Expert Insights

- Reducing Time to Diagnosis of Sepsis

MALDI-TOF

Innovation with Integrity

Reducing Time to Diagnosis of Sepsis

Analyzing costs and time-to-result of the MALDI Biotyper® and Sepsityper® diagnostic tool compared to established laboratory protocols in patients with suspected sepsis at the Royal Bolton Hospital

Working with Bruker

The Microbiology Laboratory at the Royal Bolton Hospital (RBH), UK, is pioneering the use of Bruker's Sepsityper kit, in conjunction with the MALDI Biotyper (MBT) system, for the rapid identification of organisms causing sepsis. Rushana Hussain, Clinical Scientist in the Microbiology Department of RBH, comments:

"The work we are doing with the Sepsityper has transformed the outcome for sepsis patients. Shorter hospital stays and rapid administration of targeted antimicrobial therapy was not possible with our previous methods, and has resulted in huge cost savings for the hospital."

Synopsis

Sepsis is a major worldwide healthcare issue which is life-threatening and expensive to treat. There has long been a need for rapid detection and identification of the infecting organism in blood cultures to ensure a timely response for the management of sepsis. Between 30-50% of patients presenting with clinical symptoms of sepsis have positive blood cultures [1]. It is critical that the etiology is established through the diagnostic process and appropriate treatment commenced in a timely manner.

Processes for detecting the infecting organism have remained largely unchanged since first being developed in the late 19th century, with Gram staining emerging as a popular method for classifying bacteria. This method, however, has limitations as Gram staining lacks both specificity and sensitivity. Even in the situation of accurate diagnosis, the Gram stain result provides the clinician with limited information for accurate antibiotic treatment.

A study conducted at the Royal Bolton Hospital (RBH), included a retrospective analysis of the processing of positive blood culture broths collected from patients admitted to the A&E department with suspected sepsis, to establish whether faster and more accurate diagnosis could be achieved using the (matrix-assisted laser desorption/ionization) MALDI Biotyper and Sepsityper diagnostic tools, compared to the current standard laboratory protocol (SLP).

Sepsis – a worldwide killer

There are an estimated 31 million cases of sepsis worldwide each year, with six million resulting in death. Sepsis is the largest global killer of children – more than 5 million each year. A quarter of all survivors of sepsis face life-altering physical and mental health conditions and survivors are 42% more likely to commit suicide. In the USA alone, sepsis causes or contributes to half of all deaths in hospitals and has become the leading cause of annual hospital costs, at over $24 billion per year [2] and is also the number one cause of hospital readmissions costing an additional $2 billion per year.

Sepsis is a syndromic response to infection and is the final common pathway to death from most infectious diseases. It arises when the body's response to infection causes damage to its own tissues and organs. It can lead to septic shock, multiple organ failure and death. Despite this,

sepsis is the most preventable cause of death or disability. Early diagnosis and timely and appropriate clinical management is crucial to increase the chances of survival. Whilst broad spectrum antibiotics are generally the first step in treating sepsis patients, in a high proportion of cases, an early identification of the infecting organisms enables a change in therapy where appropriate, therefore lowering mortality rates, decreasing treatment costs and improving patient outcomes [3].

Microbiology at the Royal Bolton Hospital

The Microbiology Department team at RBH consists of motivated and patient-focused Consultant Microbiologists, two Section Managers, one Clinical Scientist, eight Biomedical Scientists, 13 Support Staff and four Associate Practitioners. The laboratory processes 350,000 samples a year, of which 60% are from local GPs, with the remaining 40% of samples originating from the hospital. The laboratory has a long-standing reputation for having a strong patient-focused ethos and using LEAN methodology to develop new cost-effective services. Rushana Hussain is a Clinical Scientist within the Microbiology Department at RBH, and describes her role in the hospital:

"My main role focuses on service development and innovation.

This involves being aware of new and upcoming scientific and management innovations that will develop the service, resulting in positive contributions to the needs of the patient and the trust.

As well as being responsible for the implementation of innovation projects, I am also responsible for the evaluation of clinical impact or outcomes for the patient and cost-effectiveness for the Trust."

