# Inhaled Corticosteroid for Non-asthmatic chronic cough - PRO -

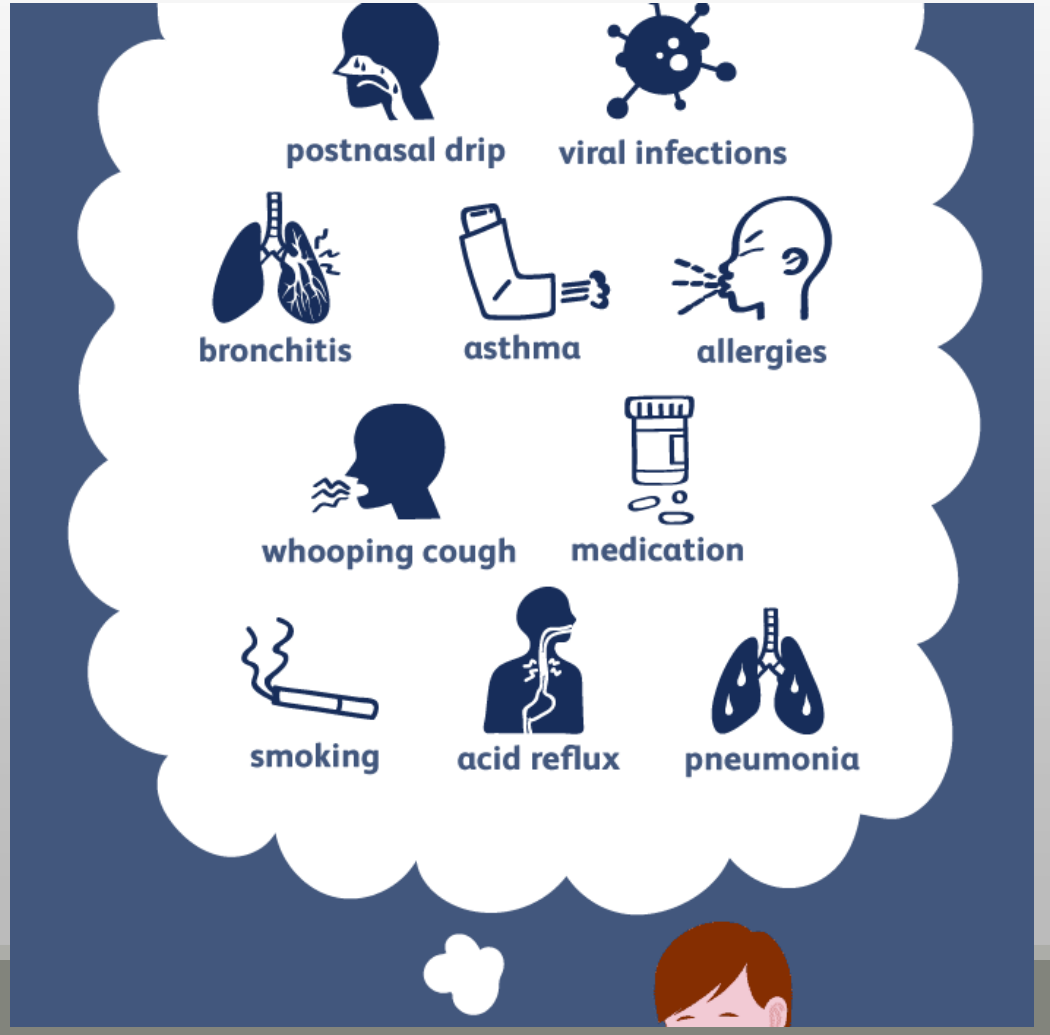
2021.4.10

INA JEONG

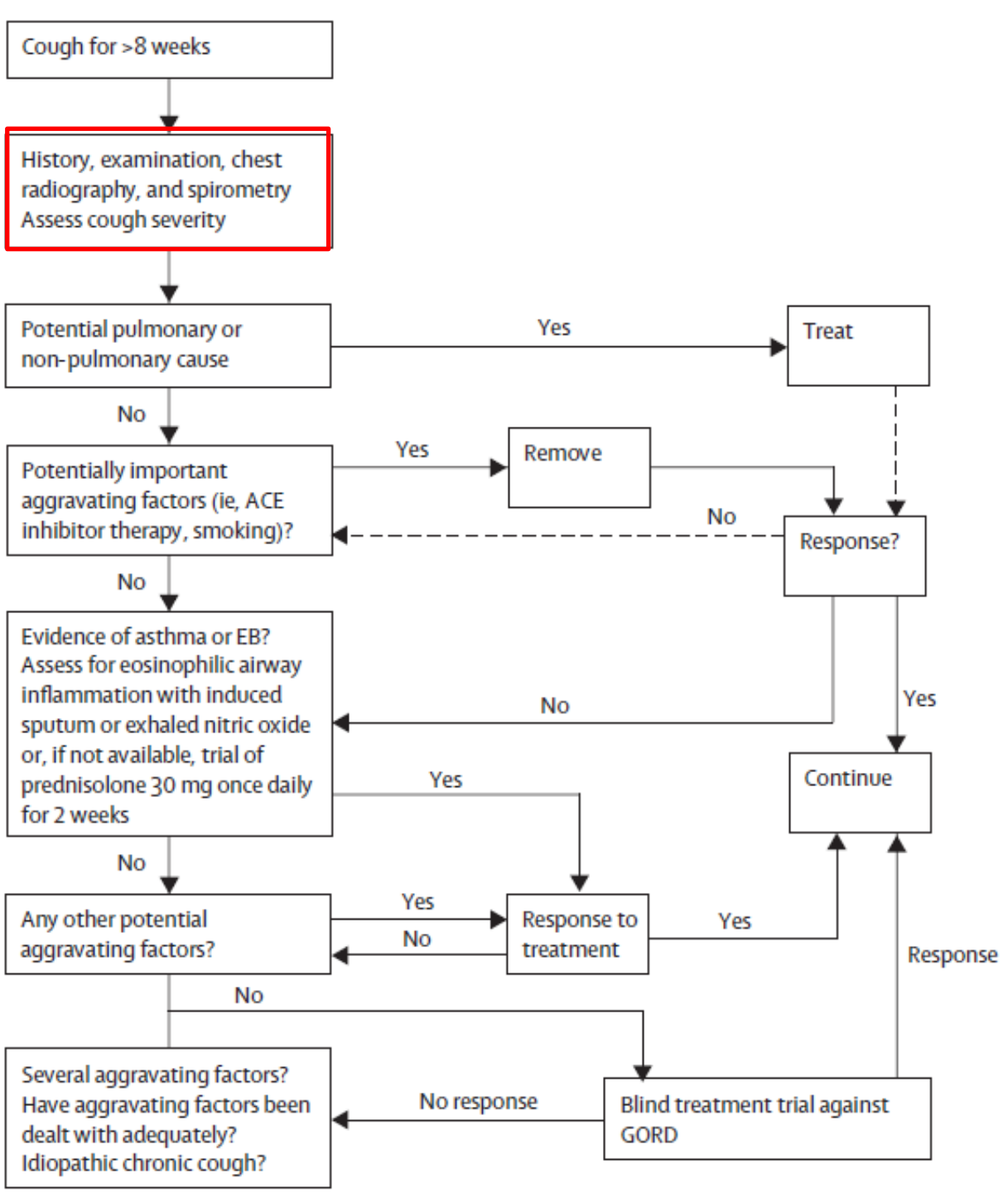
NATIONAL MEDICAL CENTER

# Contents

# Cause of cough



# Diagnosis of chronic cough




*Pavord ID, et al. The Lancet 2008;371:1375-84*

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기침진료지침

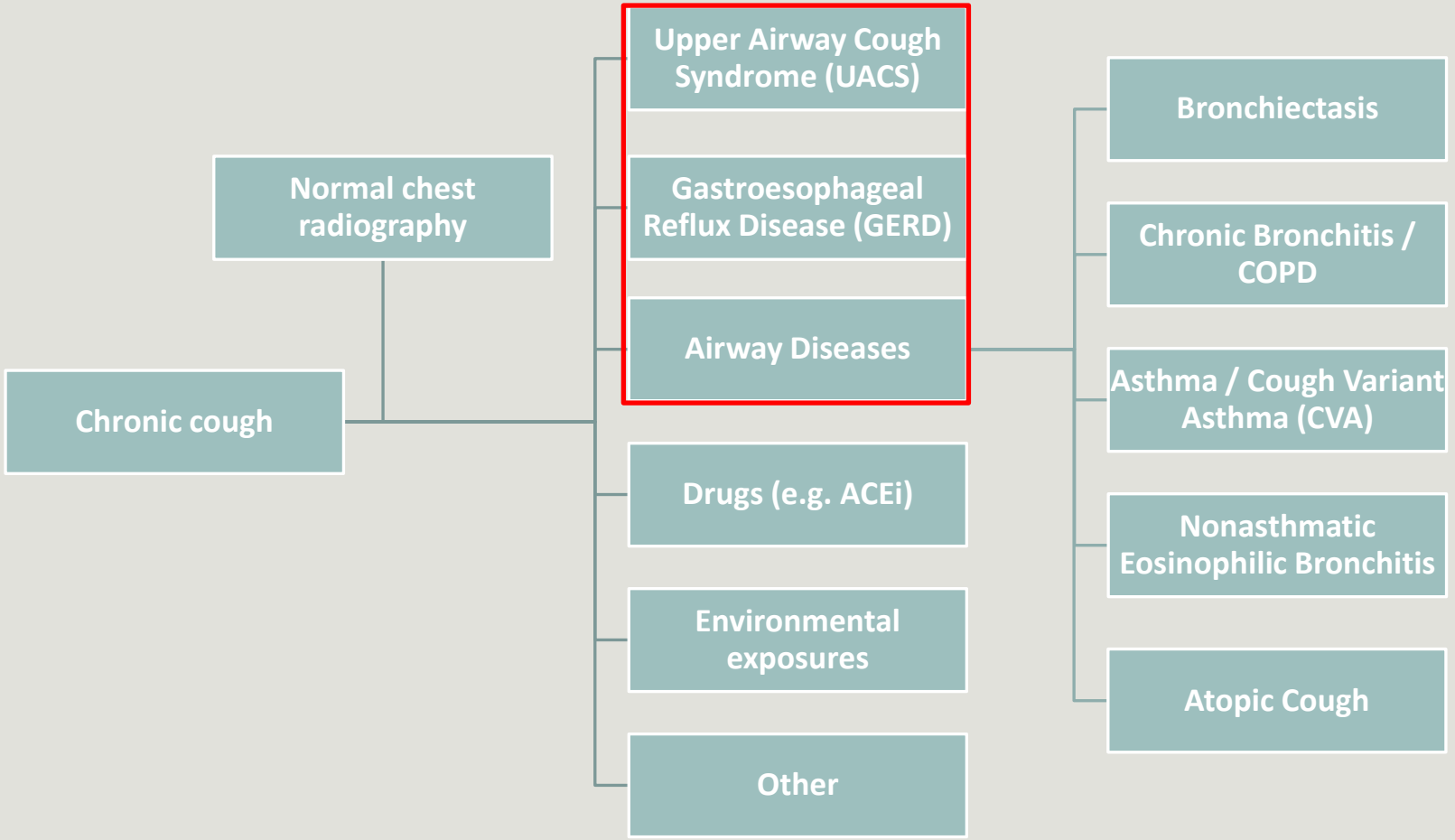


# 만성기침의 진단

**요점**

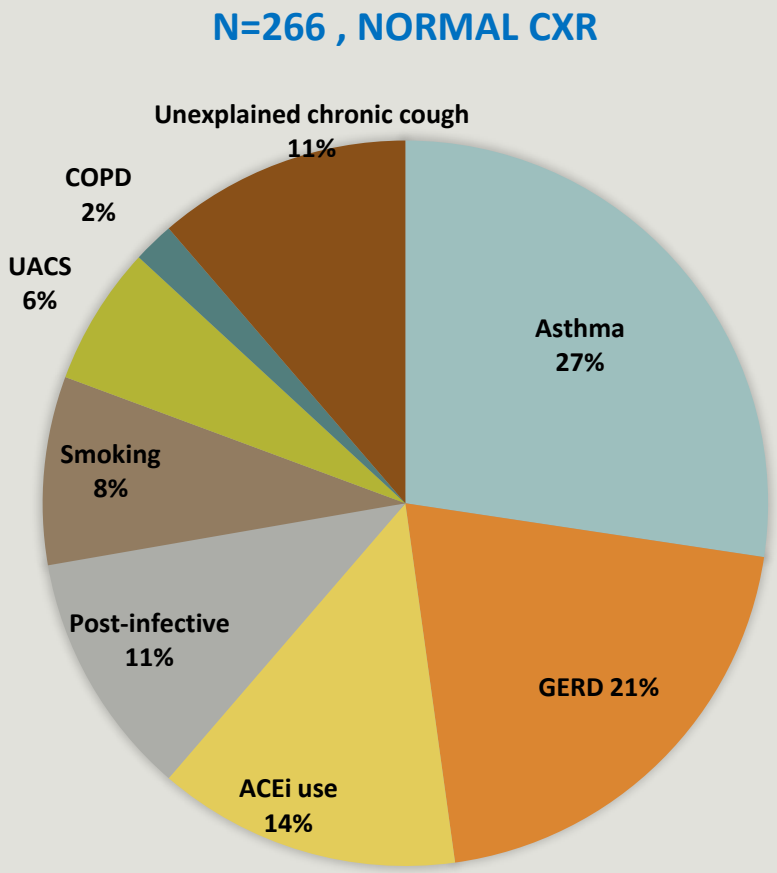
- 8주 이상 지속되는 기침을 만성기침으로 정의한다.
- 흡연력, 동반 증상, 약물력 등의 병력청취는 감별에 도움이 되며 가장 먼저 충분히 확인되어야 한다.
- 상기도기침증후군, 기침형천식, 위식도역류질환 등 장기간 기침을 유발할 수 있는 원인들을 고려하여 관련 검사를 진행한다.
- 검사는 흉부X선을 가장 우선적으로 고려하며, 병원의 실정과 환자의 증상에 따라 순차적으로 시행한다.

