

# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Diagnostics Assessment Programme

### **Sepsis: The LightCycler SeptiFast Test MGRADE, SepsiTest and IRIDICA BAC BSI assay for rapidly identifying bloodstream bacteria and fungi**

#### **Final scope**

February 2015

#### **1 Introduction**

The LightCycler SeptiFast Test MGRADE is manufactured by Roche Diagnostics. The Medical Technologies Advisory Committee identified the LightCycler SeptiFast Test MGRADE as potentially suitable for evaluation by the Diagnostics Assessment Programme on the basis of a briefing note. The final scope was informed by discussions at the scoping workshop on 9 January 2015 and the assessment subgroup meeting held on 20 January 2015.

A glossary of terms is provided in appendix A.

#### **2 Description of the technologies**

This section describes the properties of the diagnostic technologies based on information provided to NICE by manufacturers and on information available in the public domain. NICE has not carried out an independent evaluation of this description.

##### **2.1 Purpose of the medical technologies**

The LightCycler SeptiFast Test MGRADE, SepsiTest and IRIDICA BAC BSI assay are intended to rapidly detect and identify bacterial and fungal DNA which may be present in the bloodstream in people who are suspected of having sepsis. They are intended to be used in conjunction with clinical assessment and established microbiology techniques. The tests are designed to be run directly on whole blood samples and do not require prior incubation or pre-culture steps. The ability to directly test whole blood samples means that pathogens may be identified earlier when compared with microbiology techniques which require blood samples to be incubated and cultured before

the identification of viable pathogens and antimicrobial susceptibility testing. The rapid detection and identification of bacterial and fungal DNA may be of particular benefit in people who are suspected of having a severe infection and who require prompt medical intervention.

It is recommended that people who are clinically unwell and who have a suspected bloodstream infection are given empirically prescribed broad spectrum antibiotics. Broad spectrum antibiotics, and where appropriate antifungals, are administered on the basis that they are effective against a wide range of bacterial and fungal pathogens and are likely to achieve a therapeutic response. Until the identity of the pathogen is known, people are likely to remain on the empirically prescribed antimicrobial treatment. However, despite being clinically effective, the use of broad spectrum antibiotics is associated with patients developing superinfection and the development of antibiotic resistant bacteria. Reducing the length of use of broad spectrum antibiotics may contribute towards antimicrobial stewardship and help to conserve the effectiveness of existing antimicrobials. Rapidly detecting bacterial and fungal DNA may reduce the length of use of broad spectrum antibiotics and antifungals and facilitate targeted treatment earlier in the care pathway. It is anticipated that blood culture would still be required to provide definitive antimicrobial susceptibility data, where this is not provided by the rapid diagnostic test.

## **2.2 LightCycler SeptiFast Test MGRADE**

The LightCycler SeptiFast Test MGRADE (Roche Diagnostics) is a CE marked in-vitro diagnostic real-time PCR test which simultaneously detects and identifies bacterial and fungal DNA. The test requires 1.5ml of EDTA-treated whole blood which can be processed without prior incubation or culturing. The LightCycler SeptiFast Test MGRADE involves three distinct processes: specimen preparation by mechanical lysis and purification of DNA, real-time PCR amplification of target DNA in 3 parallel reactions (gram positive bacteria, gram negative bacteria, fungi) and detection using fluorescence labelled probes specific to the target DNA. The test takes around 6 hours, depending on laboratory workflow.

The SeptiFast Identification Software set v2.0 analyses the samples and generates a report including all the relevant laboratory data and details the identified species. The software also includes a crossing point cut-off rule which is intended to reduce the positive rate for Coagulase negative *Staphylococci* and *Streptococcus* spp. based on the assumption that they are contaminants and not causal agents when the crossing point value is less than 20.

Where *Staphylococcus aureus* is identified in a sample, an aliquot of the SeptiFast Test MGRADE eluate can be further tested for the presence of the MecA gene using the LightCycler SeptiFast MecA Test MGRADE. The test can determine the likely meticillin resistance of *Staphylococcus aureus* through PCR using the LightCycler 2.0 instrument.

The bacteria and fungi which can be detected by the LightCycler SeptiFast Test MGRADE are shown in table 1.

**Table 1 Bacteria and fungi detected by the LightCycler SeptiFast Test MGRADE**

Bacteria		Fungi
Gram negative	Gram positive	
<i>Escherichia coli</i>	<i>Staphylococcus aureus</i>	<i>Candida albicans</i>
<i>Klebsiella</i> (pneumonia/oxytoca)	Coagulase negative <i>Staphylococci</i> (including <i>S. epidermidis</i> , <i>S. haemolyticus</i> )	<i>Candida tropicalis</i>
<i>Serratia marcescens</i> (cloacae/aerogenes)	<i>Streptococcus pneumoniae</i>	<i>Candida parapsilosis</i>
<i>Proteus mirabilis</i>	<i>Streptococcus</i> spp. (including <i>S. pyogenes</i> , <i>S. agalactiae</i> , <i>S. mitis</i> )	<i>Candida krusei</i>
<i>Pseudomonas aeruginosa</i>	<i>Enterococcus faecium</i>	<i>Candida glabrata</i>
<i>Acinetobacter baumannii</i>	<i>Enterococcus faecalis</i>	<i>Aspergillus fumigatus</i>
<i>Stenotrophomonas maltophilia</i>		

The test has an analytical sensitivity of 100 colony forming units/millilitre for coagulase negative *Staphylococci*, *Streptococcus agalactiae*, *Streptococcus pyogenes*, *Streptococcus pneumoniae* and *Streptococcus mitis*. The minimum analytical sensitivity for all other pathogens detected by the LightCycler SeptiFast test MGRADE is 30 colony forming units/millilitre.

