Cough and Haemoptysis

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Objectives

• Describe prevalence of cough and haemoptysis in palliative care
• Understand the management of reversible causes
• Describe pharmacological management
• Describe mechanisms of action of antitussive medications
• Be aware of the evidence base (and its limitations) for the management of cough and haemoptysis
Cough

• Rapid expulsion of air from the lungs

• Estimated speed of 100 mph

• Important physiological protective reflex
  • A defense mechanism which helps clear excessive secretions and foreign material from airway

• A common symptom for which patients seek medical attention
  • Pathological when:
    – Ineffective – dry or unproductive
    – It adversely affects sleep, rest, eating or social activities
    – It causes other symptoms such as muscle strain, rib fracture, vomiting, syncope, urinary incontinence

Cough

• ‘Cough’ of all types and duration is the single most common complaint for which patients of all ages seek medical care from primary care\(^1\)
• In the UK prevalence of chronic cough in general population is 12\(^2\)
• In 2013, US- $6.8 billion and UK- $156 million on OTC remedies

Mechanism of Cough Reflex

- The cough reflex has 3 components
- Receptors – located throughout airways
- Afferent sensory limb:
  - Trigeminal, Glossopharyngeal and Vagus nerves (C and Ad fibers)
  - Majority of cough receptors are served by the vagus nerve (through pharyngeal, superior laryngeal and pulmonary branches)
- Central processing center:
  - Cough centre: Located in nucleus tractus solitarius of medulla of brainstem
  - Connected to central respiratory generator
- Efferent limb
  - Vagus to the larynx and tracheobronchial tree
  - Phrenic and spinal motor nerves of C3-S2 supply intercostal muscles, abdominal wall, diaphragm and pelvic floor
Cough Reflex: Receptors

• Located throughout the airway from the pharynx to the terminal bronchioles
• Greatest concentration located in larynx, carina and bifurcation of larger bronchi
• 3 types of receptors are predominant
  – Rapidly adapting receptors (RARs) ‘cough receptors’
    • Respond to mechanical stimuli, cigarette smoke, pulmonary congestion, bronchoconstriction
  – Slowly adapting receptors (SARs)
  – Nociceptors on C-fibers
    • Respond to chemical stimuli, inflammatory and immunological mediators (histamine, bradykinin, prostaglandins, capsaicin, substance P)
• Neuroplasticity such that a hypersensitive response is elicited over time due to the cough itself inducing chronic irritation, inflammation and tissue remodeling.
• Similarities to neuropathic pain with
  – Paraesthesia~laryngeal paraesthesia – abnormal throat sensation/tickle
  – Hyperalgesia~ hypertussia – increased cough sensitivity to irritants
  – Allodynia ~ Allotussia- cough triggered by non-tussive stimuli – talking cold air
Cough Reflex: Medulla

- Brainstem – Medulla- Complex neural network
- Sensory input mediated by relay neurones in the nucleus of the tractus solitarius (NTS) (in dorsomedial medulla)

- Columns of neurones in the ventrolateral and dorsomedial region of medulla control cough

- Different classes of neurones, with multiple receptors, interact in these regions to control
  - Inspiratory and expiratory phase durations of cough
  - Magnitude of motor drive to spinal motorneurones
  - Activation of larynx muscle motorneurones to determine the caliber of the larynx

- Xu et al also showed deep cerebellar nuclei and the inferior olive in brainstem are involved in the production of cough

- Supra pontine processes can also control cough- humans can consciously initiate cough

Categories of Cough

• Wet (productive) or Dry (non-productive)

• Acute / Sub-acute

• Chronic – lasting more than 8 weeks
  – Subtypes categorised by cause
  – Sensory neuropathic cough (SNC)
Cough in Advanced Disease

- Chronic cough - lasting > 8 weeks
- Distressing and debilitating
- Socially disruptive, physically exhausting
- Exacerbate other symptoms – breathlessness, pain, insomnia, incontinence
- Presenting symptom in 65% of lung cancer diagnoses
- High rate of cough is also reported in advanced head and neck cancer
- 115 hospitalized patients with late stage nonmalignant disease - 81% had cough as a symptom
- In last year of life ‘very distressing’ for
  - 22% of people with lung cancer
  - 26% with chronic lung disease

