

Editorial

Known knowns, known unknowns and unknown unknowns. Can systems medicine provide a new approach to sepsis?

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‘As we know, there are known knowns; there are things we know we know. We also know there are known unknowns; that is to say we know there are some things we do not know. But there are also unknown unknowns—the ones we don’t know we don’t know’.

Donald Rumsfeld’s statement as US Secretary of State for Defense during a news briefing in 2002, attracted much publicity and comment. Despite several decades of laboratory and clinical research, Rumsfeld’s assertions can be applied to the current state of knowledge about sepsis, acute illness and anaesthesia.

Known knowns

Sepsis has a high morbidity and mortality, affects all age groups worldwide and is a major, increasing area of health expenditure.¹ The evolution from the onset of infection to systemic sepsis is insidious, and it can be difficult to differentiate early sepsis from other conditions, or predict the clinical course.^{2,3} Conversely sepsis can progress rapidly with activation of widespread inflammatory pathways leading to multi-organ failure and significant clinical deterioration within hours.⁴ Prompt treatment (early resuscitation, source control, antibiotic therapy, supportive care) based on the principles of the ‘Surviving Sepsis’ campaign are beneficial.⁵ Several factors, including differing bacterial virulence/load, genetic susceptibility, interactions between inflammatory pathways, age, sex, disease or other therapies also affect outcome.^{4,6,7}

Hence we know the extent of the clinical problem, many details of the pathophysiological processes and pathways involved and several predisposing factors for good or poor outcomes, including the benefits of early diagnosis and therapy. However our widely endorsed current management strategy is recognised as a pragmatic approach that evolved partly because of a lack of effective specific therapeutic interventions.⁸ Though outcomes have improved over the last decade,⁹ increasing knowledge of the pathophysiological mechanisms involved in host responses to infection has not yet translated into changes in clinical practice directed at mechanisms, as treatments aimed at modifying the activity of single or limited pathways have been unsuccessful.^{4,7} This is frustrating for clinicians and researchers but to make further progress we need to recognise the gaps in our understanding and the reasons for this.

Known unknowns

The factors accounting for the gaps in our knowledge about sepsis include problems of diagnosis, limitations in understanding of inflammatory pathways, and the restrictions of current monitoring techniques. We know that sepsis is a syndrome comprising a non-specific group of symptoms and signs of biological responses to infection with inflammatory processes generated by many downstream and interlinked pathways.⁴ Different pathogens with a variety of clinical consequences can produce a very similar clinical picture at presentation or in the early ‘compensated’ phase of sepsis, leading to delays in diagnosis. ‘Diagnostic’ respiratory signs are generic, occurring in other non-septic causes of respiratory or circulatory failure. Disturbed central nervous system, haematological, hepatic or renal functions occur variably. Abnormal laboratory test values (such as increased lactate) occur in non-septic conditions. Cardiovascular dysfunction occurs at both macro- and microcirculatory levels. In experimental studies the relationship between macrocirculatory and microcirculatory function is disturbed, but the consequences of this are unclear and microcirculatory failure (oxygen energetics, mitochondrial dysfunction) is difficult to detect and monitor in clinical

practice. Furthermore, in contrast to cardiogenic or hypovolaemic shock, assessment of the adequacy of resuscitation is complicated by greater cellular dysfunction and regional blood flow disturbances. Consequently, clinical signs or laboratory indices are not by themselves reliable indicators of the severity of sepsis or response to resuscitation. Currently, we use direct and indirect indices alongside clinical judgement to interpret the severity of sepsis, guide therapeutic interventions and assess responses to treatment. However, clinical diagnosis relies partly on subjective judgement; the results of confirmatory diagnostic tests may be unavailable for hours (blood) or days (microbiological), leading to considerable scope for variation.

Scoring systems. Scoring systems are widely used to diagnose sepsis and monitor progress and response to treatment. However, despite their simplicity and clinical relevance, the internationally recognised diagnostic criteria for SIRS or sepsis are sensitive but have low specificity.^{2,8} They do not reflect the complexity of the mechanisms involved, differences between pathogens, the influence of genetic polymorphisms, age, sex, disease or other therapies. Furthermore, there is heterogeneity in the classification of organ dysfunction.¹⁰ Early warning 'track and trigger' scores are situation-specific, varying according to the clinical scenario and the prevalence of acute severe disease within a given patient cohort.¹¹ They are also not necessarily helpful in the early phases of sepsis before decompensation has occurred and not helpful for individual prognostication. Similarly, there is a large body of literature investigating combinations of biomarkers and clinical scoring systems. The fundamental problem with this approach is that conclusions are based inevitably with statistical associations, and although plausible mechanisms are proposed, they cannot answer questions of causality. Scoring systems do not account for changes over time in disease progression or clinical management; they do not represent the relationships between the multiple mechanisms involved in inflammation (temporal, biological, biochemical, cellular and genetic), at the cellular, organ or whole-patient level. Similarly, correlations between genetic variability or polymorphisms and clinical outcomes in acute illness or perioperative medicine do not account for the many other factors that lead to variations in disease phenotype, or provide the means to assess the effect of a particular intervention.

