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Selenocompounds and sepsis: redox bypass hypothesis for early diagnosis and treatment

Part A: Early acute phase of sepsis: an extraordinary redox situation (leukocyte-endothelium interaction leading to endothelial damage)

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Abstract

Significance: Sepsis is a health disaster. In sepsis, an initial, beneficial local immune response against infection evolves rapidly into a generalized, dysregulated response or a state of chaos, leading to multiple organ failure. Use of life-sustaining supportive therapies creates an unnatural condition, enabling the complex cascades of the sepsis response to develop in patients who would otherwise die. Multiple attempts to control sepsis at an early stage have been unsuccessful.

Recent advances: Major events in early sepsis include activation and binding of leukocytes and endothelial cells in the microcirculation, damage of the endothelial surface layer and a decrease in the plasma concentration of the antioxidant enzyme, selenoprotein-P. These events induce an increase in intracellular redox potential and lymphocyte apoptosis, whereas apoptosis is delayed in monocytes and neutrophils. They also induce endothelial mitochondrial and cell damage.

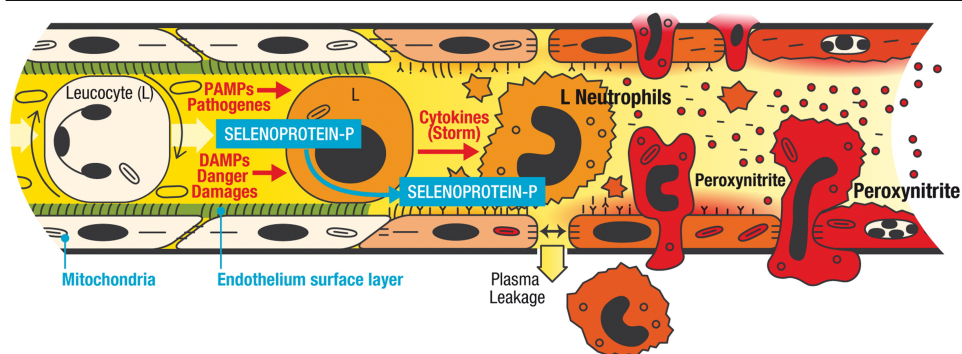
Critical issues: Neutrophil production increases dramatically and aggressive, immature forms are released. Leukocyte cross-talk with other leukocytes and with damaged endothelial cells amplifies the inflammatory response. The release of large quantities of reactive oxygen, halogen and nitrogen species as a result of the leukocyte respiratory burst, endothelial mitochondrial damage, and ischemia-reperfusion processes, along with the marked decrease in selenoprotein-P concentrations, leads to peroxynitrite damage of the endothelial surface layer, reducing flow and damaging the endothelial barrier.

Future Direction: Endothelial barrier damage by activated leukocytes is a time-sensitive event in sepsis, occurring within hours and representing the first step towards organ failure and death. Reducing or stopping this event is necessary before irreversible damage occurs.

References 340; Tables (2): 1-Main Reactive Oxygen, Halogen and Nitrogen Species Within Cells and in Plasma Near the Endothelial Vascular Membrane: Radical Species (One-Electron Oxidant) , 2- Main Reactive Oxygen, Halogen and Nitrogen Species Within Cells and in Plasma Near the Endothelial Vascular Membrane: Nonradical Species (Two-Electron Oxidant); **Figures (5):** 1- Sepsis evolution and supportive care as new survival attractors, 2- Leukocyte and endothelial activation leading to major oxidative stress and endothelial barrier dysfunction, 3-Transposition of cellular impact of increased redox potential from cancer cells to leukocytes, particularly neutrophils, 4-ROHNS production over time in sepsis and their consequences on endothelial damage, 5- Decrease in plasma Se and selenoprotein-P levels in animal sepsis and burn models and corresponding low levels on admission to the ICU in patients with sepsis or septic shock.

Selenocompounds and Sepsis: Redox Bypass Hypothesis for Early Diagnosis and Treatment: Part A – Early Acute Phase of Sepsis: An Extraordinary Redox Situation (Leukocyte/Endothelium Interaction Leading to Endothelial Damage)

Antioxidants & Redox Signaling



Conclusion: Early acute phase of sepsis: an acute oxidative stress due to dysregulated immune response, on a chaos state, leading to extensive endothelium damage.

Reference: Xavier Forceville, Pierre Van Antwerpen, and Jean-Charles Preiser

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Graphical abstract created by Dr X Forceville and Ms E Guillbert

Introduction

Sepsis is a major health problem that requires specific and early diagnostic and treatment solutions. Sepsis has been recognized for many thousands of years, with descriptions dating back to 3000 BC in ancient Egypt (169). Despite improvements in the understanding of the pathogenesis of sepsis and in therapeutic management, sepsis remains a silent public health disaster, with 337 cases occurring per 100,000 inhabitants every year in the US, associated with a 30-50% mortality rate (237). Moreover, patients who survive sepsis frequently have reduced long-term quality of life (133,228). Sepsis accounts for more than \$20 billion (5.2%) of total US hospital costs (133,276). The risk of a worldwide major infectious pandemic leading to multiple patients with sepsis is a persistent threat, as illustrated by the recent coronavirus disease 2019 (COVID-19) pandemic (60). More severe pandemics may occur in the future, of natural origin or as a result of use of biological weapons, as has already happened since medieval times, if not earlier (12,62,123,173). Severe non-infective events, such as extensive burns or irradiation, multiple trauma, some intoxications, acute pancreatitis, and major surgery, induce an acute innate response that shares similarities with sepsis (35,185,316).

Sepsis is not a disease but a complex syndrome resulting from an overwhelming dysregulated innate host response to invasive infection (59,133,187,241,276). According to the third international consensus definition for sepsis, an infection with a mild innate response is no longer called sepsis, and what was previously called “severe sepsis” is now defined as “sepsis” (169,276). Despite some progress in early management, sepsis remains a major health problem worldwide; early detection is crucial to optimize treatment, but can be difficult (11,48,187,199,215,222,315). Numerous phase III studies performed over the last few decades have failed to demonstrate improved outcomes of patients with sepsis with the interventions studied, most probably because of the great complexity of the pathophysiology of sepsis (14,90,208). Most of these interventions, including antioxidant approaches, were aimed at blocking one or more pathogenetic cascades (90,153,208,226), and it has been suggested more recently that early therapeutic interventions should rather target the microcirculation or mitochondrial dysfunction (196).

The objective of this article, written in two parts, is to provide a clearer understanding of the early events of sepsis in terms of redox potential and free radical damage, in order to propose a new approach for early diagnosis and treatment, which will be covered in a separate part B paper. Here we will focus on the oxidative consequences of the simultaneous activation and binding of activated neutrophils to endothelial cells, which induces the release of reactive oxygen, halogen and nitrogen species (ROHNS), especially peroxynitrite, compounds that are effective against pathogens but deleterious for the endothelium. As a consequence of their hyperactivation, the intracellular redox potential of leukocytes, and especially neutrophils, increases and immature forms are released by the bone marrow. Excessive release of ROHNS overwhelms plasma antioxidant defenses, especially that provided by selenoprotein P, which protects against peroxynitrite-mediated oxidation, and, to a lesser extent, by plasma glutathione peroxidase (GPX3). The ROHNS damage the inner surface of the endothelial wall, especially the endothelial surface layer (ESL), and also the endothelial cells, especially the mitochondria. These events lead to disseminated shock-induced endotheliopathy (SHINE), the first step to multiple organ failure and ultimately death.

Duality of the innate response

Beneficial against infection

The innate response is an ancient mechanism adapted from plants to mammals to counteract the exponential growth of pathogens (195). The innate reaction at the site of an infection must occur rapidly in order to control the infection locally. Toll-like receptors (TLRs) are activated by pathogen-associated molecular patterns (PAMPs) and danger-associated molecular patterns (DAMPs) (191,258). Phagocytosis, which involves phagocytic cells such as neutrophils (also called polymorphonuclear cells [PMN]), is at the crossroad of the innate response with all the cascades implicated in sepsis (108,150,154,165,192,203). This process releases ROHNS, which contribute to the killing of microorganisms (113,160).

In sepsis, the innate response changes from a beneficial localized response against infection into a dysregulated and generalized response, leading to organ dysfunction and failure, especially circulatory, and to death (108,191,263,281). The mortality rates associated with sepsis remain high, despite improvements in management, in particular more widespread, adequate early resuscitation, and improved supportive care in the intensive care unit (ICU) (24,191,241,276,280). The formal 3-h and 6-h bundles have recently been combined into a 1-h bundle, reinforcing the need for an efficient early intervention at the very early phase of sepsis (170).

Detrimental effects and cascade signaling in the early phase of sepsis

The availability of improved supportive care enables patients with sepsis to survive beyond their natural body functions. In this “unnatural” state, the innate response may be inadequate and deleterious (241,314) (Fig. 1). Thus

the different forms of supportive care in this context could be likened to survival attractors (320) (Fig. 1). In the absence of such supportive care, most patients die (148). At this stage of sepsis, the dysregulated innate and host response is mixed, with complex pro- and anti-inflammatory reactions (61,212). In such a situation, natural coping mechanisms may no longer be adequate, resulting in a state of chaos (3,8,321). Although the chaos theory is still debated, it is nevertheless widely acknowledged that the host response involves many cascades, with positive loops and complex feedback pathways and interactions (212). Numerous unsuccessful attempts, including some large multicenter randomized phase III studies, have targeted single cascade interventions, suggesting that multi-cascade interventions may be more effective (90,133,208,318). Because of lack of an early effective treatment for sepsis and improved general intensive care management, most of the associated mortality is currently related to the effects of immunodepression (76,133,317).

One of the reasons for the numerous failed attempts to demonstrate the effectiveness of immunomodulatory therapies against sepsis, may be the lack of an animal model that can adequately reflect sepsis and septic shock in critically ill patients (9,89,211). One of the important differences between animal models and patients may lie in serum proteins rather than in intrinsic cellular differences (327). Another reason for the lack of success is the complex cascade of interactions involved in the early phase of sepsis, which varies over time and with illness severity (90,133,237,318). At the extracellular level, these processes include activation of TLRs by PAMPs and DAMPs, cytokine storm (145,207), coagulation activation (87,95,166,198,257,285), formation of microparticles (236), and activation of the complement system (325), proteases, heat shock proteins, neuro-mediators and the neuro-endocrine axis (13). In addition, at the macro-circulation level, cross-talk is observed between organs. One example of this cross-talk is the effects of a decrease in perfusion of the small intestine, which induces ischemia-reperfusion injury and leads to a second hit by bacteria and compounds such as endotoxin, further enhancing the inflammatory response (110,111,255,335).

Microcirculatory dysfunction as an early event and shock-induced endotheliopathy (SHINE)

Importance of leukocyte binding to the endothelium

In the early phase of sepsis, interactions and binding between leukocytes, and more specifically neutrophils, and the endothelium are a major event at the level of the microcirculation (6,11,79,94,129,133,137,140,142,150,154,165,168,192,203,209,225,236,257,268,279,338). Initially limited to the site of infection, this process becomes generalized and dysregulated in sepsis and is involved in many of the cascades cited earlier (Fig. 2). Before, developing this concept further, we will first describe the physiological functioning of the microcirculation (Fig 2, upper panel).

Physiological functioning of the microcirculation

The endothelium, which should be considered as an organ, plays a pivotal role in the microcirculation (4,5,209). It forms a mono-cellular layer, the surface area of which is about 4,000 to 7,000 m² (4,5,6,304), and acts as a border between a liquid medium –the plasma– and a solid structure –the basal membrane (6,210). Physiologically, the endothelium is coated by glycoproteins, forming the glycocalyx (translated from the Greek meaning sugar coat) and, more broadly, the ESL (65,230,231). The endothelium has a wide range of physiological functions and can be viewed as an input-output system (5).

In blood, neutrophils account for 50 to 70% of all circulating leukocytes. They are normally produced at a rate of 10¹¹ per day and stored in the bone marrow, with only a small fraction (1-2% in mice) released each day (165,268). Under physiological conditions, neutrophils have a short half-life of 7-12 hours in the circulation, where they are quiescent, and 1-2 days in tissues, because of spontaneous apoptosis (192,219,268). During the spontaneous apoptosis of neutrophils, both mitochondria- and death receptor-mediated apoptotic signaling are activated (219). This spontaneous apoptosis is inhibited by neutrophil activation as developed later. Rolling leukocytes can be observed and red blood cells (RBCs) are flexible. RBCs and leukocytes, including neutrophils, move evenly with platelets that are not activated (Fig. 2, Upper Panel).

In health, blood flow within the microcirculation is laminar, applying shear stress evenly on the surface of the endothelial cells. The ESL, which includes the glycocalyx, covers all endothelial cells and is highly fragile (56,100,229,232) (Fig. 2 Upper panel). It is closely regulated and differs, especially in thickness, from one organ to another (e.g., in the brain, the glycocalyx is thicker in hippocampal than in cortical microvessels) (56,272,308). With a thickness ranging from 0.5 μm to 1 μm it forms a step between blood cells and the endothelium (229,232). The ESL is divided into a thin, cell-attached glycocalyx (about 70 nm) that includes proteins, glycolipids, glycoproteins and proteoglycans, and a layer of linked molecules comprised of (i) adsorbed plasma proteins, (ii) a soluble component, e.g., extracellular superoxide dismutase (SOD), derived from endothelial cells, (iii) large linear hyaluronic acid interacting with cell-surface glycoprotein CD44, and (iv) covalently bound glycosaminoglycan side chains (e.g., heparin sulfate and chondroitin sulfate), which are negatively charged (56,100,272,308). In equilibrium with the flowing plasma, the ESL generates an exclusion zone for cellular blood components, and contains about 700 ml of adult plasma. The ESL acts to reduce the filtered protein concentration, reduces the effective oncotic

pressure across the endothelium, and protects the endothelium against ROHNS (56,231,272). It plays an important role in normal vascular homeostasis, including flow resistance, transmission of shear stress, regulation of blood flow, oxygen transport, capillary barrier function including the glomerular filtration barrier, vascular permeability, creation of an anti-inflammatory and anti-coagulation phenotype, inhibition of leukocyte adhesion and angiogenesis (56,100,229,232,272). The ESL is thus intrinsically linked to vascular functionality (272). Tight junctions and adherent junctions, sealing the paracellular space between cells, join the endothelial cells and, with the ESL, form a double barrier that limits macromolecule transit (56). These components are linked to the actin-based cytoskeleton. The basal membrane is coated with pericytes, forming a layer. In this healthy state, mitochondrial activity is normal and the intracellular redox potential is low.

In endothelial cells, as in all cells, The antioxidant selenoenzymes are ubiquitously present, playing an important role in redox signaling, protection against ROHNS, and selenium (Se) metabolism in tissues and in the plasma (44,53,104,159,178,288). Every selenoprotein contains only one atom of Se per molecule; with the exception of selenoprotein-P (see later) (104). In all selenoproteins, the Se is always included in the 21st amino acid, selenocysteine (50,53,104,223). By contrast with other essential trace elements, such as iron (Fe), copper or zinc, Se is not present in ionic form, or is present in small molecules in plasma, most probably because of the oxidant properties linked to the particular electronic nature of Se (27,53,130,261,289). Se is required at the active site of all the antioxidant selenoenzymes of the 25 known selenoprotein genes in humans, as a consequence of the particular electronic properties of Se (70,158). Intracellular selenoproteins, which include glutathione peroxidases (GPXs), thioredoxin reductases (TXNRDs) and iodothyronine deiodinases, (44,103,104,205) have crucial antioxidant functions, controlling the intracellular redox potential. These proteins therefore affect, in a complex manner, many intracellular metabolic processes (44,104,282,284). The ambivalent electronic properties of Se account for its complex and highly energy-consuming intracellular metabolism (see separate part B paper) (50,53,70,130). Se can also replace sulfur in the amino acid selenomethionine, thus forming a storage pool of Se, which could be released in case of protein catabolism, but is not considered to have biological properties (53).

Se and Fe are both required for antioxidant defense and metabolism in eukaryotic cells, but also in almost all pathogens (105,162,172,283,286). Physiologically, plasma Fe, which is at physiologic pH in ferric state (Fe³⁺), is mainly complexed to transferrin. Each protein has two iron binding sites (218). Non-transferrin-bound iron (NTBI) comprises Fe³⁺ citrate, acetate and Fe loosely bound to albumin (286,287). Cells use transferrin receptors to acquire Fe.

The biologically active form of Se is transported in the plasma from the liver to the tissues within the 9 selenocysteine aminoacids of the C terminal part of selenoprotein P, which has bi-functional activity (53,104,126,249,261). Selenoprotein P binds to specific receptors (apolipoprotein E receptor-2 -ApoER2) (53,126,260) or megalin (53,157,260). During anaerobic exercise, selenoprotein P also binds to heparin sulfate proteoglycan, favored by the low pH, and has antioxidant enzymatic activity through the single selenocysteine of the N terminal part of the protein (42,52,53,85,132,193,220). Selenoprotein P accounts for about 60% of plasma Se with marked homogeneity between mammals, especially in terms of the N terminal portion (118,121,127,176,201). It has a short half-life of about 4 hours in rats (53). It is glycosylated and belongs to the heparin binding proteins (307). In physiological states, selenoprotein P has the crucial function of transporting Se and regulating the delivery of biologically active Se from the liver to the tissues (53,261). The second plasma selenoprotein, plasma glutathione peroxidase (GPX3), contains about 30% of plasma Se, and is synthesized in the kidney; it is dependent on selenoprotein P intake (128,262). GPX3 does not seem to participate in Se transport (53). GPX3 antioxidant function in plasma is unlikely in physiological conditions because of the low plasma glutathione concentration (31,115). Its possible antioxidant function during sepsis will be discussed later. The remaining plasma Se is included in proteins, notably albumin, within the non-biologically active aminoacid, selenomethionine (53).

Microcirculatory dysfunction and endothelial damage during sepsis

Large increase in neutrophil activity, redox potential, and release of immature neutrophils

During sepsis, neutrophil production dramatically increases to 10¹² per day, consisting of mature and immature forms, even very immature forms, to compensate recruitment and margination as the first line of cellular defense (190,247,268,294). Neutrophil differentiation includes the myeloblast, promyelocyte, myelocyte, meta-myelocyte, band and segmented (mature) neutrophil stages (165). This includes band cells characterized by a curved but not lobular nucleus (77,165,185,247,273). The immature forms may be more aggressive, increasing oxidative stress (185,190,294,311). During the early phase of sepsis, neutrophils also have an increased lifespan in the circulation, from less than a day to up to 5 days. This is related to delayed apoptosis and further enhances the innate response (76,192,219,268).

In neutrophil cell signaling in sepsis, the recognition of PAMPs (e.g., lipopolysaccharide [LPS], bacterial deoxyribonucleic acid [DNA], ...) and DAMPs (e.g., heat-shock proteins, uric acid, ...), and other signaling molecules, results in stimulation of neutrophils and endothelial cells by kinase activation, inducing the expression

of transcriptional factors, such as nuclear factor-kappa B (NF- κ B), and other factors of the rel family, central to the acute inflammatory response (1). Secretory neutrophil vesicles can rapidly transport their contents to the cell surface and can kill pathogens by phagocytosis and degranulation of neutrophil extracellular traps (NETs) (154,247). The ability of neutrophils to kill pathogens is immediate, non-specific, and does not depend on previous exposure (247).