### 2.3 SepsiTst

SepsiTst (Molzym Molecular Diagnostics) is a CE marked PCR test for detecting bacterial and fungal DNA in 1ml k-EDTA-or citrate-treated whole blood. The test is able to identify species from more than 200 genera of bacteria and 65 genera of fungi, with the exception of *Candida krusei*.

The SepsiTst involves 3 distinct processes: extracting and purifying microbial DNA using centrifugation, universal PCR and Sanger sequencing. The PCR result, which is available after 4 hours, indicates whether bacteria or fungi are present in the sample. Amplicons from positive samples are then sequenced to confirm the PCR result and to determine which bacteria or fungi species are present. Where readable sequences are available from sequence analysis, bacteria and fungi can be identified using the SepsiTst-BLAST

online tool. Sequencing results may be available in 3 to 4 hours depending on the analyser used.

The analytical sensitivity of SepsiT<sub>est</sub> ranges from 10 to 80 colony forming units per millilitre, depending on the target species.

## **2.4 IRIDICA BAC BSI assay**

The IRIDICA BAC BSI assay (Abbott Diagnostics) is a CE marked in vitro diagnostic test for detecting and identifying bacteria and candida DNA in 5ml EDTA-treated whole blood. The test can also detect the *mecA* (*Staphylococcus* specific meticillin resistance), *vanA* and *vanB* (*Enterococcus* specific vancomycin resistance) and KPC (gram-negative associated carbapenem resistance) genes which are associated with antibiotic resistance. The test is designed for use with the IRIDICA system which combines broad range PCR with electrospray ionisation time of flight mass spectrometry to amplify and detect pathogens. The IRIDICA analysis computer consists of a proprietary database and software which identifies the organism present in the sample by comparing the sequence of the sample with a library of known sequences.

The BAC BSI assay is able to identify over 780 bacteria and candida, with the exception of *Aspergillus fumigatus* and *Candida krusei*. The mean limit of detection for the assay is 39 colony forming units per millilitre, with a range of 0.25 to 128 colony forming units per millilitre depending on the target species. The estimated time to result is 5 hours and 55 minutes.

## **3 Target conditions**

### **Systemic inflammatory response syndrome and sepsis**

#### **3.1 Background**

##### *3.1.1 Sepsis and bloodstream infection*

Sepsis is a condition characterised by the body's inflammatory response to an infection. Sepsis is diagnosed where there is evidence of systemic inflammation, in addition to a documented or presumed infection. Systemic illness often occurs when bacteria invade normally sterile parts the body. One example of this is the invasion of bacteria or fungi into the bloodstream (bloodstream infection), a process which often causes an inflammatory immune response.

If sepsis is not treated it can progress to severe sepsis or septic shock and can lead to multiple organ failure and death. Severe sepsis occurs when the sepsis progresses to sepsis-induced organ dysfunction. That is, when the body's response to infection interferes with the functioning of vital organs, such as the heart, kidneys, lungs or liver.

Septic shock occurs in severe cases of sepsis, and is defined as persistent sepsis induced hypotension (low blood pressure) despite adequate fluid resuscitation. Septic shock prevents organs from receiving enough oxygenated blood. Complications of septic shock can include:

- Respiratory failure
- Heart failure
- Kidney injury or failure
- Abnormal blood clotting

Definitions of sepsis have been published by the following societies:

- The American College of Chest Physicians and Society of Critical Care Medicine Consensus Conference Committee (Bone et al 1992)
- 2001 SCCM / ESICM / ACCP / ATS / SIS International Sepsis Definitions Conference (Levy et al 2003)
- The German Sepsis Society (Reinhart et al 2010).

In the UK there are estimated to be 102,000 cases of sepsis per year, with around 36,800 deaths (UK Sepsis Trust). Severe sepsis is one of the most common reasons for admission to an intensive care unit, accounting for almost one third of all admissions. Severe sepsis is a time-critical condition where delays in recognition and the subsequent administration of appropriate treatment can adversely impact on outcomes.

### *3.1.2 Causes of bloodstream infections*

Bacterial infections are the most common cause of sepsis and bloodstream infection; however they can also be caused by fungal infections, and less commonly by viral infections. The most common sites of infection leading to sepsis are the lungs, urinary tract, abdomen and pelvis. Other sources of infection leading to sepsis include skin infections (such as cellulitis), post-surgical infections and infections of the nervous system (such as meningitis or encephalitis).

