



HAL
open science

Energetic dysfunction in sepsis: a narrative review

Sebastien Preau, Dominique Vodovar, Boris Jung, Steve Lancel, Lara Zafrani, Aurelien Flatres, Mehdi Oualha, Guillaume Voiriot, Youenn Jouan, Jeremie Joffre, et al.

► **To cite this version:**

Sebastien Preau, Dominique Vodovar, Boris Jung, Steve Lancel, Lara Zafrani, et al.. Energetic dysfunction in sepsis: a narrative review. *Annals of Intensive Care*, 2021, 11 (1), 10.1186/s13613-021-00893-7 . hal-03277613

HAL Id: hal-03277613

<https://hal.science/hal-03277613>

Submitted on 4 Jul 2021

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution 4.0 International License

Energetic dysfunction in sepsis: a narrative review

Sebastien Preau^{1*}, Dominique Vodovar^{2,3,4}, Boris Jung⁵, Steve Lancel¹, Lara Zafrani^{6,7}, Aurelien Flatres⁸, Mehdi Oualha⁹, Guillaume Voiriot¹⁰, Youenn Jouan^{11,12}, Jeremie Joffre¹³, Fabrice Huel¹⁴, Nicolas De Prost¹⁵, Stein Silva^{16,17}, Eric Azabou¹⁸ and Peter Radermacher¹⁹

Abstract

Background: Growing evidence associates organ dysfunction(s) with impaired metabolism in sepsis. Recent research has increased our understanding of the role of substrate utilization and mitochondrial dysfunction in the pathophysiology of sepsis-related organ dysfunction. The purpose of this review is to present this evidence as a coherent whole and to highlight future research directions.

Main text: Sepsis is characterized by systemic and organ-specific changes in metabolism. Alterations of oxygen consumption, increased levels of circulating substrates, impaired glucose and lipid oxidation, and mitochondrial dysfunction are all associated with organ dysfunction and poor outcomes in both animal models and patients. The pathophysiological relevance of bioenergetics and metabolism in the specific examples of sepsis-related immunodeficiency, cerebral dysfunction, cardiomyopathy, acute kidney injury and diaphragmatic failure is also described.

Conclusions: Recent understandings in substrate utilization and mitochondrial dysfunction may pave the way for new diagnostic and therapeutic approaches. These findings could help physicians to identify distinct subgroups of sepsis and to develop personalized treatment strategies. Implications for their use as bioenergetic targets to identify metabolism- and mitochondria-targeted treatments need to be evaluated in future studies.

Keywords: Energetic dysfunction, Metabolism, Mitochondria, Mitochondrial dysfunction, Organ dysfunction, Sepsis, Septic shock, Infection

Introduction

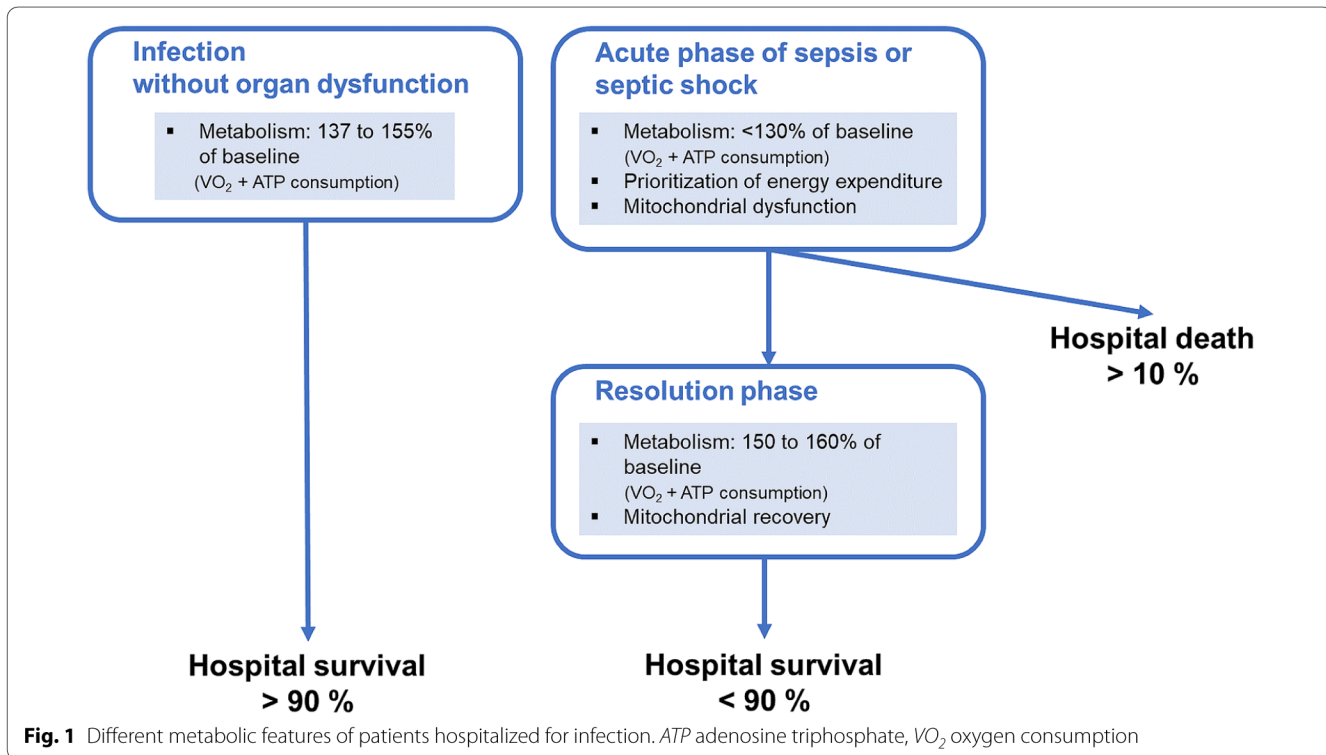
Sepsis is a well-recognized, worldwide healthcare issue defined as life-threatening organ dysfunction resulting from a dysregulated host response to an infection [1–5]. This response is generally characterized by an acute and massive release of stress hormones, leading to an overwhelming production of energy substrates in the form of glucose, fatty acids (FA), amino acids and lactate. The most severe cases tend to exhibit elevated levels of plas-matic glucose [6], triglycerides [7], and lactate [8–13],

while hypoglycaemia in combination with elevated lacta-taemia has been associated with poor outcomes [6].

Moreover, different features of oxygen (O_2) consump-tion (VO_2) characterize patients with infections accord-ing to their clinical severity (Fig. 1). In infected patients without organ dysfunction(s) and healthy humans treated with a non-lethal dose of endotoxin, systemic VO_2 and resting metabolic rate are enhanced by 37–55% com-pared with their basal metabolism [14–16]. Conversely, patients with sepsis or septic shock seem to display a less-pronounced increase in the metabolic rate from baseline (<30%) [14, 17, 18]. This metabolic attenuation has been described in patients admitted to intensive care units (ICU) for sepsis who displayed no, or only small, increases in VO_2 and energy expenditure [14] in the

*Correspondence: seb.preau@gmail.com

¹ U1167 - RID-AGE - Facteurs de Risque et Déterminants Moléculaires des Maladies Liées au Vieillissement, University Lille, Inserm, CHU Lille, Institut Pasteur de Lille, F-59000 Lille, France



absence of (tissue) hypox(aem)ia [19]. This diminished increase in these two parameters is related to the severity of sepsis [14, 17, 20], while a lack of responsiveness to the increase of systemic O_2 delivery is also associated with poorer outcome [21, 22]. The precise mechanism responsible for this attenuation of metabolic function is still a matter of debate and may be attributable to either a lack of adequate energy supply, to oxidative and nitrosative stress-related damage, or to a reprioritization of adenosine triphosphate (ATP) consumption.

Mitochondrial dysfunction participates in the pathophysiology of sepsis and is associated with patients' outcomes [23]. The key role of mitochondria in cellular homeostasis hints at a mechanistic explanation for the link between mitochondrial dysfunction and sepsis-related organ dysfunction. While the mitochondrial capacity for generating cellular ATP is decreased in sepsis, mitochondrial dysfunction is not associated with significant organ necrosis in human septic shock [24–26]. The shift in energy expenditure during sepsis, from anabolic functions like protein and nucleic acid synthesis to those essential for short-term survival such as the maintenance of ionic homeostasis [27] (i.e. Na^+/K^+ and Ca^{2+} -ATPase pumps), may preserve cells' integrity despite their dysfunction, and retain the potential for rapid recovery from organ failure among survivors [24, 26]. During the recovery phase of hospital survivors, systemic VO_2 and resting metabolic rate are enhanced

by 50–60% compared with normal basal metabolism [14, 28, 29]. A patient's ability to adequately evolve from mitochondrial dysfunction and metabolic attenuation to mitochondrial recovery and hypermetabolism is a potentially important mechanism in determining recovery during their hospital stay [2, 30].

The objectives of this review are (1) to present an integrated view of the main changes in substrate utilization by cells during sepsis; (2) to discuss the significance of mitochondrial metabolism in the course of sepsis-induced organ dysfunction; and (3) to highlight the pathophysiological relevance of energy metabolism in specific examples of sepsis-related immunodeficiency, cerebral dysfunction, cardiomyopathy, acute kidney injury (AKI), and diaphragmatic failure.

Substrate utilization for cellular energy during sepsis

Mizock has highlighted the “metabolic criteria” of stress; i.e. hypermetabolism associated with increased VO_2 , protein catabolism leading to increased urinary nitrogen loss, and insulin resistance [31]. Altered glucose metabolism comprises the key manifestations of this metabolic response, namely increased endogenous glucose production [32, 33] (unless glucose and/or insulin are exogenously supplied [33, 34]), in particular in patients with septic shock requiring catecholamine support [35–38] and impaired glucose oxidation [33, 34]. Consequently,

the predominant bedside laboratory findings are hyperglycaemia and hyperlactataemia. Although considered as a physiological stress response [31], this hyperglycaemia has marked deleterious side effects in and of itself—e.g. oxidative stress [39]—and may aggravate organ injury [40, 41]. While hyperlactataemia originates mainly from peripherally released lactate, hyperglycaemia arises from the hepatic [16] (and, during adrenergic stimulation, renal) [38, 42, 43] uptake and conversion of both lactate (i.e. the Cori cycle) and glucogenic amino acids (in particular alanine) to glucose [44, 45]; i.e. glucose formation from gluconeogenesis rather than glycogenolysis [32]. Alanine, can also directly enter the Krebs cycle with α -ketoglutarate via alanine aminotransaminase to form glutamate and pyruvate. Nevertheless, in addition to the impact of insulin resistance, hyperglycaemia can be regarded as a mirror of the metabolic capacity of the gluconeogenic tissues, i.e. the periportal hepatocytes, where the highly O_2 -dependent metabolic pathways such as gluconeogenesis and ureagenesis are located [46], and the kidney [42, 43]. Early studies described impaired hepatic glucose release, despite increased organ blood flow and O_2 uptake, in “bacteraemic burn patients with complications” [47]: it is a common clinical observation that the absence of hyperglycaemia upon catecholamine infusion and/or a sudden reduction of the amount of insulin required to achieve normoglycaemia often indicates impending liver failure. In cases of hepatic failure, the liver can no longer completely take up the circulating glucogenic amino acids. Since ureagenesis (again located in the periportal hepatocytes) is also impaired under these conditions, hepatic “detoxification” is compromised and ammonia blood levels will rise in consequence [48].

The hyperlactataemia mentioned above must not be confused [49, 50] with ischaemia-induced hyperlactataemia, which is associated with metabolic acidosis resulting from anaerobic glycolysis due to the imbalance between O_2 supply and demand in tissues [51]. In contrast, sepsis-associated hyperlactataemia has a component that is not due to “hypoxia” (i.e. impaired tissue O_2 supply [51]) or “dysoxia” (i.e. disturbed cellular O_2 utilization [52]), but instead originates from adrenergic stimulation and Na^+/K^+ -ATPase activation [53]. Perturbed O_2 utilization is at least partly due to increased superoxide anion ($O_2^{\cdot-}$) generation within mitochondria, and the subsequent impairment of electron transfer within the mitochondrial chain [54]. The $O_2^{\cdot-}$ can react with nitric oxide (NO) to form the even more toxic peroxynitrite ($ONOO^-$), which causes protein nitration detectable by increased nitrotyrosine concentrations and/or desoxyribonucleic acid (DNA) damage [55–57]. The latter will activate poly-ADP-ribose polymerase (PARP) to provide DNA repair, but this is a high-energy process and potentially contributes to

metabolic breakdown and consequent organ failure [55]. In the context of enhanced $O_2^{\cdot-}$ production, coenzyme Q10 (CoQ10—a component of the electron transport chain with antioxidant properties) plays a crucial role. Indeed, blood levels of CoQ10 are reduced in patients with sepsis or septic shock and can be restored by exogenous CoQ10 supplementation [58, 59]. Lactate released from the skeletal muscles can assume major importance in sepsis-induced, “non-dysoxic” hyperlactataemia, even in the presence of small differences in arterio-venous lactate content [50], because the contribution of muscle to total body mass is large and the vast majority of muscle cell adrenoceptors are β_2 -receptors [49, 50]. In addition, the lung can become a “lactate producer” [60, 61], whereas the splanchnic region remains an overall “lactate consumer” [35–38, 62] due to the hepatic lactate uptake and conversion to glucose [63]. Immune cell metabolic switching from oxidative phosphorylation (OXPHOS) during the quiescent state to aerobic glycolysis upon activation (see below and the glossary in Additional file 1) [64–66] also contributes to lactate release to the blood [67]; this effect is, however, quantitatively less important due to the limited total white blood cell mass. Finally, this sepsis-associated hyperlactataemia has been referred to as an adaptive phenomenon [68], which may even facilitate lactate oxidation and bioenergetic efficiency in the brain and heart [69]. The release of counter-regulatory hormones and the formation of pro-inflammatory cytokines are the main reasons for sepsis-associated metabolic disturbances [70]. Clearly, the available human data originate from studies investigating human endotoxaemia [16], but the hemodynamic, cytokine and metabolic response to endotoxin infusion in volunteers closely resembled that in patients with sepsis or septic shock [71, 72]. In addition, the so-called “triple-hormone infusion” [73, 74] allows for modelling of the metabolic response pattern, thus confirming the crucial role of the counter-regulatory hormones. This metabolic condition resembles starvation and is characterized by the breakdown of protein, carbohydrate and fat reserves [75]. Sepsis-related alterations of fat metabolism—resulting from the hormonal conditions mentioned above—are characterized by upregulation of lipolysis in white adipose tissue [16], while free FA β -oxidation may nevertheless be decreased [75]: the lipolysis-related rise in free FA blood concentrations triggers the expression of the peroxisome proliferator-activated receptor (PPAR)- α , which in turn activates ketogenesis and β -oxidation. However, sepsis may be associated with PPAR- α downregulation, so that the available free FA may not be adequately metabolized via β -oxidation, resulting in free FA accumulation [75]. Metabolomic analysis has demonstrated that this metabolic deficit seems to be due to impaired

acylcarnitine-dependent FA transport from the cytosol into the mitochondrion [76]. Sepsis-related cardiomyopathy [77], but also hospital mortality has, in part, been associated with this impaired FA oxidation [76]. Free FA accumulation may cause “lipotoxicity”, characterized by organ liver, kidney, and heart “steatosis” and, ultimately, mitochondrial injury [75]. Catecholamines assume particular importance for metabolic disturbances: all catecholamines with β -agonist properties induce “metabolic stress” [78], the extent of which relates to the substance-specific β -adrenergic potency. Due to its high β_2 -activity, adrenaline causes the most pronounced hyperlactatemic and hyperglycaemic responses [79, 80]. This hyperlactataemia may even be associated with short-term lactic acidosis [79, 81]. However, the extent of the catecholamines’ metabolic effects in relation to their immunomodulatory properties remains an open question [78, 82, 83]. Catecholamines contribute both directly and indirectly to stress-related insulin resistance [84] and while the catecholamine effect is already detectable under physi-

management of septic shock-related arterial hypotension, and the infusion rates routinely used result in a 2- to 3-fold higher concentration than observed during physiological stress conditions [86].

