Mechanisms and treatment of organ failure in sepsis

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Abstract | Sepsis is a dysregulated immune response to an infection that leads to organ dysfunction. Knowledge of the pathophysiology of organ failure in sepsis is crucial for optimizing the management and treatment of patients and for the development of potential new therapies. In clinical practice, six major organ systems — the cardiovascular (including the microcirculation), respiratory, renal, neurological, haematological and hepatic systems — can be assessed and monitored, whereas others, such as the gut, are less accessible. Over the past 2 decades, considerable amounts of new data have helped improve our understanding of sepsis pathophysiology, including the regulation of inflammatory pathways and the role played by immune suppression during sepsis. The effects of impaired cellular function, including mitochondrial dysfunction and altered cell death mechanisms, on the development of organ dysfunction are also being unravelled. Insights have been gained into interactions between key organs (such as the kidneys and the gut) and organ–organ crosstalk during sepsis. The important role of the microcirculation in sepsis is increasingly apparent, and new techniques have been developed that make it possible to visualize the microcirculation at the bedside, although these techniques are only research tools at present.

Sepsis occurs when a dysregulated host response to an infection results in life-threatening tissue damage and organ dysfunction. Indeed, the presence of unexplained organ dysfunction in a patient who is acutely ill should raise suspicion of the possible presence of sepsis and encourage an appropriate diagnostic examination. This definition is a pragmatic description of sepsis that is well recognized by physicians and has recently been reaffirmed by the Sepsis-3 definitions taskforce[1]. Sepsis is a serious condition with an associated mortality of 15–20% and considerable associated short-term and long-term morbidity[2–4].

Sepsis develops as the result of a complex, dysregulated host response to infection, which is characterized not only by increased inflammation but also by immune suppression[1,5]. The effects of this inappropriate response to infection lead to cellular dysfunction and, ultimately, organ failure. Knowledge of the pathophysiology of sepsis-related organ failure might aid in the optimization of patient management and provide valuable targets for the development of new therapies. The important role of the microcirculation in septic organ dysfunction is becoming increasingly apparent[6]. The effects of impaired cellular function, including mitochondrial dysfunction[7] and altered cell-death mechanisms (for example, apoptosis, NETosis and pyroptosis), on the development of organ dysfunction are also beginning to

be unravelled[8], and the roles of gut dysfunction and the gut microbiome in sepsis-associated organ dysfunction are increasingly recognized[9].

In this Review, we discuss some of the mechanisms that are involved in sepsis-induced organ failure, with a particular emphasis on the microcirculatory abnormalities and the cellular alterations in different organs, and how these mechanisms interact to impair organ function. We also briefly discuss how an understanding of these mechanisms might influence therapeutic approaches for the treatment of patients with sepsis.

Organ-specific dysfunction in sepsis

Although any organ system can be affected in sepsis, for practical reasons largely related to the ease with which organ function can be assessed, six organ systems are usually evaluated in clinical practice and have been the most widely studied: the cardiovascular, respiratory, renal, neurological, haematological and hepatic systems (FIG. 1). Alterations in each organ system can range from mild dysfunction to complete organ failure. Importantly, any organ can fail, but the use of the word 'failure' does not mean that the altered function is irreversible. For this reason, debate exists about the use of the term 'acute kidney injury' (AKI) as an alternative to 'acute renal failure', and many clinicians prefer to use the terms 'renal dysfunction' in milder cases and 'renal failure' in more

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REVIEWS

Key points

- Organ dysfunction is an integral part of sepsis, and the presence of unexplained organ dysfunction in a patient who is acutely ill should raise suspicion of the possible presence of sepsis and encourage an appropriate diagnostic examination.
- The pathophysiology of organ dysfunction in sepsis is similar for all organs and involves complex haemodynamic and cellular mechanisms.
- The first goal in the prevention of organ dysfunction in sepsis is to restore and maintain adequate oxygen delivery to cells.
- Single-organ dysfunction in sepsis is rare, and several organs are usually affected; mortality in patients with sepsis correlates with the number of organs that are affected.
- Most organ dysfunction in sepsis is reversible.
- Current treatment for sepsis aims to limit the development of organ dysfunction by providing rapid control of infection, haemodynamic stabilization and organ support when possible to ensure recovery of organ function.

Apoptosis
A discrete form of genetically programmed cell death that results in the efficient, non-inflammatory removal of redundant, senescent, transformed or infected cells. The basic mechanisms of apoptosis are highly conserved, and, in mammalian cells, two principal pathways of apoptosis (extrinsic and intrinsic) have been described.

NETosis
A specific cell death modality of granulocyte cells (for example, neutrophils) related to the extracellular release of neutrophil extracellular traps (NETs), which are microbicidal structures comprising nuclear chromatin, histones and granular antimicrobial proteins. NETosis shares characteristics with autophagy and regulated necrosis.

Pyroptosis
A term that was initially introduced to describe an atypical cell death modality of macrophages infected with *Salmonella enterica* subsp. *enterica* serovar Typhimurium. However, further studies showed that this process is not macrophage-specific and might be triggered by numerous other bacterial or non-bacterial stimuli. Early induction of caspase 1 is a biochemical hallmark of pyroptosis.

Hypovolaemia
An abnormally low volume of blood plasma.

severe cases. However, in this Review, we use the term AKI. The term 'acute lung injury', which refers to mild acute respiratory distress syndrome (ARDS), has now been abandoned for similar reasons[10].

Importantly, dysfunction of a single organ is rare, in part because of the existence of 'organ–organ crosstalk' or interorgan crosstalk such that the failure of one organ leads to the dysfunction of another organ. Consequently, the function of several organ systems is usually disrupted simultaneously[11]. The pattern of failing organs can influence outcomes, and the greater the number of organs that are affected, the higher the mortality[11,12]. If objective quantification of the organ dysfunction is required (for example, for research purposes), the Sequential Organ Failure Assessment (SOFA) score[13] can be used. Although the SOFA score was developed as a measure of the severity of organ dysfunction, this score also has prognostic value and has been used for this purpose in many studies. The laboratory values and treatment aspects that are required for calculation of the SOFA score can be easily obtained from computerized information, and this score can now be obtained automatically on mobile devices[14]. Importantly, calculation of the various elements of the SOFA score is not necessary for the clinical management of patients.

Cardiovascular dysfunction

Arterial hypotension is the most common feature of cardiovascular dysfunction in patients with sepsis. The main factors contributing to the pathophysiology of arterial hypotension are hypovolaemia, reduced vascular tone and myocardial depression, which can be severe and is associated with global decreases in left and right ventricular ejection fractions[15]. The predominant clinical presentation in patients with sepsis-associated cardiovascular dysfunction is poor tolerance to fluid administration, which is associated with low central venous oxygen saturation ($ScvO_2$).

