COUGH

Dr.Vishwanath Gella

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Definition & mechanism of cough

- Cough is an act of forceful expiration with the glottis closed followed by sudden explosive release of the pent-up air along with sputum or other irritant matter
- Phases-

1. Rapid inspiration
2. Closure of the glottis
3. Contraction of the abdominal and expiratory thoracic muscles
4. Abrupt increase in pleural and intrapulmonary pressures
5. Opening of glottis and expulsion of burst of air from mouth

- High intrathoracic pressure and high velocity of air
- Offending particles are propelled out
- Sound is produced by setting into vibration airway secretion, tracheobronchial walls and lung parenchyma

Pathophysiology of cough

- Cough receptors- rapid acting receptors (RAR), slow acting receptors (SAR), C fibers, and other cough receptors. Mechanosensitive and chemosensitive.
- Impulses from these receptors are all carried by the vagus nerve
- Stimuli- aspiration, inhalation, accumulation of secretions, post-nasal drip and inflammation

- RARs

1. Dynamic receptors-respond well to inflation, deflation/collapse and bronchospasm
2. Not directly activated by chemical stimuli
3. RAR activation-reflex bronchospasm and mucus secretion through parasympathetic pathways
4. Vagal cooling ⟶ blocks myelinated fibres ⟶ inhibits coughing

- SARs
- Important in Hering-breuer reflex(termination of inspiration and initiation of expiration when lungs are inflated)
- Role in cough still not clear

- C-fibres respond both to chemical and mechanical(high threshold) stimuli

1. Important in airway defensive reflexes
2. Activates parasympathetic pathway
3. Chemoreflex-apnea(followed by rapid shallow breathing), bradycardia & hypotension
4. Stimulation of C-fibres by braydkinin, capsaicin will cause cough, neurokinin antagonists block cough

- Cough receptor(unnamed)- myelinated, respond to mechanical but not to capsaicin, arise from nodose ganglion of the vagus and found in larynx, trachea and bronchi(predominantly the extrapulmonary airways)
- TRPV1-Chemical stimuli(heat,cold, capsaicin, citric acid) stimulate TRPV1(Transient receptor potential vanilloid 1)

common complications of cough

1. Subjective perception of exhaustion
2. Self-consciousness
3. Insomnia
4. Hoarseness
5. Musculoskeletal pain
6. Sweating
7. Urinary incontinence

Types of cough

- Dry cough & productive cough
- Bovine cough- non explosive cough of person who is unable to close the glottis, seen in vagus nerve lesions, associated with dysphonia
- Whooping cough- paroxysms of cough, post-tussive vomiting and inspiratory whooping sound- common in patients with pertussis infection
- Brassy cough- aortic aneurysm