# Chronic cough with normal chest X-ray



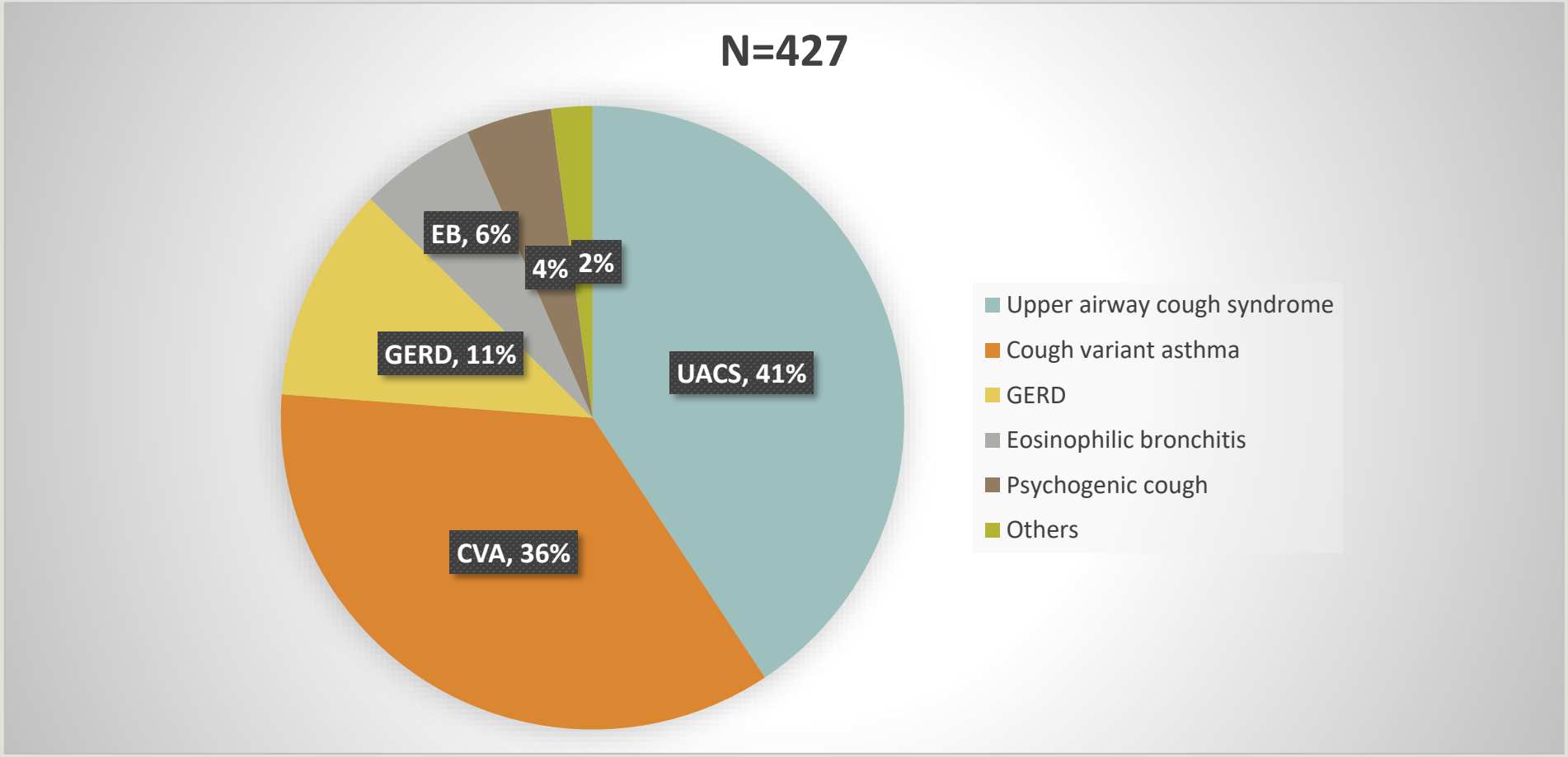

*Am Rev Respir Dis 1981;123:413-417.*
*Thorax 1998;53:738-743.*

# Cause of chronic cough with normal chest X-ray – Primary care center, British



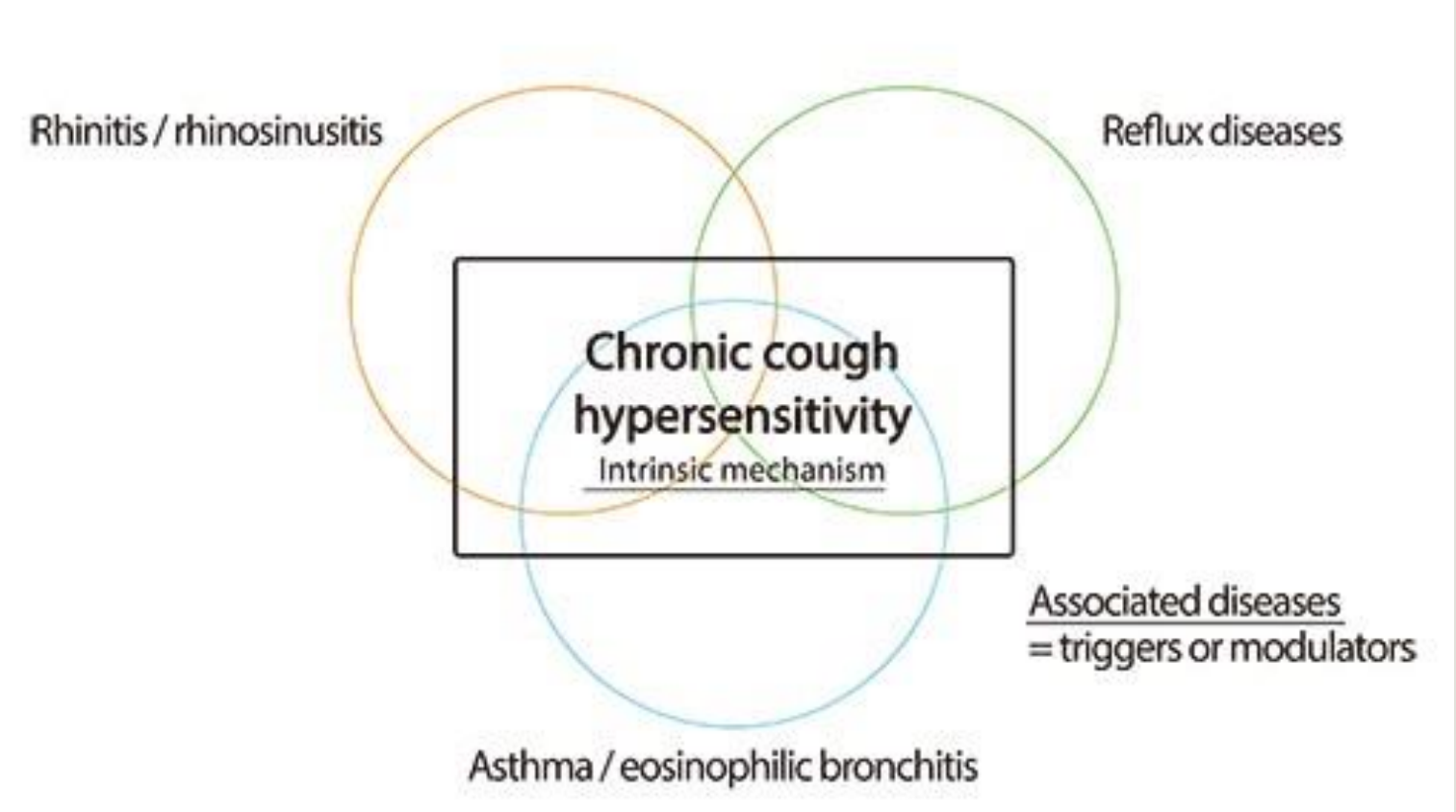

*npj Primary Care Resp. Med. 2016*

# Cause of chronic cough – Multicenter study, Korea




*Tuberc Respir Dis 2020*

# Pathogenesis ; chronic cough hypersensitivity




Airway Inflammation
; inflammatory cell+
; epithelial cell injury
; basal membrane thickening

*Lancet, 371 1364–74, 2008*
*Asia Pac Allergy. 2014 Jan;4(1):3-13.*

# Common cause of Chronic cough

**UACS**

Chronic cough d/t Airway disease

; Asthmatic Vs. non-asthmatic cough

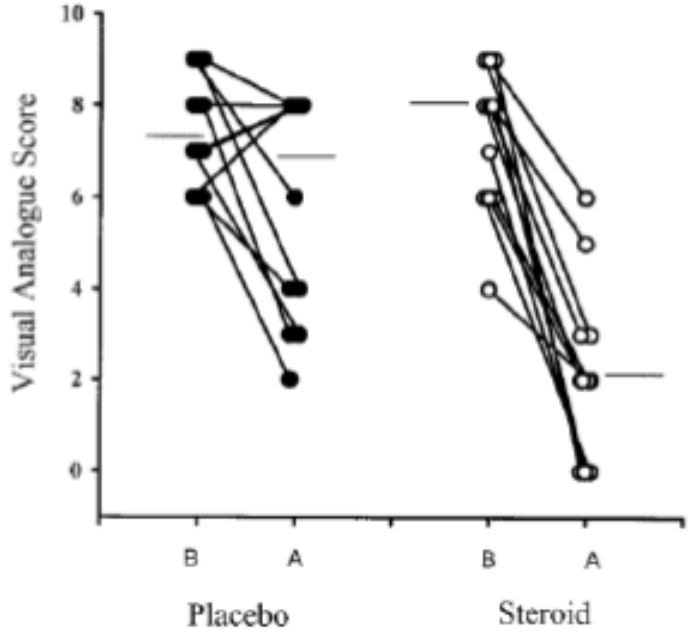
; Eosinophilic vs. non-eosinophilic

Gastroesophageal reflex disease

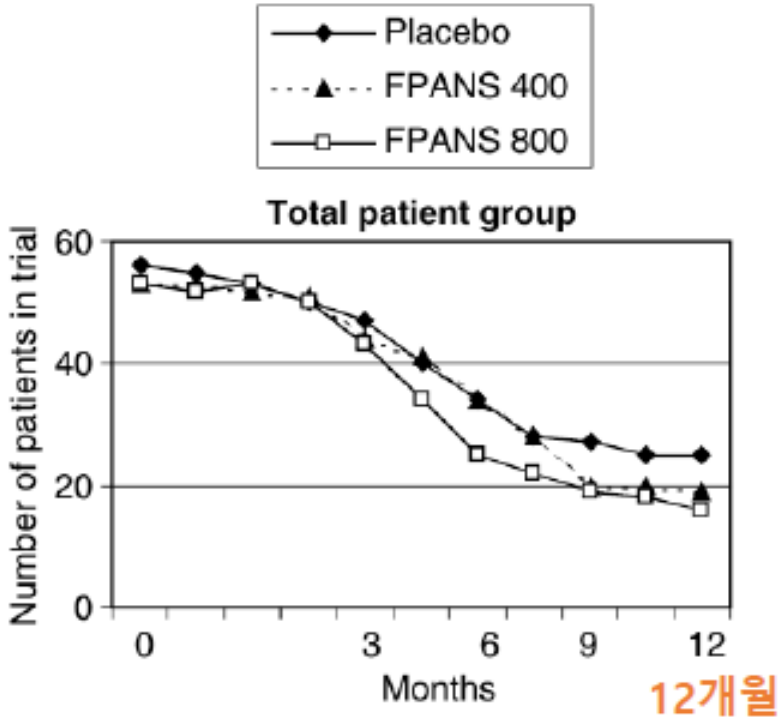
**Unexplained cough**

# Effect of intranasal steroid for chronic rhinosinusitis

항생제를 써도 증상이 지속되는 26명 x 3주




*Laryngoscope*, 112:858–864, 2002




Clin Exp Allergy 2004; 34:1395–1400

# The medical management of rhinosinusitis

**MICHAEL S. BENNINGER, MD, JACK ANON, MD,** and **RICHARD L. MABRY, MD,** Detroit, Michigan, Pittsburgh, Pennsylvania, and Dallas, Texas

**Table 1.** Medical treatment options in rhinosinusitis

| Classification | General treatment measures | Antibiotics | Antihistamines | Steroid nasal spray | Ipratropium bromide nasal spray | Systemic steroids | Immunotherapy |
|---|---|---|---|---|---|---|---|
| Acute adult rhinosinusitis | + | + | ± | – | ± | – | – |
| Subacute adult rhinosinusitis | + | ± | ± | + | + | ± | – |
| Recurrent acute adult rhinosinusitis | + | + | ± | ± | ± | – | ± |
| Chronic adult rhinosinusitis | + | ± | ± | + | + | ± | ± |
| Acute exacerbation of chronic adult rhinosinusitis | + | + | ± | + | + | ± | ± |

+, Beneficial; –, not beneficial; ±, beneficial in some cases.

