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M. Bauer; Jena
M. Singer, London

P. Arina · V. Moro · M. Singer

Bloomsbury Institute of Intensive Care Medicine, University College London, London, UK

From “bad infection” to organ failure

*“I neither know nor think that I know”
(Attribute to Socrates by Plato, Apology 21d)*

Since ancient times, sepsis (from the Greek *sepsē*, putrefaction) has been a companion of humanity. From the first Egyptian medical scriptures to the Hippocratic corpus, physicians have been well aware of the consequences of infection. The development of fever, purulent secretions and gangrene were associated with a poor prognosis [1].

For centuries scientists and physicians have tried to understand this process characterized by rapid alterations in physiology and decay of the human body. Nonetheless, the definition of sepsis remains in a state of flux. Twenty years ago, the main emphasis was placed on an exaggerated host systemic inflammatory response (deemed “sepsis”) which could progress to organ dysfunction (“severe sepsis”) or septic shock [2]. Prominence is now firmly placed on a failure of host regulatory control, with sepsis currently defined as “life-threatening organ dysfunction caused by a dysregulated host response to infection”, and septic shock as a subset in whom “profound circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality” [3].

Sepsis continues to have a major impact on public health and is associated with more than 50% of hospital deaths, albeit predominantly in elderly and/or

frail patients with multiple comorbidities [4, 5]. This syndrome has an overall hospital mortality of 25–30% which increases to over 40% in patients with septic shock [3]. Despite medical advances, no specific therapy has yet been shown to be effective. Nevertheless, the need for early recognition and timely intervention remain key to reducing illness progression, short- and long-term morbidity and mortality, and related personal and healthcare costs [5].

How patients progress from infection to multiple organ failure (MOF) is complex and still incompletely understood [6, 7]. The immune system plays a fundamental role in modulating different pathways in response to a wide range of exogenous (pathogen-associated molecular patterns [PAMPs]) and endogenous (damage-associated molecular patterns [DAMPs]) mediators. Examples of PAMPs include lipopolysaccharide from Gram-negative organisms and lipoteichoic acid from Gram-positive organisms, whereas DAMPs are host molecules released from damaged tissue into the circulation such as mitochondria [8], DNA, histones and heat shock proteins. Recognition of these mediators by a variety of extra- and intracellular pattern recognition receptors (such as the Toll-like receptors) results in activation of endothelial, epithelial and innate immune system cells, releasing cytokines, nitric oxide, eicosanoids and many other inflammatory mediators. These induce either downstream activation or suppression of multiple pathways including circula-

tory, hormonal, bioenergetic, metabolic and adaptive immunity. Transcriptomic studies in various tissues show predominant downregulation of gene expression but, notably, transcript changes vary both temporally and between organs [9].

The inflammatory response involves a simultaneous activation of both pro- and anti-inflammatory cascades [6, 7], with both the magnitude and persistence of response relating to subsequent outcome [10]. Early death in septic patients is commonly associated with an overwhelming, hyperactive inflammatory response manifest by increased levels of pro-inflammatory mediators, metabolic acidosis and cardiorespiratory dysfunction [11]. Survivors generally re-establish normal immune functioning and restoration of organ function. However, later deaths are often due to persisting immunosuppression with an increased risk of secondary infection [12, 13]. Improvements in technological capability has resulted in a large shift from predominantly early cardiovascular deaths [14] towards withdrawal of life-prolonging organ support subsequent to a failure to recover organ function over weeks [15]. Mortality risk remains high in sepsis survivors over the first few years following ICU discharge [16]; this is frequently related to new infection or to cardiovascular deaths (myocardial infarction, stroke) related to accelerated atheroma from ongoing inflammation.

Despite the increasing knowledge base, sepsis remains incompletely understood and, as a consequence, novel therapeutic strategies have consistently

P. Arina and V. Moro contributed equally to this work.

failed. For each of these strategies, this may represent one or more of the following factors: misplaced faith in the strategy though flawed understanding of the pathophysiology, poor patient selection, inappropriate timing or dosing, or unanticipated harm. For example, aggressive attempts to correct tissue hypoxia in patients in early septic shock failed to reduce mortality or morbidity [17], with organ dysfunction still developing notwithstanding preservation or even elevation of tissue oxygen delivery [18].

The circulation is involved early in a local infective process. Blood flow increases to the site of infection, with local vasodilation and increased capillary leak to facilitate movement of immune cells and nutrients into the tissues, and activation of cellular and non-cellular coagulation pathways to prevent systemic spread of the infecting micro-organisms. However, in sepsis, these processes become activated systemically, with noninfected tissues becoming involved. Vascular leak becomes generalised with loss of intravascular fluid. An elevated cardiac output is, in general, a feature of early sepsis, delivering oxygen and more substrate to tissues to assist the body's enhanced metabolic activity needed to combat the infection. However, as illness severity progresses, cardiac output may become significantly compromised, due in part to loss of circulating volume but also due to direct ventricular dysfunction triggered by circulating myocardial depressant factors ("septic cardiomyopathy") [18]. This depression is offset to some extent by a fall in systemic vascular resistance due to decreased vascular tone; however, at the microcirculatory level, there are heterogeneous regions of dilation and constriction with stop-go flow [19]. Paradoxically, in most cases of sepsis there is remarkably little histological or imaging evidence of intravascular clot obstruction [20] despite laboratory evidence of often marked coagulation activation [21]. "Disseminated intravascular coagulation" is a historical term but may be a misnomer. Nonetheless, thrombin generation is a potent stimulus of inflammation [21]. Notably, a distinguishing characteristic of sepsis-induced MOF