Respiratory dysfunction

Hypoxaemia — a decrease in the arterial partial pressure of oxygen (PaO_2) — is a hallmark of pulmonary dysfunction in patients with sepsis and is evident clinically as hyperventilation (an increased respiratory rate), which may lead to a low arterial partial pressure of carbon

dioxide ($PaCO_2$). The resulting respiratory alkalosis can be magnified if there is also metabolic (lactic and/or renal) acidosis. Treatment of hypoxaemia requires oxygen administration, and in the most severe cases, mechanical ventilation is necessary.

Renal dysfunction

Renal dysfunction in sepsis presents clinically as oliguria that is usually secondary to septic shock but sometimes also to hypovolaemia. Other factors may also contribute to renal dysfunction, including adverse effects of nephrotoxic antibiotics (for example, aminoglycosides) or exposure to contrast dyes that are used for imaging[16]. Increases in serum urea (or blood urea nitrogen) and creatinine are common, and even a minor increase in creatinine concentration is associated with worse outcomes in patients who are critically ill[17]. In the past decade, several urinary and plasma biomarkers (for example, cystatin C, neutrophil gelatinase-associated lipocalin (NGAL) and tissue inhibitor of metalloproteinases 2 (TIMP2)) for the early diagnosis of sepsis-associated renal dysfunction or for prognostic purposes have been described. Although potentially promising, the clinical efficacy of these biomarkers and their role in the diagnosis of sepsis-related renal dysfunction are unclear[18], and their availability is limited[16].

Neurological dysfunction

Cerebral dysfunction in sepsis is characterized by an altered mental state, including disorientation and confusion; although focal neurological signs are usually absent, electroencephalogram abnormalities are commonly present[19]. Coma can develop in patients with severe forms of sepsis-associated cerebral dysfunction. Importantly, sepsis-associated cerebral dysfunction can be present without other organ dysfunctions that might be associated with encephalopathy, such as hepatic failure. Patients with sepsis-associated cerebral dysfunction have high mortality and often have prolonged cognitive and functional sequelae[20].

Haematological dysfunction

The majority of patients with sepsis have coagulopathy, which ranges in severity from subtle, subclinical coagulation disorders to a prolongation of prothrombin time and activated partial thromboplastin time. Other common features of haematological dysfunction in sepsis include a low platelet count and elevated D-dimer levels. Fulminant disseminated intravascular coagulation (DIC), which is characterized by widespread thrombosis in small and midsize vessels with simultaneous haemorrhage at various sites, may occur in cases of meningococcaemia or overwhelming post-splenectomy infections. DIC is indicative of severe disease and is associated with a poor prognosis[21,22].

Hepatic dysfunction

Altered liver function in the absence of a structural hepatobiliary abnormality is common in sepsis and is related to the deleterious effects of pathogens, toxins and/or cytokines. The abnormalities in liver function are primarily reflected by an increase in bilirubin
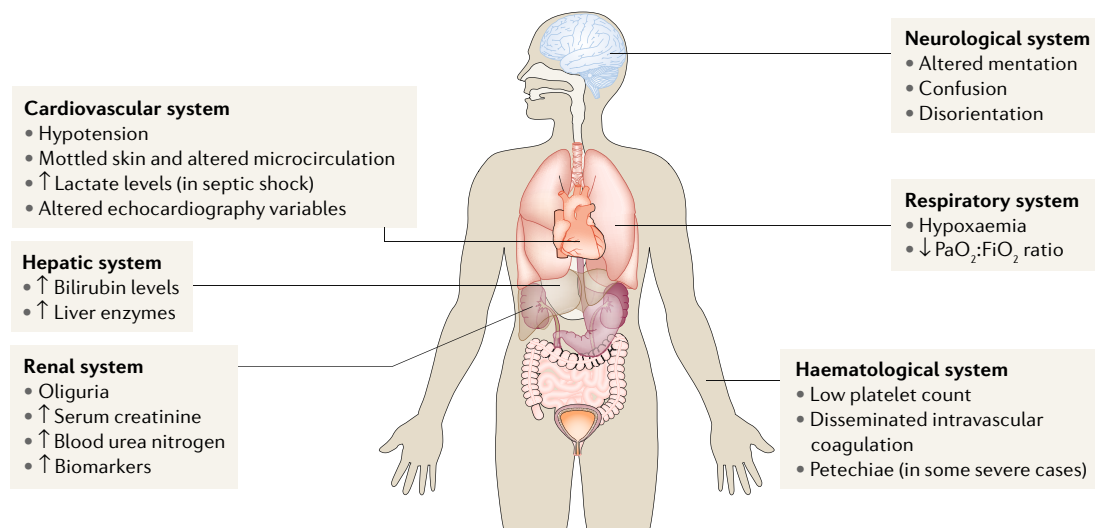
Fig. 1 | **The major organ systems that are clinically monitored in patients with sepsis.** Although dysfunction can occur in any organ in patients with sepsis, dysfunction in some organs, such as the gastrointestinal tract, is difficult to quantify. Six organ systems for which dysfunction has severe consequences or in which dysfunction is readily detectable (namely, the cardiovascular, respiratory, renal, neurological, haematological and hepatic systems) are usually monitored in clinical practice. For each organ, the signs or diagnostic characteristics that are widely used to indicate dysfunction are listed. FiO_2, fraction of inspired oxygen; PaO_2, arterial partial pressure of oxygen.

levels or transaminases, although these substances might also be released by other organs, such as the muscles. Sepsis-induced liver injury has a substantial effect on outcome in sepsis, owing mostly to altered bacterial or lipopolysaccharide (LPS) clearance, to increased release of pro-inflammatory cytokines that promote dysfunction of distal organs (such as lung injury) and to increased release of anti-inflammatory cytokines, such as IL-10 (REF.[23]).

Mechanisms of organ dysfunction

Not surprisingly, many of the mechanisms that underlie organ dysfunction in sepsis are similar for all organs and include a combination of haemodynamic and cellular alterations that develop as a result of the effects of the numerous sepsis mediators that are involved in the host response to infection (FIG. 2).

