Oxford Primary Care 2015

Cutting-edge research in the consulting room

18 May 2015
@OxPrimaryCare

In partnership with:

National Institute for Health Research
Clinical Research Network Thames Valley and South Midlands
Postinfectious cough and pertussis

Dr Kay Wang, GP and Academic Clinical Lecturer

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Twitter: @kaywang9
Thank you

- 19 Beaumont Street Surgery
- Bampton Surgery
- Bicester Health Centre
- Broadshires Health Centre
- Burnham Health Centre
- Church Street Practice
- Denham Medical Centre
- Eynsham Medical Group
- Holyport Surgery
- Horsefair Surgery
- Langley Health Centre
- Malthouse Surgery
- Mill Stream Surgery
- Morland House Surgery
- Newbury Street Practice
- Red House Surgery
- Summertown Health Centre
- Temple Cowley Health Centre
- Thatcham Medical Practice
- Trinity Health
- Waterfield Surgery
- West Bar Surgery
- Westongrove Research Centre
- Woosehill Surgery
Objectives

• To consider the differential diagnosis of postinfectious cough

• To summarise the prognosis of postinfectious cough

• To examine the role of pertussis (whooping cough) in postinfectious cough
Case scenario 1

- 35-year-old teacher
- Persistent cough for 6/52
- Cough triggered by talking
- Ticklish sensation in throat leading to bouts of coughing
- Not helped by over the counter cough medication
- Never smoked, no known underlying medical conditions
Case scenario 1

- 35-year-old teacher
- Persistent cough for 6/52
- Cough triggered by talking
- Ticklish sensation in throat leading to bouts of coughing
- Not helped by over the counter cough medication
- Never smoked, no known underlying medical conditions

Differential diagnosis?
Classification of cough$^{1,2}$

• Acute cough - less than 3 weeks

• Subacute cough - 3 to 8 weeks

• Chronic cough - More than 8 weeks

$^1$Morice AH et al. Thorax 2006;61(Suppl I):i1–i24

$^2$Pratter MR et al. Chest 2006;129;222S-231S
Causes of subacute cough

<table>
<thead>
<tr>
<th>Cause</th>
<th>Number of patients (%) (n=184)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postinfectious</td>
<td>89 (48.4%)</td>
</tr>
<tr>
<td>Post nasal drip</td>
<td>61 (33.2%)</td>
</tr>
<tr>
<td>Cough-variant asthma</td>
<td>29 (15.8%)</td>
</tr>
<tr>
<td>Other (e.g. eosinophilic bronchitis)</td>
<td>5 (2.7%)</td>
</tr>
</tbody>
</table>

Kwon et al. Chest 2006;129;1142-1147
Post viral cough reflex hypersensitivity

Cough reflex hypersensitivity

• Cough triggered by ‘low threshold’ stimuli
  – Talking, laughing, scents/odours, changes in temperature

• Bouts of coughing

• Abnormal throat sensation
  – Itch, tickle, ‘urge to cough’, choking sensation
Post viral cough reflex hypersensitivity

Post viral cough reflex hypersensitivity

Post viral cough reflex hypersensitivity

Cough Visual Analogue Scale Scores

Number of paroxysms of cough

• **Inhaled ipratropium bromide** (Holmes *et al.* Respir Med 1992)
  – Improvement in cough severity after 3 weeks (n=14)
  – used unvalidated patient-reported cough outcome

• **Nociceptin opioid 1 (NOP1) agonist** (Woodcock *et al.* Lung 2010)
  – No improvement in cough severity scores
  – Difficulties with recruitment

• **Inhaled corticosteroids** (El-Gohary *et al.* Fam Pract 2013)
  – 2/4 trials reported improvement in cough

• **Montelukast** (Wang *et al.* Lancet Respir Med 2014)
  – No improvement in cough-specific quality of life
Managing postinfectious cough

• Explain mechanism
  – Transient increase in cough reflex sensitivity

• Explain prognosis
  – Virtually resolves around 2 weeks after initial presentation in around 50% of patients.

• No proven effective treatments
Case scenario 2

- 11-year-old boy
- Persistent cough for 5/52
- Bouts of coughing
- SOB and vomiting after bouts of coughing
- All vaccinations up to date
Case scenario 2

- 11-year-old boy
- Persistent cough for 5/52
- Bouts of coughing
- SOB and vomiting after bouts of coughing
- All vaccinations up to date

Diagnosis?
WHO clinical case definition of whooping cough (pertussis)

• Cough lasting ≥2 weeks, **plus** at least one of:
  – Paroxysms of coughing
  – Inspiratory whooping
  – Post-tussive vomiting

• [http://www.whoopingcough.net/](http://www.whoopingcough.net/)
Whooping cough (pertussis)

- One of commonest vaccine preventable diseases

- UK pertussis vaccinations:
  - Primary course at 2, 3 and 4 months
  - Pre-school booster at 3 years 4 months (introduced in October 2001)
Oral fluid test for pertussis

Anti-pertussis toxin IgG

>= 70 arbitrary units (aU): pertussis positive
60-69 aU: borderline; <60 aU: pertussis negative
Laboratory-confirmed pertussis

• Total cohort
  – 56/279 (20%, 95% CI 16% to 25%)

• Fully vaccinated* children
  – 39/215 (18%, 95% CI 13% to 24%)

*Three doses of primary pertussis vaccine + pre-school pertussis booster vaccination