Changes in substrate uptake and utilization during sepsis or septic shock are summarized in Fig. 2. The main energetic impairments potentially responsible for sepsis-induced liver dysfunction are summarized in Fig. 3.

Sepsis-related mitochondria dysfunction

Mitochondria generate ATP through OXPHOS and are crucial for numerous cellular functions. Far from being isolated, independent cell structures with their own DNA, mitochondria constitute a dynamic network, the quantity (biogenesis), shape and size (fusion and fission dynamics) and degradation (mitophagy) of which are tightly regulated (see the glossary in Additional file 1). Although mitochondrial impairment has been described in human sepsis for more than 18 years [23], mitochondria-targeted management remains absent from clinical

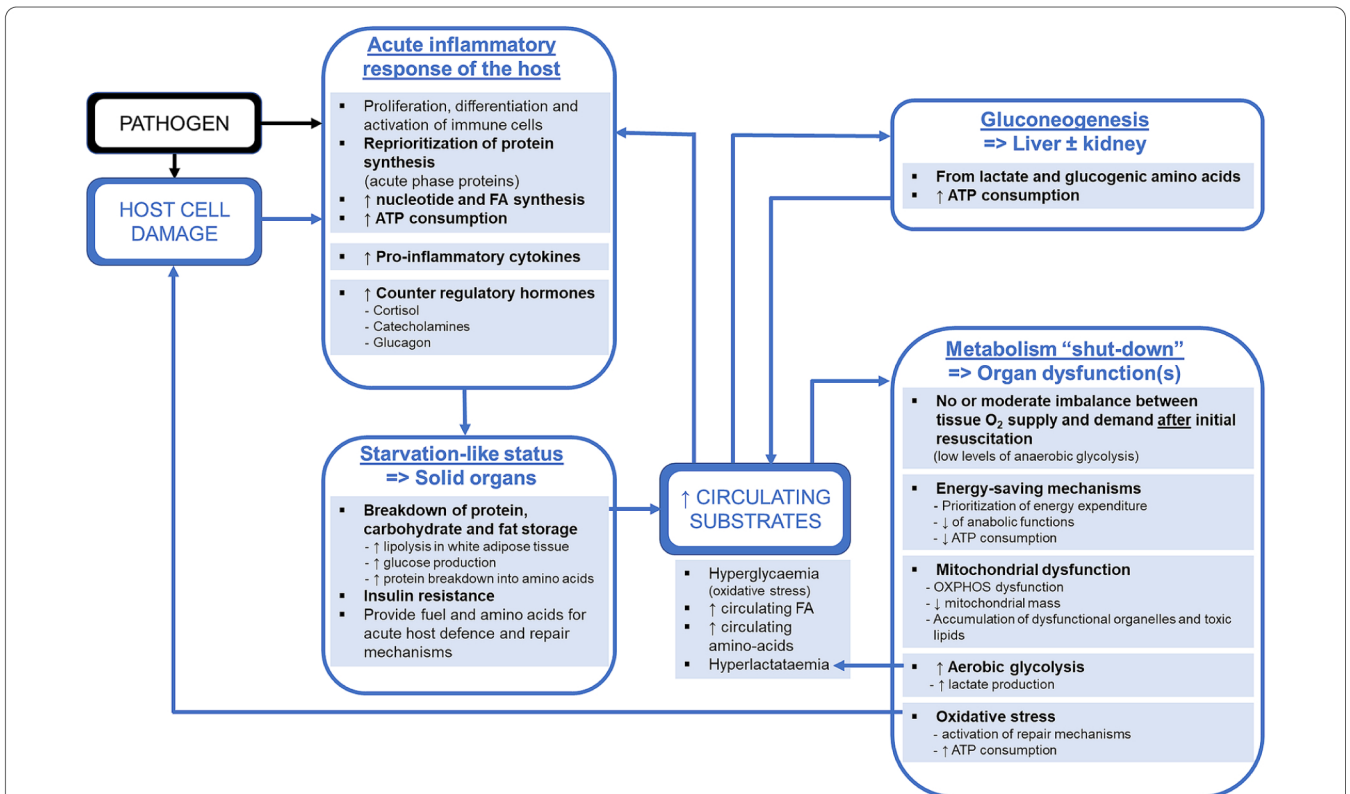


Fig. 2 Major changes in substrate uptake and utilization in patients with sepsis. *ATP* adenosine triphosphate, *FA* fatty acids, *O₂* oxygen, *OXPHOS* oxidative phosphorylation

ological conditions [45, 63], a sepsis- and/or treatment-related catecholamine desensitization due to reduced receptor density and/or affinity [85] may markedly modify this response. Noradrenaline is the first line for the

practice. Moreover, many experimental models studying sepsis-related mitochondrial dysfunction involve endotoxic mice, which display an abrupt, severe cardiovascular dysfunction and a marked hypodynamic phenotype

with significant falls in body temperature and metabolism [87, 88]. These models are poorly representative of the human condition, and caution should be applied in extrapolating findings in murine models to septic patients. Here, we describe the current knowledge of mitochondrial features in critically ill patients.

Mitochondrial haplogroups

The mitochondrial DNA, localized in the matrix, encodes 13 respiratory chain subunits. Although mitochondrial DNA comprises 16,569 base pairs, its genetic background, originating from single nucleotide polymorphisms, differs among individuals and gives rise to different haplogroups. Depending on the mitochondrial DNA haplogroup, mitochondrial complex activities may differ and impact sepsis survival. In Europe, for instance, haplotypes JT and H are associated with enhanced respiratory chain activity and are associated with better survival upon admission for sepsis [[89–91]. In Asia, the mitochondrial DNA haplogroup R represents an independent factor for the outcome of sepsis in the Chinese Han population [92]. Besides haplotypes, single point mutations in mitochondrial genes can lead to increased production of reactive O₂ species (ROS) by lymphocytes and apoptosis upon endotoxin stimulation, reinforcing the idea of a genetic component in mitochondrial susceptibility to sepsis [93].

Mitochondrial morphology

Mitochondria are distinctive double-membrane structures with an outer membrane delimiting the organelle from the cytosol, and an involuted inner membrane forming cristae that contain respiratory complex chain proteins. Their very specific ultrastructure has been evaluated by electron microscopy in different tissues from septic patients, although caution must be used in interpreting these observations since samples were often obtained from post-mortem patients. Overall, depending on the organ (skeletal muscle, heart, liver, kidneys), biopsies from septic patient displayed only limited alterations of mitochondrial morphology, including herniation of the outer membrane, vacuoles, granules and oedematous matrix [26, 40, 94–96].

Mitochondrial respiration and electron transport chain

Reductions in both expression and activity of complex I, III and IV have been reported in muscle obtained from

critically ill subjects [97–99], and may partly explain the muscle fatigue observed in ICU patients. However, it remains equivocal as to whether altered mitochondrial bioenergetic status measured within 24 h of ICU admission is causal—i.e. responsible for the patient outcome—or merely an epiphenomenon [23, 100].

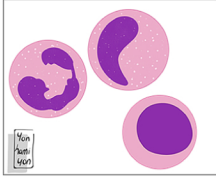
Circulating blood cell mitochondrial activity (easily measurable) has also been studied to establish whether the sepsis-related crisis in bioenergetics is detectable and could serve as a prognostic tool. Platelets from septic patients, or healthy platelets incubated with septic serum, both exhibit an increase in leak respiration (i.e. disconnected from ATP synthesis) and a higher respiratory capacity [101, 102]. Surprisingly, overall respiratory capacity is elevated in non-surviving septic patients relative to survivors and correlates with lactate levels [101, 102], suggesting a defective coupling between glucose metabolism and mitochondrial function. Conversely, cytochrome c oxidase (complex IV) activity, which decreases during sepsis [103, 104], remains higher in surviving septic patients compared to non-survivors (when measured within the first week of admission) [104]. Measuring mitochondrial function in platelets has also been reported to predict the clinical outcome in septic patients [104], but its use as a surrogate measure of mitochondrial function in other organs must be cautioned against [103]. Finally, immune cell metabolism is also of interest, though with the caveat of cell type-specific alterations of bioenergetics and metabolism (see below for details) [105]. For instance, peripheral blood mononuclear cells (PBMC) leak respiration is increased during sepsis [106, 107], meaning that mitochondrial respiration (i.e. mitochondrial VO₂) may be rapidly uncoupled [107] and disconnected from ATP synthesis [106, 108]. Consistently, respiration coupled with ATP synthesis is lowest among non-surviving septic patients [109]. Other studies indicate no mitochondrial respiratory dysfunction in PBMC [110] or even show an increase in citrate synthase-normalized activities of complex I and IV in septic monocytes [111]. In this last study, since citrate synthase activity in monocytes from septic patients was significantly lower than in controls, a relative increase in the activity of complexes I and IV may have been magnified.

Altogether, these results highlight the tissue specificity of mitochondrial dysfunction, which can also vary according to the time of the measurement and the severity of the patient's symptoms. Nevertheless, obtained *ex vivo*, the data may not precisely reflect what

(See figure on next page.)

Fig. 3 Potential sepsis-related energetic changes leading to organ dysfunction. *ATP* adenosine triphosphate, *FA* fatty acids, *OXPPOS* oxidative phosphorylation, *PPP* pentose phosphate pathway, *TEC* tubular epithelial cell

IMMUNE CELLS



- **Resting metabolism:**
 - Low levels of ATP consumption
 - Specific of cell-phenotype
- **Activation of immune cells:**
 - Reprioritization of protein synthesis
 - ↑ nucleotide and FA synthesis
 - ↑ ATP consumption
 - => aerobic glycolysis
 - => PPP / aerobic glycolysis

Energetic changes potentially leading to IMMUNE-PARALYSIS

- Cell phenotype-specific mechanisms
- Impaired metabolism plasticity

BRAIN

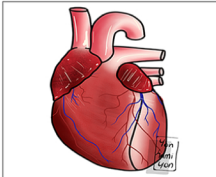


- **Basal metabolism:**
 - High levels of ATP consumption
 - Neuronal signalling
 - Maintenance of brain functions
 - => glucose oxidation / OXPHOS
- **Brain acute stimulation:**
 - Moment-to-moment variations
 - ↑ ATP consumption
 - => aerobic glycolysis

Energetic changes potentially leading to ENCEPHALOPATHY

- Mitochondrial dysfunction
- Impaired ATP production

HEART

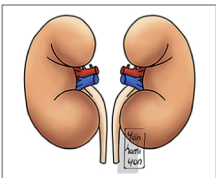


- **Basal metabolism:**
 - High levels of ATP consumption
 - Continuous rhythmic contractile activity
 - => OXPHOS
 - => 60 to 100% FA oxidation
- **Metabolism adaptation to sepsis:**
 - ↑ lactate uptake and oxidation
 - ↓ expression of genes involved in ATP consumption (e.g. sarcomere proteins)

Energetic changes potentially leading to CARDIOMYOPATHY

- Mitochondrial dysfunction
- ↓ glucose and FA oxidation
- Accumulation of toxic lipids and dysfunctional mitochondria

KIDNEY

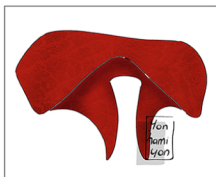


- **Basal metabolism:**
 - High levels of ATP consumption
 - Tubular reabsorption by TECs
 - => OXPHOS
- **Metabolism adaptation to sepsis:**
 - ↓ protein synthesis
 - ↑ gluconeogenesis during adrenergic stimulation

Energetic changes potentially leading to RENAL FAILURE

- Time-dependent metabolic switch from OXPHOS to a more glycolytic phenotype
- Mitochondrial dysfunction
- ↓ FA oxidation

DIAPHRAGM

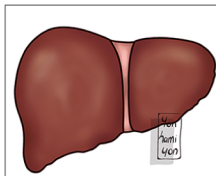


- **Basal metabolism:**
 - High levels of ATP consumption
 - Continuous rhythmic contractile activity
 - => OXPHOS

Energetic changes potentially leading to MUSCLE WEAKNESS and/or MUSCLE FATIGUE

- Mitochondrial dysfunction
- ↓ FA oxidation
- Intracellular lipid accumulation

LIVER



- **Basal metabolism:**
 - High levels of ATP consumption
 - => OXPHOS
- **Metabolic alterations during sepsis:**
 - ↑ gluconeogenesis

Energetic changes potentially leading to LIVER DYSFUNCTION

- Mitochondrial dysfunction
- ↓ FA oxidation
- Accumulation of lipids and dysfunctional mitochondria

Fig. 3 (See legend on previous page.)

happens in vivo due to changes in temperature, O₂ concentration, cytokine environment, NO concentration or light-induced nitrosylated bonds that may also change complex activities. Results may also vary according to the parameters used for normalization (i.e. citrate synthase activity, protein concentration, amount of mitochondrial DNA). Identification of other factors controlling the mitochondrial population, as well as the appropriate use of adequate experimental models, could both improve our understanding of the importance of mitochondria during sepsis.

Mitochondrial biogenesis

Mitochondrial biogenesis arises from multiple cellular mechanisms involving several transcription factors (e.g. PPAR- γ coactivator-1 α (PGC-1 α), nuclear respiratory factor 1 (NRF1) and mitochondrial transcription factor A (TFAM)) which lead to new mitochondrial component synthesis and assembly, including respiratory chain subunits, antioxidant enzymes and the DNA polymerase γ .

In post-mortem biopsies, partial mitochondrial biogenesis is present in the liver and the *rectus abdominis* skeletal muscle [112] from critically ill patients vs. controls. Indeed, while TFAM expression and respiratory complex I activity was greater in cases' liver and muscle than controls, DNA polymerase γ was only more expressed in the liver while mitochondrial DNA was not greater in either liver or muscle. Moreover, results may be influenced by the muscle selected, since no differences in those biogenesis markers were detected in *vastus lateralis* biopsies from the same study [112]. A decrease in mitochondrial content was also reported for intercostal and leg muscles of critically ill patients with sepsis-induced multiple organ failure [97]. Interestingly, despite no increase in respiratory complex expression or activity, the major transcription factor for mitochondrial biogenesis, PGC-1 α , was 2.5-fold more expressed in *vastus lateralis* from critically ill survivors compared with controls [95], whereas PGC-1 α transcription remained unchanged in non-survivors [95]. These results suggest that biogenesis activation may participate in the recovery phase.

A less invasive way to explore mitochondrial biogenesis in critical illness is available through the study of peripheral PBMC, and these studies tend to support data obtained in muscle biopsies. On admission, PGC-1 α , NRF1 and TFAM messenger ribonucleic acids (RNA) from ICU patients' PBMC were lower compared with controls, but their expression increases and remains elevated at days 3 and 5 [113], pointing to a restorative response to sepsis-induced mitochondrial depletion. The amount of mitochondrial DNA in these septic patients is consistently higher at day 5 than on admission [113], while patients with higher PGC-1 α expression left the

ICU after one week [113]. In line with these findings a multicentre, genome-wide expression database of 180 children ≤ 10 years old presenting with septic shock and 53 healthy controls, reported that cases with a high number of organ dysfunction were also those with the most downregulated expression of the mitochondrial, nuclear-encoded, respiratory chain complex gene in blood cells [114]. These data point to a compromised mitochondrial biogenesis in the more severe patients and, overall, activation of the biogenesis pathway may therefore represent a key prognosis factor in critically ill patients.

Mitochondrial fission and fusion

The mitochondrial network is governed by a dynamic fusion and fission process that maintains a healthy mitochondrial population [115] by ensuring mitochondrial DNA exchange, mitochondrial DNA integrity, and also controls the size, number, distribution and maintenance of OXPHOS capacity [116].

Mitochondrial fusion is the process of by which mitochondria merge their membranes, and is controlled mainly by mitofusins 1 and 2 (MFN1/MFN2) as well as the optic atrophy 1 (OPA1) protein. On the other hand, mitochondrial fission is the process by which mitochondria divide, a process controlled mainly by dynamin-related protein 1 (DRP1) and the fission 1 (FIS1) protein.