Biomarkers. Partly in response to the limitations of clinical data, much research has been directed at identifying novel biomarkers that might aid diagnosis and therapy. Indeed, over 170 biomarkers have been studied in sepsis but all have limitations, including lack of specificity, time required, costs and imprecision.^{12 13} Though some are used, no biomarker (alone or in combination) has sufficient discriminatory power for lone use in clinical practice, probably because no single marker reflects the complex underlying mechanisms.^{7 14} Likewise, early alterations and patterns of abnormalities in cytokines after major blunt trauma have been identified but the relationship to outcomes remains unclear.¹³ Reasons include the huge variation in the values of individual biomarkers used to diagnose inflammation, the vast mismatch between the many different biomarker patterns during sepsis and the few blunt clinical outcome measures available, meaning that enormous datasets are required to make conclusions.

Limitations of current monitoring. Further problems arise because of the limitations of currently available monitoring devices both within and outside the Intensive Care environment. Variables monitored non-invasively outside ICU (heart and respiratory rate, arterial pressure, oxygen saturation) are relatively poor indicators of the complex pathophysiological processes (cellular dysfunction, disturbed regional blood flow) occurring. Current modalities used routinely in ICU are

slightly better in this regard but also have disadvantages: they are invasive with potential complications, require specialised nursing capabilities or technical support and are often not portable outside ICU. Despite the introduction of new technologies, the accuracy of these is variable, and all monitors (new and established) are subject to inter-observer variation.¹⁵ In addition, there are always delays, the 'lead-time', between inoculation and physiological decompensation, the onset of sepsis or acute illness, presentation and diagnosis. This is well recognised but measurements described as 'early' in the current literature are almost invariably taken hours after hospital admission and physiological deterioration, often after admission to ICU using invasive monitoring techniques. In the truly "early" stages, at presentation to the emergency department, or in medical and surgical wards, only basic monitoring is used and at discrete time points. Critical Care 'Outreach' teams outside ICU have extended the application and reporting of basic monitoring to promote early intervention and interdisciplinary working, but have not addressed the inherent problems of current monitoring or detection of early pathological processes.

Limitations of current treatments. Most interventional studies aiming to modify specific parts of the relevant pathways have been unsuccessful and the mortality from sepsis remains high. Despite positive results from animal data, usually involving interventions to block specific receptors or inflammatory pathways, of over 100 interventional clinical trials in sepsis, none have provided a robust and effective solution. Reasons for this include the non-specific multi-pathway adaptive host responses to sepsis with heterogeneity in different models or populations. Furthermore, studies have used different endpoints ranging from mortality to various biomarkers, with overoptimistic estimates of effect based on assumed optimal dose or duration.¹⁶ An individual patient's outcome may also be affected by local availability of resources and clinicians' judgements about futility. It is unsurprising that there is no single effective treatment for sepsis, even though ICU outcomes appear to be improving.⁹

The need for a new approach. The limitations of current approaches relate to several 'known knowns': limitations in our understanding of the pathophysiology of sepsis, diagnostic criteria, clinical monitoring and assumptions that targeted therapy can effectively alter the clinical course of a syndrome that effectively comprises a group of symptoms rather than a specific disease process. Most clinical information is derived as single-point measures and the information from physiological monitoring is not integrated. Indeed relatively few mechanistic studies have been carried out in the early phase of sepsis. Different components of the inflammatory response have different thresholds for changing their behaviour from anti-inflammatory to pro-inflammatory, but the complex dynamic inter-relationships between cellular (e.g. mitochondrial function, cytokine production) and physiological processes (tissue oxygenation, energy pathways) are poorly understood. We have major gaps in understanding of these, how different pathways interact over time and how 'tipping points' in one biological system affect another. One of the main barriers to improved care is early diagnosis and recognition of sepsis, and the target times for delivery of care bundles recommended by the Surviving Sepsis Campaign have been reduced to within 3h and 6 h.^{8 17} Sepsis 'champions' who ensure timely resuscitation and delivery of interventions should help. However, in order to make further progress, we need a paradigm shift, using accurate combined multimodality data to enable understanding of the dynamic processes occurring in early sepsis (often before ICU admission) to predict the clinical course and target treatment at patients most likely to deteriorate. This requires a 'systems medicine' approach.^{13 18}

Modelling and systems medicine

Mathematical modelling is used in a variety of disciplines ranging from ecology and aviation to drug development and logistics. Within medicine it has been used for modelling in diabetes, acute lung injury and other conditions.¹⁸ Systems biology, established as a scientific field for over 20 years, combines biological research with engineering, mathematics and computer science, aiming to develop tools for analysing complex datasets from different sources, termed 'complex systems analysis'. Human responses to disease include many facets (multiple processes, immeasurable variables, genetic factors, random effects) which lead to unpredictable consequences, different clinical effects and outcomes in individual patients. Systems medicine amalgamates systems biology techniques with medical treatment decision-making where information from many biological measurements are combined and analysed for complex patterns of change.¹⁹ This is relevant to acute illness such as sepsis or inflammation where the relationships between cellular, tissue and organ dysfunction may be hierarchical and non-linear, hard to predict and the critical control points difficult to identify. The use of modelling in ICU is attractive because we have large amounts of physiological and clinical data, with rapid changes and measurable mediators and outcomes. It could also be used to investigate delivery of care.