Patients who are currently or have recently been hospitalised, are at risk of acquiring a healthcare associated infection and are therefore at increased risk of sepsis and bloodstream infection. It is thought that the increasing number of invasive procedures such as catheterisation, immunosuppressive therapy, antibiotic therapy and life support measures has resulted in an increase in healthcare associated bloodstream infections (Public Health England 2014b). In 2011, a total of 3,360 people in England were diagnosed with a healthcare associated infection, 255 (7.6%) of whom had a bloodstream infection (Health Protection Agency 2012). Septic shock is most commonly associated with gram negative bacterial bloodstream infections, but shock can also be associated with bloodstream infections caused by gram positive bacteria, particularly with fulminant pneumococcal, Lancefield Group A streptococcal and staphylococcal infections (Public Health England 2014a). Community acquired bloodstream infections may also occur in people who have not had recent contact with healthcare services. The pathogens isolated from these people may differ from those associated with hospital acquired bloodstream infection (Public Health England 2014b).

Bloodstream infection is also a risk for people who are immunocompromised, particularly amongst people with neutropenia, who are at risk of developing neutropenic sepsis. People who are immunocompromised often have a high incidence of infections caused by pathogens such as non-fermentative Gram-negative rods, *Listeria monocytogenes*, *Corynebacterium* species, *Candida* species, coagulase negative *Staphylococci*, *Enterococci* and *Viridans streptococci*. Polymicrobial infections are also more common amongst people who are immunocompromised (Public Health England 2014b).

The bacteria most commonly associated with bloodstream infection in adults in England, Wales and Northern Ireland are outlined below in Table 2.

**Table 2: Bacteria species isolated from adults with bloodstream infections**

Gram negative		Gram positive	
<i>Escherichia coli</i>	36%	<i>Staphylococcus aureus</i> (MSSA)	9.7%
<i>Klebsiella</i> spp.	7.8%	<i>Non-pyogenic streptococci</i>	7.1%
Other gram-negative	6.4%	<i>Enterococcus</i> spp.	6.3%
<i>Pseudomonas</i> spp.	4.3%	<i>Streptococcus pneumoniae</i>	4.2%
<i>Proteus</i> spp.	3.1%	Other gram-positive	4.2%
<i>Enterobacter</i> spp.	2.2%	<i>Staphylococcus aureus</i> (MRSA)	1.6%
<i>Bacteroides</i> spp.	1.5%	Group B <i>Streptococci</i>	1.4%
<i>Serratia</i> spp.	1.0%	Group A <i>Streptococci</i>	1.4%
<i>Acinetobacter</i> spp.	0.7%	<i>Diphtheroids</i>	1.2%

MSSA: meticillin-sensitive *staphylococcus aureus*; MRSA: meticillin resistant *staphylococcus aureus*.

Source: Annual Report of the Chief Medical Officer, Volume 2 2011, Infections and the rise of antimicrobial resistance (Davies 2013).

The types of pathogens causing bloodstream infection can also differ in children as compared to those isolated from adults with bloodstream infection. Pathogens known to cause community acquired bloodstream infection in children include *Streptococcus pneumoniae*, *Neisseria meningitidis*, *Staphylococcus aureus*, and *Escherichia coli*. The profile of pathogens associated with healthcare associated infections in children is thought to be similar to that associated with healthcare associated infections in adults; however polymicrobial infection and anaerobic bacteraemia are thought to occur less frequently amongst children (Public Health England 2014b).

### 3.1.3 Antimicrobial resistance

Antimicrobial resistance describes the development of resistance to existing antimicrobial medications (including antibiotics, anti-fungals and anti-virals) amongst bacteria, viruses and fungi. As existing antimicrobial medications are becoming less effective, strategies such as the [UK five year antimicrobial resistance strategy](#) (Department of Health 2013) have been introduced to help conserve the effectiveness of existing treatments. One of the key priorities outlined in the UK five year antimicrobial resistance strategy is the introduction of antimicrobial stewardship programmes which aim to promote the rational prescribing of antimicrobial medications and the use of existing and new rapid diagnostic tests.

Recent surveillance data for England suggest that rates of meticillin-resistant *Staphylococcus aureus* have fallen whilst there is an increase in the incidence of bloodstream infections caused by resistant gram-negative Enterobacteriaceae bacteria such as *Klebsiella* species and *Escherichia coli* (Public Health England 2014a). Of particular concern in some regions of England, such as the North West and Greater London, is the increasing resistance to carbapenem antibiotics which are often used as a last resort for treating severe infections.

A summary of key antibiotic resistance amongst bacteria causing bloodstream infection is shown in Table 3.

**Table 3: Summary of key antibiotic resistance in bacterial bloodstream infection in England**

Pathogen	Rate per 100,000	Antibiotic or antibiotic class	% of resistant cases 2013
<i>Escherichia coli</i>	52.6	Ciprofloxacin	18.2
		3 <sup>rd</sup> generation cephalosporins	10.9
		Gentamicin	9.7
		Imipenem/meropenem	0.1
<i>Klebsiella pneumoniae</i>	8.8	Ciprofloxacin	11.1
		3 <sup>rd</sup> generation cephalosporins	11.4
		Gentamicin	8.5
		Imipenem/meropenem	1.0
<i>Pseudomonas spp.</i>	6.3	Ciprofloxacin	10.4
		Ceftazidime	6.7
		Gentamicin	3.6
		Imipenem/meropenem	9.5
<i>Streptococcus pneumoniae</i>	6.1	Penicillin	3.1
		Macrolides	8.1
		Tetracycline	6.1

Source: English surveillance programme for antimicrobial utilisation and resistance (Public Health England 2014a).