Very few studies have explored mitochondrial dynamics in septic patients, and data may differ according to the tissue. For instance, mitofusins, OPA1 and DRP1 proteins, but not FIS1, are more expressed in post-mortem liver tissue from critically ill patients who received conventional insulin therapy than controls [112]. We could therefore speculate that the balance among septic patients may be in favour of mitochondrial fusion, since expression of the FIS1 protein apparently remains unchanged. Increased fusion could be a cellular response to improve mitochondrial function, reduce oxidative stress [117] and compensate sepsis-induced mitochondrial dysfunction. However, it may also impair the cellular process of removing damaged mitochondria (see below).

As for the biogenesis program, results differ between muscles: MFN1, MFN2, OPA1, DRP1 and FIS1 were all upregulated in *rectus abdominis* skeletal muscle biopsies from critically ill patients, while their expression was comparable to controls in the *vastus lateralis* [112]. No changes in either mitochondrial fusion or fission events in PBMC were detected between septic patients and controls [118].

Therefore, whether the balance between fusion and fission is modified by sepsis, and whether it impacts mitochondrial function and patient survival, is far from fully

understood. Further studies are required to decipher the role of mitochondrial dynamics in humans with sepsis.

Mitophagy

Dysfunctional mitochondria can be degraded by a mitochondria-targeted process called mitophagy, which shares features with the untargeted macro-autophagy. Macro-autophagy markers in the liver and skeletal muscle are more expressed in critically ill patients compared with controls, likely due to insufficient autophagic flux [119]. While the mitophagy-related proteins BCL2/adenovirus E1B 19 kDa protein-interacting protein 3 (BNIP3) and Parkin are unaltered [119], the global reduction in the autophagic flux may contribute to the accumulation of dysfunctional organelles, and hence organ failure. Autophagy activation seems to be different in renal and cardiac biopsies between septic patients and controls [26]. Although data in humans are lacking, animal and in vitro models point to an important role of auto- and mitophagy in sepsis-induced organ dysfunction, which can have either protective or deleterious effects depending on the organ [120].

Cellular consequences of mitochondrial alterations

Oxidative stress

Under physiological conditions, mitochondria consume ~90% of the cellular O_2 , but 1–4% of the respiratory chain reactions lead to a leak of electrons that directly react with O_2 to form $O_2^{\bullet-}$, which can oxidize lipids, DNA or proteins. During sepsis, as described above, many mitochondrial-related features are altered, leading to increased generation of reactive oxygen species (ROS) [121]. This pro-inflammatory environment also triggers inducible NO synthase (NOS)-dependent NO production which, in turn, may react with $O_2^{\bullet-}$ to form the highly reactive ONOO– that has been shown to impair mitochondrial function [122]. Enzymatic defences such as the mitochondrial superoxide dismutase 2 (SOD2, also known as Mn-SOD) converts $O_2^{\bullet-}$ into hydrogen peroxide (H_2O_2), which can then be detoxified into water by the catalase or the selenium-containing glutathione peroxidase. SOD2 expression, as for PGC-1 α , is more expressed in survivors of critical illness [95], suggesting a protective role of this detoxifying enzyme. However, higher SOD activity observed in septic patients with the SOD2 gene 47C>T single nucleotide polymorphism [123] increases the risks of developing septic shock. The authors suggest that the excess of SOD2 activity may increase the production of H_2O_2 , which would amplify mitochondrial dysfunction. Glutathione and CoQ10 (known as the lipid-soluble ubiquinone, carrying electrons from complex I and II to complex III)

are also important antioxidants localized in mitochondria. Studies indicate that CoQ10 levels are significantly lower in septic shock patients than in healthy controls, which could contribute to mitochondrial dysfunction [58]. However, initial studies on oral CoQ10 administration did not report modified amounts of cytochrome c, mitochondrial DNA, mitochondrial RNA or inflammatory parameters [59]. But these results have recently been challenged, administration of 100 mg CoQ10 twice a day for seven days, added to standard sepsis treatment, having been shown to reduce inflammation, oxidative stress and mortality, and improve mitochondrial function [124].

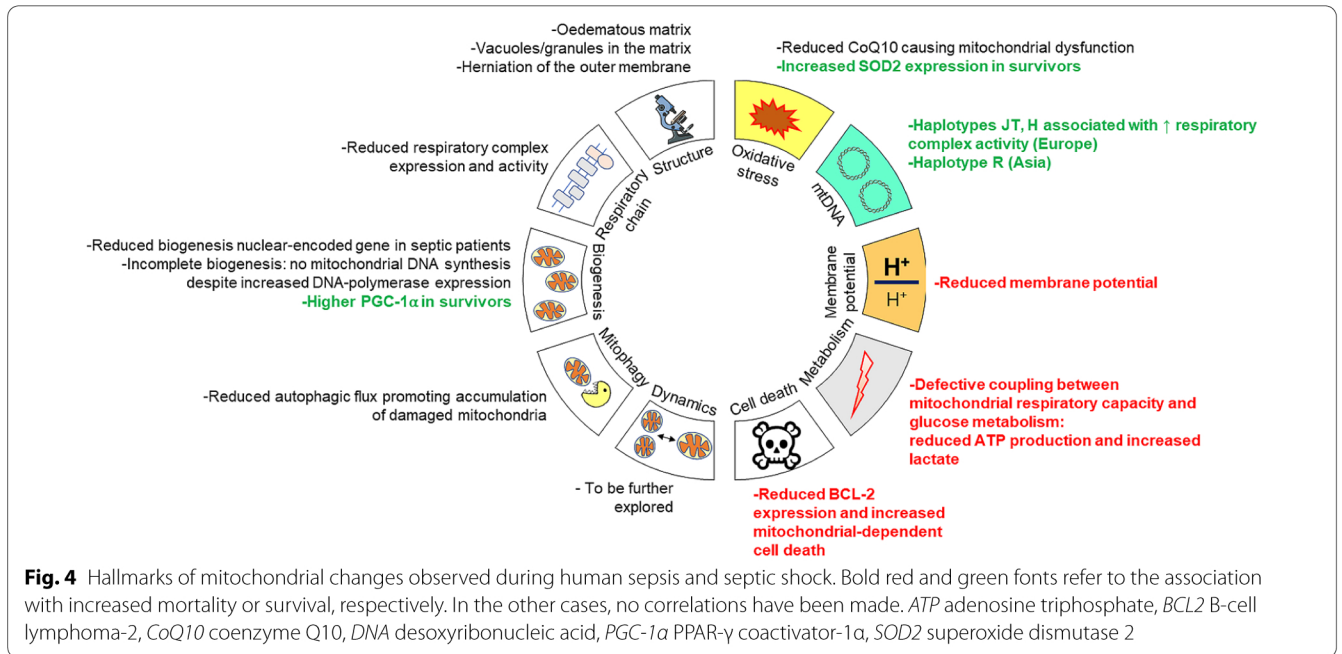
Cell death

Mitochondria may also be viewed as a signalling platform regulating cell death [125]. Upon mitochondrial stress (e.g. oxidative stress, calcium overload), they can release pro-apoptotic factors such as cytochrome c. Interestingly, total B and T lymphocytes are reduced in critically ill patients: these cells undergo apoptosis [126, 127]. Importantly, caspase-9 activation has been detected, suggesting the involvement of mitochondria [126]. Moreover, patients with sepsis or septic shock exhibit lower levels of the mitochondrial anti-apoptotic protein B-cell lymphoma 2 (BCL2) in their lymphocytes [127]. Mitochondrial depolarization, which occurs during apoptosis, is also detected in septic monocytes [128, 129]. A positive correlation has been found between the number of cells with depolarized mitochondria and mortality [129]. Moreover, sepsis survivors exhibited higher BCL2 levels [129]. Mitochondrial-dependent apoptosis may therefore contribute to the sepsis-associated immune-paralysis and in-hospital mortality.

The hallmarks of mitochondrial changes observed during human sepsis or septic shock are summarized in Fig. 4.

Immuno-metabolism

During inflammation, immune cell responses are highly dynamic and require continuous metabolic adaption to maintain a sufficient host defence. The bioenergetic demands are usually met by the interconnected metabolic pathways of glycolysis, the tricarboxylic acid (TCA) cycle and OXPHOS. Other sources, such as FA and glutamine, can fuel the TCA cycle. Some types of immune cell preferentially use aerobic glycolysis for ATP production (similar to the so-called Warburg effect in cancer cells, where glucose is converted to pyruvate and then diverted to lactate rather than entering the Krebs' cycle with carbon dioxide (CO_2) production in the presence of sufficient amounts of O_2 [130]).



Aerobic glycolysis (2 mol ATP/mol glucose) is far less efficient than complete glucose oxidation via glycolysis and the subsequent TCA cycle and OXPHOS (theoretical maximum $\approx 30\text{--}33$ mol ATP/mol glucose [131]). This difference can be at least partly offset by the rapidity of aerobic glycolysis [132]. High-throughput aerobic glycolysis subsequently increases the flux of glucose 6-phosphate through the pentose phosphate pathway (PPP), a metabolic shunt that parallels glycolysis. The PPP generates five-carbon sugars for nucleotide synthesis and reduced nicotinamide adenine dinucleotide phosphate (NADPH), crucial for the NADPH-dependent respiratory burst and FA biosynthesis (Fig. 5, reproduced with permission from Zhang et al. [105]).

The high plasticity of immune cell metabolism is crucial to their ability to fulfil different changing functions, and, consequently, loss of this plasticity has been referred to as a potential reason for sepsis-associated immune-paralysis [133, 134].

Granulocytes

Neutrophils have only a few mitochondria, and consequently, at rest, consume only small amounts of O_2 . Upon activation—that is, with initiation of chemotaxis and phagocytosis [135]—ATP turnover remains mostly unaffected [136, 137], whereas O_2 requirements markedly increase due to the respiratory burst. Glycolysis is crucial for phagocytosis and the formation of neutrophil extracellular traps (NETs) [65, 138]. The high

flux through the glycolytic pathway increases the flux through the PPP, in order to generate NADPH, which is then used by the NADPH oxidase (NOX-2) [139] to generate $O_2^{\cdot -}$, which is converted to H_2O_2 mainly via its reaction with SOD [140]. This mechanism is widely referred to as the “oxidative burst” [140].

Monocytes

Activated monocytes eliminate pathogens via phagocytosis, ROS and cytokine production (among other mechanisms), by shifting their metabolism to a more glycolytic phenotype (Fig. 5, reproduced with permission from Zhang et al. [105]), though “maintenance functions” remain dependent upon OXPHOS activation-related processes. In addition, monocytes are recruited to inflammatory tissue and continue to differentiate into two subtypes: M1 macrophages, promoting a pro-inflammatory response; or else the anti-inflammatory M2 macrophages, which play a crucial role in inflammation resolution and tissue healing. The pro-inflammatory M1 subtype relies upon aerobic glycolysis, and hence exhibits low VO_2 rates. During the resolution of inflammation, macrophages differentiate into the M2 phenotype, which primarily utilises OXPHOS metabolism fuelled by FA oxidation. In other words, the two functional macrophage states (M1 vs. M2) correspond to a time-dependent sequence of metabolic activity, with enhanced glycolysis and PPP turnover during the activation phase, and a return to TCA and OXPHOS during the resolution phase of inflammation [141, 142].

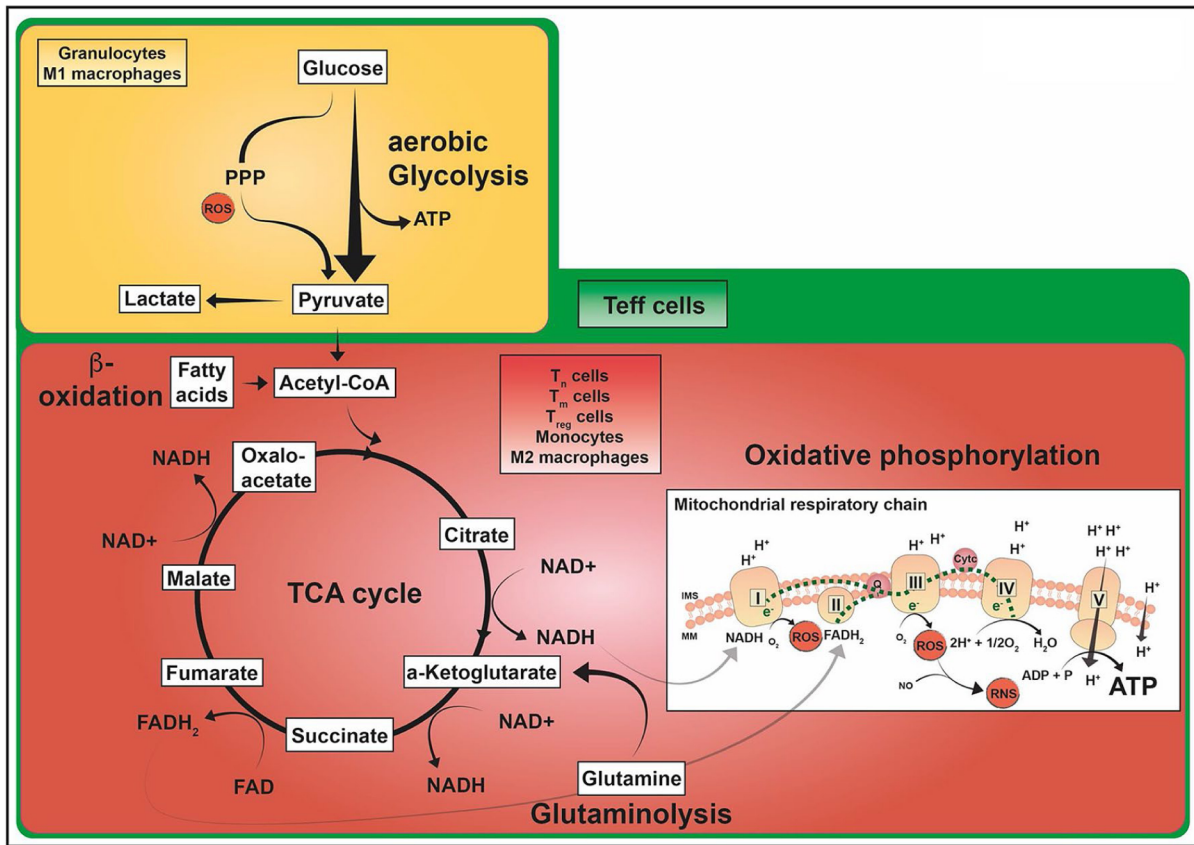


Fig. 5 ATP-producing metabolic pathways in distinct immune cell subsets. Glucose oxidation to pyruvate via glycolysis is a fast reaction generating 2 mol of ATP per mol glucose. This aerobic glycolysis is complemented by the PPP that can produce further metabolic precursor molecules and is involved in ROS production. Pyruvate can be converted to lactate or further oxidized to acetyl-CoA entering the mitochondrial TCA cycle (yellow box). The TCA cycle (red box) generates reducing equivalents NADH and FADH₂ which are utilized in the mitochondrial respiratory chain to build up the proton gradient across the mitochondrial inner membrane by complexes I–IV of the respiratory chain. As a by-product, ROS and RNS are produced. OXPHOS produces larger amounts of ATP (~30 mol/mol glucose) by complex V. Immune cells are also able to utilize substrates such as glutamine, which enters these pathways via the TCA metabolite α -ketoglutarate and FA, which are oxidized to acetyl-CoA via β -oxidation. Granulocytes and M1 macrophages (yellow box) have a highly glycolytic metabolism even when O₂ is available. Their TCA cycle and respiratory chain activity are maintained at a low level. T_{nv}, T_{mv}, and T_{reg} cells, as well as monocytes and M2 macrophages, primarily perform OXPHOS and are also able to metabolize FA and glutamine in order to fuel the TCA cycle (red box). T_{eff} cells (green box) have a highly active metabolism including all of the pathways described. ADP adenosine diphosphate, ATP adenosine triphosphate, CoA coenzyme A, FADH₂/FAD flavin adenine dinucleotide in its reduced/oxidized form, H₂O water, IMS intermembrane space, MM mitochondrial membrane, NADH/NAD⁺ nicotinamide adenine dinucleotide in its reduced/oxidized form, O₂ oxygen, OXPHOS oxidative phosphorylation, PPP pentose phosphate pathway, ROS reactive O₂ species, RNS reactive nitrogen species, TCA tricarboxylic acid cycle, T_{eff} effector T cell, T_n naïve T cell, T_m memory T cell, T_{reg} regulatory T cell. Reprinted with permission from Zhang et al. 2020 [105]

T-lymphocytes

Unstimulated, naïve T lymphocytes primarily use OXPHOS to generate ATP, and their function is related to their metabolic activity [143]. Activated T-lymphocytes rapidly proliferate and differentiate into subpopulations, such as effector T cells (T_{eff}), regulatory T cells (T_{reg}), and memory T cells (T_m). The T_{eff} cells have a low mitochondrial mass, a correspondingly low spare respiratory capacity, and generate ATP predominantly through aerobic glycolysis; in contrast, T_{reg} cells and T_m cells depend mainly on OXPHOS and FA oxidation

for ATP generation. The T_{reg} cells use oxidative metabolism, but also exhibit aerobic glycolysis, while T_m cells embody features of both naïve and effector cells. Finally, T_m cells have more mitochondrial mass and a higher spare respiratory capacity than naïve cells.