Over the last 15 years there has been interest in applying mathematical modelling techniques to acute illness, supported by US National Institutes of Health, who recognised that new approaches are needed to big datasets, drawing from information science, informatics, computer science, and computational biology.²⁰ Progress has been made in some areas. Homeostasis requires interactions between different organs: it has been demonstrated that these interactions change constantly and oscillate to produce, for example, small variations in heart and respiratory rate in health, mediated probably by the autonomic nervous system. Diurnal variations in the HPA axis and responses to stress depend on oscillatory feedback systems and have been modelled to demonstrate changes in transcription of glucocorticoid-responsive genes.^{21 22} In sepsis, this oscillatory feedback is disrupted so that variations in heart rate and respiratory rate are reduced. This means that lack of heart rate variability could potentially be used as a diagnostic tool to alert clinicians to early phases of heart rate decompensation and to a lesser extent respiratory rate variability.²² Thus it has been suggested that analysis of *changing* patterns in monitored physiological data (heart rate, temperature and possibly respiratory rate or blood glucose variability) may associate with clinical outcomes in sepsis.³

Further relevant concepts include data mining and mechanistic modelling. Data mining is a technique in which all possible data are collected and analysed to identify patterns and relationships between variables, with the goal of developing hypotheses about the mechanistic relationships. This would be the first step in defining the most important variables and correlating them with outcome. However, it is limited in that it relies on the data quality, signal to noise ratios and optimal sampling rates; these are not yet defined. It can generate hypotheses based on statistical associations, similar to biomarkers and scoring systems, but data mining alone does not address the underlying mechanisms.²³ Hence additional approaches are needed. Mechanistic modelling techniques have provided insights into drug actions and have been used to study individual inflammatory responses.¹³ Modelling techniques (including cluster analysis, decision tree approaches) may illuminate the mechanisms underlying altered physiological control in inflammation and diagnosis of sepsis. Other potential applications are in the analysis of simulated datasets or '*in silico*' clinical trials aiming to predict individuals' inflammatory responses.^{13 23 24} Rather than seeking statistical

correlations associations between predefined clinical groups (e.g. trauma or sepsis) and associated biomarker patterns, principal component analysis can be used to identify groups of patients with similar patterns of biomarkers, then correlate these groups of patients with relevant outcomes. However these approaches have not yet been studied in an integrated way in human sepsis.

Despite vigorous support and the creation in 2004 of the Society for Complex Acute Illness, the field of systems medicine has received limited attention in some quarters, with no publications in the major anaesthesia journals in the field of systems biology or medicine. This is changing and a number of papers have recently been published in the ICU literature.^{18 24} Indeed, recent investigations into modelling of the effect of propofol on EEG at different sites within the brain have suggested that it might be possible to clarify the mechanism of action of propofol more precisely, including monitoring depth of anaesthesia.²⁵

Some might consider that using modelling (based on mathematical assumptions and statistical associations) to determine therapy is contrary to current ethos of patient-centred, individualised care. However, the converse is true. Most therapeutic trials in sepsis and acute illness have been based on the tenet that a single intervention will produce a meaningful effect, sometimes involving thousands of patients in an attempt to account for biological variability. The failure of many of these studies shows clearly that 'one size does not fit all' and different approaches are needed. Inflammation and sepsis are complex processes that are both robust and fragile, sensitive to multiple factors, influenced by positive and negative feedback pathways and random or unpredictable effects. To really understand the mechanistic responses in acute illness, our view is that modelling with complex pattern analysis of an array of physiological variables, in conjunction with more sophisticated early monitoring outside ICU to predict responses and outcomes; only then are we likely to be able to translate this into new treatments effective for individuals. The 'known unknowns' to be addressed include: How do inflammatory pathways and physiological responses to infection interact dynamically? At what point does cardiovascular compensation begin to fail? Which individual factors (genetics, age, disease, sex etc) are most important and how? What treatments would be best for individuals? Why do different patients react differently to anaesthesia, analgesia or other aspects of perioperative care? Paradoxically the question of whether modelling can increase understanding of inflammatory or other pathways and direct new clinical trials is not fully resolved, but data from other scientific fields suggest clear potential. At the very least, it will generate new questions or avenues of enquiry, and perhaps reduce the unknown unknowns in sepsis.

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