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► **To cite this version:**

Xavier Forceville, Pierre van Antwerpen, Jean-Charles Preiser. 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 and Redox Signaling*, 2021, 35 (2), pp.113-138. 10.1089/ars.2020.8063 . hal-03156442

**HAL Id: hal-03156442**

**<https://hal.science/hal-03156442>**

Submitted on 10 Nov 2023

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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)*

Review article, Antioxid Redox Signal. 2022;37(13):998-1029

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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.

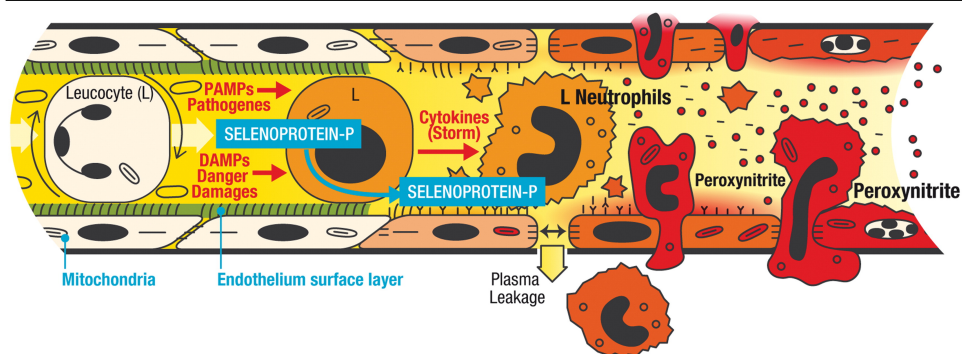
**Critical issues:** Neutrophil production increases dramatically and aggressive, immature forms are released. Leukocyte cross-talk with other leukocytes and with damaged endothelial cells amplifies the inflammatory response. The release of large quantities of reactive oxygen, halogen and nitrogen species 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

DOI: 10.1089/ars.2020.8063

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 m<sup>2</sup> (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 10<sup>11</sup> 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 21<sup>st</sup> 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 (Fe<sup>3+</sup>), is mainly complexed to transferrin. Each protein has two iron binding sites (218). Non-transferrin-bound iron (NTBI) comprises Fe<sup>3+</sup> 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 10<sup>12</sup> 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- $\kappa$ 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  $\text{Ca}^{2+}$ ), 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- $\kappa$ B (293), nitration of protein tyrosine by peroxynitrite ( $\text{ONOO}^-$ ) (57,293), and mitochondrial one electron way blockage (41). Extracellular formation of ROHNS, such as oxygen peroxide ( $\text{H}_2\text{O}_2$ ) and  $\text{ONOO}^-$ , 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  $\text{H}_2\text{O}_2$  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  $\text{H}_2\text{O}_2$  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 ( $\text{NO}^{\bullet}$ ) 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 $\beta$  (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<sup>-</sup> (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 O<sub>2</sub><sup>-</sup> and H<sub>2</sub>O<sub>2</sub>, Fe catalyzes Fenton/Haber-Weiss reactions leading to production of the extremely reactive <sup>•</sup>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 O<sub>2</sub><sup>-</sup> by antioxidant enzymes, such as SOD, and against H<sub>2</sub>O<sub>2</sub> by catalase (CAT) and intracellular cytosolic glutathione peroxidase (GPX1) (28,99). Auto-oxidation of Hb, or oxidation by plasma nitrite, may release H<sub>2</sub>O<sub>2</sub> or diffusible protein radicals (28,147,175). Nevertheless, in the acute phase of sepsis, the main impact of ROHNS, especially ONOO<sup>-</sup>, 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 (Fe<sup>3+</sup> 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 hypoferrremia 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 Fe<sup>2+</sup> 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<sup>-</sup> 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 (O<sub>2</sub>•<sup>-</sup>) 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<sup>-</sup> 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 (O<sub>2</sub>•<sup>-</sup>) (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 PO<sub>2</sub> 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 O<sub>2</sub>•<sup>-</sup>, but also in ONOO<sup>-</sup>, 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- $\alpha$  (TNF- $\alpha$ ) increases ROS production via mitochondria, especially in tumor cells (67). In human endothelial cells, TNF- $\alpha$  induced rapid mitochondrial ROS production at the ubisemiquinone site; the ceramide-dependent signaling pathway was implicated (67). H<sub>2</sub>O<sub>2</sub> is involved in NF- $\kappa$ 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<sup>-</sup> and HOCl toxicity, is the first step of this damage. The role of mitochondrial dysfunction, especially as a result of ONOO<sup>-</sup> 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<sup>-</sup>. 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.

