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Moving towards delivering precision medicine in sepsis

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Overview of talk

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

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

- **Recent NICE diagnsotic 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"*

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

Sepsis V3.0 definition *(JAMA 2016)*

Sepsis: a medical syndrome

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- 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

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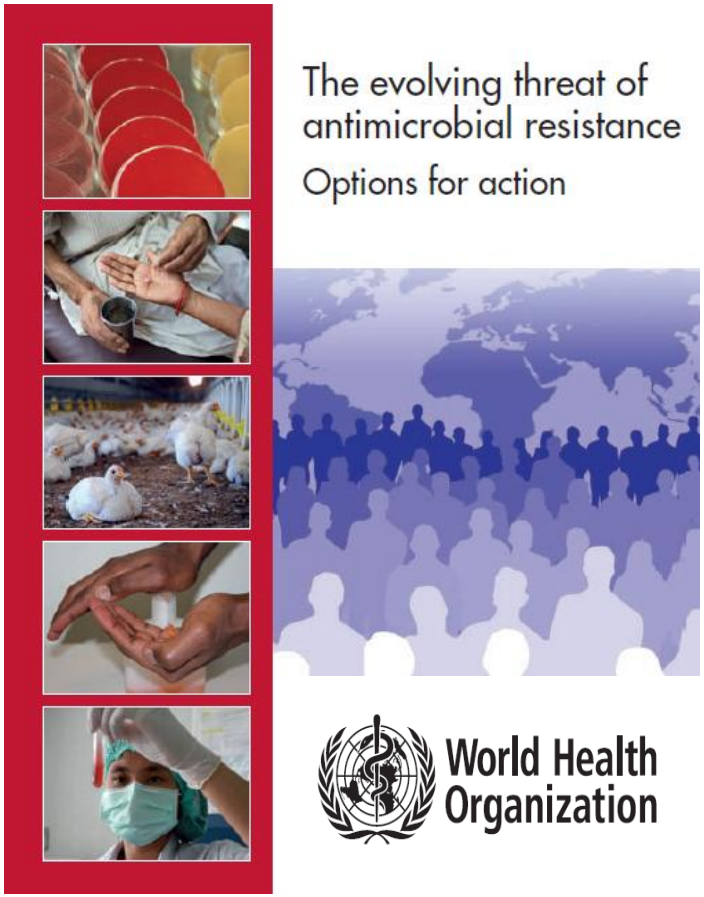
NICE National Institute for Health and Care Excellence

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

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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

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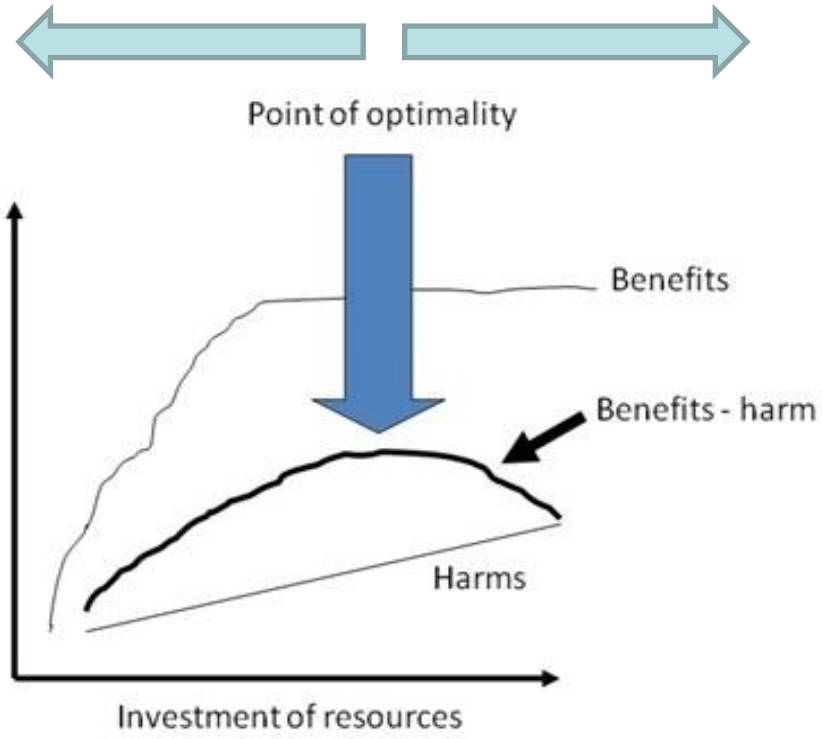
Under diagnosis leading to under treatment **Over diagnosis leading to over treatment**