B-lymphocytes

While data on B-cell lymphocyte metabolism are scarce, recent evidence indicates that resting B-cells have lower energy requirements than resting T-cells as they consume less glucose and FA and, consequently, produce less

ATP [144]. Nevertheless, they rely primarily on OXPHOS to meet their metabolic demands and have a higher mitochondrial mass. Despite these differences in the resting state, B cells share some metabolic characteristics with T cells upon activation.

The main energetic impairments potentially responsible for sepsis-induced immune-paralysis are summarized in Fig. 3.

Sepsis-related encephalopathy

The brain's energy demands are remarkable, both in intensity and in their dynamic range from moment-to-moment. It is well established that the brain consumes a disproportionate amount of ATP compared to other organs, estimated at as much as 20% of total ATP consumption for an organ that represents only 2% of the body's mass [145]. This makes sense: the electrochemical reactions that drive neuronal signalling are energetically expensive. Neurons maintain a hyperpolarized resting membrane potential, ship proteins throughout an expansive cellular architecture, maintain an enormous membrane surface area, and continuously release and recycle synaptic vesicles at each of the trillions of synapses throughout the brain. In addition, there is an enormous dynamic variation in the ATP consumption of brain cells from moment to moment as the brain engages in its signalling.

Fuelling thought: mechanisms of brain energy homeostasis

Despite the importance of metabolic signalling for the maintenance of brain function, our understanding of how the metabolic pathways responsible for the homeostatic maintenance of cellular ATP is limited. Unlike other tissues, there is only a tiny metabolization of long-chain FA in the brain, which probably minimizes peroxidation of polyunsaturated long-chain FA. Nevertheless, at least under conditions of limited O₂ supply, neurons are capable of oxidizing ketone bodies as well as odd-numbered, medium-chain FA, the latter to maintain citric cycle intermediate levels [146, 147]. Furthermore, unlike muscles, the brain does not maintain appreciable fuel stocks in the form of glycogen. Although astrocytes maintain a glycogen reserve, resting neurons rely primarily on fuel delivered in the form of blood glucose, with a near-stoichiometric utilization of O₂ and glucose [148]. The coupling of cerebral blood flow and metabolism is the main strength of this well-tuned energy supply machinery. During neural activation, an increase in neuronal activity is associated with increased blood flow, providing both O₂ and glucose and eliminating CO₂. Nevertheless, the dynamic control of blood supply does not explain the entire story and the energy demands of neurons

throughout the brain change constantly on a cell-by-cell basis. Interestingly, evidence is accumulating that neurons must synthesize ATP as required, responding to continually changing demands of fluctuating neural activity [149]. To do so, neurons seem to take advantage of both glycolysis and OXPHOS to produce ATP from circulating glucose. In fact, aerobic glycolysis occurs during the transient metabolic response of the brain to acute stimulation [149]. Overall, like fast-twitch muscle fibres, the brain may temporarily allow glycolysis to exceed OXPHOS in the face of acute energy demand.

Septic encephalopathy: metabolic underpinnings

In sepsis, cerebral metabolism is radically altered and experimental evidence has shown that oxidative stress occurs in the brain in the early stages of sepsis, and that this results in decreased ATP synthesis [150]. Oxidative stress and the enhanced production of cytokines (interleukin-1 β and interleukin-2) seem to have neurotoxic effects on the brain, mediated by by-products of the interaction between free electrons and O₂ production such as O₂^{•-}, H₂O₂, or hydroxyl radicals. Although only a small amount of O₂ consumed is converted to ROS, these short-lived and highly reactive molecules can inflict damage on the mitochondrial electron transport chain and destroy mitochondrial structural components. For example, studies have shown increased brain SOD-to-catalase activity, leading to increased H₂O₂ production in rats during early sepsis [151]. In fact, inhibition of mitochondrial function during sepsis may be a significant cause of impaired O₂ utilization and metabolism in the brain, probably driven by NO-mediated mechanisms [151]. Bacterial toxins directly induce activation of cerebral microglia by increased expression of cell-specific targeted antigen, leading to amplified production of NO and provoking significant dysfunction in redox signalling [152]. Further studies are needed to explore the potential therapeutic use of this mechanistic knowledge in patients.

Sepsis, ATP and higher brain functions

Sepsis-induced encephalopathy is clinically characterized by an alteration of consciousness, which ranges from confusion (i.e. *delirium*) to coma and is associated with increased mortality and long-term cognitive dysfunction [150, 152, 153]. The pathophysiology of sepsis-induced, multiple organ dysfunction is not fully understood [154]. However, existing data indicate an important role for inflammatory processes and diffuse endothelial activations with microcirculatory and blood-brain barrier dysfunction, triggered by the release of inflammatory mediators. In animal models and septic patients, microglial activation has been reported in multiple

neuropathological studies [154]. Neurotoxic and neural apoptosis processes occurring during sepsis have been documented by converging neuroanatomical studies [152, 154]. Interestingly, long-term cognitive impairment in sepsis survivors seems to be related to brain mitochondrial dysfunction, and activators of autophagy, mitophagy and mitochondrial biogenesis rescue septic animals from cognitive impairment [155]. Ultimately, an understanding of the connections between basic metabolic biochemistry and higher brain functions is likely to significantly impact the clinical management of sepsis-associated encephalopathy.

The main energetic impairments potentially responsible for sepsis-induced encephalopathy are summarized in Fig. 3.

Septic cardiomyopathy

Growing evidence associates septic cardiac dysfunction with impaired metabolism and limited energy production leading to changes in substrates consumption and accumulation of toxic lipids in cardiomyocytes.

The normal heart produces approximately 60–100% of its energy from free FA and the remainder from glucose and lactate (0–20% from each) [156]. In 1987, Dhainaut et al. demonstrated that patients in septic shock undergo significant changes in myocardial substrate uptake when compared with control patients [157]: lactate uptake was increased, while free FA, glucose and ketone body uptake were all significantly decreased. Non-survivors had lower myocardial FA and glucose uptake than survivors.

Surprisingly, despite reduced cardiac lipid uptake, sepsis is associated with intracellular lipid accumulation in the myocardium of patients who died from sepsis [158]. Lipid accumulation in the heart has been attributed to an impaired FA oxidation in animal models of sepsis [159]. The decrease in both FA and glucose oxidation in the myocardium is a potential cause of reduced ATP turnover, which leads to myocardial contractile dysfunction and sometimes death [157, 159–163]. Moreover, during sepsis, the lipid accumulation (e.g. sphingosine) in cardiomyocytes may be toxic and directly provoke contractile and mitochondrial dysfunction [159, 164, 165].

Prevention or reversal of sepsis-related alteration of FA oxidation may be a therapeutic target. Interventional studies on mammal models suggest that modulating PPAR's activity may promote the transcription of β -oxidation- and mitochondrial biogenesis-related genes, and ultimately prevent mitochondria and contractile dysfunction of the heart in sepsis cases. Firstly, systemic pharmacological activation of PPAR- γ or PPAR- β/δ [159, 166, 167], and prevention of PPAR- α decrease [163], attenuated myocardial dysfunction and increased survival in murine models of sepsis.

Secondly, genetic stimulation of PGC-1 β expression, a transcriptional coactivator of PPARs which promotes cardiac FA oxidation and mitochondrial biogenesis, prevented contractile dysfunction of the heart in mice challenged with an endotoxin injection [168]. Of note, Standage et al. have shown that PPAR- α was necessary to induce the hyperdynamic cardiac response in the early stage of sepsis in a mouse model of caecal ligation and puncture [169].

Sepsis-related mitochondrial dysfunction in the myocardium is multifactorial, and detailed mechanisms underlying this dysfunction have been reviewed elsewhere [170–172]. Mitochondrial dysfunction in murine septic cardiomyopathy is characterized by both decreased rates of mitochondrial respiration coupled with ATP synthesis, and increased rates of leak respiration [173–176]. Respiratory chain malfunction has been associated with contractile defects, and prevention of OXPHOS impairment is known to prevent cardiac dysfunction in murine models of sepsis [173–177].

Since the mitochondrial capacity for generating ATP is decreased in sepsis, reducing the expression of genes involved in ATP consumption (i.e. sarcomeric contraction and excitation–contraction coupling) may be a protective mechanism against myocardial necrosis in human septic shock [24, 26, 178]. The importance of mitochondria in cellular signalling and homeostasis could provide a mechanistic explanation for the link between mitochondrial dysfunction and heart failure in septic cardiomyopathy [179]. Indeed, mitochondrial ROS production [180, 181], or externalization of other mitochondrial components in the cytosol (e.g. cytochrome c, SMAC/diablo, PGAM5, and mitochondrial DNA) [182–184], are involved in both caspase activation and inflammation, both important features in the pathophysiology of endotoxin-induced cardiac dysfunction [185, 186].

Once mitochondrial damage has occurred, recovery may depend upon the efficiency of removal and replacement of damaged mitochondria. In the septic cardiomyocyte, there is an early decrease in mitochondrial mass, in parallel with an early activation of biogenesis [166, 187–189] and mitochondrial autophagy [175, 190–192]. Genetic or pharmacological activation of mitochondrial biogenesis or autophagy prevented mitochondrial and contractile dysfunction in the heart of different murine models of sepsis [175, 177, 190, 191]. Moreover, Parkin E3 ubiquitin ligase, a key effector of mitophagy in mammal cells, was shown to be required for complete recovery of mitochondrial and cardiac function in endotoxic mice [193]. Nonetheless, the beneficial effects of autophagy stimulation and/or mitochondrial biogenesis activation are not always consistent and may, for example, be blunted in the heart of mature subjects [194, 195].

The main energetic impairments potentially responsible for sepsis-induced cardiomyopathy are summarized in Fig. 3.

Sepsis-induced acute kidney injury

The kidney has one of the highest metabolic resting rates among organs of the body [196] and, after the heart, contains the second-highest number of mitochondria [197, 198]. The kidney consumes almost 7% of the body's daily ATP expenditure [199] to perform various functions, but most of the ATP produced is used to generate ion gradients across cellular membranes to enable active reabsorption [200]. Consequently, renal tubular epithelial cells (TECs), which actively reabsorb 80% of the filtrate filtered by the glomeruli, have the highest mitochondria density and are highly impacted in the event of mitochondrial dysfunction [201].

During sepsis-induced AKI, significant metabolic adaptations occur. These include:

- **A reprioritization of ATP consumption to prevent epithelial cell death** [202]: a decrease in energy expenditure for non-vital functions is observed in TECs during sepsis. A translation shut-down (blockade of protein synthesis) occurs in murine endotoxaemia, and endotoxins and/or pro-inflammatory cytokines have been shown to downregulate renal transporters/channels [202–205]. The energy thus economized is used to maintain TECs' vital functions, including membrane Na⁺/K⁺ATPase pump that has an essential role in cell life and death [202].
- **A reprogramming of renal cell metabolism** [202]: during sepsis, a biphasic metabolic reprogramming is observed in TECs. First, sepsis induces an early and acute pro-inflammatory phase (shift of metabolism from OXPHOS towards a more glycolytic phenotype), followed by a late catabolic anti-inflammatory response (inverse shift; restoration of predominant OXPHOS metabolism) [206]. In TECs, the first switch has been described in murine endotoxaemia [206–208], while the second remains more hypothetical and is derived from studies in actively proliferating tumour cells [206]. The temporary increase in aerobic glycolysis is surprising since it is less efficient than OXPHOS for generating ATP [209]. Hypotheses regarding the usefulness of this switch include the limitation of oxidative damage (decrease in ROS production, regeneration of glutathione), and providing the opportunity for TECs to generate anti-inflammatory response/signals while still producing enough energy to prevent cell death by supplying key components necessary for vital functions and mitosis (FA, amino acids and nucleotides) [206]. Interest-

ingly, experimental studies in animals have shown that induction of OXPHOS/inhibition of aerobic glycolysis was associated with less AKI onset and reduced mortality [210, 211]. However, the harmfulness of aerobic glycolysis seems to be time-dependant: sirtuin-1 inhibition in mice coincident with caecal ligation and puncture increased mortality, while it improved survival when inhibited 24 h later (sirtuin-1 inhibits aerobic glycolysis and promotes β -oxidation of FA and OXPHOS) [212].

- **A restoration of the mitochondrial pool** [202]: mitochondrial dysfunction contributes to sepsis-induced AKI. In a murine model of sepsis, Tran et al. demonstrated mitochondrial swelling and disruption of cristae in renal TECs (which occurs prior to the onset of AKI), suggesting a pathogenic role of mitochondrial dysfunction in sepsis-induced AKI [213]. Mitochondrial biogenesis is also an important process that occurs during sepsis-induced AKI. A positive regulator of mitochondrial biogenesis, PGC-1 α , decreased in a manner proportional to the degree of renal impairment [213]. When mice recovered from sepsis, PGC-1 α returned to normal levels. Moreover, aberrant fission/fusion has been observed during sepsis-induced AKI in mice [214]. Along with mitochondrial biogenesis, mitophagy is also necessary to preserve the mitochondrial pool. Dysfunctional mitochondria can be degraded by mitophagy allowing the turnover of injured mitochondria by signaling, and engulfing them into autophagosomes for degradation. Kidney mitophagy was elevated in early stage, sepsis-induced AKI, while it was impaired in the later phase [214].

The main energetic impairments potentially responsible for sepsis-induced AKI are summarized in Fig. 3.

Sepsis-induced diaphragmatic dysfunction

The diaphragm has unique properties compared with other striated muscles:

- It contracts with a continuous rhythmic activity through the life span.
- Its resting position and length change with numerous variables such as body position, elastic recoil of the lungs, gravity effects on the chest wall, and content of the abdomen and the thorax.
- Diaphragm myofibres have a higher oxidative capacity, higher capillary density, higher maximal blood flow and resistance to fatigue than limb muscles [215].