Classification of cough

- Cough classified based on duration

1. Acute- < 3 weeks
2. Sub-acute- 3-8 weeks
3. Chronic->8 weeks

Common cold - URI

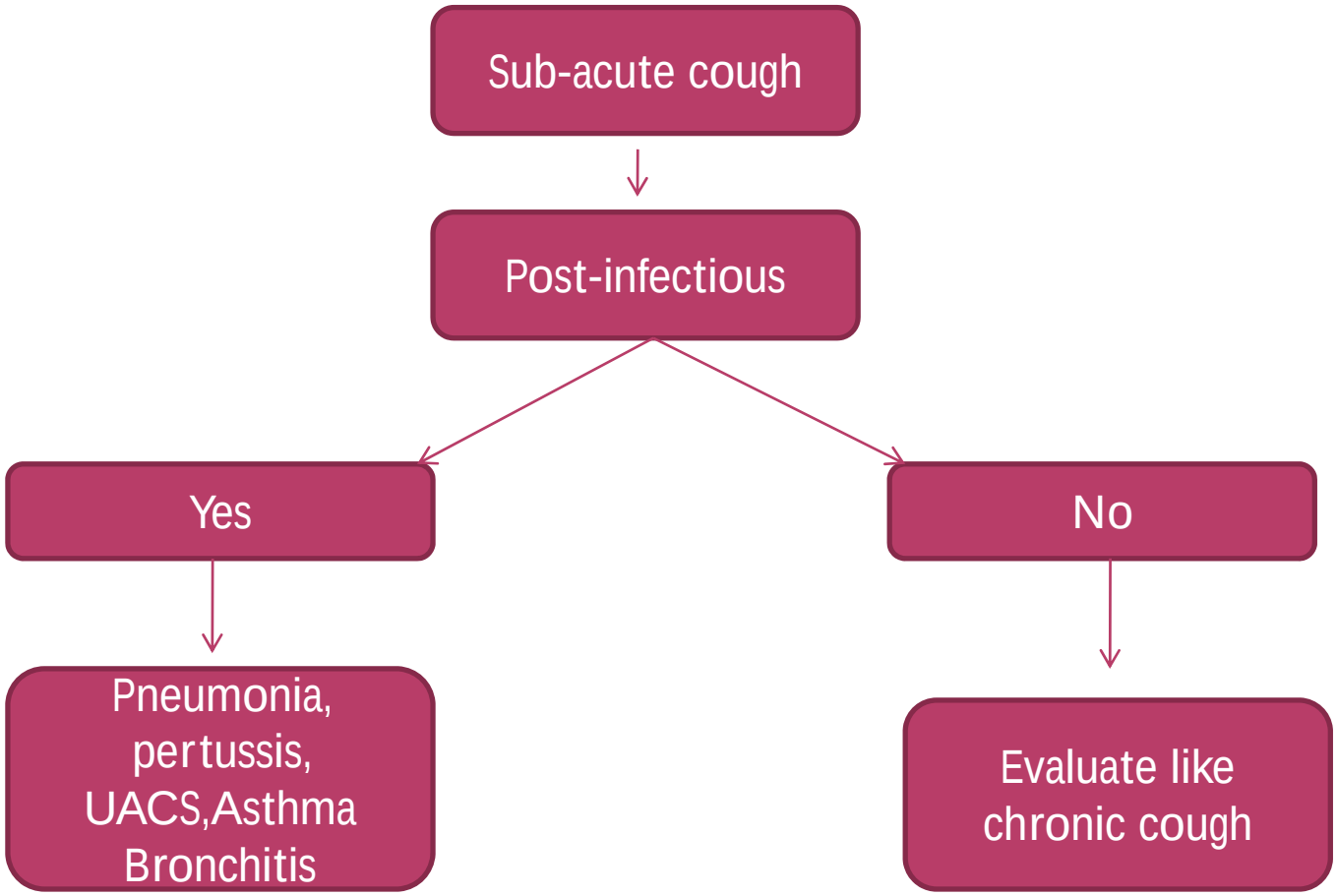
- Most common cause of acute cough
- Cough due to irritation of upper airways
- First generation antihistamine/decongestant therapy, naproxen, topical sympathomimetics and anticholinergics
- Non-sedating antihistaminic agents are not helpful

Cough due to acute bronchitis

- Acute bronchitis- sudden onset of cough, with or without sputum expectoration, and without evidence of pneumonia, the common cold, acute asthma, or an acute exacerbation of chronic bronchitis, usually lasts< 3 weeks
- Most common cause-viral(influenza, parainfluenza and RSV), <10% cases are bacterial,lasts no more than 3 weeks
- Cough-multifactorial, AHR & BDR documented in few individuals