Causes of Cough in Advanced Disease

- Acute cause - infection
- Related to disease
  - Lung metastasis
  - Airway involvement
  - Pleural effusion or pleural involvement
  - SVCO
  - Paraneoplastic cough
- Related to treatment
  - Certain chemotherapies – bleomycin, methotrexate
  - Radiotherapy
  - Drugs for other conditions – ACE inhibitors
- Preexisting condition
  - Asthma, other airways disease
  - Heart failure
  - GORD
Assessment and Investigation

- Assess- Impact on QOL, Severity, time of onset and duration of cough
- Pattern and character of cough
  - Dry cough, barking, short lived – reversible- pharyngitis, tracheobronchitis
  - Dry cough, persisting over weeks
  - Prolonged, low ‘bovine’ cough- left recurrent laryngeal nerve palsy (from thoracic compression) – abductor paralysis of vocal cords
  - Loose cough – secretions
  - Cough with food or after meals – aspiration
- Associated symptoms
  - Nasal discharge – cough from post-nasal drip
  - Sputum
  - Purulent/coloured – infection, Frothy sputum – LVF, Large volumes (>100mls/day) (Bronchorrhoea)- bronchiolo-alveolar cancer, asthma or TB
  - Haemoptysis
  - Dyspnoea – worsening effusion, lung collapse, lymphangitis

Evidence Base for Management of Cough in Advanced Disease\textsuperscript{10,11,12}


Evidence Base for Management of Cough in Advanced Disease$^{10,11,12}$

- Very Limited evidence
  - Small number of studies
  - Total number of participants small
  - Cough not often the primary outcome measure
  - Measurement of cough varies between studies
  - Study population heterogeneous

- Grade of evidence
  - Very few RCTs in cough and advanced illness
  - Most published data is uncontrolled studies or case reports
  - Evidence is Grade 2-4, case control, cohort studies, case reports, expert opinion

- Therefore need to also look at wider evidence
  - Systematic review Chronic Cough Yancy WS et al$^{13}$. Efficacy and tolerability of treatments for chronic cough: a systematic review and meta-analysis. *Chest* 2013;144:1827
  - Clinical Guidelines in Use: CHEST 2016

Dry Cough: Management Strategy

1. Treat the Cause

2. Demulcent

3. Demulcent +/- antitussive
**Dry Cough Step 1: Treat the Cause**

<table>
<thead>
<tr>
<th>Nature of Cough</th>
<th>Possible causes</th>
<th>Potential Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset related to commencing medication</td>
<td>ACE inhibitors</td>
<td>Discontinue or switch to alternative medication</td>
</tr>
<tr>
<td>Rapid onset of cough, associated with SOB</td>
<td>Pleural effusion</td>
<td>Consider drainage/pleurodesis</td>
</tr>
<tr>
<td></td>
<td>Pericardial effusion</td>
<td>Consider drainage</td>
</tr>
<tr>
<td></td>
<td>PE (usually dry cough but may also have haemoptysis)</td>
<td>Consider Ix and LMWH</td>
</tr>
<tr>
<td>Barking cough (short duration)</td>
<td>Pharyngitis/ Tracheobronchitis / Early pneumonia</td>
<td>Humidify room air</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Consider antibiotics</td>
</tr>
<tr>
<td>Bovine Cough</td>
<td>Recurrent laryngeal nerve palsy (intrathoracic compression or disease)</td>
<td>? Consider ENT referral for vocal cord injection</td>
</tr>
<tr>
<td>Hard brassy cough (with or without wheeze/stridor)</td>
<td>Tracheal compression or SVC CO</td>
<td>Consider radiotherapy, steroids, stenting</td>
</tr>
<tr>
<td>Wheezy Cough</td>
<td>Airflow obstruction (Asthma/COPD)</td>
<td>Inhaled therapy, steroids</td>
</tr>
</tbody>
</table>