## **Acknowledgments:**

We thank Prof. Anne Marie Roussel, emeritus Professor in Biochemistry at Grenoble University, for her thorough re-reading of this article and valuable advice and Prof. Jean Neve, *emertitus* Professor at the *Université Libre de Bruxelles* for his valuable advice on oxidative stress and septic shock. We thank also Ms Evelaine Guilbert for her help in the realization of the graphic illustrations.

## **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.

## **Funding statement:**

There is no funding information to declare

## **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  
ROHS = 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

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

**Radical species (one-electron oxidant)**

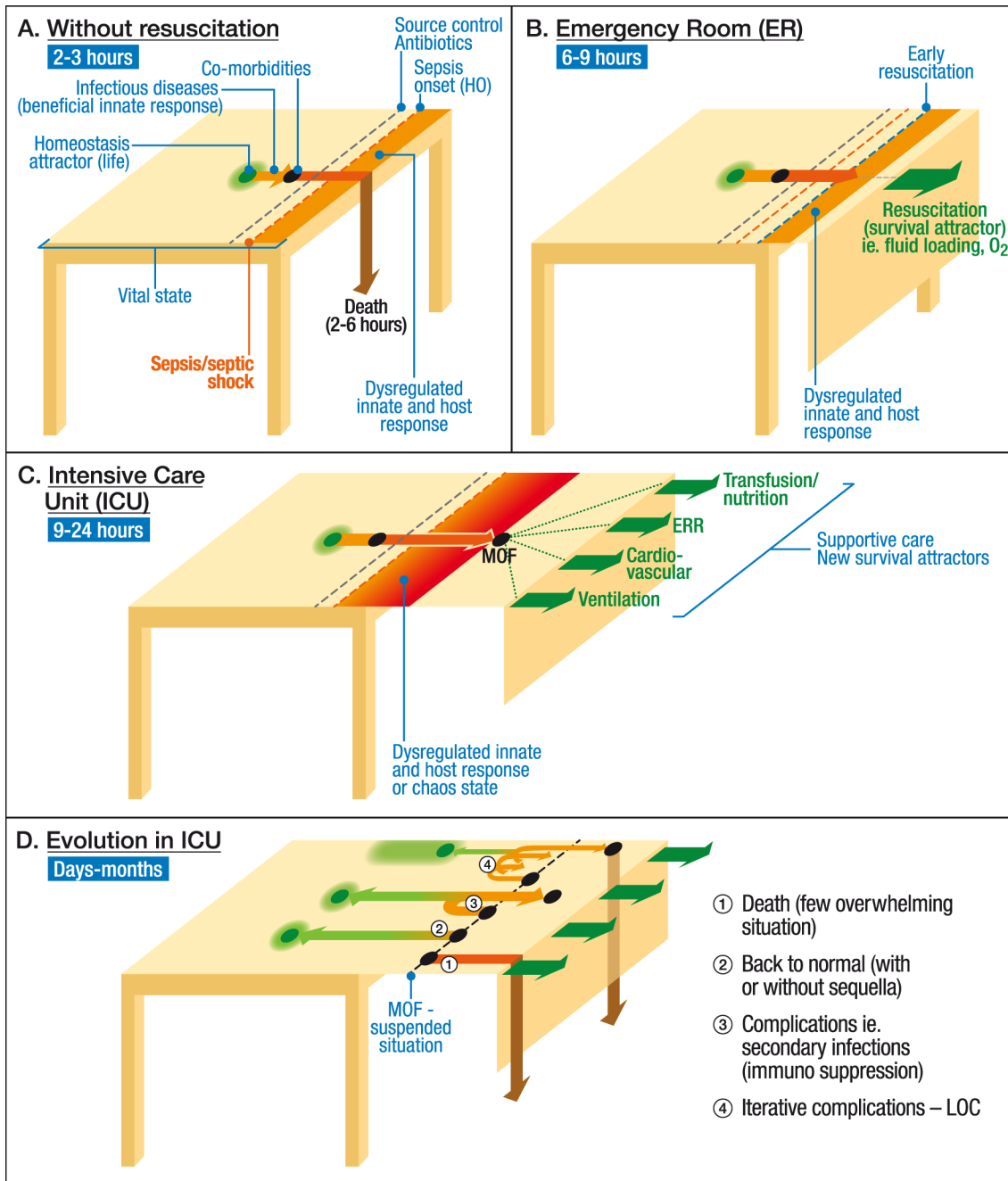
Name (113,114,271,334)	Chemical formula	Concentration from physiology to pathology	Diffusion	Half life at 37°C (271)	Reactivity
Superoxide anion	$O_2^{\bullet-}$	<ul style="list-style-type: none"> <li>- <b>Respiratory burst</b> (NOX)</li> <li>- Into neutrophil phagosome or extracellularly: increase from 3 to &gt;100 <math>\mu\text{mol/L}</math> (if limited MPO and no <math>H_2O_2</math> efflux) otherwise <math>\neq</math> 30 <math>\mu\text{mol/L}</math> (333)</li> <li>- Increase by a factor of 30 in stimulated neutrophils (266).</li> <li>- In macrophage exudate: <math>9.7 \pm 3</math> nmol/min. <math>\times 10^7</math> cells and for neutrophils: <math>26.9 \pm 3</math> nmol/min. <math>\times 10^7</math> cells (224).