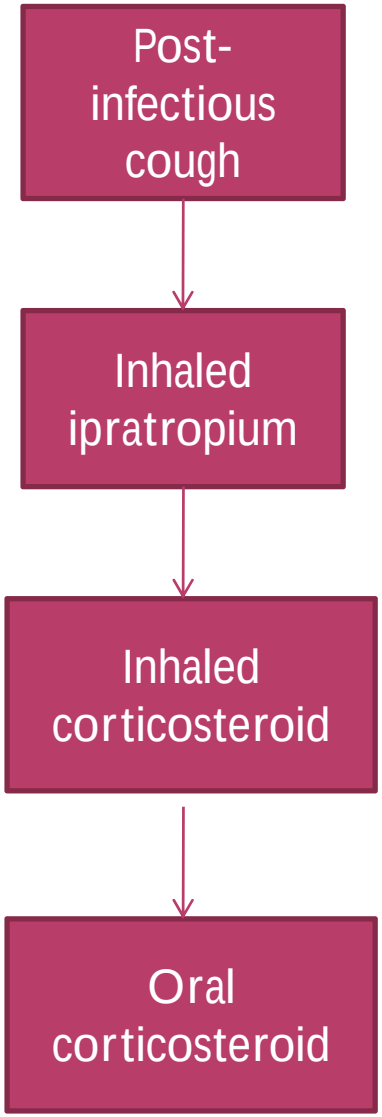
- Distinction between acute bronchitis and pneumonia important
- Temp>38^{o}C, RR>24/min, HR > 100/min and examination findings suggestive of focal consolidation, egophony increase the likelihood of pneumonia(purulent sputum bad predictor)
- Antibiotics routinely not recommended except in cases of pertussis

Approach to sub-acute cough



Post infectious cough

- Def: persisting cough after respiratory infection without other explainable cause, sub-acute(3-8 weeks), resolves spontaneously
- Airway inflammation and disruption of epithelial integrity, mucus hypersecretion and bronchial hyperresponsiveness, impaired mucociliary clearance
- Incidence-11%-25%, 25%-50% in patients with mycoplasma pneumonia and B. pertussis
- Antibiotics no role except in patients with pertussis infection


Post-infectious cough
Inhaled ipratropium
Inhaled corticosteroid
Oral corticosteroid

A Pathogenic Triad in Chronic Cough*

Asthma, Postnasal Drip Syndrome, and Gastroesophageal Reflux Disease

Methods: Seventy-eight nonsmoking patients of both genders who complained of cough for ≥ 3 weeks and had normal findings on plain chest radiographs were studied prospectively. Their histories were obtained, and physical examinations were performed. The diagnostic workup included pulmonary function tests, CT of the paranasal sinuses and chest, carbachol provocation test, fiberoptic rhinoscopy, fiberoptic bronchoscopy, and 24-h esophageal pH monitoring. The final diagnosis depended on clinical, radiologic, and laboratory findings; a successful response to therapy was required for confirmation.

Results: The causes of chronic cough were determined in all patients. Coughing was due to a single cause in 30 patients (38.5%) and multiple causes in 48 patients (61.5%). The five most important causative factors were asthma (46 patients; 58.9%), postnasal drip syndrome (PNDS; 45 patients; 57.6%), gastroesophageal reflux disease (GERD; 32 patients; 41.1%), bronchiectasis (14 patients; 17.9%), and tracheobronchial collapse (11 patients; 14.1%).

Interpretation: Asthma, PNDS, and GERD, alone or in combination, were responsible for 93.6% of the cases of chronic cough. The presence of these three conditions was so frequent that the expression "pathogenic triad of chronic cough" should be acknowledged in specialized literature. It is essential to consider pulmonary and extrapulmonary causes in order to prescribe a successful specific therapy for chronic cough.

