ofloxacin 400 mg/d	Placebo
In-hospital mortality	4 %	22 %
Duration of MV	6.4 days	10.6 days
Duration of hospitalization	14.9 days	24.5 days

Less nosocomial pneumonia
(high failure rate NIPPV, no steroids, infrequent *P. aeruginosa*)

Nouira S, Marghli S, Belghith M, Besbes L, Elatrous S, Abroug F. Once daily oral ofloxacin in COPD exacerbation requiring mechanical ventilation: a randomised placebo-controlled trial. Lancet 2001; 358: 2020-5

A) WHEN ANTIBIOTICS (cont)?

Other criteria to take into account ?

- Severity of the AE according to Anthonisen's criteria and symptoms/signs of respiratory failure (ABG/S_aO_2) [Nouria 01]

- Severity of underlying COPD (GOLD class III or IV) and active smoking [Miravitlles 1999]

  In patients with *milder* COPD antibiotics do not accelerate recovery nor reduce recurrence rate [Sachs 95/09]

  Patients with *severe* functional impairment and higher frequency of AE derived the greatest benefit of antibiotic treatment [Allegra 01]

Clinical response to antibiotic treatment and baseline severity of COPD

Retrospective analysis of a prospective, placebo- controlled trial of antibiotic Rx (amoxi/clav):

Cluster		Antibiotic	Placebo
I	(FEV_1 33%)	90.2%	30.2%
II	(FEV_1 54%)	84.8%	59.4%
III	(FEV_1 72%)		

→ **patients with severe functional impairment and higher frequency of AE derived the greatest benefit of antibiotic treatment**

Allegra L et al. Pulm Pharmacol Ther 2001; 14: 149-55

Empiric Antibiotic Therapy in AECOPD

IDAB Recommendation

	GOLD I	GOLD II	GOLD III or IV
Anthonisen 3/3	No / ?	Yes	Yes
Anthonisen 2/3 (incl. sputum purulence)	No / ?	Yes	Yes
Anthonisen 1/3	No	No	Yes
Acute resp. failure	Yes	Yes	Yes

B) WHICH ANTIBIOTICS ?

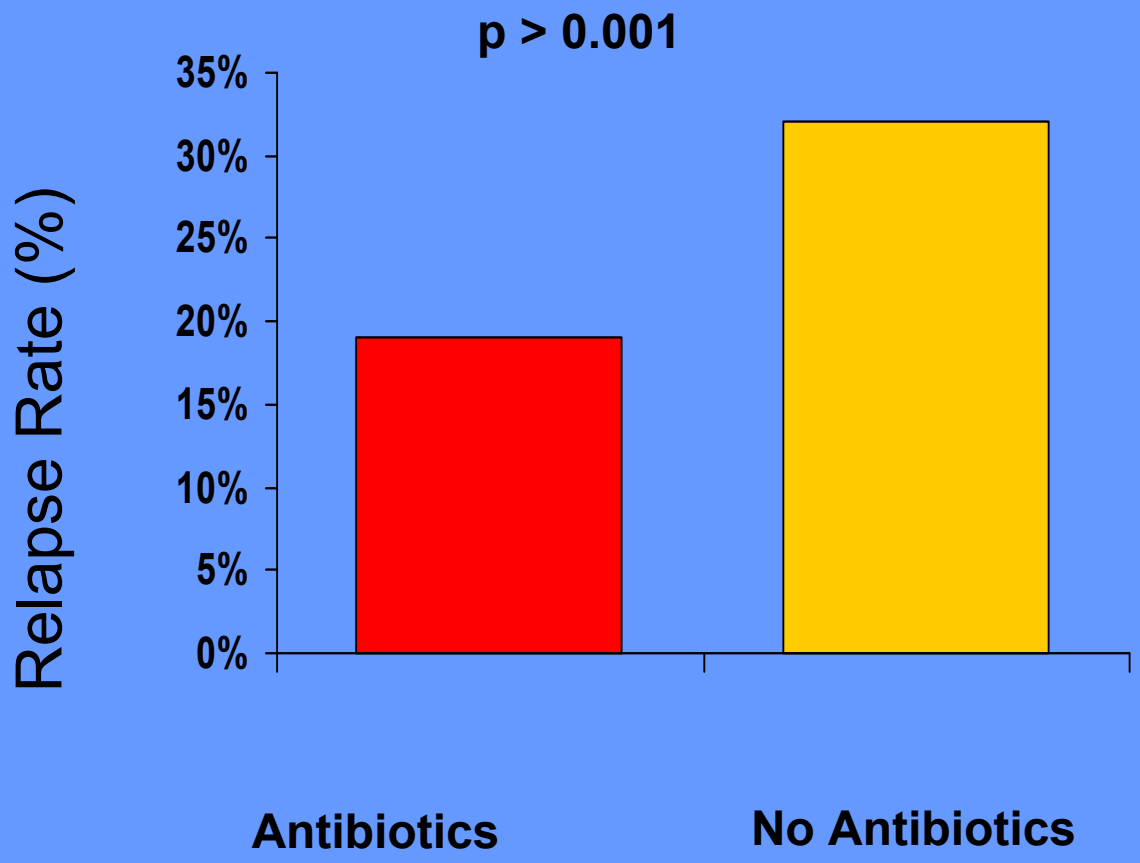
- **spectrum to include "infernal trio",** taking into account local susceptibility patterns and policies
- **"newer" drugs** (amoxi-clav, cephalo II, neomacrolides, neofluoroquinolones) :
  less treatment failure and lower relapse rates, but higher costs and possible resistance development issues [Adams 97/06] [Destache 99/08]

