Moving towards delivering precision medicine in sepsis

Paul Dark

Professor of Critical Care Medicine,
Division of Infection and Immunity,
University of Manchester

NIHR CRN National Specialty Lead (Critical Care),
King’s College London

Honorary NHS Consultant in Critical Care Medicine,
Salford Royal NHS Foundation Trust

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Overview of talk

- **Sepsis:** highlight challenges in delivering effective care to individuals & populations

- **Personalised care / precision medicine:** role for ‘high-value’ laboratory diagnostics

- **Recent NICE diagnostic guidance:** focus on CE-marked pathogen and host response rapid diagnostics

- **New NIHR-funded research:** response to evidence gaps identified by NICE
Sepsis: “new definition”

Infections associated with dysregulated host responses leading to life-threatening organ dysfunction

Sepsis V3.0 definition (JAMA 2016)
Sepsis: a medical syndrome

- Non-specific indicators:
  - clinical presentations (*limits potential for clinical early warning*)
  - host responses (*limits potential for biomarker diagnostic efficacy*)

- Range of potential causative pathogens = *empiric broad-spectrum antimicrobials*

- Routine (culture-based) tests = *not time-critical and ?diagnostic accuracy*

- Need to act quickly with **anti-infection interventions** to limit mortality/morbidity

Leads to a clinical ‘*culture*’ of educated guess-work
Room for improvement

Rapid ‘infection’ diagnostics (CE-marked):

- Host inflammatory mediators?
- Pathogen detection?

Clinical guidance CG 31 (first hours) feeding into NHS ‘Sepsis CQUINs’
Unintended consequences

- Surveillance systems
- **Better use of available antibiotics** (humans and animals)
- Hygiene
- Innovation *(rapid diagnostics* and drugs)*
- Political commitment to enable
Disruptive diagnostics

Key diagnostic decision problems to deliver precision

- **Within hour(s):**
  - Is it infection?
  - Which, if any, empiric antimicrobial treatments?

- **Within the day:**
  - What’s the causative pathogen and its phenotype?
  - Can antimicrobial treatments be refined safely?

- **Within days:**
  - What is optimal duration of antimicrobial treatment?
High-value diagnostics

Under diagnosis leading to under treatment  Over diagnosis leading to over treatment

Adapted from Avedis Donabedian
(with thanks to Muir Gray at Oxford)
Guidance on diagnostics

• Culture samples crucial (at least blood samples)

• Biomarkers for rapid diagnosis in sepsis?

  - Host response biomarkers (e.g. CRP, IL6, PCT...) not recommended as rapid diagnostics (? utility to guide stewardship)

  - Rapid, non-culture-based diagnostic methods ? rapid identification of pathogens and major antimicrobial resistance determinants (limited clinical diagnostic experience)
Tests to rapidly identify **bacteria and fungi:**
NICE-DG20 (2016)

**Problem to address**
- Rapid identification of pathogens
- Targeted treatment and shorten duration of broad-spectrums
- Conserve effectiveness of existing antimicrobials

**Focus**
- Bloodstream
- CE-marked **non-culture-based** diagnostic technologies

**Purpose**
- Evaluate clinical and cost effectiveness of available technologies
Tests to rapidly identify bacteria and fungi: NICE-DG20 (2016)