The Children And Persistent cough Study Wang et al. BMJ 2014;348:g3668
### Laboratory-confirmed pertussis

<table>
<thead>
<tr>
<th></th>
<th>Montelukast (n=137)</th>
<th>Placebo (n=139)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pertussis positive</td>
<td>31 (23%)</td>
<td>39 (28%)</td>
</tr>
<tr>
<td>Vaccinated*</td>
<td>52 (38%)</td>
<td>58 (42%)</td>
</tr>
</tbody>
</table>

* 3 doses of pertussis vaccine documented in medical records

**Montelukast for Adults with persistent Cough**  
<table>
<thead>
<tr>
<th>Age</th>
<th>Clinical symptoms</th>
<th>≤ 2 weeks cough</th>
<th>&gt; 2 weeks cough*</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 1 yr</td>
<td></td>
<td>NPA/NPS/PNS for PCR (RVPBRU)</td>
<td>NPA/NPS/PNS for PCR (RVPBRU)</td>
</tr>
<tr>
<td>Hospitalised</td>
<td>or</td>
<td>or</td>
<td>or</td>
</tr>
<tr>
<td></td>
<td>NPS/PNS for culture (local laboratory)¹</td>
<td>NPS/PNS for culture (local laboratory)¹</td>
<td></td>
</tr>
<tr>
<td>≤ 1 yr²</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Community</td>
<td>NPS/PNS for culture (local laboratory)¹</td>
<td>Serum for serology (RVPBRU)</td>
<td></td>
</tr>
<tr>
<td>&gt; 1 yr to 6 yrs²</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 6 yrs³</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

¹ For children aged ≤ 1 year, consider NPS/PNS for culture at a local laboratory when there is a high suspicion of pertussis.
% with laboratory-confirmed pertussis

Duration since pre-school pertussis booster vaccination received (years)
Cough frequency in pertussis

Number of coughs in 24 hours

Participant

Night
Day

0 1200 1400 1600 1800
0 200 400 600 800 1000 1200 1400 1600 1800
1 2 3 4 5 6

1 2 3 4 5 6

Night
Day
Duration of pertussis-induced cough

- 6 weeks 95% CI: 24–54 days
- 10 weeks 95% CI: 40–101 days
- 4 months 95% CI: 82–154 days

Role of macrolides

*Mycoplasma pneumoniae*

- Recommended for the treatment of suspected *M. pneumoniae* infections
- Insufficient evidence to demonstrate efficacy of macrolide antibiotics in the treatment of laboratory-confirmed *M. pneumoniae*

*Whooping cough*

- Start within 3 weeks of onset of cough
- Recommended to reduce risk of ongoing pertussis transmission
- Have not been shown to reduce duration or severity of cough

## Treatments for cough due to pertussis

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mean difference (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diphenhydramine*</td>
<td>1.90 (-4.66 to 8.46)</td>
</tr>
<tr>
<td>Salbutamol*</td>
<td>-0.22 (-4.13 to 3.69)</td>
</tr>
<tr>
<td>Pertussis immunoglobulin**</td>
<td>-0.07 (-0.42 to 0.27)</td>
</tr>
</tbody>
</table>

*Number of paroxysms of cough per 24 hours

** Mean paroxysmal coughs per hour

## Montelukast for Pertussis

<table>
<thead>
<tr>
<th></th>
<th>Montelukast (n=31)</th>
<th>Placebo (n=39)</th>
<th>Between group difference (unadjusted)</th>
<th>Between group difference (adjusted)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in LCQ total score (baseline to 2 weeks)</td>
<td>2.2 (1.0 to 3.3)</td>
<td>3.1 (2.1 to 4.1)</td>
<td>-0.9 (-2.4 to 0.6) p=0.2</td>
<td>-0.8 (-2.3 to 0.7) p=0.3</td>
</tr>
<tr>
<td>Change in LCQ total score (baseline to 4 weeks)</td>
<td>4.5 (3.1 to 6.0)</td>
<td>5.6 (4.5 to 6.8)</td>
<td>-1.1 (-2.9 to 0.7) p=0.2</td>
<td>-1.0 (-2.8 to 0.8) p=0.3</td>
</tr>
<tr>
<td>Overall cough severity</td>
<td>550.8 (452.1 to 649.6)</td>
<td>623.0 (529.4 to 716.5)</td>
<td>-72.1 (-207.9 to 63.5) p=0.3</td>
<td>-110.3 (-208.6 to -11.9) p=0.03</td>
</tr>
<tr>
<td>Paroxysmal cough severity</td>
<td>138.6 (92.2 to 185.0)</td>
<td>162.4 (101.6 to 223.3)</td>
<td>-23.9 (-104.2 to 56.5) p=0.6</td>
<td>-9.1 (-27.4 to 45.6) p=0.6</td>
</tr>
</tbody>
</table>

Managing pertussis

• Consider pertussis as potential diagnosis in patients with persistent cough, even if previously vaccinated

• Start macrolides if within first 21 days of onset of cough

• Role of macrolides is to prevent transmission
Summary

• Postinfectious cough accounts for nearly 50% of subacute coughs and is predominantly caused by cough reflex hypersensitivity

• Most subacute cough resolves within 2 weeks of clinical presentation, but duration of cough varies according to type of infection

• Pertussis should still be considered in adults and fully vaccinated individuals
Thank you for listening

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C-reactive protein and other point-of-care tests in primary care

Dr Ann Van den Bruel
Associate Professor
Director NIHR Diagnostic Evidence Co-operative
C-reactive protein

- Plasma protein
- Produced in the liver
- Inflammatory marker:
  - Levels increase during inflammation and after tissue damage

- Used for:
  - Diagnosis
  - Prediction
  - Management decisions
CRP for the diagnosis of …

- Serious infections in children
- Pneumonia
- Complicated urinary tract infection
- Sepsis and meningitis
- Osteomyelitis, cellulitis
Diagnostic value of inflammatory markers for serious infection in febrile children.

