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REVIEW

The Use of Redox Expression and Associated Molecular Damage to Evaluate the Inflammatory Response in Critically Ill Patient with Severe Burn

Lavinia Melania Bratu[1] · Alexandru Florin Rogobete[2,3] · Dorel Sandesc[2,3] · Ovidiu Horea Bedreag[2,3] · Sonia Tanasescu[2] · Razvan Nitu[2] · Sonia Elena Popovici[2] · Zorin Petrisor Crainiceanu[2]

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Abstract The patient with severe burns always represents a challenge for the trauma team due to the severe biochemical and physiopathological disorders. Although there are many resuscitation protocols of severe burn patient, systemic inflammatory response, oxidative stress, decreased immune response, infections, and multiple organ dysfunction syndromes are still secondary complications of trauma, present at maximum intensity in this type of patients. Currently there are numerous studies regarding the evaluation, monitoring, and minimizing the side effects induced by free radicals through antioxidant therapy. In this study, we want to introduce biochemical and physiological aspects of oxidative stress in patients with severe burns and to summarize the biomarkers used presently in the intensive care units. Systemic inflammations and infections are according to the literature the most important causes of death in these type of patients, being directly involved in multiple organ dysfunction syndrome and death.

Keywords Oxidative stress · Severe burns · microRNAs · Molecular damage · Antioxidants

✉ Alexandru Florin Rogobete
alexandru.rogobete@umft.ro

[1] Faculty of Pharmacy, "Victor Babes" University of Medicine and Pharmacy, Timisoara, Romania

[2] Faculty of Medicine, "Victor Babes" University of Medicine and Pharmacy, Timisoara, Romania

[3] Clinic of Aneshtesia and Intensive Care, Emergency County Hospital "Pius Brinzeu", Bd. Iosif Bulbuca nr.10, 300736 Timisoara, Romania

Abbreviations

SIRS	Systemic inflammatory response syndrome
MODS	Multiple organ dysfunction syndrome
ARDS	Acute respiratory distress syndrome
AKI	Acute kidney injury
FR	Free radicals
OS	Oxidative stress
ICU	Intensive care unit
MDA	Malondialdehyde
4-HNE	4-Hydroxy-2-nonenal
DNA	Deoxyribonucleic acid
RNA	Ribonucleic acid
SOD	Superoxide dismutase
CAT	Catalase
GSH	Glutathione
GRXs	Glutaredoxins
PRXs	Peroxiredoxins
NAD(P)H	Nicotinamide adenine dinucleotide phosphate oxidases
ROS	Oxygen reactive species
IL-1	Interleukin 1
IL-2	Interleukin 2
IL-6	Interleukin 6
IL-8	Interleukin 8
IL-12	Interleukin 12
IL-17	Interleukin 17
IL-23	Interleukin 23
TNF-alpha	Tumor necrosis alpha
CRP	C-reactive protein
PCT	Procalcitonin
C3a, C5a	Complement components
NT-CNP	N-terminal natriuretic peptide
microRNAs	MicroRNA species
NF-k B	Nuclear transcription factor-k B
Sirt1	Sirtuin 1
iNOS	Inducible nitric oxide synthase

Introduction

A high percentage of worldwide deaths is due to traumatic injuries caused by severe burns (Alencar de Castro et al. 2013; Lindahl et al. 2013). For patients with severe burns, there are several complications that increase morbidity and mortality, such as inflammation, compromised immune system, infections, respiratory disorders, cardiovascular and renal dysfunction. Another important factor that participates in increasing the mortality rate is the increased length of stay in hospital (Liberati et al. 2006).

Burns are responsible for modifying the functionality of the immune system, making patients vulnerable to infections. Systemic infections are according to the literature the most important causes of death in these type of patients, being directly involved in multiple organ dysfunction syndrome (MODS) and death (Rosanova et al. 2014).

The burned patient also presents pathophysiological disorders with strong implications in the survival rate, such as acute respiratory distress syndrome (ARDS), acute kidney injury (AKI), hypercatabolism, and bacterial translocation due to increased intestinal permeability (Arlati et al. 2007; Vf et al. 2012).

Moreover, inflammation influences the fluid coagulation balance by activating the coagulation cascade, which has as results the compromise of the microvascular system (Mühl et al. 2011; Farina et al. 2013; Rosanova et al. 2014). One of the most significant side effect in patients with severe burns is the systemic inflammatory response syndrome (SIRS), which occurs in a few hours postburn. This is responsible for increased capillary permeability, the release of proinflammatory factors, and for inducing the production of highly reactive molecular species, commonly known as free radicals (FR) (Lazarus et al. 2015). Excess production of FR leads to inflammation and infection potentiation, forming a vicious circle in terms of biochemical and metabolic reactions. By high concentrations of FR and by decreased antioxidant capacity, physiological redox balance is severely disrupted, thus setting up as oxidative stress (OS).