Otolaryngol Head Neck Surg 1997;117:S41-S49.

# Decrease in VAS ; PND

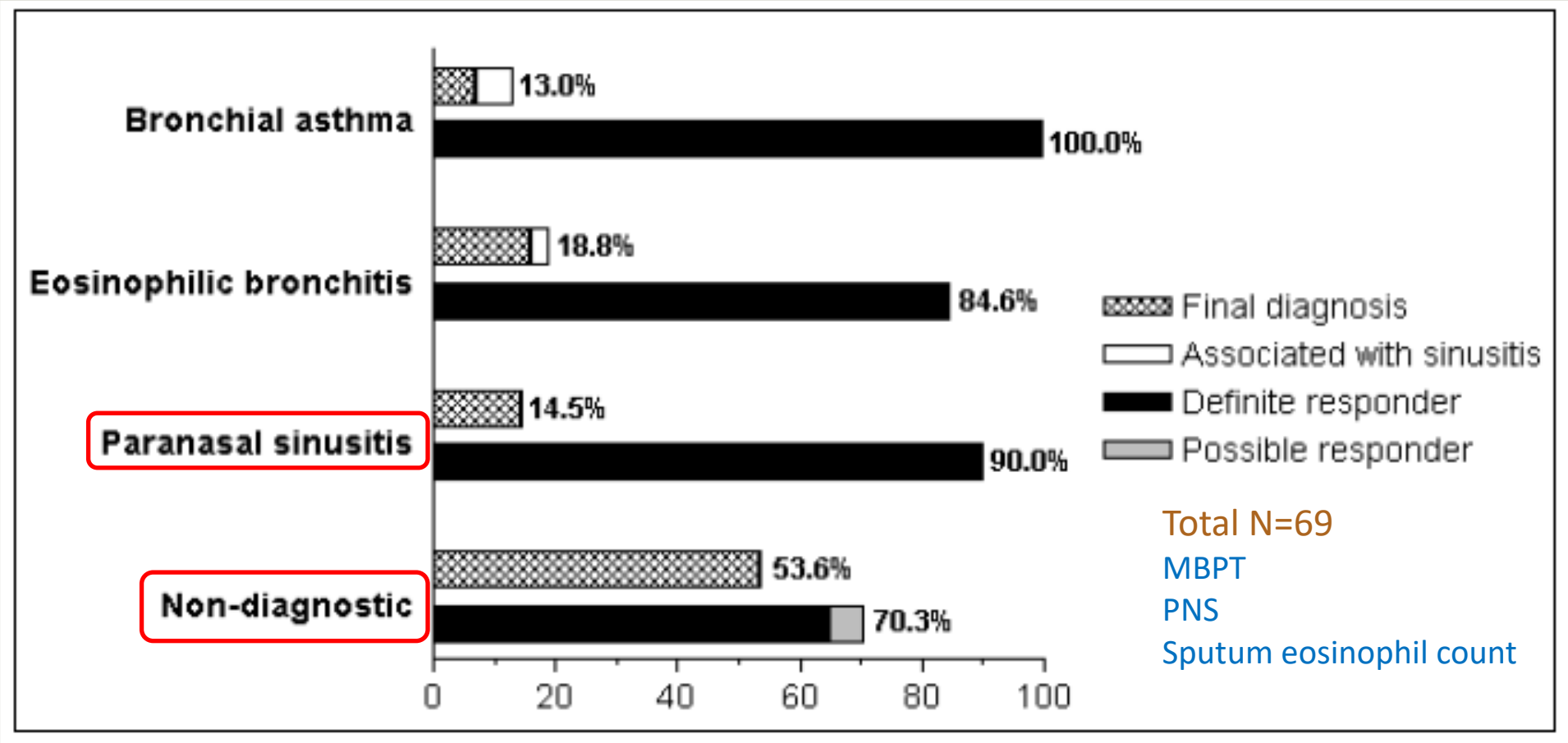
**TABLE III.** Change in cough VAS, noninvasive tests of inflammation, and sputum cells and mediators after inhaled corticosteroids compared with after placebo

| | All causes | PNDS | GERD | CVA | Bronchiectasis | Idiopathic cough |
|---|---|---|---|---|---|---|
| No. | 88 | 30 | 18 | 13 | 9 | 10 |
| Δ Cough VAS, cm | 1.0† (0.4 to 1.5) | 0.9* (−0.0 to 1.8) | 1.2 (0.0 to 2.3) | 1.4* (−0.0 to 2.7) | 0.7 (−0.9 to 2.4) | 0.5 (−1.0 to 2.1) |
| Δ eNO, ppb | −2.1* (−3.6 to −0.6) | 0.0 (−2.0 to 2.0) | −3.1* (−5.8 to −0.5) | −3.3* (−6.5 to −0.2) | −0.9 (−4.5 to 2.7) | −1.4 (−4.8 to 2.1) |
| Δ Exhaled CO, ppm | −0.3* (−0.6 to −0.0) | −0.1 (−0.6 to 0.4) | −0.3 (−1.0 to 0.4) | −0.3 (−1.1 to 0.5) | −0.7 (−1.6 to 0.2) | −0.1 (−1.0 to 0.7) |
| Induced sputum | | | | | | |
| Δ Total cells, × 106 | −1.0 (−7.4 to 7.7) | −1.5 (−11.9 to 9.0) | −4.6 (−12.3 to 3.1) | 3.4 (−7.0 to 13.9) | 5.1 (−6.3 to 16.4) | −2.8 (−15.2 to 9.6) |
| Δ Neutrophils, % | 1.1 (−7.5 to 9.7) | −1.2 (−18.6 to 16.2) | −13.8 (−29.8 to 2.1) | 0.9 (−19.9 to 21.7) | 0.6 (−20.2 to 21.4) | 5.3 (−14.2 to 24.8) |
| Δ Eosinophils, % | −0.7 (−1.8 to 0.3) | −0.0 (−2.0 to 2.1) | −0.1 (−2.0 to 1.8) | −4.6† (−7.1 to −2.1) | 1.5 (−1.0 to 3.9) | 0.1 (−2.2 to 2.4) |
| Δ Lymphocytes, % | −0.1 (−0.2 to 0.1) | 0.0 (−0.3 to 0.4) | 0.1 (−0.3 to 0.4) | −0.3 (−0.7 to 0.1) | −0.1 (−0.5 to 0.3) | −0.1 (−0.5 to 0.3) |

Data are depicted as mean differences (95% CI).
Δ, Change in value after inhaled fluticasone compared with after placebo; *ND*, not detectable.
*$P < .05$,
†$P \leq .001$.

*J Allergy Clin Immunol,2004,113:1063-70*

# ICS response in chronic cough patients (Korea)




**AE**
New respiratory infection 2.2%

Tuberculosis and Respiratory Diseases Vol. 60. No. 2, Feb. 2006

# Efficacy of ICS in treatment of chronic cough (68 UACS, 33 UCC)

ORIGINAL ARTICLE

Korean J Intern Med 2019;34:559-568
https://doi.org/10.3904/kjim.2017.291

Check for updates

KJIM

## Efficacy and predictors of response to inhaled corticosteroid treatment for chronic cough

Ji Young Hong[1,2], Joo-Hee Kim[2,3], Sunghoon Park[2,3], Yong Il Hwang[2,3], Ki-Suck Jung[2,3], and Seung Hun Jang[2,3]

# Methods

INCLUSION CRITERIA

1) Older than 18 years old

2) Chronic cough longer than 8 weeks

3) normal chest X-ray

4) no evidence of asthma by normal metacholine test (a provocation concentration of methacholine 8 mg/mL failed to cause a fall in FEV1 of 20% [PC20] or more)

5) no previous wheezing history

EXCLUSION CRITERIA

1) symptoms suggestive of respiratory infection, such as fever, sore throat, or suppurative nasal discharge in the preceding 8 weeks;

2) use of other drugs that account for the cough, such as angiotensin-converting enzyme inhibitors

3) current treatment that might influence the cough status within the 5 days before enrollment;

4) frequent gastroesophageal reflux symptoms;

5) sputum eosinophil count ≥ 3% ;

The Korean Journal of Internal Medicine Vol. 34, No. 3, May 2019

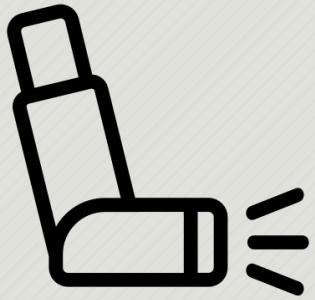
# Methods

OUTCOME MEASUREMENT

- Primary
  - the degree of persistent cough after 2-week treatment
- Secondary outcome measurements
  - drug compliance and adverse events.

TREATMENT

- Inhaled fluticasone propionate 250 μg twice a day by diskus device or
- budesonide 400 μg twice a day by turbuhaler device



# Results

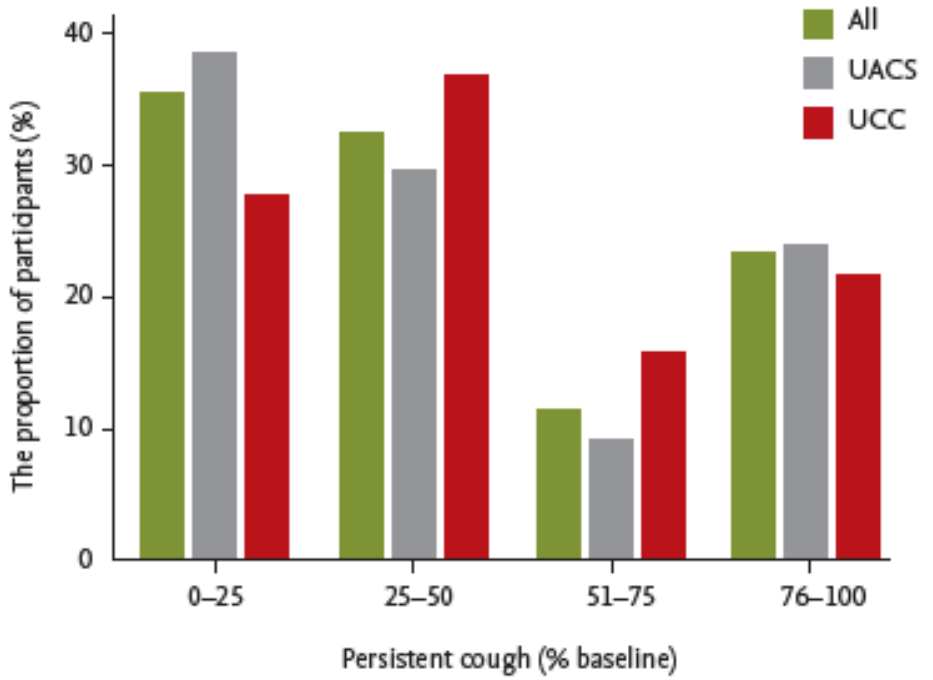



**Figure 1.** The proportion of study participants according to the degree of persistent cough after 2-week treatment with inhaled corticosteroid. A good response to 2-week inhaled corticosteroid treatment was defined as having a persistent cough after treatment that was ≤ 50% of baseline cough frequency level (100%) after treatment. UACS, upper airway cough syndrome; UCC, unexplained chronic cough.

