Sepsis: the LightCycler SeptiFast Test MGRADE®, SepsiTest™ and IRIDICA BAC BSI assay for rapidly identifying bloodstream bacteria and fungi – a systematic review and economic evaluation

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Scientific summary

Three sepsis tests for identifying bloodstream bacteria and fungi

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Scientific summary

Background

Sepsis is a condition characterised by the body's inflammatory response to a bacterial, viral or fungal infection. In the UK, sepsis is estimated to be responsible for 100,000 hospital admissions and 37,000 deaths per year. As a consequence, the cost to the NHS is considerable. Current standard practice for detecting pathogens in those patients with a suspected bloodstream infection or sepsis consists of clinical assessment in conjunction with blood culture [with or without matrix-absorbed laser desorption/ionisation time-of-flight (MALDI-TOF) mass spectrometry (MS)]. However, positive blood culture results for bacteria or fungi can take several days. Several new tests have been developed that can detect minute amounts of pathogens' deoxyribonucleic acid in patients' whole-blood samples, with results available within approximately 6 hours under optimal conditions, although this time is likely to be increased if the tests are introduced routinely into clinical practice. It is noted that recently published guidelines, if followed, are likely to reduce the consequences of sepsis.

Objectives

To evaluate the clinical effectiveness and cost-effectiveness of three tests [LightCycler SeptiFast Test MGRADE® (Roche Diagnostics, Risch-Rotkreuz, Switzerland), SepsiTest™ (Molzym Molecular Diagnostics, Bremen, Germany) and the IRIDICA BAC BSI assay (Abbott Diagnostics, Lake Forest, IL, USA)] for the rapid identification of bloodstream bacteria and fungi compared with standard practice.

Methods

Clinical evidence review

A systematic review was conducted in accordance with established guidelines. Thirteen electronic databases and research registers were searched (including MEDLINE, EMBASE and The Cochrane Library) from January 2006 to May 2015. Searches were supplemented by hand-searching of relevant articles (including citation searching and screening company submissions) and contacting experts in the field. The methodological quality of each included study was performed using the Quality Assessment of Diagnostic Accuracy Studies tool. Data were extracted at the pathogen level, where reported in the published literature, otherwise data were extracted at the patient level. Results were summarised in tables and text. Data analysis comprised a narrative synthesis and pairwise meta-analysis.

Cost-effectiveness assessment

A systematic review of evidence relating to the cost-effectiveness of the interventions was undertaken. A mathematical model was constructed with two key scenarios evaluated: base case 1, in which only published statistically significant data were used within the model; and base case 2, in which data provided by clinical experts were used. Further analyses were conducted where studies had compared interventions where MALDI-TOF MS was used in conjunction with blood culture and where studies had compared two of the interventions simultaneously. Evaluations were undertaken assuming a range (2.4–68) of blood samples that need analysing per day for all scenarios. Threshold analyses were also undertaken to provide further information for the Diagnostic Appraisal Committee on the gains required in reduced mortality, reduced intensive care unit length of stay and in reduced costs of antimicrobial drugs.

Results

Clinical effectiveness results

The literature searches identified 2892 citations. Of these, 66 studies met the inclusion criteria. The methodological quality of the included studies was variable, with the majority having deficiencies in reporting and study quality. For the review of diagnostic test accuracy, a meta-analysis of 54 studies comparing SeptiFast with blood culture found that SeptiFast had an estimated specificity of 0.86 [95% credible interval (CrI) 0.84 to 0.89] and sensitivity of 0.65 (95% CrI 0.60 to 0.71). However, there was substantial heterogeneity between studies, particularly for sensitivity. Reasons for the observed heterogeneity in sensitivity and specificity between studies were explored using metaregression for several potentially relevant characteristics: age category (adults, and children and neonates), antibiotic use at the time of blood sampling, community- or health-acquired infection, patients with febrile neutropenia and studies with inclusion/exclusion of contaminants. There was no evidence to suggest that the pooled sensitivity and specificity was affected by these subgroups. Comparison with blood culture plus MALDI-TOF MS in a single study showed higher specificities than sensitivity [0.74, 95% confidence interval (CI) 0.64 to 0.85, and 0.58, 95% CI 0.30 to 0.86, respectively]. Pooled effects across four studies comparing SepsiTest with blood culture suggest that SepsiTest had an estimated specificity of 0.86 (95% CrI 0.78 to 0.92) and a sensitivity of 0.48 (95% CrI 0.21 to 0.74). Although there was substantial heterogeneity between studies, analyses for potential causes of this heterogeneity could not be explored because of the small number of included studies. Comparison with blood culture plus MALDI-TOF MS in a single study also showed higher specificities than sensitivity (0.96, 95% CrI 0.92 to 1.00 and 0.11, 95% CrI 0.00 to 0.23, respectively). A meta-analysis of four studies comparing IRIDICA with blood culture found that IRIDICA had an estimated specificity of 0.84 (95% CrI 0.71 to 0.92) and a sensitivity of 0.81 (95% CrI 0.69 to 0.90). However, there was substantial heterogeneity between studies. Moreover, owing to the deficiencies in study quality for all interventions, diagnostic accuracy data may not be reliable and should be treated with caution.