</li> <li>- <b>Endogenous sources</b></li> <li>• <b>Ischemia-reperfusion (I/R)</b> Rapid increase by a factor of 6 (120,242,339) through XO and COX</li> <li>• <b>Mitochondrial dysfunction</b> Produced by complex I and later IV blocked by <math>NO^{\bullet}</math> (40,235) (&gt;3 time increase)(213)</li> </ul>	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"> <li>- Reacts rapidly with <math>NO^{\bullet}</math> to form toxic peroxynitrite <math>ONO_2^-</math> (below) (114).</li> <li>- Inactivates key enzymes containing [Fe-] cluster (energy metabolism and aminoacid metabolism) releasing <math>Fe^{2+}</math> leading to the Fenton reaction (113).</li> <li>- Undergoes enzyme (or non-enzyme) catalyzed dismutation in <math>H_2O_2</math> that can diffuse and form <math>OH^{\bullet}</math> by the Fenton reaction (113). If not it has been calculated an <math>O_2^{\bullet-}</math> production at millimolar range/sec (334).</li> <li>- Facilitates protease action (113).</li> </ul>
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"> <li>- Lipid peroxidation, targets especially PUFA</li> <li>- Diminution of membrane fluidity</li> </ul>
Nitric oxide	$NO^{\bullet}$	<ul style="list-style-type: none"> <li>- Increased by 33% in LPS rat muscle (312).</li> <li>- Baseline <math>\neq</math> 50 nmol/L; after cNOS stimulation highest <math>NO^{\bullet}</math> at cell membrane: <math>950 \pm 0.05</math> nmol/L, undetectable beyond 50 <math>\mu\text{m}</math>; After LPS: 6-fold increase in <math>NO_x</math>, max increase after 2-6h; after I/R: <math>NO^{\bullet}</math> increase from <math>52 \pm 15</math> to 140 (during I), and decrease at 10 nmol/L at R (reacts with <math>O_2^{\bullet-}</math>) (46)</li> <li>- Endothelial synthesis (151):</li> <li>- cNOS: picomolar range</li> <li>- iNOS: nanomolar range</li> <li>- Mitochondrial isoform of NOS (101,235)</li> </ul>		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)**