The immune response to sepsis

The inappropriate presence of microorganisms (usually bacteria) and their products induces a host immune response that is of paramount importance for the maintenance and restoration of homeostasis[24] but which can lead to tissue damage if excessive. Indeed, the greater the inflammatory response, the greater the cellular damage and thus the greater the risk of organ dysfunction. The first phase of the host response involves the detection of pathogen-associated molecular patterns (PAMPs) by innate immune cells via pattern recognition receptors. Although many PAMPs have been described, including flagellin, peptidoglycans and viral RNAs, the most widely studied is LPS (or endotoxin), which is a component of the outer membrane of Gram-negative bacteria[25]. The detection of LPS by immune cells involves multiple cofactors, including Toll-like receptor 4 (TLR4), myeloid differentiation factor 2 (MD2; also known as

LY96), CD14 and LPS-binding protein (LBP), which elicits activation of numerous downstream intracellular signalling pathways, including those involving members of the IL-1 receptor-associated kinase (IRAK) and tumour necrosis factor (TNF) receptor-associated factor (TRAF) families[26]. This signalling ultimately leads to activation of the mitogen-activated protein kinase kinase kinase (MAP3K) transforming growth factor-β-activated kinase 1 (TAK1; also known as MAP3K7)[27] and downstream activation of the JUN N-terminal kinase (JNK)–p38–extracellular-signal-regulated kinase (ERK) pathways, interferon regulatory factors (IRFs) and, importantly, the nuclear factor-κB (NF-κB) pathway[28]. Finally, activation of these pathways triggers the transcription of numerous genes that are involved in the early innate immune response[24,29].

Multiple cell-derived mediators termed damage-associated molecular patterns (DAMPs) may be released following tissue injury[30], including high mobility group protein B1 (HMGB1)[31], heat shock proteins, S100 proteins, mitochondrial DNA and metabolic molecules, such as ATP. As DAMPs can activate the same sequence of events as PAMPs, they may amplify the initial host response[30,32]. Other elements that are released during infection can influence cell function both locally and distally, including proteolytic enzymes, reactive oxygen species (ROS; which damage the vascular endothelium[33] and mitochondria[34]), microparticles (which are formed as the result of microvascular injury[35]) and neutrophil extracellular traps (NETs; which are chromatin fibre structures that are extruded by activated neutrophils and contain embedded antimicrobial peptides and enzymes, including histones)[36,37].

The immune response in sepsis is regulated in part by a neuro-immune reflex, in which the vagal nerve influences the immune response in the so-called cholinergic
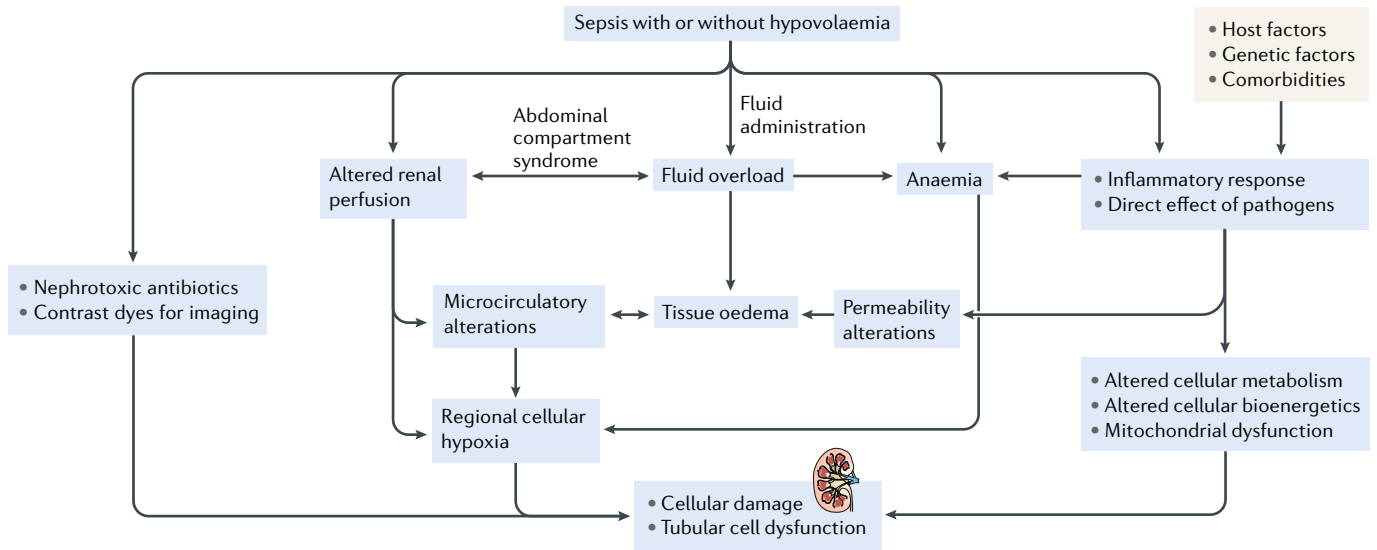
Fig. 2 | **Pathophysiology of acute kidney injury in patients with sepsis.** Multiple factors can combine to induce cellular damage in the kidneys during sepsis, including altered renal perfusion that leads to cellular hypoxia and the release of various mediators that lead to altered cellular metabolism. Cellular hypoxia might also be aggravated by anaemia, which can be caused by multiple factors, such as inflammation, blood loss and/or haemodilution. Furthermore, acute kidney injury in sepsis might, in part, be iatrogenic as a consequence of administration of nephrotoxic drugs or iodinated contrast agents that are used for imaging.

anti-inflammatory pathway[38–41]. In this process, stimulation of afferent nerve fibres by immunogenic mediators leads to efferent signalling to the spleen and other organs via the vagus nerve, resulting in the release of acetylcholine. In turn, acetylcholine activates cholinergic receptors (α7-nicotinic receptors) on macrophages, which reduces their release of pro-inflammatory cytokines. In animal models of sepsis, blockade of this reflex pathway by vagotomy increases systemic inflammation[42], but the therapeutic potential of manipulating this pathway in patients with sepsis is still controversial[41].

Circulatory abnormalities

Many patients with sepsis develop circulatory failure that results in abnormal cellular oxygen metabolism[43]. Important causes of circulatory failure include hypovolaemia, which is associated with external and internal (oedema formation) losses, and decreased vascular tone, which is mostly related to increased levels of nitric oxide and peroxynitrites[44]. Sepsis-induced myocardial depression may also occur as a result of direct toxicity of sepsis mediators to the cardiomyocyte[15]. At the systemic level, these alterations manifest as hypotension, which typically requires treatment with vasopressor agents, and as altered tissue perfusion, which is characterized by altered skin perfusion, altered renal perfusion with decreased diuresis and altered mentation with confusion and disorientation — the three clinical 'windows' of the body for the detection of altered perfusion[43]. Abnormal cellular oxygen metabolism manifests as an increase in blood lactate levels, typically to values >2 mEq per litre. Patients who require vasopressors to maintain a minimum mean arterial pressure despite adequate volume resuscitation and who have raised blood lactate levels are clinically diagnosed as having septic shock[1].