Implementing the MALDI Biotyper and Sepsityper

In January 2015, the Microbiology Laboratory began using Bruker's MBT with Sepsityper for the accurate identification of organisms in sepsis cases. Rushana explains the decision-making process behind the acquisition:

"We were initially informed about the Sepsityper through another laboratory. We very quickly established that this tool would enable us to progress the laboratory and implement good service improvements.

We were extremely confident of the impact it would make on the laboratory, the patients, and the hospital as a whole.

We sat down as a team and looked at every possible area where the Sepsityper could make an impact and it was a no-brainer, as there are no comparative tools out there."

The laboratory altered the SLP to incorporate the MBT + Sepsityper, and trained staff to use this new technique. With the previous biochemical methods used, results were extremely variable and could not be used directly from the blood cultures. Previously, the blood culture would be placed on the analyzer, and within 24-48 hours it would go positive and then be cultured on solid agar for the Gram film to be completed. The Gram film would aid with initial diagnosis of the causative agent, however would provide limited information about the organism, only being able to differentiate between Gram negative and Gram positive bacteria. Although the limited information provided by the Gram film would be available to the clinician within 60 minutes, (Royal College of Pathologist critical results turn-around-time (TAT)), more organism specific information would not be available until the organism had grown at 24 hours. In the meantime the patient would be treated according to the Gram film result, very often with a broad spectrum antibiotic.
Figure 1 shows the previous SLP and Figure 2 shows the MBT Sepsityper IVD workflow now used in the laboratory.

Rushana describes the laboratory staff's reaction to the Sepsityper's introduction:

"Everyone in the laboratory was incredibly keen to receive the training required to adopt the Sepsityper into our workflow.

We are driven by the need to provide the very best treatment for the patient, and because we knew what a positive impact the end result would have, we all put in the hours to learn.

It was also a benefit to staff, to learn a new skill and technique, which they may not have had the chance to do in another laboratory."

About the MALDI Biotyper® (MBT) with Sepsityper®

The MBT is based on MALDI-TOF mass spectrometry technology, which has emerged as a potent tool for the rapid identification of microorganisms grown on solid media. The IVD-CE approved Sepsityper kit provides the reagents and a successful method for separation of blood products from microorganisms in positively flagged liquid culture specimens of blood, to allow rapid identification of the pathogenic organism on the MBT. The MBT acquires the spectrum pattern of the organism, which is then reliably and accurately identified by matching thousands of reference spectra of known microorganisms. The MBT + Sepsityper can offer an improved turn-around-time of up to 22 hours over a standard lab procedure for a presumptive identification.

With the introduction of the new 'Rapid' MBT Sepsityper IVD kit a turn-around-time of 15-20 minutes is achievable from a positive blood culture alert.

