The Need for Rapid Diagnostic Tests for Antimicrobial Resistance

Till T Bachmann
Division of Infection and Pathway Medicine
University of Edinburgh

Antibiotic Guardian Webinar
"Fighting the Growing Threat of Antimicrobial Resistance"
16th November 2016
Bachmann Group Mission

Enhance **understanding** and **diagnostic technologies** to enable **targeted** and **effective antimicrobial therapy**
The Global Challenge of Antimicrobial Resistance

Deaths attributable to AMR every year compared to other major causes of death

AMR now 700,000 (low estimate)

- Tetanus: 60,000
- Road traffic accidents: 1.2 million
- Measles: 130,000
- Diarrhoeal disease: 1.4 million
- Cholera: 100,000–120,000
- Diabetes: 1.5 million
- Cancer: 8.2 million

AMR in 2050
10 million

North America: 317,000
Europe: 390,000
Africa: 4,150,000
Latin America: 392,000
Asia: 4,730,000
Oceania: 22,000

Mortality per 10,000 population

Correlation of Antibiotic Use and Resistance

- The more antibiotics used the higher the likelihood of antibiotic resistance
- The overall uptake of antibiotics in a population, as well as how antibiotics are consumed, has an impact on antibiotic resistance


[http://amr-review.org](http://amr-review.org)
Global MRSA Trends

**FIGURE ES-1**: Percentage of *Staphylococcus aureus* isolates that are methicillin resistant (MRSA) in selected countries, 1999–2014

*Source: CDDEP 2015*
Global Spread of NDM-1 (New Delhi Metallo-lactamase-1)

**FIGURE 1-4:** Spread of New Delhi metallo-beta-lactamase-1: first detection

*Source: Johnson and Woodford 2013 (adapted)*

http://cddep.org/publications/state_worlds_antibiotics_2015
Global Policy Response to AMR

18 November 2016
EUROPEAN ANTIBIOTIC AWARENESS DAY
A European Health Initiative
TACKLING ANTIMICROBIAL RESISTANCE ON TEN FRONTS

- Public awareness
- Sanitation and hygiene
- Antibiotics in agriculture and the environment
- Vaccines and alternatives
- Surveillance
- Rapid diagnostics
- Human capital
- Drugs
- Global Innovation Fund
- International coalition for action

Unmet Need in Clinical Microbiology

Rapid Diagnostic Test to
- Support Therapy Decision & Choice of Antibiotic
- Support Patient Management Decision
AMR Diagnostics Prizes to Win

• **EU Reducing the Mis-use of Antibiotics Prize**
  – €1 million
  – Avoid antibiotics for viral upper respiratory tract infections

• **UK Longitude Prize**
  – £10 million
  – Point of Care Test
  – Any type of bacterial infection

• **US Antimicrobial Resistance Rapid, Point-of-Need Diagnostic Test’ Challenge**
  – $20 million
  – Rapid, Point-of-Care Diagnostic Tests
  – Identify highly resistant bacterial infections
Early stage AMR Diagnostics Prizes & Initiatives

• **UK Discovery Awards**
  - small seed grants to help teams and individuals further develop their ideas for the Longitude Prize
  - **Up to £20,000 each**
  - Point of Care Test
  - Deadline 26 August 2016.
  - [https://longitudeprize.org/discoveryawards](https://longitudeprize.org/discoveryawards)

• **AMR DxC**
  - Innovative diagnostics to tackle AMR
  - Early Career Researcher Competition
  - **2017 Winter School in Bangalore**
  - **2017 Winter School in Edinburgh**
  - @AMR_DxC
You must develop a point-of-care diagnostic test that can rule out antibiotic use or help identify an effective antibiotic to treat a patient.

https://longitudeprize.org/prize-rules
Which markers should we measure?

- **Susceptibility** *(which antibiotics *can I use?*)
- **Resistance** *(which antibiotics *should I not use?*)
- **Bacterial type**
- **Bacterial or viral**

Sample to Answer Diagnostic Test Format

Sample → Disposable Cartridge → Reusable Reader → Answer → Result
Chronic Wound Care Programme

- Development of an easy-to-use, portable medical device that can be readily applied to diagnose and treat chronic wounds in a clinical environment and in the community.
- University of Edinburgh, NHS Lothian, Zisys Ltd. research provider
- Aim: Molecular MRSA detection from clinical specimen without PCR
Electrochemical Impedance Spectroscopy (EIS) for Molecular Detection