Step 2: Demulcent

- Demulcents
- Contain soothing substance such as syrup or glycerol
  - Simple Linctus
  - Honey
- High sugar content – stimulates production of saliva and soothes oropharynx
- Sweet taste antitussive by stimulating endogenous opioid release in brain stem\(^\text{14}\)

- No evidence but simple and safe
- Recommended in APM and Molassiotis guidelines

- Dose Simple Linctus BP 5mls tds/qds

\(^{14}\) PCF 5 http://www.palliativedrugs.com/formulary/en/drugs-for-cough.html
Step 3: Demulcent + Antitussive

• Antitussive
  – Peripheral
    • Sodium Cromoglicate
    • Nebulized local anaesthetic
  – Central
    • Opioids and opioid derivatives
      – Codeine, Morphine, Methadone
      – Dextromethorphan (OTC), pholcodine
    • GABA agonists
      – Gabapentin, Baclofen and Diazepam

• Preferred strategy is to use opioids
  – Most evidence and familiarity
Central Antitussive: Opioids

- Mechanism of actions
- Not fully understood, complex and unclear
- Animal studies have shown:
  - Act on opioid receptors
  - Primarily central action on μ receptors in the brainstem NTS
    - In addition both κ receptor agonists can inhibit cough
    - δ receptor shows conflicting responses in animal studies
  - μ receptors presynaptically inhibit excitatory glutamate postsynaptic impulses
- Opioids antagonists do not influence the cough reflex, suggesting endogenous opioids are not critical in the production of cough
- Role that different opioid receptor subtypes have in humans is unclear

Opioids Evidence Base

• Systematic review and APM recommendations in patients receiving palliative care¹¹

• 2 RCTs (small studies < 20 patients in each)
  – Matthys et al – compared dextromethorphan, codeine and placebo
    • Both significantly more effective than placebo
    • Dextromethorphan preferred
  – Sevelius et al – different doses of codeine v placebo for 4 days
    • Reduction in cough counts of between 29-67% in six hours post codeine dose
    • No dose relationship

• 2 uncontrolled studies
  – Homsi et al – reduction in cough frequency with hydrocodone in patients with advanced cancer
  – Luporini et al – significant reduction in cough severity in patients with lung ca with dihydrocodeine

• Lack of trials with morphine or head to head trials of different opioids

Opioid Evidence Base

• Systematic review and APM recommendations in patients receiving palliative care

• 2 other trials considered in development of recommendations

• Morice et al - RCT in a regional cough clinic
  – Patients excluded if had significant lung disease
  – 27 patients randomised to Morphine 5mg bd for 4 weeks or placebo
  – Morphine arm showed a significant reduction (p<0.01) by 40% in daily cough scores from baseline (after 1 week)

• Smith et al – RCT cross-over study
  – 21 patients given Codeine 60mg or placebo in random order
  – No significant difference between codeine and placebo in cough symptom score, VAS

• Overall data on Codeine conflicting
• Recommend Morphine in preference to Codeine or other opioids

Morice A et al. Opiate therapy in chronic cough. *A J Respir Crit Care Med* 2007; 175: 312-315
Opioids Evidence Base

• In absence of data specifically derived from palliative care populations
  – Extrapolate from patients with chronic cough from a variety of conditions

• Yancy WS et al. Efficacy and tolerability of treatments for chronic cough: a systematic review and meta-analysis. *Chest* 2013;144:1827

• Treatment of unexplained chronic cough: CHEST guideline and expert panel report confirm evidence for morphine.

Yang et al Systematic review

- 49 trials (3067 patients) comparing 68 therapeutic comparisons
- 8/11 trials comparing opioids to placebo found opioids more effective
  - Decreased cough frequency and severity
  - Improvement in QoL
  - Meta-analysis: Moderate effect size for severity and rate of cough
  - SMD cough severity 0.55 (95%CI 0.38-0.72), frequency 0.57 (95%CI 0.36-0.91)
- 4/6 trials of Dextromethorphan
  - Opioid derivative and NMDA antagonist
  - Ingredient in most OTC cough syrups
  - More effective than placebo at reducing cough severity and frequency
  - Meta-analysis: Smaller effect size compared to other opioids
- No studies comparing opioids or opioids versus protussives

