Variation in antibiotic prescribing, and patient outcomes of uncomplicated urinary tract infection: a prospective four-country primary care cohort study. The POETIC Observational study.

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16.06.2105
Wonca Europe
GRACE-Observational study
Types of Antibiotic Prescribed

Butler etc. al. BMJ. 2009 Jun 23; 338:b2242.
Antibiotics make little difference to outcome
But no microbiology data in the GRACE Observational Study (WP8)

“\textit{I need to prescribe broad spectrum agents because:}

\begin{itemize}
  \item My patients are different
  \item There is more resistance where I practice
\end{itemize}
Aim of POETIC Stage 2:

“To describe presentation, management and outcome of women with suspected UTI in contrasting European countries (Wales, England, The Netherlands, and Spain)”

Design:

A prospective observational study of approx. 800 women.
- Clinicians recorded presenting features and management decisions
- Aimed to collect urine sample from all participants
- Participant-completed 11 symptom diary each day for 14 days
# UTI definitions

<table>
<thead>
<tr>
<th>Primary</th>
<th>Secondary (for sensitivity analysis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pure or predominant* culture at $\geq 10^5$ CFU/mL of any organism</td>
<td>Pure culture at $\geq 10^3$ CFU/mL of any organism</td>
</tr>
<tr>
<td>*Predominant defined as a $10^3$ difference between the first and the second most abundant isolate on any subsequent organisms</td>
<td></td>
</tr>
</tbody>
</table>
**Recovery definitions**

<table>
<thead>
<tr>
<th>Full recovery</th>
<th>Resolution of moderately bad symptoms</th>
<th>Resolution of daytime frequency, night-time frequency, and urgency</th>
</tr>
</thead>
<tbody>
<tr>
<td>First day that all 11 symptoms were scored 0 (normal/not a problem)</td>
<td>First day that all symptoms were scored 2 (slight problem) or lower</td>
<td>First day that these three symptoms are all scored 0*</td>
</tr>
</tbody>
</table>

* Based on a factor analysis that demonstrated strong correlation between these symptoms
Participants recruited (N=797)

- Baseline CRF (n=793, 99.5%)
- Samples analysed at local lab (n=726, 91.1%)
- Diary (n=568, 71.6%)

Positive culture at local lab (n=259, 35.7%)

Sample analysed at central lab (n=209, 80.7%)
Participant characteristics

• Mean clinician-rated symptom severity score* 9.5 / 18 (95% CI: 9.2 to 9.8)
• Median age 45 years (IQR: 30 to 61 years)
• 342 participants not in paid employment (43%)
• 57 had been off work because of their illness (13%)
• 459 had urine infection diagnosed by a doctor in the past (82%)
• 300 had treated for at least one UTI in past year (55%)
• 184 had tried managing urine infection with cranberry juice (33%)
• Wide variation between countries

*Score based on the summation of day-time frequency, night-time frequency, and urgency severities
Management / urine sample characteristics

• Dipstick test performed in 669 (85%)
• 282 had cloudy urine (43%)
• 198 had offensively smelling urine (30%)
• 103 had other tests performed (13%):
  • 50 had dipslide (all in the Netherlands)
  • 28 had MSU (mostly Wales)
• Antibiotics were prescribed to 702 at the index consultation (89%)
  • Lowest in the Netherlands (59%)
  • Comparable elsewhere (93% to 95%)
  • Wide variation by country in choice of antibiotic
Antibiotic choice by country

- **Wales**
  - Fosfomycin
  - Trimethoprim
  - Nitrofurantoin
  - Ciprofloxacin
  - Other antibiotic

- **England**
  - Fosfomycin
  - Trimethoprim
  - Nitrofurantoin
  - Ciprofloxacin
  - Other antibiotic

- **Spain**
  - Fosfomycin
  - Trimethoprim
  - Nitrofurantoin
  - Ciprofloxacin
  - Other antibiotic

- **The Netherlands**
  - Fosfomycin
  - Trimethoprim
  - Nitrofurantoin
  - Ciprofloxacin
  - Other antibiotic
Modelling approach

• Linear, logistic, and Cox PH models fitted, as appropriate
• All models controlled for clustering of patients within practices
• Country fitted as fixed effect, compared to overall average
• All explanatory variables tested in univariable analyses
  • If associated with outcome at p<0.1 level, retain for multivariable analysis
• MV analysis involved manual stepwise process
  • Variables not associated at p<0.05 level removed one-by-one until final model obtained
## Microbiological confirmation of a UTI