<table>
<thead>
<tr>
<th>Study</th>
<th>Prevalence setting</th>
<th>Cut-off value</th>
<th>Likelihood ratio (95% CI)</th>
<th>Probability of illness</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Procalcitonin (ng/mL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thayyil(^{14})</td>
<td>Intermediate</td>
<td>&gt;0.5</td>
<td>1.75 (1.22 to 2.50)</td>
<td>0.25 (0.04 to 1.59)</td>
</tr>
<tr>
<td>Andreola(^{16})</td>
<td>High</td>
<td>&gt;0.5</td>
<td>3.11 (2.47 to 3.93)</td>
<td>0.35 (0.25 to 0.49)</td>
</tr>
<tr>
<td>Galetto-Lacour(^{21})</td>
<td>High</td>
<td>&gt;0.5</td>
<td>2.96 (2.33 to 3.80)</td>
<td>0.08 (0.03 to 0.25)</td>
</tr>
<tr>
<td>C reactive protein (mg/L)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hsiao(^{22})</td>
<td>Intermediate</td>
<td>&gt;9.8</td>
<td>2.61 (1.81 to 3.76)</td>
<td>0.61 (0.44 to 0.83)</td>
</tr>
<tr>
<td>Berger(^{39})</td>
<td>High</td>
<td>&gt;20</td>
<td>2.53 (1.82 to 3.50)</td>
<td>0.25 (0.11 to 0.56)</td>
</tr>
<tr>
<td>Andreola(^{16})</td>
<td>High</td>
<td>&gt;40</td>
<td>3.79 (2.92 to 4.94)</td>
<td>0.35 (0.26 to 0.49)</td>
</tr>
<tr>
<td>Galetto-Lacour(^{21})</td>
<td>High</td>
<td>&gt;40</td>
<td>3.35 (2.45 to 4.57)</td>
<td>0.25 (0.14 to 0.43)</td>
</tr>
<tr>
<td>Thayyil(^{14})</td>
<td>Intermediate</td>
<td>&gt;50</td>
<td>2.40 (1.40 to 4.12)</td>
<td>0.36 (0.11 to 1.22)</td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate (mm/h)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Berger(^{39})</td>
<td>High</td>
<td>&gt;50</td>
<td>2.49 (1.73 to 3.59)</td>
<td>0.34 (0.17 to 0.65)</td>
</tr>
<tr>
<td>Interleukin 1 receptor antagonist (pg/L)</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Galetto-Lacour(^{19})</td>
<td>High</td>
<td>&gt;9500</td>
<td>1.90 (1.34 to 2.70)</td>
<td>0.46 (0.25 to 0.84)</td>
</tr>
<tr>
<td>Interleukin 6 (pg/L)</td>
<td></td>
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</tr>
<tr>
<td>Galetto-Lacour(^{19})</td>
<td>High</td>
<td>&gt;50</td>
<td>2.29 (1.63 to 3.20)</td>
<td>0.33 (0.16 to 0.67)</td>
</tr>
<tr>
<td>Interleukin 8 (pg/L)</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Galetto-Lacour(^{19})</td>
<td>High</td>
<td>≥70</td>
<td>1.89 (1.03 to 3.45)</td>
<td>0.77 (0.56 to 1.05)</td>
</tr>
</tbody>
</table>

Ann Van den Bruel et al. BMJ 2011;342:bmj.d3082

©2011 by British Medical Journal Publishing Group
Summary receiver operating characteristic curves for C reactive protein (CRP) and procalcitonin (PCT) levels for serious infection.

Ann Van den Bruel et al. BMJ 2011;342:bmj.d3082
NICE guideline feverish illness in children <5 years

- May 2013
- Blood tests only by paediatric specialist
- Full blood count, blood culture and CRP
- Infants <3 months with fever
- Children >3 months with 1 or more red features
<table>
<thead>
<tr>
<th>Traffic light system for identifying risk of serious illness*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Colour (of skin, lips or tongue)</td>
</tr>
<tr>
<td>Activity</td>
</tr>
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<td></td>
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<tr>
<td>Respiratory</td>
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<tr>
<td>Circulation and hydration</td>
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<tr>
<td>Other</td>
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</tbody>
</table>

CRT, capillary refill time; RR, respiratory rate

*This traffic light table should be used in conjunction with the recommendations in the guideline on investigations and initial management in children with fever. See http://guidance.nice.org.uk/CG168 (update of NICE clinical guideline 47).
CRP as a point-of-care test

- Result available in 4 minutes
- Pilot study in Oxfordshire out-of-hours services
  - Recruitment rate
  - Planning larger study
  - Finger prick test feasible and acceptable to clinicians and patients/parents
CRP as a point-of-care test

• Prospective study in Flanders in daytime general practice
• Children 1 month-16 years, with an acute illness of a maximum of 5 days
• Outcome = serious infection requiring hospital admission for at least 24h
• Incremental value CRP over and above clinical features
CRP as a point-of-care test

3147 children with an acute illness
11 with a serious infection

525 children
Serious infection: 11
At least one feature of CPR

342 children
Serious infection: 11
CRP ≥5 mg/L

2622 children
Serious infection: none
NO gut feeling
NO temperature >39.95°C
NO dyspnoea
NO diarrhoea in a child between 1-2.5y

183 children
Serious infection: none
CRP <5 mg/L

Verbakel 2015, PhD thesis KULeuven
CRP used for the diagnosis of...