(CHEST 1999; 116:279–284)

Upper airway cough syndrome

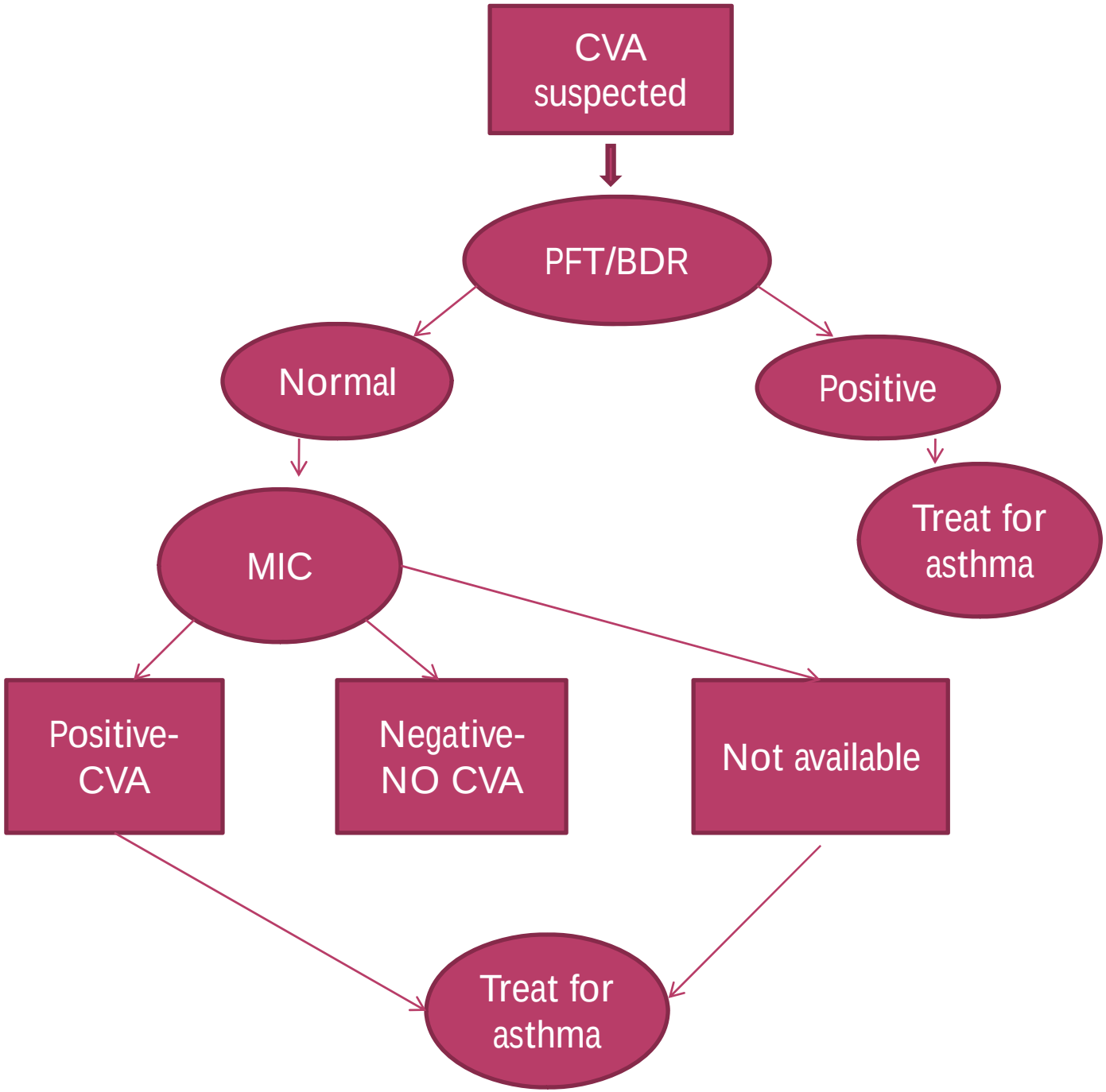
- Previously termed as ‘postnasal drip syndrome’
- Most common cause of chronic cough due to variety of rhino-sinus conditions
- Described as ‘dripping of secretions into throat’, nasal discharge, tickling sensation of throat or frequent throat clearing
- PNDS induced cough –combination of criteria-symptoms,physical examination, radiographic findings and ultimately the response to specific therapy