*Primary definition*

<table>
<thead>
<tr>
<th>Country</th>
<th>Samples analysed</th>
<th>Confirmed UTI</th>
<th>Prevalence (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>OVERALL</strong></td>
<td>726</td>
<td>259</td>
<td>36</td>
<td>32 to 39%</td>
</tr>
<tr>
<td>Wales</td>
<td>199</td>
<td>48</td>
<td>24</td>
<td>19 to 31%</td>
</tr>
<tr>
<td>England</td>
<td>218</td>
<td>53</td>
<td>24</td>
<td>19 to 30%</td>
</tr>
<tr>
<td>Spain</td>
<td>182</td>
<td>77</td>
<td>42</td>
<td>35 to 50%</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>127</td>
<td>81</td>
<td>64</td>
<td>55 to 72%</td>
</tr>
</tbody>
</table>
Microbiological confirmation of a UTI

Primary definition

• Odds of having a microbiologically-confirmed UTI compared to the overall average:
  • Higher in the Netherlands (OR = 3.4, 95% CI: 2.2 to 5.2)
  • Lower in Wales (OR = 0.5, 95% CI: 0.3 to 0.7)
  • Lower in England (OR = 0.5, 95% CI: 0.4 to 0.8)

• Higher odds for participants with positive nitrites (OR = 3.4, 95% CI: 2.2 to 5.4)

• Higher odds for participants with cloudy urine (OR = 2.5, 95% CI: 1.6 to 3.8)
Microbiological confirmation of a UTI

Definition for sensitivity analysis

- Overall prevalence increases to 39%
  - Wales – 27%
  - England – 23%
  - Spain – 55%
  - The Netherlands – 65%

- Odds of UTI in Spain higher than overall average
  (OR = 1.8, 95% CI: 1.3 to 2.4)

- High agreement between definitions (88%)
  - Disagreement mostly due to lower threshold
  - Also due to predominant growth in Wales and England
Antibiotic prescribing

<table>
<thead>
<tr>
<th>Country</th>
<th>Prevalence (%)</th>
<th>95% CI</th>
<th>Odds ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>OVERALL</td>
<td>89</td>
<td>86 to 91</td>
<td>Reference</td>
<td>category</td>
</tr>
<tr>
<td>Wales</td>
<td>93</td>
<td>89 to 96</td>
<td>0.8</td>
<td>0.3 to 1.7</td>
</tr>
<tr>
<td>England</td>
<td>95</td>
<td>92 to 97</td>
<td>2.7</td>
<td>1.1 to 6.7</td>
</tr>
<tr>
<td>Spain</td>
<td>95</td>
<td>91 to 97</td>
<td>2.3</td>
<td>0.9 to 6.2</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>59</td>
<td>51 to 67</td>
<td>0.2</td>
<td>0.1 to 0.5</td>
</tr>
</tbody>
</table>

- Odds of being prescribed antibiotics associated with:
  - Higher clinician-rated symptom severity score (OR per unit increase = 1.2, 95% CI: 1.1 to 1.3)
  - Positive leukocyte result (OR = 10.6, 95% CI: 4.5 to 25.0)
  - Positive blood result (OR = 2.3, 95% CI: 1.0 to 5.1)
Appropriate antibiotic prescribing

1. Prescribed antibiotic at index consultation
   - Yes
     - Microbiologically confirmed UTI?*
       - Yes
         - Sample sensitive to prescribed antibiotic?
           - Yes
             - 162/675 (24.0%)
           - No
             - 28/675 (4.1%)
       - No
         - 400/675 (59.3%)
   - No
     - Microbiologically confirmed UTI?*
       - Yes
         - 22/675 (3.3%)
       - No
         - 63/675 (9.3%)

Appropriate prescribing: 225/675 (33.3%)
Inappropriate prescribing: 450/675 (66.7%)
Other management outcomes

- 69 participants had purchased non-prescription medication (14%)
  - Lowest in Spain (1%), highest in England (19%)
- 669 had dipstick test performed (85%)
  - Lowest in Spain (69%), highest in The Netherlands (96%)
- In 335 instances, GP would have normally sent sample for culture (48%)
  - Lowest in The Netherlands (17%), highest in England/Wales (60%)
  - Age, Leukocytes, Protein, Cloudy urine, Smelly urine associated with higher odds of sending sample for culture
- 225 had follow-up arranged with a GP or nurse (29%)
  - Lowest in England (12%), highest in Spain (55%)
  - Age, cloudy urine, temperature associated with higher odds of follow-up
  - Leukocytes, nitrites associated with lower odds of follow-up
## Time to recovery