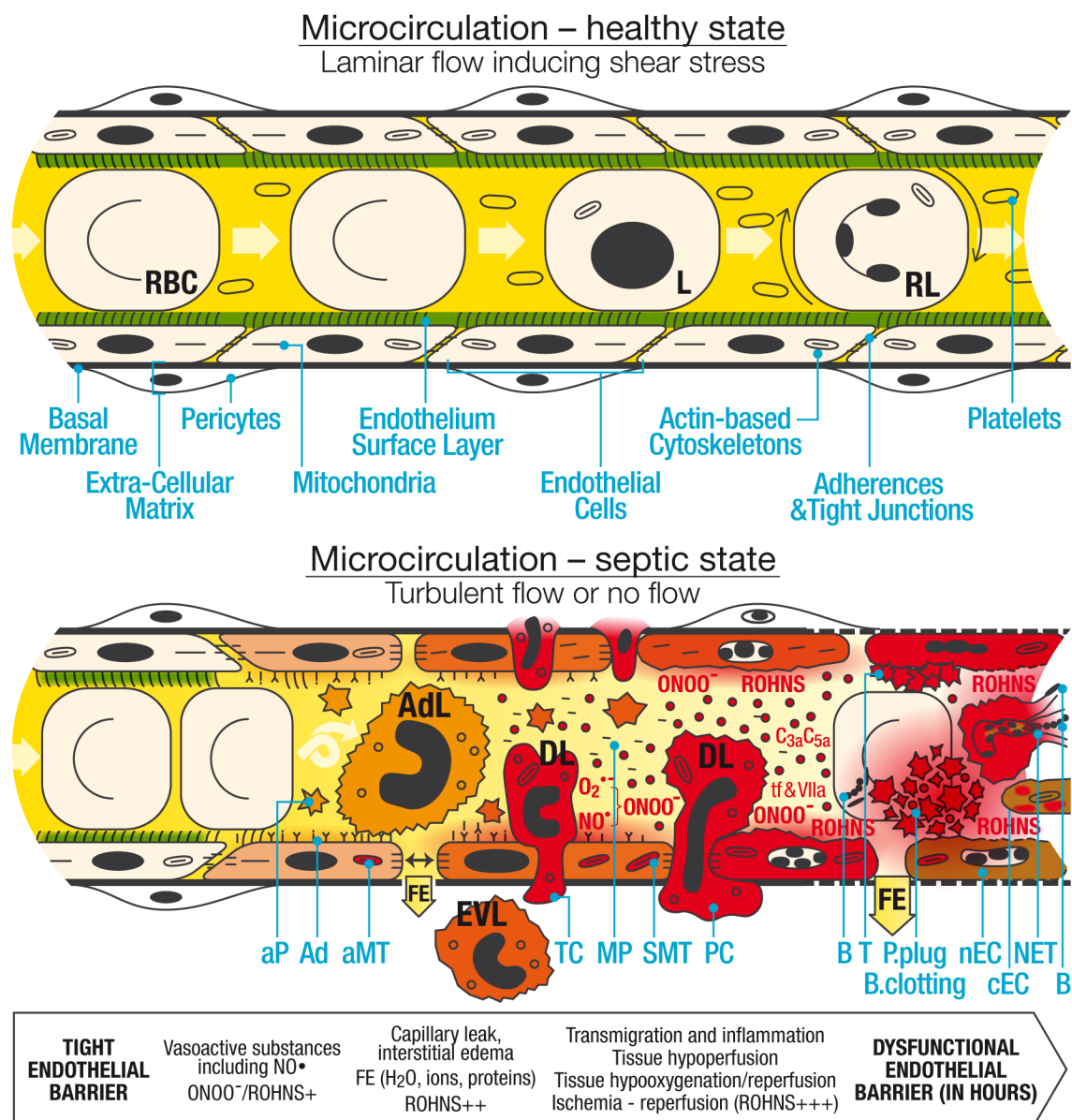
Name (113,114,271,334)	Chemical formula	Concentration from physiology to pathology	Diffusion	Half life at 37°C (271)	Reactivity
Hydrogen peroxide	H <sub>2</sub> O <sub>2</sub>	2 to 300 µmol/L, in the phagosome without H <sub>2</sub> O <sub>2</sub> efflux; ≠ 30 µmol/L in absence of MPO (333); up to 1 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)	- <b>Major antimicrobial agent in neut. phagosome</b> (80,113,141,334) - Oxidation of: cysteine, methionine, tryptophan, chlorination of tyrosine, lysine residues, ionized thiols (low pKa)
Hypothiocyanite	OSCN <sup>-</sup>	In the phagosome (MPO): - As a product of MPO or as an oxidation of SCN <sup>-</sup> by HOCl (≠ 1/2.5 of it) (22).	Not lethal to mammalian cells (22)	Possible redox buffer for HOCl especially in plasma	- <b>2<sup>nd</sup> major antimicrobial agent in phagosome.</b> Reacts with cysteine residues, low pKa thiols - Reduces ½ life of HOCl in plasma to 400 µs (22)
Peroxy-nitrite	ONO <sub>2</sub> <sup>-</sup>	- Increased by 33% in homogenate from muscle of LPS rat (312). - 100 to 200 µmol/L is achievable in vivo and induced NETs (183). - <b>Neutrophil to endothelium binding</b> Near the endothelium spatially associated with O <sub>2</sub> <sup>-</sup> sources in the plasma (297) and NO <sup>•</sup> (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). - <b>Mitochondrial dysfunction</b> that can induce toxic ONO <sub>2</sub> <sup>-</sup> formation in mitochondria (235)	<b>Crosses the membranes</b>	<b>0.05-1 sec</b>	- At physiological pH rapidly split into •OH and NO <sub>2</sub> • when protonated; or more probably to NO <sub>2</sub> • and CO <sub>3</sub> • when reacting with CO <sub>2</sub> (113,297) - <b>Major antimicrobial agent</b> (113) induces NET formation (183). - <b>Many deleterious effects on (297) **:</b> • 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 ( <sup>1</sup> O <sub>2</sub> ) 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.

