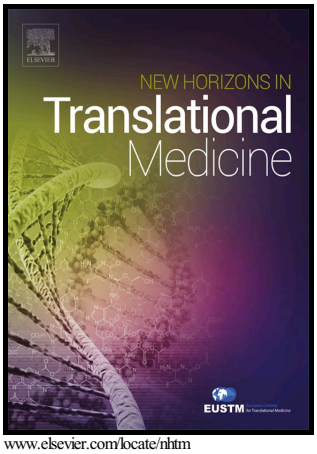

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A new horizon for sepsis: Personalised medicine: hype or hope?

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Background

Sepsis is a medical emergency and a major public health concern for society. It is estimated that there are 18 million cases of sepsis annually, and in developing countries over 6 million neonates and children die each year[1]. Data from the US supports the fact that the incidence and mortality from sepsis is rising, which reflects a global trend[2–4]. Reasons for this increasing incidence is likely due to a combination of ageing populations with multiple co-morbidities, improved life expectancy from other diseases, rising prevalence of people taking immunosuppressants and escalating antibiotic resistance[5]. Analysis of sepsis in a worldwide audit of intensive care units found that mortality was as high as 30%[6]. Within the UK, sepsis costs the NHS £830 million a year directly and between 36,000-64,0000 deaths. When sensitivity analyses are applied the estimated annual cost of sepsis to the UK is over £10 billion. [7]

The maxims of sepsis treatment include prompt administration of appropriate antimicrobial agents to kill the pathogen; fluid therapy and inotropes to support the circulation and adjunctive measures e.g. steroids for anti-inflammatory effects. Multiple adjunctive measures have been met with clinical trials which failed to demonstrate reduced mortality in cases of sepsis, notably protein C after 10 years on the market [8]. Several editorials have implored for a renewed urgency in investigating novel approaches in the treatment of sepsis[9,10].

Our knowledge of the inflammatory and regulatory processes in sepsis rely upon studies of in vitro cell lines; animal models of sepsis; inflammatory markers in human blood; and endotoxin challenges to healthy volunteers. Despite promising in vitro and ex vivo data, numerous clinical trials of immunotherapeutic agents have failed to show benefit in sepsis[11]. It is unsurprising that this approach has produced limited understanding of the processes during sepsis, and in effectively targeting clinical pathways., therefore, a completely new approach to study sepsis is needed. Furthermore, current guidelines in the management of sepsis are generic and do not account for the heterogeneity of this clinical picture[12]. They do not allow for the complex interplay between the type, location and extent of the infection combined with the individual's genetic variation, pre-morbid immune function and co-morbid conditions[13,14].

A personalised medicine approach takes into account the heterogeneity of sepsis and the need for in vivo studies to offer a more nuanced and targeted use of translational therapies. In sepsis, the inflammatory cascade is a dynamic process, in which changes need to be assessed in real-time, and specifically targeted. The development of liver or kidney dysfunction can lead to altered drug handling due to changes in pharmacokinetics or pharmacodynamics and increased likelihood of adverse drug reactions. The progression of immune exhaustion leads to an attenuated host response. Personalised medicine has been applied successfully to other fields including small molecule inhibitors in certain cancers and monoclonal antibody therapy in allergic asthma whereby it targets specific subgroups of individuals with a disease[15,16]. A tailored approach minimises the trial and error approach, which not only results in delays in administering effective therapy, but also minimised adverse drug reactions. Improvement in the stratification of patients with sepsis will provide new opportunities for current therapies within specific subgroups, allowing the targeting of specific pathways in the correct group of patients with sensitive endpoints. Implementation of improved risk stratification and targeted therapies in sepsis, may provide major breakthroughs in sepsis, not previously seen for many decades, thus improving morbidity and mortality[17],(Figure 1).

Figure 1: Cartoon depicting mode of action in potential new sepsis therapies