- Pyelonephritis in children
- Cochrane review Jan 2015 incl 13 studies
- Differentiate between cystitis and pyelonephritis
- CRP, procalcitonin and erythrocyte sedimentation rate
Pyelonephritis in children

NICE guideline UTI in children, Aug 2007

CRP alone should not be used to differentiate pyelonephritis from cystitis in infants and children
CRP used for the diagnosis of

- Inflammatory bowel disease (IBD)
  - CRP <5 mg/L excludes IBD

- Appendicitis?
  - Few studies: 3 in children and 2 in adults
  - Results heterogeneous
  - CRP 50 mg/L:
    - Not sensitive enough for ruling out
    - Slightly better for ruling in
CRP used for the diagnosis of

• Community acquired pneumonia
  – CRP 20 mg/L:
    • LR+ 2.1
    • LR- 0.33

• In primary care, signs of lower respiratory tract infection
CRP used for the diagnosis of

- Community acquired pneumonia
  - CRP 20 mg/L:
    - LR+ 2.1
    - LR- 0.33
- In primary care, signs of lower respiratory tract infection

![Pneumonia risk chart]
CRP used for the diagnosis of

- Community acquired pneumonia
  - CRP 20 mg/L:
    - LR+ 2.1
    - LR- 0.33
- In primary care, signs of lower respiratory tract infection
High-sensitivity CRP

Unfavourable long-term functional outcome after ischaemic stroke
  - 5 studies found association
  - Correction for confounders??

Coronary heart disease
  - Yes based on epidemiological data
  - No based on genetic data
  - Clinical relevance? Cost-effectiveness?

Heart failure
  - 4 studies in general population (>65y)
  - Double risk after 3-6 years if hs-CRP>2.5-7.4 mg/L
Impact on management

- Patients with acute respiratory tract infections
- Cochrane review Dec 2014 incl 6 studies
- Antibiotic prescriptions:
  - Decreased by 22% at index consultation
  - Decreased by 20% within 28 days
### 1.1.1 Individually randomised trials

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>CRP Events</th>
<th>Total Events</th>
<th>CRP Total</th>
<th>Standard care Events</th>
<th>Total Events</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melbye 1995</td>
<td>54</td>
<td>108</td>
<td>68</td>
<td>131</td>
<td>17.1%</td>
<td>0.96 [0.75, 1.24]</td>
<td>1995</td>
<td></td>
</tr>
<tr>
<td>Diederichsen 2000</td>
<td>179</td>
<td>414</td>
<td>184</td>
<td>398</td>
<td>22.7%</td>
<td>0.94 [0.80, 1.09]</td>
<td>2000</td>
<td></td>
</tr>
<tr>
<td>Cals 2010</td>
<td>56</td>
<td>129</td>
<td>73</td>
<td>129</td>
<td>17.2%</td>
<td>0.77 [0.60, 0.98]</td>
<td>2010</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>651</strong></td>
<td><strong>658</strong></td>
<td><strong>56.9%</strong></td>
<td></td>
<td></td>
<td><strong>0.90 [0.80, 1.02]</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 289 / 325
Heterogeneity: $\tau^2 = 0.00; \chi^2 = 2.11, df = 2 (P = 0.35); I^2 = 5\%$
Test for overall effect: $Z = 1.71 (P = 0.09)$

### 1.1.2 Cluster-randomised trials (modified sample size)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>CRP Events</th>
<th>Total Events</th>
<th>CRP Total</th>
<th>Standard care Events</th>
<th>Total Events</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cals 2009</td>
<td>20</td>
<td>65</td>
<td>31</td>
<td>59</td>
<td>9.4%</td>
<td>0.59 [0.38, 0.91]</td>
<td>2009</td>
<td></td>
</tr>
<tr>
<td>Little 2013a</td>
<td>304</td>
<td>920</td>
<td>407</td>
<td>844</td>
<td>24.8%</td>
<td>0.69 [0.61, 0.77]</td>
<td>2013</td>
<td></td>
</tr>
<tr>
<td>Andreeva 2013</td>
<td>18</td>
<td>49</td>
<td>22</td>
<td>38</td>
<td>8.9%</td>
<td>0.63 [0.40, 1.00]</td>
<td>2013</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>1034</strong></td>
<td><strong>941</strong></td>
<td><strong>43.1%</strong></td>
<td></td>
<td></td>
<td><strong>0.68 [0.61, 0.75]</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 342 / 460
Heterogeneity: $\tau^2 = 0.00; \chi^2 = 0.54, df = 2 (P = 0.76); I^2 = 0\%$
Test for overall effect: $Z = 7.08 (P < 0.00001)$

**Total (95% CI)**: 1685 / 1599
Heterogeneity: $\tau^2 = 0.02; \chi^2 = 15.41, df = 5 (P = 0.009); I^2 = 68\%$
Test for overall effect: $Z = 3.01 (P = 0.003)$
Test for subgroup differences: $\chi^2 = 12.08, df = 1 (P = 0.0005), I^2 = 91.7\%$
Impact on management

• Patients with acute respiratory tract infections

• Cochrane review Dec 2014 incl 6 studies

• Decreased antibiotic prescriptions:
  – Similar recovery rate at day 7 (3 studies)
  – 1 study found increased hospital admission rates after CRP test
December 2014

For people presenting with symptoms of lower respiratory tract infection in primary care

Consider a point-of-care CRP test if after clinical assessment a diagnosis of pneumonia has not been made and it is not clear whether antibiotics should be prescribed.