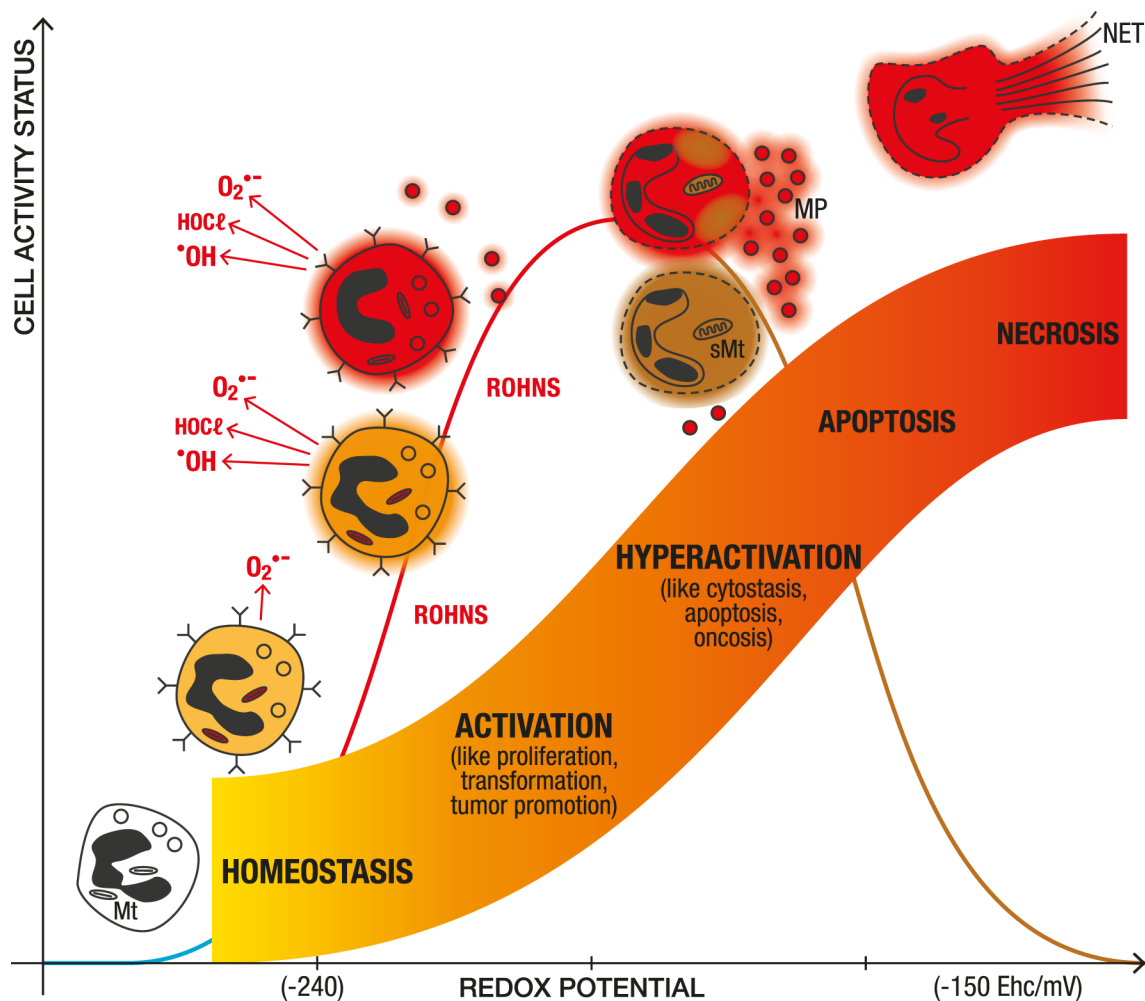
**FIG. 2. Leukocyte and endothelial activation leading to major oxidative stress and endothelial barrier dysfunction**