Although systemic circulatory abnormalities are fairly easy to identify, microcirculatory abnormalities, including a decrease in capillary density and an increase in heterogeneity of perfusion (with increased oxygen diffusion distance)[6], are typically also present (FIG. 3) and may persist even after global systemic variables, such as arterial pressure and oxygen delivery, seem to have been restored[45]. Various mechanisms have been implicated in sepsis-associated microcirculatory dysfunction, including direct effects of circulating mediators, vasodilation, oedema formation and microthrombus formation[6,46]. These microcirculatory abnormalities can be assessed at the bedside using dedicated techniques, such as sidestream dark-field imaging, which involves using a small hand-held microscope to visualize a patient's microcirculation (for example, in the sublingual area) in real time. Using this technique, a number of capillary perfusion indices have been developed and can be used to quantify the effects of therapeutic interventions on the microcirculation[47,48]. Bedside techniques, such as in vivo microdialysis, have also been developed to monitor tissue metabolic changes (for example, changes in lactate, pyruvate or glycerol levels) during sepsis and to assess the prognostic value of these changes[49].

Endothelial dysfunction

The endothelium forms the inner cell layer of blood vessels and the lymphatics and has a major role in controlling blood flow and vascular tone as well as being involved in immune responses[50]. Altered endothelial function is common in all affected organs in sepsis and has a key role in the pathogenesis of multiple organ failure. The permeability of the endothelial barrier is increased by disruption of normal cell–cell connections, including adherens junctions, which comprise
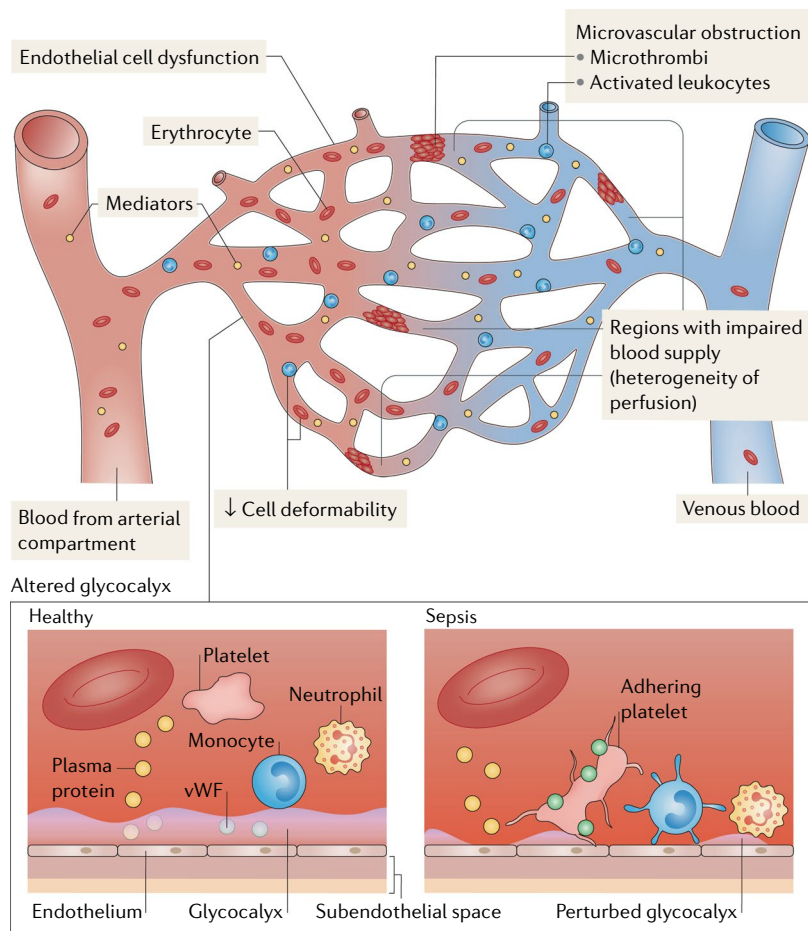
Fig. 3 | **Microvascular and cellular alterations in sepsis.** Multiple mechanisms are involved in the development of sepsis-related microvascular dysfunction, among which endothelial dysfunction (related partly to circulating host-derived and pathogen-derived mediators as well as to reactive oxygen species (ROS)) and an altered glycocalyx have major roles. The glycocalyx is a thin layer of glycosaminoglycans that covers the endothelial surface, facilitating the flow of red blood cells and limiting the adhesion of leukocytes and platelets to the endothelium. As the glycocalyx may be substantially altered during sepsis, interactions between the vascular endothelium and circulating cells (for example, leukocytes and platelets) are impaired, and leukocyte rolling and adhesion to the endothelium may occur. Activation of coagulation and the generation of microthrombi might also participate in sepsis-induced microvascular alterations, as well as alterations in erythrocyte deformability and/or their adhesion to the endothelium. All these phenomena might cause heterogeneity in microvascular blood flow, with a decrease in vascular density and non-perfused capillaries, resulting in an increased diffusion distance for oxygen and in alterations in oxygen extraction. vWF, von Willebrand factor.

Hypervolaemia
An abnormally high volume of blood plasma.

Autophagy
A process whereby organelles and portions of the cytoplasm are sequestered in vesicles (termed autophagosomes) that are delivered to lysosomes for degradation.

mainly vascular endothelial cadherin, and tight junctions (the zonula occludens), which comprise mainly occludins and claudins[5,51]. This increased permeability promotes oedema formation and associated complications, including reduced microvascular perfusion. Thrombin and matrix metalloproteinase 1 (MMP1) also contribute to endothelial dysfunction via the activation of proteinase-activated receptor 1 (PAR1)[52]. Other molecules that are implicated in endothelial disruption in sepsis include vascular endothelial growth factor (VEGF), sphingosine 1-phosphate (S1P) and angiopoietin 1 (REF.[51]).

The endothelial glycocalyx (a layer on the outer surface of the cell comprising oligosaccharides, glycoproteins and glycolipids) is also disrupted early in the sepsis

process, which further increases endothelial permeability and promotes oedema formation[53].

The increased risk of oedema in patients with sepsis highlights the importance of appropriate fluid management in these patients[54]. At one extreme, hypovolaemia can result in decreased tissue perfusion that can lead to organ dysfunction (FIG. 4). At the other extreme, hypervolaemia is associated with oedema formation that might result in altered organ function (FIG. 4). Indeed, a high central venous pressure that results in venous congestion might lead to a high venous pressure in all organs, including the kidneys, and a high central venous pressure is directly related to the severity of AKI[55]. Oedema is even greater in the presence of permeability alterations that are secondary to the inflammatory response.