Treatment of UCAS

- Specific cause apparent- therapy directed at the condition
- Patients with chronic cough if no specific cause apparent- empiric therapy for UCAS in the form of a first generation A/D prescribed before beginning extensive diagnostic w/u
- Resolution of cough in response to specific treatmentis is imp factor-confirming diagnosis of UCAS
- No response to empiric A/D & topical therapy consider sinus imaging

Chronic cough & asthma

- Asthma accounts for 24 to 29% of cases of chronic cough in adult non-smokers with normal CXR
- Cough variant asthma(CVA)-Subset of asthmatics who present with chronic cough without history of SOB or wheezing
- Reason- significantly more sensitive cough reflex, blunted bronchoconstrictor response(less rapid rise of resistance in CVA in MIC)


CVA suspected
PFT/BDR
Normal
Positive
MIC
Treat for asthma
Positive-CVA
Negative-NO CVA
Not available
Treat for asthma

Treatment of cough variant asthma

- Treatment similar to standard treatment for asthma
- Inhaled bronchodilator and corticosteroid mainstay of therapy
- Partial response in1 week and complete response in 8 weeks
- Poor response-

1. Evaluate for sputum eosinophilia
2. Increase dose of ICS
3. Oral LTRA(zafirlukast)
4. Oral corticosteroid

GERD induced chronic cough

- Common cause of chronic cough after UCAS,CVA
- Mechanisms of cough-

1. Aspiration of gastric contents into larynx
2. Stimulation of vagal afferents in oesophagus and laryngo-pharynx
3. Dysmotility

- 24 hour PH monitoring

Treatment

- If other causes have been ruled out empiric treatment with anti-reflux diet, life style modifications and PPI
- Add prokinetic therapy if symptoms persist
- Response is varible(2 weeks- 2 months)
- Refractory cough-consider adequacy of treatment, other additional causes of cough and consider 24 hr esophageal PH monitoring, UGIE or barium swallow

Systematic review and meta-analysis of randomised controlled trials of gastro-oesophageal reflux interventions for chronic cough associated with gastro-oesophageal reflux

A B Chang, T J Lasserson, T O Kiljander, F L Connor, J T Gaffney, L A Garske

Abstract

Objective To evaluate the efficacy of treatment for gastro-oesophageal reflux disease (GORD) on chronic cough in children and adults without an underlying respiratory disease.
Design Systematic review and meta-analysis.
Data sources Cochrane, Medline, and Embase databases, references from review articles.
Included studies Randomised controlled trials on GORD treatment for cough in children and adults without primary lung disease. Two reviewers independently selected studies and extracted paediatric and adult data on primary (clinical failure) and secondary outcomes.
Results 11 studies were included. Meta-analysis was limited to five studies in adults that compared proton pump inhibitors with placebo. All outcomes favoured proton pump inhibitors: the odds ratio for clinical failure (primary outcome) was 0.24 (95% confidence interval 0.04 to 1.27); number needed to treat (NNT) was 5 (harm 50 to ∞ to benefit 2.5). For secondary outcomes, the standardised mean difference between proton pump inhibitors and placebo was −0.51 (−1.02 to 0.01) for mean cough score at the end of the trial and −0.29 (−0.62 to 0.04) for change in cough score at the end of the trial. Subgroup analysis with generic inverse variance analysis showed a significant mean change in cough (−0.41 SD units, −0.75 to −0.07).
Conclusion Use of a proton pump inhibitor to treat cough associated with GORD has some effect in some adults. The effect, however, is less universal than suggested in consensus guidelines on chronic cough and its magnitude of effect is uncertain.

acid causes 21-41% of chronic non-specific cough.[1] Guidelines on chronic cough suggest use of empirical treatment for GOR,[4 5] including a therapeutic trial of three to six months of treatment for GORD.[6] Although laboratory studies have shown a temporal relation between acid in the oesophagus and cough, some studies have shown that the cough resolves only after a mean of 169-179 days after treatment.[6] Other studies have shown that acid GORD is associated with, but is not the cause of, cough.[7]

