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Authors: Rachel Hamakim[1], Noah Tattersall[2], Amal Joshy[1], Shankar Das Menon[1], Inderpreet Kaur[2], Conor Edwards[2], Magdalena Karlikowska[2], Michael Barer[1,3], Natalie Garton[1]

[1]Dept. Respiratory Sciences, University of Leicester, UK; [2]Cytecom Ltd, Coventry, UK, [3] Dept of Clinical Microbiology, University Hospitals of Leicester NHS Trust, Leicester, UK.

Title (not included in the word count):
Utilising optical electrophysiology for rapid antimicrobial susceptibility testing to enhance bloodstream infections and sepsis management

Background:
Timely administration of appropriate antibiotics for bloodstream infections is crucial as they can quickly escalate to sepsis, significantly increasing the risk of mortality. Emerging genotypic and phenotypic techniques aim to expedite the analysis of positive blood cultures. However, the existing approach still requires 2-3 days. This study aims to assess the feasibility of applying optical electrophysiology to determine antimicrobial susceptibility of pathogens in blood samples in 2.5 hours, ultimately enhancing sepsis management.

Methods:
Cytecom's cutting-edge technology uses optical electrophysiology for enumeration of proliferative bacterial populations, bypassing time-consuming culturing steps. CyteCount combines delivery of an electric shock to the sample, with microscopy to assess accumulation of a dye reporting on membrane potential; proliferative cells develop a hyperpolarised membrane potential in response to the shock.

Mock blood cultures were spiked with both resistant and susceptible *Escherichia coli* and *Staphylococcus aureus*, then cultured at 37^{o}C until reaching a concentration of 10^{7} cfu/ml. Subsequently, cultures were treated, or not, with amoxicillin for 2h and assessed using CyteCount and plate counts.

Results:
CyteCount analyses of mock blood cultures provided rapid counts of viable bacterial cells. Notably, the assay effectively revealed distinct bacterial electrophysiology profiles in 30min, distinguishing between resistant and susceptible bacteria following a 2h antibiotic exposure. Resistant cells exhibited a characteristic hyperpolarisation response indicative of viable bacteria, while susceptible cells initially showed depolarisation followed by weak hyperpolarisation. This pattern was observed in both Gram-negative and Gram-positive bacteria. Importantly, the CyteCount assay was performed directly on blood cultures after a 10-minute resting period on a lab bench. This achievement eliminates the need for complex sample preparation, simplifying the process by avoiding additional blood sample processing steps, thus streamlining the overall procedure.

Conclusion:
This work demonstrated how CyteCount rapidly differentiates resistant from susceptible bacteria directly in blood cultures, by analysing bacterial electrophysiological response profiles to electrical stimulation. Further work is required to transfer the assay to human blood samples and to determine the minimum antibiotic exposure time required to differentiate susceptible from resistant strains therein. The technology shows great potential for further development into a rapid AST device for use in a clinical setting.