- CRP <20 mg/L: Do not routinely offer antibiotic therapy
- CRP 20-100 mg/L: Consider a delayed antibiotic prescription
- CRP >100 mg/L: Offer antibiotic therapy
Point-of-care tests

• At the bedside of the patient
  – In the GP’s surgery
  – At the patient’s home
• Disruptive
  – Result available faster
  – Changes clinical pathway
  – Spectrum shift – indication creep
Spectrum effects

Test threshold will lower:

• More easily available
  – More people get tested

• Less invasive
  – Different people get tested

Effects:

• Lower prevalence of target condition
  ➔ More false positives

• Less or differently selected population
  ➔ Spectrum shift
  ➔ Different treatment efficacy
In conclusion

• CRP most useful for acute infections
  – Improves the diagnosis of serious infections in children
  – Can reduce antibiotic prescribing in adults with lower respiratory tract infection

• Rigorous studies required to estimate impact on patient outcome and healthcare resources
Uncomplicated urinary tract infection in primary care

Chris Butler, Professor of Primary Care. 18 May 2015
Disclosures

• Grants form the EU (R-Gnosis) on UTI management
• Honoraria for talks, attending meetings and supply for equipment for a publically funded research study from Alere
Case

• 38 year old woman
• “I have a UTI doctor: I need a prescription for antibiotics…”
Case continued

- 38 year old woman
- “I have a UTI doctor: I need a prescription for antibiotics…”
- Dysuria, frequency 3 days
- T36.4C, Pule 80, 130/80
- Abdo: slightly tender suprapubically
Case

- 38 year old woman
- “I have a UTI doctor: I need a prescription for antibiotics…”
- Dysuria, frequency 3 days
- T36.4°C, Pule 80, 130/80
- Abdo: slightly tender suprapubically
- Not pregnant
- Dipstick negative
Classification of UTI

- **Acute cystitis**: infection of lower urinary tract (bladder); Can occur in conjunction with *pyelonephritis* (infection of the kidney)
- **Uncomplicated**: healthy non pregnant adult women
- **Complicated**: an underlying condition which increases risk of infection or failing therapy (obstruction, anatomic abnormality, multiply-resistant uropathogen)
- **Recurrent UTI**: ≥2 infections in 6 months or ≥3 infections in a year
- **Men**
- **Children**
Percentage of women reporting a UTI in their lifetime, and information, advice and treatment sought with their most recent UTI (n=2,424)

- All women: 100%
- Had a UTI in lifetime: 37%
- Contacted a health professional: 33%
- Had a urine test: 27%
- Prescribed antibiotics: 27%
- Given other advice: 24%
- Took the antibiotics prescribed: 17%
- Went to Out of Hours service: 5%

Butler BJGP, in press
Pathogenesis

- Colonisation of vaginal intoitus by faecal flora
- Ascends via urethra to balder
- Pyelonephritis: ascends from bladder to kidneys via ureters or seeds from blood in septicaemia
- Risk factors:
  - Spermicides
  - Wiping front to back
Microbiology

- *Escherichia coli* 75-95%

Also

- *Proteus mirabilis*
- *Klebsiella pneumoniae*
- *Staphylococcus saprophyticus*

**Common contaminants:**
- Group B *Streptococci*
- *Lactobacilli*
- *Enterococci*
- Coagulase-negative *Staphylococci* (other than *S. saprophyticus*)
Diagnosis: symptoms

- Dysuria
- Frequency
- Urgency
- Suprapubically pain
- Hematuria

- Any one symptom: probability >50%
- Dysuria, frequency, no PV discharge or irritation: probability >90%

- Pyelonephritis:
  - Fever, chills, loin pain, Costovertebral angle tenderness, nausea, shock, sepsis
Diagnosis: physical examination

- Fever
- Pulse, BP
- Abdominal examination
- Costovertebral angle tenderness
- ?Pelvic exam
- ?pregnancy test
Differential diagnosis

- **Vaginitis**: discharge, odor, dyspareunia, pruritus, absence of urgency/frequency: yeast, trichomonas, bacterial vaginosis
- **Urethritis**: dysuria but no bacteria in sexually active women: chlamydia, gonorrhea, trichomonas, candida, herpes simplex virus, contraceptive gel
- **Structural urethral abnormalities**: urethral diverticula
- **Painful bladder syndrome**: diagnosis of exclusion: symptoms but no evidence of infection
- **PID**: lower abdominal pain and fever, even dysuria: mucopurulent endocervical discharge
- **Kidney stones**: flank pain, colic, macroscopic hematuria, with fever unusual
Diagnosis: point of care test: Microscopy dipsticks

- Absence of pyuria suggests an alternative diagnosis
- Microscopy of un-spun urine is most accurate POCT: \( \geq 10 \) leucocytes per microlitre. Casts = upper UTI

- **Dipstick** detects:
  - leucocyte esterase:
  - Nitrite
- Sensitivity 75%, specificity 82% for either
- When history is suggestive, a negative test does not reliably rule out UTI

