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Research Paper

Metabolic Profiling in Patients with Pneumonia on Intensive Care

David Antcliffe [a], Beatriz Jiménez [b], Kirill Veselkov [b], Elaine Holmes [b], Anthony C. Gordon [a,*]

[a] Section of Anaesthetics, Pain Medicine and Intensive Care, Department of Surgery and Cancer, Faculty of Medicine, Imperial College London, UK
[b] Division of Computational and Systems Medicine, Department of Surgery and Cancer, Faculty of Medicine, Imperial College London, UK

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ABSTRACT

Clinical features and investigations lack predictive value when diagnosing pneumonia, especially when patients are ventilated and when patients develop ventilator associated pneumonia (VAP). New tools to aid diagnosis are important to improve outcomes. This pilot study examines the potential for metabolic profiling to aid the diagnosis in critical care.

In this prospective observational study ventilated patients with brain injuries or pneumonia were recruited in the intensive care unit and serum samples were collected soon after the start of ventilation. Metabolic profiles were produced using 1D ^{1}H NMR spectra. Metabolic data were compared using multivariate statistical techniques including Principal Component Analysis (PCA) and Orthogonal Partial Least Squares Discriminant Analysis (OPLS-DA).

We recruited 15 patients with pneumonia and 26 with brain injuries, seven of whom went on to develop VAP. Comparison of metabolic profiles using OPLS-DA differentiated those with pneumonia from those with brain injuries ($R^2Y = 0.91$, $Q^2Y = 0.28$, $p = 0.02$) and those with VAP from those without ($R^2Y = 0.94$, $Q^2Y = 0.27$, $p = 0.05$). Metabolites that differentiated patients with pneumonia included lipid species, amino acids and glycoproteins.

Metabolic profiling shows promise to aid in the diagnosis of pneumonia in ventilated patients and may allow a more timely diagnosis and better use of antibiotics.

1. Introduction

Pneumonia is a frequent cause for admission to the Intensive Care Unit (ICU) and ventilator associated pneumonia (VAP) is a common complication in patients requiring mechanical ventilation, occurring in 8–28% of such patients (Chastre and Fagon, 2002). VAP is associated with increased mortality, longer intensive care unit and hospital stays, and increased healthcare costs (Chastre and Fagon, 2002).

Current diagnostic techniques are limited. Clinical features (Fabregas et al., 1999), radiological findings (Fabregas et al., 1999; Wunderink et al., 1992) and laboratory tests (Marquette et al., 1995; Fabregas et al., 1999) lack sensitivity and specificity. Biomarkers including C-reactive protein (CRP) (Povoa et al., 2005), procalcitonin (Kibe et al., 2011), and soluble triggering receptor expressed on myeloid cells (sTREM-1) (Oudhuis et al., 2009) have either failed to show strong clinical benefit or specificity for pneumonia. A new diagnostic technique is required to allow patients with VAP to be differentiated from those without, allowing a more targeted antibiotic strategy.

Metabonomics is the quantitative measurement over time of the metabolic responses of an individual or population to disease, drug treatment or intervention (Holmes et al., 2008) and provides a "top-down" integrated overview of the biochemistry in a complex system. Little work has been done characterizing pneumonia using metabonomic techniques. A few small studies have been performed including a study exploring pneumonia in Gambian children (Laiakis et al., 2010), and another looking at metabolic profiling of urine in patients with *Streptococcus pneumoniae* pneumonia (Slupsky et al., 2009b). Work within critical care has focused on outcomes of patients with community acquired pneumonia (CAP) (Seymour et al., 2013) and the ability of metabonomics to differentiate CAP as a cause for sepsis (Neugebauer et al., 2016). Despite the identification of metabolites associated with pneumonia, none have so far been used clinically as diagnostic tests.

No work has been carried out using metabonomic methods focusing specifically on VAP and limited work has been done looking at methods for differentiating patients with pneumonia from similar critically unwell patients. Most studies have used healthy volunteers as controls, this approach is limited as healthy volunteers are likely to be metabolically very different to severely ill patients. In this study we compare ventilated patients with pneumonia with a control group of patients similarly ventilated to give a more realistic background on which to develop a diagnostic for pneumonia.

* Corresponding author at: Intensive Care Unit, Charing Cross Hospital, Fulham Palace Road, London W6 8RF, UK.
E-mail address: Anthony.gordon@imperial.ac.uk (A.C. Gordon).

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2. Methods

2.1. Study Participants

Patients were recruited following written, informed assent from Imperial College Healthcare NHS Trust, London, in accordance with independent research ethics committee approval (North London REC 10/H0709/77) and conforming to the standards indicated by the Declaration of Helsinki, between December 2011 and December 2013. Patients who had two of the four criteria of the systemic inflammatory response syndrome (Bone et al., 1992) and were expected to require mechanical ventilation for ≥48 h were eligible for inclusion. Two groups were enrolled; firstly patients who had a primary diagnosis of brain injury, including subarachnoid hemorrhage, cerebrovascular accident, isolated head injury, status epilepticus or primary brain tumor, with no evidence of pneumonia. The second group were those who had pneumonia at the time of initiation of ventilation. Diagnosis was based initially on the opinion of the treating physician and then further refined by the application of the clinical pulmonary infection score (CPIS) (Pugin et al., 1991), Fig. 1. A brain injury cohort was selected as the control group as this patient group is critically unwell and often requires a period of prolonged ventilation, without having infection at the point of enrolment, thus requiring a similar degree of intensive care support to the pneumonia patients. Also this group has a significant risk of developing VAP providing a chance of being able to prospectively acquire samples from patients developing VAP without the confounding of other infection.

