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Gruppo Italiano per la Medicina Basata sulle Evidenze
Evidence-based Medicine
Le opportunità di un linguaggio comune
Como, 9-11 maggio 2003
Sezione di Como

**Workshop Interattivo 1
BPCO**

**Perché un eccesso di evidenze
non modifica i comportamenti?**

Daniela Canini

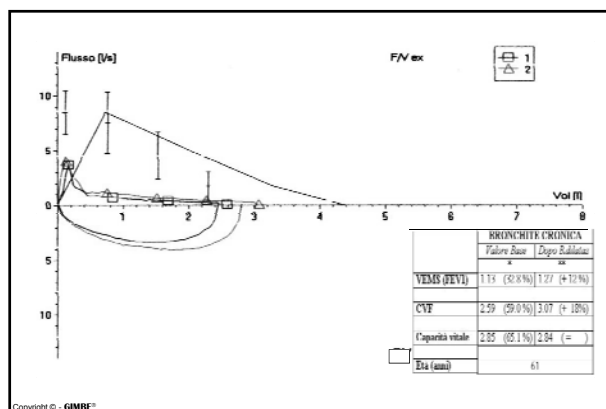
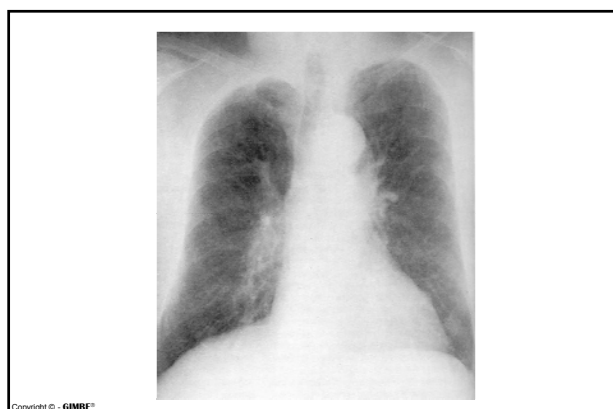
Discussant: Gian Paolo Bonini, Alfredo Potena

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Scenario Clinico (1)

- Il signor Giuseppe è un ex camionista di 61 anni, forte fumatore (30-40 sigarette/die), con pregressa diagnosi di BPCO, effettuata nel 1992 sulla base di dati clinico-anamnestici, radiologici e spirometrici
- Il paziente, inoltre, ha una storia di iperconsumo alcolico con struttura e funzione epatica perfettamente conservate
- Da quando è stata posta diagnosi di BPCO, il paziente ha praticato terapia con aminofillina retard + salbutamolo spray al bisogno

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Scenario Clinico (2)

- Sin dal 1993 il paziente va incontro a diversi episodi di riacutizzazione della BPCO, che vengono trattate con antibiotici (chinolonici e/o cefalosporine iniettive) e cortisonici per via sistemica.
- Alcuni di questi episodi hanno richiesto l'ospedalizzazione
- In occasione di uno di tali ricoveri (1996) vengono aggiunti alla terapia cronica inalatoria un anticolinergico (ipratropio) ed una combinazione di beclometasone e salbutamolo

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1. BPCO. Perché un eccesso di evidenze non modifica i comportamenti?

A. Ritieni appropriata la scelta degli antibiotici (chinolonici e/o cefalosporine iniettive) per trattare gli episodi di riacutizzazione?

1. Sì
2. No

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*American College of Chest Physicians
American College of Physicians
American Society of Internal Medicine*

Evidence Base for Management of Acute Exacerbations of Chronic Obstructive Pulmonary Disease

Ann Intern Med 2001;134:595-99

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- Although suggestions for appropriate management can be made on the basis of available evidence, the supporting literature is scarce and further high-quality research is necessary.
- Such research will require an improved, generally acceptable, and transportable definition of acute exacerbation of COPD, as well as improved methods for observing and measuring outcomes

Ann Intern Med 2001

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Antibiotics

- 11 RCTs have shown that antibiotic treatment is beneficial in selected patients with acute exacerbation of COPD.
- In particular, the studies showed that patients with more severe exacerbations (type 1) are more likely to experience benefit than those whose exacerbations are less severe.
- Typical administration periods ranged from 3 to 14 days, and tetracycline, amoxicillin, and trimethoprim-sulfamethoxazole were the most common antibiotics.

