High-value *in vitro* diagnostics in sepsis

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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

Definition hides well-rehearsed clinical challenges

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

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

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

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

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

TIME TO ACT
Severe sepsis: rapid diagnosis and treatment saves lives
Room for improvement

Rapid ‘infection’ diagnostics (CE-mark):

- Host inflammatory mediators?

- Pathogen detection?

Clinical guidance (first hours) feeding into ‘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 (and thanks to Muir Gray!)
NIHR research priority

NIHR HTA commissioned research (start 2017)
[responding to recent NICE diagnostic guidances]

Focus on potential over diagnosis/over treatment in sepsis

NHS-wide definitive pragmatic clinical trials:

- HTA 15/116: IVDs to rule-out invasive fungal sepsis (circulating fungal antigens and/or DNA)

- HTA 15/99: IVDs to guide antibiotic duration in sepsis (circulating CRP and PCT)
NIHR research priority

NHS-wide definitive pragmatic clinical trials aimed at:

- catalysing evidence-base for clinical effectiveness
- biomarkers identified but IVDs not specified
- clinical and cost effectiveness outcomes
- understanding clinical decisions behaviour
- 5-year horizon for patient impact

Coordinated/delivered by globally-leading NIHR UK research network
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