SLP starting from a positive blood culture

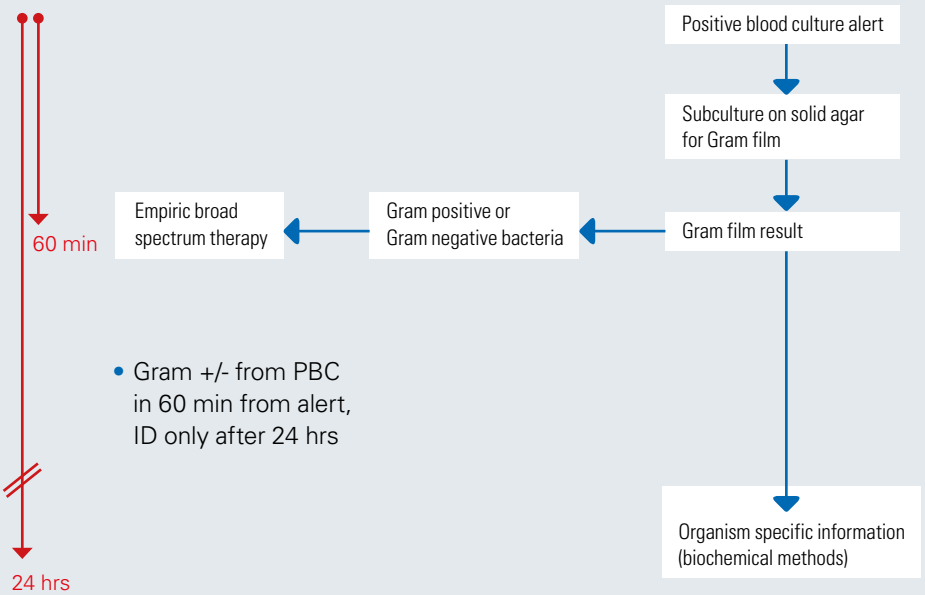
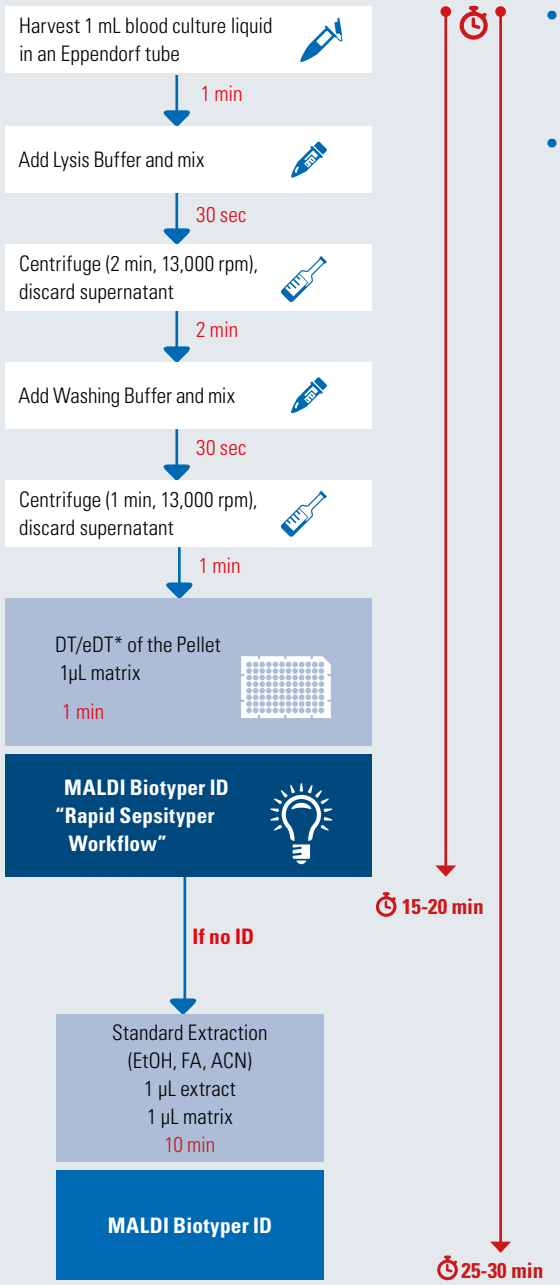


Figure 1: The standard laboratory protocol (SLP) for positive blood culture samples, previously used at the Royal Bolton Hospital.

Workflow starting from a positive blood culture bottle



- ID from PBC in 15-20 minutes from alert (or in 25-30 minutes when Standard Extraction is required)
- Less than 10 minutes hands-on time for a single PBC or a batch of multiple PBC bottles (Rapid Workflow)

* DT: Direct Transfer sample preparation method
eDT: extended Direct Transfer sample preparation method

Figure 2: The new "Rapid Sepsityper Workflow" used at the Royal Bolton Hospital.

As part of the changing workflow, biochemical methods were removed. Although useful, these tests are less specific and less sensitive compared to the MALDI time-of-flight (TOF) mass spectrometry technology used in conjunction with the Sepsityper. Additionally, biochemical tests can only be conducted from isolates after 24 hours, and are more labor-intensive. Rushana describes an example of the benefits the Sepsityper solution brings to the clinician and patient:

"Staphylococcus is an example of a common organism we see in the lab. There are many species of these bacteria on your skin which are mostly benign and don't cause infection in the majority of people. However, there are some species, such as S. aureus, which are pathogenic, so it is extremely valuable to be able to differentiate between harmless skin flora and the pathogenic organism, where antibiotic treatment is necessary. It makes a huge difference to the patient, as well as the amount of clinical work involved."

