Managing chronic cough

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Causes

- **ACUTE (<3 wks)**
  - viral URTI
  - acute bronchitis
  - allergic rhinitis

- **SUBACUTE (3-8 wks)**
  - post infection
  - asthma

- **CHRONIC (>8 wks)**
  - asthma
  - rhinitis/PND
  - GOR
Chronic cough as a ‘heart-sink’ problem

I’m sure I’ve got something serious. What does the future hold? Nobody seems to take this seriously.

I never help any of these patients. Is there really a problem? Why do those cough doctors do so well? Is it because I’m no good?
Quality of life in chronic cough

* Equivalent to patients with severe COPD

Sickness impact profile score (%)
24-hour cough frequency and cough reflex sensitivity in different groups

Problems with the ‘anatomic-diagnostic’ approach

- Absence of clinical trial evidence that interventions against ‘causes’ help
- Lack of clarity on criteria for assigning cough to a specific cause
- No relationship between objective measures of a potential cause and the success of therapy
- No evidence that specific ‘causes’ have different pattern of disease
- Almost all patients are middle aged women
Intrinsic abnormality of cough reflex + Aggravants → Cough
An approach to assessment of chronic cough syndrome

- Quantify the problem
- Is there a major aggravating factor?
- Is there eosinophilic airway inflammation?
- Is there an potential treatable aggravating factor?
- Is there anything rare or esoteric?
- Am I doing all I can to help/reassure the patient?
## Tools used to assess chronic cough

<table>
<thead>
<tr>
<th>Method</th>
<th>Available</th>
<th>Ease of use</th>
<th>Responsive</th>
<th>Useful to compare</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough VAS</td>
<td>✔️ ✔️</td>
<td>✔️ ✔️</td>
<td>✔️ ✔️</td>
<td>✗</td>
</tr>
<tr>
<td>Symptom scores</td>
<td>✔️ ✔️</td>
<td>✔️ ✔️</td>
<td>✔️</td>
<td>✔</td>
</tr>
<tr>
<td>LCQ</td>
<td>✔️ ✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔</td>
</tr>
<tr>
<td>Cough counting</td>
<td>✗</td>
<td>✗</td>
<td>✔️ ✔️</td>
<td>✔</td>
</tr>
<tr>
<td>Cough sensitivity</td>
<td>✗</td>
<td>✗</td>
<td>✔</td>
<td>✔</td>
</tr>
</tbody>
</table>

VAS = Visual analogue score  
LCQ = Leicester Cough Questionnaire
Major aggravants

- ACE inhibitor therapy
- Smoking
ACE-inhibitor associated cough

- 5-10%; Not obviously dose related
- Higher incidence in women and Southeast Asians
- Heightened cough reflex due to increased concentration of tussive mediators (i.e. bradykinin)
- Likely that all users have increased cough frequency
- Temporal association not always present
- Can take up to 2 months to resolve
- ACE-inhibitors should be stopped in all
Smoking and cough

- Active smokers 2-3 times more likely to report chronic cough.
- Passive smokers 1.3-1.6 fold more likely to report chronic cough.
- Dose-response relationship.
- No excess coughing in ex-smokers.
- Little information on time course of improvement in cough after smoking cessation.
# Eosinophilic vs non-eosinophilic chronic cough

<table>
<thead>
<tr>
<th></th>
<th>Eosinophilic</th>
<th>Non-eosinophilic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>Any</td>
<td>Middle aged</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td>Equal</td>
<td>80% female</td>
</tr>
<tr>
<td><strong>Steroid response</strong></td>
<td>Good</td>
<td>Poor</td>
</tr>
<tr>
<td><strong>Exhaled NO</strong></td>
<td>Raised</td>
<td>Low</td>
</tr>
<tr>
<td><strong>Features of asthma</strong></td>
<td>Common</td>
<td>Rare</td>
</tr>
</tbody>
</table>
Cough and eosinophilic airway disease

- Often not overt. Simple ‘asthma’ tests can be normal
- Unusual asthma phenotypes particularly prevalent (i.e. eosinophilic bronchitis)
- Assessment of airway inflammation more helpful than measuring airway responsiveness
- Unlikely to be an important aggravant if no response to prednisolone 30 mg daily for 2 weeks
- Most patients do well with inhaled corticosteroids
Exhaled NO as a means of identifying eosinophilic cough