Ann Intern Med 2001

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Antibiotics

- Although most of these RCTs were done before the emergence of multidrug-resistant organisms, they show only a minimal benefit with antibiotic treatment in the more severe exacerbations.
- On the basis of these data and the emergence over time of more resistant organisms, particularly *Streptococcus pneumoniae*, it has become common practice to use more broad-spectrum antibiotics in acute exacerbations of COPD.
- To date, however, no RCTs have proved the superiority of the newer broad-spectrum antibiotics in such cases

Ann Intern Med 2001

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*World Health Organization
National Heart Lung and Blood Institute
April 2001*

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Antibiotics: Antibiotics are only effective when patients with worsening dyspnea and cough also have increased sputum volume and purulence¹⁰⁰ (**Evidence B**). The choice of agents should reflect local patterns of antibiotic sensitivity among *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis*.



- Patients experiencing COPD exacerbations with clinical signs of airway infection (e.g., increased volume and change of color of sputum, and/or fever) may benefit from antibiotic treatment (**Evidence B**).

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3. Bronchite cronica, asma, BPCO. Pratica clinica ed eccesso di linee guida?

B. In occasione degli episodi di riacutizzazione, avresti prescritto un mucolitico per via orale?

1. Si
2. No

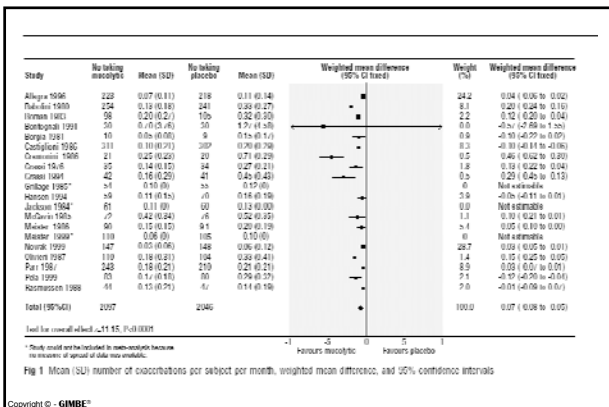
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Poole PJ, Black PN.

Mucolytic agents for chronic bronchitis or chronic obstructive pulmonary disease

In: *The Cochrane Library*, Issue 2, 2003
Oxford: Update Software

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- There was significant heterogeneity between the RCTs

• Our systematic review shows that mucolytic drugs have a modest, but significant effect on exacerbation rates in people with chronic bronchitis and chronic obstructive pulmonary disease.

• On the basis of the annualised exacerbation rate of 2.7 per patient per year in the control group, the number needed to treat for one subject to remain free of exacerbations for the study period would be 6.

Poole PJ, et al. *Cochrane Library*, 2003

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What this study adds

Regular use of mucolytic drugs for at least two months significantly reduces exacerbations and days of illness compared with placebo in patients with chronic bronchitis and chronic obstructive pulmonary disease:

Exacerbations that do occur may not be as severe, and the benefit may be greater in those with more severe disease

Reductions are modest and treatment may not be cost effective

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Poole PJ, et al. Cochrane Library, 2003



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Mucolytic (Mucokinetic, Mucoregulator) Agents

(ambroxol, erdosleine, carbocysteine, iodinated glycerol): Although a few patients with viscous sputum may benefit from mucolytics^{127,128}, the overall benefits seem to be very small. Therefore, the widespread use of these agents cannot be recommended on the basis of the present evidence (**Evidence D**).

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Scenario Clinico (3)

- Nel 1999, a causa del sopraggiungere di una insufficienza respiratoria ipossiémico-ipercapnica stabile (pO_2 54, pCO_2 50) con $FEV_1 < 50\%$, viene posta indicazione all' O_2 -terapia domiciliare
- Viene anche modificata la terapia farmacologica:
 - sostituisce lo spray combinato beclometasone-salbutamolo con l'uso sequenziale di formoterolo e fluticasone
 - sostituisce l'ipratropio con l'ossitropio
 - inizia terapia steroidea sistemica continuativa (prednisone 7,5 mg/die x os).

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3. Bronchite cronica, asma, BPCO. Pratica clinica ed eccesso di linee guida?

C. Ritieni appropriata la prescrizione della ossigenoterapia domiciliare

1. Sì
2. No

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Crockett AJ, Moss JR, Cranston JM, Alpers JH.