<table>
<thead>
<tr>
<th>Recovery definition</th>
<th>UTI</th>
<th>No UTI</th>
<th>Antibiotics</th>
<th>No Antibiotics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full recovery</td>
<td>8.5 (6, &gt;14)</td>
<td>10 (6, &gt;14)</td>
<td>9 (5, &gt;14)</td>
<td>13 (7, &gt;14)</td>
</tr>
<tr>
<td>Resolution of moderately bad symptoms</td>
<td>3 (3, 6)</td>
<td>4 (2, 7)</td>
<td>4 (2, 6)</td>
<td>3.5 (2, 8)</td>
</tr>
<tr>
<td>Resolution of daytime frequency, night-time frequency</td>
<td>7 (4, &gt;14)</td>
<td>8 (5, &gt;14)</td>
<td>7 (4, &gt;14)</td>
<td>8.5 (5, &gt;14)</td>
</tr>
</tbody>
</table>
Time to recovery

• Predictors of recovery from multivariable analysis:
  • Symptom severity and no. times treated for urine infection in past year in all three time to recovery models
  • Antibiotics prescribed at initial consultation (full recovery only)
  • Age (time to resolution of daytime/night-time frequency and urgency only)

• No evidence of country differences

• No evidence of an interaction between UTI and antibiotics

• Overall symptom burden over follow-up period higher for those:
  • With higher GP-rated symptom severity at baseline
  • Who had symptoms for 8+ days prior to consulting
  • Who had been treated for a urine infection 2/3+ times in the past year
Other post-consultation outcomes

• 169 reported they had no enablement (32%)
  • Odds higher in Spain, lower in The Netherlands
• 68 participants prescribed additional medicines during follow-up (13%)
  • Lowest in Spain (3%), highest in Wales (22%)
  • Temperature, treated for a urine infection 3+ times in past year associated with higher odds of additional prescriptions
• 130 consulted with GP or OOH during follow-up period (24%)
  • Lowest in Spain (9%), highest in Wales (34%)
<table>
<thead>
<tr>
<th>Country</th>
<th>Wales</th>
<th>England</th>
<th>Spain</th>
<th>Netherlands</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>No UTI confirmed</td>
<td>151</td>
<td>75.9</td>
<td>165</td>
<td>75.7</td>
<td>46</td>
</tr>
<tr>
<td>UTI-confirmed</td>
<td>48</td>
<td>24.1</td>
<td>53</td>
<td>24.3</td>
<td>81</td>
</tr>
<tr>
<td><strong>Urinary pathogen identification</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enterobactericeae</td>
<td>44</td>
<td>91.7</td>
<td>48</td>
<td>90.6</td>
<td>66</td>
</tr>
<tr>
<td>Coagulase negative staphylococci (S. saprophyticus)</td>
<td>2</td>
<td>4.2</td>
<td>1</td>
<td>1.9</td>
<td>9</td>
</tr>
<tr>
<td>Other organisms</td>
<td>2</td>
<td>4.2</td>
<td>4</td>
<td>7.6</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>48</td>
<td>100.0</td>
<td>53</td>
<td>100.0</td>
<td>77</td>
</tr>
<tr>
<td><strong>Antibiotic resistant</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fosfomycin</td>
<td>44</td>
<td>3 (6.8)</td>
<td>48</td>
<td>2 (4.2)</td>
<td>44</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>44</td>
<td>0 (0.0)</td>
<td>48</td>
<td>4 (8.2)</td>
<td>44</td>
</tr>
<tr>
<td>Trimethoprim</td>
<td>44</td>
<td>10 (22.7)</td>
<td>48</td>
<td>8 (16.7)</td>
<td>44</td>
</tr>
<tr>
<td>Other antibiotic</td>
<td>44</td>
<td>15 (34.1)</td>
<td>48</td>
<td>27 (56.2)</td>
<td>44</td>
</tr>
</tbody>
</table>