- **Dipslide**: quantification, not sensitivity
• Frequency, nocturia and cloudy urine = PPV of 82%

• Dipstick testing was found to only modestly increase the PPV and did not improve NPV
Resistance in Gram-Negative Organisms: Studying Intervention Strategies

R-GNOSIS WP2

POETIC
point of care testing for urinary tract infection in primary care

Observational study and RCT of clinical and cost effectiveness

Professor Chris Butler and team
Professor of Primary Care Medicine
Director of Institute of Primary Care and Public Health
Cardiff University
The POCT: FLEXICULT™ SSI-Urinary Kit

- Agar plate – 6 high-sided compartments
- Chromogenic agar: for bacterial identification
- Control compartment: for quantitation of bacteria
- Antibiotic compartments: for susceptibility testing

UK:
- Trimethoprim (3mg/l)
- Nitrofurantoin (64mg/l)
- Amoxicillin/Clavulanate (16/8mg/l)
- Ciprofloxacin (0.75mg/l)
- Cephalothin (Cephalothin)(16mg/l)

Netherlands:
- Trimethoprim (3mg/l)
- Nitrofurantoin (64mg/l)
- Amoxicillin/Clavulanate (16/8mg/l)
- Ciprofloxacin (0.75mg/l)
- Amoxicillin (Ampicillin) (8mg/l)

Spain:
- Fosfomycin (32mg/l)
- Nitrofurantoin (64mg/l)
- Amoxicillin/Clavulanate (16/8mg/l)
- Ciprofloxacin (0.75mg/l)
- Cefuroxime (8mg/l)
Flexicult™ - Identification of Bacteria:

- E. coli
- Klebsiella sp
- E. faecalis
- Proteus spp
Laboratory culture

• $\geq 10^5$ Colony Forming Units per ml usual
• Cells sometimes taken into account
• E. coli can be pathogen or contaminant

• HPA
  • Single organism $\geq 10^4$ CFU/ml
  • $\geq 10^5$ CFU/ml mixed growth with one predominant organism
  • $\geq 10^3$ CFU/ml of E. coli of Staphylococcus saprophyticus
  • $\geq 10^5$ CFU/ml white cells= inflammation: if absent, true UTI less likely
Double blind placebo controlled RCT of trimethoprim 300mg daily for 3 days

General practice

59 women with dysuria and frequency and dipstick of MSU neg. for leucocytes and nitrites

Day 3: 5 (tri) vs 20 (placebo) had ongoing symptoms

Day 7: 2 (tri) vs 7 (placebos) had ongoing symptoms

NNT 4

Dipsticks accurately predicted negative urine culture but response to antibiotic treatment
Management: HPA guideline

- If **severe**, or ≥ 3 of:
  - dysuria
  - frequency
  - suprapubic tenderness
  - urgency
  - hematuria

*And*
- No vaginal irritation or discharge:
- Then **treat empirically** (90% will be culture positive)
Management: mild or ≤ 2 symptoms

- Urine *not cloudy*, NPV 97% so consider another diagnosis
- If *cloudy*, dipstick:
  - Nitrite and leucocyte and blood, or nitrite alone, treat with first line agent
  - Nitrite negative, leucocyte positive: treat if severe, consider delayed prescription, culture
  - Negative nitrite leucocyte and blood, 76% NPV
  - Negative nitrite and leucocyte but positive blood or protein: consider other diagnosis, symptomatic treatment, safety net
Older people

- Do not send culture in asymptomatic elderly with positive dipsticks
- Only send for culture if ≥ 2 signs of infection especially dysuria, fever >38C, new incontinence
- Do not treat asymptomatic bacteriuria as it does not reduce mortality or prevent symptomatic episodes, but increases side effects and resistance
Asymptomatic bactiuria in pregnancy

• Do not treat (SIGN)
Antibiotic treatment HPA

• **First line:**
  • *Trimethoprim* 200mg or *nitrofurantoin* 100mg m/r BD for 3 days (do not use nitrofurantoin if e-GFR ≤60

• **Second line:** perform culture in all treatment failures:
  • *Nitrofurantoin*: minimal resistance; >90% sensitive, little change since 1950’s: active against ESBLs; can be used in pregnancy; few side effects from short courses
  • *Fosfomycin*: 3g single dose minimal resistance: active against ESBLs but does not treat pyelonephritis
    – *Fluoroquinolones*: reserve for other infections: rapidly increasing resistance
    – Cephpodoxime is less effective than ciprofloxacin
    – *Ampicillin and amoxicillin*: >50% resistance
Antimicrobial agents for treating uncomplicated urinary tract infection in women (Review)

Zalmanovici Trestioreanu A, Green H, Paul M, Yaph J, Leibovici L

THE COCHRANE COLLABORATION®
Cochrane Review: search 2010

- 21 studies (6016 participants)
- Trimethoprim-sulfamethoxazole as effective as fluoroquinolones short term and long term symptomatic cure
- Beta-lactams as effective as TMP-SMX short and long term
- Nitrofurantoin similar to TMP-SMX short term and longer term
- Fluoroquinolones more effective in achieving microbiological short term bacteriological cure but of uncertain clinical significance
- Minimal data on the emergence of resistance after treatment
KEEP CALM AND CHECK THE BNF
BNF recommendations

- *Uncomplicated lower urinary-tract infections* often respond to **trimethoprim, nitrofurantoin, or amoxicillin** given for 7 days (3 days may be adequate for infections in women; see also Table 1, section 5.1); those caused by fully sensitive bacteria respond to two 3-g doses of amoxicillin (section 5.1.1.3). Widespread bacterial resistance to ampicillin, amoxicillin, and trimethoprim has been reported. Alternatives for resistant organisms include co-amoxiclav (amoxicillin with clavulanic acid), an oral cephalosporin, nitrofurantoin, pivmecillinam, or a quinolone.