Enterobacteriaceae are a large group of Gram negative bacteria that are formed of numerous organisms with varying characteristics, the most significant being variation in antimicrobial sensitivity patterns. It is for this reason that the Sepsityper is extremely important when identifying *Enterobacteriaceae* in positive blood cultures.

A Gram film has limited capabilities when providing an identification of an organism, only being able to give the information that the organism is Gram negative, whereas the Sepsityper is able to provide a full identification to species level.

Knowing the identification of the organism to species level, *E. coli*, *E. cloacae* or *Pseudomonas aeruginosa* etc., enables clinicians to make more informed and calculated decisions about sepsis treatment, especially when treating a highly resistant organism.

Knowing the species of the organism is also helpful in identification of the source of the infection. Identifying an organism associated with a particular body site, i.e. the gut, or an organism associated with infection from a common site, i.e. *E. coli* in urinary tract infections, is extremely important as it can aid with targeting additional diagnostic tests, and can result in better focused and tailored treatment plans.

Evaluating the Sepsityper at the RBH

During April and May 2015, the Bruker MBT + Sepsityper protocol was implemented in the microbiology laboratory for processing positive blood culture broths, and was compared to the SLP to determine potential improvements in time to clinical results and patient pathways. In order to determine if the new protocol was more effective, an audit was performed for both methods for a period of one month at the same time of year (April – May 2014 for the SLP and April – May 2015 for the MBT + Sepsityper protocol).

Table 1: Time (minutes) taken from sample being removed from the blood culture analyser to the Gram availability and the average time taken from removing positive sample from analyzer to initial presumptive ID. SLP = Standard Laboratory Protocol; MBT-SP = Bruker MALDI Biotyper + Sepsityper; TAT = turn-around-time; GNB = Gram negative bacilli; GPC = Gram positive cocci.

Organism	SLP		MBT-SP	
	Gram TAT (min)	Presumpt ID TAT (min)	Gram TAT (min)	Presumpt ID TAT (min)
GNB	92	1415	56	93
GPC	63	1128	66	118

Blood samples of patients who were suspected as having sepsis were sent to the microbiology laboratory for processing, to determine the identity of the infecting organism. All samples with growth were flagged and subjected to Gram staining to classify as Gram positive cocci (GPC), Gram positive bacilli (GPB), Gram negative cocci (GNC) or Gram negative bacilli (GNB) and subject to further testing to complete the identification.

The MBT + Sepsityper protocol required positive blood cultures to be analyzed using the MBT Sepsityper IVD kit, with the final product processed through the MBT to establish the causative agent. The protocol involves a manual procedure whereby blood is centrifuged and manipulated before the sample is placed in the MBT for analysis. Proving that processing the blood culture with the Sepsityper kit improved the turn-around-time to result, by providing a confirmed identification within one day, was important for adoption into laboratory procedures. Clinicians no longer need to wait for 24 hours for an isolate to grow.

Results: cost savings and patient outcomes

The use of MBT + Sepsityper requires a few minutes of hands-on time to prepare the sample, however, there was no delay to the availability of the Gram stain result and there was a significant improvement with the MBT + Sepsityper over the standard laboratory procedure of up to 22 hours in TAT for a presumptive identification.

In addition there was a statistically significant reduction in the duration of hospital stay for patients with bacteraemia during the period the MBT + Sepsityper protocol was used, compared to the SLP.

This reduction in hospitalization has benefits in reducing costs and freeing hospital beds. *Based on an estimated cost per bed day of £500, the hospitalization cost savings alone are £22,600 for the study cohort of 27 patients admitted from the A&E department (or £837 per patient), which is a significant budget saving for any hospital.*

In addition to length of stay in hospital, the cost implications of implementing the MBT + Sepsityper protocol considered the use of intravenous (IV) and oral antibiotics. Analysis of this data at RBH has shown a 33% reduction in doses of IV antibiotics and a 35% reduction in oral antibiotics using the MBT + Sepsityper protocol compared to SLP over a similar time period. Rushana comments on these findings:

"In our study, this reduction is a reflection of the earlier and more accurate identification of the organism, enabling the clinical team to make informed decisions and alter antibiotic regimes 18 hours sooner.