## 3.2 Care pathway

### 3.2.1 Diagnosis of sepsis and bloodstream infection

The diagnostic work-up of sepsis and bloodstream infection is described in several guidelines:

- NICE Clinical Guideline 151: [prevention and management of neutropenic sepsis in cancer patients](#) (2012)
- The Royal College of Obstetricians and Gynaecologists: [Green-Top Guideline 64a Bacterial Sepsis in Pregnancy](#) (2012)
- The Royal College of Obstetricians and Gynaecologists: [Green Top Guideline 64b Bacterial Sepsis following Pregnancy](#) (2012)



- Surviving Sepsis Campaign: [International Guidelines for Management of Severe Sepsis and Septic Shock](#) (2012).

In addition a NICE clinical guideline Sepsis: the recognition, diagnosis and management of severe sepsis is currently in development with an estimated publication date of July 2016.

Diagnostic criteria for sepsis are listed in the Surviving Sepsis Campaign guidelines (adapted from Levy et al. 2003). In summary, regular observations of all vital signs should be taken and recorded, kidney and liver function tests should be performed, inflammatory biomarkers and serum lactate should be measured. These guidelines state that a diagnosis of sepsis should be based on infection, documented or suspected, in conjunction with hyper- or hypothermia, tachycardia and at least one indication of altered organ function of the following. The diagnostic criteria for sepsis include the following variables:

- General variables: temperature of greater than 38.3°C or less than 36°C; heart rate greater than 90 beats per minute; rapid breathing, altered mental status; significant oedema; high blood sugar in the absence of diabetes.
- Inflammatory variables: low or high white blood cell count or more than 10% immature forms; raised plasma CRP; raised plasma procalcitonin.
- Haemodynamic and tissue perfusion variables: low blood pressure; raised blood lactate (a concentration of  $\geq 4$ mmol/l suggests tissue hypoperfusion).
- Organ dysfunction variables: low blood oxygen; reduced urine output; increased creatinine levels (indicating impaired kidney function); coagulation abnormalities; absent bowel sounds; reduced platelet count; raised plasma bilirubin levels.

The Surviving Sepsis Campaign guidelines also make the following specific recommendations relating to the detection of localised and bloodstream infection:

- At least 2 blood cultures should be collected (aerobic and anaerobic) before antimicrobial therapy is initiated if such cultures do not cause significant delay (>45 minutes) in the start of antimicrobial administration. At least one should be drawn percutaneously and one drawn through each vascular access device, unless the device was recently (<48 hours) inserted. The blood cultures can be drawn at the same time if they are obtained from different sites. Cultures of other

sites such as urine, cerebrospinal fluid, wounds, respiratory secretions or other bodily fluids that may be the source of infection should be obtained before initiation of antimicrobial therapy, if doing so does not cause significant delay in the start of antimicrobial administration.

- Imaging studies such as CT or X-ray should be performed in order to confirm a potential source of infection.
- Assays to diagnose systemic fungal infection should be used if available and invasive candidiasis is suspected.

### Blood cultures and microbiology investigations

[Standards for the investigation of blood cultures](#) are available from Public Health England (2014b). A blood culture set for the diagnosis of bloodstream infection is defined as one aerobic and one anaerobic bottle (Public Health England 2014b). For adult patients it is recommended that 20-30ml of blood be cultured per set, and that two consecutive blood culture sets from two separate venepuncture sites should be collected during any 24hr period for each septic episode. The first set should be taken prior to the administration of antimicrobial treatment as the presence of antibiotics or antifungals may inhibit the growth of pathogens in the blood culture (Public Health England 2014b). Blood culture bottles should be incubated within 4 hours of the blood sample being taken with many laboratories now using automated culture systems such as the BACTEC system, which alert laboratory staff once growth has been detected.

When a blood culture has been detected as positive it is recommended that:

- Gram staining and rapid antigen testing should be performed within 2 hours.
- Direct or automated isolate identification should be performed within 24 hours (extending to 48 hours if traditional microbiology techniques such as morphological identification are used). Rapid species identification may be done following blood culture using techniques such as MALDI-TOF mass spectrometry.
- Identification should be followed by sensitivity testing to determine which antimicrobials the identified pathogen is susceptible to. If direct or automated sensitivity testing (including MALDI-TOF mass spectrometry) is used a report should be made within 24 hours, extended to 48 if traditional techniques such as the disc diffusion method are used.

- A preliminary positive report is made within 2 hours of identification and sensitivity testing, and a final positive report should be made within 5 days of the sample arriving in the laboratory (Public Health England 2014b).

If a blood culture is negative, it is recommended that a preliminary negative report is provided within 48 hours of sample receipt in the laboratory and a final negative report should be issued within 5 days unless extended culture is being undertaken for example if fungi or unusual, fastidious or slow growing organisms are suspected (Public Health England 2014b).