It is important to specify that the redox potential modifies function of all cells, from bacteria to eukaryotic cells (15,117,177,239). The redox potential depends notably on the redox environment the intracellular production of reactive oxygen species (ROS) by the mitochondria (16,277), and the peroxide-associated enzymes linked to cellular redox couples (49). An increase in the degree of oxidation of the intracellular redox potential modifies cell function from starvation to multiplication or activation (activation of transcription factors, protective enzymes, increase in Ca^{2+}), to pre-apoptosis and finally to cell death by apoptosis, necrosis, or ferroptosis (49,106,112,114,143) (Fig. 3). However, the response to an increased oxidation state varies from cell to cell (134). Immune cells, especially lymphocytes, have increased apoptosis, whereas apoptosis is delayed in monocytes/macrophages and neutrophils, which may be related to the particular properties of their mitochondria (76,247,285,309,326). The increase in intracellular superoxide anion ($\text{O}_2^{\bullet-}$) concentration, due to extra and intracellular production, and increase in redox state is involved in neutrophil priming before complete activation (74,180,247,293,298) (Table 1). The increase in redox potential increases neutrophil activation by membrane perturbation (293), activating the arachidonic acid cascade (171), Janus kinase (JAK) activation as reported by Brigelius-Flohe, especially with effects on thiol residues (43,45,57,149,293), redox activation of NF- κ B (293), nitration of protein tyrosine by peroxynitrite (ONOO^-) (57,293), and mitochondrial one electron way blockage (41). Extracellular formation of ROHNS, such as oxygen peroxide (H_2O_2) and ONOO^- , can induce neutrophil priming (293). Intracellular myeloperoxidase (MPO) activation is associated with decreased glutathione (GSH) concentration by hypochlorous acid (HOCl), resulting in irreversible protein thiols and in GSH oxidation (57,74) (Table 2), whereas H_2O_2 detoxification by GPXs leads to reversible glutathione disulfide (GSSG) (57). Irreversible GSH oxidation by HOCl decreases the antioxidant defense and may contribute to increased redox potential (57). Following phagocytosis and MPO lipid peroxidation, an increase in protein carbonyl is observed in neutrophil cytosol (330). However, additional enhanced redox potential by increased intracellular H_2O_2 concentration contributes to reduce the inflammatory phenotype (337). The initial stage of neutrophil apoptosis is linked to changes in the expression of genes encoding for the redox pathway, including glutathione-, thioredoxin- and heme metabolism (247). Nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX2) and MPO are considered as key players in post-phagocytotic events, such as activation of cell death and NETs (Fig 4). This is in accordance with the central impact of redox potential on cell function (49,106,112) (Fig. 3). When comparing the redox status in resting and oxidative burst conditions of human leukemia cell line-60 (HL-60), a cell line from an acute promyelocytic leukemia patient, to that of neutrophils, these cells share similarities (74,97). However, they also differ. For example, in resting and oxidative burst states, recycling of peroxiredoxins, thiol peroxidases with a key role in antioxidant defense and redox signaling, may be deficient in neutrophils compared to HL-60 cells (74).

Neutrophils are also implicated in many of the numerous extracellular cascades in the early phase of sepsis, such as the cytokine storm, coagulation activation, microparticle release, and complement activation, among others (90,133,237,318). Another important cellular cross-talk is the interaction of neutrophils with other immune cells, such as activation of natural killer (NK) cells, leading to (219) a self-amplifying loop of inflammation with dendritic cells, while inhibiting the proliferation of T lymphocytes (154,192). Neutrophil-macrophage interactions are important in both the initiation and the resolution phases of sepsis, especially in the process of phagocytosis-induced cell death of neutrophils by macrophages as underlined by Kennedy and colleagues (146,192,285). Finally, neutrophils interact with platelets, in particular, through microparticles displaying platelet activating factor (PAF) (192). Generation of NETs, which is an effective mechanism for bacterial trapping, is an additional deleterious neutrophil – endothelium interaction (78). Together, these mechanisms result in activation and binding of neutrophils and endothelial cells

(6,11,79,94,129,133,137,140,142,150,154,165,168,192,203,209,225,236,257,268,279,338).

Hyperactivation and interaction between endothelium and leukocytes, and ROHNS formation

In sepsis, the endothelium receives information from mediators of inflammation, including cytokines, growth factors, chemokines, complement and coagulation factors, ROHNS (including oxidized lipid), and circulating cells (leukocytes, especially neutrophils, but also RBCs and platelets). Endothelial cells in return alter the vasomotor tone, plasticity and fluidity (230,231), and interact with circulating cells, especially neutrophils. In addition, sepsis-induced microcirculatory alterations are characterized by heterogeneous abnormalities in blood flow and pathological shunt, in which the different degree of expression of inducible nitric oxide synthase (iNOS) and nitric oxide (NO^{\bullet}) production in different organ beds plays an important role in the ischemia-reperfusion process (72,73,139,209,305).

Dramatic increase in ROHNS production

ROHNS play a major role in the early phase of sepsis (Table 1 and 2) (Figs. 2 and 4) (23,113,114,188,271,334). A hyperoxidation redox state in sepsis was first reported as a major part of the innate response in 1990 by Novelli and colleagues and confirmed later by others, (96,202,204). This hyperoxidation can be related to three main mechanisms (5,92,204,217,250): (i) the respiratory burst from hyperactivated leukocytes and concomitant activation of the endothelium, which is probably the most important early event (81,113,119,136,152,180,192,204,300,329); (ii) the onset of ischemia-reperfusion (204,250); and (iii) blockage of the mitochondrial respiratory chain (39,40,98,119,274).

In the early phase of sepsis, neutrophil activation induces an abrupt increase in oxygen consumption, termed the respiratory burst (247,264,334). ROHNS are produced by activated leukocytes (especially $O_2^{\bullet-}$ and halogen species) and by endothelial cells (especially NO^{\bullet}). Neutrophils or macrophages via NOX2 and MPO represent most of the protein oxidation and lipid-derived free radicals in the very early 6-hour phase following LPS instillation (243,253). (Fig 2 and 4) (Table 1 and 2). ROHNS are ambivalent molecules that are major antimicrobial agents, and are also toxic to endothelial cells (23,113,114,188,227,236,270,271,312,331,334). Among the ROHNS, $ONOO^-$ should be highlighted as it can cross membranes, and lead to formation of extremely reactive species. $ONOO^-$ can be split into hydroxyl ($\bullet OH$) and nitrogen dioxide (NO_2^{\bullet}) radicals when protonated or to NO_2^{\bullet} and carbonate radical ($CO_3^{\bullet-}$) when reacting with carbon dioxide (CO_2) (40,80,113,141,235,297,334). Superoxide anion ($O_2^{\bullet-}$) rapidly dismutates H_2O_2 , activating MPO or producing $\bullet OH$ via Fe^{++} or copper (Cu^+) catalyzed Fenton/Haber-Weiss reactions (144,244,296,332). In addition, $ONOO^-$ enhances the release of NETs, which further increase the oxidative stress (183) (Fig. 2 and 3).

Adhesion of activated leukocytes to the endothelium is important for ROHNS production in plasma at the edge of the vascular luminal surface in the microcirculation (122). The simultaneous production of $O_2^{\bullet-}$ and NO^{\bullet} at this location leads rapidly, in less than 30 min in vitro, to the formation of $ONOO^-$ (46,141,297). Oxygen consumption by hyperactivated leukocytes increases by a factor of 20 to 100%, leading to a marked release of $O_2^{\bullet-}$ in phagosomes and in the plasma (141,238,265,266,333).

Release of NO^{\bullet} by endothelial cells increases from a picomolar range by constitutive (or endothelial) NOS (cNOS) to a nanomolar range from iNOS (151,296). The gradient of NO^{\bullet} concentration, decreasing exponentially with distance from the cell, favors a spatially increased concentration of $ONOO^-$ near the endothelial vascular membrane (46,245,290,297). This process targets the ESL, endothelial cells, especially their mitochondria, and multiple other targets (46,138,186,196,272,278,297) (Table 1 and 2) (Fig. 2 and 4). HOCl, initially synthesized in the phagosome via MPO, can be released or synthesized in the plasma, despite being buffered by hypothiocyanite (22,116,141,333) (Table 2, Fig. 4). In addition, multiple positive redox loops increase ROHNS production in the acute phase of sepsis, an unnatural, dysregulated or chaotic immune response, made possible by supportive care (122,151,296) (Fig. 1).

In the early phase of sepsis, there is also a complex alteration of the microcirculation, with closing and reopening of small vessels and opening of shunts leading to ischemia-reperfusion and NOS activation. Activated macrophages and ischemia-reperfusion processes through xanthine oxidase (XO) and cyclooxygenase participate in the plasma increase in $O_2^{\bullet-}$ and H_2O_2 concentrations (120,224,242,339) (Table 1), as do NOX2, mitochondria, and NO^{\bullet} by iNOS (69,109,115,227,243). These processes are an important part of ROHNS production and interact with neutrophil activation (109,180).

Finally in the early phase of sepsis, inside the endothelial cells, and later within tissues, mitochondrial dysfunction - by reversible blocking by NO^{\bullet} of complex I and IV and later irreversible blocking of complex I by $ONOO^-$ - increases the production of $O_2^{\bullet-}$ (40,213,235). In turn, mitochondrial isoforms of NOS further increase NO^{\bullet} synthesis within cells (101,235). NO^{\bullet} also reacts with heme to form nitrite (NO_2^-) and nitrate (NO_3^-) (151) and may react with $O_2^{\bullet-}$ to form $ONOO^-$ within the mitochondria (235) (Tables 1 and 2). Damage to mitochondria will be discussed later as part of endothelial cell dysfunction.

Other radicals, oxidants, and secondary species are produced, such as singlet oxygen 1O_2 , alkyl peroxy nitrates $RONOO^-$, alkyl radicals RO^{\bullet} in reaction with lipids (especially unsaturated), and many other reactive molecules as detailed by Halliwell (33,68,88,113,160,216,226,243,312) (Tables 1 and 2).

Decrease in plasma antioxidant defense by selenoenzymes

In parallel to the increase in ROHNS production, there is increased non-specific adhesion of selenoprotein P to the endothelium via its heparin binding domain (7,18,52,124,157), especially to the ESL, which contains heparin sulfates (17,18). This binding is favored by acidic pH (42,52,53,132); it is also sensitive to ionic strength (18). In addition, multiple mechanisms support a downregulation in the synthesis and excretion of selenoprotein P by the

liver during the acute phase of sepsis, including (i) negative regulation by inflammatory cytokines, especially interleukin (IL)-1 β (83,201); (ii) hypoxic conditions favoring the synthesis of phospholipid hydroperoxide glutathione peroxidase (GPX4) instead of selenoprotein P (30); (iii) decreased selenoprotein P excretion and selenoprotein P messenger ribonucleic acid (mRNA) in an LPS mouse model (240); (iv) decreased hepatic transcription and protein content of factors required for Se insertion into selenoproteins (269); and finally (v) liver mitochondrial dysfunction in sepsis may impair selenoprotein synthesis, which is highly energy requiring, especially for synthesis of selenoprotein P, which contains 10 selenocysteine residues (39,41,119,136,184,226,243,246,313). This counter-regulation of selenoprotein P synthesis and excretion will be further developed in a separate part B paper.

As a result of increased binding, downregulated liver excretion, and fluid extravasation, plasma Se and selenoprotein P concentrations decrease by up to 75% in a few hours in mice, rat, and sheep septic models. The more severe the model, the more rapid is this decrease (182,240,252,291,324) (Fig. 5). In a resuscitated peritonitis sheep model, a halving of plasma Se concentration was observed 4 hours after the onset of peritonitis. On admission to the ICU, a profound decrease in plasma Se and selenoprotein P concentrations is observed in patients with sepsis and septic shock (32,91,93,131,251). In the early phase of sepsis, this marked decrease in plasma selenoprotein P concentration limits the availability of Se to pathogens, but also decreases plasma antioxidant defense, especially at the ESL level; the N-terminal part of selenoprotein P has high antioxidant enzymatic activity (53,248,299), especially against ONOO⁻ (19,20,42,51,54,201,288,299,303). Later, GPX3, whose synthesis depends on selenoprotein P, may exert its antioxidant action after specific binding to basement membranes or the extracellular matrix (ECM). According to the double barrier hypothesis, this effect may play an important role, in limiting macromolecule transit and fluid extravasation (55,56,254) (Fig. 2).

Involvement of iron in ROHNS production

A parallel could be made between altered Se and Fe metabolism during sepsis. As previously indicated, bacteria, with few exceptions, require Fe for growth and proliferation (162,200,286). However, in the presence of O₂^{-•} and H₂O₂, Fe catalyzes Fenton/Haber-Weiss reactions leading to production of the extremely reactive [•]OH (Table 1) (144,332). Most of the body's Fe content (4-5 g) is incorporated into hemoglobin (Hb) (2.5 g) (162,221); the remainder is in other hemoproteins (such as myoglobin [Mb]), iron-sulfur (Fe-S), and Fe binding and storage proteins (218). Within the RBC, Hb is protected against O₂^{-•} by antioxidant enzymes, such as SOD, and against H₂O₂ by catalase (CAT) and intracellular cytosolic glutathione peroxidase (GPX1) (28,99). Auto-oxidation of Hb, or oxidation by plasma nitrite, may release H₂O₂ or diffusible protein radicals (28,147,175). Nevertheless, in the acute phase of sepsis, the main impact of ROHNS, especially ONOO⁻, on RBCs is oxidation of their membrane and their cytoplasmic proteins, including the cytoskeleton (175,206) (Table 2). This oxidation decreases RBC deformability, increases RBC aggregation (Fig. 2) (28,206,292), increases blood viscosity, and alters tissue oxygenation (28,292). In addition, oxidized RBCs may induce ROHNS formation by macrophages and neutrophils as part of multiple positive loops (206). Macrophages also play a pivotal role in erythrophagocytosis (162). Inflammatory anemia occurs at a later stage of sepsis (28,37,221,295), but anemia resulting from previous Fe deficiency, blood loss, hemodilution or frequent blood sampling, may alter tissue oxygenation (37,221).

In the acute phase of sepsis, the circulating ionic form of Fe is decreased by hepatocyte expression of hepcidin, which (i) increases H-ferritin (Fe³⁺ storage in macrophage); (ii) downregulates Fe efflux; (iii) increases secretion of ceruloplasmin, a copper ferroxidase; and (iv) decreases transferrin concentration (162,218). Lactoferrin also chaperones Fe in neutrophils (162,218). This occurs in less than 3 to 6 hours in sepsis models (162,221), inducing hypoferrinemia and low NTBI (306). In septic patients admitted to the ICU, low serum Fe, transferrin concentration, and transferrin saturation, and high ferritin concentrations are observed (37,221). In sepsis models, hepcidin agonists have been shown to decrease mortality, and intravenous Fe administration increased mortality (218,286,287,295). In septic ICU patients, a higher concentration of catalytic Fe (similar to NTBI) and a lower concentration of hepcidin have been associated with higher mortality rates (163). On the other hand, small quantities of Fe²⁺ can serve as a catalyst in the phagolysosome for Fenton/Haber-Weiss reactions (340). In neutrophils, lactoferrin may also enhance such a reaction (26). Catalytic Fe may contribute to positive inflammatory loops (197).

Cell-free Hb or Mb is released in the plasma during hemolysis, hemorrhage, and rhabdomyolysis (cell-free Mb), the latter being implicated in renal toxicity (267). These compounds induce the expression of (i) acute phase proteins hemopexin (HPX) and haptoglobin, which bind to heme and Hb; and (ii) heme oxygenase-1 (HO-1), which catabolizes HPX-bound heme by the hepatocytes (84,161,162). However, this clearance mechanism can be overwhelmed (84). During sepsis, hemolysis has been suspected to be the main source of catalytic Fe, free heme, and free Hb, which in turn further increase hemolysis (84,161,163). These products increase the severity of sepsis in mice (161,163,194,267) and also have the characteristics of a "danger signal", amplifying the innate response. Nevertheless, their importance in oxidative stress during the acute phase of sepsis is debated (84). Hemolysis is certainly an important mechanism in acute malaria and this may also be the case in infections by pathogens secreting

hemolysins, such as *Staphylococcus species (spp.)*, *Streptococcus spp.*, and *Clostridium spp.* or in case of disseminated intravascular coagulation (DIC) (84,200).

Damage of the first barrier, the endothelial surface layer

Damage of the ESL plays a major role in sepsis pathophysiology, modifying hematocrit, flow resistance, permeability, coagulation, leukocyte adhesion, and the ability to bind a variety of proteins, including selenoprotein P, to heparin sulfate (17,18,56,100,138,245,308). The damage induces positive amplification loops, through (i) destruction of the glycosaminoglycan chain and unsulfated hyaluronic acid and release of hyaluronic acid fragments (82,107,272); (ii) cleavage of heparan sulfate from proteoglycans, themselves cleaved from endothelial cells (308); and (iii) loss of the heparan sulfate-bound extracellular SOD - directly or through activation of heparanase - that further increases oxidative stress (272).

As illustrated in Fig. 2 (Lower Panel) and Fig.4, in the early phase of sepsis, ROHNS are central players in the destruction of the ESL, which is extremely sensitive to free radicals and oxidants (11,29,38,82,107,186,210,245,272) (Tables 1 and 2). ONOO⁻ and HOCl play an important role in ESL damage and enzyme activation (38,272) (Fig. 4). These oxidant molecules activate matrix metalloproteinase, a zinc-dependent endopeptidase, and heparanase (272). The damage to the ESL, the first line barrier of the blood-tissue interface, further exposes endothelial cells (Fig. 2). Adhesion molecules are unmasked (272). Following rupture of the tight junctions, according to the double barrier hypothesis, this leads to fluid extravasation and protein rich leakage (Fig. 2) (11,56,165,272).

In animal models and human volunteers, LPS administration results in reduction in the depth of the ESL and glycocalyx shedding within hours, with a similar kinetic to that of the decrease in selenoprotein P concentrations (56,82,182,240,291,308,324). This effect may be initiated within minutes during the ischemia-reperfusion process (245) and coincided with vascular dysfunction in a rat LPS study (186). As a consequence, numerous glycocalyx degradation products are under investigation as early sepsis markers (56,308). Damage may vary from one organ's circulation to another. As an illustration, the hippocampal region, which physiologically has a thicker glycocalyx than the cortex, seems to be especially susceptible to damage, altering the blood brain barrier and making it one of the first organs to suffer in sepsis, engendering long term sequelae (56). Similarly early glycocalyx damage on the thicker glycocalyx present in the pulmonary vasculature compared to that in the systemic vasculature may be an important first step towards acute respiratory distress syndrome (ARDS) (56).

Damage to endothelial cells with loss of the second barrier and mitochondrial dysfunction

During sepsis, there is a change in endothelial properties from a non-coagulant, non-adherent, vasodilator phenotype to a pro-coagulant, adherent, vasoconstrictor phenotype (6,137,139,164,167,209,301,329). Under the expression of adhesins (P- and E-selectins; vascular cell adhesion molecule [VCAM], intercellular adhesion molecule (322)), slow rolling of leukocytes is observed, leading to leukocyte arrest and adhesion to the endothelial surface, leukocyte crawling, and diapedesis. Diapedesis may be of trans-endothelial cells or para-endothelial cells. Extravascular leukocytes are observed beyond the extracellular matrix. Phagocytosis can be observed with intracellular bacteria. Degranulation by leukocytes can also contribute to killing of bacteria. Breakdown of the second endothelial barrier, after ESL degradation, is due to physical endothelial disruption with breakdown of the actin cytoskeleton, and rupture of the tight junction and the basal membrane, resulting in opening of intercellular gaps. There is increased microvascular permeability with fluid extravasation and retraction of endothelial cells. Flow is reduced, decreasing the shear stress. The endothelial cell membrane becomes unstable with formation of microparticles, which originate from endothelial cells but also platelets and leukocytes. These particles are mainly pro-coagulant, providing an increased area of tissue factor exposure and increasing activation of factor VIIa. They induce the expression of enzymes related to inflammation and ROHNS, increase cytokines and exposure of adhesion molecules, and participate in the immunosuppression (5,6,11,17,36,58,142,164,179,226,234). Abnormal coagulation leads to activated platelet aggregation, fibrin deposition and thrombus (e.g., exposure of tissue factor, activation of the complement system C3a, C5a and b, and von Willebrand factor...), which induce ischemia-reperfusion and ROHNS formation (O₂•⁻) through intermittent flow. There is a formation of platelet plugs, including microparticles, which trap bacteria. Blood clotting and thrombi are also observed, favored by impaired anticoagulant pathways and fibrinolysis. NET - DNA structures released with adherent bactericidal proteins, such as MPO, participate in the trapping and killing of bacteria and in endothelial damage (78).