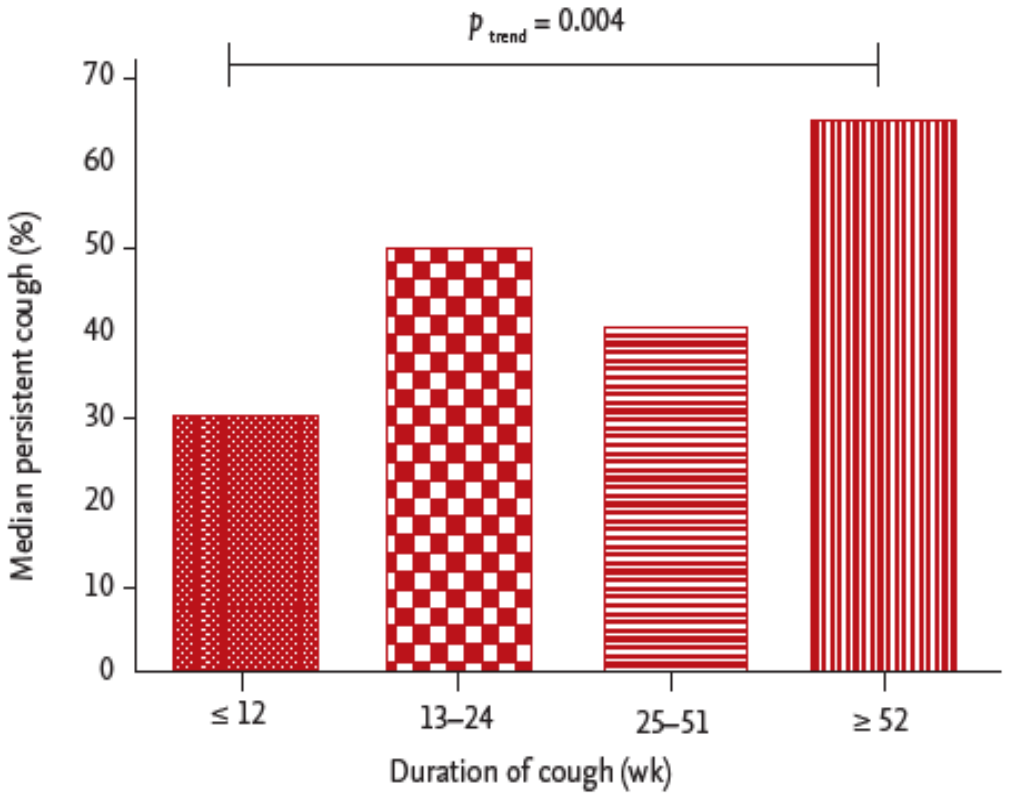



**Figure 2.** Median degree of persistent cough after 2-week treatment with inhaled corticosteroid varied according to duration of cough reported at baseline ($p = 0.004$, linear trend test).

# Adverse events of ICS

Infrequent, mild hoarse voice (5 from UACS, 1 from UCC)

The Korean Journal of Internal Medicine Vol. 34, No. 3, May 2019

# Short course inhaled corticosteroid (ICS) treatment in chronic cough

- Short course inhaled corticosteroid (ICS) treatment has modest efficacy for upper airway cough syndrome and unexplained chronic cough without significant adverse events.
- Patients with short-term cough and cough triggered by cold air exposure experienced a relatively better response to ICS.

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# 단원 6. 상기도기침증후군

## 권고사항

- 상기도기침증후군 환자에서 기침의 호전을 위해 비강분무 스테로이드제 사용을 고려한다 (근거수준: 매우낮음, 권고수준: 약함).
- 상기도기침증후군 환자에서 기침의 호전을 위해 경구 항히스타민제 사용을 권장한다 (근거수준: 매우낮음, 권고수준: 강함).
- 상기도기침증후군 환자에서 기침의 호전을 위해 비충혈제거제를 단독으로 사용하지 않을 것을 권장한다 (근거수준: 전문가의견, 권고수준: 강함).
- 상기도기침증후군 환자에서 기침의 호전을 위해 비강분무 항히스타민제를 사용하지 않을 것을 고려한다 (근거수준: 매우 낮음, 권고수준: 약함).
- 상기도기침증후군 환자에서 기침의 호전을 위해 항생제를 사용하지 않을 것을 권고한다 (근거수준: 전문가의견, 권고수준: 강함).

## 요점

- 상기도기침증후군은 다양한 상기도질환이 원인이 되어 기침을 주증상으로 하는 질환군이다.
- 상기도기침증후군은 증상, 신체검진 소견, 방사선 검사 및 경험적 약물치료에 대한 반응을 종합하여 진단한다.
- 원인 상기도질환이 확인되면 이에 대한 적절한 치료를 시작한다.
- 원인 상기도질환이 확실하지 않을 경우, 1세대 항히스타민제와 비충혈제거제를 경험적으로 투여할 수 있다.

# Common cause of Chronic cough

UACS

**Chronic cough d/t Airway disease**

**; Asthmatic Vs. non-asthmatic cough**

**; Eosinophilic vs. non-eosinophilic**

Gastroesophageal reflex disease

Unexplained cough

# Role of eosinophil airway disease

Cough d/t Airway disease

; Asthmatic Vs. non-asthmatic cough

; Eosinophilic vs. non-eosinophilic

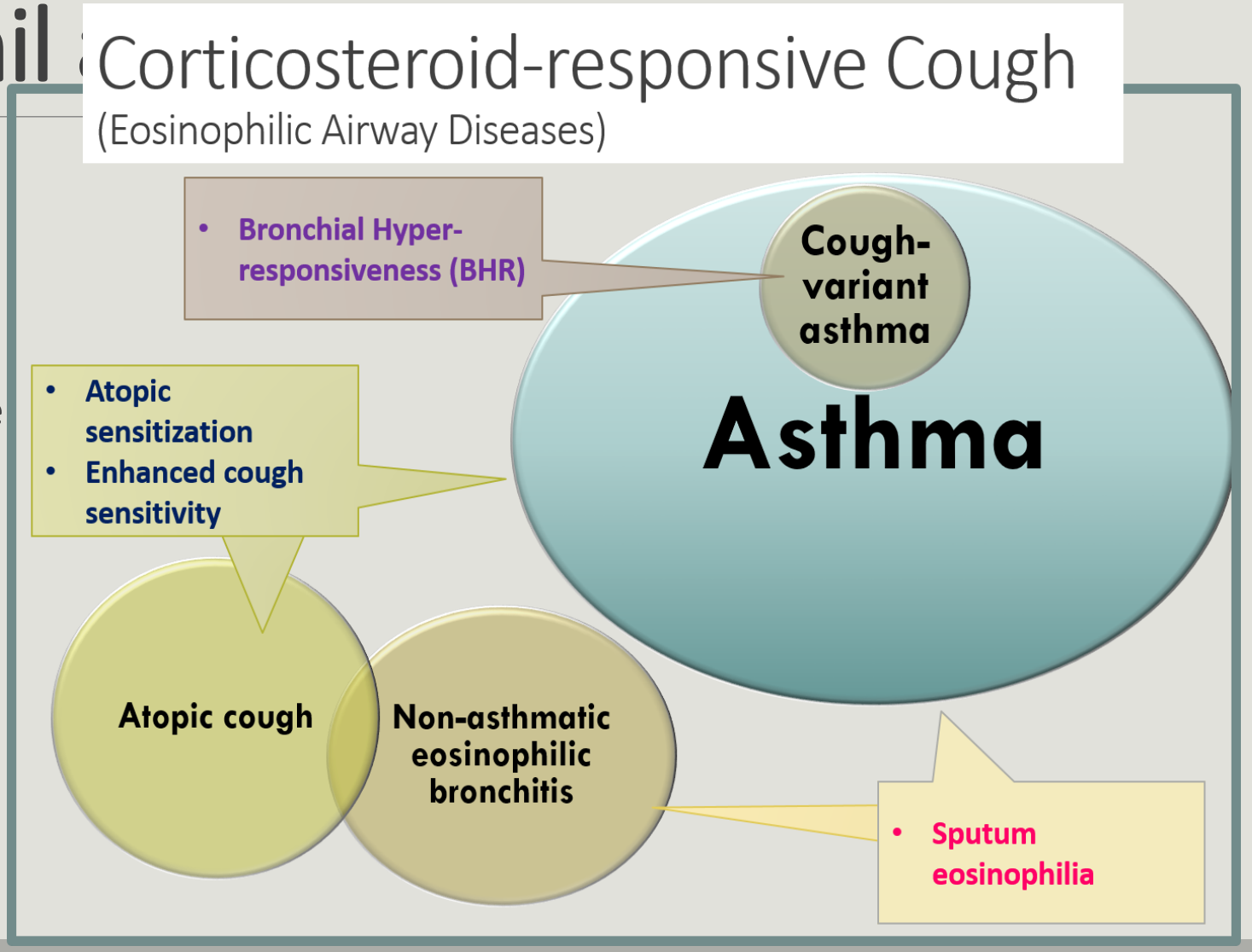
# Role of eosinophil

Cough d/t Airway disease

; Asthmatic Vs. non-asthmatic cough

; Eosinophilic vs. non-eosinophilic

; Steroid responsive vs. non-responsive




*문지용, 기침연구회 심포지엄, 2018*

# Role of eosinophil airway disease

Cough d/t Airway dis

; Asthmatic Vs. non-asthmatic cough

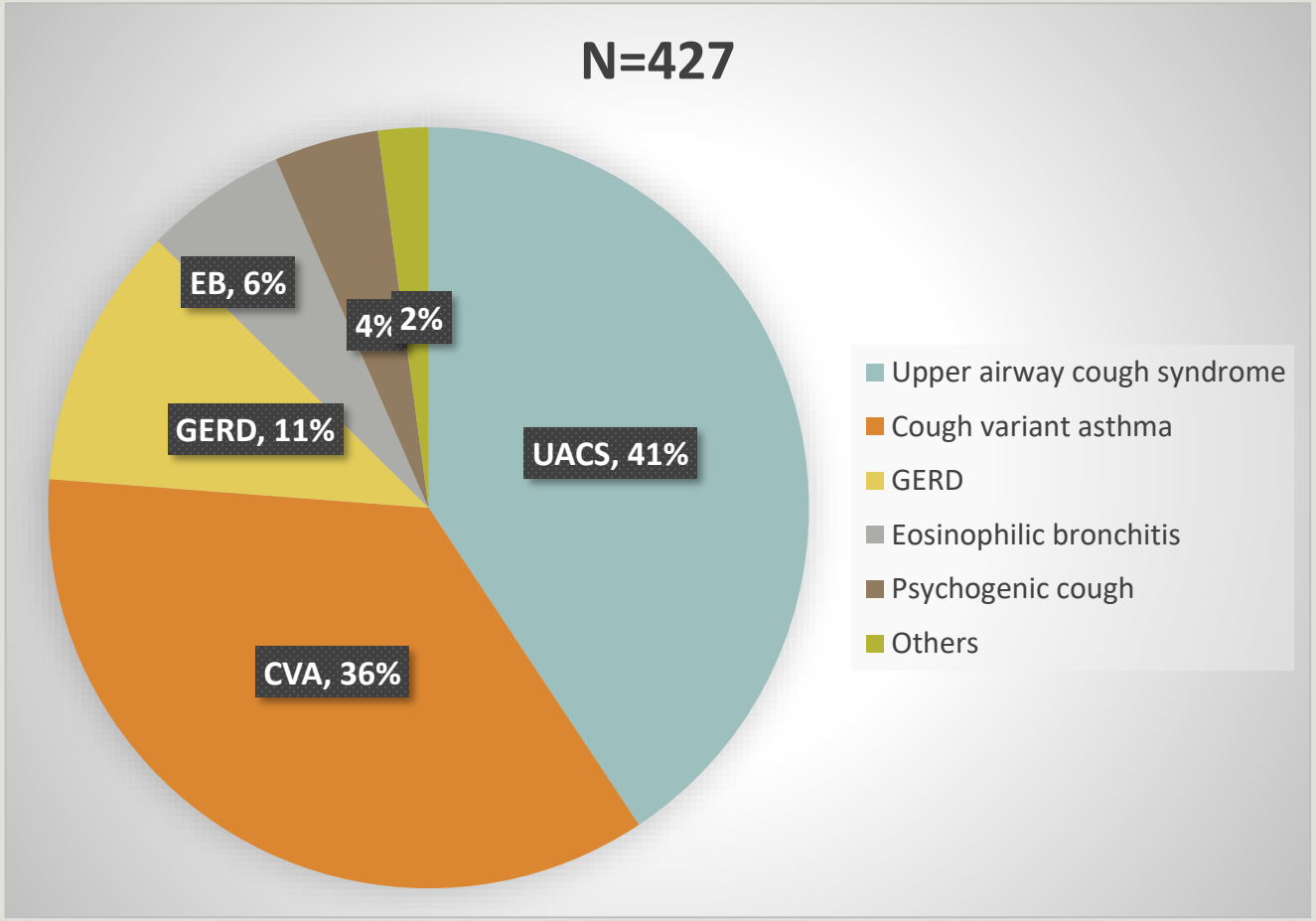
; Eosinophilic vs. non-eosinophilic

; Steroid responsive vs. non-responsive

" A chronic cough responding to a **trial of a steroid therapy**, either parenterally or by inhalation, was thought to indicate the presence of eosinophilic inflammation by the majority of the opinion leaders. "

*(ERJ 2014;44:1132-58)*

# Cause of Chronic cough




| Primary Cause of Cough (N=91) | No. of Patients (%) |
|---|---|
| Rhinitis | 20 (24%) |
| Asthma | 16 (17.6%) |
| Postviral | 12 (13.2%) |
| **Eosinophilic bronchitis** | **12 (13.2%)** |
| Gastroesophageal reflux | 7 (7.7%) |
| Unexplained | 6 (6.6%) |
| COPD | 6 (6.6%) |
| Bronchiectasis | 5 (5.5%) |
| ACE inhibitor-induced cough | 4 (4.4%) |
| Lung cancer | 2 (2.2%) |
| Cryptogenic fibrosing alveolitis | 1 (1.1%) |

*Tuberc Respir Dis 2020*

*AJRCCM 160;2 1998*

# Two Major Types of Chronic Cough

| | Eosinophilic airway diseases | Non-eosinophilic chronic cough |
|---|---|---|
| Age | Any | 40–60 years |
| Sex | Equal | Female predominant |
| Response to corticosteroids | Good | Poor |
| Pathology | Eosinophilic | Non-eosinophilic |
| Exhaled (NO) | Raised | Low |
| Variable airflow obstruction | Present in asthma | Absent |
| Airway hyper-responsiveness | Present in asthma | Absent |

NO=nitric oxide.