Prevalence of ß-lactam resistance among 'infernal trio'

	% of total isolates *	Relative frequency (%)	% ß-lactamase producers	ß-lactam resistance (%)
H. influenzae	31.2	52.5	20-25	10.5-13.1
S. pneumoniae	14.2	23.9	0	0
M. catarrhalis	14	23.6	90-95	21.2-22.4
Total	59.4	100		31.7-35.5

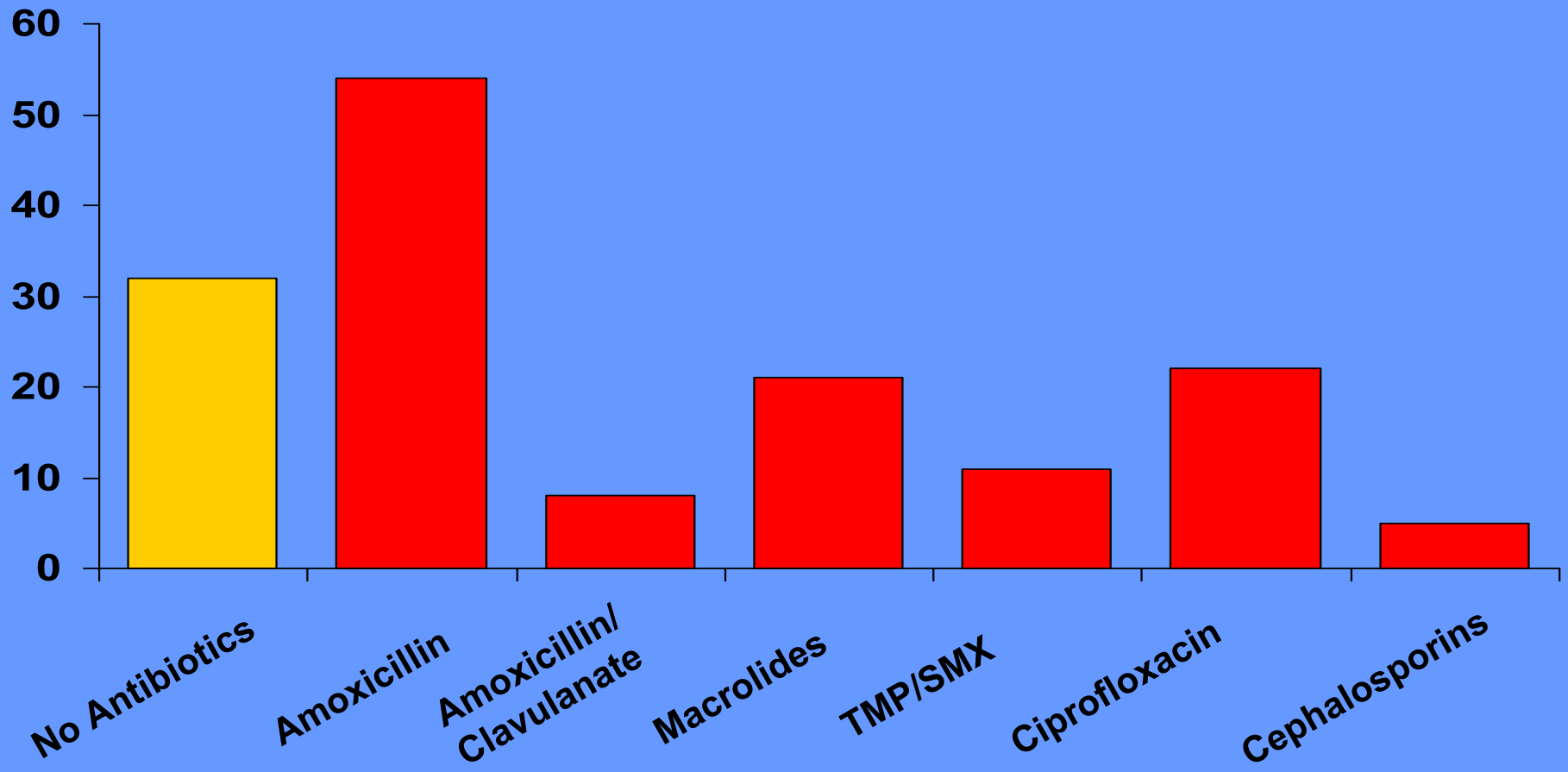
* Obaii & Sehti 2001

Association of Antibiotics with Relapse Rates in AECOPD



Adams SG *et al. Chest* 2000; 117(5): 1345-52

Association of Antibiotics with Relapse Rates in AECOPD