False negative blood culture results may occur due to the transient nature of bloodstream infections, and the number of organisms present in each blood sample may be low; often less than  $1 \times 10^3$  colony forming units per litre in adults with bloodstream infection (Public Health England 2014b). Conversely, false positive blood culture results may occur when pathogens transferred from the skin during the blood draw contaminate the culture. To reduce the incidence of false positive results current standards recommend that contamination rates are no higher than 3% (Public Health England 2014b). In addition, several criteria are used to differentiate between contamination and true bloodstream infection which include the identity and clinical significance of the pathogen, the number of positive blood culture sets and positive culture bottles and the quantity of growth detected.

Blood culture sample collection differs for infants and neonates, for whom a single aerobic bottle or low volume blood culture bottle may be requested (Public Health England 2014b). Criteria for calculating total blood culture volumes in neonates and children is based on weight rather than age and relates to total patient blood volume. It has been suggested that the volume of blood drawn should be no more than 1% of the patient's total blood volume (Public Health England 2014b). In infants and children the magnitude of bacteraemia is usually higher than that in adults and therefore the sensitivity of detection is not significantly reduced by lower blood-to-medium ratio.

### *3.2.2 Management/treatment*

The Surviving Sepsis Campaign guidelines recommend care 'bundles' which should be initiated during the diagnostic work-up of a patient. The 3-hour bundle should be completed within 3 hours of a patient developing symptoms which are indicative of sepsis:

- a. Measure lactate levels to identify tissue hypoperfusion
- b. Obtain blood cultures prior to administration of antibiotics

- c. Administer broad spectrum antibiotics
- d. Administer 30ml/kg crystalloid for hypotension or lactate  $\geq 4$ mmol/L

The 6-hour bundle should be completed within 6 hours:

- e. Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation) to maintain a mean arterial pressure  $\geq 65$ mm Hg
- f. In the event of persistent arterial hypotension despite volume resuscitation (septic shock) or initial lactate  $\geq 4$ mmol/L:
  - Measure central venous pressure (CVP)\*
  - Measure central venous oxygen saturation (ScvO<sub>2</sub>)\*
- g. Re-measure lactate if initial lactate was elevated.

The treatment of sepsis varies based on the initial infection, the organs affected and the extent of tissue damage. The management of severe sepsis and septic shock is described by the Surviving Sepsis Campaign in their International Guidelines for the Management of Severe Sepsis and Septic Shock (2012). All patients with severe sepsis or septic shock will require initial resuscitation, antimicrobial therapy, source control and fluid therapy. Some patients may require additional treatment with vasopressors, inotropic therapy, corticosteroids and other supportive therapy.

### Antimicrobial therapy

It is recommended that intravenous empiric antimicrobials should be administered within the first hour of recognition of septic shock and severe sepsis. The initial antimicrobial therapy should include one or more drugs that have activity against all likely pathogens (bacterial and/or fungal or viral) and that penetrate in adequate concentrations into the tissues presumed to be the source of sepsis (Surviving Sepsis Campaign 2012). Frequently used broad spectrum antibiotics for more serious infections include cephalosporins and aminoglycosides. Carbapenems are often the last option in patients with hard to treat infections (Department of Health 2013).

The choice of empirical antimicrobial therapy is often based on:

- the patient's history including drug intolerances
- receipt of antibiotics (previous 3 months)

- underlying disease
- the clinical syndrome
- susceptibility patterns of pathogens in the community and hospital
- previous microbiology reports identifying pathogens which have previously colonised or infected the patient.

Clinicians should also consider whether fungi is a likely causative pathogen when selecting initial therapy and administer empirical antifungal therapy where necessary.

Clinicians prescribing antimicrobial therapy should take into account the Department of Health's [guidance on antimicrobial stewardship](#) which is based on the "start smart then focus" strategy (Department of Health 2011). The guidance recommends that, when antimicrobials are administered empirically, the patient is reviewed after 48 to 72 hours to allow an "antimicrobial prescribing decision" to be made. This decision should take into account available microbiology results to determine whether therapy can be stopped or changed, that is, the de-escalation, substitution or addition of antimicrobial agents to the treatment plan (Department of Health 2011). Narrowing the spectrum of antimicrobial coverage and reducing the duration of therapy is thought to be associated with a reduction in the risk of a patient developing a superinfection, a reduction in the selection of resistant organisms and a reduction in treatment related side-effects (British National Formulary 2014). Side-effects associated with the use of broad spectrum antimicrobials may include diarrhoea, nausea, vomiting, hearing loss, damage to the kidneys and an increased risk of developing superinfection with *Clostridium difficile*. Narrowing the spectrum of antimicrobial coverage may also be associated with an increase in treatment efficacy as certain broad spectrum antibiotics may not be as effective as related narrow spectrum antibiotics against certain pathogens (Department of Health 2011), and in addition a reduction in agents may result in costs savings, particularly when empirical antifungal agents have been prescribed.

The use of antimicrobials varies from hospital to hospital and prescribing choices are influenced by local resistance and susceptibility patterns (British National Formulary 2014). The choice of antimicrobials is also influenced by the suspected source of the infection and local prescribing protocols may be developed for:

- urinary tract infections
- upper respiratory tract infections
- lower respiratory tract infections
- soft tissue infections

- central nervous system infections
- gastrointestinal infections, genital tract infections
- bloodstream infections
- eye, ear, nose and throat infections
- sepsis of unknown origin.

