A New Tool in the Clinical Management of Sepsis

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Sepsis is a common and potentially life-threatening condition triggered by an infection.

Sepsis is the body's immune response to infection and it is estimated that sepsis counts for more deaths in the UK annually than bowel cancer, breast cancer and prostate cancer combined. The focus of infection can arise anywhere but most commonly from the lungs, urinary tract or skin. In patients in intensive care, who have had surgery or are receiving therapy requiring indwelling devices there is a risk of organisms passing into the blood causing bacteremia or fungemia.

Figure 1: Sepsis definitions

SEPSIS DEFINITIONS

- INFECTION
  - Inflammatory response to microorganisms, or
  - Invasion of normally sterile tissues
- SYSTEMIC INFLAMMATORY RESPONSE SYNDROME (SIRS)
  - Systemic response to a variety of processes
- SEPSIS
  - Infection plus
  - 2 SIRS criteria
- SEVERE SEPSIS
  - Sepsis
  - Organ Dysfunction
- SEPTIC SHOCK
  - Sepsis
  - Hypotension despite fluid resuscitation

Figure 1: Sepsis definitions

Presence of infection causes stimulation of cytokines which mediate and regulate immunity, inflammation and haematopoiesis. In the case of sepsis, the presence of endotoxin or exotoxins from microorganisms triggers an inflammatory cascade which can result in systemic inflammatory response syndrome (SIRS). This inflammatory cascade may cause blood clotting and changes to circulation, resulting in end-organ dysfunction, while hypotention during septic shock can be fatal.

Due to the rapidly escalating nature of sepsis and the difficulty in early diagnosis, a number of clinical tool kits and guidelines have been produced to aid health professionals.

Figure 2 details a sepsis screening toolkit produced by the UK Sepsis Trust. Box 1 details SIRS criteria which includes temperature, respiration rate, heart rate and glucose levels as well as patient presentation. It should be noted that SIRS may arise from non-infectious causes but for a diagnosis of sepsis infection must be present. Clinical indications of infection are detailed in box 2. Red flag sepsis criteria in box 3 is to help identify patients at risk of severe sepsis i.e. possible organ dysfunction.

If any red flag is present immediate action is required.

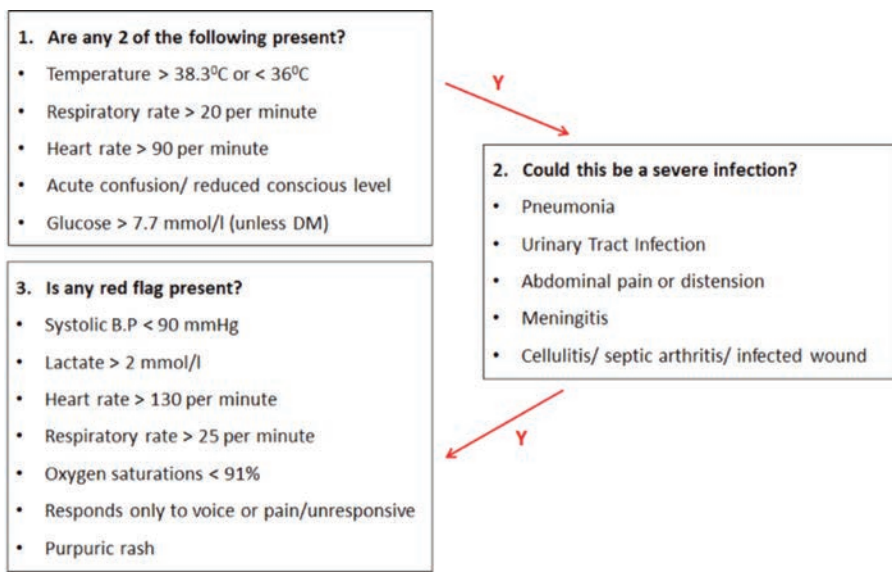


Figure 2: Sepsis screening
Taken from www.sepsistrust.org

The UK Sepsis Trust developed the 'sepsis six' toolkit which details immediate actions to be completed within the first hour of a 'red flag sepsis' event.

Figure 3: Sepsis Six

1. High-flow oxygen
2. **Blood cultures, consider source control**
3. **Intravenous antibiotics**
4. Intravenous fluid resuscitation
5. Check haemoglobin and serum lactates
6. Hourly urine output measurement

Record the time, each of these actions is completed. All actions should be completed as soon as possible but always ***within 60 minutes.***

Figure 3: Sepsis Six

As detailed above, patients suspected of bloodstream infection have samples taken and are routinely placed on high-dose, broad-spectrum intravenous antibiotics and antifungals until definitive information is available. In a high number of cases this is precautionary but has a significant impact on costs, care levels and patient outcomes. Up to 90% of blood cultures are negative but take 5 days to be confirmed as such. De-escalation of treatment reduces antibiotic resistance pressure, reduces antibiotic-associated disease (e.g. *C. difficile*) and confers significant cost savings in treatment and bed management.

