# Preliminary Blood Culture Rapid Identification and Resistance Targets Determination using GenMark Dx® ePlex® Blood Culture Identification System Improves Sepsis Management, Aids Early Antimicrobial Stewardship (AMS) Interventions and Results in Significant Cost Savings


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## Introduction

- Time to appropriate antimicrobial therapy is essential to reduce mortality and morbidity in sepsis-related bloodstream infections (BSI) (1). Standard practice for identification (ID) and antimicrobial susceptibility testing (AST) of a positive blood culture can up to 48 hours (2).
- GenMark Dx® ePlex® Blood Culture Identification (BCID) panels are an automated, qualitative nucleic acid multiplex in vitro diagnostic test, combining electrowetting and GenMark's eSensor® technology, for the simultaneous detection and ID of multiple Gram positive (GP) and Gram negative (GN) bacteria and fungi from positive blood cultures following Gram staining.
  - Electrowetting uses electrical fields to directly manipulate droplets on the surface of a hydrophobically coated printed circuit board.
  - eSensor® technology uses a solid-phase electrochemical method for determining the presence of one or more of a defined panel of bacterial or fungal target sequences.
- Molecular assays, such as the ePlex® BCID panels, enable clinicians to rapidly identify clinically relevant BSI and their resistance genes when blood culture are initially positive. This allows for early antimicrobial interventions, while quickly ruling out blood culture contamination, resulting in cost savings.

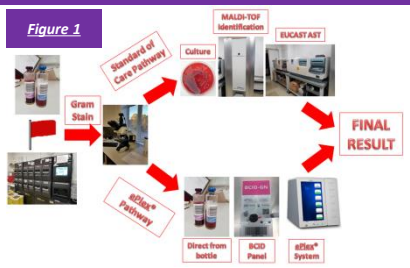
## Aim

To evaluate the **rapid laboratory, clinical, antimicrobial stewardship and health economic benefits** of the implementation of the GenMark Dx® ePlex® BCID panels.

## Methods

- At the time of initial positivity, blood cultures were Gram stained and tested in parallel as per *Figure 1*.
- Data was collected from Electronic Patient Record (EPR) and Telepath laboratory system in 2 Microsoft Excel databases.
- The data collected included:
  - Time to ID.
  - Time to resistance determinants/AST.
  - Concordance of results.
  - Clinical data:
    - Blood culture contamination.
    - Possible AMS interventions.

***Figure 1***




**ePlex® BCID Panels**

| Gram Positive Panel | Gram Negative Panel | Fungal Panel |
|---|---|---|
| *Bacillus cereus* group | *Acinetobacter baumannii* | *Candida albicans* |
| *Bacillus subtilis* group | *Bacteroides fragilis* | *Candida dubliniensis* |
| *Corynebacterium* | *Citrobacter* | *Candida famata* |
| *Enterococcus* | *Enterobacter cloacae* complex | *Candida glabrata* |
| *Enterococcus faecalis* | *Enterobacter cloacae* complex | *Candida guilliermondii* |
| *Enterococcus faecium* | *Enterobacter* (non-*cloacae* complex) | *Candida kefyr* |
| *Lactobacillus* | *Escherichia coli* | *Candida krusei* |
| *Listeria* | *Fusobacterium nucleatum* | *Candida lusitaniae* |
| *Listeria monocytogenes* | *Fusobacterium necrophorum* | *Candida parapsilosis* |
| *Micrococcus* | *Haemophilus influenzae* | *Candida tropicalis* |
| *Propionibacterium acnes* | *Klebsiella aerogenes* | *Cryptococcus gattii* |
| *Staphylococcus* | *Klebsiella pneumoniae* | *Cryptococcus neoformans* |
| *Staphylococcus aureus* | *Morganella morganii* | *Fusarium* |
| *Staphylococcus epidermidis* | *Neisseria meningitidis* | *Malassezia furfur* |
| *Staphylococcus lugdunensis* | *Proteus* | *Rhodotorula* |
| *Streptococcus* | *Proteus mirabilis* | *Trichosporon* |
| *Streptococcus agalactiae* (GBS) | *Pseudomonas aeruginosa* | |
| *Streptococcus anginosus* group | *Salmonella* | |
| *Streptococcus pneumoniae* | *Serratia* | |
| *Streptococcus pyogenes* (GAS) | *Serratia marcescens* | |
| **Resistance Genes** | *Stenotrophomonas maltophilia* | |
| *mecA* | **Resistance Genes** | |
| *mecC* | CTX-M | |
| *vanA* | IMP | |
| *vanB* | KPC | |
| **Pan Targets** | NDM | |
| Pan gram-negative | OXA | |
| Pan *Candida* | VIM | |
| | **Pan Targets** | |
| | Pan gram-positive | |
| | Pan *Candida* | |

## Results

- 21 blood cultures were tested.
- 2 blood cultures were mixed:
  - *Enterococcus faecium* and *Citrobacter* (required a GN and a GP card for ID).
  - *Staphylococcus epidermidis* and *Enterococcus faecalis* (required 1 GP card for ID).