Current treatments for GORD include conservative measures (diet, positioning, etc), pharmaceuticals (acid suppressants such as histamine H_2 receptor antagonists, and proton pump inhibitors; prokinetic agents such as domperidone, metoclopramide, and cisapride), and surgical approaches (fundoplication). These well established treatments for GOR, however, may not be beneficial for associated cough or may increase respiratory morbidity.[8] We examined the efficacy of treatments for GOR on non-specific chronic cough in adults and children in a systematic review. This review is based on a Cochrane systematic review.[9]

Methods

We used QUOROM guidelines, Cochrane collaboration method, and software (RevMan 4.2) (see bmj.com). Studies in adults and children were eligible if they were randomised controlled trials of any GORD treatment for chronic cough (lasting more than three weeks) where cough was an outcome and not primarily related to an underlying respiratory disorder. We classified the evaluated treatment regimens by type: anti-reflux conservative measures (for example, positioning, diet), H_2 receptor antagonists, proton pump inhibitor, and surgical therapy. Our primary outcome was proportion of participants who were

Non-asthmatic eosinophilic bronchitis(NAEB)

- First described in 1989 as cause of chronic cough which is corticosteroid responsive
- NAEB-

1. Chronic cough
2. No symptoms or objective evidence of variable airflow obstruction
3. Normal airway hyperresponsiveness(i.e, a provocative concentration of methacholine producing a 20% decrease in FEV1 of > 16mg/ml)
4. sputum eosinophilia(3% non squamous cell sputum eosinophil count)

- First line treatment- inhaled corticosteroids
- Avoidance of exposure to causal allergen or sensitizer if identified
- oral corticosteroid -symptoms persist despite high dose ICS
- controversial issues- Duration, type and dose
- Natural history- Persistent symptoms, progression to asthma, fixed airway obstruction and rarely resolution

ACE inhibitor induced cough

- Incidence-5-35%, constitutes 0-3% of cases of chronic cough
- Mechanism: accumulation of protussive mediators bradykinin and substance P, bradykinin induced stimulation of prostaglandin production
- Usually dry cough with tickling or scratching sensation in the throat
- Not dose dependent
- Onset- within hours to months of initiation therapy
- More common in patients treated for congestive heart failure than hypertension

- More common in women, non-smokers and chinese origin
- Discontinuation of the drug is the uniformly effective therapy and should be discontinued irrespective of time of starting therapy
- Desensitisation with rechallenge can be done
- The diagnosis is confirmed by the resolution of cough, usually within 1 to 4 weeks of the cessation of the offending agent, may take upto 3 months
- Alternative- ARBS- low incidence of cough

Cough-ILD

- Cough is a significant clinical manifestation of ILD(approx. >80% patients of IPF)
- Chronic cough- ILD considered after excluding common conditions
- Cough perse secondary to ILD - considered after excluding UCAS, GERD, cough variant asthma
- Mechanism in IPF-Increased sensitivity to substance P and capsaicin & increased sputum levels of NGF,BDNF
- Inflammatory changes of small and large airways(RA), reversible AFL(chronic eosinophilic pneumonia),chronic nasal, sinus and airway disease in churg-strauss syndrome & WG,GERD(scleroderma)

- Cough in sarcoidosis-parenchymal distortion, endobronchial disease(AFL,AHR), extrinsic airway compression
- Hypersensitivity pneumonitis-bronchiolocentric granulomatous inflammation(bronchiolitis), AFL with or without reversibility
- HP- Acute> sub-acute and chronic fibrotic forms
- Steroids for acute disease, symptomatically and physiologically severe disease- long term role still not clear

Non-specific treatment of cough

- Anti-tussive agents- Used when the intensity of cough is elevated and is more than what is required for defending the airways

(1) the etiology of cough is unknown(precluding the use of specific therapy)