Its higher susceptibility to inflammation [216] and metabolic stress [217] may predispose the diaphragm to the deleterious consequences of sepsis, namely atrophy and loss of force [218, 219]. In a seminal study, Hussain et al. showed that endotoxaemic shock was associated with hypercapnic respiratory failure [220]. Subsequent studies explored the different mechanisms of sepsis-induced diaphragmatic function and reported that several pathways are involved: oxidative stress, inflammation, altered proteostasis and metabolic/mitochondrial dysfunction [221]. Sepsis-induced metabolic/mitochondrial dysfunction can be summarized by several key findings. Sepsis is associated with a reduction of transcripts and protein levels for mitochondrial electron transport chain components and phosphofructokinase (the rate-limiting glycolysis enzyme), as well as a decrease in the rates of mitochondrial respiration (coupled with ATP synthesis) and phosphofructokinase enzyme activity [222]. Along with the reduction in mitochondrial function as the energy provider to the cell, endotoxaemic shock is associated with excessive production of ROS [223]. In septic rats, a burst in NO formation was associated with increased intramitochondrial $O_2^{\cdot-}$ concentrations and protein nitrosylations. The production of ROS was associated with a loss in production of diaphragm force, which, in turn, was prevented by the administration of a NOS inhibitor. Few studies have been performed in humans. Van den Berg et al. collected diaphragm biopsies performed during abdominal surgery in 36 critically ill patients, 58% of whom presented ongoing sepsis [224]. Biopsies were performed when surgery was needed during the ICU stay. The authors reported conserved mitochondrial respiration, energy status and morphology despite atrophy and reduced force. Nevertheless, mitochondrial fusion proteins (mitofusins and OPA1) and PGC1- α , which promote mitochondrial biogenesis, were decreased in critically ill patients compared with controls.

Sepsis and mechanical ventilation are both associated with lipid accumulation in the diaphragm [217, 225]. In mechanically ventilated, brain-dead organ donors, optical microscopy with oil red O staining showed lipid droplets in the diaphragm along with elevated transcripts for FA synthase and adipokines. The gene expression of a FA transporter to mitochondria, carnitine palmitoyl transferase-1, was also downregulated. The imbalance between an increased level of the metabolic sensor adenosine monophosphate-activated protein kinase (AMPK) and the decreased level of sirtuin-3, a mitochondrial sirtuin implicated in mitochondrial biogenesis and FA oxidation, was held to favour diaphragmatic metabolic oversupply [217]. This profile was reproduced in endotoxaemic rabbits [225]. Along with consequences for lipid metabolism, glucose metabolism is also impaired

during sepsis. In limb muscle biopsies from patients with ICU-acquired weakness, the insulin-dependent glucose transporter from plasma to adipocytes and muscle cells, GLUT4, was trapped in perinuclear spaces instead of being located at its usual location at the sarcolemma. This mis-translocation of GLUT4 was associated with insulin resistance and was reversed by electrical muscle stimulation [226], but whether GLUT4 mis-location also exists in the respiratory muscles with functional consequences is hypothetical.

Although there are numerous possibilities to treat sepsis-induced diaphragmatic dysfunction by targeting mitochondria, none have as yet been proven to improve prognosis. These opportunities may include mitochondrial antioxidants [227–229], drugs such as sirtuin activators (e.g. resveratrol) [230] or bezafibrate to promote mitochondrial biogenesis [231] (which is associated with survival in critically ill septic patients [95]), or even mitochondrial transplantation [232]. However, despite the abundant evidence for increased oxidative stress in patients with sepsis, treatment with antioxidants may have major potential pitfalls: (1) oxidative damage is related to the tissue rather than the blood antioxidant capacity, which may itself be inversely related to the severity of organ failure [233, 234]. This is, at least in part, due to bilirubin, a potent endogenous antioxidant but also one of the markers of liver dysfunction/failure; (2) clearly, depending on the surrounding “milieu” any antioxidant (at least of non-enzymatic origin) can become a pro-oxidant and thus eventually even cause harm, a phenomenon referred to as the “antioxidant paradox” [235, 236], with albumin being a prominent example [237, 238]; (3) both ROS and reactive nitrogen species (RNS) assume crucial importance, both as signalling molecules and for antimicrobial host defence, so that their complete eradication will most likely have deleterious consequences [239]. It is therefore not surprising that—except for the controversial combination of hydrocortisone, vitamin c and thiamine [221, 222, 240]—antioxidant interventions have so far failed to improve outcomes [223]. Finally, treatment may also include the promotion of spontaneous breathing, which was reported to enhance mitochondrial respiration [241], decrease ROS generation, optimize substrate utilization, avoid metabolic oversupply and prevent loss of diaphragmatic force [242, 243].

The main energetic impairments potentially responsible for sepsis-induced diaphragmatic dysfunction are summarized in Fig. 3.

Conclusion

Systemic and organ-specific changes in bioenergetics and metabolism characterize the acute phase of sepsis or septic shock. Alterations of VO_2 , increased levels of

circulating substrates, impaired glucose and lipid oxidation, and mitochondrial dysfunction are all associated with organ dysfunction and poor outcomes during ICU stay. Recent understandings in substrate utilization and mitochondrial dysfunction may pave the way for new diagnostic and therapeutic approaches. These findings could help physicians to identify distinct subgroups of sepsis and, subsequently, to personalize treatment strategies. Implications for their use as bioenergetic targets to identify metabolism- and mitochondria-targeted treatments need to be evaluated in future studies.

Abbreviations

AMPK: Adenosine monophosphate-activated protein kinase; AKI: Acute kidney injury; ANLS: Astrocyte-to-neuron lactate shuttle; ATP: Adenosine triphosphate; BCL2: B-cell lymphoma 2 protein; BNIP3: BCL2/adenovirus E1B 19 kDa protein-interacting protein 3; CO₂: Carbon dioxide; CoQ10: Coenzyme Q10; DO₂: O₂ delivery; DNA: Deoxyribonucleic acid; DRP1: Dynamin-related protein 1; FA: Fatty acids; FADH₂: Reduced flavin adenine dinucleotide; FIS1: Fission 1; H₂O: Water; H₂O₂: Hydrogen peroxide; ICU: Intensive care unit; MFN1 and MFN2: Mitofusins 1 and 2, respectively; NADH: Reduced nicotinamide adenine dinucleotide; NADPH: Reduced nicotinamide adenine dinucleotide phosphate; NETs: Neutrophil extracellular traps; NO: Nitric oxide; NOS: NO synthase; NOX: NADPH oxidase; NRF: Nuclear respiratory factor; O₂: Oxygen; O₂^{•-}: Superoxide anion; ONOO⁻: Peroxynitrite; OPA1: Poptic atrophy 1; OXPHOX: Oxidative phosphorylation; PBMC: Peripheral blood mononuclear cells; PGC-1: PPAR-γ coactivator-1; PPAR: Peroxisome proliferator-activated receptor; PPP: Pentose phosphate pathway; SOD: Superoxide dismutase; RNA: Ribonucleic acid; RNS: Reactive nitrogen species; ROS: Reactive O₂ species; TCA cycle: Tricarboxylic acid cycle; T_{eff}: Effector T lymphocyte; TEC: Tubular epithelial cell; TFAM: Mitochondrial transcription factor A; T_m: Memory T lymphocyte; T_n: Naive T lymphocyte; T_{reg}: Regulatory T lymphocyte; VO₂: O₂ Consumption.

Acknowledgements

We thank Dr. Michael Howsam for his assistance in editing and English proofreading of the article. We are grateful to Yon Kamiyon for his assistance in drawing the original pictures in Figure 3.

Authors' contributions

All authors met authorship criteria and participated significantly to the study; in particular, PR, DV, LZ, MO, GV, NDP, SS, EA, FH, BJ and SP involved in conception and design; PR, DV, LZ, BJ, AF, SL, SS, EA and SP wrote the article; and FH, YJ, JJ and NDP provided critical revisions to the manuscript. All authors read and approved the final manuscript.

Funding

This study was supported by the French Intensive Care Society (Société de Réanimation de Langue Française). PR was supported by the Deutsche Forschungsgemeinschaft (SFB 1149 and GRK 2203).

Availability of data and materials

Not applicable.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Author details

¹U1167 - RID-AGE - Facteurs de Risque et Déterminants Moléculaires des Maladies Liées au Vieillessement, University Lille, Inserm, CHU Lille, Institut Pasteur de Lille, F-59000 Lille, France. ²Centre AntiPoison de Paris, Hôpital Fernand Widal, APHP, 75010 Paris, France. ³Faculté de pharmacie, UMRS 1144, 75006 Paris, France. ⁴Université de Paris, UFR de Médecine, 75010 Paris, France. ⁵Medical Intensive Care Unit, Lapeyronie Teaching Hospital, Montpellier University Hospital and PhyMedExp, University of Montpellier, Montpellier, France. ⁶Médecine Intensive Réanimation, Hôpital Saint-Louis, AP-HP, Université de Paris, Paris, France. ⁷INSERM UMR 976, Hôpital Saint Louis, Université de Paris, Paris, France. ⁸PhyMedExp, University of Montpellier, Montpellier, France. ⁹Pediatric Intensive Care Unit, Necker Hospital, APHP, Centre - Paris University, Paris, France. ¹⁰Service de Médecine Intensive Réanimation, Sorbonne Université, Assistance Publique - Hôpitaux de Paris, Hôpital Tenon, Paris, France. ¹¹Service de Médecine Intensive Réanimation, CHRU Tours, Tours, France. ¹²Faculté de Médecine de Tours, INSERM U1100 Centre d'Etudes des Pathologies Respiratoires, Tours, France. ¹³Department of Anesthesia and Perioperative Care, University of California, San Francisco, CA 94143, USA. ¹⁴Réanimation médico-chirurgicale, Université de Paris, Assistance Publique - Hôpitaux de Paris, Hôpital Louis Mourier, Paris, France. ¹⁵Service de Réanimation Médicale, Hôpital Henri Mondor, Assistance Publique-Hôpitaux de Paris, Cedex 94010 Créteil, France. ¹⁶Réanimation URM CHU Purpan, Cedex 31300 Toulouse, France. ¹⁷Toulouse NeuroImaging Center INSERM1214, Cedex 31300 Toulouse, France. ¹⁸Clinical Neurophysiology and Neuromodulation Unit, Departments of Physiology and Critical Care Medicine, Raymond Poincaré Hospital, AP-HP, Inserm UMR 1173, Infection and Inflammation (2I), University of Versailles (UVSQ), Paris-Saclay University, Paris, France. ¹⁹Institut für Anästhesiologische Pathophysiologie und Verfahrensentwicklung, Universitätsklinikum, Ulm, Germany.

References

- Reinhart K, Daniels R, Kisson N, Machado FR, Schachter RD, Finfer S. Recognizing sepsis as a global health priority—a WHO resolution. *N Engl J Med*. 2017;377:414–7.
- Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA*. 2016;315:801–10.
- Seymour CW, Liu VX, Iwashyna TJ, Brunkhorst FM, Rea TD, Scherag A, et al. Assessment of clinical criteria for sepsis: For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA*. 2016;315:762–74.
- Dupuis C, Bouadma L, Ruckly S, Perozziello A, Van-Gysel D, Mageau A, et al. Sepsis and septic shock in France: incidences, outcomes and costs of care. *Ann Intensive Care*. 2020;10:145.
- Dong R, Tian H, Zhou J, Weng L, Hu X, Peng J, et al. External validity of Adult Sepsis Event's simplified eSOFA criteria: a retrospective analysis of patients with confirmed infection in China. *Ann Intensive Care*. 2020;10:14.
- Freire Jorge P, Wieringa N, de Felice E, van der Horst ICC, Oude Lansink A, Nijsten MW. The association of early combined lactate and glucose levels with subsequent renal and liver dysfunction and hospital mortality in critically ill patients. *Crit Care*. 2017;21:218.

