Assessment of rapid diagnostic test to exclude bacteraemia and effect on clinical decision-making

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INTRODUCTION

The emergence of multi-drug resistant Gram-negative bacteria is a major health concern. Antimicrobial stewardship is an essential means of reducing the spread of multi-drug resistant bacterial infections. Unnecessary antimicrobial therapies increase healthcare costs and may promote the emergence of resistance.

An observational cohort study was conducted to determine whether a diagnostic test which excluded the presence of bacteria from blood specimens after 12 hours may have influenced clinical decision-making. Patient treatment was not affected by the result of the test. However, decisions to continue or stop antibiotic treatment on the provision of earlier negative results was compared retrospectively.

BACKGROUND

In Critical Care, antimicrobial treatment is discussed daily. Antibiotics are stopped when clearly not needed (e.g. CRP<10) but, where there is uncertainty, the antimicrobial course is continued at least until the fifth day. Overuse of antibiotics is therefore inevitable.

Routine automated blood cultures may give positive results within 24 hours; however, blood samples are not confirmed negative until after 5 days incubation. A test that would exclude the presence of bacteria in a blood culture earlier may aid the clinical decision-making process.

Cognitor© Minus

Cognitor© Minus (Momentum Bioscience Ltd., Oxfordshire UK) is designed to provide rapid universal detection of viable microorganisms. The test is performed on negative blood samples after 12 hours incubation. Using Enzymatic Template Generation and Amplification (EGTA®) technology, the test detects microbial DNA polymerase activity common to a wide range of bacteria and fungi (Figure 1).

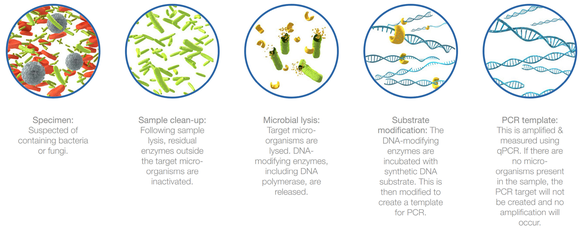

Figure 1. Enzymatic Template Generation and Amplification (EGTA®) process overview.

The test generates a high Negative Predictive Value (99.5% when compared with 5 day incubation); however, positive values cannot be reliably reported as due to infection.

Results of the test are given as:

- **'Negative'** – indicating that the sample is unlikely to contain microorganisms. Or,
- **'Not Determined'** – indicating that the sample cannot be confirmed as negative.

Used in conjunction with routine blood culture, the test may aid clinical decision-making on discontinuing antibiotic treatment in suspected cases of bacteraemia or fungaemia.

OBJECTIVES

- **To determine if Cognitor© Minus would lead to earlier negative bacteraemia results and whether this would be expected to reduce the length of antimicrobial treatment.**
- **To determine the frequency of contamination in the blood cultures collected for the Cognitor© Minus test when compared with the routine blood cultures.**
- **To determine if the removal of blood for the test has an impact on (i) the blood culture bottle result; and (ii) the time to result of the blood culture.**

METHODS

The laboratory performance of the Cognitor© Minus test was assessed and compared to routine automated blood cultures using the BD BACTEC™ FX Blood Culture System. Patient treatment was not affected by the result of the Cognitor© Minus test.

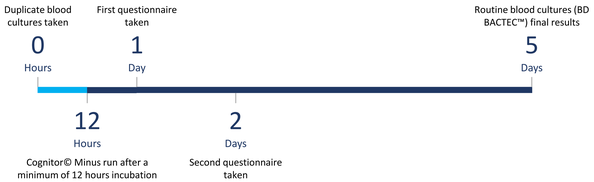

Figure 2. Study schedule.

Blood cultures were taken in duplicate from Critical Care patients at a London teaching hospital during the study. Approximately 8-10ml blood was drawn into both aerobic and anaerobic bottles for each culture set. Duplicate blood cultures were incubated and one set identified for Cognitor© Minus testing. All bottles were weighed to estimate blood sample volume. For test bottles that were negative after at least 12 hours incubation, 0.5ml aliquots from both aerobic and anaerobic bottles were taken and combined for testing. Test bottles were replaced into BACTEC™ after aliquots were taken in case growth developed. The Cognitor© Minus test was performed on the combined sample following manufacturer's instructions.

Antibiotic usage questionnaires

Clinicians and microbiologists were asked 24 and 48 hours after blood cultures were taken whether a 'Negative' or 'Not Determined' result would affect decisions to continue or stop antimicrobial treatment compared to current practice. Confidence in and reasons for the decisions were also recorded.

Antibiotic doses

It was assumed that antibiotics could have been saved where the current treatment and Cognitor© Minus decision went from 'Continue'/'Increase' to 'Stop' or from 'Increase' to 'Continue'.

