NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Centre for Health Technology Evaluation

Review decision

Review of DG20: Tests for rapidly identifying bloodstream bacteria and fungi

This guidance was issued in February 2016.

The review date for this guidance is February 2019.

NICE proposes an update of published guidance if the evidence base or clinical environment has changed to an extent that is likely to have a material effect on the recommendations in the existing guidance. Other factors such as the introduction of new technologies relevant to the guidance topic, or newer versions of technologies included in the guidance, will be considered relevant in the review process, but will not in individual cases always be sufficient cause to update existing guidance.

1. Review decision

Transfer the guidance to the 'static guidance list' after a post-publication update to the recommendations to reflect that the LightCycler SeptiFast Test MGRADE and IRIDICA BAC BSI are no longer available to the NHS.

At the Guidance Executive meeting of 28 January 2020 the proposal to transfer the guidance to the static list without consultation was agreed. A list of the options for consideration, and the consequences of each option is provided in Appendix 1 at the end of this paper.

2. Rationale

A post-publication update is needed to reflect that the LightCycler SeptiFast Test MGRADE (Roche Diagnostics) and IRIDICA BAC BSI (Abbott) have been discontinued.

The only test from the original guidance that remains available to the NHS is the SepsiTest (Molzym). No new evidence was found on this test that could have a material impact on the guidance recommendations. In addition, there have been no substantial changes to the care pathway. The guidance should be transferred to the static list after being amended to reflect that 2 of the tests are no longer available to the NHS.

3. Implications for other guidance producing programmes

No overlaps identified.

4. Original objective of guidance

To assess the clinical and cost effectiveness of LightCycler SeptiFast Test MGRADE, SepsiTest and IRIDICA BAC BSI assay (in addition to clinical assessment) for rapidly identifying bloodstream bacteria and fungi.

5. Current guidance

Adoption recommendations

There is currently insufficient evidence to recommend the routine adoption in the NHS of the LightCycler SeptiFast Test MGRADE, SepsiTest and IRIDICA BAC BSI assay for rapidly identifying bloodstream bacteria and fungi. The tests show promise and further research to provide robust evidence is encouraged, particularly to demonstrate the value of using the test results in clinical decision-making.

Research recommendations

No formal research recommendations were made in the guidance, but sections 5.18 to 5.22 set out several areas the committee thought would benefit from further research. In brief, the committee encouraged research on the clinical utility of rapid tests (including identifying clinical scenarios in which the tests may offer most benefit), the clinical utility of rapid tests in combination with other biomarkers, the impact on anti-fungal prescribing and the levels of certainty about the results of rapid molecular tests that clinicians need to have before they decide to change treatment and level of care for patients. The committee also encouraged the use of MALDI-TOF MS as a comparator in any future studies aiming to establish the clinical utility of rapid molecular tests, and that future studies should include children and neonates.

6. New evidence

The search strategy from the original diagnostics assessment report was re-run on Medline (including In Process & Other Non-Indexed Citations and Epub ahead of print); EMBASE; Cochrane Database of Systematic Reviews; Cochrane Central Register of Controlled Trials; Health Technology Assessment Database; Science Citation Index Expanded; Conference Proceedings Index Service and WHO International Clinical Trials Registry Platform. References from January 2015 onwards were reviewed. Additional searches of clinical trials registries were also carried out and relevant guidance from NICE and other professional bodies was reviewed to determine whether there have been any changes to the diagnostic and care pathways. Companies were asked to submit all new literature references

relevant to their technology along with updated costs and details of any changes to the technology itself or the CE marked indication for use for their technology. Specialist committee members for this guidance topic were also consulted and asked to submit any information regarding changes to the technologies, the evidence base and clinical practice. The results of the literature search are discussed in the 'Summary of evidence and implications for review' section below. See Appendix 2 for further details of ongoing and unpublished studies.

6.1 Technologies

LightCycler SeptiFast Test MGRADE (Roche Diagnostics)

The company has stated that this test will not be available after the end of 2019.

SepsiTest (Molzym)

The SepsiTest has been renamed as SepsiTest-UMD. The company have stated that it is widely used for routine diagnosis in hospital laboratories and private laboratories elsewhere in Europe but is not currently used in the UK. In addition to blood samples, the CE mark indication for use of test has been expanded to include other clinical specimen types, such as fluid and tissue biopsies.

IRIDICA BAC BSI (Abbott)

The company have stated that this test has been discontinued.

Additional technologies (not included in scope)

Several additional technologies are available that can be used to detect and identify pathogens that are causing sepsis. However, from manufacturer's websites these tests appear to require initial blood culture to be done before the tests are run. The purpose of the medical technologies assessed in DG20 was to rapidly detect and identify bacterial and fungal DNA which may be present in the bloodstream in people who are suspected of having sepsis. 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.