### 3.3 Patient issues and preferences

The extended use of broad spectrum antimicrobials may place patients at increased risk of developing a superinfection such as *Clostridium difficile* and contribute to the development of resistant organisms. In addition, survivors of critical illness, particularly those who have been admitted to an intensive care unit, are at risk of long term physical and psychological problems which impact upon their quality of life (Jones and Griffiths 2006). People who have survived sepsis are also thought to be at increased risk of long-term neurophysiological problems including cognitive decline (Annane and Sharshar 2014).

## 4 Scope of the evaluation

**Table 4: Scope of the evaluation**

<b>Decision question</b>	What is the clinical and cost-effectiveness of using the LightCycler SeptiFast Test MGRADE, SepsiTest and IRIDICA BAC BSI assay in addition to clinical assessment for rapidly identifying bloodstream bacteria and fungi?
<b>Populations</b>	People with suspected bloodstream infections in secondary care Potential subgroups include: <ul style="list-style-type: none"> <li>• People with a suspected healthcare associated infection</li> <li>• People with a suspected community acquired infection</li> <li>• Children and neonates</li> <li>• People who are immunocompromised</li> <li>• People exposed to antibiotics prior to blood sample collection</li> </ul>
<b>Interventions</b>	<ul style="list-style-type: none"> <li>• LightCycler SeptiFast Test MGRADE</li> <li>• SepsiTest</li> <li>• IRIDICA BAC BSI assay</li> </ul> in conjunction with clinical assessment
<b>Comparator</b>	<ul style="list-style-type: none"> <li>• Clinical assessment in conjunction with blood</li> </ul>

	<p>culture</p> <ul style="list-style-type: none"> <li>• Clinical assessment in conjunction with blood culture and MALDI-TOF</li> </ul>
<b>Healthcare setting</b>	<ul style="list-style-type: none"> <li>• Departments and wards providing care for acutely unwell patients</li> <li>• Critical care unit</li> </ul>
<b>Outcomes</b>	<p>Intermediate measures for consideration may include:</p> <ul style="list-style-type: none"> <li>• Diagnostic accuracy</li> <li>• Discordant results with blood culture</li> <li>• Time to result</li> <li>• Time to treatment decision</li> <li>• Test failure rates</li> <li>• Duration of ICU and/or hospital stay</li> <li>• Duration of broad and narrow spectrum antimicrobial therapy</li> <li>• Re-admission rate</li> <li>• Change in antimicrobial treatment plan</li> </ul> <p>Clinical outcomes for consideration may include:</p> <ul style="list-style-type: none"> <li>• Side-effects associated with broad spectrum antimicrobial use</li> <li>• Morbidity and mortality</li> <li>• Severity of disease (as measured by scoring systems such as SOFA, SAPS II and APACHEII)</li> <li>• Rates of superinfection (including <i>C. difficile</i>)</li> <li>• Rates of resistant infections</li> <li>• Health related quality of life</li> </ul> <p>Costs will be considered from an NHS and Personal Social Services perspective. Costs for consideration may include:</p> <ul style="list-style-type: none"> <li>• Cost of equipment, reagents and consumables</li> <li>• Cost of staff and associated training</li> <li>• Costs associated with treatment (for example, broad and narrow spectrum antibiotics and antifungals)</li> <li>• Medical costs arising from testing and care such as hospital stay</li> <li>• Medical costs arising from adverse events including those associated with false test results and</li> </ul>

	<p>inappropriate treatment</p> <p>Blood culture in current practice is required for the identification of bloodstream bacteria and fungi, and to provide definitive antimicrobial susceptibility data.</p> <p>It is anticipated that blood cultures would be required in addition to the rapid molecular tests, to provide definitive antimicrobial susceptibility data.</p>
	<p>The cost-effectiveness of interventions should be expressed in terms of incremental cost per quality-adjusted life year.</p>
	<p>The potential costs and health impacts associated with antimicrobial resistance should also be considered.</p>
<b>Time horizon</b>	<p>The time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.</p>

## 5 Modelling approach

### 5.1 Existing models

During scoping, two published economic evaluations were found which reported the use of PCR tests for the rapid identification of pathogens in people with sepsis (Lehmann et al 2010 and Alvarez et al 2012). Both studies are based upon PCR using the LightCycler SeptiFast test MGRADE.

Lehmann et al. (2010) report results from a mathematical prediction model populated with data from 3 observational studies to assess the impact of PCR-based rapid adjustment of antimicrobial treatment. The study reports that 80.5 days of earlier adequate antimicrobial treatment were enabled by 221 PCR tests, which the authors estimate could also translate into a 1.15 day reduction in duration of ventilation and intensive care unit stay for each day of earlier adequate treatment. The authors conclude that the cost of a PCR test (€300) could be recovered for patients with a daily treatment cost of greater than €717 and the study reports an incremental cost effectiveness ratio of €3107 per quality adjusted life year gained for PCR testing.