ROHNS and especially ONOO⁻ have a specific toxicity towards endothelial cell mitochondria (Fig. 4, lower part) (41). This disruption of the mitochondrial respiratory chain is probably due to the structural analogy between mitochondria and bacteria, as mitochondria evolved from captured bacteria (75). These damaged mitochondria swell, which increases ROHNS formation (O₂•⁻) (2,25,39,41,67,119,136,233,246,274,275,323,336) (Fig. 4, lower part). Together with the endothelial wall damage, mitochondrial damage in endothelial cells and later in tissues, especially the liver, is recognized as a key factor in the pathophysiology of the early phase of sepsis (39,41,46,119,136,184,196,226,243,246,313). ROHNS damage aerobic and anaerobic microorganisms that are

killed by exposure to oxygen, but also eukaryotic cells, especially mitochondria (75). Mitochondria in eukaryotic cells are protected against oxygen toxicity by a low PO₂ tension of around 0.5 mmHg. This allows eukaryotic cells to use oxygen for energy production (i.e., the mitochondrial respiratory chain) and metabolic transformation (i.e., by cytochrome P450). Mitochondria have a key role in energy production, supplying 80% - 90% of the adenosine triphosphate (ATP) required by mammalian cells (115,243). They are the source of most cellular free radical production in physiological conditions (277). However, they are also organelles that are sensitive to oxidative damage. The mitochondrial damage checkpoint induces apoptosis, as demonstrated in aging and cancer (277). In addition, ferroptosis or pyroptotic cell death was recently proposed as a mechanism in ischemia-reperfusion and sepsis (143), involving lipoperoxidation membrane damage that may evolve with oxidation of the inner membrane space of mitochondria in case of ferroptosis, and caspase 11 activation for pyroptosis. These effects seem to be related to overwhelming antioxidant defense by the cell membrane and mitochondrial membrane selenoenzyme GPX4, requiring reduced glutathione (GSH) (64,143,156). Acute mitochondrial damage induces a decrease in ATP production, threatening cell viability (46,243) (Fig. 4, lower part).

Blockage of the mitochondrial respiratory chain induces an increase in O₂•⁻, but also in ONOO⁻, a decrease in energy production and membrane potential, and mitochondrial damage inducing apoptosis (39,243,246,313) (Fig. 4, lower part). Mitochondrial ROS production, especially in the lung, is particularly enhanced when sepsis appears on a background of chronic ethanol abuse (47). Mitochondrial impairment is more likely to participate in functional endoplasmic reticulum (ER) stress, as shown in the LPS cellular model, inducing a pro-apoptotic state (155). The ER is a structure that is highly sensitive to increased cellular redox state and is involved in sepsis lung damage (86,155). Tumor necrosis factor- α (TNF- α) increases ROS production via mitochondria, especially in tumor cells (67). In human endothelial cells, TNF- α induced rapid mitochondrial ROS production at the ubisemiquinone site; the ceramide-dependent signaling pathway was implicated (67). H₂O₂ is involved in NF- κ B upregulation of iNOS, creating a positive loop in endothelial cells (243). NO• may also activate the ER (86).

The increased redox potential in the endothelium is associated with a decrease in reduced GSH. This reduction is partially related to mitochondrial dysfunction, which increases the oxidative stress and activates cell apoptosis (11,135,136,142,243,331). Endothelial cell metabolism is markedly modified, with resistance to insulin (302,310). Microparticles are released from the damaged and activated endothelial membrane, as well as from other cells, and play an important role in vascular redox signaling and endothelial dysfunction (189,236,319). All these phenomena increase platelet- as well as leukocyte- adhesion to endothelial cells, which in turn increases the endothelial dysfunction as already discussed (Fig. 2 and 4). At a later stage, which was achieved in 2-4 hours in a murine cecal ligation and puncture (CLP)-septic model, endothelial cells directly cause apoptosis by a caspase-dependent mechanism (102), or necrosis with the release of DAMPs, particularly mitochondrial DAMPs (192,328). This alteration of the endothelium is linked to the hyper-activation of neutrophils (72,133,137,165,192) (Fig. 2, 3 and 4). Sepsis is a time-sensitive condition ideally requiring prevention of irreversible endothelial damage (66,170). It is also an unnatural situation, made possible by supportive care, leading to a dysregulated innate response or a state of chaos (Fig.1).

The ubiquitous intracellular antioxidant selenoenzymes, GPX1, GPX4 and TXNRDs (cytosolic TXNRD1, and mitochondrial TXNRD2), play a key role in the antioxidant defense of endothelial cells. If their antioxidant capacity is exceeded, there is increased redox potential, complex modifications of cell functioning, and cell damage (10,42,44,117,152,178). In the acute phase of sepsis, intake of a biologically active form of Se by endothelial cells is reduced as a result of the previously mentioned downregulation of liver selenoprotein P synthesis. In addition, even if a biologically active form of Se is available, synthesis of selenoenzymes is an energy-intensive process, and energy production may be impaired in situations of mitochondrial dysfunction (50,53,70,130). Moreover, excess oxidative stress and hypoxia may reduce selenoenzyme synthesis (30,214,259). Finally, endothelial apoptosis and necrosis are observed as well as circulating endothelial cells. All these phenomena contribute to the dysfunction of the endothelial barrier. This dysfunction takes hours to occur in cecal ligation and puncture (CLP) models, leading to SHINE (6,11,79,94,129,133,137,140,142,150,154,165,168,192,203,209,225,236,257,268,279,338).

Consequences and deleterious effects of ROHNS in the early phase of sepsis

Endothelial damage (SHINE) is the first step to multiple organ failure (MOF) and death (63,72) (Fig. 1) and occurs within hours of the start of sepsis (5,69,71,94,125,154,165,181,192,219,256,257). As previously highlighted, the marked decrease in plasma Se and selenoproteins, specifically selenoprotein P, is an indirect argument in favor of a major deleterious effect of ROHNS (91,93,131) (Fig. 5). SHINE is a first step to sepsis-related organ dysfunction, characterized by a profound modification of tissue cell metabolism with a low degree of apoptosis, despite major organ dysfunction or failure requiring organ support in the ICU to survive. It is also associated with secondary immunosuppression that begins simultaneously with hyper-inflammation (dysregulated innate and host response) (4,6,21,34,63,133,142,209,275) (Fig. 1). Organ dysfunction is related to the severity of the early endothelial damage, coupled with immunosuppression due to immune cell apoptosis (4,63,72,94,142,174,209,210,236,243), and, in surviving patients, these two factors are most probably responsible for the long-term consequences of sepsis

(133,228).

Considering the importance of the increased redox potential and activity of leukocytes, and especially neutrophils, to ROHNS production and endothelial damage, a therapeutic intervention would conceptually need to be very potent and active at multiple sites to be effective. One target of such an intervention could be to reduce the hyperactivity of leukocytes, especially neutrophils, while protecting the endothelium. Such an approach could potentially be achieved using a combination of oxidant and antioxidant selenocompounds and might enable a major part of the complexity and heterogeneity of sepsis to be bypassed. We will develop this possibility further in a separate part B paper.

Conclusion

In summary, endothelial damage occurs rapidly in the first few hours following the onset of sepsis, largely due to the extensive interaction between activated leukocytes and the endothelium. Dysfunction of the ESL, especially as a result of ONOO⁻ and HOCl toxicity, is the first step of this damage. The role of mitochondrial dysfunction, especially as a result of ONOO⁻ toxicity, should also be stressed. Concomitantly there is a major decrease in plasma concentrations of selenoprotein P, a protein with antioxidant enzymatic functions, especially against ONOO⁻. In this early phase of sepsis, which can be considered as SHINE, ROHNS play a major role. Consequently, the hyperactivated leukocytes with myeloma and release of immature cell forms could be considered as an acute, transient, benign hematological tumor.

With development of supportive care, patients can survive in a state of dysregulated and overwhelming host response. This response involves many overlapping cascades, with positive loops and interaction of pro- and anti-inflammatory processes (dysregulated innate and host response). The result could even be likened to a state of chaos, an unstable condition falling between a stable situation controlled by homeostasis and a stable situation provided by supportive care, including the treatment of opportunistic infections.

Together, sepsis must be considered as a time-sensitive acute condition requiring early identification and efficient treatment before endothelial damage becomes established and immunosuppression occurs. Ideally, such a treatment would reduce leukocyte hyperactivity and overwhelming ROHNS production by neutrophils, while protecting the endothelium.

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Author Contribution

Xavier Forceville (XF), Pierre Van Antwerpen (PVA), Jean-Charles Preiser (JCP)

XF: conceived of the presented review, XF, PVA and JCP contributed to the writing of the manuscript. PVA especially participated and validated the biochemical data. JCP had a particular implication in the plan of the review and participated and validated the clinical implication.

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Author disclosure statement

Dr Xavier Forceville

I started a very small start-up in 2005 (Sérénité-Forceville). In 2015, Pharm. V Cotereau volunteer manager of Sérénité-Forceville, former vice president of the French pharmacist association, filed a new patent for the treatment of sepsis entitled: “Kit for treating sepsis and/or any systemic (SIRS) or damaging cellular hyper-inflammation”. Its reference numbers are: PCT number PCT/FR2016/051569, European patent application 16742342.5, US patent application Attorney Docket Number: 0727-1267.

I declare that I am the main shareholder of this company. One of my brothers is also a shareholder.

Pr Pierre Van Antwerpen and Pr Jean Charles Preiser declare no competing financial interests.

List of Abbreviations

AKI = acute kidney injury
ALI = acute lung injury
ARDS = acute respiratory distress syndrome
B. clotting = blood clotting
CLP = cecal ligation and puncture
DAMPS = danger associated molecular patterns
ER = endoplasmic reticulum
ESL = endothelial surface layer
GPX = glutathione peroxidase
GPX1 = intracellular cytosolic GPX
GPX3 = plasma GPX
GPX4 = phospholipid hydroperoxide GPX
Hb = hemoglobin
HPX = hemopexin
ICAM = intercellular adhesion molecule
ICU = intensive care unit
PAMPS = pathogen-associated molecular patterns
PMN = polymorphonuclear cells also called neutrophils
RBC = red blood cells
ROHNS = reactive oxygen, halogen and nitrogen species
TLRs = toll-like receptors
LPS = lipopolysaccharide
MPO = myeloperoxidase
MOF = Multiple organ failure
NOX = NADPH oxidase
NTBI = Non-transferrin-bound iron
NK = natural killer
NETs = neutrophil extracellular traps
PAF = platelet activating factor
SHINE = shock induced endotheliopathy
TXNRDs = thioredoxin reductases (cytosolic TXNRD1, mitochondrial TXNRD2 and testis TXNRD3)
VCAM = vascular cell adhesion protein

References

1. Abraham E. Alterations in cell signaling in sepsis. *Clin Infect Dis* 41 Suppl 7: S459-64, 2005.
2. Abraham E, Singer M. Mechanisms of sepsis-induced organ dysfunction. *Crit Care Med* 35: 2408-16, 2007.
3. Aerts JM, Haddad WM, An G, Vodovotz Y. From Data Patterns to Mechanistic Models in Acute Critical Illness. *J Crit Care* 29: 604-10, 2014.
4. Aird WC. The role of the endothelium in severe sepsis and multiple organ dysfunction syndrome. *Blood* 101: 3765-77, 2003.
5. Aird WC. Endothelium as an organ system. *Crit Care Med* 32: S271-9, 2004.
6. Ait-Oufella H, Maury E, Lehoux S, Guidet B, Offenstadt G. The endothelium: physiological functions and role in microcirculatory failure during severe sepsis. *Intensive Care Med* 36: 1286-98, 2010.
7. Akesson B, Martensson B. Heparin interacts with a selenoprotein in human plasma. *J Inorg Biochem* 33: 257-61., 1988.
8. An G, Faeder J, Vodovotz Y. Translational systems biology: introduction of an engineering approach to the pathophysiology of the burn patient. *J Burn Care Res* 29: 277-85, 2008.
9. Anas AA, Wiersinga WJ, de Vos AF, van der Poll T. Recent insights into the pathogenesis of bacterial sepsis. *Neth J Med* 68: 147-52, 2010.
10. Anema SM, Walker SW, Howie AF, Arthur JR, Nicol F, Beckett GJ. Thioredoxin reductase is the major selenoprotein expressed in human umbilical-vein endothelial cells and is regulated by protein kinase C. *Biochem J* 342: 111-7, 1999.
11. Angus DC, van der Poll T. Severe sepsis and septic shock. *N Engl J Med* 369: 2063, 2013.
12. Annane D, Antona M, Lehmann B, Kedzia C, Chevret S. Designing and conducting a randomized trial for pandemic critical illness: the 2009 H1N1 influenza pandemic. *Intensive Care Med* 38: 29-39, 2012.
13. Annane D, Bellissant E, Cavaillon JM. Septic shock. *Lancet* 365: 63-78, 2005.
14. Annane D, Renault A, Brun-Buisson C, Megarbane B, Quenot J-P, Siami S, Cariou A, Forceville X, Schwebel C, Martin C, Timsit J-F, Misset B, Ali Benali M, Colin G, Souweine B, Asehnoune K, Mercier E, Chimot L, Charpentier C, François B, Boulain T, Petitpas F, Constantin J-M, Dhonneur G, Baudin F, Combes A, Bohé J, Loriferne J-F, Amathieu R, Cook F, Slama M, Leroy O, Capellier G, Dargent A, Hissem T, Maxime V, Bellissant E. Hydrocortisone plus Fludrocortisone for Adults with Septic Shock. *New England Journal of Medicine* 378: 809-818, 2018.
15. Antelmann H, Hellmann JD. Thiol-Based Redox Switches and Gene Regulation. *Antioxid Redox Signal* 14: 1049-63, 2011.
16. Apostolova N, Victor VM. Molecular Strategies for Targeting Antioxidants to Mitochondria: Therapeutic Implications. *Antioxid Redox Signal* 22: 686-729, 2015.
17. Arteel GE, Briviba K, Sies H. Protection against peroxynitrite. *FEBS Lett* 445: 226-30, 1999.
18. Arteel GE, Franken S, Kappler J, Sies H. Binding of selenoprotein P to heparin: characterization with surface plasmon resonance. *Biol Chem* 381: 265-8., 2000.
19. Arteel GE, Klotz LO, Buchczyk DP, Sies H. Selenoprotein P. *Methods Enzymol* 347: 121-5., 2002.
20. Arteel GE, Mostert V, Oubrahim H, Briviba K, Abel J, Sies H. Protection by selenoprotein P in human plasma against peroxynitrite-mediated oxidation and nitration. *Biol Chem* 379: 1201-5, 1998.
21. Arulkumaran N, Sixma ML, Jentho E, Ceravola E, Bass PS, Kellum JA, Unwin RJ, Tam FWK, Singer M. Sequential Analysis of a Panel of Biomarkers and Pathologic Findings in a Resuscitated Rat Model of Sepsis and Recovery. *Crit Care Med* 45: e821-e830, 2017.
22. Ashby MT, Carlson AC, Scott MJ. Redox buffering of hypochlorous acid by thiocyanate in physiologic fluids. *J Am Chem Soc* 126: 15976-7, 2004.
23. Balligand JL. Molecular Mechanisms of Action of Nitric Oxide in Heart Muscle. In: *Yearbook of Intensive Care and Emergency Medicine*. edited by Vincent JL. Heidelberg: Springer-Verlag; 1998. pp. 107-124.
24. Banerjee D, Levy MM. Sepsis Definitions. In: *Sepsis, Definitions, Pathophysiology and the Challenge of Bedside Management*. edited by Ward NS, Levy M. Cham, Switzerland: Springer; 2017. pp. 7-24.
25. Banfi C, Brioschi M, Barbieri SS, Eligini S, Barcella S, Tremoli E, Colli S, Mussoni L. Mitochondrial reactive oxygen species: a common pathway for PAR1- and PAR2-mediated tissue factor induction in human endothelial cells. *J Thromb Haemost* 7: 206-16, 2009.
26. Bannister JV, Bannister WH, Hill HA, Thornalley PJ. Enhanced production of hydroxyl radicals by the xanthine-xanthine oxidase reaction in the presence of lactoferrin. *Biochim Biophys Acta* 715: 116-20, 1982.

27. Bartolini D, Sancineto L, Fabro de Bem A, Tew KD, Santi C, Radi R, Toquato P, Galli F. Selenocompounds in Cancer Therapy: An Overview. *Adv Cancer Res* 136: 259-302, 2017.
28. Bateman RM, Sharpe MD, Singer M, Ellis CG. The Effect of Sepsis on the Erythrocyte. *Int J Mol Sci* 18, 2017.
29. Becker BF, Chappell D, Bruegger D, Annecke T, Jacob M. Therapeutic strategies targeting the endothelial glycocalyx: acute deficits, but great potential. *Cardiovasc Res* 87: 300-10, 2010.
30. Becker NP, Martitz J, Renko K, Stoedter M, Hybsier S, Cramer T, Schomburg L. Hypoxia reduces and redirects selenoprotein biosynthesis. *Metallomics* 6: 1079-86, 2014.
31. Bjornstedt M, Xue J, Huang W, Akesson B, Holmgren A. The thioredoxin and glutaredoxin systems are efficient electron donors to human plasma glutathione peroxidase. *J Biol Chem* 269: 29382-4, 1994.
32. Bloos F, Trips E, Nierhaus A, Briegel J, Heyland DK, Jaschinski U, Moerer O, Weyland A, Marx G, Grundling M, Kluge S, Kaufmann I, Ott K, Quintel M, Jelschen F, Meybohm P, Rademacher S, Meier-Hellmann A, Utzolino S, Kaisers UX, Putensen C, Elke G, Ragaller M, Gerlach H, Ludewig K, Kiehntopf M, Bogatsch H, Engel C, Brunkhorst FM, Loeffler M, Reinhart K. Effect of Sodium Selenite Administration and Procalcitonin-Guided Therapy on Mortality in Patients With Severe Sepsis or Septic Shock: A Randomized Clinical Trial. *JAMA Intern Med* 176: 1266-76, 2016.
33. Bochkov VN, Oskolkova OV, Birukov KG, Levonen AL, Binder CJ, Stöckl J. Generation and Biological Activities of Oxidized Phospholipids. *Antioxid Redox Signal* 12: 1009-59, 2010.
34. Boisrame-Helms J, Kremer H, Schini-Kerth V, Meziani F. Endothelial dysfunction in sepsis. *Curr Vasc Pharmacol* 11: 150-60, 2013.
35. Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, Schein RM, Sibbald WJ. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. *Chest* 101: 1644-55, 1992.
36. Bongrazio M, Baumann C, Zakrzewicz A, Pries AR, Gaehtgens P. Evidence for modulation of genes involved in vascular adaptation by prolonged exposure of endothelial cells to shear stress. *Cardiovasc Res* 47: 384-93, 2000.
37. Boshuizen M, Binnekade JM, Nota B, van de Groep K, Cremer OL, Tuinman PR, Horn J, Schultz MJ, van Bruggen R, Juffermans NP. Iron metabolism in critically ill patients developing anemia of inflammation: a case control study. *Ann Intensive Care* 8: 56, 2018.
38. Boueiz A, Hassoun PM. Regulation of endothelial barrier function by reactive oxygen and nitrogen species. *Microvasc Res* 77: 26-34, 2009.
39. Brealey D, Brand M, Hargreaves I, Heales S, Land J, Smolenski R, Davies NA, Cooper CE, Singer M. Association between mitochondrial dysfunction and severity and outcome of septic shock. *Lancet* 360: 219-23, 2002.
40. Brealey D, Karyampudi S, Jacques TS, Novelli M, Stidwill R, Taylor V, Smolenski RT, Singer M. Mitochondrial dysfunction in a long-term rodent model of sepsis and organ failure. *Am J Physiol Regul Integr Comp Physiol* 286: R491-7, 2004.
41. Brealey D, Singer M. Mitochondrial Dysfunction in Sepsis. *Curr Infect Dis Rep* 5: 365-371, 2003.
42. Brigelius-Flohe R, Banning A, Schnurr K. Selenium-dependent enzymes in endothelial cell function. *Antioxid Redox Signal* 5: 205-15, 2003.
43. Brigelius-Flohe R, Flohe L. Basic principles and emerging concepts in the redox control of transcription factors. *Antioxid Redox Signal* 15: 2335-81, 2011.
44. Brigelius-Flohe R, Flohe L. Selenium and redox signaling. *Arch Biochem Biophys* 617: 48-59, 2017.
45. Brigelius-Flohe R, Friedrichs B, Maurer S, Schultz M, Streicher R. Interleukin-1-induced nuclear factor kappa B activation is inhibited by overexpression of phospholipid hydroperoxide glutathione peroxidase in a human endothelial cell line. *Biochem J* 328: 199-203, 1997.
46. Brovkovich V, Stolarczyk E, Oman J, Tombouljian P, Malinski T. Direct electrochemical measurement of nitric oxide in vascular endothelium. *J Pharm Biomed Anal* 19: 135-43, 1999.
47. Brown LA, Harris FL, Guidot DM. Chronic ethanol ingestion potentiates TNF-alpha-mediated oxidative stress and apoptosis in rat type II cells. *Am J Physiol Lung Cell Mol Physiol* 281: L377-86, 2001.
48. Buchan CA, Bravi A, Seely AJ. Variability analysis and the diagnosis, management, and treatment of sepsis. *Curr Infect Dis Rep* 14: 512-21, 2012.
49. Buettner GR, Wagner BA, Rodgers VG. Quantitative redox biology: an approach to understand the role of reactive species in defining the cellular redox environment. *Cell Biochem Biophys* 67: 477-83, 2013.
50. Bulteau AL, Chavatte L. Update on selenoprotein biosynthesis. *Antioxidants and Redox Signaling* 23: 775-794, 2015.
51. Burk RF, Hill KE. Selenoprotein P: an extracellular protein with unique physical characteristics and a role in selenium homeostasis. *Annu Rev Nutr* 25: 215-35, 2005.
52. Burk RF, Hill KE. Selenoprotein P-expression, functions, and roles in mammals. *Biochim Biophys Acta* 1790: 1441-7, 2009.
53. Burk RF, Hill KE. Regulation of Selenium Metabolism and Transport. *Annu Rev Nutr* 35: 109-34, 2015.