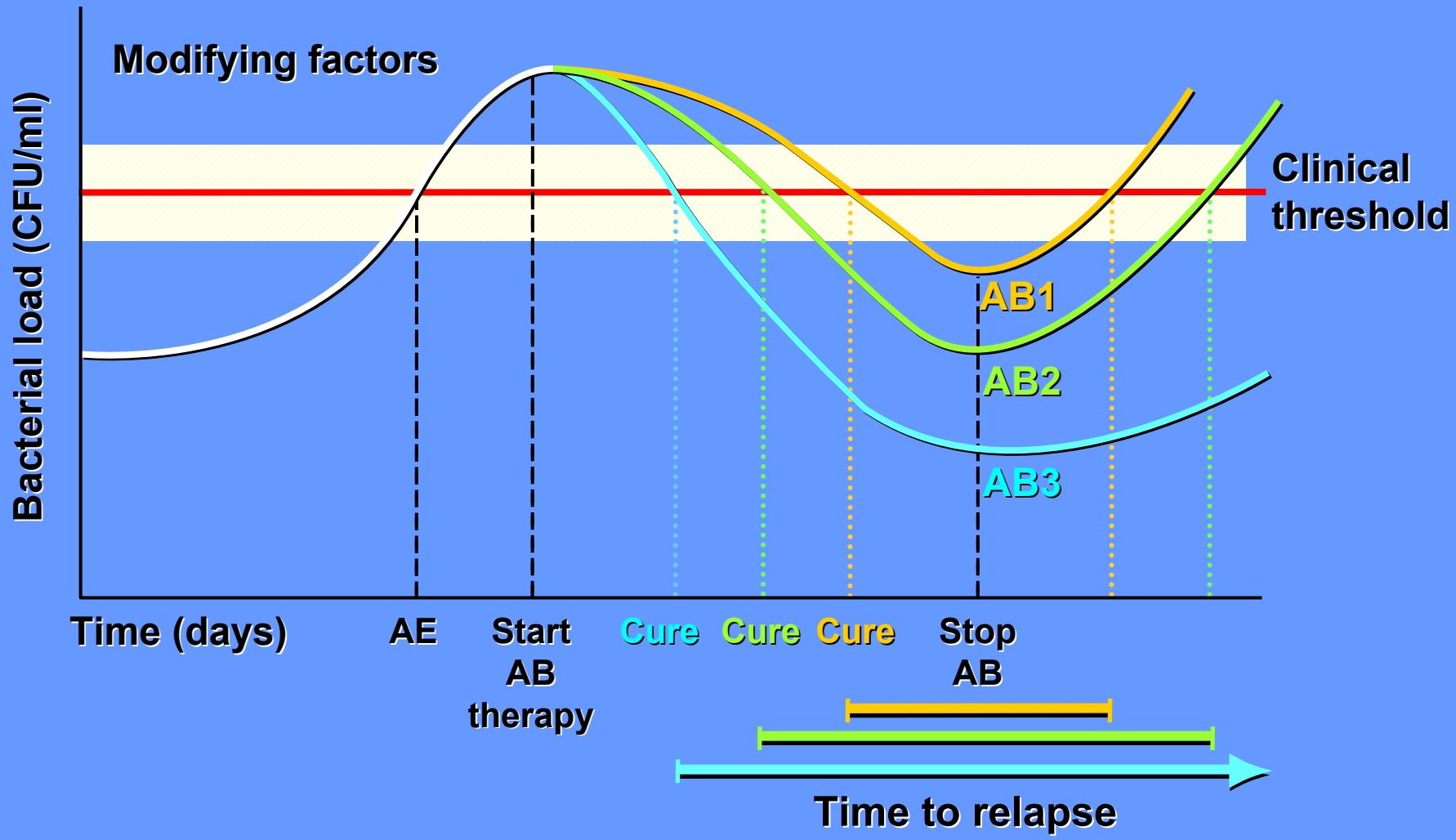
Adams SG *et al. Chest* 2000; 117(5): 1345-52

Novel outcomes in evaluation of antibiotic treatment for AECOPD

- **Clinical response : rapidity of resolution of symptoms**
- **Bacteriologic response : eradication of the causative pathogen**
  - Reducing colonising bacterial load and airway inflammation
  - Slowing progression of underlying COPD (decline in FEV_1 and HRQoL)
- **Decreased likelihood of recurrence / relapse**
  - Disease- or Infection-free interval
  - Need for additional antibiotics