Wide search by NICE DAC resulted in 3 diagnostic tests for appraisal

All based on few millilitres of fresh whole blood in EDTA

Differing sample processing and DNA extraction techniques

<table>
<thead>
<tr>
<th>Test Name</th>
<th>Biomarker target and amplification principle</th>
<th>Pathogen identification technology</th>
<th>Pathogen range</th>
<th>Resistance genes</th>
<th>Limits of detection</th>
</tr>
</thead>
<tbody>
<tr>
<td>LightCycler Septifast Test MGRADE (Roche Diagnostics)</td>
<td>Pathogen DNA Broad-range qPCR</td>
<td>Fluorescence-labelled probes Thermal melt</td>
<td>25 bacterial and fungal pathogen species</td>
<td>MecA gene (MRSA)</td>
<td>30 - 100 cfus/ml</td>
</tr>
<tr>
<td>Sepsitest (Molzym Molecular Diagnostics)</td>
<td>Pathogen DNA Broad-range qPCR</td>
<td>Sequencing technology not part of assay Sepsitest-BLAST analysis online</td>
<td>200 bacteria and 65 fungi genera</td>
<td>Nil</td>
<td>10 - 80 cfus/ml</td>
</tr>
<tr>
<td>IRIDICA BAC BSI assay (Abbott Laboratories)</td>
<td>Pathogen DNA Broad-range qPCR</td>
<td>Electrospray ionisation time-of-flight mass spectrometry</td>
<td>780 bacteria and candida</td>
<td>MecA (MRSA) vanA and vanB (VRE) KPC (wide range Gram–neg bacilli carbapenem resist.)</td>
<td>Mean 39 cfus/ml Range 0.25 -128</td>
</tr>
</tbody>
</table>
Tests to rapidly identify bacteria and fungi: NICE-DG20 (2016)

Commissioned external assessment (NIHR HTA):

- Systematic review of evidence for test performance
  - diagnostic accuracy (clinical efficacy)
  - clinical outcomes
  - clinical and cost effectiveness

- Conceptual economic model

- Comparator technology (routine care in NHS)
  - blood culture alone
  - blood culture with MALDI-TOF mass spectrometry
Tests to rapidly identify bacteria and fungi: NICE-DG20 (2016)

Systematic review results

• 66 clinical studies compared at least one of the new (index) tests with an NHS comparator

• 62 of these were diagnostic accuracy studies

• All studies were judged by independent reviewers as at risk of bias and may not be applicable to the decision problem

• With the exception of one large-scale NHS study (NIHR HTA 08/13/16: Warhurst, Chadwick and Dark)
Tests to rapidly identify bacteria and fungi: NICE-DG20 (2016)

\[
\text{Sensitivity} = \frac{\text{True positives}}{\text{True positives} + \text{False negatives}}
\]

\[
\text{Specificity} = \frac{\text{True negatives}}{\text{True negatives} + \text{False positives}}
\]

<table>
<thead>
<tr>
<th>Test</th>
<th>Number of diagnostic clinical studies</th>
<th>Pooled estimate for sensitivity</th>
<th>Pooled estimate for specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>LightCycler SeptiFast Test MGRADE (Roche Diagnostics)</td>
<td>54</td>
<td>0.65 (95%CI 0.60-0.71)</td>
<td>0.86 (95%CI 0.84-0.89)</td>
</tr>
<tr>
<td>SepsiTest (Molzym Molecular Diagnostics)</td>
<td>4</td>
<td>0.48 (95%CI 0.21-0.75)</td>
<td>0.86 (95%CI 0.78-0.92)</td>
</tr>
<tr>
<td>IRIDICA BAC BSI assay (Abbott Laboratories)</td>
<td>4</td>
<td>0.81 (95%CI 0.69-0.90)</td>
<td>0.84 (95%CI 0.50-0.96)</td>
</tr>
</tbody>
</table>
Tests to rapidly identify bacteria and fungi: NICE-DG20 (2016)

Commissioned external assessment (NIHR HTA):

• Systematic review of evidence for test performance
  - diagnostic accuracy (clinical efficacy)
    - study quality
    - lack of reference standards
    - limited studies in NHS care setting
    - clinical diagnostic efficacy
  - clinical outcomes
  - clinical and cost effectiveness

• Conceptual economic model
Tests to rapidly identify bacteria and fungi: NICE-DG20 (2016)

NICE Diagnostic Advisory Committee

Recommendations

• Insufficient evidence to recommend the routine adoption in the NHS
• The tests show promise and further research in UK

Research recommendations

• Determine clinical scenarios (adults/children) where tests may offer most benefit
• Assess utility of combination of biomarkers (e.g. PCT for bacterial infection)
• Invasive-fungal diseases – should aim to quantify the clinical utility of the rapid molecular tests, including their effect on antifungal prescribing
Tests to rapidly identify bacteria and fungi: NICE-DG20 (2016)

Rapid tests for fungal infection

Research Question:

*In patients treated for suspected fungal infection can rapid tests be used to rule out infection and guide the early discontinuation of anti-fungal treatment. Would use of these tests be cost effective?*

1. **Technology:** Rapid tests for the diagnosis or exclusion of fungal infection. (Applicants to specify one or more tests or combinations of tests, eg beta-D glucan (BDG), galactomannan or PCR methods).