For the review of other intermediary and clinical outcome measures, 41 studies across the three interventions reported data on time to pathogen identification (SeptiFast only, $n = 21$); time to treatment (SeptiFast only, $n = 3$); test failure rates [SeptiFast, $n = 7$ (confidential information has been removed)]; duration of stay in hospital or critical care units (SeptiFast only, $n = 13$); duration of broad- and narrow-spectrum antimicrobial therapy (SeptiFast only, $n = 1$); changes in antimicrobial treatment plan (SeptiFast, $n = 14$; and IRIDICA, $n = 1$); and mortality (SeptiFast, $n = 17$; SepsiTest, $n = 1$; IRIDICA, $n = 1$; and SeptiFast/SepsiTest, $n = 1$). The majority of studies reported data for the whole patient cohort, as opposed to comparative data for the index and reference test. As a result, the effects of the individual test on these outcomes remain unclear. Of the comparative studies, a small number of low-methodological-quality randomised controlled trials (all SeptiFast studies) indicated no statistically significant between-group differences for SeptiFast compared with blood culture in length of hospital stay ($n = 3$), length of intensive care unit stay ($n = 2$), duration of antimicrobial therapy ($n = 1$) or mortality ($n = 3$).

Cost-effectiveness results

Four economic evaluations were identified, three evaluating SeptiFast and one evaluating a hybrid of IRIDICA and an earlier system PLEX-ID, but none was deemed to adequately address the decision problem. The results produced by the de novo model were highly variable. In base case 1, all interventions were dominated as the tests were not assumed to provide benefit. In base case 2, all interventions were estimated to have cost per quality-adjusted life-year (QALY) gained values of < £20,000 when using the average values provided by the clinicians; however, these estimates differed markedly between individual clinicians, with a non-negligible proportion believing the tests had a cost per QALY gained in excess of £30,000. IRIDICA was estimated to have the greatest net monetary benefit, followed by SepsiTest and then SeptiFast. The additional analyses undertaken using the results from multitest studies that compared SeptiFast, SepsiTest and blood culture, when the data provided by clinicians were used, were concordant with base case 2. However, the indirect results produced when using studies directly comparing the three tests with MALDI-TOF MS produced contrary results, with SeptiFast estimated to dominate SepsiTest. Within the threshold analyses it was seen that relatively small mortality gains would be required for the interventions to achieve a cost per QALY gained of £20,000 compared with standard practice.

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Discussion

SeptiFast, SepsiTest and IRIDICA appear to have higher specificity values than sensitivity values. However, given the potentially fatal consequences of removing treatment from patients with sepsis, it is not anticipated that negative tests in isolation would be acted on in clinical practice were an intervention introduced. This is because the sensitivity of the tests is not high enough to allow them to be used in a 'rule-out' manner, such that clinicians can be reassured that a negative test is associated with a very low probability of the patient having the disease. Furthermore, because of the deficiencies in study design and poor reporting of the included studies, test characteristic data may not be reliable and should be treated with caution.

The pooled estimates of sensitivity and specificity for each test were estimated assuming that the reference standard was 100% sensitive and specific; however, this is unlikely to be the case. In practice, a wide range of factors are known to influence the diagnostic accuracy of blood cultures. For example, this may include antimicrobial treatment prior to blood sampling, low blood sample volumes, lack of replicate blood culture sets, delays in incubation and contamination during sampling. As a result, the reported estimates of sensitivity and specificity are likely to be biased (underestimated) compared with those that would be obtained using a perfect reference standard. In addition, diagnostic metrics in the included studies were measured using different units: patients, sample episodes or species/pathogen level. Such analyses create a 'unit of analyses' error and may have contributed to the heterogeneity in the results.

Although there are no existing systematic reviews of diagnostic accuracy for SepsiTest or IRIDICA, the present review includes more studies than previous reviews on SeptiFast and is therefore more comprehensive. Although an extensive literature search was conducted, it is possible that some studies may have been missed. However, such omissions are likely to have been minimal as the search included all identifiable publications in the grey literature (including contact with clinical experts in the field and checking evidence submitted by the companies that manufacture the tests). Statistical evaluation of diagnostic test accuracy was undertaken using rigorous methods, allowing for the correlation between sensitivity and specificity, and between-study heterogeneity. Reasons for the heterogeneity in sensitivity and specificity between studies were further explored using metaregression. Parameter estimates were produced using Markov chain Monte Carlo simulation.

There are no head-to-head comparisons of all these tests and there are limited robust data that report the impact of interventions on hard clinical outcomes, such as mortality and length of stay in critical care units. The data that do exist have not shown any intervention to produce a non-confounded statistically significant improvement. In addition, the three interventions provide very limited data regarding antimicrobial sensitivity. Definitive data on this need to be determined, if possible, via standard culture methods undertaken in parallel with the interventions. In order to produce a definitive conclusion on the clinical effectiveness of these interventions, appropriate studies need to be conducted.

The results from the cost-effective analyses are fundamentally limited by the lack of appropriate evidence. As such, little credence should be given to any result. However, the results from base case 2 show that there appears to be clinical support for the effectiveness of the interventions even though these data have not been proven. This lack of data results in all of the tests being dominated in base case 1. Pragmatic studies assessing the benefits of the interventions in changing real-world decisions are required to provide appropriate data.

Conclusions

Based on the current evidence, no definitive conclusions regarding either the clinical effectiveness or the cost-effectiveness of the interventions can be made. However, evidence based on expert clinical judgement suggests that the tests are likely to be beneficial to patients but this needs to be proven within appropriate studies.

Study registration

This study is registered as PROSPERO CRD42015016724.

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