A number of studies have reported an association between a more positive fluid balance and mortality risk in sepsis[56–58]. In a study of 173 patients with sepsis who were admitted to the intensive care unit (ICU) at Erasme Hospital (Belgium), a positive fluid balance was independently associated with higher mortality (adjusted HR for every 1 ml per kg increase 1.014, 95% CI 1.007–1.022, $P < 0.001$)[56]. The fact that this study was conducted in a single-centre might be viewed as a limitation but could also be considered a strength as it resulted in less heterogeneity in the management of the participants. An analysis that used data from >1,800 patients enrolled in the multicentre Intensive Care Over Nations (ICON) study reported that a higher cumulative fluid balance 3 days after admission to the ICU was independently associated with an increase in the hazard of death[58]. Of note, as optimal fluid requirements can vary over time, it would be naive to simply randomly assign patients to treatment groups in studies comparing liberal with restrictive fluid strategies; instead, fluid strategies should be individualized and be flexible over time.

These elements of fluid imbalance can influence long-term outcomes in sepsis. In the well-known Fluid and Catheter Treatment Trial (FACTT), in which two fluid management strategies were compared in stabilized patients with ARDS, the more restrictive of the two strategies was associated with a shorter duration of mechanical ventilation[59]. However, in a subsequent analysis of a subgroup of surviving patients, those who received the restrictive fluid management strategy had worse neurological recovery at 12-month follow-up, with reduced executive function and greater neurocognitive impairment, than those who received the more liberal fluid management strategy[60]. These results suggest that an overly restrictive fluid management strategy is associated with decreased cerebral perfusion and increased neurological impairment.

Cellular alterations

Cellular dysfunction in sepsis is the subject of intense research, and studies in the past 2 decades have provided important insights into numerous cellular processes that might be dysfunctional in sepsis, such as cell death pathways, intracellular recycling processes (for example, autophagy), mitochondrial dysfunction and associated phenomena (such as mitophagy and mitochondrial biogenesis), ROS biology and intracellular redox status.
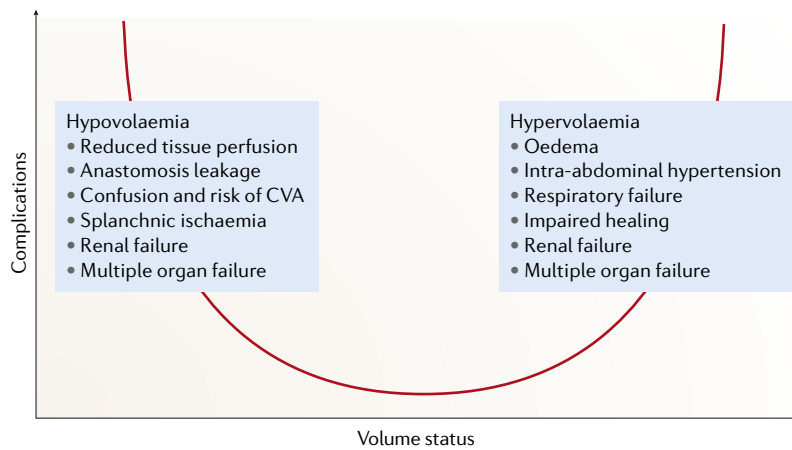
Fig. 4 | **Complications associated with hypovolaemia and hypervolaemia in sepsis.** Inadequate fluid administration can lead to an increased incidence of complications, mostly due to reduced tissue perfusion, whereas excessive fluid administration is also associated with further complications, mostly due to tissue oedema. CVA, cerebrovascular accident. Figure adapted from REF.[141], CC BY 4.0.

Cell death pathways. Various cell death pathways can be activated during sepsis, including necrosis, apoptosis, necroptosis, NETosis, pyroptosis and autophagy-induced cell death[61]. Although a comprehensive discussion of all of these pathways is beyond the scope of this Review, some important considerations must be addressed. Many of these cell death pathways are altered during sepsis, either as a direct result of the pathophysiology of sepsis and associated inflammation or via direct interaction with pathogens. These alterations may contribute to the development of sepsis-induced multiple organ failure. Necrosis is a form of non-programmed, energy-independent cell death that can be triggered by various virulence factors that are released by pathogens, although sepsis-induced alterations in organ perfusion and hypovolaemia may also promote necrosis (for example, acute renal tubular necrosis). In turn, necrosis might increase local inflammation through the extracellular release of 'alarmins' such as HMGB1 (REF.[62]).

Apoptosis is a form of programmed cell death that is dependent on the activity of caspases and cathepsins and can be triggered following exposure to stress stimuli as well as mitochondrial products such as cytochrome *c*[63]. As increased apoptosis has been observed in gut and respiratory epithelial cells, cardiomyocytes, endothelial cells and lymphocytes during sepsis, apoptosis is considered to play an important part in sepsis-induced organ dysfunction[62] and in immune dysregulation[64,65]. However, microbial products and host-derived factors can delay neutrophil apoptosis during sepsis[66] by a process that is largely dependent on the anti-apoptotic protein myeloid cell leukaemia 1 (MCL1)[67]. In turn, delayed neutrophil apoptosis can promote distal tissue injury (such as ARDS) through neutrophil accumulation and release of ROS and proteases[68]. At a local level, phagocytosed bacteria, which usually trigger neutrophil apoptosis and removal by efferocytosis in a process that favours the resolution of infection, may in some circumstances delay neutrophil apoptosis or promote necrosis or NETosis[69]. Some bacteria, such as *Listeria monocytogenes*, *Legionella*

pneumophila and *Staphylococcus aureus*, can also induce apoptosis in epithelial cells or hepatocytes, thereby contributing to organ injury[62]. In many cases, intracellular responses that are triggered by pathogen recognition involve the assembly of inflammasomes, which are macromolecular platforms at the interface between apoptosis (activation of caspase 1) and inflammation (maturation of IL-1β and IL-18)[70]. Activation of inflammasomes can also induce pyroptosis, which is a highly inflammatory form of cell death that has been observed during *Salmonella* sp. infections[71]. Alterations in other cell death functions have also been described during sepsis and are associated with the occurrence of sepsis-associated organ dysfunction. For example, deficient autophagy in rabbit liver and kidneys is associated with mitochondrial dysfunction and organ damage severity[72], and the inability to activate autophagy in the livers of mice worsens mitochondrial injury and dysfunction and ultimately promotes liver damage[73].