6.2 Clinical practice

No evidence was identified that suggested changes to the care pathway have occurred since publication of the guidance.

A clinical expert commented that microbiologists in the NHS are not using any of these rapid tests and that almost all diagnostic laboratories are using MaldiTOF because it is cheap and gives more information.

NICE guidance on Sepsis: recognition, diagnosis and early management (NG51; published July 2016) recommended carrying out a venous blood test for blood culture (among other things) for:

- adults, children and young people aged 12 years and over who have suspected sepsis and 1 or more high risk criteria (recommendation 1.6.1) and 2 or more moderate to high risk criteria, or systolic blood pressure 91–100 mmHg (recommendation 1.6.8)
- children aged 5–11 years who have suspected sepsis and 1 or more high risk criteria (recommendation 1.6.16) and 2 or more moderate to high risk criteria (recommendation 1.6.23)
- children aged under 5 years who have suspected sepsis and 1 or more high risk criteria (recommendation 1.6.31) and 2 or more moderate to high risk criteria (recommendation 1.6.39).

6.3 New studies

Several new studies were identified on technologies included in the scope for this guidance and were considered potentially relevant. However, as the SeptiFast test and IRIDICA test are no longer available on the NHS, or soon will not be, studies reporting on these tests are not discussed here.

A single study by Nieman et al. (2016) assessed the SepsiTest. This was a multicentre observational study which tested blood samples from people with suspected sepsis (166 patients, 236 samples) between November 2010 and September 2012 from 2 centres in Germany and 1 in the Netherlands. When blood culture was used as a reference standard, the SepsiTest had:

- Sensitivity of 25.6% and specificity of 82.9% per sample
- Sensitivity of 28.9% and specificity of 79.7% per patient

To assess any issues with blood culture used as a reference standard, the authors also used clinical interpretation to assess positive results and determine if detected bacteremia was true, probable, possible or questionable[1]. The adjusted sensitivity and specificity calculated using this methodology were 66.7% and 94.4%, respectively. In addition, the authors commented that of the 36 positive samples, 15 were detected by SepsiTest only, and 10 were detected by blood culture only.

7. Summary of new evidence and implications for review

The estimates of sensitivity and specificity reported in Nieman et al. (2016) for the SepsiTest compared with blood culture as a reference standard were both lower

[1] *True bacteremia* occurred when blood culture and SepsiTest identified the same bacteria; if results between the tests differed, bacteremia was considered *probable* if the detected bacterium was also cultured in other specimens from the same patient and was consistent with the clinical diagnosis, and *possible* bacteremia if the bacterium was not confirmed in other cultures, but was considered to be consistent with the clinical diagnosis (Nieman et al. 2016).

than pooled estimates of this tests produced for the DG20 assessment (reported in section 4.10 of the guidance).

No new evidence was identified on the effect of using the SepsiTest on clinical outcomes. In the base case economic analysis done for DG20 based on clinical effectiveness data (base case 1), the SepsiTest was dominated by blood culture because no data were available showing clinical benefits associated with the test (for 30-day mortality, duration of stay in the intensive care unit or duration of stay in hospital).

In conclusion, no evidence was found that could have a material impact on the guidance recommendations. The guidance transferred to the static list after being amended to reflect that 2 of the tests are no longer available to the NHS.

8. Implementation

Clinical experts and manufacturers have commented that these tests are not in use in the NHS.

9. Equality issues

No new equality issues have been identified since the publication of the guidance.

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Appendix 1 – explanation of options

If the published Diagnostics Guidance needs updating NICE must select one of the options in the table below:

Options	Consequence	Selected – 'Yes/No'
Standard update of the guidance	A standard update of the Diagnostics Guidance will be planned into NICE's work programme.	No
Accelerated update of the guidance	An accelerated update of the Diagnostics Guidance will be planned into NICE's work programme. Accelerated updates are only undertaken in circumstances where the new evidence is likely to result in minimal changes to the decision problem, and the subsequent assessment will require less time to complete than a standard update or assessment.	No
Update of the guidance within another piece of NICE guidance	The guidance is updated according to the processes and timetable of that programme.	No

If the published Diagnostics Guidance does not need updating NICE must select one of the options in the table below:

Options	Consequences	Selected – 'Yes/No'
Transfer the guidance to the 'static guidance list'	The guidance remains valid and is designated as static guidance. Literature searches are carried out every 5 years to check whether any of the Diagnostics Guidance on the static list should be flagged for review.	Yes
Produce a technical supplement	A technical supplement describing newer versions of the technologies is planned into NICE's work programme.	No
Defer the decision to review the guidance to [specify date or trial].	NICE will reconsider whether a review is necessary at the specified date.	No
Withdraw the guidance	The Diagnostics Guidance is no longer valid and is withdrawn.	No