Assessment: GOR and rhinitis associated cough

- Symptoms and objective evidence of reflux/abnormal motility/rhinitis common in chronic cough population
- Many potential mechanisms for a causal link
- Aggressive treatment trials often disappointing
- Difficulty relating treatment response to objective markers of GOR/rhinitis
- Epiphenomenon or manifestation of global abnormality of upper aero-digestive tract function
- Unlikely to be an important aggravant if no response to 3 months PPI and alginate/nasal corticosteroids
Cough and proton pump inhibitor therapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Proton pump inhibitor Not cured/ No in group</th>
<th>Placebo Not cured/ No in group</th>
<th>Odds ratio (random) (95% CI)</th>
<th>Weight (%)</th>
<th>Odds ratio (random) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ours 1999</td>
<td>7/8</td>
<td>9/9</td>
<td></td>
<td>25.34</td>
<td>0.26 (0.01 to 7.43)</td>
</tr>
<tr>
<td>Kijander 2000</td>
<td>7/9</td>
<td>12/12</td>
<td></td>
<td>28.17</td>
<td>0.12 (0.01 to 2.85)</td>
</tr>
<tr>
<td>Eherer 2003</td>
<td>2/5</td>
<td>4/6</td>
<td></td>
<td>46.49</td>
<td>0.33 (0.03 to 3.93)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>22</td>
<td>27</td>
<td></td>
<td>100.00</td>
<td>0.24 (0.04 to 1.27)</td>
</tr>
</tbody>
</table>

Total events: 16 (PPI), 25 (placebo)

Test for heterogeneity: $\chi^2=0.26$, df=2, $P=0.88$, $I^2=0$

Test for overall effect: $z=1.69$, $P=0.09$

Fig 2 Meta-analysis of primary outcome (clinical failures—that is, patients still had cough at the end of the trial or reporting period), analyses by intention to treat (49 participants included in meta-analysis)

Chang et al. BMJ 2006;332;11-17
Other potential causes of cough

- Infections
- Occupational factors
- Subtle ILD or bronchiectasis
- Rheumatoid arthritis, inflammatory bowel disease
- Genetic cough, associated with Hereditary Sensory Neuropathy type 1 and GOR*
- Cough and Holmes-Aide syndrome**
- Chronic tonsillitis#
- Obstructive sleep apnoea##
- Tic cough
- Post radiotherapy
- Complication of interferon therapy
- As a manifestation of HIV infection

**Kimber et al. J Neurol Neurosurg Psychiatry 1998;65:583-6  
Diffuse panbronchiolitis

- Adult onset productive cough
- Neutrophilic sputum
- Rhinosinusitis
- Crackles and squeaks
- Nodules and tree-in-bud changes on CT
- Often pre-existing airway disease
- Positive sputum cultures (H. Influenzae, Pseudomonas)
- Good response to long-term low dose macrolide antibiotics

\[ FEV_1 \]

1.2

2.7
Unexplained chronic cough

- Around 40% of patients seen in tertiary clinic
- Normal examination and PFT
- Normal CXR / HRCT
- Negative PC20 / induced sputum
- Negative treatment trials for GORD and rhinitis
- Most (80-90%) females aged 45-55
- Association with autoimmune disease (particularly thyroid disease)*
- BAL lymphocytosis and low blood lymphocyte count in 40%

Bronchoalveolar lavage (BAL) differential lymphocyte count (%)

- Normal (n=11)
- Unexplained Cough (n=19)
- Explained Cough (n=14)

Mean (SEM)

History of autoimmune disease or positive autoantibodies

**p = 0.01 ANOVA

Birring et al. Thorax 2003;58:1066-70
The menopause and lung immunity

• Increased BAL CD4+ lymphocytes and CD4/CD8 ratio in BAL from healthy women after menopause
• May lead to amplification of chronic immune responses at this age

Mund et al. Thorax 2001;56:450-5
Predisposed individual

Low grade airway inflammation

Menopause associated change in lung immunity

Amplified inflammatory response

Clinical problem
Helping patients with unexplained chronic cough

- Reassurance: no serious disease found
- If anything a heightened cough reflex is a health advantage
- Longer-term prognosis is probably good
- Speech therapy/physiotherapy input may help
  - Voluntary cough suppression
  - Nose breathing
  - Avoidance strategies
- Better treatments may become available
Gabapentin and chronic cough

- 62 patients with unexplained chronic cough randomly assigned to gabepentin (300 mg tds; n=32) or placebo (n=30) for 10 weeks
- Change in Leicester Cough Questionnaire at 8 weeks was primary outcome
Cough reflex hypersensitivity and P2X3 antagonist

Abdulqawi et al. Lancet 2014
Conclusions

- Assess cough objectively
- Don’t miss important aggravants
- Eosinophilic and non-eosinophilic cough are distinct
- Non-eosinophilic cough probably mainly due to an intrinsic abnormality prevalent in females and worse at menopause
- Treatment confined to identifying and treating aggravants
- Importance of GORD and rhinitis overplayed
- Association with chronic inflammatory conditions
- Accept that many will be unexplained
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