*Based on those who have a microbiologically confirmed UTI
†Other antibiotic includes: Amoxicillin, Ceftriaxone, Gentamicin, Cephalaxin, Cefixime, Ceftazidime, Ciprofloxacin, Methicillin, Temocillin and Ertapenem
Percentage of UTI pathogens identified in urine samples*
*The height of each stack reflects the percentage of participants with a microbiologically-confirmed UTI
Resistance to antibiotics commonly prescribed for UTIs in those with confirmed UTIs*

*“Other antibiotics” has been removed from this chart to make the main three UTI treatments stand out a bit more.
Same data as presented in slides 4, but legend and axis switched.
Time to full recovery by country - Unadjusted

### Countries compared to the overall average

<table>
<thead>
<tr>
<th>Country</th>
<th>HR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wales</td>
<td>0.95</td>
<td>0.79-1.44</td>
<td>0.589</td>
</tr>
<tr>
<td>England</td>
<td>1.00</td>
<td>0.85-1.19</td>
<td>0.959</td>
</tr>
<tr>
<td>Spain</td>
<td>1.06</td>
<td>0.89-1.26</td>
<td>0.556</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>0.99</td>
<td>0.82-1.21</td>
<td>0.945</td>
</tr>
</tbody>
</table>

### The Netherlands as the reference category

<table>
<thead>
<tr>
<th>Country</th>
<th>HR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wales</td>
<td>0.96</td>
<td>0.69-1.32</td>
<td>0.786</td>
</tr>
<tr>
<td>England</td>
<td>1.01</td>
<td>0.75-1.36</td>
<td>0.941</td>
</tr>
<tr>
<td>Spain</td>
<td>1.06</td>
<td>0.78-1.45</td>
<td>0.699</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>Reference category</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Time to full recovery by country – Adjusted for case-mix*

<table>
<thead>
<tr>
<th>Country</th>
<th>HR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Countries compared to the overall average</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wales</td>
<td>0.97</td>
<td>0.79-1.18</td>
<td>0.747</td>
</tr>
<tr>
<td>England</td>
<td>1.08</td>
<td>0.91-1.29</td>
<td>0.365</td>
</tr>
<tr>
<td>Spain</td>
<td>1.04</td>
<td>0.86-1.25</td>
<td>0.714</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>0.92</td>
<td>0.75-1.13</td>
<td>0.429</td>
</tr>
<tr>
<td><strong>The Netherlands as the reference category</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wales</td>
<td>1.05</td>
<td>0.75-1.48</td>
<td>0.774</td>
</tr>
<tr>
<td>England</td>
<td>1.18</td>
<td>0.86-1.61</td>
<td>0.303</td>
</tr>
<tr>
<td>Spain</td>
<td>1.12</td>
<td>0.81-1.55</td>
<td>0.475</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>Reference category</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Case-mix variables: GP-rated symptom severity score, number of times a urine infection had been treated in the past year
Time to full recovery by country – Adjusted for case-mix and management*†

<table>
<thead>
<tr>
<th>Country</th>
<th>HR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Countries compared to the overall average</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wales</td>
<td>0.94</td>
<td>0.77-1.15</td>
<td>0.547</td>
</tr>
<tr>
<td>England</td>
<td>1.03</td>
<td>0.87-1.23</td>
<td>0.725</td>
</tr>
<tr>
<td>Spain</td>
<td>0.99</td>
<td>0.82-1.20</td>
<td>0.944</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>1.04</td>
<td>0.84-1.29</td>
<td>0.738</td>
</tr>
</tbody>
</table>

| The Netherlands as the reference category |
| Wales        | 0.91   | 0.64-1.28| 0.580   |
| England      | 1.00   | 0.72-1.38| 0.976   |
| Spain        | 0.96   | 0.69-1.34| 0.799   |

*Case-mix variables: GP-rated symptom severity score, number of times a urine infection had been treated in the past year. †Management variable: Whether participant was prescribed antibiotics at the index consultation.
In summary: at a country level...

- Minor variations in case mix
- Wide variation in UIT on culture
- Wide variation in investigation
- Wide variation in overall antibiotic prescribing and antibiotic choice
- Differences in outcome if UTI positive or antibiotic given
- Overall, no differences in recovery
- We need to identify most cost effective strategy and apply it EUROPE WIDE
Antibiotic choice by country

- Wales
- England
- Spain
- The Netherlands

- Fosfomycin
- Trimethoprim
- Nitrofurantoin
- Co-amoxiclav
- Cephalosporins
- Ciprofloxacin
- Other antibiotic