When Cognitor© Minus was to 'Stop' antibiotics, it was assumed that all doses of antibiotics given from the next day onwards would be saved. As the Cognitor© Minus decisions were assessed twice per patient, the clinical decision could differ between days. One decision was chosen based on the relative time of the questionnaires to the time of the Cognitor© Minus test (i.e. if the test was run before the first questionnaire, this result was used; however, if run after the first questionnaire, the second was used).

RESULTS

Time to Cognitor© Minus test

Over a six month period, 125 patients were enrolled. The median time from initial incubation to Cognitor© Minus test was 27.1 hours (Figure 3). In all instances where blood cultures were incubated for ≥48 hours prior to the Cognitor© Minus test (31 patients), blood samples were collected on a Friday or weekend.

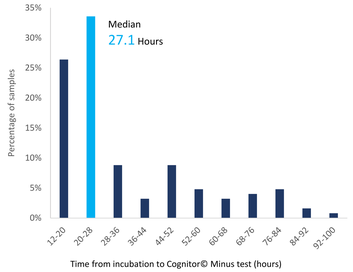

Figure 3. Histogram of time from incubation of blood cultures in BACTEC™ to Cognitor© Minus test run in laboratory.

Blood volume taken

Figure 4. Mean estimated blood volumes in culture bottles.

Estimated volumes of blood taken ranged from 0.1ml to 23.6ml per bottle. Significantly more blood was taken in aerobic routine bottles compared to study bottles (p=0.03).

Diagnostic ability of Cognitor© Minus

When compared to 5 day blood culture results from the routine and study samples, Cognitor© Minus gave Negative Predictive Values (NPVs) of 99% and 100% respectively (Table 1).

Table 1. Cognitor© Minus results from study set compared with results of routine and study 5 day blood cultures.

		Cognitor© Minus result (number of patients)		
Blood culture set	**5 day blood culture result**	**Negative**	**Not Determined**	**Negative Predictive Value (NPV)**
Routine	Negative	104	18	99%
	Positive	1	2	
Study	Negative	105	18	100%
	Positive	0	2	

Compared with routine bottles, Cognitor© Minus identified 2 of 3 positive blood cultures as 'Not Determined'; however, 1 was identified as 'Negative'. Compared with study bottles, 2 positive blood cultures were identified as 'Not Determined'. With both sets, 18 samples were identified as 'Not Determined' of the 122 (routine) and 123 (study) negative blood culture samples.

Acknowledgments

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Antibiotic usage

Current antibiotic actions were compared with questionnaire results (Figure 5). Decisions to 'Narrow' or 'Stop' were considered downgrading of antibiotic treatment. Questionnaires suggested that 'Negative' Cognitor© Minus results would have led to antibiotic treatments being downgraded in 14% (17/119) of patients at 24 and 48 hours when compared with routine blood culture. Antibiotics would have been downgraded for 24% of patients at either or both time points.

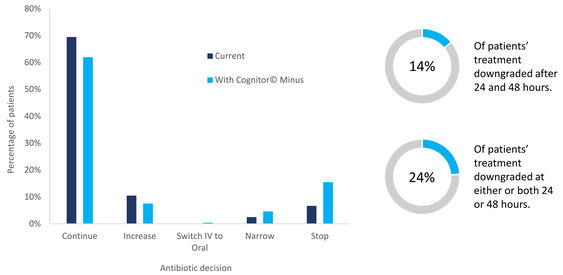

Figure 5. Summary of antibiotic action taken compared with questionnaire decisions on provision of negative Cognitor© Minus test results. Results from first and second questionnaires combined. Patients with no antibiotic treatment not shown.

119 Doses — An estimated 119 doses of antibiotics would have been saved from 12 patients where the Cognitor© Minus decision went from 'Continue'/'Increase' to 'Stop' or from 'Increase' to 'Continue'.

Impact of Cognitor© Minus on blood cultures

No contamination was found in the study bottles when compared to routine bottles. With the sample set which had a positive routine bottle but negative study bottle, the bottle weight of the routine anaerobic bottle indicated a greater volume of blood had been taken compared to the study bottle (6.48g vs 1.97g) which may have affected the result.

CONCLUSION

Cognitor© Minus was run on samples at a median of 27.1 hour after incubation. Samples run after 48 hours coincided with weekends, hence in a routine hospital laboratory, results may be available sooner. Negative Predictive Values were 99% when compared with routine bottles and 100% compared with study bottles. Questionnaires suggested antibiotics would have been downgraded in 24% of patients overall and saved 119 doses of antibiotics.

The availability of ETGA® technology could assist antimicrobial decision-making and lead to a reduction in length of antimicrobial treatment. Reducing doses would have potential cost savings and reduce the risk of antimicrobial resistance emerging.

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