2. **Patient group:** Patients at high risk and receiving presumptive treatment for suspected systemic or invasive fungal infection.
Host response circulating inflammatory mediators as diagnostic markers: 

**Procalcitonin - NICE-DG18 (2015)**

**Background**

- Released into the circulation in response to **acute pro-inflammatory stimuli**
- Bacterial stimuli associated with rapid and highest responses
- Rapid fall with correct treatment for bacterial infection
- Potential to aid antibiotic initiation and discontinuation decisions (duration)
- No direct information about causative pathogen or antibiotic susceptibility
Host response circulating inflammatory mediators as diagnostic markers:

Technologies under assessment

<table>
<thead>
<tr>
<th>Test</th>
<th>Manufacturer</th>
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</thead>
<tbody>
<tr>
<td>BRAHMS PCT Sensitive Kryptor assay</td>
<td>Thermo Fisher Scientific</td>
</tr>
<tr>
<td>VIDAS BRAHMS PCT assay</td>
<td>bioMérieux</td>
</tr>
<tr>
<td>ADVIA Centaur BRAHMS PCT assay</td>
<td>Siemens Healthcare Diagnostics</td>
</tr>
<tr>
<td>Elecsys BRAHMS PCT assay</td>
<td>Roche Diagnostics</td>
</tr>
<tr>
<td>LIAISON BRAHMS PCT assay</td>
<td>DiaSorin</td>
</tr>
</tbody>
</table>
ADULT SEPSIS

- 8 RCTs focused on daily serum/plasma PCT algorithms aimed at antibiotic discontinuation in sepsis

- All studies used:
  - PCT algorithms with multiple decision thresholds to guide antibiotic treatment in intervention arms
  - common decision thresholds (definitive <0.25µg/l; advisory <0.50µg/l)
  - final decision resting with treating clinician
  - consistency of advice around discontinuation rules in intervention arms

Summary (adults with sepsis)

Addition of PCT algorithm to standard clinical care to **discontinue** antibiotics:

- reduced antibiotic duration
- reduced resource use (accounted for by reduced hospital and ICU stay)
- no evidence of any adverse consequences on clinical outcomes (but studies were often under-powered for safety)
- No evidence found of variation in effect between commonly used assays
Summary (adults with sepsis)

Addition of PCT algorithm to standard clinical care to **discontinue** antibiotics:

- Studies were of unclear quality, with some at high risk of bias with real concerns about ‘**performance bias**’ contributing to study effect size
- Standard clinical care not identified in studies
- No RCTs based in UK with lower antibiotic duration than other jurisdictions

Recommendations (adults with sepsis)

Lab-based procalcitonin tests:

- Show promise for the safe reduction of antibiotic exposure
- Insufficient evidence to recommend routine adoption in the NHS

Research recommendations:

- Further NHS research on the clinical and cost effectiveness to stop antibiotics
- Is there a role for CRP?
- NHS centres currently using procalcitonin tests encouraged to participate in research and data collection

Research Question:

*Does a treatment protocol based on serial monitoring of C-reactive protein or procalcitonin safely allow reduction in duration of antibiotic therapy in hospitalised patients with sepsis?*

Specifies: definitive 3-arm RCT

- adequately powered for antibiotic duration (superiority) and safety (non-inferiority)
- assess clinical and cost effectiveness
Summary

**Rapid infection diagnosis** is the key to improvements in sepsis care

Highlighted some key decision problems for care disruption

*Donabedian* framework to conceptualise high-value IVDs

Important roles for NICE and NIHR to catalyse evidence for IVDs

Max. 5-year horizon to impact, responding to patient need