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<sup>-</sup>) formed by the simultaneous production of superoxide anion (O<sub>2</sub><sup>-•</sup>) 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](http://www.liebertpub.com/ars).

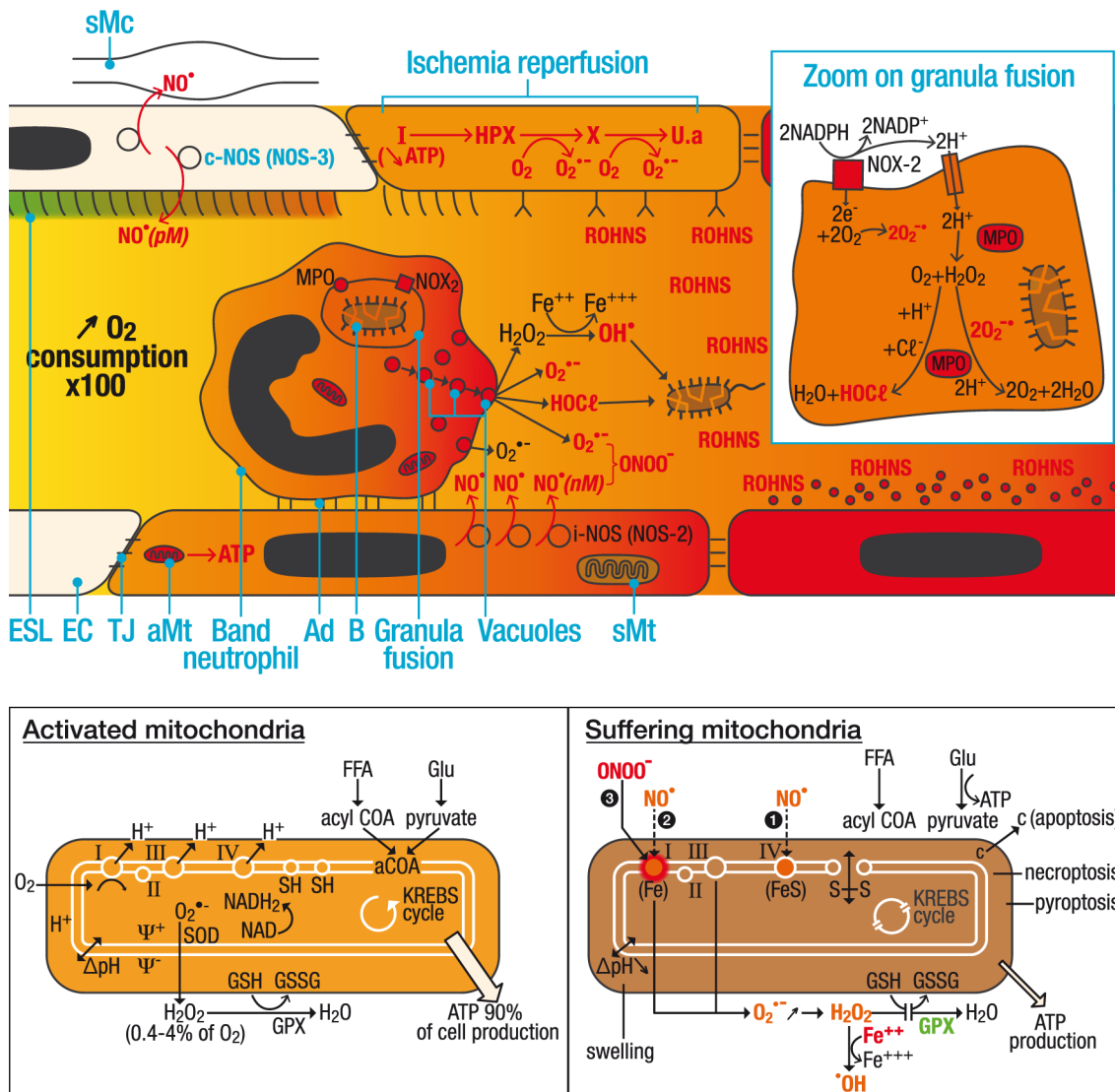
**FIG. 3. Transposition of cellular impact of increased redox potential from cancer cells to leukocytes, particularly neutrophils.**