Mitochondrial dysfunction. The importance of mitochondrial dysfunction in the pathogenesis of sepsis-induced organ damage is increasingly recognized[34]. This importance is not too surprising, as the mitochondrion is a key organelle for multiple essential cellular processes, including ATP production, intracellular calcium homeostasis, thermoregulation and the production of ROS, reactive nitrogen species and some hormones[74]. Mitochondria are also involved in triggering of the so-called intrinsic pathway of apoptosis, which is facilitated by mitochondrial outer membrane permeabilization[75].

During sepsis, various mitochondrial functions are altered, which include reduced oxidative phosphorylation and thus ATP production, increased ROS production, increased apoptosis and altered mitochondrial biogenesis[34]. Affected mitochondria also release DAMPs, which further augment the immune response[32]. Various mechanisms have been proposed to explain mitochondrial dysfunction in sepsis, including the effects of tissue hypoxia on oxidative phosphorylation, the inhibitory effects of nitric oxide and ROS on mitochondrial respiration, the effects of sepsis-induced hormonal changes (for example, thyroid hormone) on mitochondrial function and downregulation of the genes encoding mitochondrial proteins[74]. One hypothesis to explain the altered mitochondrial function that occurs early in the sepsis response is that it is an adaptive mechanism to protect cells; for example, decreased oxidative phosphorylation might lead to reduced production of potentially harmful ROS[34,74]. Interestingly, mitophagy (the autophagic removal of damaged mitochondria) and mitochondrial biogenesis (the production of new, healthy mitochondria) might increase early in sepsis as a mechanism to limit the harmful effects of mitochondrial dysfunction[34,76,77]. Therefore, it seems probable that the various mitochondrial alterations occur at different times during the progression of sepsis. To what extent and at what stage these alterations influence organ function and how ongoing organ dysfunction further affects mitochondrial function are unclear, but these questions are the subject of intense translational research, as these complex responses represent clear targets for potential therapies to limit sepsis-induced organ dysfunction.

Necrosis
A type of premature cell death that lacks the features of apoptosis and autophagy. Although necrosis is usually considered to be uncontrolled and accidental, it may also occur in a regulated manner (regulated necrosis) and includes distinct subtypes (for example, necroptosis).

Role of the gut in sepsis

The gut was first proposed as the "motor of multiple organ failure" in the 1980s[78]. Functionally, the gut consists of a vast, single-layered epithelium that is in direct contact with a complex lymphoid immune system that includes Peyer's patches, intraepithelial lymphocytes and mesenteric lymph nodes. In a healthy host, a symbiotic relationship exists between the host and its surrounding abundant flora, the gut microbiome, which comprises over 100 trillion bacteria of varying taxonomic diversity[79]. In the past few decades, various hypotheses have been proposed to explain how the gut might be involved in the development of sepsis-associated organ dysfunction. An early hypothesis proposed that altered gut mucosal permeability, increased apoptosis of epithelial cells and altered mucus integrity enabled bacteria to directly translocate through the gut wall into the portal circulation[80]. However, data in support of this hypothesis in patients who are critically ill are conflicting[79]. An alternative hypothesis that is supported by considerable experimental evidence proposes that toxic mediators released from the injured gut mucosa are transported through the mesenteric lymph nodes and might cause dysfunction of distant organs[80].

Increasing evidence suggests that the intestinal microbiome also has a crucial role in mediating pathology in critical illness[9]. In healthy individuals, the composition of the gut microbiome can influence the cytokine response to infection[81]. In animal models, alveolar macrophages that were harvested from gut microbiota-depleted mice had reduced responsiveness to microbial stimulation and an impaired phagocytic capacity[82]. In patients who are critically ill, the composition and diversity of the intestinal microbiome are profoundly altered through a series of factors, including hypoxic injury and the use of antibiotics, proton pump inhibitors, vasopressors or parenteral feeding (FIG. 5). The effects of these microbiome alterations might negatively affect morbidity and mortality in patients with sepsis[9,83] as well as organ function. Indeed, crosstalk might occur between the gut microbiome and remote organs, such as the kidneys, partly through the effects of short-chain fatty acids, which are the end-products of fermentation of non-digestible dietary carbohydrates by the intestinal microbiota. In a mouse model of ischaemia–reperfusion-induced AKI, the administration of short-chain fatty acids attenuated renal dysfunction through various mechanisms, including epigenetic modification[84]. Although improving gut integrity might thus seem a valid approach to limit sepsis-associated organ dysfunction, difficulties in measuring or assessing gut integrity make it difficult to determine the efficacy of potential therapeutic agents. Gastric tonometry was proposed as a method to evaluate the extent of gut perfusion but has been largely abandoned because there are too many associated artefacts. A number of other surrogate markers of gut integrity have been proposed[85], including plasma or urinary intestinal-type fatty acid-binding protein (I-FABP; also known as FABP2, a marker of enterocyte damage)[86] and plasma citrulline[87], a marker of functional enterocyte mass. In prospective observational studies of patients who are critically ill, elevated I-FABP levels or decreased citrulline levels were independently associated with reduced survival[88], and catecholamine use, which indicates greater disease severity, was associated with raised I-FABP concentrations[89].

Inter-organ crosstalk

As discussed earlier, the failure of one organ can lead to the dysfunction of another organ via inter-organ crosstalk, in which the dysfunction of one organ influences the function of another. This crosstalk probably occurs between all organs, but in this Review, we focus on the kidney. AKI might affect heart and lung functions when associated with oliguria (or even anuria) and overt fluid overload. Another clear mechanism by which AKI might affect the function of other organs is through the impaired elimination of toxins and metabolites, which then influence the correct functioning of other organ systems. For example, AKI induced by ischaemia in mice is associated with increased levels of IL-6 (REF.[90]), which can cause lung inflammation and impair lung function[91,92]. Bilateral nephrectomy in mice resulted in similar increases in IL-6 and in pulmonary dysfunction[93]. Elevated IL-6 levels after renal ischaemia or bilateral nephrectomy are also associated with liver and intestinal dysfunction[94]. The brain is also affected by renal dysfunction: in mice with ischaemia-induced renal failure, increased levels of inflammatory mediators were evident in brain tissue, and the blood–brain barrier was disrupted[95]. In a prospective cohort study of 466 patients in the ICU who had respiratory failure and/or septic shock, renal failure was a risk factor for delirium and coma[96]. Renal failure can also reduce the elimination of drugs, notably antibiotics, analgesics and sedatives, and elevated levels of these drugs can result in toxicity to distant organs, such as the ototoxicity of aminoglycosides[97,98]. Furthermore, the use of renal replacement therapy (RRT) to treat renal failure can influence drug elimination, which makes the appropriate dose of medication in these patients difficult to determine[99–101].

