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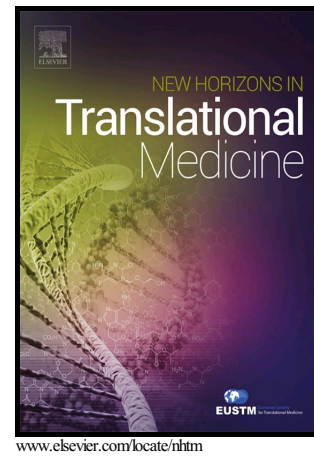
A new horizon for sepsis: Personalised medicine: Hype or hope?

R.J. McGalliard, E.D. Carrol

Cite this article as: R.J. McGalliard and E.D. Carrol, A new horizon for sepsis: Personalised medicine: Hype or hope?, *New Horizons in Translational Medicine* http://dx.doi.org/10.1016/j.nhtm.2017.06.002

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

McGalliard R J*, Carrol E D
University of Liverpool
*Corresponding author: Department of Clinical Infection, Microbiology and Immunology, University of Liverpool Institute of Infection and Global Health, Ronald Ross Building, 8 West Derby Street, Liverpool, L69 7BE. Rachel.mcgalliard@liverpool.ac.uk

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
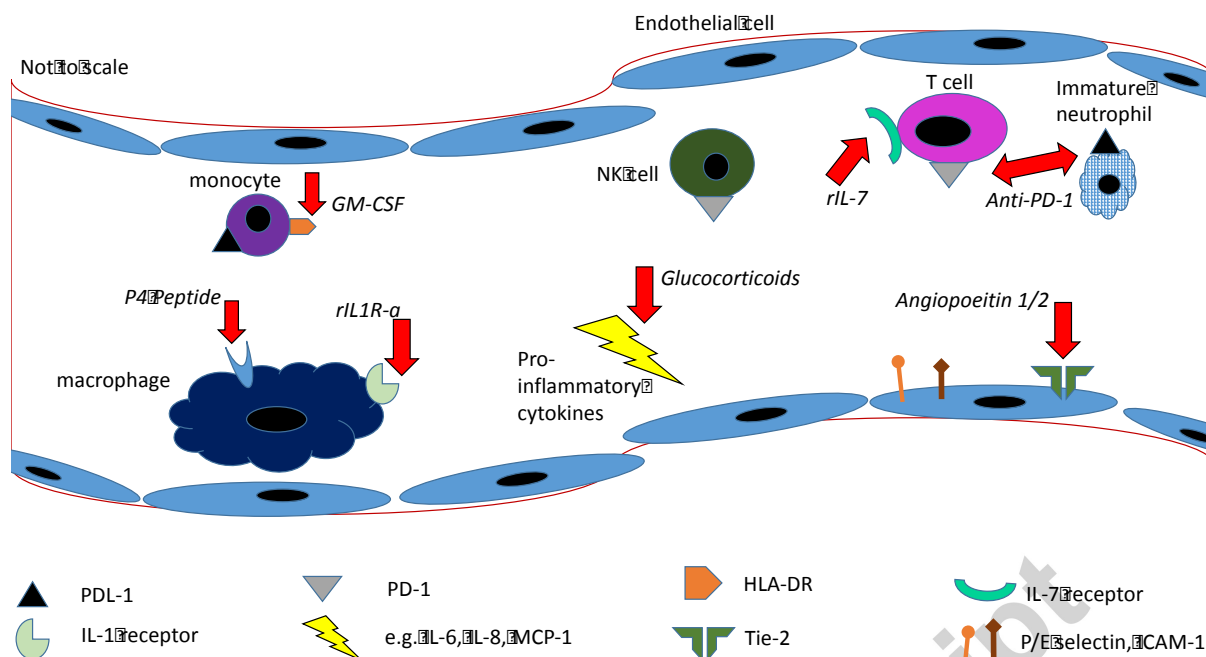
Personalised medicine targeting the microcirculation: refining fluid and inotrope therapy