PAVORD ID, *ET AL. THE LANCET 2008;371:1375-84.*

# Eosinophilic Airway disease

| | Eosinophilic Bronchitis |
|---|---|
| Symptoms | Cough, sputum |
| Atopy | Same as general population |
| Airway hyperresponsiveness | - |
| Cough reflex hypersensitivity | Increased |
| Response to bronchodilator | - |
| **Response to corticosteroids** | **Good** |
| Sputum eosinophilia(>3%) | Always |
| Bronchial biopsy eosinophilia | Very common |
| Mast cells within airway smooth m uscle bundles | - |

*ACCP Evidence-Based Clinical Practice Guidelines, CHEST 129;1, 116S-121S, 2006*

# Non-asthmatic eosinophilic bronchitis (NAEB)

Prevalence
- Unknown
- 10-30%

Diagnosis
- Require measurement of eosinophilic inflammation

Etiology
- Usually unknown
- Possibility of association with exposure to a common inhaled allergen or occupational sensitizers

# Non-asthmatic eosinophilic bronchitis (NAEB)

Immunopathological features

- Eosinophilia in sputum, BAL, biopsy
- Basement membrane (BM) thickening

Clinical course

- A 10-year follow up evaluation of 12 patients with NAEB suggested that this condition is generally benign and self-limiting. (*Lancet.* 2001; **358**: 1104)
- Progress to BHR

# PICO study for NAEB

Key Question : ***How is cough due to non-asthmatic eosinophilic bronchitis (NAEB) best treated?***

| | |
|---|---|
| **Patient population** | Humans•Adults and adolescents (aged ≥ 13 y) |
| **Intervention** | Treatments of NAEB: inhaled corticosteroids, bronchodilators, theophylline, anti-cholinergic, beta-agonist, cromoglycate, montelukast, leukotriene antagonists, oral corticosteroids, systemic corticosteroids, prednisolone, prednisone, omalizumab |
| **Comparator** | No treatment |
| **Outcome** | Improvement of cough |

*ASTHMA: GUIDELINES AND CONSENSUS STATEMENTS , CHEST 158;1, P68-96, 2020*

| Authors, Year | Setting | Study Design | Treatment Period | Centers (No.) | Subjects (No.) | Age (years, mean ± SD *or* mean range]) | Sex, Male (No.) | Treatment | Control | Outcomes |
|---|---|---|---|---|---|---|---|---|---|---|
| Bao et al, 2015[87] | Outpatient China | Randomized, open-label, parallel-group | 4 weeks | 3 | 65 | T 43.76 ± 9.65<br>C 48.34 ± 12.40 | 36 | Montelukast 10 mg QD and budesonide 200 μg BID | Budesonide 200 μg BID | [a]**CVAS** ↓ both groups with significant between-group difference favoring treatment group.<br>[a]**LCQ** ↑ both groups with significant between-group difference favoring treatment group.<br>Sputum eosinophils ↓ both groups with no between-group difference.<br>Sputum ECP ↓ both groups with significant between-group difference favoring treatment group. |
| Brightling et al, 2000[88] | Outpatient UK | Open-label, observational | 4 weeks | 1 | 11 | 51 (24) median (IQR) | 6 | Budesonide 400 μg BID | n/a | **CVAS** ↓<br>Sputum eosinophils ↓<br>Cough threshold (capsaicin) ↑ |
| Cai et al, 2012[89] | Outpatient China | Randomized, open-label, parallel-group | 4 weeks | 1 | 26 | T 38.6 ± 12.5<br>C 36. 2 ± 12.4 | 9 | Montelukast 10 mg QD and Budesonide 200 μg BID | Budesonide 400 μg BID | **CVAS** ↓ both groups with no between-group difference.<br>Sputum eosinophils ↓ both groups with no between-group difference. |
| Gibson et al, 1995[90] | Outpatient Canada | Open-label, observational | 7 days | 1 | 9 | 48 ± 16 | 4 | Beclomethasone dipropionate 400 μg BID | n/a | **Cough frequency score** ↓<br>Sputum eosinophils ↓ |
| Park et al, 2004[19] | Outpatient Korea | Open-label, observational | 1 month | 1 | 36 | 46.8 ± 12.5 | 17 | Budesonide 800 μg/day or equivalent fluticasone | n/a | **Cough severity score** ↓<br>Sputum eosinophils ↓ |
| Shioya et al, 2004[91] | Outpatient Japan | Randomized, double-blind, placebo controlled | 4 weeks | 1 | 20 | T 35.6 ± 8.1<br>C 39.8 ± 9.2 | 8 | Epinastine 20 mg QD | Placebo | **Cough frequency score** ↓ with epinastine compared with baseline. No change with placebo.<br>Cough threshold (capsaicin) ↑ with epinastine compared with baseline. No change with placebo.<br>NB. Diagnosis of NAEB using sputum cytology was not reported for all subjects. |

*ASTHMA: GUIDELINES AND CONSENSUS STATEMENTS , CHEST 158;1, P68-96, 2020*

# Treatment of chronic cough d/t NAEB

- **Inhaled corticosteroids (ICS)** as first-choice treatment (Grade 2B)
- If response to ICS is incomplete, stepping-up the ICS dose and considering a therapeutic trial of a leukotriene inhibitor (Grade 2C)

*ASTHMA: GUIDELINES AND CONSENSUS STATEMENTS , CHEST 158;1, 68-96, 2020*
*ACCP Evidence-Based Clinical Practice Guidelines, CHEST 129;1, 116S-121S, 2006*

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## 7.2. 호산구기관지염

### 권고사항

- 호산구기관지염 환자에서 기침의 호전을 위해 항류코트리엔제를 사용하지 않을 것을 권장한다(근거수준: 전문가의견, 권고수준: 강함).
- 호산구기관지염 환자에서 기침의 호전을 위해 흡입스테로이드제 사용을 권장한다(근거수준: 전문가의견, 권고수준: 강함).

### 요점

- 호산구기관지염은 기침 외 다른 천식의 증상이나 가역적인 기도 폐쇄의 증거가 없고, 기도과민성이 정상이면서, 기도의 호산구염증 소견이 있는 경우로 정의한다.
- 흡입스테로이드가 주된 치료이다.

*대한결핵및호흡기학회, 개정기침진료지침, 2020*

# Common cause of Chronic cough

UACS

Chronic cough d/t Airway disease

; Asthmatic Vs. non-asthmatic cough

; Eosinophilic vs. non-eosinophilic

**Gastroesophageal reflex disease**

Unexplained cough

# GERD chronic cough

(1) endorsed the use of a diagnostic/therapeutic algorithm addressing causes of common cough, including symptomatic reflux;

(2) advised that although lifestyle modifications and weight reduction may be beneficial in suspected reflux-cough syndrome, **PPIs** demonstrated **no benefit** when used in isolation;

*CHEST **2016**, 150(6), 1341-60*

# Decrease in VAS ; GERD

**TABLE III.** Change in cough VAS, noninvasive tests of inflammation, and sputum cells and mediators after inhaled corticosteroids compared with after placebo

| | All causes | PNDS | GERD | CVA | Bronchiectasis | Idiopathic cough |
|---|---|---|---|---|---|---|
| No. | 88 | 30 | 18 | 13 | 9 | 10 |
| Δ Cough VAS, cm | 1.0† (0.4 to 1.5) | 0.9* (−0.0 to 1.8) | 1.2 (0.0 to 2.3) | 1.4* (−0.0 to 2.7) | 0.7 (−0.9 to 2.4) | 0.5 (−1.0 to 2.1) |
| Δ eNO, ppb | −2.1* (−3.6 to −0.6) | 0.0 (−2.0 to 2.0) | −3.1* (−5.8 to −0.5) | −3.3* (−6.5 to −0.2) | −0.9 (−4.5 to 2.7) | −1.4 (−4.8 to 2.1) |
| Δ Exhaled CO, ppm | −0.3* (−0.6 to −0.0) | −0.1 (−0.6 to 0.4) | −0.3 (−1.0 to 0.4) | −0.3 (−1.1 to 0.5) | −0.7 (−1.6 to 0.2) | −0.1 (−1.0 to 0.7) |
| Induced sputum | | | | | | |
| Δ Total cells, × 106 | −1.0 (−7.4 to 7.7) | −1.5 (−11.9 to 9.0) | −4.6 (−12.3 to 3.1) | 3.4 (−7.0 to 13.9) | 5.1 (−6.3 to 16.4) | −2.8 (−15.2 to 9.6) |
| Δ Neutrophils, % | 1.1 (−7.5 to 9.7) | −1.2 (−18.6 to 16.2) | −13.8 (−29.8 to 2.1) | 0.9 (−19.9 to 21.7) | 0.6 (−20.2 to 21.4) | 5.3 (−14.2 to 24.8) |
| Δ Eosinophils, % | −0.7 (−1.8 to 0.3) | −0.0 (−2.0 to 2.1) | −0.1 (−2.0 to 1.8) | −4.6† (−7.1 to −2.1) | 1.5 (−1.0 to 3.9) | 0.1 (−2.2 to 2.4) |
| Δ Lymphocytes, % | −0.1 (−0.2 to 0.1) | 0.0 (−0.3 to 0.4) | 0.1 (−0.3 to 0.4) | −0.3 (−0.7 to 0.1) | −0.1 (−0.5 to 0.3) | −0.1 (−0.5 to 0.3) |

Data are depicted as mean differences (95% CI).
Δ, Change in value after inhaled fluticasone compared with after placebo; *ND*, not detectable.
*$P < .05$,
†$P \leq .001$.

*J Allergy Clin Immunol,2004,113:1063-70*

# Common cause of Chronic cough

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; Eosinophilic vs. non-eosinophilic

Gastroesophageal reflex disease

**Unexplained cough**

# Idiopathic, Unexplained, Refractory cough

Definition

1) 진단적 검사에서 원인을 찾을 수 없는 경우,

2) 진단적 검사에서 원인을 찾았지만 치료에 내성을 보이는 경우,

3) 진단적 검사에서 원인을 찾지도 못하고, 치료에 대한 내성을 보이는 경우

Pathophysiologic feature

- 기침반사경로의 비정상적 항진
- 기관지점막에 비특이적 염증관찰

**Treatment of unexplained chronic cough: CHEST guideline and expert panel report.**
*Chest 2016;149:27-44.*

# Unexplained chronic cough

2016 CHEST guideline

**4. In adult patients with unexplained chronic cough and negative tests for bronchial hyperresponsiveness and eosinophilia (sputum eosinophils, exhaled nitric oxide), we suggest that inhaled corticosteroids not be prescribed** (Grade 2B).

근거연구?

# Nonasthmatic chronic cough: No effect of treatment with an inhaled corticosteroid in patients without sputum eosinophilia

Marcia MM Pizzichini MD[1], Emilio Pizzichini MD[1], Krishnan Parameswaran MD[2], Lynda Clelland RN[2], Ann Efthimiadis MLT[2], Jerry Dolovich MD[2], Frederick E Hargreave MD[2]

*[1]Respiratory Division (NUPAIVA), Department of Internal Medicine, University of Santa Catarina (UFSC), Florianópolis, Brazil; [2]Asthma Research Group, Departments of Medicine and Paediatrics, St Joseph's Hospital and McMaster University, Hamilton, Ontario*

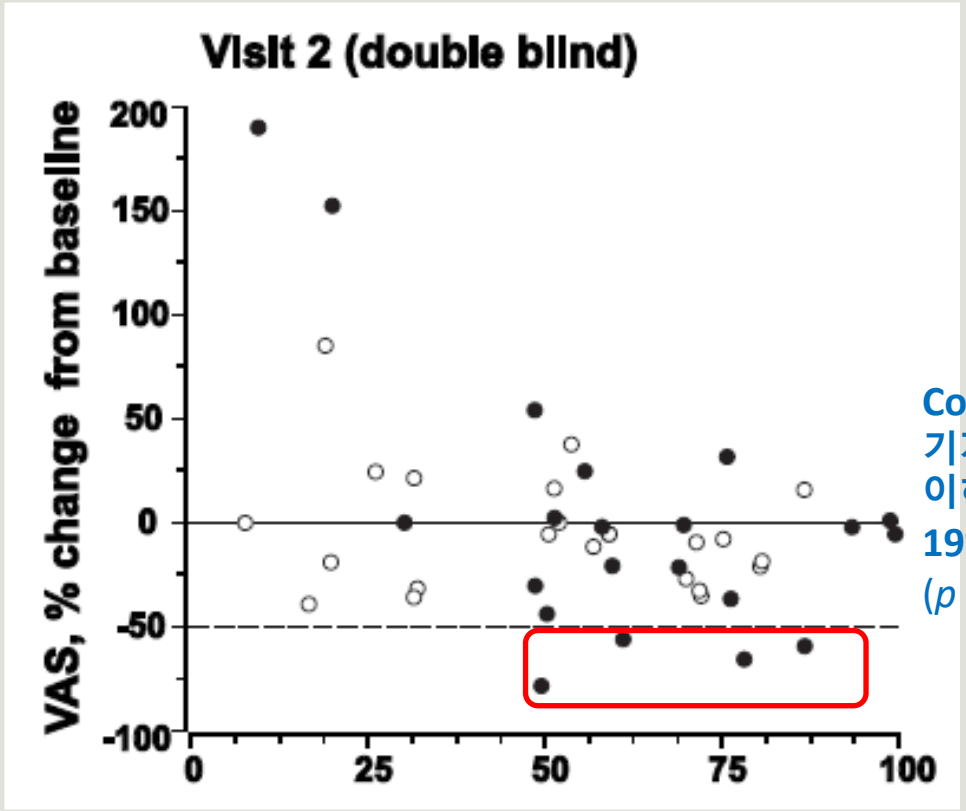
**MMM Pizzichini, E Pizzichini, K Parameswaran, et al. Nonasthmatic chronic cough: No effect of treatment with an inhaled corticosteroid in patients without sputum eosinophilia. Can Respir J 1999;6(4):323-330.**

each treatment period. Cough severity was documented by a visual analogue scale.