Although the kidneys influence the function of other organs, changes in other organs can in turn affect the kidneys[102]. For example, hypoxaemia due to respiratory dysfunction is associated with reduced renal blood flow, which can potentially lead to renal dysfunction[102]. Mechanical ventilation is associated with an increased risk of renal failure[103], which is probably related to mechanical ventilation-induced release of inflammatory mediators and to associated haemodynamic changes, including increased intrathoracic pressures that limit cardiac output and oxygen delivery, and might impair right ventricular function[102,104]. Impaired renal function might also occur as a consequence of the abdominal compartment syndrome, in which excessive intra-abdominal pressure can alter renal perfusion[105].

Recovery from organ failure

In the past decade, attention has been focused on two particularly important mechanisms that are involved in the resolution of inflammation and the recovery from organ failure after sepsis. First, a number of leukocyte-derived bioactive lipids that originate from fatty acids have been implicated in the resolution of inflammatory

Gut microbiome
The human gut microbiome refers to the genomic elements of the >1,000 different species of microorganisms that are present in the digestive tract.

Gastric tonometry
A technique enabling measurement of the partial pressure of carbon dioxide inside the stomach (using a saline-filled balloon) to assess and monitor splanchnic (gut) mucosal perfusion.
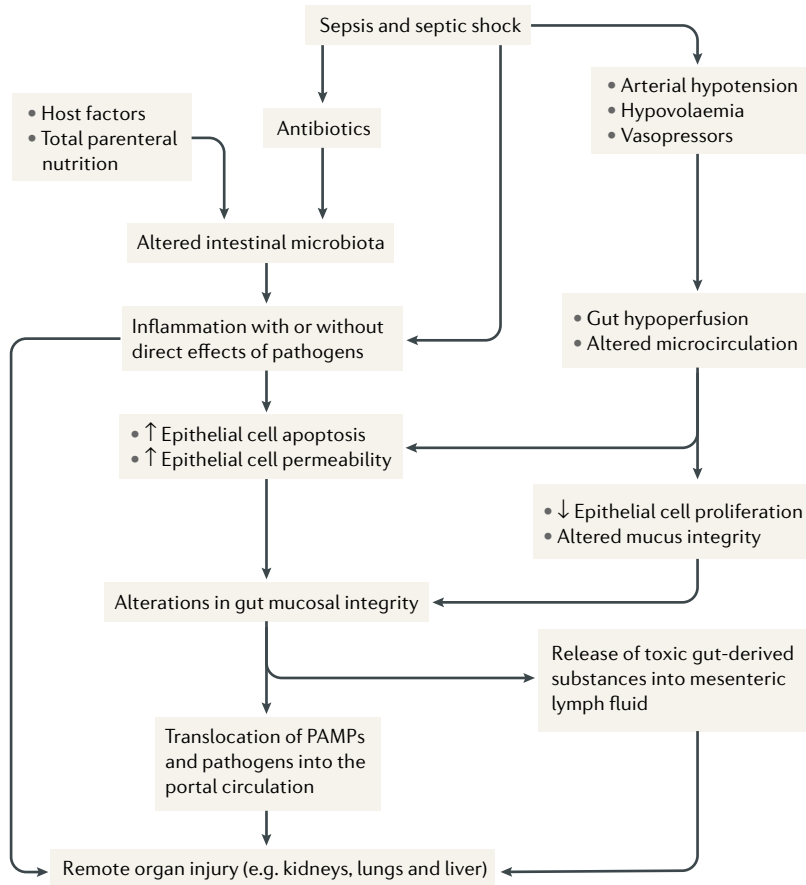
Fig. 5 | **Interplay between the gut and other organs in sepsis.** Various factors can result in gut dysfunction during sepsis, and functional disruption of the gut (for example, gut microbiome dysbiosis) can lead to tissue damage and dysfunction in other organ systems. PAMPs, pathogen-associated molecular patterns.

processes[106]. These lipid mediators, which belong to three distinct but related families termed resolvins, protectins and maresins, act as counter-regulators of the initial inflammation by stimulating the clearance of apoptotic cells and the uptake and killing of bacteria by innate immune cells, especially macrophages, and by promoting tissue repair and regeneration[107]. Second, autophagy is increasingly recognized as a crucial factor for recovery from critical illness-induced organ failure[72,108].

Biomarkers of sepsis and organ failure

Only a few markers are currently available for use at the bedside to assess the severity of organ dysfunction and inflammatory status — notably, C-reactive protein (CRP) and procalcitonin (PCT). The intensity of the inflammatory response is assessed by measuring the plasma levels of these markers. Importantly, however, changes in these markers can also reflect an inflammatory response to conditions other than sepsis; thus, assessment of these markers must be interpreted in the context of a patient's individual characteristics, including the results of a clinical examination, the patient's history and other laboratory and imaging tests. The lack of specificity of these two biomarkers means that they are more useful to exclude a diagnosis of sepsis than to

establish such a diagnosis[109]. Biomarker levels can also be useful for determining the severity of the inflammatory response, the risk of death and responses to therapy. For these roles, in particular, changes in biomarker concentrations over time are more valuable than single measurements[110,111].

Serum levels of soluble triggering receptor expressed on myeloid cells 1 (sTREM1) and soluble CD14 (also known as presepsin) and cell-surface levels of CD64 (also known as immunoglobulin G (IgG) Fc receptor 1) in neutrophils are also potential biomarkers of sepsis[112–114].

Potential therapeutic implications

Cellular alterations and circulatory abnormalities are related and interact to cause organ dysfunction and organ failure (FIG. 2). Global and distal microcirculatory abnormalities are associated with endothelial cell dysfunction, oedema formation and release of many molecules that may alter cellular function. The prevention and management of organ dysfunction in sepsis encompass three therapeutic approaches, of which two approaches — the elimination of the underlying infection and haemodynamic stabilization to ensure adequate microcirculatory perfusion — are the mainstay of current sepsis treatment. The third approach — immunomodulatory therapies that are targeted at some of the many pathways that are involved in cellular dysfunction and the sepsis response — is the subject of ongoing research.