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

Guidance on diagnostics

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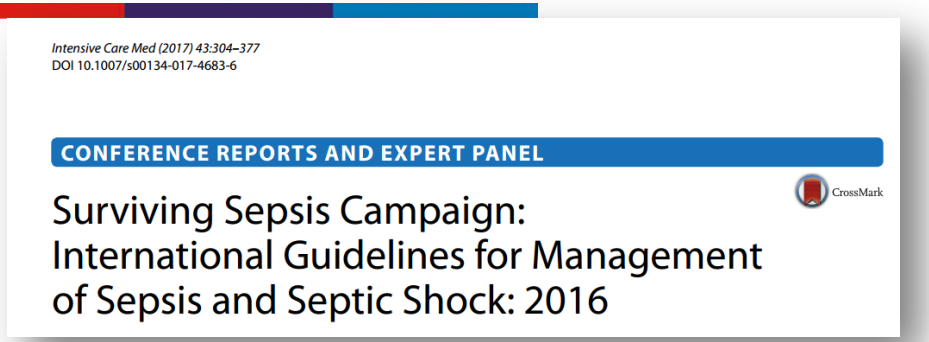

- **Culture samples crucial (**at least blood samples**)**

- **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)

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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)

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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

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

Tests to rapidly identify bacteria and fungi: NICE-DG20 (2016)

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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

The University Of Sheffield.

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Tests to rapidly identify bacteria and fungi: NICE-DG20 (2016)

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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)

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

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

	Number of diagnostic clinical studies	Pooled estimate for sensitivity	Pooled estimate for specificity
LightCycler SeptiFast Test MGRADE (Roche Diagnostics)	**54**	**0.65** (95%CI 0.60-0,71)	**0.86** (95%CI 0.84-0.89)
SepsiTest (Molzym Molecular Diagnostics)	**4**	**0.48** (95%CI 0.21-0.75)	**0.86** (95%CI 0.78-0.92)
IRIDICA BAC BSI assay (Abbott Laboratories)	**4**	**0.81** (95%CI 0.69-0.90)	**0.84** (95%CI 0.50-0.96)

Tests to rapidly identify bacteria and fungi: NICE-DG20 (2016)

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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

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Tests to rapidly identify bacteria and fungi: NICE-DG20 (2016)

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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)

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Health Technology Assessment Programme

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HTA no 15/116

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)

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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: Procalcitonin - NICE-DG18 (2015)

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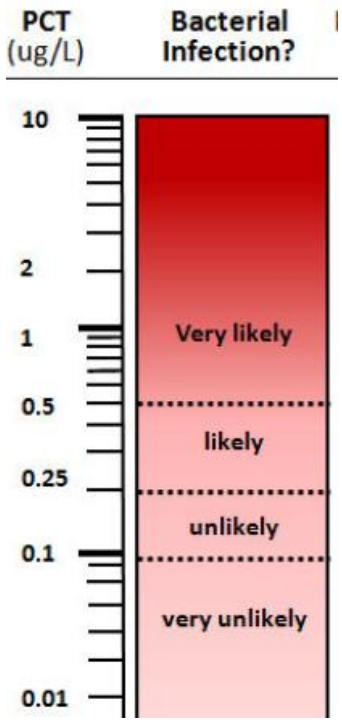

Technologies under assessment

Test	Manufacturer
BRAHMS PCT Sensitive Kryptor assay	Thermo Fisher Scientific
VIDAS BRAHMS PCT assay	bioMérieux
ADVIA Centaur BRAHMS PCT assay	Siemens Healthcare Diagnostics
Elecsys BRAHMS PCT assay	Roche Diagnostics
LIAISON BRAHMS PCT assay	DiaSorin

Host response circulating inflammatory mediators as diagnostic markers: Procalcitonin - NICE-DG18 (2015)

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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

Host response circulating inflammatory mediators as diagnostic markers: Procalcitonin - NICE-DG18 (2015)

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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

Host response circulating inflammatory mediators as diagnostic markers: Procalcitonin - NICE-DG18 (2015)

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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

Host response circulating inflammatory mediators as diagnostic markers: Procalcitonin - NICE-DG18 (2015)

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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

Host response circulating inflammatory mediators as diagnostic markers: Procalcitonin - NICE-DG18 (2015)

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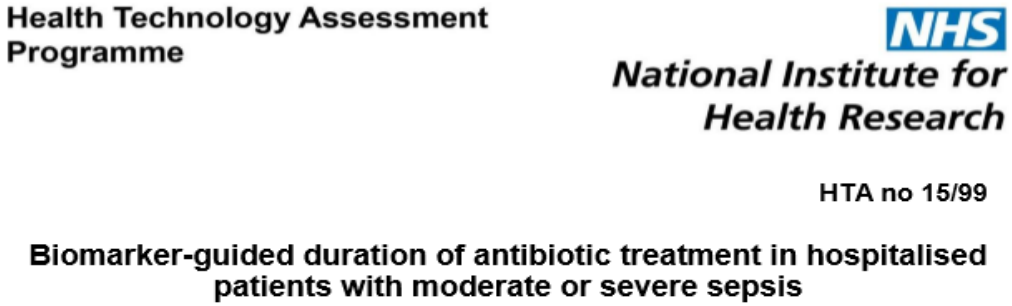
Health Technology Assessment Programme

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HTA no 15/99

Biomarker-guided duration of antibiotic treatment in hospitalised patients with moderate or severe sepsis

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