is the scarcity of histological findings of cell death that is disproportionately minimal compared to the degree of organ dysfunction, even in non-survivors [22]. This implies that tissue hypoxia is not severe enough to cause significant necrosis yet may still play a role in amplifying inflammatory processes and inducing multiple pathways, e.g. through induction/activation of hypoxia-inducible factor [23].

To explain the biochemical and physiological dysfunction seen in vivo in the absence of major structural damage suggests a metabolic shutdown analogous to hibernation or estivation [24]. We have previously proposed mitochondrial dysfunction to play a major role in the development of organ failure in sepsis [25]. Mitochondria are present in all cell lines, except red blood cells. They are not just responsible for producing the bulk of the body's energy currency (adenosine triphosphate [ATP]) through oxidative phosphorylation thus enabling metabolism to occur, but also have important roles in fatty acid metabolism, intracellular calcium regulation, hormone production, cell death, and generation of body heat [26–28]. Mitochondria are the major site within the body of reactive oxygen species (ROS) production. In health, ROS play an important part in signalling; however, in systemic inflammatory conditions such as sepsis, ROS are generated in significant excess, overwhelming endogenous anti-oxidant defences and causing damage to proteins (through carbonylation), lipids (through peroxidation), DNA and RNA. Sepsis may also induce a shift of respiration away from ATP generation towards uncoupling, with excess production of heat. This may explain in part the pyrexia associated with sepsis. Multiple factors are implicated in inducing mitochondrial dysfunction in sepsis including initial tissue hypoxia, excess production of ROS and reactive nitrogen species, downregulated transcription of genes encoding mitochondrial proteins, increased uncoupling, and altered hormonal influences such as the sick euthyroid syndrome [25, 29]. Further support for this postulate arises from the finding that tissue oxygen tension is maintained or elevated in sepsis, implying local

availability but non-utilisation of oxygen ("dysoxia") [25]. Mitochondrial abnormalities have now been demonstrated in multiple tissues including muscle, heart and immune cells [30–32], with the degree of both dysfunction and markers of mitochondrial biogenesis (recovery of healthy mitochondria) relating to prognosis [30, 33].

A decrease in energy substrate availability may initiate the metabolic reprogramming that underlies organ dysfunction in sepsis. From an evolutionary point of view, mitochondrial ATP production has enabled complexity within eukaryotic cells [34] but, by necessity, this requires a delicate energy management mechanism based on the balance between oxygen availability and ATP production, known as oxygen conformance [35, 36]. A decrease in ATP production, resulting from either a lack of sufficient oxygen availability and/or an inability to utilize the oxygen though the consequences of inflammation, triggers a shutdown in metabolic activity other than those processes responsible for maintaining cellular integrity. Multiple neural and hormonal influences, acting on both mitochondrial and metabolic pathways, serve to facilitate this shutdown. The corollary is a decline in cellular functionality but by preventing a sufficient decline in intracellular ATP levels sufficient to trigger cell death pathways, the cell may be able to both survive and recover once the stress elapses. Indeed, this may represent an adaptive mechanism whereby the cell is able to enter into a state akin to hibernation or estivation following exposure to a prolonged stressor [37, 38]. In support of this notion, glycogen deposition and other markers indicative of hibernation have been reported within the myocardium of a murine mouse model [39].

Assuming this hypothesis is indeed valid, recovery from MOF depends upon restoration of healthy mitochondria through mitochondrial biogenesis [33]. Strategies to protect mitochondria or enhance their recovery may be advantageous [40], albeit with the proviso that correct timing is observed. Similarly, minimisation or avoidance of iatrogenic interventions such as antibiotics [41] and sedatives [42] that can either exac-

erbate mitochondrial damage or impair biogenesis should also increase the odds of survival.

In conclusion, sepsis is a syndrome with a highly complex pathophysiology that affects the whole organism, albeit in a variable manner and to variable degrees. Multiple pathways are either activated or suppressed by the exaggerated inflammatory process that ensues on occasion following an infectious insult. This leads to organ dysfunction that appears to be functional rather than structural, and in which a bioenergetic–metabolic shutdown is strongly implicated. Whether this shutdown offers protection and facilitates the capability of longer term cell survival is an intriguing possibility.

Corresponding address

Prof. Dr. M. Singer

Bloomsbury Institute of Intensive Care Medicine, University College London
Cruciform Building, Gower St, WC1E 6BT London, UK
m.singer@ucl.ac.uk

Compliance with ethical guidelines

Conflict of interest. P. Arina, V. Moro and M. Singer declare that they have no competing interests.

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