- **Fosfomycin** [unlicensed] can be used, on the advice of a microbiologist, for the treatment of uncomplicated lower urinary-tract infections caused by multiple-antibacterial resistant organisms when other antibacterials cannot be used; in adults, it is given as a single oral dose of 3 g.
Duration of antibacterial treatment for uncomplicated urinary tract infection in women (Review)

Milo G, Katchman E, Paul M, Christiaens T, Baerheim A, Leibovici L
Duration of antibiotics

• Meta analysis of 32 trials showed that a 3 day course of antimicrobials was equivalent to a 5 to 10 day course in achieving symptomatic cure.

• Shorter courses were associated with fewer adverse effects.
Actual practice: the POETIC Study
(in progress, unpublished, not peer reviewed!)

• Explore the resistance profiles of isolated pathogens
• Symptomatic recovery
• UTI related use of health service resources
## Antibiotic Prescription

<table>
<thead>
<tr>
<th></th>
<th>Wales</th>
<th>England</th>
<th>Spain</th>
<th>The Netherlands</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Any antibiotic prescribed?</td>
<td>196 92.9</td>
<td>232 95.1</td>
<td>195 95.1</td>
<td>79 59.4</td>
<td>702 88.5</td>
</tr>
<tr>
<td>Trimethoprim</td>
<td>150 76.5</td>
<td>107 46.1</td>
<td>0 0.0</td>
<td>9 11.4</td>
<td>266 37.9</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>34 17.3</td>
<td>112 48.3</td>
<td>6 3.1</td>
<td>63 79.7</td>
<td>215 30.6</td>
</tr>
<tr>
<td>Fosfomycin</td>
<td>0 0.0</td>
<td>0 0.0</td>
<td>148 75.9</td>
<td>5 6.3</td>
<td>153 21.8</td>
</tr>
<tr>
<td>Co-amoxiclav</td>
<td>1 0.5</td>
<td>1 0.4</td>
<td>21 10.8</td>
<td>0 0.0</td>
<td>23 3.3</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>2 1.0</td>
<td>0 0.0</td>
<td>17 8.7</td>
<td>1 1.3</td>
<td>20 2.8</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>4 2.0</td>
<td>6 2.6</td>
<td>0 0.0</td>
<td>0 0.0</td>
<td>10 1.4</td>
</tr>
<tr>
<td>Cefalexin</td>
<td>3 1.5</td>
<td>5 2.2</td>
<td>0 0.0</td>
<td>0 0.0</td>
<td>8 1.1</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>0 0.0</td>
<td>0 0.0</td>
<td>2 1.0</td>
<td>0 0.0</td>
<td>2 0.3</td>
</tr>
</tbody>
</table>
Why is better targeted treatment important?
Antibiotic use and resistance

Correlation between penicillin use and prevalence of penicillin non-susceptible S pneumoniae
• Risk of ampicillin resistant E coli in 903 women associated with amoxicillin prescription ≥ 7 days in the previous month (OR 3.9; 1.65-9.34)
• And in 2-3 months (OR 2.29; 1.12-4.70)
• Higher doses, shorter duration associated with lower risk
• Trimethoprim resistant E. coli infections: Tri ≥ 7 days in previous month (OR 8.44; 3.12-22.86)
• And 2-3 months (OR 13.91; 3.31-58.3)
Antibiotic-resistant infections in primary care are symptomatic for longer and increase workload:

outcomes for patients with E. coli UTIs

Christopher C. Butler, Sharon Hillier, Zoe Roberts, Frank Dunstan, Anthony Howard and Stephen Palmer

ABSTRACT

Background

Antimicrobial resistance is considered to be one of the major threats to public health. However, the practical implications for patients and workload in primary care are largely unknown.

AIM

To determine outcomes for patients managed in primary care with an antibiotic-resistant strain compared to an antibiotic-sensitive Escherichia coli (E. coli) urinary tract infection (UTI).

Design

Nested case control study with prospective measurement of outcomes.

Setting

Ten general practices in South Wales.

Methods

Patients consulting with symptoms suggestive of UTI identified through systematic sampling, and with a laboratory-proven E. coli infection, were followed up by interview 1 month after their consultations and by searching of their medical records.

Results

Nine hundred and thirty-two patients were interviewed and had their medical records reviewed. The risk of patients reporting feeling poorly, “frequent or pain on urinating” and being “out of action” for more than 5 days after consulting was significantly increased for patients with resistant compared to sensitive infections. After adjusting for risk factors, there was an increased risk of “frequent or pain on urinating” and “being out of action” for those infected with a resistant E. coli. The median number of maximum reported days with at least one symptom was 17 days for patients with E. coli infections resistant to trimethoprim, 7 days for infections resistant to ampicillin, 7 days for infections resistant to any antibiotics, and 5 days for infections sensitive to all tested antibiotics. Even if treated with an appropriate antibiotic, infections caused by a resistant strain were asymptomatic for longer. For those infected with an organism resistant to at least one antibiotic, the odds ratio (OR) for re-visiting their GP within the next 30 days for the UTI was 1.47 (95% confidence interval [CI] = 1.10 to 1.96). The OR was 1.49 (95% CI = 1.11 to 2.00) for ampicillin resistance and 2.48 (95% CI = 1.30 to 4.59) for trimethoprin resistance.