54. Burk RF, Hill KE, Motley AK. Selenoprotein metabolism and function: evidence for more than one function for selenoprotein P. *J Nutr* 133: 1517S-20S, 2003.
55. Burk RF, Olson GE, Winfrey VP, Hill KE, Yin D. Glutathione peroxidase-3 produced by the kidney binds to a population of basement membranes in the gastrointestinal tract and in other tissues. *Am J Physiol Gastrointest Liver Physiol* 301: G32-8, 2011.
56. Butler MJ, Down CJ, Foster RR, Satchell SC. The Pathological Relevance of Increased Endothelial Glycocalyx Permeability. *Am J Pathol* 190: 742-751, 2020.
57. Carr AC, Winterbourn CC. Oxidation of neutrophil glutathione and protein thiols by myeloperoxidase-derived hypochlorous acid. *Biochem J* 327 (Pt 1): 275-81, 1997.
58. Cavaillon JM. Inflammation locale et générale. In: *Sepsis*. edited by Mira JP, Vallet B. Paris: Masson; 2004. pp. 45-73.
59. Cavaillon JM, Adib-Conquy M. Immune status in sepsis: the bug, the site of infection and the severity can make the difference. *Crit Care* 14: 167, 2010.
60. Cevik M, Bamford CGG, Ho A. COVID-19 pandemic-a focused review for clinicians. *Clin Microbiol Infect* 26: 842-847, 2020.
61. Chun T, Potz B, Young W, Ayala A. Overview of the Molecular Pathways and Mediators of Sepsis. In: *Sepsis, Definitions, Pathophysiology and the Challenge of Bedside Management*. edited by Ward N, Levy M. Cham, Switzerland: Springer; 2017. pp. 47-69.
62. Cole J. Antimicrobial resistance, infection control and planning for pandemics: the importance of knowledge transfer in healthcare resilience and emergency planning. *J Bus Contin Emerg Plan* 6: 122-35, 2012.
63. Coletta C, Modis K, Olah G, Brunyanszki A, Herzig DS, Sherwood ER, Ungvari Z, Szabo C. Endothelial dysfunction is a potential contributor to multiple organ failure and mortality in aged mice subjected to septic shock: preclinical studies in a murine model of cecal ligation and puncture. *Crit Care* 18: 511, 2014.
64. Conrad M, Friedmann Angeli JP. Glutathione peroxidase 4 (Gpx4) and ferroptosis: what's so special about it? *Mol Cell Oncol* 2, 2015.
65. Constantinescu AA, Vink H, Spaan JA. Endothelial cell glycocalyx modulates immobilization of leukocytes at the endothelial surface. *Arterioscler Thromb Vasc Biol* 23: 1541-7, 2003.
66. Coopersmith CM, De Backer D, Deutschman CS, Ferrer R, Lat I, Machado FR, Martin GS, Martin-Loeches I, Nunnally ME, Antonelli M, Evans LE, Hellman J, Jog S, Kesecioglu J, Levy MM, Rhodes A. Surviving sepsis campaign: research priorities for sepsis and septic shock. *Intensive Care Med*, 2018.
67. Corda S, Laplace C, Vicaut E, Duranteau J. Rapid reactive oxygen species production by mitochondria in endothelial cells exposed to tumor necrosis factor-alpha is mediated by ceramide. *Am J Respir Cell Mol Biol* 24: 762-8, 2001.
68. Costa NA, Gut AL, Azevedo PS, Tanni SE, Cunha NB, Fernandes AAH, Polegato BF, Zornoff LAM, de Paiva SAR, Balbi AL, Ponce D, Minicucci MF. Protein carbonyl concentration as a biomarker for development and mortality in sepsis-induced acute kidney injury. *Biosci Rep* 38, 2018.
69. Crimi E, Sica V, Williams-Ignarro S, Zhang H, Slutsky AS, Ignarro LJ, Napoli C. The role of oxidative stress in adult critical care. *Free Radic Biol Med* 40: 398-406, 2006.
70. Cupp-Sutton KA, Ashby MT. Biological Chemistry of Hydrogen Selenide. *Antioxidants (Basel)* 5, 2016.
71. De Backer D, Hollenberg S, Boerma C, Goedhart P, Buchele G, Ospina-Tascon G, Dobbe I, Ince C. How to evaluate the microcirculation: report of a round table conference. *Crit Care* 11: R101, 2007.
72. De Backer D, Orbegozo Cortes D, Donadello K, Vincent JL. Pathophysiology of microcirculatory dysfunction and the pathogenesis of septic shock. *Virulence* 5: 73-9, 2014.
73. De Backer D, Ospina-Tascon G, Salgado D, Favory R, Creteur J, Vincent JL. Monitoring the microcirculation in the critically ill patient: current methods and future approaches. *Intensive Care Med*, 2010.
74. de Souza LF, Pearson AG, Pace PE, Dafre AL, Hampton MB, Meotti FC, Winterbourn CC. Peroxiredoxin expression and redox status in neutrophils and HL-60 cells. *Free Radic Biol Med* 135: 227-234, 2019.
75. Degli Esposti M. Bioenergetic evolution in proteobacteria and mitochondria. *Genome Biol Evol* 6: 3238-51, 2014.
76. Delano M, Ward P. Sepsis-induced immune dysfunction: can immune therapies reduce mortality? *J Clin Invest* 126: 23-31, 2016.
77. Delano MJ, Kelly-Scumpia KM, Thayer TC, Winfield RD, Scumpia PO, Cuenca AG, Harrington PB, O'Malley KA, Warner E, Gabilovich S, Mathews CE, Laface D, Heyworth PG, Ramphal R, Strieter RM, Moldawer LL, Efron PA. Neutrophil mobilization from the bone marrow during polymicrobial sepsis is dependent on CXCL12 signaling. *J Immunol* 187: 911-8, 2011.
78. Delgado-Rizo V, Martínez-Guzmán MA, Iñiguez-Gutiérrez L, García-Orozco A, Alvarado-Navarro A, Fafutis-Morris M. Neutrophil Extracellular Traps and Its Implications in Inflammation: An Overview. *Frontiers in Immunology* 8: 81, 2017.

79. Dewitte A, Lepreux S, Villeneuve J, Rigotherier C, Combe C, Ouattara A, Ripoche J. Blood platelets and sepsis pathophysiology: A new therapeutic prospect in critical ill patients? *Annals of Intensive Care* 7: 115, 2017.
80. Dickerhof N, Isles V, Pattemore P, Hampton MB, Kettle AJ. Exposure of *Pseudomonas aeruginosa* to bactericidal hypochlorous acid during neutrophil phagocytosis is compromised in cystic fibrosis. *J Biol Chem* 294: 13502-13514, 2019.
81. Dinoso J, Gutierrez J, Choy D, Kummerfeld S, Baruch A, Chambers H, Rosenberger C. Understanding heterogeneity in the host response to *Staphylococcus aureus* infection for prognostic biomarker discovery. *Crit Care* 18: P14, 2014.
82. Dogné S, Flamion B. Endothelial Glycocalyx Impairment in Disease: Focus on Hyaluronan Shedding. *Am J Pathol* 190: 768-780, 2020.
83. Dreher I, Jakobs TC, Kohrle J. Cloning and characterization of the human selenoprotein P promoter. Response of selenoprotein P expression to cytokines in liver cells. *J Biol Chem* 272: 29364-71, 1997.
84. Effenberger-Neidnicht K, Hartmann M. Mechanisms of Hemolysis During Sepsis. *Inflammation* 41: 1569-1581, 2018.
85. Emre MH, Düzova H, Sancak B, Polat A, Erdoğan H, Yologlu S. Serum selenium response to maximal anaerobic exercise among sportsmen trained at various levels. *The Journal of Trace Elements in Experimental Medicine* 17: 93-100, 2004.
86. Endo M, Oyadomari S, Suga M, Mori M, Gotoh T. The ER stress pathway involving CHOP is activated in the lungs of LPS-treated mice. *J Biochem* 138: 501-7, 2005.
87. Esmon CT. The interactions between inflammation and coagulation. *Br J Haematol* 131: 417-30, 2005.
88. Fink MP. Reactive oxygen species as mediators of organ dysfunction caused by sepsis, acute respiratory distress syndrome, or hemorrhagic shock: potential benefits of resuscitation with Ringer's ethyl pyruvate solution. *Curr Opin Clin Nutr Metab Care* 5: 167-74, 2002.
89. Fink MP. Animal models of sepsis. *Virulence* 5: 143-53, 2014.
90. Fink MP, Warren HS. Strategies to improve drug development for sepsis. *Nat Rev Drug Discov* 13: 741-58, 2014.
91. Forceville X, Mostert V, Pierantoni A, Vitoux D, Le Toumelin P, Plouvier E, Dehoux M, Thuillier F, Combes A. Selenoprotein P, Rather than Glutathione Peroxidase, as a Potential Marker of Septic Shock and Related Syndromes. *Eur Surg Res* 43: 338-347, 2009.
92. Forceville X, Van Antwerpen P. Selenocompounds and selenium: A Biochemical Approach to Sepsis. In: *Yearbook of Intensive Care and Emergency Medicine 2008*. edited by Vincent JL. Berlin: Springer-Verlag; 2008. pp. 454-469.
93. Forceville X, Vitoux D, Gauzit R, Combes A, Lahilaire P, Chappuis P. Selenium, systemic immune response syndrome, sepsis, and outcome in critically ill patients. *Crit Care Med* 26: 1536-44, 1998.
94. Fox ED, Heffernan DS, Cioffi WG, Reichner JS. Neutrophils from critically ill septic patients mediate profound loss of endothelial barrier integrity. *Crit Care* 17: R226, 2013.
95. Franco RF, de Jonge E, Dekkers PE, Timmerman JJ, Spek CA, van Deventer SJ, van Deursen P, van Kerkhoff L, van Gemen B, ten Cate H, van der Poll T, Reitsma PH. The in vivo kinetics of tissue factor messenger RNA expression during human endotoxemia: relationship with activation of coagulation. *Blood* 96: 554-9., 2000.
96. Frein D, Schildknecht S, Bachschmid M, Ullrich V. Redox regulation: a new challenge for pharmacology. *Biochem Pharmacol* 70: 811-23, 2005.
97. Gallagher R, Collins S, Trujillo J, McCredie K, Ahearn M, Tsai S, Metzgar R, Aulakh G, Ting R, Ruscetti F, Gallo R. Characterization of the continuous, differentiating myeloid cell line (HL-60) from a patient with acute promyelocytic leukemia. *Blood* 54: 713-33, 1979.
98. Galley HF. Oxidative stress and mitochondrial dysfunction in sepsis. *Br J Anaesth* 107: 57-64, 2011.
99. Gamarra Y, Santiago FC, Molina-López J, Castaño J, Herrera-Quintana L, Domínguez Á, Planells E. Pyroglutamic acidosis by glutathione regeneration blockage in critical patients with septic shock. *Crit Care* 23: 162, 2019.
100. Gaudette S, Hughes D, Boller M. The endothelial glycocalyx: Structure and function in health and critical illness. *J Vet Emerg Crit Care (San Antonio)* 30: 117-134, 2020.
101. Ghafourifar P, Richter C. Nitric oxide synthase activity in mitochondria. *FEBS Lett* 418: 291-6, 1997.
102. Gill SE, Rohan M, Mehta S. Role of pulmonary microvascular endothelial cell apoptosis in murine sepsis-induced lung injury in vivo. *Respir Res* 16, 2015.
103. Gladyshev VN. Eukaryotic Selenoproteomes. In: *Selenium: Its Molecular Biology and Role in Human Health*. edited by Hatfield DL, Schweizer U, Tsuji PA, Gladyshev VN. Cham: Springer International Publishing; 2016. pp. 127-139.
104. Gladyshev VN, Arnér ES, Berry MJ, Brigelius-Flohé R, Bruford EA, Burk RF, Carlson BA, Castellano S, Chavatte L, Conrad M, Copeland PR, Diamond AM, Driscoll DM, Ferreira A, Flohé L, Green FR, Guigó R, Handy DE, Hatfield DL, Hesketh J, Hoffmann PR, Holmgren A, Hondal RJ, Howard MT, Huang K, Kim HY, Kim IY, Köhrle J, Krol A, Kryukov GV, Lee BJ, Lee BC, Lei XG, Liu Q, Lescure A, Lobanov AV, Loscalzo J, Maiorino M, Mariotti M, Sandeep Prabhu K, Rayman MP, Rozovsky S, Salinas G, Schmidt EE, Schomburg L, Schweizer U, Simonović M, Sunde RA, Tsuji PA, Tweedie S,

- Ursini F, Whanger PD, Zhang Y. Selenoprotein Gene Nomenclature*. *J Biol Chem* 291: 24036-40, 2016.
105. Gladyshev VN, Kryukov GV. Evolution of selenocysteine-containing proteins: significance of identification and functional characterization of selenoproteins. *Biofactors* 14: 87-92., 2001.
106. Gloire G, Legrand-Poels S, Piette J. NF-kappaB activation by reactive oxygen species: fifteen years later. *Biochem Pharmacol* 72: 1493-505, 2006.
107. Goligorsky MS, Sun D. Glycocalyx in Endotoxemia and Sepsis. *Am J Pathol* 190: 791-798, 2020.
108. Gordon S. Phagocytosis: An Immunobiologic Process. *Immunity* 44: 463-475, 2016.
109. Granger DN, Kvietys PR. Reperfusion injury and reactive oxygen species: The evolution of a concept☆. *Redox Biol* 6: 524-51, 2015.
110. Grootjans J, Lenaerts K, Buurman WA, Dejong CH, Derikx JP. Life and death at the mucosal-luminal interface: New perspectives on human intestinal ischemia-reperfusion. *World J Gastroenterol* 22: 2760-70, 2016.
111. Grootjans J, Lenaerts K, Derikx JP, Matthijsen RA, de Bruine AP, van Bijnen AA, van Dam RM, Dejong CH, Buurman WA. Human intestinal ischemia-reperfusion-induced inflammation characterized: experiences from a new translational model. *Am J Pathol* 176: 2283-91, 2010.
112. Hail N, Jr., Cortes M, Drake EN, Spallholz JE. Cancer chemoprevention: a radical perspective. *Free Radic Biol Med* 45: 97-110, 2008.
113. Halliwell B. Phagocyte-derived reactive species: salvation or suicide? *Trends Biochem Sci* 31: 509-15, 2006.
114. Halliwell B. Reactive species and antioxidants. Redox biology is a fundamental theme of aerobic life. *Plant Physiol* 141: 312-22, 2006.
115. Halliwell B, Gutteridge JMC. *Free Radicals in Biology and Medicine* Oxford: Oxford university Press; 1999. 936 p.
116. Hampton MB, Kettle AJ, Winterbourn CC. Inside the neutrophil phagosome: oxidants, myeloperoxidase, and bacterial killing. *Blood* 92: 3007-17, 1998.
117. Hanschmann EM, Godoy JR, Berndt C, Hudemann C, Lillig CH. Thioredoxins, Glutaredoxins, and Peroxiredoxins—Molecular Mechanisms and Health Significance: from Cofactors to Antioxidants to Redox Signaling. *Antioxid Redox Signal* 19: 1539-605, 2013.
118. Harrison I, Littlejohn D, Fell GS. Distribution of selenium in human blood plasma and serum. *Analyst* 121: 189-194, 1996.
119. Harrois A, Huet O, Duranteau J. Alterations of mitochondrial function in sepsis and critical illness. *Curr Opin Anaesthesiol* 22: 143-9, 2009.
120. Hashimoto Y, Itoh K, Nishida K, Okano T, Miyazawa Y, Okinaga K. Rapid superoxide production by endothelial cells and their injury upon reperfusion. *J Surg Res* 57: 693-7, 1994.
121. Hatfield DL, Gladyshev VN. How selenium has altered our understanding of the genetic code. *Mol Cell Biol* 22: 3565-76., 2002.
122. He P, Talukder MAH, Gao F. Oxidative Stress and Microvessel Barrier Dysfunction. *Front Physiol* 11: 472, 2020.
123. Henderson DA, Inglesby TV, Bartlett JG, Ascher MS, Eitzen E, Jahrling PB, Hauer J, Layton M, McDade J, Osterholm MT, O'Toole T, Parker G, Perl T, Russell PK, Tonat K. Smallpox as a biological weapon: medical and public health management. Working Group on Civilian Biodefense. *Jama* 281: 2127-37, 1999.
124. Herrman JL. The properties of a rat serum protein labelled by the injection of sodium selenite. *Biochim Biophys Acta* 500: 61-70, 1977.
125. Heyland DK, Dhaliwal R, Suchner U, Berger MM. Antioxidant nutrients: a systematic review of trace elements and vitamins in the critically ill patient. *Intensive Care Med* 31: 327-37. Epub 2004 Dec 17., 2005.
126. Hill KE, Wu S, Motley AK, Stevenson TD, Winfrey VP, Capecchi MR, Atkins JF, Burk RF. Production of Selenoprotein P (Sepp1) by Hepatocytes Is Central to Selenium Homeostasis*. *J Biol Chem* 287: 40414-24, 2012.
127. Hill KE, Xia Y, Akesson B, Boeglin ME, Burk RF. Selenoprotein P concentration in plasma is an index of selenium status in selenium-deficient and selenium-supplemented Chinese subjects. *J Nutr* 126: 138-45, 1996.
128. Hill KE, Zhou J, McMahan WJ, Motley AK, Atkins JF, Gesteland RF, Burk RF. Deletion of selenoprotein P alters distribution of selenium in the mouse. *J Biol Chem* 278: 13640-6, 2003.
129. Hirase T, Node K. Endothelial dysfunction as a cellular mechanism for vascular failure. *Am J Physiol Heart Circ Physiol* 302: H499-505, 2012.
130. Hoefig CS, Renko K, Kohrle J, Birringer M, Schomburg L. Comparison of different selenocompounds with respect to nutritional value vs. toxicity using liver cells in culture. *J Nutr Biochem* 22: 945-55, 2011.
131. Hollenbach B, Morgenthaler NG, Struck J, Alonso C, Bergmann A, Kohrle J, Schomburg L. New assay for the measurement of selenoprotein P as a sepsis biomarker from serum. *J Trace Elem Med Biol* 22: 24-32, 2008.
132. Hondal RJ, Ma S, Caprioli RM, Hill KE, Burk RF. Heparin-binding histidine and lysine residues of rat selenoprotein P. *J Biol Chem* 276: 15823-31., 2001.