Yancy WS et al. Efficacy and tolerability of treatments for chronic cough: a systematic review and meta-analysis. Chest 2013;144:1827
Suggested Opioids and Dose

• Codeine (linctus or tablet) 15mg (5mls) tds/qds
• Morphine I/R liquid 2.5-5mg qds
• Morphine M/R formulation start at 5mg bd
• Titrate to effect or undesirable effects
• If already on opioid titrate further to suppress cough
Central Antitussive: GABA agonists

• Mechanism of action
  – Central inhibitory effects
  – May increase inhibitory neurones effects in medulla on cough reflex
  – May reduce the central sensitization and hypersensitivity in chronic cough

• Suggested GABA agonists and dose
  – Gabapentin 300mg tds increased up to 600mg tds (could start with smaller doses – 100mg bd)
  – Baclofen titrate up to 10mg tds or 20mg od
  – Diazepam 5mg PO/nocte
GABA agonist Evidence Base

- Gabapentin
- Not included in systematic review
  - 62 adults with refractory chronic cough (> 8 weeks) without active respiratory disease or infection
  - Randomised to Gabapentin (up to 1800mg /day) or placebo
  - Gabapentin significantly improved cough specific QOL (p=0.004) NNT 3.58
  - Side effects occurred in 10 (31%) of the Gabapentin group (nausea and vomiting)
- Gibson et al (2015) systematic review
  - Case series and reports supporting the results of this RCT
  - Likely greatest effect in patients with central sensitisation (hypertussia, allotussia)

- Treatment of Unexplained Chronic Cough: CHEST guideline and expert panel report 2016 recommend Gabapentin

GABA agonist Evidence Base

- Baclofen
  - Not included in systematic review
  - Level of evidence: Case reports
    - Additional action of inhibiting relaxation of lower oesophageal sphincter and reducing reflux
    - Effective in ACEi cough

- Diazepam
  - Not included in systematic review
  - Level of evidence: Case reports

Peripheral Antitussives

• Suppresses peripheral transmission of afferent vagal impulses in cough reflex

• Sodium Cromoglicate
  – Suppresses peripheral C-fibers transmission of afferent vagal impulses in cough reflex
  – Dose: 10mg inhaled qds\(^1\)
  – Small RCT (n=20), lung cancer patients
  – Sodium cromoglicate versus placebo
  – Improved cough severity after 36-48hrs

• Nebulised local anaesthetic
  – Likely inhibit sensory nerves in airways
  – 5ml 2% lidocaine or 0.25% bupivacaine nebulised tds
  – No RCT data
  – Case series data – showed 20% of participants reported improved cough, many side effects including bronchospasm
  – USE ONLY WHEN OTHER ANTITUSSIVES HAVE FAILED

Truesdale K et al Nebulised lidocaine in the treatment of intractable cough. *American journal of Hospital Palliative Care* 2013p 587-589
Disease specific and Experimental

• Thalidomide and cough in IPD

  – Double blind cross-over study n= 24
  – Cough QOL scores significantly improved with thalidomide (MD -11.4 (95%CI -15.7 to -7.0) p<0.001)
  – 74% of patients receiving thalidomide had side effects
Wet Cough: Strategy for management