7. Lee SH, Park MS, Park BH, Jung WJ, Lee IS, Kim SY, et al. Prognostic Implications of Serum Lipid Metabolism over Time during Sepsis. *BioMed Res Int*. 2015;2015:789298.
8. Shankar-Hari M, Phillips GS, Levy ML, Seymour CW, Liu VX, Deutschman CS, et al. Developing a New Definition and Assessing New Clinical Criteria for Septic Shock: For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA*. 2016;315:775–87.
9. Shankar-Hari M, Harrison DA, Rowan KM. Differences in Impact of Definitional Elements on Mortality Precludes International Comparisons of Sepsis Epidemiology—A Cohort Study Illustrating the Need for Standardized Reporting. *Crit Care Med*. 2016;44:2223–30.
10. Mikkelsen ME, Miliades AN, Gaieski DF, Goyal M, Fuchs BD, Shah CV, et al. Serum lactate is associated with mortality in severe sepsis independent of organ failure and shock. *Crit Care Med*. 2009;37:1670–7.
11. Nichol AD, Egi M, Pettila V, Bellomo R, French C, Hart G, et al. Relative hyperlactatemia and hospital mortality in critically ill patients: a retrospective multi-centre study. *Crit Care*. 2010;14:R25.
12. Puskarich MA, Illich BM, Jones AE. Prognosis of emergency department patients with suspected infection and intermediate lactate levels: a systematic review. *J Crit Care*. 2014;29:334–9.
13. Casserly B, Phillips GS, Schorr C, Dellinger RP, Townsend SR, Osborn TM, et al. Lactate measurements in sepsis-induced tissue hypoperfusion: results from the Surviving Sepsis Campaign database. *Crit Care Med*. 2015;43:567–73.
14. Kreyman G, Grosser S, Buggisch P, Gottschall C, Matthaei S, Greten H. Oxygen consumption and resting metabolic rate in sepsis, sepsis syndrome, and septic shock. *Crit Care Med*. 1993;21:1012–9.
15. Soop A, Albert J, Weitzberg E, Bengtsson A, Lundberg JON, Sollevi A. Complement activation, endothelin-1 and neuropeptide Y in relation to the cardiovascular response to endotoxin-induced systemic inflammation in healthy volunteers. *Acta Anaesthesiol Scand*. 2004;48:74–81.
16. Fong YM, Marano MA, Moldawer LL, Wei H, Calvano SE, Kenney JS, et al. The acute splanchnic and peripheral tissue metabolic response to endotoxin in humans. *J Clin Invest*. 1990;85:1896–904.
17. Kao CC, Guntupalli KK, Bandi V, Jahoor F. Whole-body CO₂ production as an index of the metabolic response to sepsis. *Shock*. 2009;32:23–8.
18. Liggitt SB, Renfro AD. Energy expenditures of mechanically ventilated nonsurgical patients. *Chest*. 1990;98:682–6.
19. Boekstegers P, Weidenhöfer S, Kapsner T, Werdan K. Skeletal muscle partial pressure of oxygen in patients with sepsis. *Crit Care Med*. 1994;22:640–50.
20. Zauner C, Schuster BI, Schneeweiss B. Similar metabolic responses to standardized total parenteral nutrition of septic and nonseptic critically ill patients. *Am J Clin Nutr*. 2001;74:265–70.
21. Hayes MA, Timmins AC, Yau EH, Palazzo M, Watson D, Hinds CJ. Oxygen transport patterns in patients with sepsis syndrome or septic shock: influence of treatment and relationship to outcome. *Crit Care Med*. 1997;25:926–36.
22. Dyson A, Rudiger A, Singer M. Temporal changes in tissue cardiorespiratory function during faecal peritonitis. *Intensive Care Med*. 2011;37:1192–200.
23. Brealey D, Brand M, Hargreaves I, Heales S, Land J, Smolenski R, et al. Association between mitochondrial dysfunction and severity and outcome of septic shock. *Lancet*. 2002;360:219–23.
24. Hotchkiss RS, Swanson PE, Freeman BD, Tinsley KW, Cobb JP, Matuschak GM, et al. Apoptotic cell death in patients with sepsis, shock, and multiple organ dysfunction. *Crit Care Med*. 1999;27:1230–51.
25. Hotchkiss RS, Coopersmith CM, McDunn JE, Ferguson TA. The sepsis seesaw: tilting toward immunosuppression. *Nat Med*. 2009;15:496–7.
26. Takasu O, Gaut JP, Watanabe E, To K, Fagley RE, Sato B, et al. Mechanisms of cardiac and renal dysfunction in patients dying of sepsis. *Am J Respir Crit Care Med*. 2013;187:509–17.
27. Buttgeriet F, Brand MD. A hierarchy of ATP-consuming processes in mammalian cells. *Biochem J*. 1995;312:163–7.
28. Uehara M, Plank LD, Hill GL. Components of energy expenditure in patients with severe sepsis and major trauma: a basis for clinical care. *Crit Care Med*. 1999;27:1295–302.
29. Whittle J, Molinger J, MacLeod D, Haines K, Wischmeyer PE, LEEP-COVID Study Group. Persistent hypermetabolism and longitudinal energy expenditure in critically ill patients with COVID-19. *Crit Care*. 2020;24:581.
30. Besen BAMP, Romano TG, Nassar AP, Taniguchi LU, Azevedo LCP, Mendes PV, et al. Sepsis-3 definitions predict ICU mortality in a low-middle-income country. *Ann Intensive Care*. 2016;6:107.
31. Mizock BA. Alterations in carbohydrate metabolism during stress: a review of the literature. *Am J Med*. 1995;98:75–84.
32. Dahn MS, Mitchell RA, Lange MP, Smith S, Jacobs LA. Hepatic metabolic response to injury and sepsis. *Surgery*. 1995;117:520–30.
33. Saeed M, Carlson GL, Little RA, Irving MH. Selective impairment of glucose storage in human sepsis. *Br J Surg*. 1999;86:813–21.
34. Scheeren T, Susanto F, Reinauer H, Tarnow J, Radermacher P. Prostacyclin improves glucose utilization in patients with sepsis. *J Crit Care*. 1994;9:175–84.
35. Reinelt H, Radermacher P, Fischer G, Geisser W, Wachter U, Wiedeck H, et al. Effects of a dobutamine-induced increase in splanchnic blood flow on hepatic metabolic activity in patients with septic shock. *Anesthesiology*. 1997;86:818–24.
36. Reinelt H, Radermacher P, Kiefer P, Fischer G, Wachter U, Vogt J, et al. Impact of exogenous beta-adrenergic receptor stimulation on hepato-splanchnic oxygen kinetics and metabolic activity in septic shock. *Crit Care Med*. 1999;27:325–31.
37. Kiefer P, Tugtekin I, Wiedeck H, Vogt J, Wachter U, Bracht H, et al. Effect of dopexamine on hepatic metabolic activity in patients with septic shock. *Shock*. 2001;15:427–31.
38. Kiefer P, Tugtekin I, Wiedeck H, Bracht H, Vogt J, Wachter U, et al. Hepato-splanchnic metabolic effects of the stable prostacyclin analogue iloprost in patients with septic shock. *Intensive Care Med*. 2001;27:1179–86.
39. Leverve X. Hyperglycemia and oxidative stress: complex relationships with attractive prospects. *Intensive Care Med*. 2003;29:511–4.
40. Vanhorebeek I, De Vos R, Mesotten D, Wouters PJ, De Wolf-Peeters C, Van den Berghe G. Protection of hepatocyte mitochondrial ultrastructure and function by strict blood glucose control with insulin in critically ill patients. *Lancet*. 2005;365:53–9.
41. Chao W-C, Tseng C-H, Wu C-L, Shih S-J, Yi C-Y, Chan M-C. Higher glycaemic variability within the first day of ICU admission is associated with increased 30-day mortality in ICU patients with sepsis. *Ann Intensive Care*. 2020;10:17.
42. Stumvoll M, Chintalapudi U, Perriello G, Welle S, Gutierrez O, Gerich J. Uptake and release of glucose by the human kidney. Postabsorptive rates and responses to epinephrine. *J Clin Invest*. 1995;96:2528–33.
43. Stumvoll M, Meyer C, Mitrakou A, Nadkarni V, Gerich JE. Renal glucose production and utilization: new aspects in humans. *Diabetologia*. 1997;40:749–57.
44. Träger K, Radermacher P, Debacker D, Vogt J, Jakob S, Ensinger H. Metabolic effects of vasoactive agents. *Curr Opin Anaesthesiol*. 2001;14:157–63.
45. Träger K, DeBacker D, Radermacher P. Metabolic alterations in sepsis and vasoactive drug-related metabolic effects. *Curr Opin Crit Care*. 2003;9:271–8.
46. Jungermann K, Katz N. Functional specialization of different hepatocyte populations. *Physiol Rev*. 1989;69:708–64.
47. Wilmore DW, Goodwin CW, Aulick LH, Powanda MC, Mason AD, Pruitt BA. Effect of injury and infection on visceral metabolism and circulation. *Ann Surg*. 1980;192:491–504.
48. Woźnica EA, Inglot M, Woźnica RK, Łysenko L. Liver dysfunction in sepsis. *Adv Clin Exp Med*. 2018;27:547–51.
49. Levy B. Lactate and shock state: the metabolic view. *Curr Opin Crit Care*. 2006;12:315–21.
50. Garcia-Alvarez M, Marik P, Bellomo R. Sepsis-associated hyperlactatemia. *Crit Care*. 2014;18:503.
51. Vincent J-L, De Backer D. Circulatory shock. *N Engl J Med*. 2013;369:1726–34.
52. Gattinoni L, Vasques F, Camporota L, Meessen J, Romitti F, Pasticci I, et al. Understanding lactatemia in human sepsis. Potential impact for early management. *Am J Respir Crit Care Med*. 2019;200:582–9.
53. Levy B, Gibot S, Franck P, Cravoisy A, Bollaert P-E. Relation between muscle Na⁺K⁺ ATPase activity and raised lactate concentrations in septic shock: a prospective study. *Lancet*. 2005;365:871–5.
54. Singer M. Critical illness and flat batteries. *Crit Care*. 2017;21:309.

55. Berger NA, Besson VC, Boulares AH, Bürkle A, Chiarugi A, Clark RS, et al. Opportunities for the repurposing of PARP inhibitors for the therapy of non-oncological diseases. *Br J Pharmacol*. 2018;175:192–222.
56. Lanone S, Mebazaa A, Heymes C, Henin D, Poderoso JJ, Panis Y, et al. Muscular contractile failure in septic patients: role of the inducible nitric oxide synthase pathway. *Am J Respir Crit Care Med*. 2000;162:2308–15.
57. Qian J, You H, Zhu Q, Ma S, Zhou Y, Zheng Y, et al. Nitrotyrosine level was associated with mortality in patients with acute kidney injury. *PLoS ONE*. 2013;8:e79962.
58. Donnino MW, Cocchi MN, Saliccioli JD, Kim D, Naini AB, Buettner C, et al. Coenzyme Q10 levels are low and may be associated with the inflammatory cascade in septic shock. *Crit Care*. 2011;15:R189.
59. Donnino MW, Mortensen SJ, Andersen LW, Chase M, Berg KM, Balkema J, et al. Ubiquinol (reduced Coenzyme Q10) in patients with severe sepsis or septic shock: a randomized, double-blind, placebo-controlled, pilot trial. *Crit Care*. 2015;19:275.
60. Kellum JA, Kramer DJ, Lee K, Mankad S, Bellomo R, Pinsky MR. Release of lactate by the lung in acute lung injury. *Chest*. 1997;111:1301–5.
61. Iscra F, Gullo A, Biolo G. Bench-to bedside review: lactate and the lung. *Crit Care*. 2002;6:327–9.
62. De Backer D, Creteur J, Silva E, Vincent JL. The hepatosplanchnic area is not a common source of lactate in patients with severe sepsis. *Crit Care Med*. 2001;29:256–61.
63. Bearn AG, Billing B, Sherlock S. The effect of adrenaline and noradrenaline on hepatic blood flow and splanchnic carbohydrate metabolism in man. *J Physiol*. 1951;115:430–41.
64. Haji-Michael PG, Ladrrière L, Sener A, Vincent JL, Malaisse WJ. Leukocyte glycolysis and lactate output in animal sepsis and ex vivo human blood. *Metabolism*. 1999;48:779–85.
65. Pearce EL, Pearce EJ. Metabolic pathways in immune cell activation and quiescence. *Immunity*. 2013;38:633–43.
66. Kramer PA, Ravi S, Chacko B, Johnson MS, Darley-Usmar VM. A review of the mitochondrial and glycolytic metabolism in human platelets and leukocytes: implications for their use as bioenergetic biomarkers. *Redox Biol*. 2014;2:206–10.
67. Denk S, Neher MD, Messerer DAC, Wiegner R, Nilsson B, Rittirsch D, et al. Complement C5a functions as a master switch for the pH balance in neutrophils exerting fundamental immunometabolic effects. *J Immunol*. 2017;198:4846–54.
68. Leverve XM. Lactate in the intensive care unit: pyromaniac, sentinel or fireman? *Crit Care*. 2005;9:622–3.
69. Garcia-Alvarez M, Marik P, Bellomo R. Stress hyperlactataemia: present understanding and controversy. *Lancet Diabetes Endocrinol*. 2014;2:339–47.
70. Losser M-R, Damoiseil C, Payen D. Bench-to bedside review: Glucose and stress conditions in the intensive care unit. *Crit Care*. 2010;14:231.
71. Agwunobi AO, Reid C, Maycock P, Little RA, Carlson GL. Insulin resistance and substrate utilization in human endotoxemia. *J Clin Endocrinol Metab*. 2000;85:3770–8.
72. Soop M, Duxbury H, Agwunobi AO, Gibson JM, Hopkins SJ, Childs C, et al. Euglycemic hyperinsulinemia augments the cytokine and endocrine responses to endotoxin in humans. *Am J Physiol Endocrinol Metab*. 2002;282:E1276–85.
73. Bessey PQ, Watters JM, Aoki TT, Wilmore DW. Combined hormonal infusion simulates the metabolic response to injury. *Ann Surg*. 1984;200:264–81.
74. Gore DC, O'Brien R, Reines HD. Derangements in peripheral glucose and oxygen utilization induced by catabolic hormones. *Crit Care Med*. 1993;21:1712–6.
75. Van Wyngene L, Vandewalle J, Libert C. Reprogramming of basic metabolic pathways in microbial sepsis: therapeutic targets at last? *EMBO Mol Med*. 2018;10:e8712.
76. Langley RJ, Tsalik EL, van Velkinburgh JC, Glickman SW, Rice BJ, Wang C, et al. An integrated clinico-metabolomic model improves prediction of death in sepsis. *Sci Transl Med*. 2013. <https://doi.org/10.1126/scitranslmed.3005893>.
77. Drosatos K, Lympelopoulou A, Kennel PJ, Pollak N, Schulze PC, Goldberg JJ. Pathophysiology of sepsis-related cardiac dysfunction: driven by inflammation, energy mismanagement, or both? *Curr Heart Fail Rep*. 2015;12:130–40.
78. Hartmann C, Radermacher P, Wepler M, Nußbaum B. Non-hemodynamic effects of catecholamines. *Shock*. 2017;48:390–400.
79. Levy B, Bollaert PE, Charpentier C, Nace L, Audibert G, Bauer P, et al. Comparison of norepinephrine and dobutamine to epinephrine for hemodynamics, lactate metabolism, and gastric tonometric variables in septic shock: a prospective, randomized study. *Intensive Care Med*. 1997;23:282–7.
80. De Backer D, Creteur J, Silva E, Vincent J-L. Effects of dopamine, norepinephrine, and epinephrine on the splanchnic circulation in septic shock: which is best? *Crit Care Med*. 2003;31:1659–67.
81. Meier-Hellmann A, Reinhart K, Brede DL, Specht M, Spies CD, Hanne-mann L. Epinephrine impairs splanchnic perfusion in septic shock. *Crit Care Med*. 1997;25:399–404.
82. Stolk RF, van der Poll T, Angus DC, van der Hoeven JG, Pickkers P, Kox M. Potentially inadvertent immunomodulation: norepinephrine use in sepsis. *Am J Respir Crit Care Med*. 2016;194:550–8.
83. Stolk RF, van der Pasch E, Naumann F, Schouwstra J, Bressers S, van Herwaarden AE, et al. Norepinephrine dysregulates the immune response and compromises host defense during sepsis. *Am J Respir Crit Care Med*. 2020;202:830–42.
84. Barth E, Albuszies G, Baumgart K, Matejovic M, Wachter U, Vogt J, et al. Glucose metabolism and catecholamines. *Crit Care Med*. 2007;35:S508–518.
85. Silverman HJ, Penaranda R, Orens JB, Lee NH. Impaired beta-adrenergic receptor stimulation of cyclic adenosine monophosphate in human septic shock: association with myocardial hyporesponsiveness to catecholamines. *Crit Care Med*. 1993;21:31–9.
86. Ensinger H, Stein B, Jäger O, Grünert A, Ahnefeld FW. Relationship between infusion rates, plasma concentrations, and cardiovascular and metabolic effects during the infusion of norepinephrine in healthy volunteers. *Crit Care Med*. 1992;20:1250–6.
87. Guillon A, Preau S, Aboab J, Azabou E, Jung B, Silva S, et al. Preclinical septic shock research: why we need an animal ICU. *Ann Intensive Care*. 2019;9:66.
88. Zolfaghari PS, Pinto BB, Dyson A, Singer M. The metabolic phenotype of rodent sepsis: cause for concern? *Intensive Care Med Exp*. 2013;1:25.
89. Baudouin SV, Saunders D, Tiangyou W, Elson JL, Poynter J, Pyle A, et al. Mitochondrial DNA and survival after sepsis: a prospective study. *Lancet*. 2005;366:2118–21.
90. Lorente L, Iceta R, Martín MM, López-Gallardo E, Solé-Violán J, Blanquer J, et al. Survival and mitochondrial function in septic patients according to mitochondrial DNA haplogroup. *Crit Care*. 2012;16:R10.
91. Lorente L, Martín MM, López-Gallardo E, Ferreres J, Solé-Violán J, Labarta L, et al. Septic patients with mitochondrial DNA haplogroup JT have higher respiratory complex IV activity and survival rate. *J Crit Care*. 2016;33:95–9.
92. Yang Y, Shou Z, Zhang P, He Q, Xiao H, Xu Y, et al. Mitochondrial DNA haplogroup R predicts survival advantage in severe sepsis in the Han population. *Genet Med*. 2008;10:187–92.
93. Shen X, Han G, Li S, Song Y, Shen H, Zhai Y, et al. Association between the T6459C point mutation of the mitochondrial MT-CO1 gene and susceptibility to sepsis among Chinese Han people. *J Cell Mol Med*. 2018;22:5257–64.
94. Fredriksson K, Hammarqvist F, Strigård K, Hultenby K, Ljungqvist O, Wernerman J, et al. Derangements in mitochondrial metabolism in intercostal and leg muscle of critically ill patients with sepsis-induced multiple organ failure. *Am J Physiol Endocrinol Metab*. 2006;291:E1044–50.
95. Carré JE, Orban J-C, Re L, Felsmann K, Iffert W, Bauer M, et al. Survival in critical illness is associated with early activation of mitochondrial biogenesis. *Am J Respir Crit Care Med*. 2010;182:745–51.
96. Watanabe E, Muenzer JT, Hawkins WG, Davis CG, Dixon DJ, McDunn JE, et al. Sepsis induces extensive autophagic vacuolization in hepatocytes: a clinical and laboratory-based study. *Lab Invest*. 2009;89:549–61.
97. Fredriksson K, Tjäder I, Keller P, Petrovic N, Ahlman B, Schéele C, et al. Dysregulation of mitochondrial dynamics and the muscle transcriptome in ICU patients suffering from sepsis induced multiple organ failure. *PLoS ONE*. 2008;3:e3686.
98. Gasparetto A, Corbucci GG, Candiani A, Gohil K, Edwards RH. Effect of tissue hypoxia and septic shock on human skeletal muscle mitochondria. *Lancet*. 1983;2:1486.