Alvarez et al. (2012) report results from a cost minimisation study where the use of the LightCycler SeptiFast test MGRADE was found to be associated with a net average saving of €9970 per patient. The cost savings were driven by reductions in both the length of intensive care unit stay and use of antibiotics, however the analysis is based on the assumption that the use of the LightCycler SeptiFast test MGRADE is associated with a mortality rate equivalent to that of current practice.



In addition economic models based on the care pathway for people with suspected sepsis are currently under development for both the NICE clinical guideline on the recognition, diagnosis and management of severe sepsis and the NICE diagnostics assessment of procalcitonin testing.

## **6 *Potential equality issues***

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others.

Bloodstream infection may be a particular risk for neonates, older people, people who are immunocompromised and pregnant women. People with cancer are at risk of neutropenic sepsis.

The volume of blood required for a sample may make molecular tests less suitable for testing in neonatal and paediatric patients.

## **7 *Potential implementation issues***

The adoption of direct sample whole blood molecular tests may require changes to laboratory processes and workflow to achieve rapid turn-around times for processing and reporting samples. It may also be difficult to obtain the volume of blood required for a sample for direct whole blood molecular testing in some critically ill neonates and paediatric patients.

## **Appendix A      Glossary of terms**

### **Anaerobic bacteriaemia**

Bloodstream infections caused by anaerobic bacteria. Anaerobic bacteria are the most common flora in the body but may cause serious infection after injury or trauma to the body. Anaerobic bacteria include Gram Positive and Gram Negative cocci and rods.

### **Broad spectrum antibiotic**

An antibiotic which is effective against a broad range of bacteria. Broad spectrum antibiotics typically include coverage against gram-positive and gram-negative bacteria.

### **Carbapenems**

Broad spectrum antibiotics which are often used as the last line of treatment for hard to treat human infections caused by gram-negative bacteria.

### **Carbapenemases**

Enzymes produced by bacteria that destroy carbapenems and other beta-lactam antibiotics.

### **Disc diffusion method**

A method of antimicrobial susceptibility testing which involves placing antimicrobial impregnated discs onto an agar plate containing bacterial cultures. If the antibiotic is effective against the bacteria, there will be a visible zone which is devoid of bacterial growth surrounding the disc.

### **Empiric antibiotic**

An antibiotic given to a person before a specific microorganism or source of the potential infection is known. It is usually a broad-spectrum antibiotic and the treatment may change if the pathogen or source is confirmed.

### **Extended-spectrum beta-lactamases**

Enzymes produced by bacteria making them resistant to penicillins and cephalosporins.

### **Gram-negative bacteria**

Bacteria that do not retain crystal violet dye in the Gram-staining procedure. They can cause many types of infection and include *E. coli* and *Pseudomonas aeruginosa*.

### **Gram-positive bacteria**

Bacteria that are stained dark blue or violet in the Gram-staining procedure. They include *Staphylococcus aureus* and *Clostridium difficile*.

### **Healthcare associated infections**

Infections acquired via the provision of healthcare in either a hospital or community setting.

### **MALDI-TOF mass spectrometry**

MALDI-TOF (matrix-absorbed laser desorption/ionization- time of flight) mass spectrometry may be used to identify bacteria and fungi from positive blood cultures.

### **Meticillin-resistant *Staphylococcus aureus* (MRSA)**

A strain of *Staphylococcus aureus* that is resistant to beta lactam antibiotics which include penicillins (e.g. meticillin and oxacillin) and almost all cephalosporin antibiotics.

### **Neutropenia**

An abnormally low number of neutrophils which are a type of white blood cells that help to fight off infections by destroying bacteria and fungi. People who have neutropenia are therefore at an increased risk of developing a serious infection.

### **Polymicrobial infection**

An infection which is caused by more than one pathogen and which may include a combination of bacteria, fungi and viruses.

### **Sepsis**

A life-threatening systemic inflammatory response caused by the presence of an infectious agent (i.e. bacterial, viral, fungal or parasitic).

### **Severe sepsis**

A septic infection that is associated with signs of organ dysfunction, damage and altered cerebral function leading to septic shock. Most patients with severe sepsis require treatment in intensive care units and severe sepsis can lead to death.

### **Septic shock**

Sepsis-induced hypotension persisting despite adequate fluid resuscitation.

### **Superinfection**

A new infection occurring in a patients with a pre-existing infection.

### **Systemic Inflammatory Response Syndrome**

A life-threatening condition which arises from a severe systemic response to either an infectious or non-infectious insult.