133. Hotchkiss RS, Moldawer LL, Opal SM, Reinhart K, Turnbull IR, Vincent JL. Sepsis and septic shock. *Nat Rev Dis Primers* 2: 16045, 2016.
134. Hotchkiss RS, Strasser A, McDunn JE, Swanson PE. Cell death. *N Engl J Med* 361: 1570-83, 2009.
135. Huet O, Cherreau C, Nicco C, Dupic L, Conti M, Borderie D, Pene F, Vicaut E, Benhamou D, Mira JP, Duranteau J, Batteux F. Pivotal role of glutathione depletion in plasma-induced endothelial oxidative stress during sepsis. *Crit Care Med* 36: 2328-34, 2008.
136. Huet O, Dupic L, Harrois A, Duranteau J. Oxidative stress and endothelial dysfunction during sepsis. *Front Biosci (Landmark Ed)* 16: 1986-95, 2011.
137. Iba T, Levy JH. Inflammation and thrombosis: roles of neutrophils, platelets and endothelial cells and their interactions in thrombus formation during sepsis. *J Thromb Haemost*, 2017.
138. Iba T, Levy JH. Derangement of the endothelial glycocalyx in sepsis. *J Thromb Haemost* 17: 283-294, 2019.
139. Ince C. The microcirculation is the motor of sepsis. *Crit Care* 9: S13-9. Epub 2005 Aug 25., 2005.
140. Ince C, Mayeux PR, Nguyen T, Gomez H, Kellum JA, Ospina-Tascon GA, Hernandez G, Murray P, De Backer D. The endothelium in sepsis. *Shock* 45: 259-70, 2016.
141. Jiang Q, Griffin DA, Barofsky DF, Hurst JK. Intrapagosomal chlorination dynamics and yields determined using unique fluorescent bacterial mimics. *Chem Res Toxicol* 10: 1080-9, 1997.
142. Johansson PI, Stensballe J, Ostrowski SR. Shock induced endotheliopathy (SHINE) in acute critical illness - a unifying pathophysiologic mechanism. *Crit Care* 21: 25, 2017.
143. Kang R, Zeng L, Zhu S, Xie Y, Liu J, Wen Q, Cao L, Xie M, Ran Q, Kroemer G, Wang H, Billiar TR, Jiang J, Tang D. Lipid Peroxidation Drives Gasdermin D-Mediated Pyroptosis in Lethal Polymicrobial Sepsis. *Cell Host Microbe* 24: 97-108.e4, 2018.
144. Kehrer JP. The Haber-Weiss reaction and mechanisms of toxicity. *Toxicology* 149: 43-50, 2000.
145. Kellum JA, Kong L, Fink MP, Weissfeld LA, Yealy DM, Pinsky MR, Fine J, Krichevsky A, Delude RL, Angus DC. Understanding the inflammatory cytokine response in pneumonia and sepsis: results of the Genetic and Inflammatory Markers of Sepsis (GenIMS) Study. *Arch Intern Med* 167: 1655-63, 2007.
146. Kennedy AD, DeLeo FR. Neutrophil apoptosis and the resolution of infection. *Immunol Res* 43: 25-61, 2009.
147. Keszler A, Mason RP, Hogg N. Immuno-spin trapping of hemoglobin and myoglobin radicals derived from nitrite-mediated oxidation. *Free Radic Biol Med* 40: 507-15, 2006.
148. Khan IA. Plague: the dreadful visitation occupying the human mind for centuries. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 98: 270-277, 2004.
149. Kim IY, Stadtman TC. Inhibition of NF-kappaB DNA binding and nitric oxide induction in human T cells and lung adenocarcinoma cells by selenite treatment. *Proc Natl Acad Sci U S A* 94: 12904-7, 1997.
150. Kim ND, Luster AD. The role of tissue resident cells in neutrophil recruitment. *Trends Immunol* 36: 547-55, 2015.
151. Kirkeboen KA, Strand OA. The role of nitric oxide in sepsis--an overview. *Acta Anaesthesiol Scand* 43: 275-88, 1999.
152. Kirsch J, Schneider H, Pagel JI, Rehberg M, Singer M, Hellfritsch J, Chillo O, Schubert KM, Qiu J, Pogoda K, Kameritsch P, Uhl B, Pircher J, Deindl E, Muller S, Kirchner T, Pohl U, Conrad M, Beck H. Endothelial Dysfunction, and A Prothrombotic, Proinflammatory Phenotype Is Caused by Loss of Mitochondrial Thioredoxin Reductase in Endothelium. *Arterioscler Thromb Vasc Biol* 36: 1891-9, 2016.
153. Koekkoek WA, van Zanten AR. Antioxidant Vitamins and Trace Elements in Critical Illness. *Nutr Clin Pract* 31: 457-74, 2016.
154. Kolaczowska E, Kubes P. Neutrophil recruitment and function in health and inflammation. *Nature Reviews Immunology* 13: 159-175, 2013.
155. Kozlov AV, Duvigneau JC, Miller I, Nurnberger S, Gesslbauer B, Kungl A, Ohlinger W, Hartl RT, Gille L, Staniek K, Gregor W, Haindl S, Redl H. Endotoxin causes functional endoplasmic reticulum failure, possibly mediated by mitochondria. *Biochim Biophys Acta* 1792: 521-30, 2009.
156. Krause K, Daily K, Estfanous S, Hamilton K, Badr A, Abu Khweek A, Hegazi R, Anne MN, Klamer B, Zhang X, Gavrilin MA, Pancholi V, Amer AO. Caspase-11 counteracts mitochondrial ROS-mediated clearance of Staphylococcus aureus in macrophages. *EMBO reports* 20: e48109-e48109, 2019.
157. Kurokawa S, Eriksson S, Rose KL, Wu S, Motley AK, Hill S, Winfrey VP, McDonald WH, Capecchi MR, Atkins JF, Arnér ESJ, Hill KE, Burk RF. Sepp1UF forms are N-terminal selenoprotein P truncations that have peroxidase activity when coupled with thioredoxin reductase-1. *Free Radic Biol Med* 69: 67-76, 2014.
158. Kyriakopoulos A, Behne D. Selenium-containing proteins in mammals and other forms of life. *Rev Physiol Biochem Pharmacol* 145: 1-46., 2002.
159. Labunskyy VM, Hatfield DL, Gladyshev VN. Selenoproteins: Molecular Pathways and Physiological Roles. *Physiol Rev* 94: 739-77, 2014.
160. Lamy M, Mathy-Hartert M, DEby-Dupont G. Neutrophil-induced Oxidative Stress. In: *Yearbook of Intensive Care and Emergency Medic.* edited by Vincent JL. Heidelberg: Springer-Verlag; 1996.

161. Larsen R, Gozzelino R, Jeney V, Tokaji L, Bozza FA, Japiassú AM, Bonaparte D, Cavalcante MM, Chora A, Ferreira A, Marguti I, Cardoso S, Sepúlveda N, Smith A, Soares MP. A central role for free heme in the pathogenesis of severe sepsis. *Sci Transl Med* 2: 51ra71, 2010.
162. Latunde-Dada GO. Iron metabolism: microbes, mouse, and man. *Bioessays* 31: 1309-17, 2009.
163. Leaf DE, Rajapurkar M, Lele SS, Mukhopadhyay B, Boerger EAS, Mc Causland FR, Eisenga MF, Singh K, Babitt JL, Kellum JA, Palevsky PM, Christov M, Waikar SS. Iron, Hecpidin, and Death in Human AKI. *J Am Soc Nephrol* 30: 493-504, 2019.
164. Legrand M, Klijn E, Payen D, Ince C. The response of the host microcirculation to bacterial sepsis: does the pathogen matter? *J Mol Med* 88: 127-33, 2010.
165. Lerman YV, Kim M. Neutrophil migration under normal and sepsis conditions. *Cardiovasc Hematol Disord Drug Targets* 15: 19-28, 2015.
166. Levi M, van der Poll T. Inflammation and coagulation. *Crit Care Med* 38: S26-34, 2010.
167. Levi M, van der Poll T. Endothelial injury in sepsis. *Intensive Care Med* 39: 1839-42, 2013.
168. Levi M, van der Poll T. Coagulation and sepsis. *Thromb Res* 149: 38-44, 2017.
169. Levy M, Ward NS. Introduction. In: *Sepsis, Definitions, Pathophysiology and the Challenge of Bedside Management*. edited by Ward NS, Levy M. Cham, Switzerland: Springer; 2017. pp. 3-5.
170. Levy MM, Evans LE, Rhodes A. The Surviving Sepsis Campaign Bundle: 2018 update. *Intensive Care Med*, 2018.
171. Levy R, Dana R, Hazan I, Levy I, Weber G, Smoliakov R, Pesach I, Riesenber K, Schlaeffer F. Elevated cytosolic phospholipase A(2) expression and activity in human neutrophils during sepsis. *Blood* 95: 660-5, 2000.
172. Li Z, Tan J, Shao L, Dong X, Ye RD, Chen D. Selenium-mediated protection in reversing the sensitivity of bacterium to the bactericidal antibiotics. *J Trace Elem Med Biol* 41: 23-31, 2017.
173. Ligon BL. Plague: A Review of its History and Potential as a Biological Weapon. *Seminars in Pediatric Infectious Diseases* 17: 161-170, 2006.
174. Lin SM, Wang YM, Lin HC, Lee KY, Huang CD, Liu CY, Wang CH, Kuo HP. Serum thrombomodulin level relates to the clinical course of disseminated intravascular coagulation, multiorgan dysfunction syndrome, and mortality in patients with sepsis. *Crit Care Med* 36: 683-9, 2008.
175. Linares E, Nakao LS, Augusto O, Kadiiska MB. EPR studies of in vivo radical production by lipopolysaccharide: potential role of iron mobilized from iron-nitrosyl complexes. *Free Radic Biol Med* 34: 766-73, 2003.
176. Lobanov AV, Hatfield DL, Gladyshev VN. Reduced reliance on the trace element selenium during evolution of mammals. *Genome Biol* 9: R62, 2008.
177. Loi VV, Rossius M, Antelmann H. Redox regulation by reversible protein S-thiolation in bacteria. *Front Microbiol* 6, 2015.
178. Lopes Junior E, Leite HP, Konstantyner T. Selenium and selenoproteins: from endothelial cytoprotection to clinical outcomes. *Transl Res* 208: 85-104, 2019.
179. Lorigados CB, Soriano FG, Szabo C. Pathomechanisms of myocardial dysfunction in sepsis. *Endocr Metab Immune Disord Drug Targets* 10: 274-84, 2010.
180. Lorne E, Zmijewski JW, Zhao X, Liu G, Tsuruta Y, Park YJ, Dupont H, Abraham E. Role of extracellular superoxide in neutrophil activation: interactions between xanthine oxidase and TLR4 induce proinflammatory cytokine production. *Am J Physiol Cell Physiol* 294: C985-93, 2008.
181. Macdonald J, Galley HF, Webster NR. Oxidative stress and gene expression in sepsis. *Br J Anaesth* 90: 221-32, 2003.
182. Maehira F, Luyo GA, Miyagi I, Oshiro M, Yamane N, Kuba M, Nakazato Y. Alterations of serum selenium concentrations in the acute phase of pathological conditions. *Clin Chim Acta* 316: 137-46, 2002.
183. Manda-Handzlik A, Bystrzycka W, Cieloch A, Glodkowska-Mrowka E, Jankowska-Steifer E, Heropolitanska-Pliszka E, Skrobot A, Muchowicz A, Ciepiela O, Wachowska M, Demkow U. Nitric oxide and peroxynitrite trigger and enhance release of neutrophil extracellular traps. *Cell Mol Life Sci* 77: 3059-3075, 2020.
184. Mantzaris K, Tsolaki V, Zakynthinos E. Role of Oxidative Stress and Mitochondrial Dysfunction in Sepsis and Potential Therapies. *Oxid Med Cell Longev* 2017: 5985209, 2017.
185. Mare TA, Treacher DF, Shankar-Hari M, Beale R, Lewis SM, Chambers DJ, Brown KA. The diagnostic and prognostic significance of monitoring blood levels of immature neutrophils in patients with systemic inflammation. *Crit Care* 19: 57, 2015.
186. Marechal X, Favory R, Joulin O, Montaigne D, Hassoun S, Decoster B, Zerimech F, Neviere R. Endothelial glycocalyx damage during endotoxemia coincides with microcirculatory dysfunction and vascular oxidative stress. *Shock* 29: 572-6, 2008.
187. Marshall JC, Reinhart K. Biomarkers of sepsis. *Crit Care Med* 37: 2290-8, 2009.
188. Martinez-Cayueta M. Oxygen free radicals and human disease. *Biochimie* 77: 147-61, 1995.
189. Mastronardi ML, Mostefai HA, Meziani F, Martinez MC, Asfar P, Andriantsitohaina R. Circulating microparticles from septic shock patients exert differential tissue expression of enzymes related to inflammation and oxidative stress. *Crit Care Med* 39: 1739-48, 2011.

190. Mathias B, Delmas A, Ozrazgat-Baslanti T, Vanzant E, Szpila B, Mohr A, Moore F, Brakenridge S, Brumback B, Moldawer L, Efron P, and the Sepsis C. Human Myeloid-derived Suppressor Cells are Associated With Chronic Immune Suppression After Severe Sepsis/Septic Shock. *Ann Surg* 265: 827-834, 2017.
191. Matzinger P. The danger model: a renewed sense of self. *Science* 296: 301-5, 2002.
192. Mayadas TN, Cullere X, Lowell CA. The Multifaceted Functions of Neutrophils. *Annu Rev Pathol* 9: 181-218, 2014.
193. Maynar M, Munoz D, Alves J, Barrientos G, Grijota FJ, Robles MC, Llerena F. Influence of an Acute Exercise Until Exhaustion on Serum and Urinary Concentrations of Molybdenum, Selenium, and Zinc in Athletes. *Biol Trace Elem Res* 186: 361-369, 2018.
194. Meegan JE, Shaver CM, Putz ND, Jesse JJ, Landstreet SR, Lee HNR, Sidorova TN, McNeil JB, Wynn JL, Cheung-Flynn J, Komalavilas P, Brophy CM, Ware LB, Bastarache JA. Cell-free hemoglobin increases inflammation, lung apoptosis, and microvascular permeability in murine polymicrobial sepsis. *PLoS One* 15: e0228727, 2020.
195. Merlino R, Gaillard JL, Fauchere JL, Chaumont P, Droy-Lefaix MT, Descamps P, Ricour C, Veron M. In vitro quantitative model of catheter infection during simulated parenteral nutrition. *J Clin Microbiol* 26: 1659-64, 1988.
196. Merz T, Denoix N, Huber-Lang M, Singer M, Radermacher P, McCook O. Microcirculation vs. Mitochondria—What to Target? *Frontiers in Medicine* 7, 2020.
197. Metcalfe DD, Thompson HL, Klebanoff SJ, Henderson WR, Jr. Oxidative degradation of rat mast-cell heparin proteoglycan. *Biochem J* 272: 51-7, 1990.
198. Middleton E, Rondina MT. Platelets in infectious disease. *Hematology Am Soc Hematol Educ Program* 2016: 256-261, 2016.
199. Miller A. Identifying sepsis too late. *Nursing* 44: 12-4, 2014.
200. Mooney JP, Galloway LJ, Riley EM. Malaria, anemia, and invasive bacterial disease: A neutrophil problem? *J Leukoc Biol* 105: 645-655, 2019.
201. Mostert V. Selenoprotein P: properties, functions, and regulation. *Arch Biochem Biophys* 376: 433-8., 2000.
202. Muhl D, Woth G, Drenkovics L, Varga A, Ghosh S, Csontos C, Bogar L, Weber G, Lantos J. Comparison of oxidative stress & leukocyte activation in patients with severe sepsis & burn injury. *Indian J Med Res* 134: 69-78, 2011.
203. Nourshargh S, Alon R. Leukocyte migration into inflamed tissues. *Immunity* 41: 694-707, 2014.
204. Novelli GP. Role of free radicals in septic shock. *J Physiol Pharmacol* 48: 517-27, 1997.
205. Oldfield JE. Selenium: A historical perspective. In: *Selenium: Its molecular biology and role in human health*. edited by Hatfield DL, J. BM, N. GV. New York: Springer; 2006. pp. 1-6.
206. Oliveira YPAd, Pontes-de-Carvalho LC, Couto RD, Noronha-Dutra AA. Oxidative stress in sepsis. Possible production of free radicals through an erythrocyte-mediated positive feedback mechanism. *The Brazilian Journal of Infectious Diseases* 21: 19-26, 2017.
207. Opal S. Severe Sepsis and Septic Shock. In: *Surgery, Basic Science and Clinical Evidence*. New York: Springer; 2008. pp. 287-304.
208. Opal SM, Dellinger RP, Vincent JL, Masur H, Angus DC. The next generation of sepsis clinical trial designs: what is next after the demise of recombinant human activated protein C?*. *Crit Care Med* 42: 1714-21, 2014.
209. Opal SM, van der Poll T. Endothelial barrier dysfunction in septic shock. *J Intern Med* 277: 277-293, 2015.
210. Ostrowski SR, Haase N, Muller RB, Moller MH, Pott FC, Perner A, Johansson PI. Association between biomarkers of endothelial injury and hypocoagulability in patients with severe sepsis: a prospective study. *Crit Care* 19: 191, 2015.
211. Osuchowski MF, Remick DG, Lederer JA, Lang CH, Aasen AO, Aibiki M, Azevedo LC, Bahrami S, Boros M, Cooney R, Cuzzocrea S, Jiang Y, Junger WG, Hirasawa H, Hotchkiss RS, Li XA, Radermacher P, Redl H, Salomao R, Soebandrio A, Thiemermann C, Vincent JL, Ward P, Yao YM, Yu HP, Zingarelli B, Chaudry IH. Abandon the mouse research ship? Not just yet! *Shock* 41: 463-75, 2014.
212. Osuchowski MF, Welch K, Siddiqui J, Remick DG. Circulating cytokine/inhibitor profiles reshape the understanding of the SIRS/CARS continuum in sepsis and predict mortality. *J Immunol* 177: 1967-74, 2006.
213. Packer MA, Porteous CM, Murphy MP. Superoxide production by mitochondria in the presence of nitric oxide forms peroxynitrite. *Biochem Mol Biol Int* 40: 527-34, 1996.
214. Papp LV, Lu J, Striebel F, Kennedy D, Holmgren A, Khanna KK. The Redox State of SECIS Binding Protein 2 Controls Its Localization and Selenocysteine Incorporation Function. *Molecular and Cellular Biology* 26: 4895, 2006.
215. Parlato M, Cavaillon JM. Host response biomarkers in the diagnosis of sepsis: a general overview. *Methods Mol Biol* 1237: 149-211, 2015.