- Label free
- Surface sensitive
- Functionalisation introduces specificity
- Small AC potential $\rightarrow$ current response
- Frequencies $10^{-1}$ – $10^6$ Hz

Fe(CN)$_6^{3/-4}$

E - Excitation potential
I - current response

Nyquist Plot

Z 'im'
Z 're'
Amplification-free NDM-1 **Plasmid** Detection

Amplification-free MRSA Genomic DNA Detection

Signal Ratios caused by incubation with gDNA extracted from MRSA cells spiked into human wound fluid and uninoculated human wound fluid. Signal Ratio measured 10 min after sample addition.
**One Detection Technology – Many Targets**

**MRSA gDNA**


**Pathogen rRNA**


**microRNA**

Ongoing, In collaboration with Dr. James Dear, University of Edinburgh

**EIS platform**

**TREM-1, MMP9 protein infection biomarker**


**Homo Serine Lactone (HSL) quorum sensing biomarker**


**VEGF Aptamer**

Ongoing, In collaboration with Prof. Kazuoh Ikekuburo, Tokyo University of Agriculture and Technology
Contact

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- Deputy Head of Division of Infection and Pathway Medicine
- Programme Director Clinical Microbiology and Infectious Diseases

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The diagnostic process for serious infections in children

Prof Ann Van den Bruel
Director NIHR Diagnostic Evidence Cooperative
Nuffield Department of Primary Care Health Sciences
University of Oxford
Introduction

• Acute infections common in primary care
  – Cough, cold, earache and fever most common symptoms

• Pressure on secondary care is increasing
  – 20% paediatric ED visits for febrile illness
  – Unplanned paediatric hospital admissions increased by 20% over last decade

• Diagnostic uncertainty leads to care escalation to the next level up
1/300 will have a serious infection
Clinical tools in primary care

- History, observation, clinical examination
- Laboratory tests, radiology
- Watchful waiting
Evidence accumulation

- Prospective cross-sectional study, n=4,000
- Prospective validation study, n=8,962
- Cluster randomised controlled trial, n=3,147
Fever:
Different setting – Different diagnostic value

Temperature threshold used in study:

\[ pr > 38.5 - 38.9°C \]
\[ TM \geq 39 \text{ or } 39.5°C \]
\[ \Phi \ £ > 40°C \]

Van den Bruel et al., Lancet 2010
### Alarm symptoms

<table>
<thead>
<tr>
<th>Study reference</th>
<th>Prevalence</th>
<th>Age range</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>Cyanosis</td>
<td>5</td>
<td>Low</td>
<td>&lt;17 years</td>
<td>52.20 (10.50–258)</td>
</tr>
<tr>
<td></td>
<td>33</td>
<td>High</td>
<td>3 months to 16 years</td>
<td>2.66 (1.73–4.10)</td>
</tr>
<tr>
<td></td>
<td>45†</td>
<td>High</td>
<td>1 month to 15 years</td>
<td>50.20 (2.97–846)</td>
</tr>
<tr>
<td>Poor peripheral circulation</td>
<td>5†</td>
<td>Low</td>
<td>&lt;17 years</td>
<td>38.80 (11.20–134)</td>
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<tr>
<td></td>
<td>425</td>
<td>Intermediate</td>
<td>1 month to 5 years</td>
<td>4.71 (2.07–10.7)</td>
</tr>
<tr>
<td></td>
<td>425†</td>
<td>Intermediate</td>
<td>1 month to 5 years</td>
<td>10.50 (5.00–22.1)</td>
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<td></td>
<td>33</td>
<td>High</td>
<td>3 months to 16 years</td>
<td>17.70 (2.36–132)</td>
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<tr>
<td></td>
<td>41†</td>
<td>High</td>
<td>1 month to 5 years</td>
<td>11.70 (4.78–28.7)</td>
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<tr>
<td></td>
<td>45†</td>
<td>High</td>
<td>1 month to 15 years</td>
<td>3.71 (2.32–5.93)</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>High</td>
<td>1–36 months</td>
<td>2.39 (1.50–3.82)</td>
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<tr>
<td>Crackles</td>
<td>5</td>
<td>Low</td>
<td>&lt;17 years</td>
<td>6.00 (2.52–10.10)</td>
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<tr>
<td></td>
<td>46∥</td>
<td>Intermediate</td>
<td>2–59 months</td>
<td>1.51 (0.81–2.83)</td>
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<tr>
<td>Decreased breathing sounds</td>
<td>5</td>
<td>Low</td>
<td>&lt;17 years</td>
<td>9.30 (4.42–19.70)</td>
</tr>
<tr>
<td></td>
<td>46∥</td>
<td>Intermediate</td>
<td>2–59 months</td>
<td>2.21 (0.89–5.50)</td>
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<tr>
<td>Short of breath</td>
<td>5</td>
<td>Low</td>
<td>&lt;17 years</td>
<td>9.30 (5.83–14.80)</td>
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<tr>
<td></td>
<td>46∥</td>
<td>Intermediate</td>
<td>2–59 months</td>
<td>1.11 (0.70–1.74)</td>
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<tr>
<td></td>
<td>24</td>
<td>High</td>
<td>1–36 months</td>
<td>3.60 (2.06–6.28)</td>
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<tr>
<td>Rapid breathing</td>
<td>5</td>
<td>Low</td>
<td>&lt;17 years</td>
<td>9.78 (5.71–16.70)</td>
</tr>
<tr>
<td></td>
<td>47∥</td>
<td>Intermediate</td>
<td>&lt;2 years</td>
<td>3.08 (2.41–3.94)</td>
</tr>
<tr>
<td></td>
<td>33</td>
<td>High</td>
<td>3 months to 16 years</td>
<td>1.26 (1.07–1.49)</td>
</tr>
</tbody>
</table>