Insults in sepsis, including pathogen toxins and destruction of host cells, result in a dynamic release of inflammatory mediators which damage the endothelium causing impaired perfusion of the microcirculation. This results in hypotension, multi-organ failure and shock, requiring large fluid volumes resuscitation. Fluid therapy and vasoactive drugs support the systemic circulation by increasing perfusion to tissues and organs. Early goal directed therapy was initially thought to reduce multi-organ dysfunction and mortality but the recently published ProCESS, ProMISe and ARISE trials established no benefit in survival with protocol driven resuscitation in severe sepsis[18–21]. Tissue hypoperfusion may also arise from abnormal distribution of blood flow[22,23]. Interestingly Brierley and Peters found that there are two distinct subgroups of microcirculatory patterns in paediatric intensive care unit (PICU) populations as characterised by community acquired or central venous catheter (CVC) associated fluid refractory septic shock. Community acquired septic shock was associated with high systemic venous resistance and low cardiac index deemed 'cold shock' and contrarily, CVC related septic shock with low systemic venous resistance and high cardiac index- 'hot shock'[24]. They suggest that this would influence management with vasopressors for CVC related septic shock and inotropes for community acquired cases.

Sidestream dark-field (SDF) imaging is a technique that allows observation of the microcirculation at the bedside with a hand-held device, thus allowing the classification of microcirculatory flow patterns[25]. Microcirculatory assessment provides an important intermediary value to correlate microvascular flow derangements with clinical and laboratory parameters, assessment of current fluid and inotrope resuscitation and ultimately new therapies. Hollenberg and colleagues correlated early microcirculatory dysfunction with poor prognosis in patients with septic shock and such persistent alterations also correlated with multi-organ failure and death[26,27]. Paize et al. found, in children with severe meningococcal disease, that microcirculatory dysfunction was associated with increased soluble markers of endothelial activation, such as E and P selectin and ICAM-1; and that microvascular dysfunction improved, alongside clinical recovery[28]. There is also evidence that low angiopoietin-1 and, inversely, high angiopoietin-2 concentrations are associated with mortality and are significantly lower in septic shock compared to patients with systemic inflammatory response syndrome (SIRS) or sepsis[29–32]. Both studies suggest means of investigating those with microcirculation dysfunction in vivo and providing further tools to guide prognosis. These studies also implicate dysregulation of angiopoietin- Tie-2 signaling pathway in endothelial dysfunction in severe sepsis and provides new therapeutic targets for investigation[33]. Recent studies have shown that fluid bolus administration improves microvascular perfusion in the early but not the late phase of

sepsis with reduced multi-organ failure outcomes, and that this effect is independent of the haemodynamic effects of fluid[34,35].

Personalised medicine targeting immune dysregulation

Granulocyte-macrophage colony stimulating factor (GM-CSF) is widely and safely used in oncology and it was initially postulated to improve outcomes in sepsis through reversal of monocyte deactivation and reduced antigen presentation and thereby immunosuppression that characterises the later stages of sepsis. However studies of GM-CSF in sepsis in vivo did not demonstrate a mortality benefit despite increased TNF-α production ex vivo[36,37]. Low HLA-DR has been associated with increased hospital acquired infections and mortality in septic shock[38,39]. Meisel and colleagues used low HLA-DR expression as a biomarker of monocyte immune dysfunction and stratified such patients in ICU to receive GM-CSF or placebo. They demonstrated that HLA-DR expression recovered significantly with GM-CSF, demonstrating monocyte function improvement which persisted throughout disease duration. Moreover, GM-CSF administration in this subset resulted in reduced length of mechanical ventilation, ICU and overall hospital stay[40].