Step 1
- Treat the Cause

Step 2
- Aid expectoration
- Physiotherapy, Nebulized Saline

Step 3
- Protussive +/- antitussive

## Wet Cough Step 1: Treat the cause

<table>
<thead>
<tr>
<th>Nature of Cough</th>
<th>Possible cause</th>
<th>Potential treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Productive</strong></td>
<td>COPD (no infection)</td>
<td>Optimise inhaled therapy, consider steroids</td>
</tr>
<tr>
<td></td>
<td>Infection, pneumonia</td>
<td>Antibiotics (?PO/IV)</td>
</tr>
<tr>
<td></td>
<td>COPD exacerbation</td>
<td>Antibiotics (?PO/IV) and steroids</td>
</tr>
<tr>
<td></td>
<td>Tracheo-oesophageal fistula</td>
<td>Consider ? Possible stenting</td>
</tr>
<tr>
<td></td>
<td>Aspiration of saliva</td>
<td>Antimuscarinics /anticholinergics, antibiotics</td>
</tr>
<tr>
<td></td>
<td>Gastro-oesophageal reflux</td>
<td>PPI, prokinetic</td>
</tr>
<tr>
<td></td>
<td>Cardiac failure</td>
<td>Optimise medical management</td>
</tr>
<tr>
<td><strong>After food</strong></td>
<td>Fatigue or weakness causing a poor swallow</td>
<td>SALT assessment</td>
</tr>
<tr>
<td><strong>Weak ineffective</strong></td>
<td>MND, Amyotrophic lateral sclerosis</td>
<td>Consider antisecretory (e.g Hyoscine)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Titrate carefully</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Consider suction or cough assist machine</td>
</tr>
</tbody>
</table>

Step 2 & Step 3

- **Step 2: Aid Expectoration**
  - Physiotherapy
  - Nebulized Saline
- **Step 3: Protussive**
- **Chemical mucolytics**
  - Reduce viscosity of bronchial secretions by breaking links between mucin polymers
  - Anti-inflammatory effect
  - Suggests drugs and dose
    - Carbocisteine – start 750mg tds, reduce to bd once satisfactory response occurs
    - Erdosteine – 300mg bd for up to 10 days (in COPD)
    - ? N-acetylcysteine
Disease specific and Experimental

• Systematic Review for treatment of Bronchoalveolar Ca
• 48 studies identified, 20 eligible for review
• No controlled trials
• All 20 case reports and case series
• Treatments with reported effect on symptoms were: Corticosteroids, macrolide antibiotics, indomethacin, octreotide
Evidence Base for Management of Cough in Cancer


Molassiotis et al recommendations\textsuperscript{10},

- For lung cancer
- Combination of synthesis of 2 systematic reviews and expert panel
- Higher up the pyramid – less evidence and less confidence in recommendation

Evidence Base for Management of Cough in Advanced Disease

  - 60 studies, 11 full text assessed for eligibility
  - 6 excluded as only case reports, small series
  - 5 included in recommendations (only 3 RCTs) with 2 additional studies considered (2 RCTs)
- Limited evidence in both quantity and quality to support robust guidelines.
- Recommendations are also based on convenience, minimising burden and harm and toxicity
# APM recommendations

<table>
<thead>
<tr>
<th>Recommendations (Grade D)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Consider potential for disease-directed treatment</td>
</tr>
<tr>
<td>2. Review medications and consider if appropriate to discontinue those that exacerbate cough (ACEi)</td>
</tr>
<tr>
<td>3. Consider co-existing benign causes of chronic cough (Asthma, GORD) and treat</td>
</tr>
<tr>
<td>4. Prescribe simple linctus: a demulcent cough preparation (no evidence but safe)</td>
</tr>
<tr>
<td>5. Therapeutic trial of sodium cromoglycate inhaler (one small RCT, relatively safe)</td>
</tr>
<tr>
<td>6. Prescribe an opioid or opioid derivative:</td>
</tr>
<tr>
<td>a. Dextromethorphan: weak evidence, low toxicity</td>
</tr>
<tr>
<td>b. Morphine: most recent evidence suggests significant benefit over placebo. 5mg MR BD, unless already on morphine and then titrate upwards</td>
</tr>
<tr>
<td>c. Codeine: conflicting evidence – historical evidence is weak, most recent evidence shows no benefit. Probably should not choose codeine over morphine</td>
</tr>
<tr>
<td>d. ? Trial a GABA agonist - Gabapentin</td>
</tr>
</tbody>
</table>

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Evidence Base for Management of Cough in Cancer

- This review did not identify any additional trials to the original version in 2010
- Shows overall ‘almost complete absence of any credible evidence on the management of cough in cancer patients’