## **Appendix B      Related guidance**

### **Published NICE guidance**

[Antibiotics for neonatal infection](#) (2014) NICE Quality standard QS75

[Pneumonia: Diagnosis and management of community- and hospital-acquired pneumonia in adults](#) (2014) NICE Clinical guideline CG191

[Surgical site infection](#) (2014) NICE Quality standard QS49

[Faecal microbiota transplant for recurrent \*Clostridium difficile\* infection](#) (2014) NICE Interventional procedure guidance IPG485

[Acute kidney injury](#) (2013) NICE Clinical guideline CG169

[Feverish illness in children: Assessment and initial management in children younger than 5 years](#) (2013) NICE Clinical guideline CG160

[Intravenous fluid therapy in adults in hospital](#) (2013) NICE Clinical guideline CG174

[Antibiotics for the prevention and treatment of early-onset neonatal infection](#) (2012) NICE Clinical guideline CG149

[Neutropenic sepsis: prevention and management of neutropenic sepsis in cancer patients](#) (2012) NICE Clinical guideline CG151

[Prevention and control of healthcare-associated infections: Quality improvement guide](#) (2011) NICE guidelines PH36

[Management of bacterial meningitis and meningococcal septicaemia in children and young people younger than 16 years in primary and secondary care](#) (2010) NICE Clinical guideline CG102

[Management of acute diarrhoea and vomiting due to gastroenteritis in children under 5](#) (2009) NICE Clinical guideline CG84

[Rehabilitation after critical illness](#) (2009) NICE Clinical guideline CG83

[Prevention and treatment of surgical site infection](#) (2008) NICE Clinical guideline CG74

[Surgical site infection](#) (2008) NICE Clinical guideline CG74

[Acutely ill patients in hospital](#) (2007) NICE Clinical guideline CG50

[Diagnosis, treatment and long-term management of urinary tract infection in children](#) (2007) NICE Clinical guideline CG54

### **NICE guidance under development**

Antimicrobial stewardship. NICE medicines practice guideline. Publication expected March 2015.

Diagnosis and monitoring of sepsis: procalcitonin testing (ADVIA Centaur BRAHMS PCT assay, BRAHMS PCT Sensitive Kryptor assay, Elecsys BRAHMS PCT assay, LIAISON BRAHMS PCT assay and VIDAS BRAHMS PCT assay). NICE Diagnostic guidance. Publication expected October 2015.

Intravenous fluids therapy in children. NICE Clinical guideline. Publication expected October 2015.

Antimicrobial resistance - changing risk-related behaviours in the general population. NICE public health guidance. Publication expected March 2016.

Sepsis. NICE Clinical guideline. Publication expected July 2016.

Acute Medical Emergencies in adults and young people, service guidance. NICE clinical guideline. Publication expected November 2016.

### **NICE pathways**

The rapid pathogen identification guidance will be included in several NICE pathways, for example: neutropenic sepsis, feverish illness in children and antibiotics for early onset neonatal infection.

In some of these pathways, it may be appropriate to include the full recommendations of the guidance, in others it will only be necessary to give a link to the guidance.

### **Relevant guidance from other organisations**

British Thoracic Society (2011) [Guidelines for the management of community acquired pneumonia in children: update 2011](#)

British Thoracic Society (2005) [Guidelines for the management of pleural infection in children](#)

College of Emergency Medicine (2012) [Standards for Severe Sepsis and Septic Shock Management in Adults \(revised 2012\)](#)

Diagnosis and therapy of Candida infections (2011) Joint recommendations of the German Speaking Mycological Society and the Paul-Ehrlich-Society from Chemotherapy

European Society of Clinical Microbiology and Infectious Diseases (2014) [ESCMID and ECMM guidelines for the management of rare and emerging fungal infections](#)

European Society of Clinical Microbiology and Infectious Diseases (2012) [ESCMID guideline for the diagnosis and management of Candida diseases](#)

Fourth European Conference on Infections in Leukaemia (2014) Guidelines for diagnosis, prevention, and treatment of invasive fungal diseases in paediatric patients with cancer or allogeneic haemopoietic stem-cell transplantation

Infectious Diseases Society of America (2009) Clinical Practice Guidelines for the Diagnosis and Management of Intravascular Catheter-Related Infection: 2009 update by the Infectious Diseases Society of America

Infectious Diseases Society of America (2009) Clinical Practice Guidelines for the Management of Candidiasis: 2009 update by the Infectious Diseases Society of America

Infectious Diseases working Party in Hematology and Oncology of the German Society for Haematology and Oncology (2011) Diagnosis of invasive fungal infections in haematology and oncology

Parliamentary and Health Service Ombudsman (2013) [Time to act. Severe sepsis: rapid diagnosis and treatment saves](#) lives

Royal College of Obstetricians and Gynaecologists (2012) Bacterial Sepsis in Pregnancy

Royal College of Obstetricians and Gynaecologists (2012) Bacterial Sepsis following Pregnancy

Scottish Intercollegiate Guidelines Network (2008) Management of invasive meningococcal disease in children and young people

Scottish Intercollegiate Guidelines Network (2012) Management of suspected bacterial urinary tract infection in adults

Scottish Intercollegiate Guidelines Network (2014) Antibiotic [prophylaxis in surgery](#)

Scottish Intercollegiate Guidelines Network (2014) Care [of deteriorating patients](#)

Surviving Sepsis Campaign (2012) International Guidelines for Management of Severe Sepsis and Septic Shock

## Appendix C      References

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- Public Health England (2014a) English surveillance programme for antimicrobial utilisation and resistance (ESPAUR). London: Public Health England.
- Public Health England (2014b) UK standards for microbiology investigations: Investigation of blood cultures (for organisms other than Mycobacterium species). London: Public Health England.
- Sepsis: The LightCycler SeptiFast Test MGRADE, SepsiTtest and IRIDICA BAC BSI assay for rapidly identifying bloodstream bacteria and fungi  
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