Domiciliary oxygen in chronic obstructive pulmonary disease

The Cochrane Library, Issue 2, 2003
Oxford: Update Software

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- We found limited evidence that domiciliary oxygen treatment improves survival in people with COPD and hypoxaemia.
- One RCT found that continuous treatment was more effective than nocturnal treatment.
- Domiciliary oxygen treatment seems to be more effective in people with severe hypoxaemia, than in people with moderate hypoxaemia or those who have arterial desaturation only at night.

Crockett AJ, et al. Cochrane Library 2003

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The long-term administration of oxygen (>15 hours per day) to patients with chronic respiratory failure has been shown to increase survival^{126,127,153,154} (**Evidence A**). It can also have a beneficial impact on hemodynamics, hematologic characteristics, exercise capacity, lung mechanics, and mental state¹⁵⁵.

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Long-term oxygen therapy is generally introduced in Stage III (severe COPD) for patients who have:

- PaO₂ at or below 55 mm Hg or SaO₂ at or below 88%, with or without hypercapnia; or
- PaO₂ between 55 and 60 mm Hg or SaO₂ 89%, if there is evidence of pulmonary hypertension, peripheral edema suggesting congestive heart failure, or polycythemia (hematocrit > 55%).

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3. Bronchite cronica, asma, BPCO. Pratica clinica ed eccesso di linee guida?

D. In quale delle seguenti categorie collocheresti l'uso degli steroidi inalatori nella BPCO

1. Utile
2. Probabilmente utile
3. Da valutare caso per caso
4. Di efficacia sconosciuta
5. Probabilmente inutile
6. Inutile o dannoso

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Chronic Obstructive Pulmonary Disease

Clinical Evidence
April 2003

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Inhaled corticosteroids

Unlikely to be beneficial

- Short term RCTs found no evidence of benefit of inhaled corticosteroids.
- Large RCTs of at least 6 months have found that inhaled steroids increase FEV₁ during the first 3–6 months of use, but found no subsequent effect on decline of lung function.
- Two studies also found a reduction in exacerbation frequency and an improvement in health status.

Clinical Evidence. April 2003

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- Regular treatment with inhaled glucocorticosteroids should only be prescribed for symptomatic COPD patients with a documented spirometric response to glucocorticosteroids or for those with an FEV₁ < 50% predicted and repeated exacerbations requiring treatment with antibiotics and/or oral glucocorticosteroids (**Evidence B**).

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- E. Ritieni che il rapporto rischio/beneficio sull'uso long-term degli steroidi orali nella BPCO sia:
1. Verosimilmente favorevole
 2. Verosimilmente sfavorevole

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Chronic Obstructive Pulmonary Disease

*Clinical Evidence
April 2003*

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Oral Corticosteroids

- One systematic review of short term RCTs has found that steroids versus placebo significantly improves lung function.
- We found no RCT of the effects of long term treatment on lung function.
- We found evidence of potentially serious adverse effects, including osteoporosis and induction of diabetes

Clinical Evidence. March 2003

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McEvoy CE, Niewoehner DE.

Adverse effects of corticosteroid therapy for COPD: a critical review

Chest 1997;111:732-743.

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Long-term treatment with oral glucocorticosteroids is not recommended in COPD¹¹⁷⁻¹¹⁸ (**Evidence A**). There is no evidence of long-term benefit from this treatment. Moreover, a side effect of long-term treatment with systemic glucocorticosteroids is steroid myopathy^{118,119}, which contributes to muscle weakness, decreased functionality, and respiratory failure in patients with advanced COPD.



- Chronic treatment with systemic glucocorticosteroids should be avoided because of an unfavorable benefit-to-risk ratio (**Evidence A**).

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Scenario Clinico (4)

- Nell'agosto del 2000, a seguito di un trauma banale, il signor Giuseppe riportava la frattura non mielica di L1.
- Tutti i tentativi di sospendere la terapia steroidea sistemica comportavano un peggioramento soggettivo del quadro respiratorio
- Il paziente, comunque, continua a fumare

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Scenario Clinico (5)

- Nel febbraio 2002 ricovero per insufficienza respiratoria acuta in terapia intensiva, dove viene sottoposto a ventilazione meccanica invasiva.
- Il paziente viene dimesso dopo circa 20 giorni di degenza in discrete condizioni generali
- Attualmente, il paziente continua a fumare (di nascosto)

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3. Bronchite cronica, asma, BPCO. Pratica clinica ed eccesso di linee guida?