99. Jirutková K, Krajčová A, Ziak J, Fric M, Waldauf P, Džupa V, et al. Mitochondrial function in skeletal muscle of patients with protracted critical illness and ICU-acquired weakness. *Crit Care*. 2015;19:448.
100. Svistunenko DA, Davies N, Brealey D, Singer M, Cooper CE. Mitochondrial dysfunction in patients with severe sepsis: an EPR interrogation of individual respiratory chain components. *Biochim Biophys Acta*. 2006;1757:262–72.
101. Puskarich MA, Kline JA, Watts JA, Shirey K, Hosler J, Jones AE. Early alterations in platelet mitochondrial function are associated with survival and organ failure in patients with septic shock. *J Crit Care*. 2016;31:63–7.
102. Sjövall F, Morota S, Hansson MJ, Friberg H, Gnaiger E, Elmér E. Temporal increase of platelet mitochondrial respiration is negatively associated with clinical outcome in patients with sepsis. *Crit Care*. 2010;14:R214.
103. Protti A, Fortunato F, Caspani ML, Pluder M, Lucchini V, Grimoldi N, et al. Mitochondrial changes in platelets are not related to those in skeletal muscle during human septic shock. *PLoS ONE*. 2014;9:e96205.
104. Lorente L, Martín MM, López-Gallardo E, Blanquer J, Solé-Violán J, Labarta L, et al. Decrease of oxidative phosphorylation system function in severe septic patients. *J Crit Care*. 2015;30:935–9.
105. Zhang X, Zink F, Hezel F, Vogt J, Wachter U, Wepler M, et al. Metabolic substrate utilization in stress-induced immune cells. *Intensive Care Med Exp*. 2020;8:28.
106. Belikova I, Lukaszewicz AC, Faivre V, Damoiseil C, Singer M, Payen D. Oxygen consumption of human peripheral blood mononuclear cells in severe human sepsis. *Crit Care Med*. 2007;35:2702–8.
107. Weiss SL, Selak MA, Tuluc F, Perales Villarreal J, Nadkarni VM, Deutschman CS, et al. Mitochondrial dysfunction in peripheral blood mononuclear cells in pediatric septic shock. *Pediatr Crit Care Med*. 2015;16:e4–12.
108. Clere-Jehl R, Helms J, Kassem M, Le Borgne P, Delabranche X, Charles A-L, et al. Septic shock alters mitochondrial respiration of lymphoid cell-lines and human peripheral blood mononuclear cells: the role of plasma. *Shock*. 2019;51:97–104.
109. Japiassú AM, Santiago APSA, da d'Avila JCP, Garcia-Souza LF, Galina A, Castro Faria-Neto HC, et al. Bioenergetic failure of human peripheral blood monocytes in patients with septic shock is mediated by reduced F1Fo adenosine-5'-triphosphate synthase activity. *Crit Care Med*. 2011;39:1056–63.
110. Sjövall F, Morota S, Persson J, Hansson MJ, Elmér E. Patients with sepsis exhibit increased mitochondrial respiratory capacity in peripheral blood immune cells. *Crit Care*. 2013;17:R152.
111. Merz TM, Pereira AJ, Schürch R, Scheffold JC, Jakob SM, Takala J, et al. Mitochondrial function of immune cells in septic shock: a prospective observational cohort study. *PLoS ONE*. 2017;12:e0178946.
112. Vanhorebeek I, Gunst J, Derde S, Derese I, Boussemaere M, D'Hoore A, et al. Mitochondrial fusion, fission, and biogenesis in prolonged critically ill patients. *J Clin Endocrinol Metab*. 2012;97:E59–64.
113. Kraft BD, Chen L, Suliman HB, Piantadosi CA, Welty-Wolf KE. Peripheral blood mononuclear cells demonstrate mitochondrial damage clearance during sepsis. *Crit Care Med*. 2019;47:651–8.
114. Weiss SL, Cvijanovich NZ, Allen GL, Thomas NJ, Freishtat RJ, Anas N, et al. Differential expression of the nuclear-encoded mitochondrial transcriptome in pediatric septic shock. *Crit Care*. 2014;18:623.
115. Yu R, Lendahl U, Nistér M, Zhao J. Regulation of mammalian mitochondrial dynamics: opportunities and challenges. *Front Endocrinol*. 2020;11:374.
116. Chen L, Knowlton AA. Mitochondria and heart failure: new insights into an energetic problem. *Minerva Cardioangiol*. 2010;58:213–29.
117. Willems PHGM, Rossignol R, Dieteren CEJ, Murphy MP, Koopman WJH. Redox homeostasis and mitochondrial dynamics. *Cell Metab*. 2015;22:207–18.
118. Jang DH, Greenwood JC, Owiredu S, Ranganathan A, Eckmann DM. Mitochondrial networking in human blood cells with application in acute care illnesses. *Mitochondrion*. 2019;44:27–34.
119. Vanhorebeek I, Gunst J, Derde S, Derese I, Boussemaere M, Güiza F, et al. Insufficient activation of autophagy allows cellular damage to accumulate in critically ill patients. *J Clin Endocrinol Metab*. 2011;96:E633–45.
120. Yin X, Xin H, Mao S, Wu G, Guo L. The role of autophagy in sepsis: protection and injury to organs. *Front Physiol*. 2019;10:1071.
121. Prauchner CA. Oxidative stress in sepsis: pathophysiological implications justifying antioxidant co-therapy. *Burns*. 2017;43:471–85.
122. Brown GC, Borutaite V. Inhibition of mitochondrial respiratory complex I by nitric oxide, peroxynitrite and S-nitrosothiols. *Biochim Biophys Acta*. 2004;1658:44–9.
123. de Paludo FJO, Picanço JB, Fallavena PRV, da Fraga LR, Graebin P, de Nóbrega OT, et al. Higher frequency of septic shock in septic patients with the 47C allele (rs4880) of the SOD2 gene. *Gene*. 2013;517:106–11.
124. Soltani R, Alikiaie B, Shafiee F, Amiri H, Mousavi S. Coenzyme Q10 improves the survival and reduces inflammatory markers in septic patients. *Bratisl Lek Listy*. 2020;121:154–8.
125. Galluzzi L, Vitale I, Aaronson SA, Abrams JM, Adam D, Agostinis P, et al. Molecular mechanisms of cell death: recommendations of the Nomenclature Committee on Cell Death 2018. *Cell Death Differ*. 2018;25:486–541.
126. Hotchkiss RS, Tinsley KW, Swanson PE, Schmiege RE, Hui JJ, Chang KC, et al. Sepsis-induced apoptosis causes progressive profound depletion of B and CD4+ T lymphocytes in humans. *J Immunol*. 2001;166:6952–63.
127. Hotchkiss RS, Osmon SB, Chang KC, Wagner TH, Coopersmith CM, Karl IE. Accelerated lymphocyte death in sepsis occurs by both the death receptor and mitochondrial pathways. *J Immunol*. 2005;174:5110–8.
128. Martínez-García JJ, Martínez-Banauloch H, Angosto-Bazarra D, de Torre-Minguela C, Baroja-Mazo A, Alarcón-Vila C, et al. P2X7 receptor induces mitochondrial failure in monocytes and compromises NLRP3 inflammasome activation during sepsis. *Nat Commun*. 2019;10:2711.
129. Adrie C, Bachelet M, Vayssier-Taussat M, Russo-Marie F, Bouchaert I, Adib-Conquy M, et al. Mitochondrial membrane potential and apoptosis peripheral blood monocytes in severe human sepsis. *Am J Respir Crit Care Med*. 2001;164:389–95.
130. Warburg O. On the origin of cancer cells. *Science*. 1956;123:309–14.
131. Mookerjee SA, Gerencser AA, Nicholls DG, Brand MD. Quantifying intracellular rates of glycolytic and oxidative ATP production and consumption using extracellular flux measurements. *J Biol Chem*. 2017;292:7189–207.
132. Epstein T, Gatenby RA, Brown JS. The Warburg effect as an adaptation of cancer cells to rapid fluctuations in energy demand. *PLoS ONE*. 2017;12:e0185085.
133. Williams DL, Li C, Sherwood ER. Loss of monocyte metabolic plasticity in endotoxin tolerance: a model for understanding sepsis-induced immune paralysis? *J Leukoc Biol*. 2019;106:7–9.
134. Grondman I, Arts RJW, Koch RM, Leijte GP, Gerretsen J, Bruse N, et al. Frontline Science: Endotoxin-induced immunotolerance is associated with loss of monocyte metabolic plasticity and reduction of oxidative burst. *J Leukoc Biol*. 2019;106:11–25.
135. Fossati G, Moulding DA, Spiller DG, Moots RJ, White MRH, Edwards SW. The mitochondrial network of human neutrophils: role in chemotaxis, phagocytosis, respiratory burst activation, and commitment to apoptosis. *J Immunol*. 2003;170:1964–72.
136. Borregaard N, Herlin T. Energy metabolism of human neutrophils during phagocytosis. *J Clin Invest*. 1982;70:550–7.
137. Jeon J-H, Hong C-W, Kim EY, Lee JM. Current Understanding on the Metabolism of Neutrophils. *Immune Netw*. 2020;20:e46.
138. Pearce EL, Poffenberger MC, Chang C-H, Jones RG. Fueling immunity: insights into metabolism and lymphocyte function. *Science*. 2013;342:1242454.
139. Nauseef WM. The phagocyte NOX2 NADPH oxidase in microbial killing and cell signaling. *Curr Opin Immunol*. 2019;60:130–40.
140. Root RK, Metcalf JA. H2O2 release from human granulocytes during phagocytosis. Relationship to superoxide anion formation and cellular catabolism of H2O2: studies with normal and cytochalasin B-treated cells. *J Clin Invest*. 1977;60:1266–79.
141. Patil NK, Bohannon JK, Sherwood ER. Metabolism drives monocytes during inflammation: What we do and do not know. *J Leukoc Biol*. 2019;105:211–3.
142. Zhu X, Meyers A, Long D, Ingram B, Liu T, Yoza BK, et al. Frontline Science: Monocytes sequentially rewire metabolism and bioenergetics during an acute inflammatory response. *J Leukoc Biol*. 2019;105:215–28.
143. Geltink RIK, Kyle RL, Pearce EL. Unraveling the complex interplay between T cell metabolism and function. *Annu Rev Immunol*. 2018;36:461–88.

144. Khalsa JK, Chawla AS, Prabhu SB, Vats M, Dhar A, Dev G, et al. Functionally significant metabolic differences between B and T lymphocyte lineages. *Immunology*. 2019;158:104–20.
145. Rolfe DF, Brown GC. Cellular energy utilization and molecular origin of standard metabolic rate in mammals. *Physiol Rev*. 1997;77:731–58.
146. Schönfeld P, Reiser G. Brain energy metabolism spurns fatty acids as fuel due to their inherent mitotoxicity and potential capacity to unleash neurodegeneration. *Neurochem Int*. 2017;109:68–77.
147. White H, Venkatesh B. Clinical review: ketones and brain injury. *Crit Care*. 2011;15:219.
148. Davis GW. Not fade away: mechanisms of neuronal ATP homeostasis. *Neuron*. 2020;105:591–3.
149. Ashrafi G, de Juan-Sanz J, Farrell RJ, Ryan TA. Molecular tuning of the axonal mitochondrial Ca^{2+} uniporter ensures metabolic flexibility of neurotransmission. *Neuron*. 2020;105:678–687.e5.
150. Gofton TE, Young GB. Sepsis-associated encephalopathy. *Nat Rev Neurol*. 2012;8:557–66.
151. Lyu J, Zheng G, Chen Z, Wang B, Tao S, Xiang D, et al. Sepsis-induced brain mitochondrial dysfunction is associated with altered mitochondrial Src and PTP1B levels. *Brain Res*. 2015;1620:130–8.
152. Annane D, Sharshar T. Cognitive decline after sepsis. *Lancet Respir Med*. 2015;3:61–9.
153. Hotchkiss RS, Moldawer LL, Opal SM, Reinhart K, Turnbull IR, Vincent J-L. Sepsis and septic shock. *Nat Rev Dis Primer*. 2016;2:16045.
154. Sharshar T, Bozza F, Chrétien F. Neuropathological processes in sepsis. *Lancet Neurol*. 2014;13:534–6.
155. Bozza FA, D'Avila JC, Ritter C, Sonnevile R, Sharshar T, Dal-Pizzol F. Bioenergetics, mitochondrial dysfunction, and oxidative stress in the pathophysiology of septic encephalopathy. *Shock*. 2013;39(Suppl 1):10–6.
156. Bing RJ, Siegel A, Vitale A, Balboni F, Sparks E, Taeschler M, et al. Metabolic studies on the human heart in vivo. I. Studies on carbohydrate metabolism of the human heart. *Am J Med*. 1953;15:284–96.
157. Dhainaut JF, Huyghebaert MF, Monsallier JF, Lefevre G, Dall'Ava-Santucci J, Brunet F, et al. Coronary hemodynamics and myocardial metabolism of lactate, free fatty acids, glucose, and ketones in patients with septic shock. *Circulation*. 1987;75:533–41.
158. Rossi MA, Celes MRN, Prado CM, Saggioro FP. Myocardial structural changes in long-term human severe sepsis/septic shock may be responsible for cardiac dysfunction. *Shock*. 2007;27:10–8.
159. Drosatos K, Khan RS, Trent CM, Jiang H, Son N-H, Blaner WS, et al. Peroxisome proliferator-activated receptor- γ activation prevents sepsis-related cardiac dysfunction and mortality in mice. *Circ Heart Fail*. 2013;6:550–62.
160. Lado-Abeal J, Martínez-Sánchez N, Cocho JA, Martín-Pastor M, Castro-Piedras I, Couce-Pico ML, et al. Lipopolysaccharide (LPS)-induced septic shock causes profound changes in myocardial energy metabolites in pigs. *Metabolomics*. 2018;14:131.
161. Raymond RM, McLane MP, Law WR, King NF, Leutz DW. Myocardial insulin resistance during acute endotoxin shock in dogs. *Diabetes*. 1988;37:1684–8.
162. Tessier J-P, Thurner B, Jüngling E, Lückhoff A, Fischer Y. Impairment of glucose metabolism in hearts from rats treated with endotoxin. *Cardiovasc Res*. 2003;60:119–30.
163. Drosatos K, Drosatos-Tampakaki Z, Khan R, Homma S, Schulze PC, Zannis VI, et al. Inhibition of c-Jun-N-terminal kinase increases cardiac peroxisome proliferator-activated receptor α expression and fatty acid oxidation and prevents lipopolysaccharide-induced heart dysfunction. *J Biol Chem*. 2011;286:36331–9.
164. Hassoun SM, Lancel S, Pettillot P, Decoster B, Favory R, Marchetti P, et al. Sphingosine impairs mitochondrial function by opening permeability transition pore. *Mitochondrion*. 2006;6:149–54.
165. Favory R, Lancel S, Marchetti P, Mordon S, Chopin C, Formstecher P, et al. Endotoxin-induced myocardial dysfunction: evidence for a role of sphingosine production. *Crit Care Med*. 2004;32:495–501.
166. Reynolds CM, Suliman HB, Hollingsworth JW, Welty-Wolf KE, Carraway MS, Piantadosi CA. Nitric oxide synthase-2 induction optimizes cardiac mitochondrial biogenesis after endotoxemia. *Free Radic Biol Med*. 2009;46:564–72.
167. Uji Y, Yamamoto H, Tsuchihashi H, Maeda K, Funahashi T, Shimomura I, et al. Adiponectin deficiency is associated with severe polymicrobial sepsis, high inflammatory cytokine levels, and high mortality. *Surgery*. 2009;145:550–7.
168. Schilling J, Lai L, Sambandam N, Dey CE, Leone TC, Kelly DP. Toll-like receptor-mediated inflammatory signaling reprograms cardiac energy metabolism by repressing peroxisome proliferator-activated receptor γ coactivator-1 signaling. *Circ Heart Fail*. 2011;4:474–82.
169. Standage SW, Bennion BG, Knowles TO, Ledee DR, Portman MA, McGuire JK, et al. PPAR α augments heart function and cardiac fatty acid oxidation in early experimental polymicrobial sepsis. *Am J Physiol Heart Circ Physiol*. 2017;312:H239–49.
170. Durand A, Duburcq T, Dekeyser T, Neviere R, Howsam M, Favory R, et al. Involvement of mitochondrial disorders in septic cardiomyopathy. *Oxid Med Cell Longev*. 2017;2017:4076348.
171. Stanzani G, Duchon MR, Singer M. The role of mitochondria in sepsis-induced cardiomyopathy. *Biochim Biophys Acta Mol Basis Dis*. 2019;1865:759–73.
172. Mantzarlis K, Tsolaki V, Zakyntinos E. Role of oxidative stress and mitochondrial dysfunction in sepsis and potential therapies. *Oxid Med Cell Longev*. 2017;2017:5985209.
173. Larche J, Lancel S, Hassoun SM, Favory R, Decoster B, Marchetti P, et al. Inhibition of mitochondrial permeability transition prevents sepsis-induced myocardial dysfunction and mortality. *J Am Coll Cardiol*. 2006;48:377–85.
174. Hassoun SM, Marechal X, Montaigne D, Bouazza Y, Decoster B, Lancel S, et al. Prevention of endotoxin-induced sarcoplasmic reticulum calcium leak improves mitochondrial and myocardial dysfunction. *Crit Care Med*. 2008;36:2590–6.
175. Preau S, Delguste F, Yu Y, Remy-Jouet I, Richard V, Saulnier F, et al. Endotoxemia engages the RhoA kinase pathway to impair cardiac function by altering cytoskeleton, mitochondrial fission, and autophagy. *Antioxid Redox Signal*. 2016;24:529–42.
176. Joshi MS, Julian MW, Huff JE, Bauer JA, Xia Y, Crouser ED. Calcineurin regulates myocardial function during acute endotoxemia. *Am J Respir Crit Care Med*. 2006;173:999–1007.
177. Lancel S, Hassoun SM, Favory R, Decoster B, Motterlini R, Neviere R. Carbon monoxide rescues mice from lethal sepsis by supporting mitochondrial energetic metabolism and activating mitochondrial biogenesis. *J Pharmacol Exp Ther*. 2009;329:641–8.
178. Matkovich SJ, Al Khiami B, Efimov IR, Evans S, Vader J, Jain A, et al. Widespread down-regulation of cardiac mitochondrial and sarcomeric genes in patients with sepsis. *Crit Care Med*. 2017;45:407–14.
179. Azevedo LCP. Mitochondrial dysfunction during sepsis. *Endocr Metab Immune Disord Drug Targets*. 2010;10:214–23.
180. Aoi W, Naito Y, Yoshikawa T. Potential role of oxidative protein modification in energy metabolism in exercise. *Subcell Biochem*. 2014;77:175–87.
181. Cherry AD, Suliman HB, Bartz RR, Piantadosi CA. Peroxisome proliferator-activated receptor γ co-activator 1- α as a critical co-activator of the murine hepatic oxidative stress response and mitochondrial biogenesis in *Staphylococcus aureus* sepsis. *J Biol Chem*. 2014;289:41–52.
182. Cadenas S, Aragonés J, Landázuri MO. Mitochondrial reprogramming through cardiac oxygen sensors in ischaemic heart disease. *Cardiovasc Res*. 2010;88:219–28.
183. Sekine S, Ichijo H. Mitochondrial proteolysis: its emerging roles in stress responses. *Biochim Biophys Acta*. 2015;1850:274–80.
184. Kroemer G, Galluzzi L, Brenner C. Mitochondrial membrane permeabilization in cell death. *Physiol Rev*. 2007;87:99–163.
185. Lancel S, Joulin O, Favory R, Goossens JF, Kluz J, Chopin C, et al. Ventricular myocyte caspases are directly responsible for endotoxin-induced cardiac dysfunction. *Circulation*. 2005;111:2596–604.
186. Neviere R, Hassoun SM, Decoster B, Bouazza Y, Montaigne D, Maréchal X, et al. Caspase-dependent protein phosphatase 2A activation contributes to endotoxin-induced cardiomyocyte contractile dysfunction. *Crit Care Med*. 2010;38:2031–6.
187. Vanasco V, Saez T, Magnani ND, Pereyra L, Marchini T, Corach A, et al. Cardiac mitochondrial biogenesis in endotoxemia is not accompanied by mitochondrial function recovery. *Free Radic Biol Med*. 2014;77:1–9.
188. Suliman HB, Welty-Wolf KE, Carraway M, Tatro L, Piantadosi CA. Lipopolysaccharide induces oxidative cardiac mitochondrial damage and biogenesis. *Cardiovasc Res*. 2004;64:279–88.