**RESULTS**: Thirty-nine (89%) patients produced mucoid sputum after induction on at least one study visit. At baseline, the majority (59%) had a mild elevation in the median pro-

**TABLE 1**
**Subject characteristics in a study of patients with nonasthmatic chronic cough**

| Characteristic | Placebo (n=23) | Budesonide (n=21) |
|---|---|---|
| Age (years)* | 47 (22-72) | 43 (20-75) |
| Sex, male | 10 | 6 |
| Smoking (non [ex]) | 17 (6) | 15 (6) |
| Atopic (n) | 9 | 8 |
| $FEV_1$ (L) | 3.5 (3.0,3.6) | 3.6 (3.9,4.0) |
| $FEV_1$ (% predicted) | 102 (99,103) | 101 (95,106) |
| $FEV_1/VC$ (%) | 80 (77,83) | 82 (78,85) |
| $\Delta FEV_1$ after bronchodilator (% from predicted) | 2.5 (1.2,3.8) | 3.5 (1.2,5.1) |
| $PC_{20}$ methacholine (mg/mL) | >8.0 | >8.0 |
| Previous cough investigation (n) | 14 | 14 |
| Previous cough treatment (n) | 14 | 12 |
| Previous inhaled steroid trial (n) | 4 | 3 |
| Cough duration (years) | 11.8 (4.6,19.2) | 9.8 (5.3,14.2) |
| Cough questionnaire score† | 5.2 (4.6,5.9) | 4.6 (3.7,5.5) |
| Cough VAS (mm)‡ | 51.0 (41,61) | 61.4 (51,72) |




Cough VAS가 기저치 대비 50% 이하로 감소비율:
19% Vs. 0%
($p$ = 0.028)

Can Respir J Vol 6 No 4 July/August 1999

# Unexplained chronic cough

2016 CHEST guideline

**4. In adult patients with unexplained chronic cough and negative tests for bronchial hyperresponsiveness and eosinophilia (sputum eosinophils, exhaled nitric oxide), we suggest that inhaled corticosteroids not be prescribed** (Grade 2B).

**2.** In adult patients with chronic cough, we suggest that patients with chronic cough undergo a guideline/protocol based assessment process that includes **objective testing for bronchial hyperresponsiveness and eosinophilic bronchitis, or a therapeutic corticosteroid trial.**

(Ungraded Consensus-Based Statement)

*CHEST* ***2016****, 149(1), 27-44*

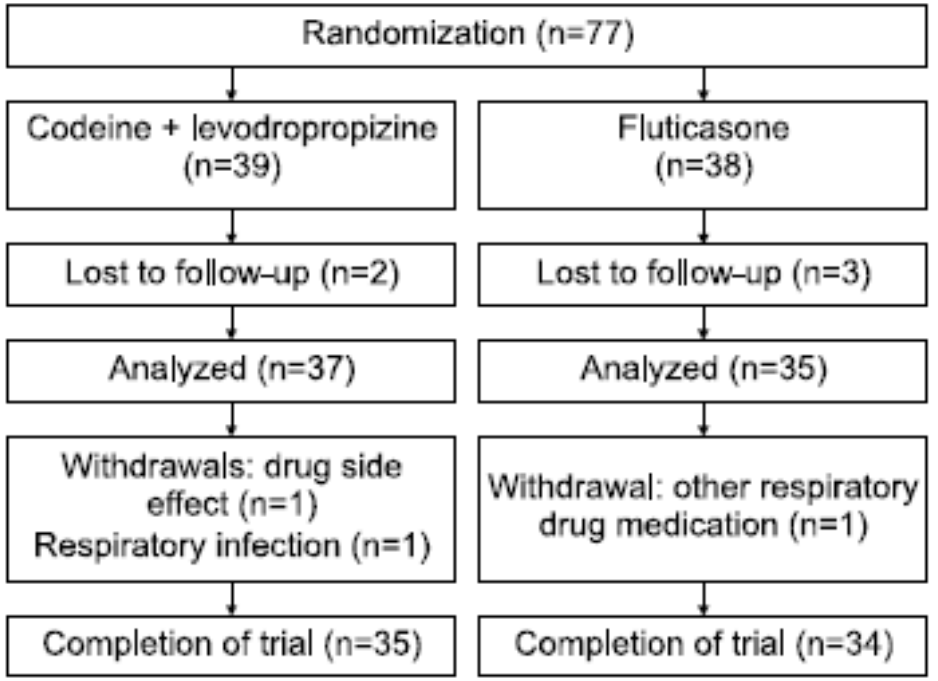
DOI: 10.4046/trd.2009.67.5.422
ISSN: 1738-3536(Print)/2005-6184(Online)
Tuberc Respir Dis 2009;67:422-429


Original Article

# 만성 특발성 기침에 대한 흡입 스테로이드의 치료 효과

[1]한림대학교 의과대학 내과학교실, [2]한림대학교성심병원 호흡기-알레르기내과, [3]한강성심병원 호흡기-알레르기내과
**한보람[1,2], 장승훈[1,2], 김유진[1,2], 박성훈[1,2], 황용일[1,2], 김동규[1,2], 김철홍[1,3], 현인규[1,3], 정기석[1,2]**

- Chronic idiopathic cough ≥ 3 week
- Nonsmoker (<평생 100개피)
- Induced sputum Eo < 1%
- Exclusion
  - Hx of wheezing
  - GERD sx
  - 8주 이내의 fever, pharyngitis, PND sx
  - ACE inhibitor, 3일 이내 antihistamine, antitussive
- Inhaled fluticasone vs. codeine + levodropropizine for 2 week
- Hx taking/PE/CPA/PNS/induced sputum/PFT/MBPT



# Treatment effect and AEs

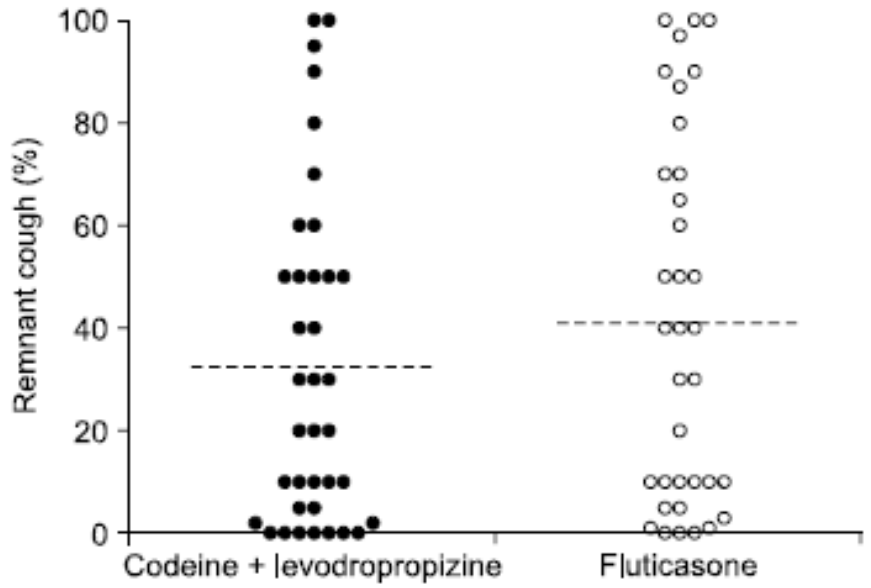



Figure 2. Remnant cough after two-week treatment. Remnant cough (% baseline) were 32.4±32.0% in the codeine+levodropropizine group and 41.0±35.8% in the fluticasone group (p=0.288). Dashed lines represent the mean.

Table 3. Summary of adverse events

| Adverse events | Codeine+Levodropropizine (n=37) | Fluticasone (n=35) |
|---|---|---|
| Epigastric pain, n (%) | 2 (5.4%) | 0 (0.0%) |
| Dizziness, n (%) | 1 (2.7%) | 0 (0.0%) |
| Drowsiness, n (%) | 3 (8.1%) | 0 (0.0%) |
| Headache, n (%) | 2 (5.4%) | 0 (0.0%) |
| Nausea, n (%) | 1 (2.7%) | 0 (0.0%) |
| Hoarseness, n (%) | 0 (0.0%) | 1 (2.9%) |
| Respiratory infection, n (%) | 1 (2.7%) | 0 (0.0%) |
| Total, n (%) | 9 (24.3%)* | 1 (2.9%) |

*One patient simultaneously had drowsiness and headache.

# 2wks of ICS showed efficacy in UCC

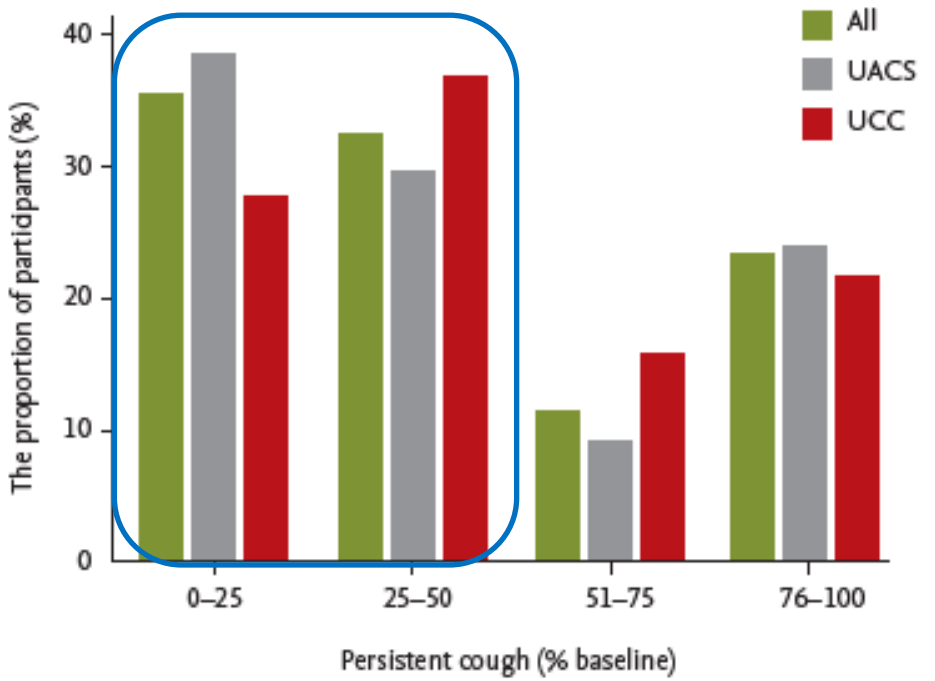
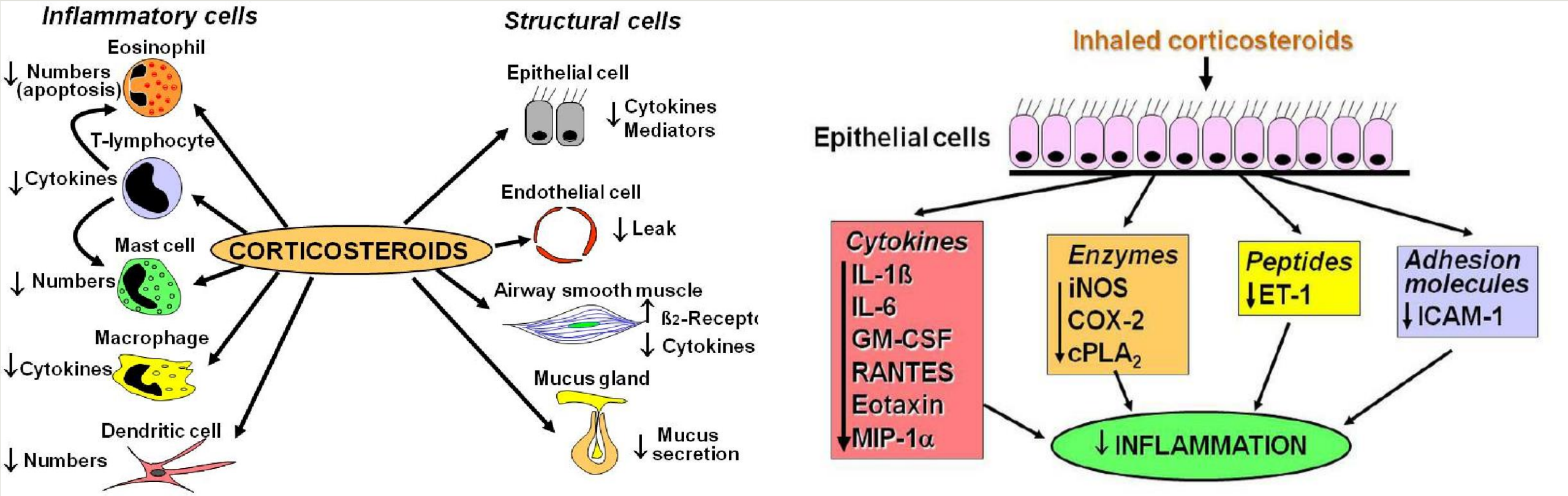



**Figure 1.** The proportion of study participants according to the degree of persistent cough after 2-week treatment with inhaled corticosteroid. A good response to 2-week inhaled corticosteroid treatment was defined as having a persistent cough after treatment that was ≤ 50% of baseline cough frequency level (100%) after treatment. UACS, upper airway cough syndrome; UCC, unexplained chronic cough.