Enrolment occurred within the first 48 h of ICU admission, as soon as written consent could be obtained from a personal or professional consultee. Blood samples were collected as soon after enrolment as possible, all were taken within the first 72 h of ventilation with an average time to the first sample of 43 h, and then at 48 h intervals until either the patient left the ICU or four samples had been collected. Serum was separated immediately by allowing whole blood to clot on ice for 30 min. The serum fraction was isolated by centrifugation for 10–15 min and then stored at −80 °C prior to batch analysis.

Patients with brain injuries were reviewed daily and clinical, routine laboratory and radiological data were collected from the clinical notes. A diagnosis of VAP was made, prospectively, in patients who had been ventilated for >48 h in whom the CPIS was >6. Not all components of the CPIS score were routinely measured at our institution, specifically Gram staining of tracheal secretions and the measurement of circulating band forms, so patients with borderline scores were assessed by an independent clinician blinded to the metabonomics results and classified as pneumonia, VAP or no VAP, Fig. 1. As this was an exploratory study no power calculation could be performed to determine the number of participants needed. We aimed to ensure that we recruited six patients to each group. Given an assumed VAP rate of 25% this meant that we needed to recruit at least 24 patients in the brain injured group.

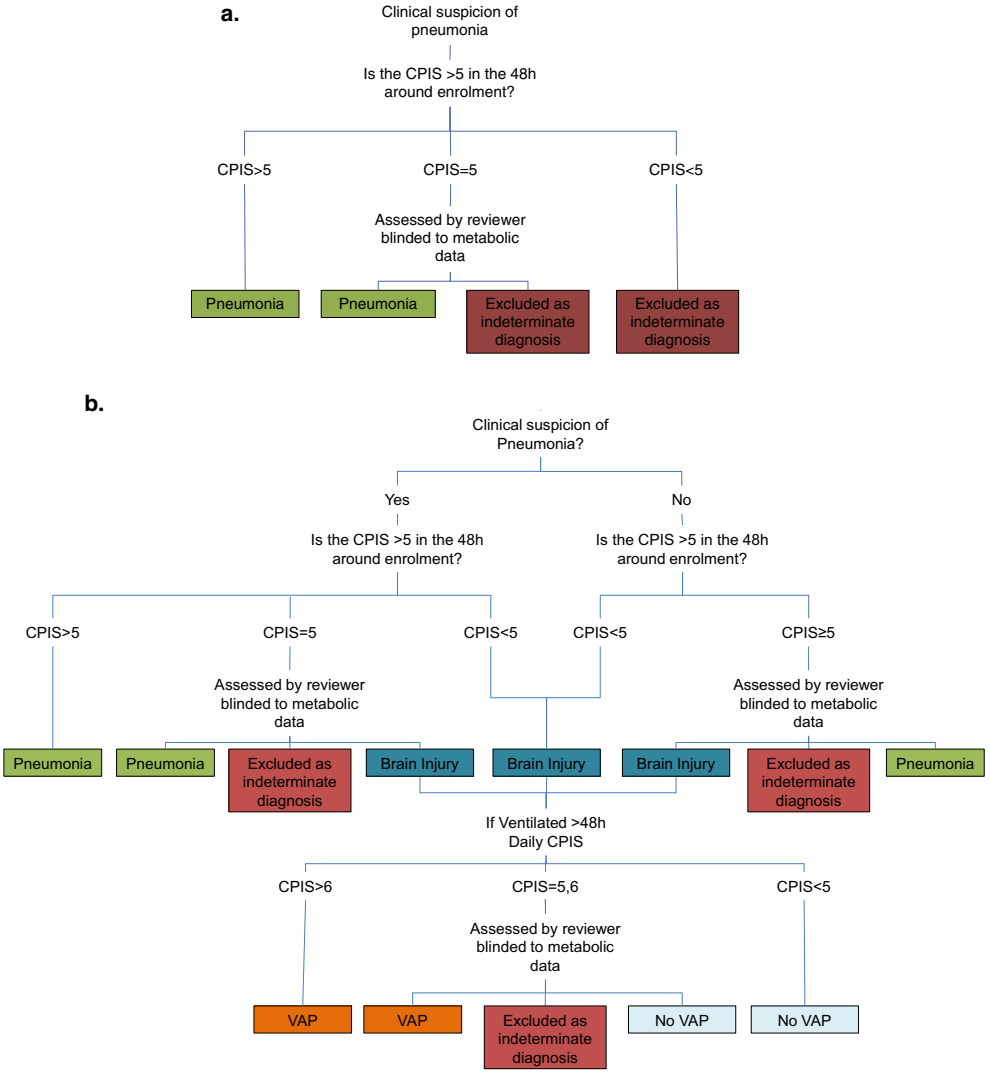

Fig. 1. Diagnostic pathway for a) patients admitted with pneumonia ($n = 15$) and b) patients admitted with brain injury ($n = 26$) when enrolled into the study.

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