189. Hickson-Bick DLM, Jones C, Buja LM. Stimulation of mitochondrial biogenesis and autophagy by lipopolysaccharide in the neonatal rat cardiomyocyte protects against programmed cell death. *J Mol Cell Cardiol.* 2008;44:411–8.
190. Hsieh C-H, Pai P-Y, Hsueh H-W, Yuan S-S, Hsieh Y-C. Complete induction of autophagy is essential for cardioprotection in sepsis. *Ann Surg.* 2011;253:1190–200.
191. Sun Y, Yao X, Zhang Q-J, Zhu M, Liu Z-P, Ci B, et al. Beclin-1-dependent autophagy protects the heart during sepsis. *Circulation.* 2018;138:2247–62.
192. Zi Z, Song Z, Zhang S, Ye Y, Li C, Xu M, et al. Rubicon deficiency enhances cardiac autophagy and protects mice from lipopolysaccharide-induced lethality and reduction in stroke volume. *J Cardiovasc Pharmacol.* 2015;65:252–61.
193. Piquereau J, Godin R, Deschênes S, Bessi VL, Mofarrahi M, Hussain SN, et al. Protective role of PARK2/Parkin in sepsis-induced cardiac contractile and mitochondrial dysfunction. *Autophagy.* 2013;9:1837–51.
194. Pang J, Peng H, Wang S, Xu X, Xu F, Wang Q, et al. Mitochondrial ALDH2 protects against lipopolysaccharide-induced myocardial contractile dysfunction by suppression of ER stress and autophagy. *Biochim Biophys Acta Mol Basis Dis.* 2019;1865:1627–41.
195. Inata Y, Piraino G, Hake PW, O'Connor M, Lahni P, Wolfe V, et al. Age-dependent cardiac function during experimental sepsis: effect of pharmacological activation of AMP-activated protein kinase by AICAR. *Am J Physiol Heart Circ Physiol.* 2018;315:H826–37.
196. Wang Z, Ying Z, Bopsy-Westphal A, Zhang J, Schautz B, Later W, et al. Specific metabolic rates of major organs and tissues across adulthood: evaluation by mechanistic model of resting energy expenditure. *Am J Clin Nutr.* 2010;92:1369–77.
197. O'Connor PM. Renal oxygen delivery: matching delivery to metabolic demand. *Clin Exp Pharmacol Physiol.* 2006;33:961–7.
198. Pagliarini DJ, Calvo SE, Chang B, Sheth SA, Vafai SB, Ong S-E, et al. A mitochondrial protein compendium elucidates complex I disease biology. *Cell.* 2008;134:112–23.
199. Duann P, Lin P-H. Mitochondria damage and kidney disease. *Adv Exp Med Biol.* 2017;982:529–51.
200. Soltoff SP. ATP and the regulation of renal cell function. *Annu Rev Physiol.* 1986;48:9–31.
201. Bhargava P, Schnellmann RG. Mitochondrial energetics in the kidney. *Nat Rev Nephrol.* 2017;13:629–46.
202. Peerapornratana S, Manrique-Caballero CL, Gómez H, Kellum JA. Acute kidney injury from sepsis: current concepts, epidemiology, pathophysiology, prevention and treatment. *Kidney Int.* 2019;96:1083–99.
203. Schmidt C, Höcherl K, Schweda F, Bucher M. Proinflammatory cytokines cause down-regulation of renal chloride entry pathways during sepsis. *Crit Care Med.* 2007;35:2110–9.
204. Schmidt C, Höcherl K, Schweda F, Kurtz A, Bucher M. Regulation of renal sodium transporters during severe inflammation. *J Am Soc Nephrol.* 2007;18:1072–83.
205. Hato T, Maier B, Syed F, Myslinski J, Zollman A, Plotkin Z, et al. Bacterial sepsis triggers an antiviral response that causes translation shutdown. *J Clin Invest.* 2019;129:296–309.
206. Gómez H, Kellum JA, Ronco C. Metabolic reprogramming and tolerance during sepsis-induced AKI. *Nat Rev Nephrol.* 2017;13:143–51.
207. Smith JA, Stallons LJ, Schnellmann RG. Renal cortical hexokinase and pentose phosphate pathway activation through the EGFR/Akt signaling pathway in endotoxin-induced acute kidney injury. *Am J Physiol Renal Physiol.* 2014;307:F435–44.
208. Waltz P, Carchman E, Gomez H, Zuckerbraun B. Sepsis results in an altered renal metabolic and osmolyte profile. *J Surg Res.* 2016;202:8–12.
209. Heiden MG, Cantley LC, Thompson CB. Understanding the warburg effect: the metabolic requirements of cell proliferation. *Science.* 2009;324:1029–33.
210. Escobar DA, Botero-Quintero AM, Kautza BC, Luciano J, Loughran P, Darwiche S, et al. Adenosine monophosphate-activated protein kinase activation protects against sepsis-induced organ injury and inflammation. *J Surg Res.* 2015;194:262–72.
211. Opal SM, Ellis JL, Suri V, Freudenberg JM, Vlasuk GP, Li Y, et al. Pharmacological SIRT1 activation improves mortality and markedly alters transcriptional profiles that accompany experimental sepsis. *Shock.* 2016;45:411–8.
212. Vachharajani VT, Liu T, Brown CM, Wang X, Buechler NL, Wells JD, et al. SIRT1 inhibition during the hypoinflammatory phenotype of sepsis enhances immunity and improves outcome. *J Leukoc Biol.* 2014;96:785–96.
213. Tran M, Tam D, Bardia A, Bhasin M, Rowe GC, Kher A, et al. PGC-1 α promotes recovery after acute kidney injury during systemic inflammation in mice. *J Clin Invest.* 2011;121:4003–14.
214. Liu J, Yang C, Zhang W, Su H, Liu Z, Pan Q, et al. Disturbance of mitochondrial dynamics and mitophagy in sepsis-induced acute kidney injury. *Life Sci.* 2019;235:116828.
215. Sieck GC, Ferreira LF, Reid MB, Mantilla CB. Mechanical properties of respiratory muscles. *Compr Physiol.* 2013;3:1533–67.
216. Demoule A, Divangahi M, Yahiaoui L, Danelou G, Gvozdic D, Labbe K, et al. Endotoxin triggers nuclear factor-kappaB-dependent up-regulation of multiple proinflammatory genes in the diaphragm. *Am J Respir Crit Care Med.* 2006;174:646–53.
217. Picard M, Jung B, Liang F, Azuelos I, Hussain S, Goldberg P, et al. Mitochondrial dysfunction and lipid accumulation in the human diaphragm during mechanical ventilation. *Am J Respir Crit Care Med.* 2012;186:1140–9.
218. Jung B, Nougaret S, Conseil M, Coisel Y, Futier E, Chanques G, et al. Sepsis is associated with a preferential diaphragmatic atrophy: a critically ill patient study using tridimensional computed tomography. *Anesthesiology.* 2014;120:1182–91.
219. Demoule A, Jung B, Prodanovic H, Molinari N, Chanques G, Coirault C, et al. Diaphragm dysfunction on admission to the intensive care unit. Prevalence, risk factors, and prognostic impact—a prospective study. *Am J Respir Crit Care Med.* 2013;188:213–9.
220. Hussain SN, Simkus G, Roussos C. Respiratory muscle fatigue: a cause of ventilatory failure in septic shock. *J Appl Physiol.* 1985;58:2033–40.
221. Petrof BJ. Diaphragm weakness in the critically ill: basic mechanisms reveal therapeutic opportunities. *Chest.* 2018;154:1395–403.
222. Callahan LA, Supinski GS. Downregulation of diaphragm electron transport chain and glycolytic enzyme gene expression in sepsis. *J Appl Physiol.* 2005;99:1120–6.
223. Boczkowski J, Dureuil B, Branger C, Pavlovic D, Murciano D, Pariente R, et al. Effects of sepsis on diaphragmatic function in rats. *Am Rev Respir Dis.* 1988;138:260–5.
224. van den Berg M, Hooijman PE, Beishuizen A, de Waard MC, Paul MA, Hartemink KJ, et al. Diaphragm atrophy and weakness in the absence of mitochondrial dysfunction in the critically ill. *Am J Respir Crit Care Med.* 2017;196:1544–58.
225. Yang Y, Yu T, Pan C, Longhini F, Liu L, Huang Y, et al. Endotoxemia accelerates diaphragm dysfunction in ventilated rabbits. *J Surg Res.* 2016;206:507–16.
226. Weber-Carstens S, Schneider J, Wollersheim T, Assmann A, Bierbrauer J, Marg A, et al. Critical illness myopathy and GLUT4: significance of insulin and muscle contraction. *Am J Respir Crit Care Med.* 2013;187:387–96.
227. Supinski GS, Schroder EA, Callahan LA. Mitochondria and critical illness. *Chest.* 2020;157:310–22.
228. Dridi H, Yehya M, Barsotti R, Reiken S, Angebault C, Jung B, et al. Mitochondrial oxidative stress induces leaky ryanodine receptor during mechanical ventilation. *Free Radic Biol Med.* 2020;146:383–91.
229. Powers SK, Hudson MB, Nelson WB, Talbert EE, Min K, Szeto HH, et al. Mitochondria-targeted antioxidants protect against mechanical ventilation-induced diaphragm weakness. *Crit Care Med.* 2011;39:1749–59.
230. Sung MM, Byrne NJ, Robertson IM, Kim TT, Samokhvalov V, Levasseur J, et al. Resveratrol improves exercise performance and skeletal muscle oxidative capacity in heart failure. *Am J Physiol Heart Circ Physiol.* 2017;312:H842–53.
231. Komen JC, Thorburn DR. Turn up the power - pharmacological activation of mitochondrial biogenesis in mouse models. *Br J Pharmacol.* 2014;171:1818–36.
232. McCully JD, Cowan DB, Emani SM, Del Nido PJ. Mitochondrial transplantation: From animal models to clinical use in humans. *Mitochondrion.* 2017;34:127–34.
233. Pascual C, Karzai W, Meier-Hellmann A, Oberhoffer M, Horn A, Bredle D, et al. Total plasma antioxidant capacity is not always decreased in sepsis. *Crit Care Med.* 1998;26:705–9.

234. Chuang C-C, Shiesh S-C, Chi C-H, Tu Y-F, Hor L-I, Shieh C-C, et al. Serum total antioxidant capacity reflects severity of illness in patients with severe sepsis. *Crit Care*. 2006;10:R36.

235. Halliwell B. The antioxidant paradox. *Lancet*. 2000;355:1179–80.

236. Halliwell B. The antioxidant paradox: less paradoxical now? *Br J Clin Pharmacol*. 2013;75:637–44.

237. Quinlan GJ, Martin GS, Evans TW. Albumin: biochemical properties and therapeutic potential. *Hepatology*. 2005;41:1211–9.

238. Aldecoa C, Llau JV, Nuvials X, Artigas A. Role of albumin in the preservation of endothelial glycocalyx integrity and the microcirculation: a review. *Ann Intensive Care*. 2020;10:85.

239. Magder S. Reactive oxygen species: toxic molecules or spark of life? *Crit Care*. 2006;10:208.

240. Wang Y, Lin H, Lin B-W, Lin J-D. Effects of different ascorbic acid doses on the mortality of critically ill patients: a meta-analysis. *Ann Intensive Care*. 2019;9:58.

241. Martin AD, Joseph A-M, Beaver TM, Smith BK, Martin TD, Berg K, et al. Effect of intermittent phrenic nerve stimulation during cardiothoracic surgery on mitochondrial respiration in the human diaphragm. *Crit Care Med*. 2014;42:e152–6.

242. Jung B, Constantin J-M, Rossel N, Le Goff C, Sebbane M, Coisel Y, et al. Adaptive support ventilation prevents ventilator-induced diaphragmatic dysfunction in piglet: an in vivo and in vitro study. *Anesthesiology*. 2010;112:1435–43.

243. Reynolds SC, Meyyappan R, Thakkar V, Tran BD, Nolette M-A, Sadarangani G, et al. Mitigation of ventilator-induced diaphragm atrophy by transvenous phrenic nerve stimulation. *Am J Respir Crit Care Med*. 2017;195:339–48.