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Van den Bruel et al., Lancet 2010
Alarm symptoms

<table>
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<tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>Meningeal irritation</td>
<td>Low</td>
<td>&lt;17 years</td>
<td>25.70 (3.09-213)</td>
<td>0.97 (0.91-1.03)</td>
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<tr>
<td>44†</td>
<td>Intermediate</td>
<td>3 months to 6 years</td>
<td>275 (1670-4526)</td>
<td>0.52 (0.35-0.76)</td>
</tr>
<tr>
<td>48‡</td>
<td>Intermediate</td>
<td>&gt;1 month to 16 years</td>
<td>13.90 (5.41-35.60)</td>
<td>0.61 (0.47-0.79)</td>
</tr>
<tr>
<td>45†</td>
<td>High</td>
<td>1 month to 15 years</td>
<td>2.57 (2.16-3.06)</td>
<td>0.01 (0.00-0.15)</td>
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<tr>
<td>Petechial rash</td>
<td>Low</td>
<td>&lt;17 years</td>
<td>12.50 (1.66-94.19)</td>
<td>0.97 (0.91-1.03)</td>
</tr>
<tr>
<td>44†</td>
<td>Intermediate</td>
<td>3 months to 6 years</td>
<td>83.70 (4.50-1475)</td>
<td>0.86 (0.73-1.01)</td>
</tr>
<tr>
<td>48§</td>
<td>Intermediate</td>
<td>&gt;1 month to 6 years</td>
<td>9.00 (5.26-15.3)</td>
<td>0.28 (0.16-0.48)</td>
</tr>
<tr>
<td>49§</td>
<td>Intermediate</td>
<td>≤15 years</td>
<td>7.00 (4.60-10.70)</td>
<td>0.19 (0.08-0.46)</td>
</tr>
<tr>
<td>45†</td>
<td>High</td>
<td>1 month to 15 years</td>
<td>6.18 (2.68-14.30)</td>
<td>0.81 (0.73-0.91)</td>
</tr>
<tr>
<td>Seizures</td>
<td>Low</td>
<td>&lt;17 years</td>
<td>20.70 (4.83-88.60)</td>
<td>0.94 (0.86-1.03)</td>
</tr>
<tr>
<td>43¶</td>
<td>Intermediate</td>
<td>6 months to 6 years</td>
<td>5.90 (1.79-19.00)</td>
<td>0.80 (0.59-1.08)</td>
</tr>
<tr>
<td>44†</td>
<td>Intermediate</td>
<td>3 months to 6 years</td>
<td>3.50 (1.69-7.17)</td>
<td>0.76 (0.58-1.00)</td>
</tr>
<tr>
<td>Unconsciousness</td>
<td>Low</td>
<td>&lt;17 years</td>
<td>1.68 (0.66-4.27)</td>
<td>0.96 (0.90-1.04)</td>
</tr>
<tr>
<td>45†</td>
<td>High</td>
<td>1 month to 15 years</td>
<td>19.80 (6.17-63.50)</td>
<td>0.91 (0.81-1.02)</td>
</tr>
<tr>
<td>Decreased skin elasticity</td>
<td>High</td>
<td>1 month to 5 years</td>
<td>155 (9.03-2677)</td>
<td>0.73 (0.57-0.93)</td>
</tr>
<tr>
<td>Hypotension**</td>
<td>Low</td>
<td>&lt;17 years</td>
<td>10.70 (3.87-29.8)</td>
<td>0.67 (0.56-0.81)</td>
</tr>
<tr>
<td>49‡</td>
<td>Intermediate</td>
<td>≤15 years</td>
<td>9.40 (1.99-44.70)</td>
<td>0.74 (0.56-0.99)</td>
</tr>
<tr>
<td>Any abnormal finding in history or physical examination</td>
<td>Intermediate</td>
<td>&lt;24 months</td>
<td>4.42 (2.87-6.80)</td>
<td>0.18 (0.71-0.44)</td>
</tr>
</tbody>
</table>
### Alarmsymptomen