Interleukin-1 α and β are pivotal pro-inflammatory cytokines produced during microbial infection, which have also been implicated in the development of multiorgan dysfunction in septic shock. The recombinant IL-1 receptor antagonist (rILR-a) was demonstrated to have immune regulatory roles, postulated to be through blocking IL-1 alpha and beta binding monocytes and endothelial cells[41]. However, initial clinical studies of rILR-a, Anakinra, did not show any survival benefit in sepsis or with further analysis in septic shock[42,43]. However, when stratified by patients with sepsis and macrophage activation syndrome (MAS), rILR-a was shown to reduce mortality[44]. MAS is characterised by a cytokine storm with liver dysfunction and coagulopathy and a similar phenotype is seen in some cases of severe sepsis with disseminated intravascular coagulopathy (DIC) or liver failure. Subsequent work by Shakoory et al, elucidated that in patients with severe sepsis and DIC or hepatobiliary dysfunction, rIL-1Ra significantly improved 28-day survival but had no effect on survival in severe sepsis without features of DIC or hepatobiliary dysfunction[45]. These studies suggest a role for rIL-Ra use in sepsis patients with specific clinical phenotype of hepatobiliary dysfunction and coagulopathy.

Programmed death-1 (PD-1) and its ligand (PDL-1) act as T cell checkpoint inhibitors. When co-stimulated with the T cell receptor, it produces intracellular inhibitory signal cascades resulting in cell cycle arrest and reduced production of pro-inflammatory cytokines[46]. PD-1: PDL-1 interactions have been strongly implicated in T cell exhaustion and approved monoclonal antibodies are already in clinical use[47]. Chang and colleagues exhibited that septic patients had increased PD-1 expression on CD8 T cells which increased during the course of the illness and was associated with reduced IL-2 and IFN-gamma production. Increased expression of PD-1 also correlated with an increased immune exhaustion phenotype and propensity to secondary infections, which was reversed by ex vivo blockade of the PD-1 system[48]. Shao et al studied PDL-1 expression on cell lines in patients with severe sepsis and septic shock via flow cytometry. Using multivariate logistic regression, they showed that monocyte PDL-1 expression is an independent marker of 28-day mortality in severe sepsis and provides more accurate prognosis when combined with conventional clinical parameters[49]. Patera and colleagues showed that this increased PDL-1 expression on monocytes and neutrophils correlated with reduced ex vivo phagocytic function in these cells. Reduced NK and T cell activation and function, as measured by CD107a, IFN- γ and granzyme b production, was significantly associated with increased PDL-1 expression on immature, low density neutrophils (LDNs) which suggests PD-1: PDL-1 plays an inhibitory role in both innate and adaptive response. Additionally, they demonstrated that PD-1 and PDL-1 monoclonal antibodies significantly restored monocyte function in patients with sepsis[50]. These results suggest that a group of patients with sepsis who exhibit highest levels of PD-1 on monocytes and T cells are at greatest risk of mortality and nosocomial infections and may be appropriate for targeted therapy to this pathway to restore innate and adaptive immune responses. Although there are safety concerns about autoimmune disease with prolonged anti-PDL1 use in oncology, in sepsis, therapy would be short term.

IL-7 is an important cytokine in T cell function through Bcl-2 signaling to increase proliferation and concomitant broadening of repertoire. It binds to its receptor via the common gamma cytokine subunit and alpha unit, also known as CD127. Studies have shown elevated endogenous IL-7 in plasma in

septic patients but in septic shock, increased plasma soluble CD127 (sCD127) was also observed. sCD127 is able to bind IL-7 like a decoy receptor. Perronet et al demonstrated that increased soluble CD127 concentrations as measured by ELISA, was associated with increased mortality in ICU patients with septic shock compared to controls[51]. rIL-7 administration ex vivo restored both intracellular markers of T cell activation and IFN-gamma production[52]. In combination, these studies suggest sCD127 is a useful marker of patients with septic shock, who may also derive benefit from exogenous IL-7 administration.