Haemodynamics and eliminating infection

The primary goal of the first two approaches for the management of organ dysfunction in sepsis is to initiate treatment as early as possible using rapid administration of appropriate antibiotics, controlling the source of infection whenever indicated and achieving haemodynamic stabilization with fluids and with vasoactive agents when required[115]. The salvage, optimization, stabilization, de-escalation (SOSD) mnemonic summarizes the optimal management of altered tissue perfusion using fluid administration[43]. Initial resuscitation (the salvage phase) must include immediate administration of fluids and vasopressors to restore a minimum perfusion pressure. The next phase, optimization, involves more careful titration of fluids (for example, using repeated fluid challenges[43,116]) guided by some form of monitoring, typically of cardiac output and mixed venous oxygen saturation[43]. As soon as a patient's fluid status has stabilized (the stabilization phase), de-escalation must follow by the use of diuretics if spontaneous diuresis is not sufficient, although diuretics are seldom effective in this situation and ultrafiltration with RRT is generally required. Indeed, the use of diuretics in patients with sepsis-associated AKI has been controversial[117]. Although studies in animal models found that furosemide might have renoprotective effects through inhibition of the sodium–potassium–chloride cotransporter and decreased tubular medullary oxygen demand[118], the use of diuretics to prevent the development of AKI in patients is not helpful and is not recommended[119]. Similarly, the use of diuretics in

patients with AKI has no clear benefit for recovery of renal function or for mortality, unless overt fluid overload is present[119]. The importance of the de-escalation phase was illustrated in a review of 18,000 critically ill patients who were hospitalized in the eight ICUs at the University of Pittsburgh (USA): a positive fluid balance was associated with higher mortality throughout a 1-year follow-up, but this higher mortality was attenuated in patients who received RRT, suggesting that this intervention can help to prevent prolonged fluid overload and its harmful effects in some patients[120].

Noradrenaline is the vasopressor of choice to restore perfusion pressure, but angiotensin II has also been shown to be effective[121]. Once arterial pressure has been restored, oxygen delivery to the organs should be optimized, which includes maintaining arterial pressure, assuring adequate blood flow and correcting anaemia and hypoxaemia. An inotropic agent may be required to increase cardiac output when the response to fluids is limited, and dobutamine is usually the inotrope of choice. Attempts to improve the distribution of blood flow with dopamine[122] or fenoldopam[123] have been disappointing. The mnemonic PaFloV can be used to remind the clinician of the three fundamental circulatory elements that are involved in organ dysfunction: arterial pressure (Pa), organ blood flow (Flo) and blood volume (V). These three facets are intertwined and must be considered and managed together using a personalized approach that is adapted to each patient. For example, hypotension, hypovolaemia and inadequate cardiac output are all potentially very harmful for the kidneys. However, raising blood pressure alone without fluid therapy can result in excessive vasoconstriction, whereas giving excessive amounts of fluids to a patient who is profoundly vasodilated could result in excessive oedema formation, and excessive use of inotropic agents also has adverse effects, especially in patients with coronary artery disease.

Immunomodulation

Immunomodulation is the third arm of sepsis management. Initially, attention was focused on the pro-inflammatory aspects of the immune response in sepsis, mostly because the typical early pro-inflammatory cytokines TNF and IL-1 were the first to be shown to induce organ failure in animals and thus became the target for initial anti-sepsis drug development. However, anti-inflammatory strategies, including anti-TNF agents, IL-1 receptor antagonists and many others, have not been shown to influence outcomes in clinical trials in sepsis[124]. Indeed, it is increasingly acknowledged that the amplitude of the initial pro-inflammatory host response differs between individuals and that an early anti-inflammatory response occurs nearly simultaneously in sepsis[8]. Depending on a series of host-related factors, the immune system may then evolve to a progressive resolution of the inflammatory response or, by contrast, to a state of complex immune dysregulation that is sometimes termed post-aggressive immune depression[125–127]. This concept of a 'dysregulated host response', although somewhat vague, better reflects the nature of this complex immune response in which many cytokines have both pro-inflammatory and anti-inflammatory effects, rather than separate pro-inflammatory and anti-inflammatory phases, which are quite artificial, especially when taking into account the results of transcriptomic analyses[128,129].

The recognition that patients with sepsis also develop immunosuppression, including lymphopenia and decreased expression of human leukocyte antigen D-related (HLA-DR), has led to the development of immunostimulation strategies, such as treatment with interferon-γ (IFNγ), granulocyte–macrophage colony stimulating factor (GM-CSF), IL-7 or antiprogrammed cell death protein 1 (PD1) antibodies[130]. However, the balance between pro-inflammatory and anti-inflammatory components varies among patients and within each patient during the course of their disease. Consequently, generalized approaches are not optimal, and similar to anti-inflammatory strategies, an immunostimulatory strategy may not benefit all patients. Furthermore, patient mortality due to complications of sepsis-associated immunosuppression is rare. In a study of more than 1,719 patients with sepsis, development of nosocomial infections as a result of sepsis-associated immunosuppression contributed only modestly to attributable mortality[131]. The results of ongoing clinical trials should clarify whether an immunostimulatory approach proves more successful than anti-inflammatory strategies.

Monitoring the host response in sepsis

Improved monitoring of the host response (for example, by using transcriptomic and/or metabolomic profiling[132,133]) could be helpful to guide immunological therapies, but the situation is complicated by the lack of knowledge of the dynamics of specific cellular responses at different stages of sepsis[134]. For example, cellular responses can vary among cells and at different stages of sepsis, cellular responses might change quite rapidly over time and the degree of activation of circulating cells in the blood might be different from that of cells within organs or in the septic focus.

Therapies targeting specific organs

Another therapeutic approach in the treatment of sepsis is to protect individual organs. For example, the results of a randomized controlled trial that evaluated the effects of recombinant human alkaline phosphatase on renal protection in patients with sepsis are awaited with interest[135]. In an interesting study in rats, administration of thrombomodulin protected the kidneys against ischaemia[136], and soluble thrombomodulin is being tested in a multicentre randomized controlled trial in patients with sepsis-associated coagulopathy[137]. The neuropeptide ghrelin is another potential therapeutic option to protect the kidneys, as it may limit inflammation in the kidneys in sepsis conditions[138].

Therapeutic approaches to specifically protect the lungs during sepsis are also being investigated. A study in patients with ARDS that is testing the efficacy of IFNβ, which acts by increasing adenosine availability in tissues and so might help to restore endothelial integrity[139], will soon be completed[140].

Conclusions

Many factors can contribute to the development of organ dysfunction in sepsis, including cellular dysoxia, inter-organ interactions and cellular metabolic alterations. Effective treatment of sepsis requires measures to limit organ failure as quickly and effectively as possible, although such limitation is challenging given the complexity of sepsis-associated organ dysfunction. Sepsis therapy currently comprises two approaches: eradication of the initial infection and organ support (including haemodynamic stabilization). In the future, immunomodulatory therapies targeted according to an individual patient's needs will have an increasingly important role in the treatment of sepsis. Alterations in organ function are potentially entirely reversible in sepsis[108]. Patients can recover fully from even the most severe forms of ARDS, AKI or mental alterations. The long-term consequences of sepsis have been clearly characterized, but the fact that recovery can occur highlights the possibility that effective interventions can be found.

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