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Editorial

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

> 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 to predict the clinical course.[2 3] Conversely, sepsis can progress rapidly, with activation of widespread inflammatory pathways leading to multiorgan failure and significant clinical deterioration within hours.[4] Prompt treatment (early resuscitation, source control, antibiotic therapy, and supportive care) based on the principles of the 'Surviving Sepsis Campaign' are beneficial.[5] Several factors, including differing bacterial virulence and 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 recognized as a pragmatic approach that evolved partly because of a lack of effective specific therapeutic interventions.[8] Although 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, because treatments aimed at modifying the activity of single or limited pathways have been unsuccessful.[4 7]

This is frustrating for clinicians and researchers, but in order to make further progress we need to recognize 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 macro- 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 recognized diagnostic criteria for systemic inflammatory response syndrome or sepsis are sensitive but have low specificity.[2 8] They do not reflect the complexity of the mechanisms involved, the differences between pathogens, or 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. Likewise, 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 inevitably based on 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. Likewise, 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, more than 170 biomarkers have been studied in sepsis, but all have limitations, including lack of specificity, time required, costs, and imprecision.[12 13] Although 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 data sets are required to draw 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 the intensive care unit (ICU) (heart rate and respiratory rates, arterial pressure and oxygen saturation) are relatively poor indicators of the complex pathophysiological processes occurring (cellular dysfunction and disturbed regional blood flow). Current modalities used routinely in the ICU are slightly better in this regard but also have disadvantages: they are invasive, with potential complications, require specialized nursing capabilities or technical support, and are often not portable outside the ICU. Despite the introduction of new technologies, the accuracy of these is variable, and all monitors (new and established) are subject to interobserver 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 recognized, but measurements described as 'early' in the current literature are almost invariably made hours after hospital admission and physiological deterioration, often after admission to the 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 the 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 more than 100 interventional clinical trials in sepsis, none has provided a robust and effective solution. Reasons for this include the non-specific multipathway adaptive host responses to sepsis, with heterogeneity in different models or populations. Furthermore, studies have used different end points, 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 and 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 3 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]