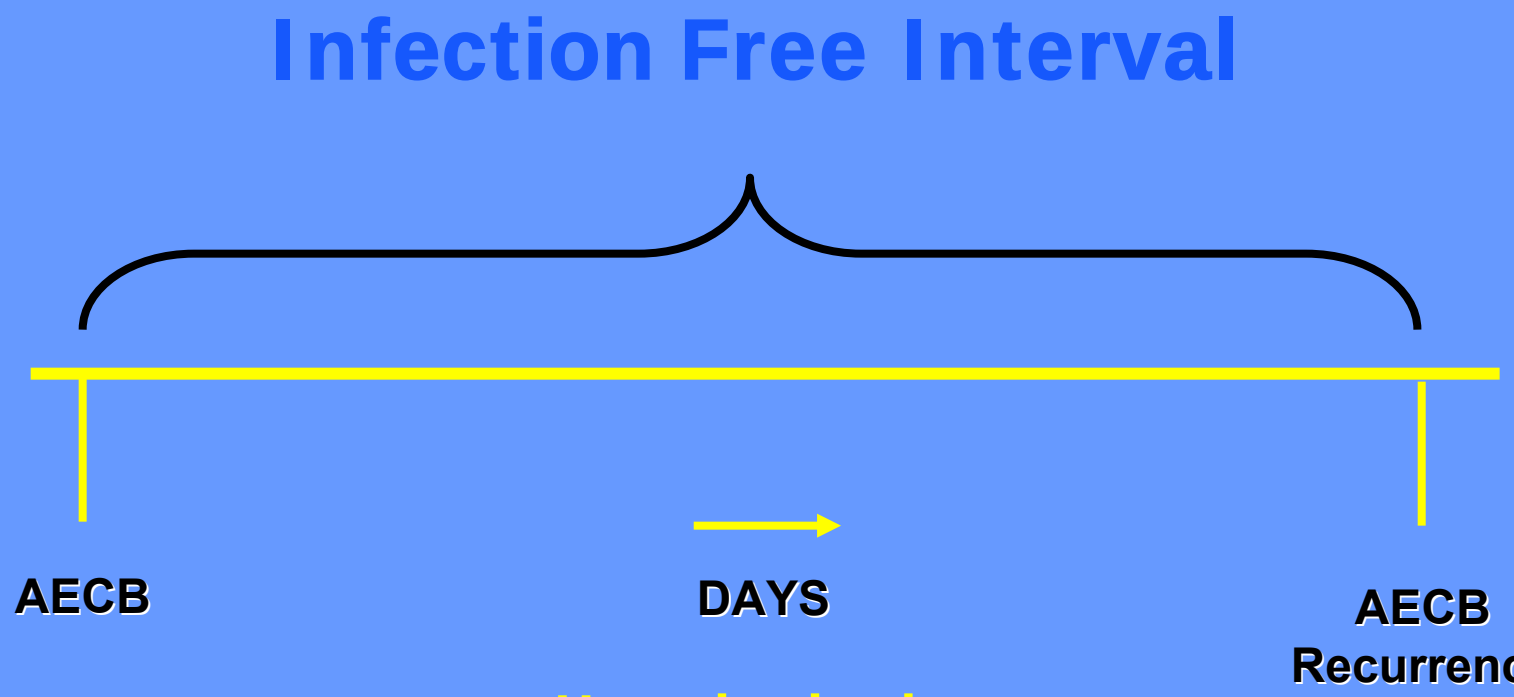
Martinez and Anzueto. Am J Med 2005; 118 (7A)

The ‘fall & rise’ of bacterial AECOPD



Miravitlles M. *Eur Respir J* 2002; 20(Suppl 36): 9-19

Infection free interval in AECB



Hypothesized to:

Relate to decreased number of colonizing bacteria

Influence cost of treatment of AECB

Aid in contrasting antimicrobials in AECB

Empiric antibiotic therapy for AECOPD

IDAB 2007

1. Treatment outside the hospital possible

- **amoxicillin-clavulanic acid PO**
  875/125 mg TID *or* 2000/125 mg BID

- **moxifloxacin PO 400 mg OD**
  if ß-lactam allergy or intolerance

- **cycling between amoxicillin-clavulanic acid and moxifloxacin if frequent AECOPD (i.e., ≥ 3 in the previous year)**

2. In-hospital treatment necessary
Mild or moderate COPD: GOLD stage I or II (i.e., FEV_1 > 50 %P)

- **oral treatment possible: same therapy as under 1.**

- **IV treatment necessary:**
  - **amoxicillin-clavulanic acid 1g QID**
  - **moxifloxacin 400 mg OD**

  if ß-lactam allergy or intolerance

  - **sequential IV>PO therapy ASAP within the same drug class**

- **cycling between amoxicillin-clavulanic acid and moxifloxacin if frequent AECOPD (i.e., ≥ 3 in the previous year)**

3. In-hospital treatment necessary

Severe or very severe COPD: GOLD stage III or IV (i.e., FEV_1 < 50 %P)

No risk factors for *Pseudomonas aeruginosa*

- **amoxicillin-clavulanic acid IV 1g QID**
- **moxifloxacin PO 400 mg OD if intact GI function**
- **moxifloxacin PO or IV 400 mg OD if ß-lactam allergy or intolerance**
- **sequential IV>PO therapy ASAP within the same drug class**
- **cycling between amoxicillin-clavulanic acid and moxifloxacin if frequent AECOPD (i.e., ≥ 3 in the previous year)**