**Graph 1 - ePlex® Panels used (n=22)**

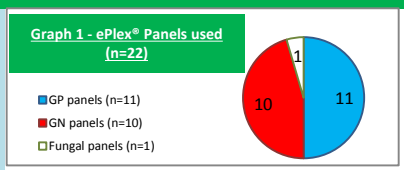
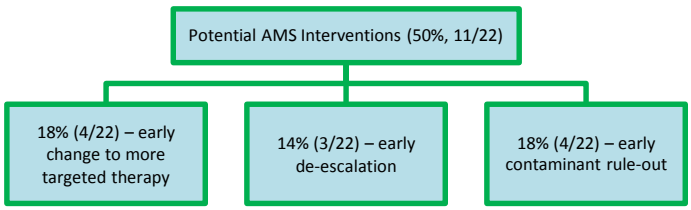



***Table 1 – Average Time to Identification and Resistance Profiles for GN/GP Bacteria***

| | ePlex® System | Standard Methodology | Average Differential Time |
|---|---|---|---|
| Average Time to Identification (n=21 panels) | **297 min *** (4 hr 47 min) | **1874 min** (31 hr 14 min) | **1577 min** (26 hr 17 min) |
| Average Time to Resistance Determinants (n=15 panels) | **293 min** (4 hr 53 min) | **3755 min** (62 hr 35 min) | **3462 min** (57 hr 42 min) |

*ePlex® processing time = 90 mins. ePlex® BCID panels were only used during working hours so there was a delay in some cases between blood culture flagging positive and being loaded onto the ePlex® machine (i.e. if flagged positive overnight).

- The fungal ePlex® ID was *Malassezia furfur*.
  - This failed to grow in our laboratory.
  - ID and AST was performed at the UK Mycology Reference Laboratory – the final report was received 38 days after the blood culture initially flagged positive.
  - Early ID allowed for an early change to an appropriate antifungal agent.
- Taking into account the selection of organisms and resistance determinants on the ePlex® panel, **concordance with final culture ID and AST results** was **100%**.
- Three isolates had no targets determined on the ePlex® BCID panels and were not detected – *Prevotella denticola*, *Pseudomonas fluorescens/Pseudomonas pickettii* and *Raoultella* spp.




- Although the sample set was small, the results of ePlex® BCID panels could have resulted in potentially **50% earlier AMS interventions** for positive blood cultures with GN/GP bacteria. This may increase with the sample size.
- Early ID of *Serratia marcesens*, *Enterobacter cloacae complex* and *Citrobacter* would have allowed for early change from empiric treatment to more appropriate treatment based on clinical picture, allowing for **more targeted therapy and improved sepsis management**.
- Early ID of *Staphylococcus aureus* without detection of *mecA* or *mecC* resistant determinants would allow for **early de-escalation** from empiric vancomycin to targeted flucloxacillin.
- Early ID of *Enterococcus faecalis* without detection of *vanA* or *vanB* resistant determinants would allow for **early de-escalation** from empiric linezolid to targeted amoxicillin.
- Early ID of blood culture contaminants in the four cases could have resulted in **potential savings of over €16,000** (based on local financial costings).
- While no Multi-Drug Resistant Organisms (MDROs) were included, the ePlex® would have potentially allowed for the early exclusion of VRE BSI in 2 cases and the potential early exclusion of ESBL/CPE BSI in 7 cases.

## Conclusion

The potential benefits of the ePlex® BCID system include:

- Reduced laboratory time to result.
- Earlier ID of MDROs (e.g. VRE, MRSA, ESBL and CPE) resulting in earlier infection prevention and control interventions.
- Earlier appropriate treatment on the basis of ID and resistance profile, thereby improving sepsis management.
- AMS interventions - earlier more targeted treatment, escalation or de-escalation of treatment as appropriate, and early ID of blood culture contaminants.
- Cost saving related to early blood culture contaminant recognition.


DECLARATION: This evaluation was supported by Syntec Scientific Ltd.



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**References:**

1. Pfaller et al. Clinical Microbiology Reviews. Jan 2007, p133-163.
2. Tabak et el. Blood Culture Turnaround Time in US Acute Care Hospitals and Implications for Laboratory Process Optimisation. JCM. Aug 2018 22 [Epub ahead of print]