# Anti-inflammatory role of steroids in airway




*Pharmaceuticals* ***2010***, *3(3), 514-54*

## Anti-inflammatory effect of ICS in airway inflammation

Lung disease by cigarette smoking; ICS are largely ineffective in reducing neutrophil-mediated inflammation

Nonsmokers may have a heightened baseline cough-reflex sensitivity

Cough duration

# Efficacy of fluticasone on cough: a randomised controlled trial

**B.P. Ponsioen*, W.C.J. Hop#, N.A. Vermue¶, P.N.R. Dekhuijzen+ and A.M. Bohnen***

N=135,
2주 이상 기침
primary care center

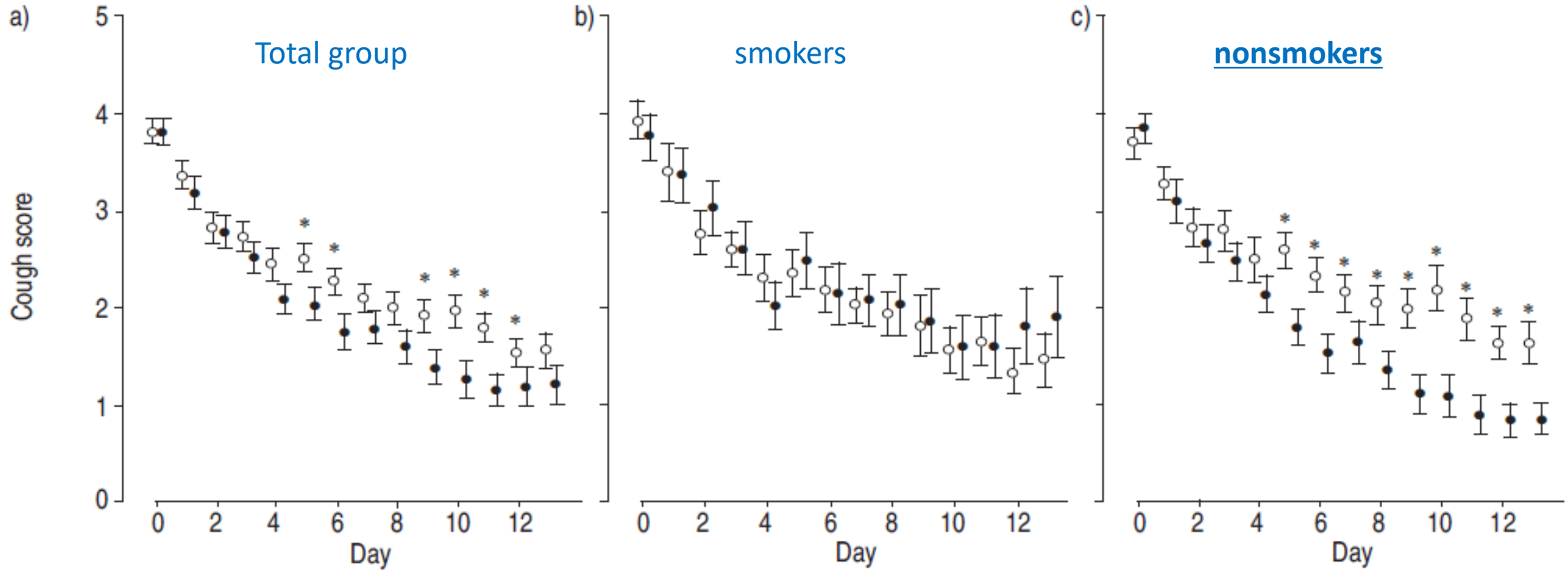



**FIGURE 2.** Mean±SEM of daily cough score (scale 0–6) during the 2-week treatment period. Scores are given for a) the total group, and the subgroups of b) smokers and c) nonsmokers. Day 0 corresponds with baseline cough score. ●: fluticasone; ○: placebo. *: $p<0.05$ placebo compared with fluticasone.

Eur Respir J 2005; 25: 147–152

# Effect of inhaled corticosteroids on symptom severity and sputum mediator levels in chronic persistent cough

Rekha Chaudhuri, MD,[a] Alex D. McMahon, PhD,[b] Lorna J. Thomson, BA,[a]
Kirsten J. MacLeod, BSc,[c] Charles P. McSharry, PhD,[c] Eric Livingston, MRCP,[a]
Anne McKay, MRCP,[a] and Neil C. Thomson, FRCP[a] *Glasgow, Scotland*

Inclusion

- 1년 이상 기침환자 88명 (평균 기침 기간 16.2 yr)
- normal CPA/spirometry

Exclusion

- Any other lung disease
- No steroid within 3 wk
- URI within 6 wk
- ACEi, smoking within year

*J Allergy Clin Immunol,2004,113:1063-70*

# Effect of inhaled corticosteroids on symptom severity and sputum mediator levels in chronic persistent cough

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**TABLE I.** Baseline characteristics of patients with chronic cough

| | All causes | PNDS | GERD | CVA | Bronchiectasis | Idiopathic cough |
|---|---|---|---|---|---|---|
| No. | 88 | 30 | 18 | 13 | 9 | 10 |
| Age, y* | 59.0 (12.7) | 58.8 (12.4) | 67.7 (4.4) | 48.5 (17.3) | 64.0 (9.6) | 57.7 (8.7) |
| Sex, male/female | 32/57 | 12/18 | 8/10 | 2/11 | 3/6 | 4/6 |
| Duration of cough, y | 16.2 (16.1) | 18.6 (17.4) | 14.9 (15.8) | 13.6 (9) | 17.8 (19.4) | 13.9 (18.6) |
| Baseline cough VAS, cm | 4.1 (2.0) | 3.9 (2.3) | 3.9 (1.9) | 4.7 (2.1) | 4.3 (1.7) | 4.4 (2.2) |
| Exsmokers, n | 35 | 13 | 8 | 4 | 4 | 4 |
| Years quit smoking | 19.7 (12. 9) | 20.7 (13.7) | 21.6 (13.9) | 7.1 (8.9) | 20.3 (6.9) | 25.8 (16.4) |
| Pack-years smoked | 14.8 (15.8) | 10.0 (13.1) | 24.7 (19.9) | 14.6 (24.4) | 20.3 (8.7) | 7.4 (7.0) |
| Previous inhaled corticosteroids, n (%) | 48 (55) | 15 (50) | 8 (44) | 6 (46) | 6 (67) | 6 (60) |
| $FEV_1$, L | 2.6 (0.8) | 2.7 (0.8) | 2.4 (0.6) | 2.4 (1.0) | 2.1 (0.8) | 2.9 (0.9) |
| $FEV_1$, % predicted | 94 (16) | 96 (12) | 94 (15) | 86 (24) | 88 (12) | 101 (13) |
| Total serum IgE, IU/L | 96 (195) | 61 (72) | 110 (162) | 32 (35) | 75 (99) | 168 (419) |
| Positive specific IgE level, n (%) | 18 (21) | 4 (13) | 4 (22) | 4 (33) | 1 (14) | 4 (13) |

*J Allergy Clin Immunol,2004,113:1063-70*

**TABLE II.** Baseline values of exhaled gases, sputum cell counts, sputum mediators, and blood counts in subjects with chronic cough

| | Normal/ cutoff | All causes | PNDS | GERD | CVA | Bronchiectasis | Idiopathic cough |
|---|---|---|---|---|---|---|---|
| No. | | 88 | 30 | 18 | 13 | 9 | 10 |
| Exhaled NO, ppb | 9 | 10.4* (5.7) | 8.9 (3.5) | 10.0 (3.8) | 12.6 (7.6) | 11.2 (3.7) | 8.6 (4.3) |
| CO, ppm | 4 | 3.7 (1.1) | 3.6 (1.0) | 3.7 (1.4) | 3.4 (0.9) | 3.5 (1.2) | 4.1 (0.9) |
| Induced sputum | | | | | | | |
| Total cell count, × 106 | 8 | 10.4* (9.1) | 10.1 (7.0) | 6.1 (5.6) | 7.9 (4.9) | 21.3* (12.1) | 14.6 (12.9) |
| Neutrophils, % | 53 | 62 (22.9)† | 60.4 (25) | 58.1 (20.6) | 68.1* (21.2) | 81.2 (13)† | 62.7 (26.9) |
| Eosinophils, % | 2 | 1.0 (2.3) | 0.3 (0.4) | 0.4 (0.5) | 2.4 (4.3) | 1.4 (3.3) | 0.3 (0.8) |
| Lymphocytes, % | 3 | 0.2 (0.4) | 0.3 (0.6) | 0.2 (0.4) | 0.2 (0.5) | 0.1 (0.2) | 0.1 (0.2) |
| ECP, ng/mL | 363 (249) | 1082* (891) | 1055 (931) | 1182* (966) | 895 (904) | 1479* (812) | 661 (305) |
| MPO, µg/mL | 5.2 (4.1) | 17.8 (24.6) | 11.6 (19.0) | 16.6 (23.0) | 14.7 (15.8) | 57 (32.2)† | 8.8 (6.0) |
| $PGE_2$, ng/mL | 0.1 (0.2) | 16.0 (10.7)† | 10.2 (6.5)† | 21.0 (14.2)† | 11.5 (7.1)† | 17.5 (8.0)† | 27.9 (10.7)† |
| $LTB_4$, ng/mL | 4.58 (5.4) | 28.2 (12.7)† | 35.3 (13.7)† | 25.3 (14.3)† | 25.9 (10.7)† | 32.7 (8.4)† | 33.3 (6.6)† |
| Cys-LT, ng/mL | 0.3 (0.8) | 1.4 (1.0)† | 1.3 (0.9)* | 1.4 (1.3)* | 1.5 (1.2)* | 1.2 (0.6)* | 1.7 (1.6)* |
| IL-8, ng/mL | 4.8 (2.1) | 29.7 (65.4)* | 9.0 (6.9) | 25.1 (47) | 14.6 (23.1) | 142 (126)† | 12.9 (18.6) |
| TNF-α, ng/mL | 0.02 (0.02) | 1.3 (4.1) | 0.04 (0.1) | 1.0 (2.8) | 0.05 (0.1) | 6.0 (8.1)* | 0.01 (0.0) |
| Blood cell counts, ×109/L | | | | | | | |
| Total white cells | 4.0-11.0 | 7.9 (1.7) | 8.1 (1.4) | 7.7 (1.5) | 7.9 (2.3) | 8.5 (2.2) | 7.5 (1.7) |
| Neutrophils | 2.0-7.5 | 3.97 (1.3) | 3.98 (1.0) | 4.2 (1.1) | 3.6 (1.2) | 4.6 (2.0) | 3.8 (1.7) |
| Eosinophils | 0.04-0.4 | 0.09 (0.1) | 0.09 (0.1) | 0.1 (0.1) | 0.1 (0.1) | 0.1 (0.1) | 0.07 (0.1) |
| Lymphocytes | 1.5-4.0 | 3.43 (1.01) | 3.7 (0.9) | 3.1 (0.9) | 3.8 (1.4) | 3.3 (1.1) | 3.3 (1.1) |

Eosinophil activity marker

Neutrophil activity marker

Realease from neutrophil

Neutrophil chemoattractant

Proinflammatory from mast cell, macrophage

*J Allergy Clin Immunol,2004,113:1063-70*

# The mean percentage change in VAS : 22.3% (95% CI, - 3.5% to 48.2%).

**TABLE III.** Change in cough VAS, noninvasive tests of inflammation, and sputum cells and mediators after inhaled corticosteroids compared with after placebo