With improved understanding of single pathways involved in immune dysfunction, Shindo et al examined the effect of IL-7 and anti-PD-1 on various markers of immune activation. IL-7, but not anti-PD-1 increased T cell proliferation as measured by nuclear protein Ki-67 staining; and leukocyte tracking by intercellular adhesion molecule 1 (ICAM-1) and very late antigen (VLA-4) expression on T cells. IL-7 also increased intracellular and extracellular IFN-γ as assessed by staining and ELISA respectively. Conversely anti-PD-1 increased MHC class II in splenic macrophages and dendritic cells, suggesting its effects are partially mediated through antigen presentation[53].

Personalised medicine re-targeting adjunctive therapies

Sepsis is characterised by a pro-inflammatory state and a concomitant ant-inflammatory process with a dysfunctional immune response. This is recognised to be phenomena of both innate and adaptive immune systems. Immune dysfunction and the plethora of pathways involved in the immunosuppressant late stages of sepsis are being investigated[54]. Targeting therapies to specific subgroups will improve immunosuppression and associated risk of nosocomial infection.

Glucocorticoids have had a controversial role in the management of sepsis with regards to their multifaceted immunosuppressant and systemic vascular resistance effects. Clear clinical benefit has been difficult to elucidate, either in prevention of progression to septic shock or in mortality[55]. A study by Remmelts et al. identified patients with community acquired infections with pro-inflammatory cytokine profiles (IL-6, IL-8, MCP-1) and low cortisol had significantly reduced ICU admissions and mortality when given dexamethasone compared to placebo[56]. Currently, glucocorticoids are indicated in the treatment of bacterial meningitis to reduce the incidence of neurological sequelae including hearing loss[57]. Latest sepsis guidelines appraised the limited evidence for glucocorticoids and currently recommend the use of hydrocortisone if adequate fluid resuscitation and vasopressor therapy fail to restore haemodynamic stability[58]. Cvijanovich and colleagues analysed three glucocorticoid receptor polymorphisms in patients with septic shock. They found that individuals who were homozygous for the wild type glucocorticoid receptor allele and received corticosteroids had increased odds of morbidity and mortality.[59]

P4 peptide is a 28 peptide fragment of pneumococcal surface adhesin A (PsaA), which is pivotal for the adherence of PsaA to nasopharyngeal cells, thus was originally investigated as a vaccine candidate.[60] However it was noted to increased opsonisation of bacteria and rates of phagocytosis and subsequently was investigated as a potential therapy through augmented passive immunity[61]. Morton et al reviewed the in vivo murine models of sepsis which showed significantly reduced mortality with S. aureus septicaemia and both primary and secondary S. pneumoniae infection mediated through increased activitation of phagocytes with diminished bacterial burden in tissues [62] P4 coadministration with intravenous immunoglobulin (IVIG) in mice reduced mortality in S. pneumoniae septicaemia from 100% to 40% and in models of pneumonia, when administered early, prevented bacteraemia and sepsis in 100% of cases[63].
In a critical care cohort with severe sepsis, P4 peptide administration ex vivo increased phagocytic activity, independent of microbiology or source of infection [64]. Further investigation of subsets in sepsis should be investigated for this promising adjunctive therapy and its efficacy with IVIG.

Conclusion

Personalised medicine does not only pertain to genetic predisposition and epigenetic changes influencing choice of drug therapy, but with regards to sepsis, serves to improve understanding of the host-pathogen interaction and how a particular individual might benefit from novel targeted therapy[65,66]. As discussed in this article, personalised medicine has the potential to risk-stratify

patients allowing accurate predictions of response and prognosis, which could guide clinicians' decisions regarding tiers of care e.g. intensive care, tailor resuscitation fluid and inotrope measures and employ particular adjunctive therapies to augment the host immune response. Precision diagnostics are also crucial to allow timely personalised medicine decisions for the treatment of patients with sepsis. In the future, biomarker panels at the bedside could sub-classify patients presenting with sepsis to appropriate therapies alongside antimicrobial agents. In summary, with a shift from treating sepsis using a "one size fits all" approach to using a dynamic approach, which allows risk stratification of a heterogenous clinical syndrome in individuals, there is potential for improvement in sepsis outcomes, through understanding the pathways involved in specific groups and targeting them appropriately.

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