Knowing the actual identification of the organism means that clinicians can tailor the antibiotic treatment and reduce overall antimicrobial use across the hospital."

Table 2: Duration of hospital stay (days) for patients with bacteraemia with the standard laboratory protocol (SLP) compared with the Bruker MALDI Biotyper (MBT) + Sepsityper (SP) protocol. GNB = Gram negative bacilli; GPC = Gram positive cocci.

Organism	SLP	MBT-SP
	Days	Days
GNB	8.1	6.5
GPC	7.3	5.5

An associated positive effect of a reduction in IV antibiotic usage is the expected reduction in nursing time to administer the therapy. In addition, reducing antibiotic use falls in line with NICE Guidelines (National Institute for Health and Clinical Excellence) on Antimicrobial Stewardship [4], by reducing the risk of multi-drug resistance through hospital acquired infections.

Hospital- and economy-wide advantages

For the clinical management of septicemia patients, it is important to identify the organism quickly in order to change empiric antibiotic regimens to a more targeted therapy. The MBT + Sepsityper protocol has shown 90% sensitivity and 100% specificity in laboratory investigations [5]. This level of information enables clinicians to make confident, informed decisions in personalizing antibiotic regimes, or altering patient pathways, which typically lead to better patient outcomes.

The MBT reference library used alongside the Sepsityper reinforces the aim of the NICE guidelines [6] to improve molecular methods, as it covers thousands of organisms compared to the 10-20 covered with polymerase chain reaction (PCR) methods. These guidelines highlight three areas: identifying sepsis, testing for sepsis, and treating sepsis, which were included in a letter sent to all Hospital Trusts by the government, providing guidance about the new changes that need to be made for organizations to abide to the NICE and Public Health England (PHE) guidelines.

"This letter will have a massive impact to close the gap on what needs to be done to address the problem of sepsis, and how it needs to be done"

explains Rushana, continuing:

"When we look at those targets, RBH is already doing two of them: improving diagnostics and reducing broad spectrum antimicrobial usage. We have already improved diagnostics, so we are implementing the best practice to improve treatment times and reduce antimicrobial resistance. One target we are trying to implement further is looking at the impact of taking two blood cultures, and how this will improve our workflow. We are already ahead of the game, and those organizations that don't have the Sepsityper won't be able to meet these targets."

MBT Sepsityper IVD Kit

Rushana comments on the collaborative approach the hospital has had towards adopting the Sepsityper:

"For me, this has been such a rewarding project to be a part of.

One thing I'm really proud of at the RBH, is that we are able to take a step back and realize that by investing in a diagnostic test that costs slightly more at the outset, you can prevent re-admissions and reap long-lasting economic benefits.

The finance team works with the clinicians to get an overall picture, and we build a business case with procurement. Not many organizations work like that but we believe that it's vital to pass on the benefit of our experience."

The benefits of treating sepsis in a targeted manner have significant impact on quality of life for many patients who have sepsis. Faster diagnosis and treatment of the condition reduce the risk of long-term patient morbidity (sometimes referred to as Post Sepsis Syndrome or PSS) or life-changing physical and mental conditions.

"I genuinely can't understand why other organizations aren't doing this" Rushana comments, adding: *"With the media coverage around the dangers of sepsis, plus all the available data from studies such as this at RBH, it makes adoption of this technique an easy decision – in my opinion."*

MALDI Biotyper smart

Fighting sepsis in the future

The MBT and Sepsityper can provide identification of an infecting organism in the blood approximately 18-22 hours earlier than the traditional method of identification. This faster TAT provides the clinician with timely and accurate information to enable them to make an informed clinical assessment of the patient, prescribe the correct antibiotic regime faster, and instruct the removal of lines and indwelling catheters where possible.