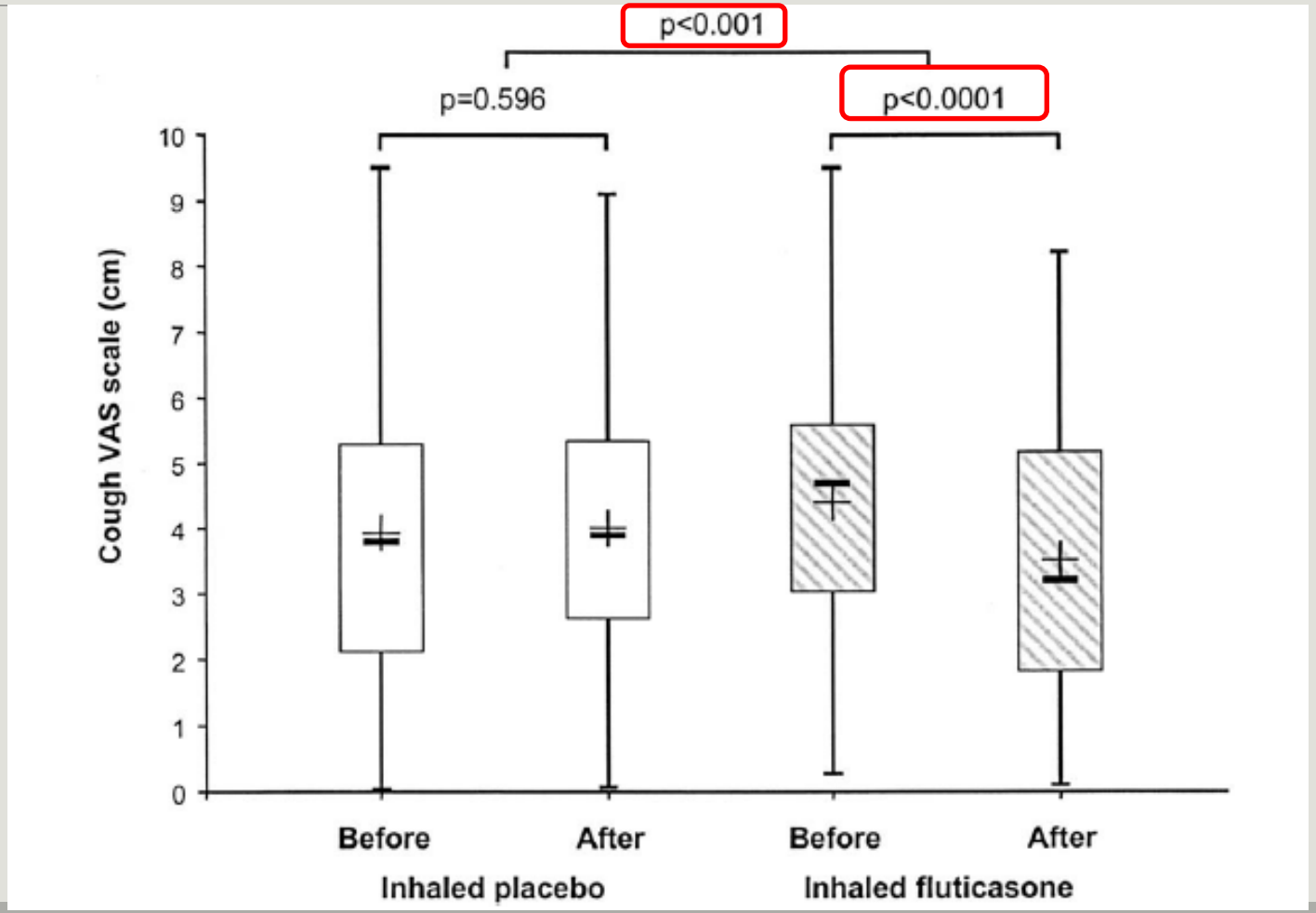
| | All causes | PNDS | GERD | CVA | Bronchiectasis | Idiopathic cough |
|---|---|---|---|---|---|---|
| No. | 88 | 30 | 18 | 13 | 9 | 10 |
| Δ Cough VAS, cm | 1.0† (0.4 to 1.5) | 0.9* (−0.0 to 1.8) | 1.2 (0.0 to 2.3) | 1.4* (−0.0 to 2.7) | 0.7 (−0.9 to 2.4) | 0.5 (−1.0 to 2.1) |
| Δ eNO, ppb | −2.1* (−3.6 to −0.6) | 0.0 (−2.0 to 2.0) | −3.1* (−5.8 to −0.5) | −3.3* (−6.5 to −0.2) | −0.9 (−4.5 to 2.7) | −1.4 (−4.8 to 2.1) |
| Δ Exhaled CO, ppm | −0.3* (−0.6 to −0.0) | −0.1 (−0.6 to 0.4) | −0.3 (−1.0 to 0.4) | −0.3 (−1.1 to 0.5) | −0.7 (−1.6 to 0.2) | −0.1 (−1.0 to 0.7) |
| Induced sputum | | | | | | |
| Δ Total cells, × 106 | −1.0 (−7.4 to 7.7) | −1.5 (−11.9 to 9.0) | −4.6 (−12.3 to 3.1) | 3.4 (−7.0 to 13.9) | 5.1 (−6.3 to 16.4) | −2.8 (−15.2 to 9.6) |
| Δ Neutrophils, % | 1.1 (−7.5 to 9.7) | −1.2 (−18.6 to 16.2) | −13.8 (−29.8 to 2.1) | 0.9 (−19.9 to 21.7) | 0.6 (−20.2 to 21.4) | 5.3 (−14.2 to 24.8) |
| Δ Eosinophils, % | −0.7 (−1.8 to 0.3) | −0.0 (−2.0 to 2.1) | −0.1 (−2.0 to 1.8) | −4.6† (−7.1 to −2.1) | 1.5 (−1.0 to 3.9) | 0.1 (−2.2 to 2.4) |
| Δ Lymphocytes, % | −0.1 (−0.2 to 0.1) | 0.0 (−0.3 to 0.4) | 0.1 (−0.3 to 0.4) | −0.3 (−0.7 to 0.1) | −0.1 (−0.5 to 0.3) | −0.1 (−0.5 to 0.3) |

Data are depicted as mean differences (95% CI).
Δ, Change in value after inhaled fluticasone compared with after placebo; *ND*, not detectable.
*$P < .05$,
†$P \leq .001$.

*J Allergy Clin Immunol,2004,113:1063-70*

# Decreased cough VAS after ICS

- Inhaled fluticasone 500mcg bid
  vs. placebo for 2 week in 88 patients




*J Allergy Clin Immunol,2004,113:1063-70*

Cochrane Library

Cochrane Database of Systematic Reviews

**Inhaled corticosteroids for subacute and chronic cough in adults (Review)**

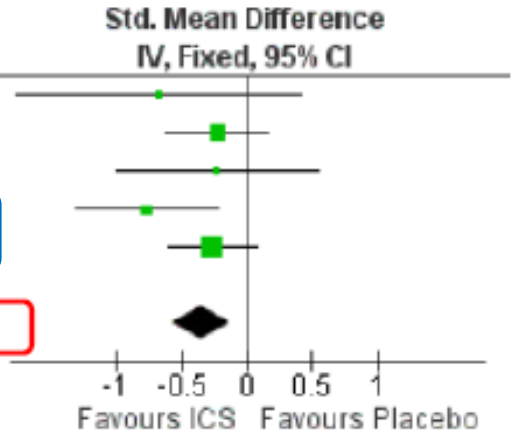
Johnstone KJ, Chang AB, Fong KM, Bowman RV, Yang IA

## Mean reduction in cough severity

| Study or Subgroup | ICS Mean | ICS SD | ICS Total | Placebo Mean | Placebo SD | Placebo Total | Weight | Std. Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Boulet 1994 | -1.15 | 1.56 | 7 | -0.24 | 0.88 | 7 | 3.9% | -0.67 [-1.76, 0.42] |
| Ponsioen 2005 (1) | -2.3846 | 1.76484 | 52 | -2 | 1.66599 | 50 | 30.7% | -0.22 [-0.61, 0.17] |
| Pornsuriyasak 2005 | -1.36 | 1.74 | 14 | -1 | 1.28 | 12 | 7.8% | -0.23 [-1.00, 0.55] |
| Ribeiro 2007 | -1.37 | 1.21 | 44 | -0.54 | 0.7 | 20 | 15.6% | -0.76 [-1.31, -0.21] |
| Rytilä 2008 (2) | -0.44 | 0.669328 | 70 | -0.26 | 0.66933 | 70 | 42.0% | -0.27 [-0.60, 0.07] |
| **Total (95% CI)** | | | **187** | | | **159** | **100.0%** | **-0.34 [-0.56, -0.13]** |

Heterogeneity: Chi² = 3.25, df = 4 (P = 0.52); I² = 0%

Test for overall effect: Z = 3.12 (P = 0.002)




Chronic cough ;

*Cochrane Database Syst Rev 2013;(3)*

# Inhaled Corticosteroids and Placebo Treatment Effects in Adult Patients With Cough: A Systematic Review and Meta-analysis

Seung-Eun Lee,[1†] Ji-Hyang Lee,[2†] Hyun Jung Kim,[3] Byung-Jae Lee,[4] Sang-Heon Cho,[5] David Price,[6] Alyn H. Morice,[7] Woo-Jung Song[2*]

- A total of 9 studies
- Overall ICS treatment effects in cough severity outcomes
  - small-to-moderate (standardized mean difference [SMD], −0.38; 95% confidence interval [CI], −0.54, −0.23)

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# ICS effect on Chronic cough

| Study | Outcome (scale) | Placebo treatment group | | | | ICS treatment group | | | | Therapeutic gain |
|---|---|---|---|---|---|---|---|---|---|---|
| | | No. (%) | Baseline score | Absolute change from baseline (mean ± SD) | Relative change from baseline (A, %) | No. (%) | Baseline score | Absolute change from baseline (mean ± SD) | Relative change from baseline (B, %) | (A-B) |
| Chronic cough | | | | | | | | | | |
| Engel *et al.* (1989)[30] | Cough score (0–3) (at 4 wk)‡ | 10 | 1.79 ± 0.76 | −0.16 ± 0.54 | −8.9% | 8 | 1.48 ± 0.41 | 0.15 ± 0.67 | 10.1% | −19.0% |
| | Cough score (0–3) (at 12 wk) | 10 | 1.79 ± 0.76 | −0.43 ± 0.55 | −24.0% | 8 | 1.48 ± 0.41 | −0.46 ± 0.37 | −31.1% | +7.1% |
| Boulet *et al.* (1994)[22] | Daily cough score (0–10) | 7 | 1.91 ± 0.9 | −0.24 ± 0.88 | −12.6% | 7 | 3.35 ± 2.28 | −1.15 ± 1.56 | −34.3% | +21.7% |
| Pizzichini *et al.* (1999)[23] | Cough severity VAS (0–100) | 23 | 51 ± 24.6 | −3.7 ± 12.1 | −7.3% | 23 | 61.4 ± 24.0 | −7.7 ± 23.7 | −12.5% | +5.2% |
| Ribeiro *et al.* (2007)[28] | Cough severity diary score (0–4) | 20 | 1.5 ± 0.7 | −0.6 ± 0.5 | −40.0% | 44 | 1.39 ± 0.7 | −1.19 ± 0.52 | −85.6% | +45.6% |
| | Cough frequency diary score (0–4) | | 2.1 ± 0.85 | −0.77 ± 0.74 | −36.7% | | 1.98 ± 1.07 | −1.71 ± 0.79 | −86.4% | +49.7% |
| | Cough severity VAS (0–100) | | 93* | −2* | −2.2% | | 94* | −91* | −96.8% | +94.6% |
| Rytila *et al.* (2008)[24] | Cough diary score for morning and evening (combined; 0–3) (at 4 wk)‡ | 60 | 1.39 ± 0.46 | −0.29 ± 0.58 | −20.9% | 61 | 1.42 ± 0.47 | −0.46 ± 0.58 | −32.4% | +11.5% |
| | Cough diary score for morning and evening (combined; 0–3) (at 8 wk) | 60 | 1.39 ± 0.46 | −0.55 ± 0.77 | −39.5% | 61 | 1.42 ± 0.47 | −0.58 ± 0.70 | −40.8% | +1.3% |
| Price *et al.* (2018)[27] | Cough severity VAS (0–100) | 112 | 42.52 ± 25.5 | −11.06 ± 21.05 | −26.0% | 123 | 45.09 ± 28.42 | −19.96 ± 20.89 | −44.3% | +18.3% |

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# Summary
# ICS in treatment of Non-asthmatic chronic cough

- ICS showed efficacy in patients with **UACS**
- ICS is effective in cough d/t **NAEB** without significant AE
- ICS showed efficacy in **Unexplained cough**
- Empirical ICS therapy could be considered in non asthmatic chronic cough


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