216. Parra-Ortiz E, Browning KL, Damgaard LSE, Nordström R, Micciulla S, Bucciarelli S, Malmsten M. Effects of oxidation on the physicochemical properties of polyunsaturated lipid membranes. *J Colloid Interface Sci* 538: 404-419, 2019.
217. Pascual C, Bredle D, Karzai W, Meier-Hellmann A, Oberhoffer M, Reinhart K. Effect of plasma and LPS on respiratory burst of neutrophils in septic patients. *Intensive Care Med* 24: 1181-6., 1998.
218. Patruta SI, Hörl WH. Iron and infection. *Kidney Int Suppl* 69: S125-30, 1999.
219. Paunel-Görgülü A, Kirichevska T, Lögters T, Windolf J, Flohé S. Molecular Mechanisms Underlying Delayed Apoptosis in Neutrophils from Multiple Trauma Patients with and without Sepsis. *Mol Med* 18: 325-35, 2012.
220. Persson-Moschos M. Selenoprotein P. *Cell Mol Life Sci* 57: 1836-45., 2000.
221. Piagnerelli M, Cotton F, Herpain A, Rapotec A, Chatti R, Gulbis B, Vincent JL. Time course of iron metabolism in critically ill patients. *Acta Clin Belg* 68: 22-7, 2013.
222. Pierrakos C, Vincent JL. Sepsis biomarkers: a review. *Crit Care* 14: R15, 2010.
223. Pinkerton MH, Copeland PR. Eukaryotic Mechanisms of Selenocysteine Incorporation and Its Reconstitution In Vitro. In: *Selenium: Its Molecular Biology and Role in Human Health*. edited by Hatfield DL, Schweizer U, Tsuji PA, Gladyshev VN. Cham: Springer International Publishing; 2016. pp. 13-24.
224. Pollock JD, Williams DA, Gifford MA, Li LL, Du X, Fisherman J, Orkin SH, Doerschuk CM, Dinauer MC. Mouse model of X-linked chronic granulomatous disease, an inherited defect in phagocyte superoxide production. *Nat Genet* 9: 202-9, 1995.
225. Pomara C, Riezzo I, Bello S, De Carlo D, Neri M, Turillazzi E. A Pathophysiological Insight into Sepsis and Its Correlation with Postmortem Diagnosis. *Mediators Inflamm* 2016, 2016.
226. Prauchner CA. Oxidative stress in sepsis: Pathophysiological implications justifying antioxidant co-therapy. *Burns* 43: 471-485, 2017.
227. Preiser JC. Oxidative stress. *JPEN J Parenter Enteral Nutr* 36: 147-54, 2012.
228. Prescott HC, Angus DC. Enhancing Recovery From Sepsis: A Review. *Jama* 319: 62-75, 2018.
229. Pries AR, Kuebler WM. Normal endothelium. *Handb Exp Pharmacol*: 1-40, 2006.
230. Pries AR, Reglin B, Secomb TW. Structural response of microcirculatory networks to changes in demand: information transfer by shear stress. *Am J Physiol Heart Circ Physiol* 284: H2204-12, 2003.
231. Pries AR, Secomb TW. Microvascular blood viscosity in vivo and the endothelial surface layer. *Am J Physiol Heart Circ Physiol* 289: H2657-64, 2005.
232. Pries AR, Secomb TW, Gaetgens P. The endothelial surface layer. *Pflugers Arch* 440: 653-66, 2000.
233. Protti A, Singer M. Oxidative stress and critical illness. *Minerva Anesthesiol* 73: 255-7, 2007.
234. Radi R. Peroxynitrite, a Stealthy Biological Oxidant. *Journal of Biological Chemistry* 288: 26464-26472, 2013.
235. Radi R, Cassina A, Hodara R, Quijano C, Castro L. Peroxynitrite reactions and formation in mitochondria. *Free Radic Biol Med* 33: 1451-64, 2002.
236. Reid VL, Webster NR. Role of microparticles in sepsis. *Br J Anaesth* 109: 503-13, 2012.
237. Reinhart K, Bauer M, Riedemann NC, Hartog CS. New approaches to sepsis: molecular diagnostics and biomarkers. *Clin Microbiol Rev* 25: 609-34, 2012.
238. Reiss M, Roos D. Differences in oxygen metabolism of phagocytosing monocytes and neutrophils. *J Clin Invest* 61: 480-8, 1978.
239. Ren X, Zou L, Zhang X, Branco V, Wang J, Carvalho C, Holmgren A, Lu J. Redox Signaling Mediated by Thioredoxin and Glutathione Systems in the Central Nervous System. *Antioxid Redox Signal* 27: 989-1010, 2017.
240. Renko K, Hofmann PJ, Stoedter M, Hollenbach B, Behrends T, Kohrle J, Schweizer U, Schomburg L. Down-regulation of the hepatic selenoprotein biosynthesis machinery impairs selenium metabolism during the acute phase response in mice. *Faseb J* 23: 1758-65, 2009.
241. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, Kumar A, Sevransky JE, Sprung CL, Nunnally ME, Rochweg B, Rubinfeld GD, Angus DC, Annane D, Beale RJ, Bellinghan GJ, Bernard GR, Chiche J-D, Coopersmith C, De Backer DP, French CJ, Fujishima S, Gerlach H, Hidalgo JL, Hollenberg SM, Jones AE, Karnad DR, Kleinpell RM, Koh Y, Lisboa TC, Machado FR, Marini JJ, Marshall JC, Mazuski JE, McIntyre LA, McLean AS, Mehta S, Moreno RP, Myburgh J, Navalesi P, Nishida O, Osborn TM, Perner A, Plunkett CM, Ranieri M, Schorr CA, Seckel MA, Seymour CW, Shieh L, Shukri KA, Simpson SQ, Singer M, Thompson BT, Townsend SR, Van der Poll T, Vincent J-L, Wiersinga WJ, Zimmerman JL, Dellinger RP. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. *Intensive Care Medicine*: 1-74, 2017.
242. Rieger JM, Shah AR, Gidday JM. Ischemia-reperfusion injury of retinal endothelium by cyclooxygenase- and xanthine oxidase-derived superoxide. *Exp Eye Res* 74: 493-501, 2002.
243. Rocha M, Herance R, Rovira S, Hernandez-Mijares A, Victor VM. Mitochondrial dysfunction and antioxidant therapy in sepsis. *Infect Disord Drug Targets* 12: 161-78, 2012.
244. Rosen GM, Pou S, Ramos CL, Cohen MS, Britigan BE. Free radicals and phagocytic cells. *Faseb j* 9: 200-9, 1995.
245. Rubio-Gayosso I, Platts SH, Duling BR. Reactive oxygen species mediate modification of glycocalyx during ischemia-reperfusion injury. *Am J Physiol Heart Circ Physiol* 290: H2247-56, 2006.

246. Rudiger A, Stotz M, Singer M. Cellular processes in sepsis. *Swiss Med Wkly* 138: 629-34, 2008.
247. Rungelrath V, Kobayashi SD, DeLeo FR. Neutrophils in innate immunity and systems biology-level approaches. *Wiley Interdiscip Rev Syst Biol Med* 12: e1458, 2020.
248. Saito Y, Hayashi T, Tanaka A, Watanabe Y, Suzuki M, Saito E, Takahashi K. Selenoprotein P in human plasma as an extracellular phospholipid hydroperoxide glutathione peroxidase. Isolation and enzymatic characterization of human selenoprotein p. *J Biol Chem* 274: 2866-71, 1999.
249. Saito Y, Sato N, Hirashima M, Takebe G, Nagasawa S, Takahashi K. Domain structure of bi-functional selenoprotein P. *Biochem J* 381: 841-6, 2004.
250. Sakaguchi S, Furusawa S. Oxidative stress and septic shock: metabolic aspects of oxygen-derived free radicals generated in the liver during endotoxemia. *FEMS Immunol Med Microbiol* 47: 167-77, 2006.
251. Sakr Y, Reinhart K, Bloos F, Marx G, Russwurm S, Bauer M, Brunkhorst F. Time course and relationship between plasma selenium concentrations, systemic inflammatory response, sepsis, and multiorgan failure. *Br J Anaesth* 98: 775-84, 2007.
252. Sandre C, Agay D, Ducros V, Van Uye A, Cruz C, Chancerelle Y, Rousset AM. Early evolution of selenium status and oxidative stress parameters in rat models of thermal injury. *J Trace Elem Med Biol* 17: 313-8, 2004.
253. Sato K, Kadiiska MB, Ghio AJ, Corbett J, Fann YC, Holland SM, Thurman RG, Mason RP. In vivo lipid-derived free radical formation by NADPH oxidase in acute lung injury induced by lipopolysaccharide: a model for ARDS. *Faseb j* 16: 1713-20, 2002.
254. Schamberger AC, Schiller HB, Fernandez IE, Sterclova M, Heinzelmann K, Hennen E, Hatz R, Behr J, Vašáková M, Mann M, Eickelberg O, Staab-Weijnitz CA. Glutathione peroxidase 3 localizes to the epithelial lining fluid and the extracellular matrix in interstitial lung disease. *Sci Rep* 6, 2016.
255. Schiller HJ, Reilly PM, Bulkley GB. Tissue perfusion in critical illnesses. Antioxidant therapy. *Crit Care Med* 21: S92-102, 1993.
256. Schouten M, Wiersinga WJ, Levi M, van der Poll T. Inflammation, endothelium, and coagulation in sepsis. *J Leukoc Biol*, 2007.
257. Schouten M, Wiersinga WJ, Levi M, van der Poll T. Inflammation, endothelium, and coagulation in sepsis. *J Leukoc Biol* 83: 536-45, 2008.
258. Schromm A, Alexander C, Gutschmann T, Andrä J, Stamme C. Pathogen in Sepsis: Gram-negative Bacterial PAMPs and PRRs. In: *Sepsis and Non-Infectious Systemic Inflammation*. edited by Cavailon JM, Adrie C. Wainheim: Willey-VCH; 2009. pp. 79-108.
259. Schwarz M, Lossow K, Schirl K, Hackler J, Renko K, Kopp JF, Schwerdtle T, Schomburg L, Kipp AP. Copper interferes with selenoprotein synthesis and activity. *Redox Biol* 37: 101746, 2020.
260. Schweizer U. Selenoproteins in Nervous System: Development, Function and Degeneration. In: *Selenium: Its Molecular Biology and Role in Human Health*. edited by Hatfield DL, Schweizer U, Tsuji PA, Gladyshev VN. Cham: Springer International Publishing; 2016. pp. 427-433.
261. Schweizer U, Schomburg L, Köhrle J. Selenoprotein P and Selenium Distribution in Mammals. In: *Selenium: Its Molecular Biology and Role in Human Health*. edited by Hatfield DL, Schweizer U, Tsuji PA, Gladyshev VN. Cham: Springer International Publishing; 2016. pp. 261-274.
262. Schweizer U, Streckfuss F, Pelt P, Carlson BA, Hatfield DL, Köhrle J, Schomburg L. Hepatically derived selenoprotein P is a key factor for kidney but not for brain selenium supply. *Biochem J* 386: 221-6., 2005.
263. Seeley EJ, Matthay MA, Wolters PJ. Inflection points in sepsis biology: from local defense to systemic organ injury. *Am J Physiol Lung Cell Mol Physiol* 303: L355-63, 2012.
264. Segal AW, Clark J, Allison AC. Tracing the fate of oxygen consumed during phagocytosis by human neutrophils with $^{15}O_2$. *Clin Sci Mol Med* 55: 413-5, 1978.
265. Segal AW, Coade SB. Kinetics of oxygen consumption by phagocytosing human neutrophils. *Biochem Biophys Res Commun* 84: 611-7, 1978.
266. Shapira L, Borinski R, Sela MN, Soskolne A. Superoxide formation and chemiluminescence of peripheral polymorphonuclear leukocytes in rapidly progressive periodontitis patients. *J Clin Periodontol* 18: 44-8, 1991.
267. Shaver CM, Paul MG, Putz ND, Landstreet SR, Kuck JL, Scarfe L, Skrypnik N, Yang H, Harrison FE, de Caestecker MP, Bastarache JA, Ware LB. Cell-free hemoglobin augments acute kidney injury during experimental sepsis. *Am J Physiol Renal Physiol* 317: F922-f929, 2019.
268. Shen XF, Cao K, Jiang JP, Guan WX, Du JF. Neutrophil dysregulation during sepsis: an overview and update. *J Cell Mol Med*, 2017.
269. Sherlock LG, Sjöstrom K, Sian L, Delaney C, Tipple TE, Krebs NF, Nozik-Grayck E, Wright CJ. Hepatic-Specific Decrease in the Expression of Selenoenzymes and Factors Essential for Selenium Processing After Endotoxemia. *Frontiers in Immunology* 11: 2901, 2020.
270. Shiloh MU, MacMicking JD, Nicholson S, Brause JE, Potter S, Marino M, Fang F, Dinauer M, Nathan C. Phenotype of mice and macrophages deficient in both phagocyte oxidase and inducible nitric oxide synthase. *Immunity* 10: 29-38, 1999.
271. Sies H. Oxidative stress: from basic research to clinical application. *Am J Med* 91: 31S-38S, 1991.

272. Sieve I, Münster-Kühnel AK, Hilfiker-Kleiner D. Regulation and function of endothelial glycocalyx layer in vascular diseases. *Vascul Pharmacol* 100: 26-33, 2018.
273. Silvestre-Roig C, Fridlender ZG, Glogauer M, Scapini P. Neutrophil Diversity in Health and Disease. *Trends Immunol* 40: 565-583, 2019.
274. Singer M. Mitochondrial function in sepsis: acute phase versus multiple organ failure. *Crit Care Med* 35: S441-8, 2007.
275. Singer M. Critical illness and flat batteries. *Crit Care* 21: 309, 2017.
276. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, Bellomo R, Bernard GR, Chiche JD, Coopersmith CM, Hotchkiss RS, Levy MM, Marshall JC, Martin GS, Opal SM, Rubenfeld GD, van der Poll T, Vincent JL, Angus DC. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *Jama* 315: 801-10, 2016.
277. Singh KK. Mitochondria damage checkpoint, aging, and cancer. *Ann N Y Acad Sci* 1067: 182-90, 2006.
278. Song JW, Zullo J, Lipphardt M, Dragovich M, Zhang FX, Fu B, Goligorsky MS. Endothelial glycocalyx--the battleground for complications of sepsis and kidney injury. *Nephrol Dial Transplant* 33: 203-211, 2018.
279. Souza AC, Yuen PS, Star RA. Microparticles: markers and mediators of sepsis-induced microvascular dysfunction, immunosuppression, and AKI. *Kidney Int* 87: 1100-8, 2015.
280. Souza-Fonseca-Guimaraes F, Adib-Conquy M, Cavaillon JM. Natural killer (NK) cells in antibacterial innate immunity: angels or devils? *Mol Med* 18: 270-85, 2012.
281. Souza-Fonseca-Guimaraes F, Cavaillon JM, Adib-Conquy M. Bench-to-bedside review: Natural killer cells in sepsis - guilty or not guilty? *Crit Care* 17: 235, 2013.
282. Stadtman TC. Selenium biochemistry. *Science* 183: 915-22, 1974.
283. Stadtman TC. New biologic functions--selenium-dependent nucleic acids and proteins. *Fundam Appl Toxicol* 3: 420-3, 1983.
284. Stadtman TC. Selenoproteins--tracing the role of a trace element in protein function. *PLoS Biol* 3: e421, 2005.
285. Stearns-Kurosawa DJ, Osuchowski MF, Valentine C, Kurosawa S, Remick DG. The pathogenesis of sepsis. *Annu Rev Pathol* 6: 19-48, 2011.
286. Stefanova D, Raychev A, Arezes J, Ruchala P, Gabayan V, Skurnik M, Dillon BJ, Horwitz MA, Ganz T, Bulut Y, Nemeth E. Endogenous hepcidin and its agonist mediate resistance to selected infections by clearing non-transferrin-bound iron. *Blood* 130: 245-257, 2017.
287. Stefanova D, Raychev A, Deville J, Humphries R, Campeau S, Ruchala P, Nemeth E, Ganz T, Bulut Y. Hepcidin Protects against Lethal Escherichia coli Sepsis in Mice Inoculated with Isolates from Septic Patients. *Infect Immun* 86, 2018.
288. Steinbrenner H, Speckmann B, Klotz L-O. Selenoproteins: Antioxidant selenoenzymes and beyond. *Archives of Biochemistry and Biophysics* 595: 113-119, 2016.
289. Stewart MS, Spallholz JE, Neldner KH, Pence BC. Selenium compounds have disparate abilities to impose oxidative stress and induce apoptosis. *Free Radic Biol Med* 26: 42-8, 1999.
290. Strand OA, Leone A, Giercksky KE, Kirkeboen KA. Nitric oxide indices in human septic shock. *Critical care medicine* 28: 2779-2785, 2000.
291. Su F, Wang Z, Xavier F, Vincent J-L. Blood Selenium Concentrations in Septic Shock Due to Peritonitis. *Shock* 26: 38-39, 2006.
292. Subramani K, Raju SP, Chu X, Warren M, Pandya CD, Hoda N, Fulzele S, Raju R. Effect of plasma-derived extracellular vesicles on erythrocyte deformability in polymicrobial sepsis. *Int Immunopharmacol* 65: 244-247, 2018.
293. Swain SD, Rohn TT, Quinn MT. Neutrophil priming in host defense: role of oxidants as priming agents. *Antioxid Redox Signal* 4: 69-83, 2002.
294. Sweeney TE, Perumal TM, Henao R, Nichols M, Howrylak JA, Choi AM, Bermejo-Martin JF, Almansa R, Tamayo E, Davenport EE, Burnham KL, Hinds CJ, Knight JC, Woods CW, Kingsmore SF, Ginsburg GS, Wong HR, Parnell GP, Tang B, Moldawer LL, Moore FE, Omberg L, Khatri P, Tsalik EL, Mangravite LM, Langley RJ. A community approach to mortality prediction in sepsis via gene expression analysis. *Nat Commun* 9: 694, 2018.
295. Swenson ER, Porcher R, Piagnerelli M. Iron deficiency and infection: another pathway to explore in critically ill patients? *Intensive Care Med* 44: 2260-2262, 2018.
296. Szabó C. Role of nitric oxide in endotoxic shock. An overview of recent advances. *Ann N Y Acad Sci* 851: 422-5, 1998.
297. Szabó C, Módis K. Pathophysiological roles of peroxynitrite in circulatory shock. *Shock* 34 Suppl 1: 4-14, 2010.
298. Tadie JM, Bae HB, Banerjee S, Zmijewski JW, Abraham E. Differential activation of RAGE by HMGB1 modulates neutrophil-associated NADPH oxidase activity and bacterial killing. *Am J Physiol Cell Physiol* 302: C249-56, 2012.
299. Takebe G, Yarimizu J, Saito Y, Hayashi T, Nakamura H, Yodoi J, Nagasawa S, Takahashi K. A Comparative Study on the Hydroperoxide and Thiol Specificity of the Glutathione Peroxidase Family and Selenoprotein P. *J Biol Chem* 277: 41254-41258., 2002.

300. Tanaka S, Harrois A, Duranteau J. Leukodepleted versus nonleukodepleted red blood cell transfusion in septic patients: a microcirculatory vision. *Crit Care* 18: 128, 2014.
301. Teboul JL, Duranteau J. Alteration of microcirculation in sepsis: a reality but how to go further? *Crit Care Med* 40: 1653-4, 2012.
302. Thiessen SE, Van den Berghe G, Vanhorebeek I. Mitochondrial and endoplasmic reticulum dysfunction and related defense mechanisms in critical illness-induced multiple organ failure. *Biochim Biophys Acta* 1863: 2534-2545, 2017.
303. Traulsen H, Steinbrenner H, Buchczyk DP, Klotz LO, Sies H. Selenoprotein P protects low-density lipoprotein against oxidation. *Free Radic Res* 38: 123-8, 2004.
304. Trzeciak S, Cinel I, Phillip Dellinger R, Shapiro NI, Arnold RC, Parrillo JE, Hollenberg SM. Resuscitating the microcirculation in sepsis: the central role of nitric oxide, emerging concepts for novel therapies, and challenges for clinical trials. *Acad Emerg Med* 15: 399-413, 2008.
305. Trzeciak S, Dellinger RP, Parrillo JE, Guglielmi M, Bajaj J, Abate NL, Arnold RC, Colilla S, Zanotti S, Hollenberg SM. Early microcirculatory perfusion derangements in patients with severe sepsis and septic shock: relationship to hemodynamics, oxygen transport, and survival. *Ann Emerg Med* 49: 88-98, 98 e1-2, 2007.
306. Tsukano K, Shimamori T, Fukuda T, Nishi Y, Otsuka M, Kitade Y, Suzuki K. Serum iron concentration as a marker of inflammation in young cows that underwent dehorning operation. *The Journal of veterinary medical science* 81: 626-628, 2019.
307. Tujebajeva RM, Harney JW, Berry MJ. Selenoprotein P expression, purification, and immunochemical characterization. *J Biol Chem* 275: 6288-94., 2000.
308. Uchimido R, Schmidt EP, Shapiro NI. The glycocalyx: a novel diagnostic and therapeutic target in sepsis. *Crit Care* 23: 16, 2019.
309. Vaki I, Kranidioti H, Karagianni V, Spyridaki A, Kotsaki A, Routsis C, Giamarellos-Bourboulis EJ. An early circulating factor in severe sepsis modulates apoptosis of monocytes and lymphocytes. *J Leukoc Biol* 89: 343-9, 2011.
310. van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, Vlasselaers D, Ferdinande P, Lauwers P, Bouillon R. Intensive insulin therapy in the critically ill patients. *N Engl J Med* 345: 1359-67, 2001.
311. van Grinsven E, Textor J, Hustin LSP, Wolf K, Koenderman L, Vrisekoop N. Immature Neutrophils Released in Acute Inflammation Exhibit Efficient Migration despite Incomplete Segmentation of the Nucleus. *J Immunol* 202: 207-217, 2019.
312. Vanasco V, Evelson P, Boveris A, Alvarez S. In situ and real time muscle chemiluminescence determines singlet oxygen involvement in oxidative damage during endotoxemia. *Chem Biol Interact* 184: 313-8, 2010.
313. Victor VM, Espulgues JV, Hernandez-Mijares A, Rocha M. Oxidative stress and mitochondrial dysfunction in sepsis: a potential therapy with mitochondria-targeted antioxidants. *Infect Disord Drug Targets* 9: 376-389, 2009.
314. Vincent J-L. Safety considerations of septic shock treatment. *Expert Opinion on Drug Safety*: 1-7, 2015.
315. Vincent JL, Marshall JC, Namendys-Silva SA, Francois B, Martin-Loeches I, Lipman J, Reinhart K, Antonelli M, Pickkers P, Njimi H, Jimenez E, Sakr Y. Assessment of the worldwide burden of critical illness: the Intensive Care Over Nations (ICON) audit. *Lancet Respir Med* 2: 380-6, 2014.
316. Vincent JL, Mira JP, Antonelli M. Sepsis: older and newer concepts. *Lancet Respir Med* 4: 237-40, 2016.
317. Vincent JL, Singer M, Marini JJ, Moreno R, Levy M, Matthay MA, Pinsky M, Rhodes A, Ferguson ND, Evans T, Annane D, Hall JB. Thirty years of critical care medicine. *Crit Care* 14: 311, 2010.
318. Vincent JL, Van Nuffelen M. Septic shock: new pharmacotherapy options or better trial design? *Expert Opin Pharmacother* 14: 561-70, 2013.
319. Vink H, Constantinescu AA, Spaan JA. Oxidized lipoproteins degrade the endothelial surface layer : implications for platelet-endothelial cell adhesion. *Circulation* 101: 1500-2, 2000.
320. Viret J. Reaction of the organism to stress: the survival attractor concept. *Acta Biotheor* 42: 99-109, 1994.
321. Vodovotz Y, Csete M, Bartels J, Chang S, An G. Translational systems biology of inflammation. *PLoS Comput Biol* 4: e1000014, 2008.
322. Volpi S, Heaton C, Mack K, Hamilton JB, Lannan R, Wolfgang CD, Licamele L, Polymeropoulos MH, Lavedan C. Whole genome association study identifies polymorphisms associated with QT prolongation during iloperidone treatment of schizophrenia. *Mol Psychiatry* 14: 1024-31, 2009.
323. Wang CN, Duan GL, Liu YJ, Yu Q, Tang XL, Zhao W, Li XH, Zhu XY, Ni X. Overproduction of nitric oxide by endothelial cells and macrophages contributes to mitochondrial oxidative stress in adrenocortical cells and adrenal insufficiency during endotoxemia. *Free Radic Biol Med* 83: 31-40, 2015.
324. Wang Z, Forceville X, Van Antwerpen P, Piagnerelli M, Ahishakiye D, Macours P, De Backer D, Neve J, Vincent JL. A large-bolus injection, but not continuous infusion of sodium selenite improves outcome in peritonitis. *Shock* 32: 140-6, 2009.