"Resistance to antibiotics risks health 'catastrophe' to rank with terrorism and climate change." Chief Medical Officer Dame Sally Davies

Antimicrobial-resistant infections claim at least 50,000 lives each year across Europe and the US alone. Approximately 5,000 patients a year in the UK die from bloodstream infections, half of them caused by drug-resistant organisms. The prevalence of antimicrobial resistance has risen alarmingly over the last 40 years and few truly novel antimicrobials have been developed. This has led to increased pressure on existing antibiotics and greater challenges in treating patients.

Inappropriate use of antimicrobials increases the risk to patients of colonisation and infection with resistant organisms. Reviewing the clinical diagnosis and de-escalating antibiotics at the earliest opportunity is considered highly desirable.

In relation to this, the UK government published a guidance document in 2011 called 'Antimicrobial Stewardship: Start smart - then focus'. It was updated in 2015 and the summary of actions is detailed in *Figure 4*.

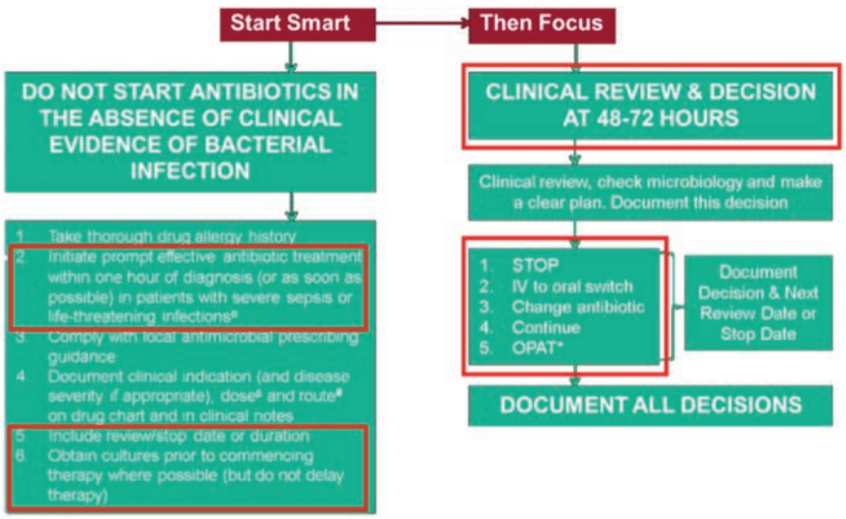


Figure 4: Antimicrobial Stewardship Toolkit for English Hospitals: Start Smart – Then Focus www.gov.uk March 2015

Cognitor® Minus is the first in a new range of diagnostic products specifically designed for the rapid detection and exclusion of infection, giving a confirmed negative result direct from blood with a negative predictive value of 99.5%.

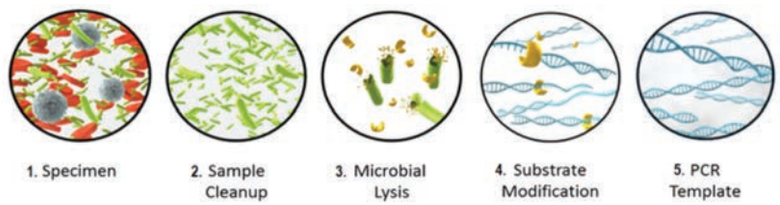
Universal detection of all bacteria and fungi.

Detects only viable organisms.

NPV = 99.5%

Results available after 12 hours incubation on a blood culture machine.

Utilising patented ETGA® technology, the test is able to rapidly and universally detect viable micro-organisms using a unique combination of a phenotypic marker and ultra-sensitive molecular PCR measurement.
ETGA® (Enzymatic Template Generation & Amplification) is a technology that detects the activity of nucleic acid modifying enzymes from micro-organisms. The Cognitor® Minus test utilises ETGA® technology to detect micro-organisms by measuring microbial DNA polymerase activity. This means that Cognitor® Minus can be used to universally detect any micro-organism because DNA polymerase activity is common to all living things. Cognitor® Minus does not identify micro-organisms.



When bacterial or fungal cells die, enzymes such as DNA polymerase are rapidly lost to the surrounding media. The diagram above shows how the Cognitor® Minus test detects living organisms by separating intact (viable) organisms from the specimen and neutralising background levels of enzyme activity. Following microbial lysis, DNA polymerase activity is then detected using a proprietary synthetic DNA substrate that can be modified by DNA polymerase. Cognitor® Minus does not detect microbial or human DNA or RNA. The amount of modified Cognitor® Minus substrate is indicative of microbial DNA polymerase activity and can be measured by quantitative/real-time PCR (qPCR), so when the amount of modified substrate exceeds a threshold level, the result is 'positive'. Because Cognitor® Minus has been designed to provide a high negative predictive value 'positive' results cannot be reliably reported as due to infection and these results are reported as 'not determined'.

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