Appendix 2 – supporting information

Relevant Institute work

Published

- Sepsis: recognition, diagnosis and early management (2016) NICE guideline NG51
- Antimicrobial stewardship: systems and processes for effective antimicrobial medicine use (2015) NICE guideline NG15
- Pneumonia in adults: diagnosis and management (2014) NICE guideline CG191
- Procalcitonin testing for diagnosing and monitoring sepsis (ADVIA Centaur BRAHMS PCT assay, BRAHMS PCT Sensitive Kryptor assay, Elecsys BRAHMS PCT assay, LIAISON BRAHMS PCT assay and VIDAS BRAHMS PCT assay) (2015) NICE diagnostics guidance DG18

In progress

- Meningitis (bacterial) and meningococcal septicaemia: recognition, diagnosis and management NICE guideline. Publication expected February 2022

Registered and unpublished trials

No ongoing studies relevant to the SepsiTest were identified. Ongoing studies use other tests from the scope of the assessment or newer tests.

Trial name and registration number	Details
A rapid DNA-test for early detection of bloodstream infections in intestinal failure patients NL7716	Observational study (n=125) using the SeptiFast test for adults with intestinal failure and clinical suspicion of bloodstream infection. Primary outcome: Sensitivity of ddPCR and SeptiFast to correctly detect pathogens (identical to results from blood cultures and clinical course). Netherlands Currently recruiting (accessed 18 September 2019)

Trial name and registration number	Details
Randomized Trial of Fast Bacterial Identification and Phenotypic Antimicrobial Susceptibility Testing in Patients With Positive Blood Cultures Using the Accelerate PhenoTest™ BC Kit, Performed on the Accelerate Pheno™ System as Compared With the Verigene® BC-GP/GN NCT03744728	Open-label randomised trial (n=466) of adults with positive blood cultures using the Accelerate PhenoTest BC kit or Standard culture and AST of positive blood culture bottles plus the Verigene BC-GP/GN. Primary outcomes: Duration of anti-pseudomonal β-lactam therapy and Duration of anti-MRSA therapy USA Estimated study completion date: March 2020
Ultra Rapid Culture Independent Detection of High-Priority Carbapenem Resistant Enterobacteriaceae Directly From Blood NCT02482051	Prospective observational study (n=2,500) comparing the Accelerate ID/AST system to conventional microbiological methods of gram negative bacilli detection Primary outcomes: Bacteria identification and Accuracy of carbapenem susceptibility testing USA Estimated study completion date: January 2020
Impact of Rapid Pathogen Identification From Blood Cultures (RABbIT) NCT02743585	Randomised trial (n=832) comparing participants in a rapid diagnostic arm (standard care, FilmArray Blood Culture ID (BCID) Panel test and Rosco Diagnostica ESBL and carbapenemase screen kit) with standard care. Primary outcome: Time from positive blood culture result to effective/optimal antibiotics. Secondary outcomes include costs, quality of life (EQ-5D-5L/SF-12) and a cost-effectiveness analysis. Singapore. Estimated study completion date: July 2020
Assessment of the Use and Impact of a Molecular Identification Assay in the Diagnosis and Management of Bloodstream Infections at in Healthcare Settings in Princess Marina Hospital, Botswana NCT03255759	Randomised trial (n=560) comparing the BIOFIRE FilmArray system with standard care. Primary outcome: 1.Time from blood collection to definitive treatment initiation (optimal treatment defined as time from blood culture collection to the initiation of a predetermined pathogen-specific antimicrobial therapy) Botswana Estimated study completion date: June 2019

Trial name and registration number	Details
Clinical and Medico-economic Evaluation of a Rapid Test (ePlex-BCID®, GenMark) for the Diagnosis of Bacteremia or Fungemia From Positive Blood Culture Bottles, Combining Fast Identification of Bacteria and Fungi and Evaluation of Bacterial Resistance to First Line Antibiotics (HEMOFAST) NCT03876990	Randomised trial (n=400) comparing the use of multiplex PCR (ePlex BCID) and current strategy with current strategy alone. Primary outcome: Delay from suspicion of sepsis to optimized antibiotic/antifungal treatment. Secondary outcomes include economic evaluations. France Estimated study completion date: December 2020
Fast Assay for Pathogen Identification and Characterization - Prospective Observational Study NCT03841162 (follow-up to NCT03025802)	Prospective observational study of adults with suspected sepsis, for whom blood cultures are drawn (n=700). Primary outcomes: Confirmed bacteremia based on positive blood cultures with (i) SOFA score, (ii) Serum Lactate and (iii) Ferritin, and Test performance (sensitivity, specificity and accuracy) Belgium Estimated study completion date: September 2019

References

Nieman, A.E. et al. (2016) A prospective multicenter evaluation of direct molecular detection of blood stream infection from a clinical perspective. *BMC Infectious Diseases.* 16: 314.