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](http://www.liebertpub.com/ars).

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



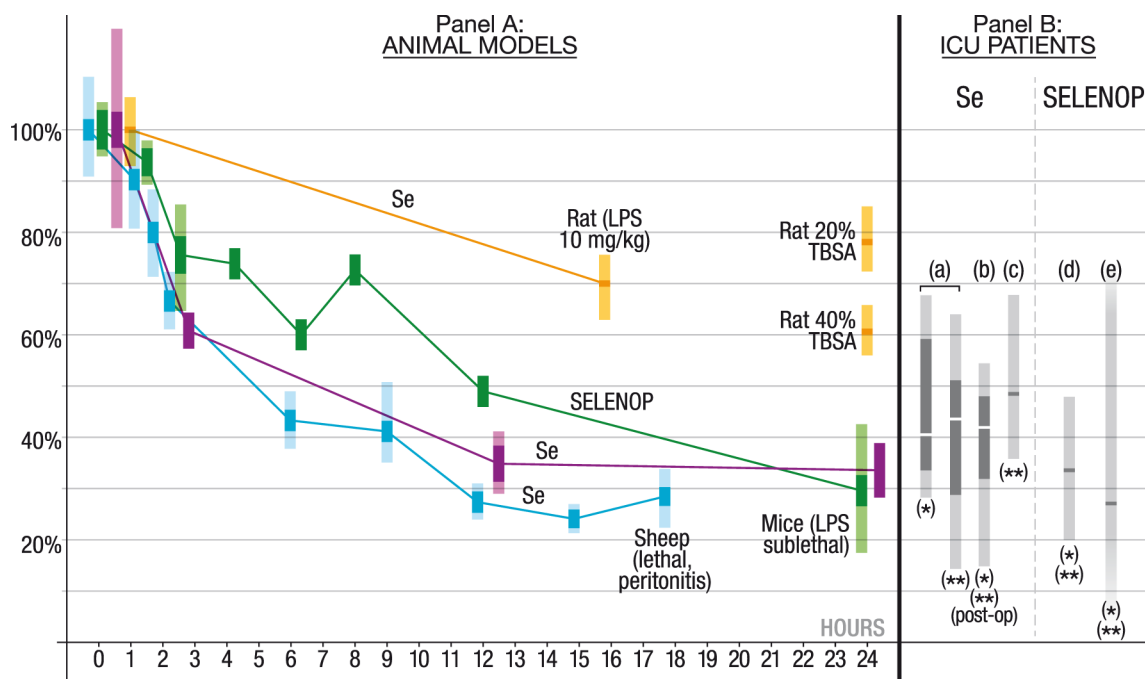
In the *upper part of the figure*, the illustrated leukocyte is a band neutrophil (immature form produced by activated bone marrow). Cell colors, from orange to red, illustrate increased activation. Damaged mitochondria (sMT) are in brown.

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 ( $O_2^{\bullet-}$ ), hydrogen peroxide ( $H_2O_2$ ) leading to the bactericidal hypochlorous acid (HOCl) by MPO, hydroxyl radical ( $\bullet OH$ ) in the presence of ferrous ( $Fe^{++}$ ) or copper ( $Cu^+$ ) cations or  $H_2O$  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 ( $NO^\bullet$ ) concentration and  $O_2^{\bullet-}$ .

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  $NO^\bullet$  leading to increased  $O_2^{\bullet-}$  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  $O_2^{\bullet-}$  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  $\mu$ 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 25<sup>th</sup> and 75<sup>th</sup> percentiles as the top and the bottom of the box and capped lines indicating the 10<sup>th</sup> to the 90<sup>th</sup> 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.

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