Haemoptysis – Definition, incidence

• Expectoration of blood that originates from the lower respiratory tract (lung parenchyma or airway)
• Most is self-limiting, but in 5%-15% it may be severe or massive (MH)
  – life threatening requiring urgent investigation and treatment
  – Mortality of MH is 50%
• Massive haemoptysis
  – no agreed volume definition (100-1000mls) - > 200mls
  – Associated with haemodynamic instability
• Asphyxia – due to flooded airway- is usually the cause of death
# Causes – Differential Diagnosis

<table>
<thead>
<tr>
<th>Parenchymal source</th>
<th>Vascular source</th>
<th>Airway source</th>
</tr>
</thead>
<tbody>
<tr>
<td>TB</td>
<td>AV malformation</td>
<td>Cancer</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>PE</td>
<td>Bronchitis</td>
</tr>
<tr>
<td>Lung Abscess / Mycetoma</td>
<td>Pulmonary artery rupture</td>
<td>Broncholithiasis</td>
</tr>
<tr>
<td>Lung contusion</td>
<td></td>
<td>Airway trauma</td>
</tr>
<tr>
<td>Small vessel vasculitis</td>
<td></td>
<td>Foreign Body</td>
</tr>
<tr>
<td><strong>Pseudohaemoptysis</strong></td>
<td><strong>Others</strong></td>
<td></td>
</tr>
<tr>
<td>Upper airway or GI source</td>
<td></td>
<td>Coagulopathy/thrombolytic agents</td>
</tr>
</tbody>
</table>
Assessment

• Indications for admission / urgent management
• Etiology with high risk of repeat/massive bleeding (pulmonary artery involvement)
• Breathing difficulties
  – RR > 30, Sats 88% RA or need for high flow oxygen
• Haemodynamic instability
  – Hb < 80 or a drop of > 20, hypotension, coagulopathy
• Massive haemoptysis
  – >200mls or less in lung disease
• Other comorbidities

## Predictors of in-hospital mortality

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>CXR shows involvement of 2 or more quadrants</td>
<td>1</td>
</tr>
<tr>
<td>Chronic alcoholism</td>
<td>1</td>
</tr>
<tr>
<td>Pulmonary artery involvement</td>
<td>1</td>
</tr>
<tr>
<td>Aspergillosis</td>
<td>2</td>
</tr>
<tr>
<td>Malignancy</td>
<td>2</td>
</tr>
<tr>
<td>Mechanical ventilation required</td>
<td>2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Score</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>1%</td>
<td>2%</td>
<td>6%</td>
<td>16%</td>
<td>34%</td>
<td>58%</td>
<td>79%</td>
<td>91%</td>
</tr>
</tbody>
</table>

Adapted from Fortoukh M et al. Early prediction of in-hospital mortality of patients with haemoptysis: an approach to defining severe haemoptysis. *Respiration* 2012; 83 (2) 111

Active Management

• Aim: stabilise and reverse haemoptysis
  – Admit, consider ITU
  – ABC
  – Hb, platelets, coagulation, G&S, Xmatch, CXR
  – Place patient in lateral decubitus position with the affected lung down
    • to prevent pooling of blood in unaffected bronchial tree
  – Reverse abnormal clotting, haemodynamic support
  – Treat cause
  – IV Terlipressin
  – Bronchoscopy/ CT angiography and/or arteriography with embolisation

Palliative management

- Paucity of evidence
- Case series or expert opinion

Tranexamic acid
- 1 pilot study with 3 patients (1997). All 3 experienced cessation of bleeding within 1-4 days
- Dosing 1.5g initially, 1g tds

Etamsylate
- Expert opinion – 500mg qds

Corticosteroids
- Expert opinion and anecdotal evidence, no optimal dose

Pressins – vasoconstrictors
- IV terlipressin 1 case series in 20 patients severe haemoptysis
- 14/20 ‘total success’, 5/20 ‘partial success’
- Case series n=2 of nebulised Vasopressin (2005)
- Initial improvement and then rebleed

Is this a terminal catastrophic bleed?
- Stay with the patient, consider sedation if time allows
Objectives

• Describe prevalence of cough and haemoptysis in palliative care
• Understand the management of reversible causes
• Describe pharmacological management
• Describe mechanisms of action of antitussive medications
• Be aware of the evidence base (and its limitations) for the management of cough and haemoptysis