Conclusions

Resistant E. coli UTIs are asymptomatic for longer and cause increased workload in general practice.

Keywords

anti-bacterial agents; cohort study; drug resistance; bacterial; primary health care; treatment outcomes; urinary tract infections.

INTRODUCTION

Antibiotic resistance increases the length of hospital stay and mortality in secondary care, but the situation in primary care is far from clear. Primary care clinicians are concerned about the issue, but only infrequently report anecdotally treatment failure associated with antibiotic resistance and may see it as a ‘public health or hospital issue’, remote from prescribers’ decisions for their individual patients. If it could be shown clearly that resistant infections were associated with poorer outcomes for patients managed in primary care, this may concentrate attention on the impact of antibiotic resistance for primary care and further promote the appropriate use of antibiotics. We therefore set out to compare outcomes for patients infected with resistant and sensitive Escherichia coli (E. coli) urinary tract infections (UTIs).

We chose to study UTI because UTI is one of the commonest bacterial infections managed in general practice. UTIs are very common and one in five patients is treated for a UTI each year in primary care. UTIs are classified as uncomplicated if there are no signs of infection in the urinary system and if the symptoms have been present for less than 7 days. Complicated UTIs are those that have symptoms for more than 7 days, those that recur, or those for which the patient has been prescribed antibiotics in the past 3 months.

932 patients with lab proven E. coli UTI

• Median number of maximum reported days with at least one symptom
  • 12 days if resistant to tri
  • 7 days if resistant to ampicillin
  • 7 days if resistant to any antibiotic
  • 5 days if sensitive to all
• Even if treatment with appropriate antibiotic, resistant infections were symptomatic for longer
• Resistant to 1 antibiotic, re-consulting in 30 days more common (OR 1.47; 1.10-2.00)
• R. to Ampicillin (OR 1.49; 1.11-2.00)
• R. to Tri (OR 2.48; 1.70-3.59)
The additional costs of antibiotics and re-consultations for antibiotic-resistant *Escherichia coli* urinary tract infections managed in general practice

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**ABSTRACT**

The emergence of antibiotic resistance is a major threat to public health. In the UK, most antibiotics are prescribed in general practice but the extra costs to general practice of resistant infections have not previously been well described. We compared the costs of treating patients presenting with resistant *Escherichia coli* urinary tract infections (UTIs) (resistant to ampicillin, trimethoprim or at least one antibiotic) with the costs of treating patients with UTIs that were sensitive to all six tested antibiotics (ampicillin, trimethoprim, amoxicillin/clavulanic acid, cefalexin, ciprofloxacin and nitrofurantoin) with regard to re-consultations and antibiotics prescribed. There were significantly higher antibiotic costs (mean extra antibiotic cost £1.19/€1.75), re-consultation costs (£2.42/€3.55) and total costs (£3.62/€5.31) for patients whose infections were resistant to at least one antibiotic compared with those with sensitive infections.

Extra costs of trimethoprim resistant infections = £11.21
Resistant bacteraemias in Wales 2005–2011

Figure 1: All-Wales resistance rates for *E. coli* bacteraemia (2005 to 2011).
Resistance in coliforms in the community in Wales 2005–2011

Figure 16: All-Wales antimicrobial resistance rates for coliforms from community urine samples (2005 to 2011)
E. Coli bacteremia by age group 2002-2011
Trends in Usage of Antibacterials in General Practice in England

Prescription Services

ADQs per Patient

Apr.96 - Mar.97
Apr.97 - Mar.98
Apr.98 - Mar.99
Apr.99 - Mar.00
Apr.00 - Mar.01
Apr.01 - Mar.02
Apr.02 - Mar.03
Apr.03 - Mar.04
Apr.04 - Mar.05
Apr.05 - Mar.06
Apr.06 - Mar.07
Apr.07 - Mar.08
Apr.08 - Mar.09
Apr.09 - Mar.10
Apr.10 - Mar.11

- Penicillins
- Cephalosporins
- Macrolides
- Tetracyclines
- Sulphonamides & trimethoprim
- Quinolones
- All other antibacterial drugs
- Metronidazole & tinidazole

NB If no ADQ is available, the DDD was used instead.
Consequences

• 400,000 resistant infections in EU on 2007
• 25,000 excess deaths
• 2.5M extra hospital days
• Costs 1.5BN Euro (excluding preventative measures)
• In US hospitalizations for resistant infections cost extra $6000 to $30000
• Antibiotics of last resort (carbapenems, tigecycline, linezolid, colistin, daptomycin) have high side effect burden and resistance has been reported in rapid time; totally resistant Klebsiella now in Southern Europe

European CDC and European Medicines Agency, 2009
• 7 year study
• 164 225 Coliform isolates routinely submitted from 240 general practices serving 1.7 M people
• Quartile that had the greatest reduction in total antibiotic prescribing has a 5.2% reduction in ampicillin resistance
• Changes of 0.4%, 2.4%, and -0.3% in other quartiles
• Decrease in trimethoprim resistance in the two quartiles that reduced prescribing the most
Case revisited

- Urine not cloudy
- Probably don’t send urine for culture
- Explain natural history and triggers to re-consult
- No prescription or delayed prescription of antibiotics
Infection Q&A