*Van den Bruel et al., Lancet 2010*

<table>
<thead>
<tr>
<th>Study reference</th>
<th>Prevalence*</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td><strong>All serious infections</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yale Observation Scale†</td>
<td>30</td>
<td>Intermediate</td>
<td>0.16 (0.13-0.53)</td>
<td>0.01 (0.00-0.26)</td>
</tr>
<tr>
<td></td>
<td>28</td>
<td>Low</td>
<td>0.97 (0.82-1.15)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>32</td>
<td>Low</td>
<td>0.19 (0.03-1.17)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>22</td>
<td>Low</td>
<td>0.68 (0.50-0.93)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>21</td>
<td>Low</td>
<td>0.68 (0.55-0.85)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>25</td>
<td>Intermediate</td>
<td>0.91 (0.74-1.12)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>26</td>
<td>Intermediate</td>
<td>0.93 (0.74-1.18)</td>
<td></td>
</tr>
</tbody>
</table>

Yale Observation Scale or any normal finding in history or physical examination

Five-stage decision tree‡

**Pneumonia**

- Short of breath and parent concerned illness different
- Short of breath and clinician concerned something is wrong

**Meningitis**

- Any abnormal neurological finding or sought care <48 h
- Petechiae or nuchal rigidity or coma

**Dehydration from gastroenteritis**

- Any two of:
  - Absent tears, dry mucous membranes, ill appearance, poor peripheral circulation

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Sensitivity 32.5%
Specificity 78.9%
LR+ 2.9
LR- 0.86
# Alarm symptoms

<table>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>Global assessment</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Parental concern†</td>
<td>5</td>
<td>Low</td>
<td>1:00 (0:51-1:89)</td>
<td>0:99 (0:51-1:89)</td>
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<tr>
<td>Clinician instinct that something wrong</td>
<td>5</td>
<td>Low</td>
<td>1:00 (0:51-1:89)</td>
<td>0:99 (0:51-1:89)</td>
</tr>
<tr>
<td>Clinical impression</td>
<td>5</td>
<td>Low</td>
<td>1:00 (0:51-1:89)</td>
<td>0:99 (0:51-1:89)</td>
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<tr>
<td></td>
<td>36</td>
<td>Intermediate</td>
<td>1:00 (0:51-1:89)</td>
<td>0:99 (0:51-1:89)</td>
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<tr>
<td></td>
<td>40</td>
<td>Intermediate</td>
<td>1:00 (0:51-1:89)</td>
<td>0:99 (0:51-1:89)</td>
</tr>
<tr>
<td></td>
<td>49‡</td>
<td>Intermediate</td>
<td>1:00 (0:51-1:89)</td>
<td>0:99 (0:51-1:89)</td>
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<tr>
<td></td>
<td>42§</td>
<td>Intermediate</td>
<td>1:00 (0:51-1:89)</td>
<td>0:99 (0:51-1:89)</td>
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<tr>
<td>Child appears ill</td>
<td>27</td>
<td>Intermediate</td>
<td>1:00 (0:51-1:89)</td>
<td>0:99 (0:51-1:89)</td>
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<tr>
<td></td>
<td>24</td>
<td>High</td>
<td>1:00 (0:51-1:89)</td>
<td>0:99 (0:51-1:89)</td>
</tr>
<tr>
<td>Child behaviour</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Changed crying pattern</td>
<td>5</td>
<td>Low</td>
<td>1:00 (0:51-1:89)</td>
<td>0:99 (0:51-1:89)</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>High</td>
<td>1:00 (0:51-1:89)</td>
<td>0:99 (0:51-1:89)</td>
</tr>
<tr>
<td></td>
<td>45‡</td>
<td>High</td>
<td>1:00 (0:51-1:89)</td>
<td>0:99 (0:51-1:89)</td>
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<tr>
<td>Child drowsy</td>
<td>5</td>
<td>Low</td>
<td>1:00 (0:51-1:89)</td>
<td>0:99 (0:51-1:89)</td>
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<td></td>
<td>44¶</td>
<td>Intermediate</td>
<td>1:00 (0:51-1:89)</td>
<td>0:99 (0:51-1:89)</td>
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<td></td>
<td>45¶</td>
<td>High</td>
<td>1:00 (0:51-1:89)</td>
<td>0:99 (0:51-1:89)</td>
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<tr>
<td>Child moaning</td>
<td>5</td>
<td>Low</td>
<td>1:00 (0:51-1:89)</td>
<td>0:99 (0:51-1:89)</td>
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<tr>
<td>Child inconsolable</td>
<td>5</td>
<td>Low</td>
<td>1:00 (0:51-1:89)</td>
<td>0:99 (0:51-1:89)</td>
</tr>
</tbody>
</table>

