Differentiation of Bacterial versus Viral Infection in Acute Respiratory Conditions using a Point of Care Assay to detect Human Neutrophil Lipocalin.

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CONTENTS

KEY POINTS

Every 4 minutes worldwide someone dies from infection caused by bacteria that are resistant to antibiotics and it is predicted by 2050 ten million could die (Ref 1: Health and Social Care Committee- AMR eleventh report for House of Commons published October 2018)

Published studies report that at least 50% of antibiotic prescriptions are unnecessary due to a viral source of infection (Ref 2: Journal of Antimicrobial Chemotherapy, Volume 73, Issue suppl_2, 1 February 2018)

Unnecessary use of antibiotics is the primary cause of the increased antibiotic resistance and adverse reaction to commonly prescribed drugs

Diagnostic uncertainty in combination with patient pressure influences physicians to prescribe antibiotics in a large number of patients presenting with acute respiratory infections.

Here we report the measurement of HNL to distinguish between bacterial and viral cause of an acute infection with superior accuracy to accepted biomarkers such as CRP or procalcitonin (PCT).

The invention is IP-protected and was awarded the prestigious EU Horizon prize (€1MM) for being the most promising POC assay for delivering a "better use of antibiotics" in acute respiratory infections.

A PoC solution would cut costs for the healthcare systems and improve patient outcomes.

INTRODUCTION

Millions of antibiotic prescriptions are written annually in primary care settings around the world and it is estimated that more than 50% of these prescriptions are unnecessary due to a viral source of infection (Ref 2). Unnecessary antibiotic use has resulted in a global surge in both antibiotic resistance and adverse drug reactions (ADR's). Patients who experience ADRs tend to stay in hospital longer and require increased outpatient care thereby burdening health care systems. In the EU, for example, it is estimated that antibiotic resistance is responsible for > 2 M extra hospital stays and > 25,000 deaths annually (Ref 1) which results in an annual economic cost in excess of €1.5Billion.

Acute respiratory infections are very common and result in many patients seeking medical attention. These infections range from the common cold to influenza, pneumonia and Strep infections amongst others. The overlap in symptoms presents a significant challenge to physicians and the uncertainty of whether the underlying cause is bacterial or viral can result in mismanagement of patients.
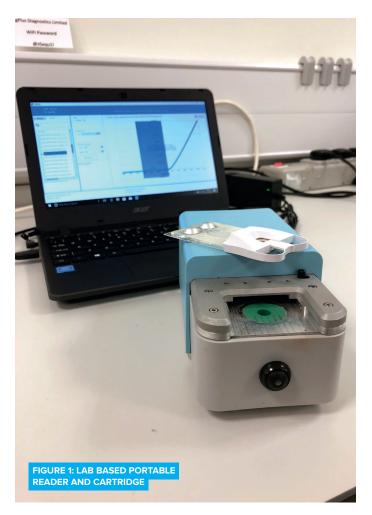
Human Neutrophil Lipocalin (HNL), is a complex protein produced by neutrophil leukocytes and secreted as monomers (22kDa), homodimers (45 kDa) and heteromers (>90 kDa). The different forms have been associated with different diagnostic capabilities, the major ones being (i) the detection of bacterial infections and discriminating such infections from those caused by viruses and (ii) the early detection and monitoring of acute kidney injury (AKI).

Here we report on the ability of HNL to distinguish between bacterial and viral causes of acute respiratory infections in comparison to validated biomarkers such as CRP and PCT.

METHODS

Using antibodies with epitope specificities against the different variants of HNL, we have developed immunoassays that specifically and accurately determine the concentrations in body fluids of different HNL molecular entities. These assays are critical to enabling specific diagnoses of, say, bacterial infections and AKI, respectively.

A rapid point-of-care (POC) assay is being developed by AgPlus and Diagnostics Development based in Upsala. This POC assay measures the release from the neutrophil granulocytes in whole blood after 5 minutes of incubation with a neutrophil activator and a total time to result of <10 minutes.

FIGURE 1: LAB BASED PORTABLE READER AND CARTRIDGE

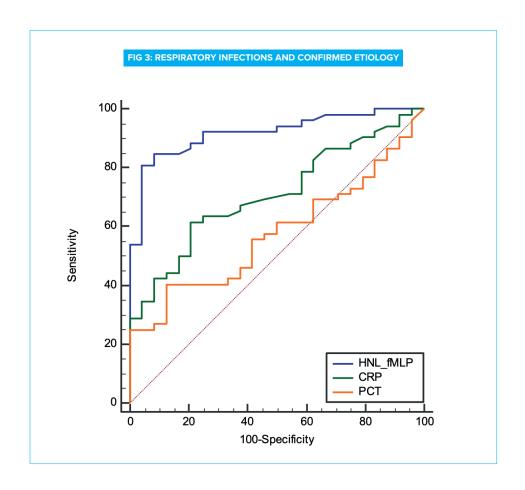**FIGURE 2: CONCEPT FOR POC READER AND CARTRIDGE**

METHODS (CONTD)

Some initial work has been completed to assess the HNL suitability. Samples were collected from 162 patients with acute respiratory disease and tested with an HNL ELISA assay. Results were compared with expert evaluations using standard microbiological (eg PCR, culture) and lab testing (eg CRP, PCT).

Results are shown below:

A Sensitivity and Specificity of 81% and 96 %, respectively, in the distinction between bacterial and viral infection was obtain with a positive likelihood ratio of bacterial infection of 9.9 and negative likelihood ratio of bacterial infection of 0.19

In addition, ROC-curve analysis was performed the results of which are illustrated in figure 3 below:

FIG 3: RESPIRATORY INFECTIONS AND CONFIRMED ETIOLOGY

CONCLUSIONS

These results confirm that HNL delivers superior results to both CRP and PCT to diagnose bacterial causes of acute respiratory infections. Consequently HNL can be used to triage patients presenting with these common respiratory conditions thereby enabling physicians to improve patient management for example by reducing the administration of unnecessary antibiotics and avoiding both antibiotic resistance and ADRs. The test will trigger the need for pathogen-specific testing and will help guide therapeutic decision making with regards antibiotic need

CONTACT

CONTACT DETAILS

For further information please contact:

AgPlus Diagnotics
The Exchange,
Colworth Science Park,
Sharnbrook,
Bedfordshire,
MK44 1LZ
(sat nav: MK44 1ET)

t: +44 (0)1234 867 100
e: info@agplusdiagnostics.com