(2) specific therapy requires a period of time before it can become effective

(3) specific therapy will be ineffective, such as in patients with inoperable lung cancer

- Drugs acting on muco-ciliary factors
- Peripheral anti-tussive agents- drugs acting on sensory receptors modifying their excitability supressing cough
- Central anti-tussive agents- drugs acting in the brain-stem
- Protussive- any drug that may increase cough clearance (diseases in which thickened or accumulated mucus leads to morbidity)

Drugs affecting muco-ciliary factors

- Drugs affecting mucociliary factors-

(1) Expectorant, increasing mucus volume

(2) Suppression of mucus production

(3) Alteration of mucus consistency

(4) Enhancement of ciliary function

- Numerous agents-Ipratropium, oxitropium, tiotropium, bromhexine, guaifensin, iodinated glycerol, acetylcysteine ,carbocysteine, etc

Drugs affecting muco-ciliary factors

- Ipratropium bromide-Inhalation of ipratropium bromide - shown to suppress subjective measures of cough in patients with URI or chronic bronchitis(blocks efferent limb of cough reflex & decreases stimulation of cough receptors by altering muco-ciliary factors)

- Antihistaminic drugs-H1 antihistamines- effective in the suppression of cough due to URI(mucus production)
- Sedating > non-sedating- greater CNS penetration & anticholinergic activity on M1(both in nasal airways and CNS) & on H1 histaminergic receptors

Drugs That Affect the Afferent Limb of the Cough Reflex

- Peripheral acting drugs- supression of pulmonary afferent activity
- Levodropropizine- acts on c-fibre sensory afferents & reflexly inhibit cough
- In patients with chronic or acute bronchitis, peripheral cough suppressants, such as levodropropizine and moguisteine, are recommended for the short-term symptomatic relief of coughing
- Cough due to lung cancer- sensitive to peripheral acting cough supressants(inhaled sodium chromoglycate, Levodropropizine)

- In patients with cough due to URI, peripheral cough suppressants have limited efficacy and are not recommended for this use
- Benzonotate- peripheral acting antitussive acts by anesthetising stretch receptors in lungs and pleura
- One report showed that a combination of 200 mg of benzonotate + 600 mg of guaiphensin(g) significantly supressed capsaicin-induced cough compared to g alone
- Palliative treatment of cough in advanced cancer

Drugs affecting central mechanism of cough

- central acting supressants – act in the brainstem
- Codeine and dextrometharphan(No sedation potential)

- Drugs affecting the efferent limb of cough reflex- not recommended(Baclofen)
- Drugs affecting skeletal muscles- for cough supression during anesthesia in conjunction with anesthetics(succinylcholine & other NMBs)

Protussive agents

- Enhance cough effectiveness to promote clearance of airway secretions
- Useful in disorders like cystic fibrosis, bronchiectasis, pneumonia, post-operative atelectasis and chronic bronchitis
- Require the motor control system to be intact
- Erdosteine- anti-inflammatory, antioxidant, rheological action on bronchial secretions
- Erdosteine and hypertonic saline are effective agents for enhancing cough clearance in patients with chronic bronchitis

	Central acting	Peripheral	Mucociliary factors	Protussive
Common cold & URI	No	No	A/D, Ipratropium	No
Acute bronchitis	No	Levodropropizine(L), Moguiestine	No	No
Chronic bronchitis	Short term	L,M	No except Ipratropium	Erdosteine 3% saline
Post-infectious	No	No	Ipratropium	No
Lung cancer	No	Benzonotate Sodium chromoglycate& L	No	No

CONCLUSIONS

- Cough is a defence mechanism, can be debilitating
- Most common causes of acute cough are common cold and acute bronchitis
- Post-infectious cough is a common cause of sub-acute cough and antibiotics are not indicated in the treatment
- Consider UCAS, CVA, GERD & NAEB in patients with chronic cough
- Chronic cough may be due to single or multiple causes