*Prevalence:* Low, Intermediate, High

Van den Brueel et al., Lancet 2010
Clinical prediction rule

- No gut feeling
- No dyspnoea
- No fever ≥40°C

Van den Bruel et al., BJGP 2007
Verbakel BMJ Open 2015
<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>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Procalcitonin (ng/ml)</td>
<td></td>
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<tr>
<td>Thayil</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</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</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>
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<tr>
<td>C reactive protein (mg/L)</td>
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<td></td>
</tr>
<tr>
<td>Hsiao</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>
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<tr>
<td>Berger</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</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</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>Thayil</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>
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<tr>
<td>Erythrocyte sedimentation rate (mm/h)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Berger</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>
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<tr>
<td>Interleukin 1 receptor antagonist (pg/L)</td>
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<tr>
<td>Galetto-Lacour</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>
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<td>Interleukin 6 (pg/L)</td>
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<tr>
<td>Galetto-Lacour</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>
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<tr>
<td>Galetto-Lacour</td>
<td>Intermediate</td>
<td>≥100</td>
<td>2.74 (1.33 to 5.61)</td>
<td>0.50 (0.24 to 1.01)</td>
</tr>
<tr>
<td>Interleukin 8 (pg/L)</td>
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<td></td>
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</tr>
<tr>
<td>Galetto-Lacour</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>
Stepwise exclusion
Stepwise exclusion

STEP 1
NO
• Gut feeling
• Dyspnoea
• Temperature ≥40°C
Stepwise exclusion

STEP 2
NO
• CRP >5 mg/L
Stepwise exclusion

STEP 3
Additional testing or referral
Conclusions

• Serious infections rare among very common presentation acute illness

• Clinical features limited in its value
  – Gut feeling

• Laboratory tests to further exclude serious infections
C-Reactive Protein
Point of Care Testing

Fighting the growing threat of antimicrobial resistance

Dr Jayne Ellis, Medical Director Western Europe & Nordics, Alere
Antimicrobial Stewardship and Diagnostics

- Over 78.5% of antibiotic prescribing is in Primary Care\(^1\)
- Over half of antibiotic prescribed in Primary Care are for respiratory tract infections (RTI) \(^2\)
- There is strong evidence that primary care CRP testing for RTI in adults reduces antibiotic prescribing and enables patient education and the consultation discussion\(^3\). Especially:
  (i) where there is a high degree of diagnostic uncertainty
  (ii) for patients who are very worried and/or demanding antibiotics
  (iii) to differentiate the seriously ill from the non-seriously ill.
NICE guideline CG191 recommends that GPs should consider carrying out a **point of care (POC) C-reactive protein (CRP)** test for people presenting in primary care with symptoms of lower respiratory tract infection.

- CRP rapid test
  - < 20 mg/L: Do not routinely offer antibiotic therapy
  - 20-100 mg/L: Consider a delayed antibiotic prescription
  - >100 mg/L: Offer antibiotic therapy

Pneumonia not diagnosed or not clear if antibiotic should be prescribed

Pneumonia diagnosed

See NICE pathway

Reducing unnecessary prescribing

- Evidence based POC CRP testing has been shown to reduce unnecessary antibiotic prescriptions without compromising patient care.\(^5,6,7\)

- European studies have demonstrated that the use of CRP testing in patients presenting with RTI symptoms reduces antibiotic prescribing by up to 41%.\(^5,6,7,8\)
In line with Policy Making

• Use of CRP POCT is in line with key NICE guidance (CG 191, NG 15) \(^4,9\)

• Also supports ambitions set out in the final report of the AMR Review, for increased use of diagnostic testing to inform prescribing of antibiotics

‘I call on the governments of the richest countries to mandate now that by 2020, all antibiotic prescriptions will need to be informed by up-to-date surveillance information and a rapid diagnostic test wherever one exists.’