F. In occasione delle riaccerbazioni di BPCO, ritieni appropriata la ventilazione meccanica non-invasiva?

1. Sì
2. No

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Lightowler JV, Wedzicha JA, Elliott MW, et al.

Non-invasive positive pressure ventilation to treat respiratory failure resulting from exacerbations of COPD **Cochrane systematic review and meta-analysis**

The Cochrane Library, Issue 2, 2003
Oxford: Update Software

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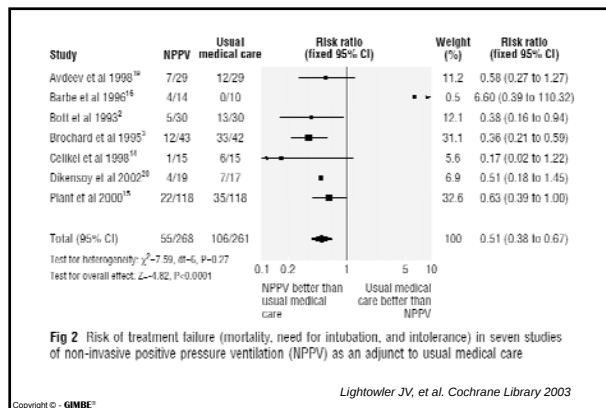


Table 1 Effects of non-invasive positive pressure ventilation as an adjunct to usual medical care, compared with usual care alone: overall results of the review for dichotomous outcome measures

Outcome	Number of studies contributing data	Total number of patients	Relative risk (95% CI)	Number needed to treat (95% CI)
Treatment failure	7 ² 2 11-16 18 20	529	0.51 (0.38 to 0.67)	5 (4 to 7)
Mortality	7 ² 2 11-16 18 20	528	0.41 (0.26 to 0.64)	8 (6 to 13)
Intubation	8 ² 2 14 17 19 20	546	0.42 (0.31 to 0.59)	5 (4 to 7)
Complications	2 ⁸ 10	143	0.32 (0.18 to 0.56)	3 (2 to 4)

Lightowler JV, et al. Cochrane Library 2003

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Table 2 Effects of non-invasive positive pressure ventilation as an adjunct to usual medical care, compared with usual care alone: overall results of the review for continuous outcome measures

Outcome	Number of studies contributing data	Total number of patients	Weighted mean difference (95% CI)
Length of stay in hospital (days):			
Trials in intensive care units	3 ⁸ 14 17	138	3.28 (6.09 to -0.67)
Trials in wards	5 ² 16 18 20	408	3.20 (4.51 to 1.89)
Total	8 ² 3 14 17 18 20	546	-3.24 (-4.42 to -2.06)

Lightowler JV, et al. Cochrane Library 2003

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What this study adds

Evidence from good quality, randomised controlled trials shows that NPPV is an effective treatment for acute exacerbations of COPD

NPPV should be considered early in the course of respiratory failure and before severe acidosis ensues, to avoid the need for endotracheal intubation and reduce mortality in patients with COPD

Lightowler JV, et al. Cochrane Library 2003

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- Noninvasive intermittent positive pressure ventilation (NIPPV) in acute exacerbations improves blood gases and pH, reduces in-hospital mortality, decreases the need for invasive mechanical ventilation and intubation, and decreases the length of hospital stay (**Evidence A**).

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**Table 14 - Selection and Exclusion Criteria
for NIPPV¹²⁷**

Selection criteria (at least 2 should be present)

- Moderate to severe dyspnea with use of accessory muscles and paradoxical abdominal motion.
- Moderate to severe acidosis (pH 7.30-7.35) and hypercapnia (PaCO₂ 6.0-8.0 kPa, 45-60 mm Hg).
- Respiratory frequency > 25 breaths per minute.

Exclusion criteria (any may be present)

- Respiratory arrest.
- Cardiovascular instability (hypotension, arrhythmias, myocardial infarction).
- Somnolence, impaired mental status, uncooperative patient.
- High aspiration risk; viscous or copious secretions.
- Recent facial or gastroesophageal surgery.
- Craniofacial trauma, fixed nasopharyngeal abnormalities.
- Extreme obesity.