4. In-hospital treatment necessary

Severe or very severe COPD: GOLD stage III or IV (i.e., FEV_1 < 50 %P)

With risk factors for *Pseudomonas aeruginosa*

- **recent hospitalization**
- **frequent administration of antibiotics** (>4 courses in last year)
- **recent administration of antibiotics (last 3 months)**
- **very severe COPD (Stage IV)**
- **isolation of P. aeruginosa during previous AECOPD**
- **colonization with P. aeruginosa during stable period**
- **presence of bronchiectasis**

4. In-hospital treatment necessary

Severe or very severe COPD: GOLD stage III or IV (i.e., FEV_1 < 50 %P)

With risk factors for *Pseudomonas aeruginosa*

- **if oral therapy possible: ciprofloxacin PO 750 mg BID**

- **if IV treatment necessary:**
  - **anti-Pseudomonas ß-lactam:**
    - **ceftazidime 2 g TID**
    - **cefepime 2 g TID**
    - **piperacillin-tazobactam 4 g QID**
  - **ciprofloxacin 400 mg TID**

- **add IV aminoglycoside active against *Pseudomonas aeruginosa* if**
  - **instability on the hospital ward**
  - **requirement for ICU admission**

Thank you for your attention

On behalf of the
IDAB WORKGROUP AECOPD

Herman Goossens
Paul Jordens
Willy Peetermans
Yves Sibille
Yvan Valcke
Pascal Van Bleyenbergh
Jan Vandevoorde
Johan Van Eldere
Yves Van Laethem
Walter Vincken (coordinator)

And the plenary IDAB presided by Dirk Vogelaers

ACUTE EXACERBATIONS OF COPD : Overview of topics

1. DEFINITIONS : COPD & AECOPD

2. IMPORTANCE / IMPACT OF AECOPD

3. ETIOLOGY OF AECOPD : non-infectious
   infectious

4. DIAGNOSIS OF AECOPD

5. TREATMENT OF AECOPD

6. PREVENTION OF AECOPD

Prevention of AECOPD

- **Smoking cessation**
  Only intervention with proven effect on mortality
- **Regular maintenance treatment [GOLD guideline]**
  especially tiotropium, LABA, iGCS (in GOLD class 3 or 4), NAC[4], rehabilitation
- **Vaccination (influenza, S. pneumoniae)**
- **Prevention of infection (viral, bacterial) [1] : AB associated with lower relapse rates [2]**
- **Immunostimulating agents [3]**

[1] Black et al. Cochrane Database Syst Rev 2003;(1):CD004105

[2] Adams et al. Chest 2000;17:1345-52

[3] Collet et al. Can Respir J 2001;8:27-33; Collet et al. AJRCCM 1997;156:1719-24

[4] [Stey 2000]

Indications for hospital assessment or admission for acute exacerbations of COPD

- Marked increase in intensity of symptoms, such as sudden development of resting dyspnea
- Onset of new physical signs (e.g., cyanosis, peripheral edema, newly occurring arrhythmias)
- Failure of exacerbation to respond to initial medical management
- Severe background COPD and patients on LTOT
- History of frequent AE and hospitalizations (>3 in the past year)
- Chronic oral steroid use
- Significant comorbidities
- Older age
- Poor or deteriorating general condition with little activity
- Insufficient home support
- Diagnostic uncertainty

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Indications for ICU admission of patients with acute exacerbations of COPD

- Severe dyspnea that responds inadequately to initial emergency therapy
- Persistent or worsening hypoxemia (P_aO_2 < 50 mmHg), and/or severe/worsening hypercapnia (P_aCO_2 > 70 mmHg), and/or severe/worsening respiratory acidosis (pH < 7.30) despite supplemental oxygen and NIPPV
- Presence of other end-organ dysfunction
- Confusion, lethargy, coma
- Hemodynamic instability

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