Lord Jim O’Neill
CRP Testing

- Tiny blood sample – 1.5µL
- Integrated sampling tube in test – no messy test tubes.
- Quantitative result displayed on the screen in just 4 minutes
- Can be attached to a small printer
- Can be connected

‘It was quite simple and the result was fairly soon’

*Anglesey GP Practice*
NHS UK Adoption

- Alere developed and launched the Afinion CRP testing for point of care in 2005 in Europe
- Following NICE Pneumonia Guidance (Dec 2014), a number of UK Pilots have been completed and reported.
  - In England, Scotland and Wales
  - In GP setting & Acute Care Setting
CRP UK Pilot Results

Consistency with data from Randomised controlled trials and European users

Data summarised from 8 pilot studies includes 1653 patients (adults)\textsuperscript{13}

Most patients who present with RTI / acute cough and were tested had low CRP (mean %)
- 73% CRP < 20 mg/L
- 22% CRP 20-100 mg/L
- 5% CRP > 100 mg/L
Figure 1: CRP test results (mg/L) n= 231

- CRP >100: 4%
- CRP 20-100: 24%
- CRP <20: 72%

Percentage of patient tests
CRP Pilot Results

Antibiotic prescribing reduction = mean 33%

- Measured by comparison with previous year before CRP testing was introduced

| Table 2. Antibiotic prescribing for patients presenting with a chesty cough Winter 2014/15 and Winter 2015/16, and unscheduled follow up within 28 days. |
|---|---|---|---|
| No antibiotics prescribed | Delayed antibiotics | Immediate antibiotics prescribed | Unscheduled follow up within 28 days |
| Winter 2014/15 No CRP testing (n=106) | 51% | 18% | 31% | 28% |
| Winter 2015/16 CRP testing (n=67) | 84% | 9% | 8% | 13%* |

*No admissions to secondary care, presentations to A&E/OOH

Re-attendance was reduced by >50%
- In acute care setting, antibiotic prescribing was compared with the month prior to introduction of CRP testing (70% to 20% prescribing reduction observed)

Table 2: Antibiotic prescribing rate by POC CRP group

<table>
<thead>
<tr>
<th>POC CRP result (mg/L)</th>
<th>Number of patients</th>
<th>Proportion given antibiotics (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;20</td>
<td>69</td>
<td>0</td>
</tr>
<tr>
<td>20-100</td>
<td>19</td>
<td>74</td>
</tr>
<tr>
<td>&gt;100</td>
<td>5</td>
<td>100</td>
</tr>
</tbody>
</table>
• Study evaluated feasibility of CRP testing to support clinical decision-making in patients presenting with LRTIs
• Results were informed by data from 246 individual patient consultations and the results of a questionnaire completed by 15 GPs
• Over 90% of respondents felt that CRP POCT provided reassurance when not prescribing an antibiotic
• Almost two-thirds (60%) of GPs thought that CRP POCT was a useful additional tool to support clinical practice
• 40% of GPs subjectively thought that CRP POCT reduced levels of patient re-attendance
• Patient experience of the test appeared to be positive and the majority of respondents would like to see CRP testing used routinely
CRP Pilot Results – benefits

More focussed antibiotic prescribing. Has been helpful in clinical decision making.

I think it has been a big influence in how much antibiotics have been prescribed and reduction in cost.

Helpful when patient keen for antibiotics but CRP normal to reassure patients.

Saves time, instant results, antibiotics given less often.
Summary

• CRP point of care testing can represent an important component of antimicrobial stewardship (AMS) programmes

• The test has been supporting AMS programmes in a number of European countries for many years (such as the Netherlands and across Scandinavia)

• Increasingly being used across the UK, with numerous pilots demonstrating its effectiveness

• Increasing uptake of CRP point of care testing can:
  • Reduce levels of inappropriate antibiotic prescribing
  • Reduce patient re-attendance
  • Lead to cost-savings
  • Strengthen clinical decision-making and reassure patients
References

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