325. Ward PA. Sepsis, apoptosis and complement. *Biochemical Pharmacology* 76: 1383-1388, 2008.
326. Warren HS. Editorial: Control issues in sepsis: what modulates apoptosis? *J Leukoc Biol* 89: 325-6, 2011.
327. Warren HS, Fitting C, Hoff E, Adib-Conquy M, Beasley-Topliffe L, Tesini B, Liang X, Valentine C, Hellman J, Hayden D, Cavaillon JM. Resilience to bacterial infection: difference between species could be due to proteins in serum. *J Infect Dis* 201: 223-32, 2010.
328. Wenceslau CF, McCarthy CG, Goulopoulou S, Szasz T, NeSmith EG, Webb RC. Mitochondrial-derived N-formyl peptides: novel links between trauma, vascular collapse and sepsis. *Med Hypotheses* 81: 532-5, 2013.
329. Wiersinga WJ, Leopold SJ, Cranendonk DR, van der Poll T. Host innate immune responses to sepsis. *Virulence* 5: 36-44, 2014.
330. Wilkie-Grantham RP, Magon NJ, Harwood DT, Kettle AJ, Vissers MC, Winterbourn CC, Hampton MB. Myeloperoxidase-dependent lipid peroxidation promotes the oxidative modification of cytosolic proteins in phagocytic neutrophils. *J Biol Chem* 290: 9896-905, 2015.
331. Wink DA, Hines HB, Cheng RY, Switzer CH, Flores-Santana W, Vitek MP, Ridnour LA, Colton CA. Nitric oxide and redox mechanisms in the immune response. *J Leukoc Biol* 89: 873-91, 2011.
332. Winterbourn CC. Toxicity of iron and hydrogen peroxide: the Fenton reaction. *Toxicol Lett* 82-83: 969-74, 1995.
333. Winterbourn CC, Hampton MB, Livesey JH, Kettle AJ. Modeling the reactions of superoxide and myeloperoxidase in the neutrophil phagosome: implications for microbial killing. *J Biol Chem* 281: 39860-9, 2006.
334. Winterbourn CC, Kettle AJ, Hampton MB. Reactive Oxygen Species and Neutrophil Function. *Annu Rev Biochem* 85: 765-92, 2016.
335. Yoseph BP, Klingensmith NJ, Liang Z, Breed ER, Burd EM, Mittal R, Dominguez JA, Petrie B, Ford ML, Coopersmith CM. Mechanisms of intestinal barrier dysfunction in sepsis. *Shock* 46: 52-9, 2016.
336. Zhang DX, Gutterman DD. Mitochondrial reactive oxygen species-mediated signaling in endothelial cells. *Am J Physiol Heart Circ Physiol* 292: H2023-31, 2007.
337. Zmijewski JW, Banerjee S, Bae H, Friggeri A, Lazarowski ER, Abraham E. Exposure to hydrogen peroxide induces oxidation and activation of AMP-activated protein kinase. *J Biol Chem*, 2010.
338. Zonneveld R, Martinelli R, Shapiro NI, Kuijpers TW, Plotz FB, Carman CV. Soluble adhesion molecules as markers for sepsis and the potential pathophysiological discrepancy in neonates, children and adults. *Crit Care* 18: 204, 2014.
339. Zweier JL, Flaherty JT, Weisfeldt ML. Direct measurement of free radical generation following reperfusion of ischemic myocardium. *Proc Natl Acad Sci U S A* 84: 1404-7, 1987.
340. Zwilling BS, Kuhn DE, Wikoff L, Brown D, Lafuse W. Role of iron in Nramp1-mediated inhibition of mycobacterial growth. *Infect Immun* 67: 1386-92, 1999.

TABLE 1 MAIN REACTIVE OXYGEN, HALOGEN AND NITROGEN SPECIES WITHIN CELLS AND IN PLASMA NEAR THE ENDOTHELIAL VASCULAR MEMBRANE

Radical species (one-electron oxidant)

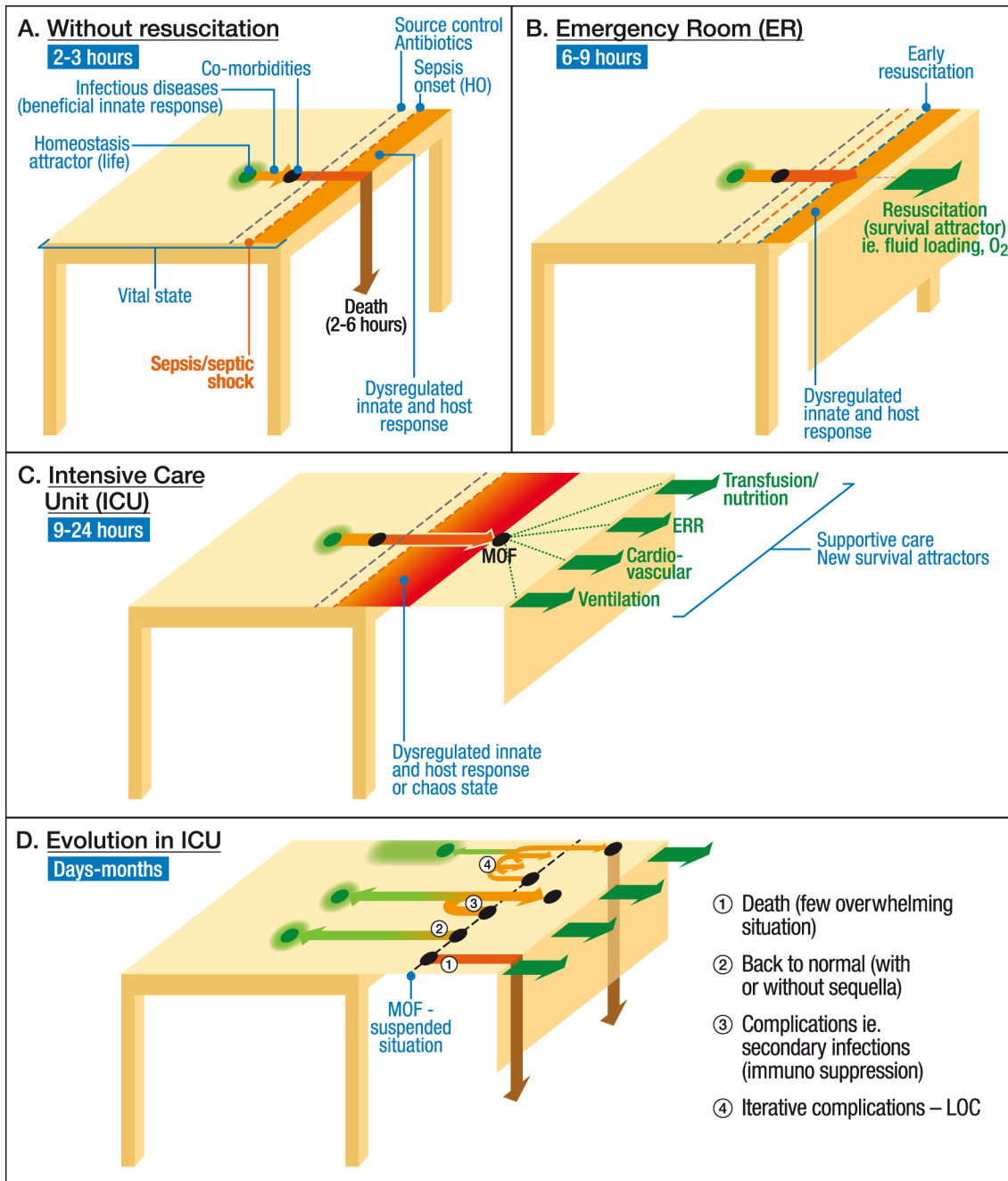
Name (113,114,271,334)	Chemical formula	Concentration from physiology to pathology	Diffusion	Half life at 37°C (271)	Reactivity
Superoxide anion	$O_2^{\bullet-}$	<ul style="list-style-type: none"> - Respiratory burst (NOX) - Into neutrophil phagosome or extracellularly: increase from 3 to >100 $\mu\text{mol/L}$ (if limited MPO and no H_2O_2 efflux) otherwise \neq 30 $\mu\text{mol/L}$ (333) - Increase by a factor of 30 in stimulated neutrophils (266). - In macrophage exudate: 9.7 ± 3 nmol/min. $\times 10^7$ cells and for neutrophils: 26.9 ± 3 nmol/min. $\times 10^7$ cells (224). - Endogenous sources • Ischemia-reperfusion (I/R) Rapid increase by a factor of 6 (120,242,339) through XO and COX • Mitochondrial dysfunction Produced by complex I and later IV blocked by NO^{\bullet} (40,235) (>3 time increase)(213) 	Limited membrane permeability (113,116)	<p>Spontaneous dismutation or enzymatic</p> <p>Reacts quickly with only a few molecules</p>	<p>Weak oxidant, highly selective but:</p> <ul style="list-style-type: none"> - Reacts rapidly with NO^{\bullet} to form toxic peroxynitrite ONO_2^- (below) (114). - Inactivates key enzymes containing [Fe-] cluster (energy metabolism and aminoacid metabolism) releasing Fe^{2+} leading to the Fenton reaction (113). - Undergoes enzyme (or non-enzyme) catalyzed dismutation in H_2O_2 that can diffuse and form OH^{\bullet} by the Fenton reaction (113). If not it has been calculated an $O_2^{\bullet-}$ production at millimolar range/sec (334). - Facilitates protease action (113).
Singlet Oxygen	1O_2	2-fold increase in muscle of LPS rat (312)	Immediate reaction	10^{-6} sec	++++ (114) Proteins, DNA and lipids
Hydroxyl radical	$\bullet OH$	By Fenton reaction or peroxynitrite fission (\neq 1% - 4% of this fission) (244)	Immediate reaction	10^{-9} sec	+++++ Extremely reactive
Alkoxy	RO^{\bullet}	Formed by similar to Fenton reaction: $ROOH (Fe^{2+}) \rightarrow RO^{\bullet}$	Chain reactions	10^{-6} sec	+++
Peroxy and Organic radicals	ROO^{\bullet} R^{\bullet}	$RH + ROO^{\bullet} \rightarrow R^{\bullet} + ROOH$		7 sec	<ul style="list-style-type: none"> - Lipid peroxidation, targets especially PUFA - Diminution of membrane fluidity
Nitric oxide	NO^{\bullet}	<ul style="list-style-type: none"> - Increased by 33% in LPS rat muscle (312). - Baseline \neq 50 nmol/L; after cNOS stimulation highest NO^{\bullet} at cell membrane: 950 ± 0.05 nmol/L, undetectable beyond 50 μm; After LPS: 6-fold increase in NO_x, max increase after 2-6h; after I/R: NO^{\bullet} increase from 52 ± 15 to 140 (during I), and decrease at 10 nmol/L at R (reacts with $O_2^{\bullet-}$) (46) - Endothelial synthesis (151): - cNOS: picomolar range - iNOS: nanomolar range - Mitochondrial isoform of NOS (101,235) 		Broadly diffusible	0.1 to 5.6 sec relatively stable

TABLE 2 MAIN REACTIVE OXYGEN, HALOGEN AND NITROGEN SPECIES WITHIN CELLS AND IN PLASMA NEAR THE ENDOTHELIAL VASCULAR MEMBRANE

Non radical species (two-electron oxidant)

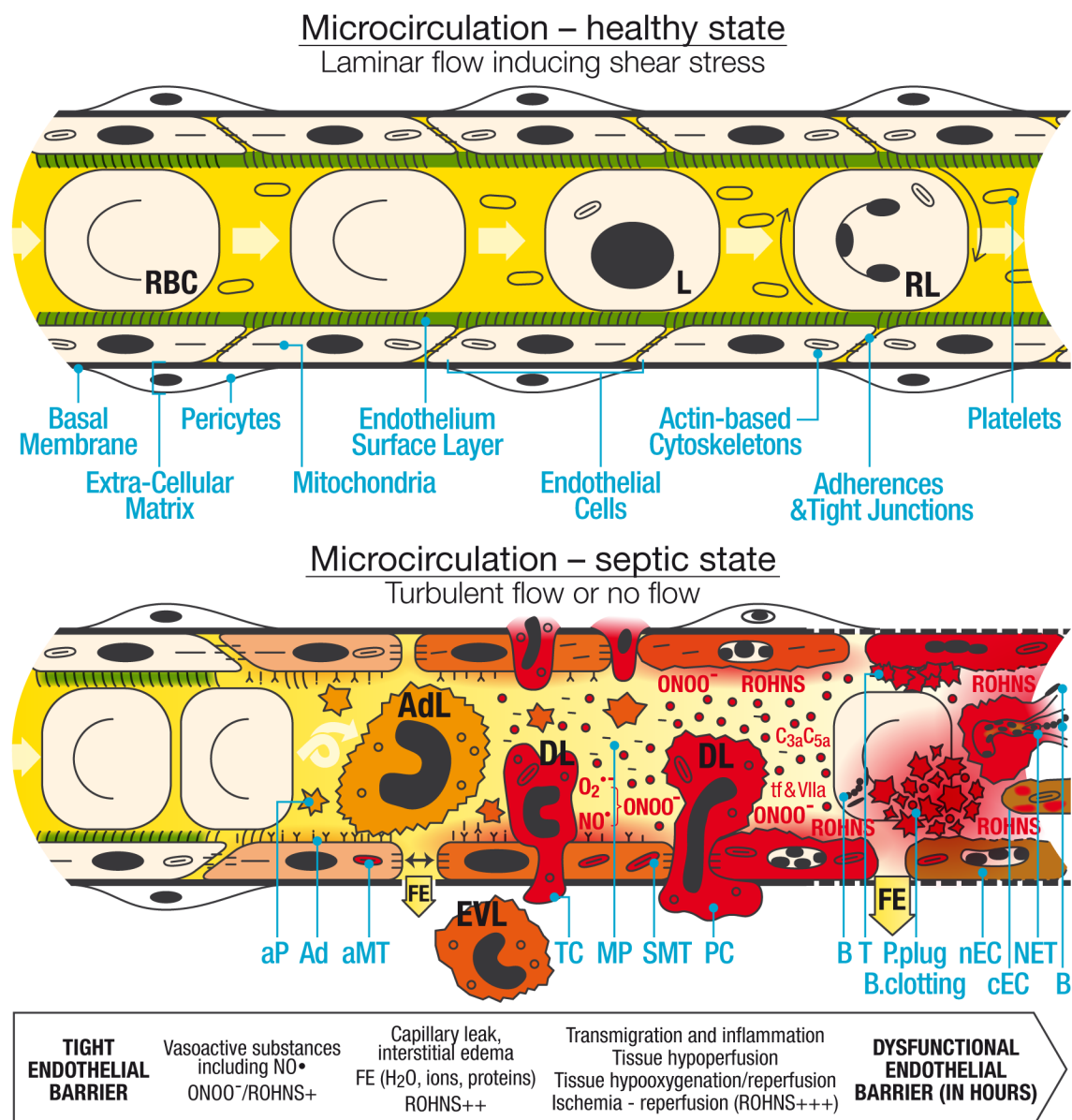
Name (113,114,271,334)	Chemical formula	Concentration from physiology to pathology	Diffusion	Half life at 37°C (271)	Reactivity
Hydrogen peroxide	H ₂ O ₂	2 to 300 µmol/L, in the phagosome without H ₂ O ₂ efflux; ≠ 30 µmol/L in absence of MPO (333); up to 1 mmol/L in plasma during respiratory burst (22)	Cross the membranes (pref. through aquaporins)	Stable	Strong oxidant (but limited substrates esp. thiols, transition metal centers)
Hypochlorous acid	HOCl	In the phagosome (MPO): - 12 % of consumed oxygen can be converted into HOCl within the phagosome (116). - Might increase up to 91% (333) - Up to 50-70 mmol/L (141,333)	Membrane permeable	pH depending stability (less stable in acidic medium)	- Major antimicrobial agent in neut. phagosome (80,113,141,334) - Oxidation of: cysteine, methionine, tryptophan, chlorination of tyrosine, lysine residues, ionized thiols (low pKa)
Hypothiocyanite	OSCN ⁻	In the phagosome (MPO): - As a product of MPO or as an oxidation of SCN ⁻ by HOCl (≠ 1/2.5 of it) (22).	Not lethal to mammalian cells (22)	Possible redox buffer for HOCl especially in plasma	- 2nd major antimicrobial agent in phagosome. Reacts with cysteine residues, low pKa thiols - Reduces ½ life of HOCl in plasma to 400 µs (22)
Peroxy-nitrite	ONO ₂ ⁻	- Increased by 33% in homogenate from muscle of LPS rat (312). - 100 to 200 µmol/L is achievable in vivo and induced NETs (183). - Neutrophil to endothelium binding Near the endothelium spatially associated with O ₂ ⁻ sources in the plasma (297) and NO [•] (245). - Elevated plasma NOx: 144 ± 39 vs. 20 ± 3 µmol/L and elevated plasma nitrotyrosine: 102 ± 19 vs. 14 ± 6 pmol/L in 16 septic shock patients vs. 9 healthy volunteers (290). - Mitochondrial dysfunction that can induce toxic ONO ₂ ⁻ formation in mitochondria (235)	Crosses the membranes	0.05-1 sec	- At physiological pH rapidly split into •OH and NO ₂ • when protonated; or more probably to NO ₂ • and CO ₃ • when reacting with CO ₂ (113,297) - Major antimicrobial agent (113) induces NET formation (183). - Many deleterious effects on (297) **: • Mitochondria (complex I) (40,235). • Protein functions • Lipid peroxidation • Arachidonic acid • Pulmonary surfactant • Nucleic acids • ESL, glycocalyx • Endothelial epithelial, and myocyte injury • Induce NET formation
Phospholipid oxidation		Chemoluminescence (¹ O ₂) correlates with TBARS muscle and mitochondria content (30% and 45% increase respectively in LPS rat) (312)		(In hours, after UV-induced oxidation)	• Alters membrane properties (thickness, lateral structure, & permeability). • Amplifies inflammation (danger signal)(216) • Endothel. procoagulant shift (33)
Protein carbonyl	R-CO-R'	Increased by 23% in muscle mitochondria of LPS rat (312) 29.5±6.6 vs. 11.3±6.3 nmol/L in survivor vs. non survivor ICU septic shock patients (68)			Marker of protein damage more stable than lipid peroxidation (68)

FIG. 1. Sepsis evolution and supportive care as new survival attractors



As an adaptation to Thom's Catastrophe Theory, as made by Viret, supportive care in the emergency room (ER) and later in the intensive care unit (ICU) are new survival attractors that prevail over homeostasis life attractors. They enable patients to survive outside a natural living state as illustrated by the table during their ICU stay. A) (*Upper-left corner*) Developing an infection, the body reacts by producing a beneficial innate immune response illustrated by an orange arrow. If the infection is not treated in time, this innate response may evolve a few day(s) (hours) later into sepsis, illustrated by a red arrow. Sepsis is often lethal as illustrated by the brown arrow that falls from the table of life. B) (*Upper-right corner*) A septic patient (in the ER) has a dysregulated innate and host response. He/she can survive because of early resuscitation, which thus becomes a new mild survival attractor. C) (*Middle of the figure*) Worsening sepsis (septic shock) increases the complexity of the reaction - even corresponding to a state of chaos - and finally leads to multiple organ failure (MOF). In the ICU, different forms of supportive care, illustrated in green, become new survival attractors enabling patients to survive. D) (*Bottom*) Depending in part on the initial severity of the sepsis, evolution may be (1) lethal in a few cases because of an overwhelming reaction; (2) favorable with rapid withdrawal of supportive care as illustrated by the green arrow returning to the homeostasis attractor; (3) less favorable with secondary infection(s) or various other complications illustrated by a zig-zag orange arrow; (4) associated with a high risk of *sequelae* if recovering or, in the worst cases, supportive cares become futile, and a decision of limitation of care (LOC) leads to death. ERR, extra-renal replacement.