"More and more hospitals want to adopt the Sepsityper" comments Rushana, continuing: "There's been a lot of interest in it. Many laboratories in the UK are familiar with MALDI-TOF technology, but the Sepsityper is relatively new to the field. Despite this, I've spoken to a lot of people who can see the benefits that this tool brings."

In the current financial climate, it is important to ensure that any new diagnostic process is cost-effective. The cost of the MBT Sepsityper IVD Kit is significantly lower than the traditional molecular kits used by the lab, meaning that the purchase of the kits is no barrier to changing protocol.

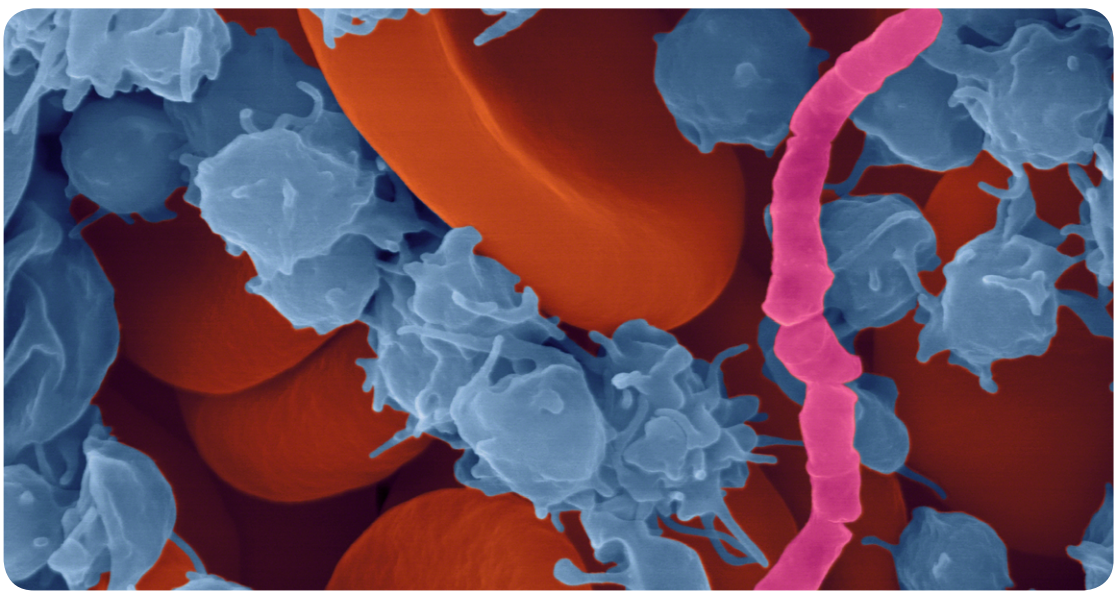
Although it is difficult to calculate all the financial implications across the patient pathway, data from RBH show additional cost savings arising from a reduced length of hospitalization and reduced use of antibiotics following the implementation of the MBT + Sepsityper protocol into the hospital microbiology laboratory workflow.

Rushana describes how working with Bruker has made adopting the Sepsityper a smooth process:

> *"Working with Bruker has been really positive. They are very keen to evaluate developments for the MBT and Sepsityper.*

For example, based on our feedback as customers, they are coming up with shorter methods to benefit lab staff and patients even further. Like us, Bruker are patient-focused and are passionate about what they do."

For more information about the Royal Bolton Hospital please visit http://www.boltonft.nhs.uk/about-us/. For more information on Bruker's MBT Sepsityper IVD diagnostic kit, please visit https://www.bruker.com/products/mass-spectrometry-and-separations/ivd-ce-certified-maldi-biotyper/mbt-sepsityper-ivd-kit.html



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About Royal Bolton Hospital

Bolton NHS Foundation Trust provides patient care at the Royal Bolton Hospital. Laboratory Medicine underpins the diagnosis, monitoring and management of disease and, within this department, Microbiology specializes in diagnosing infectious diseases caused by microorganisms and assisting clinicians reach the most appropriate treatment decision.

About Bruker Corporation (NASDAQ: BRKR)

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For more information, please visit: **www.bruker.com/microbiology**

MBT Sepsityper IVD Module and Kit currently not available in the USA.

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