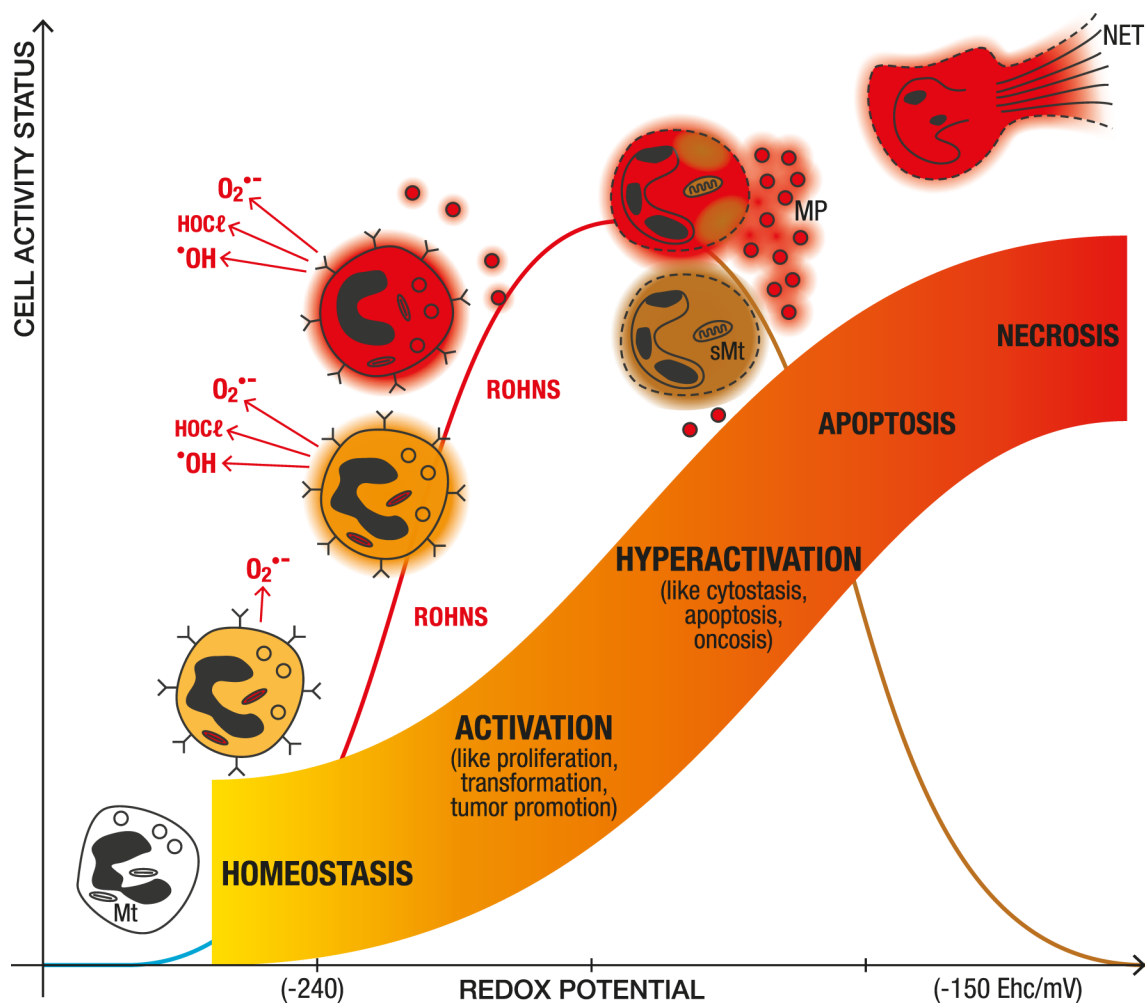
FIG. 2. Leukocyte and endothelial activation leading to major oxidative stress and endothelial barrier dysfunction



In health (*Upper Panel*), blood flows evenly in the microcirculation applying shear stress evenly on endothelial cells (EC). The endothelial surface layer (ESL) covering the ECs is shown in green to illustrate its protective properties. Leukocytes (L) flow evenly, although rolling leukocytes can be observed. Red blood cells are flexible. Platelets are not activated.

In sepsis (*Lower Panel*), reactive oxygen, halogen and nitrogen species (ROHNS) - such as peroxynitrite (ONOO⁻) formed by the simultaneous production of superoxide anion (O₂^{-•}) and nitric oxide (NO•) - are released by both activated adherent leukocytes (AdL) and ECs. The ESL is severely damaged and finally disappears. ECs evolve into a pro-coagulant, adherent, vasoconstrictor phenotype. Flow becomes turbulent. *From left to right*, the evolution of the damaged endothelium is illustrated in the light of sepsis evolution (septic clock). *Cell colors, from orange to red, illustrate increased activation*. Activated mitochondria (aMT) and highly reactive ROHNS are in red. By contrast, plasma colors change from yellow to off-white, due to fluid and protein extravasation. Damaged ECs and swollen mitochondria (SMT) are illustrated in brown. aP, activated platelet; Ad, adhesins; B, Bacteria; B clotting, blood clotting; cEC, circulating endothelial cells; C3a, C5a, complement system activation; DL and EVL, diapedesis and extra-vascular leukocyte; FE, fluid extravasation; ICG, inter-cellular gap; MP, microparticle; NET, neutrophil extracellular traps; PC and TC para-endothelial and trans-endothelial cells diapedesis; P. plug, platelet plugs; tf & VIIa, tissue factor and VIIa factor activation; T, thrombi. To see this illustration in color, the reader is referred to the web version of this article at www.liebertpub.com/ars.

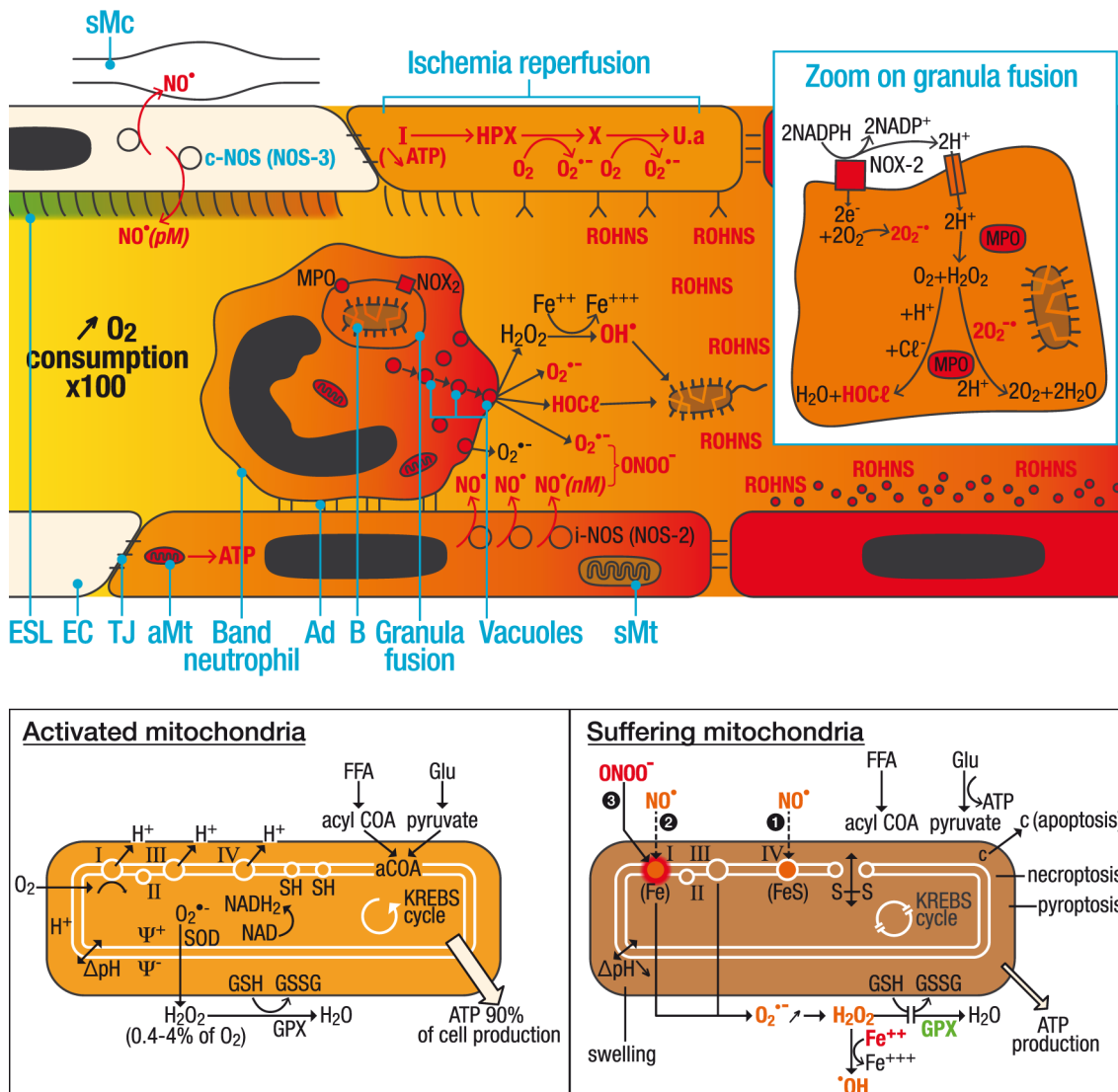
FIG. 3. Transposition of cellular impact of increased redox potential from cancer cells to leukocytes, particularly neutrophils.



Increased redox potential is a central event in cell signaling and transformation in cancer. Similarly, during sepsis, increased intracellular $O_2^{\bullet-}$ concentration - due to extra or intracellular production - is involved in activation of neutrophils and other leukocytes. *Cell colors, from orange to red, illustrate increased activation.* Damaged endothelial cells and swelling mitochondria (SMT) are illustrated in brown. During sepsis (see Fig. 2), neutrophils (i) have an expanded lifetime; (ii) increase their secretion of reactive oxygen, halogen and nitrogen sepsis (ROHNS), especially $O_2^{\bullet-}$, leading to peroxynitrite ($ONOO^-$) and hypochlorous acid (HOCl) formation (see Fig. 4); and (iii) express adhesins. Band immature neutrophils are released from the bone marrow. Microparticles (MP) are also released. Neutrophil extracellular traps (NETs) are an alternative pathway distinct from apoptosis or necrosis, and participate in bactericidal function. The redox potential values of -240 to -150 E_{hc}/mV are purely indicative (see Buettner and other related articles). E_{hc} is the standard cell potential according to the Nernst reaction adapted to the GSH/GSSG ratio in millivolts (mV) at 37°C, pH 7.2.

To see this illustration in color, the reader is referred to the web version of this article at www.liebertpub.com/ars.

FIG. 4. Reactive oxygen, halogen and nitrogen species (ROHNS) production over time in sepsis and their consequences on endothelium damage.

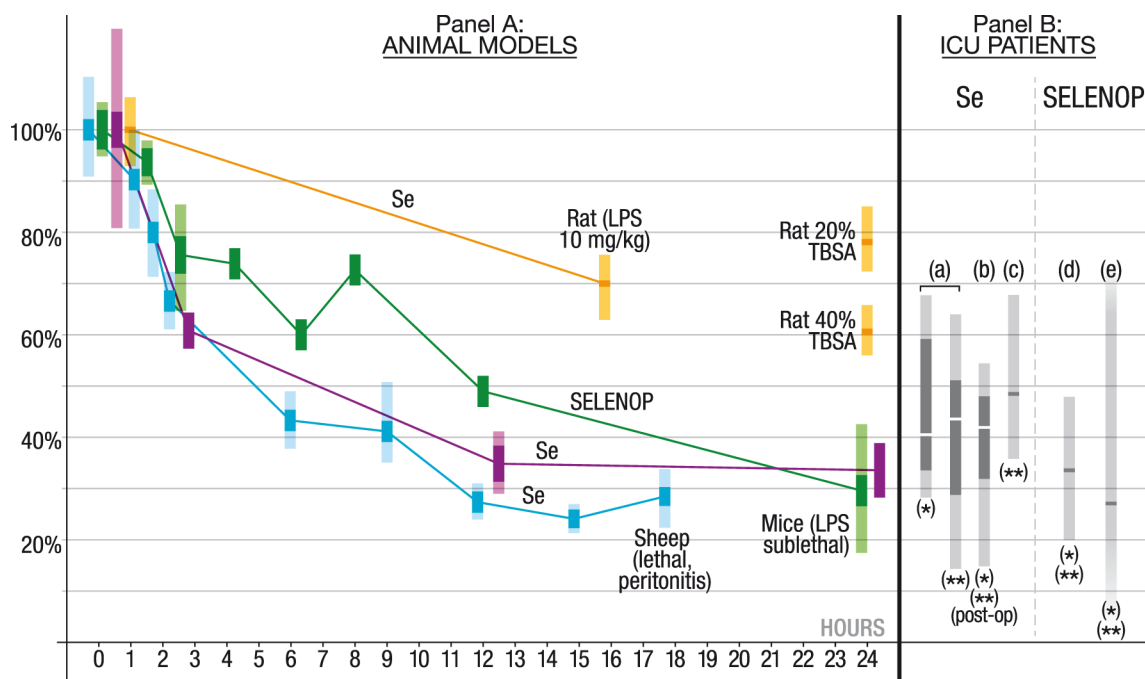


In the *upper part of the figure*, the illustrated leukocyte is a band neutrophil (immature form produced by activated bone marrow). Cell colors, from orange to red, illustrate increased activation. Damaged mitochondria (sMT) are in brown.

Neutrophils can generate the whole spectrum of reactive oxygen, halogen and nitrogen species (ROHNS) required for the innate response (see Table 1 and 2) (334). During sepsis, oxygen consumption of neutrophils can increase up to 100 times, in about 6 hours. Nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX-2) and myeloperoxidase (MPO) play a crucial role in ROHNS generation. Along with antimicrobial and hydrolytic proteins, ROHNS are secreted in leukocyte phagosomes - illustrated with a dying bacteria (B) – but also in the blood with production of RHONS such as superoxide anion (O₂^{•-}), hydrogen peroxide (H₂O₂) leading to the bactericidal hypochlorous acid (HOCl) by MPO, hydroxyl radical (•OH) in the presence of ferrous (Fe⁺⁺) or copper (Cu⁺) cations or H₂O according to the available antioxidant defenses (such as reduced glutathione and functioning glutathione peroxidase GPX). Binding of activated endothelial cells (EC) and neutrophils contributes to the formation of bactericidal peroxynitrite (ONOO⁻) due to simultaneous nanomolar (nM) nitric oxide (NO[•]) concentration and O₂^{•-}.

But ROHNS are a double-edge sword. Mitochondria (MT) (*lower-left corner*), share many features with bacteria. In ECs, activated MT are particularly targeted by RHONS (*lower-right corner*). Within hours, factor I, and later factor IV, are reversibly blocked by NO[•] leading to increased O₂^{•-} production. Finally, ONOO⁻ non-reversibly blocks complex I. This results in major suffering of mitochondria (sMT) with opening of ionic pores (S-S), loss of pH gradient, and swelling. ATP production dramatically decreases and cytochrome c is released leading to apoptosis of ECs. In addition (*upper part of the figure*), ATP is degraded during ischemia-reperfusion into inosine (I), leading to hypoxanthine (HPX), xanthine (X) and uric acid (U.a) and O₂^{•-} release by oxidases, such as xanthine oxidase (XO). Other mechanisms also contribute to RHONS production. Ad, adhesins; ESL, endothelial surface layer; GPX, glutathione peroxidase; SOD, superoxide dismutase; Fe-S iron sulfur clusters; i-NOS (NOS-2), inducible endothelial nitric oxide synthase; c-NOS (NOS 3), constitutive NOS; TJ, tight junction.

FIG 5. Decrease in plasma selenium and selenoprotein-P levels in animal sepsis and burn models and corresponding low levels on admission to the ICU in patients with sepsis or septic shock.



Panel A: in all animal models, plasma selenium (Se) levels decrease rapidly. The values are expressed as a percentage of the initial level (see respective publications below). Although rats and humans share a similar Se body content (see table 2), reference plasma Se and selenoprotein P levels are similar in rats and mice, about 6 times higher than in humans, and about 7 times higher than in sheep. Results are given as mean \pm SD. The corresponding studies are: (i) non-lethal lipopolysaccharide (LPS) rat model “Rat (LPS 10 mg/kg)” (n=5 at each time point) (182); (ii) “Mice (LPS sub-lethal)” (LPS 100 μ g/mouse; n=8 at each time points) with similar decrease in Se and selenoprotein P - in addition selenoprotein P mRNA decreased from onset to 6 h - (240); (iii) “Sheep (lethal, peritonitis)” fluid resuscitated and ventilated lethal model (18 h). Significant decrease in plasma Se from 3 h preceded the onset of septic shock (H10) and the increase in lactate (12 h) (n=21) (291,324); in a non-exudative burn rat model “Rat 20% TBSA” and “Rat 40% TBSA” the decrease in plasma Se levels at 24 h were linked to the size of the total body surface area (TBSA) (252).

Panel B: On admission to the ICU, low Se and selenoprotein P levels are observed in septic (*) and septic shock (**) patients expressed as a percentage of the reference value. Results are given as medians with 25th and 75th percentiles as the top and bottom of the box and capped lines indicating the 10th to the 90th percentile, or median and interquartile range. The corresponding studies are (a) (93), (b) (251), (c) (32). For the Bloos et al (2016) study performed in Germany (32), the reference plasma Se value from the German study by Sakr was chosen (251). For plasma selenoprotein P, the corresponding studies are: (d) (131), (e) (91). Post-op, post-operative patients.

To see this illustration in color, the reader is referred to the web version of this article at www.liebertpub.com/ars.