Numerous studies correlate OS in patients with severe burns with an increased rate of severe posttraumatic complications and with a high mortality rate (Rosenfeldt et al. 2013). For increasing the body's antioxidant capacity, a number of studies recommend the administration of substances with antioxidant capacity. At the moment, a number of research groups are studying intensively the action of antioxidant therapy regarding the clinical outcomes of patients with severe burns (Oudemans-van Straaten et al. 2014).

In this current work, we want to present the pathophysiology of the OS in patients with severe burns, as well as the implications of the antioxidant therapy on the outcome of such patients.

Molecular Damage in Critically Ill Patients with Severe Burns

FR are molecular or ionic species with an increased reactivity, mainly due to their electronic configuration. In the human body, this reactive species are produced in a physiological pathway following biochemical processes, their destructive action being inhibited by the endogenous antioxidant systems (Lazarus et al. 2015). Along with the disturbance of physiological metabolisms due to trauma, the production of FR is accelerated. Moreover, the body's antioxidant capacity progressively decreases because it is susceptible to OS aggression (Scheibmeir et al. 2005; Rao et al. 2011) (Fig. 1).

The most common FR described in the case of severe burns are represented by the hydroxyl radical, the superoxide radical, hydrogen peroxide, the alkylperoxyl radical, nitric oxide, nitroperoxide, and the lipid radical (Horton 2003; Chaturvedi

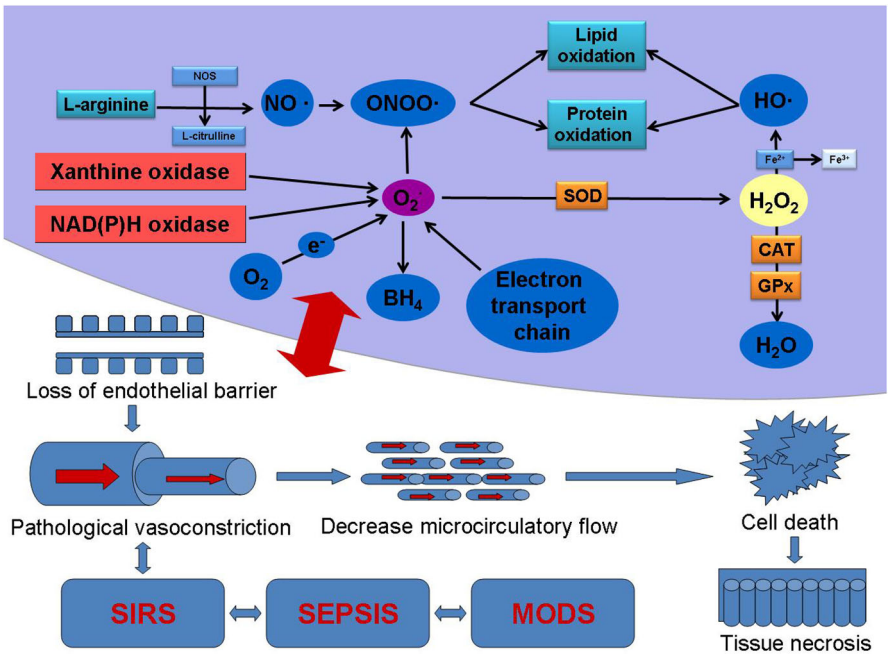

Fig. 1 The diagram of biochemical mechanisms of free radicals. Pathophysiological implications of oxidative stress. The massive losses of fluids through the burned area have as effect a decrease of the blood flow. Following the peripheral ischemia, the cell metabolism goes from the aerobic phase to the anaerobic one, leading to modifications of the enzyme systems and to free radicals production. The overproduction of free radicals occurs through various biochemical pathways, such as xanthine oxidase pathway, NAD(P)H oxidase pathway, electron transport chain, lipid peroxidation, and protein peroxidation pathway. Lipid oxidation is responsible for destroying the mitochondrial cell membranes. Also, the intense redox activity is responsible for the destruction of the vascular endothelium. Cell apoptosis and tissue necrosis emphasizes *SIRS* increasing MODS and the death rate

and Beal 2013; Tsakiridis et al. 2014). The main sources of FR generation are represented by mitochondria, the peroxisomal oxidases, the xanthine oxidase, the nicotinamide adenine dinucleotide phosphate NAD(P)H oxidases, and by the cytochrome P450 enzymes (Halliwell 2007; Lazzarino et al. 2014).

By the action of reactive oxygen species (ROS) on the polyunsaturated fatty acids, a series of important lipid reactive species are being produced, which are responsible for initiating the lipid peroxidation chain reactions. The aggression of lipid peroxidation on the physiological function of the human body is given especially by high spreading ability of the redox chain reactions, as well as by toxicity and by high concentrations of metabolites, which include malondialdehyde (MDA), 4-hydroxy-2-nonenal (4-HNE) si F2-isoprostanes (Leipnitz et al. 2011; Le Lay et al. 2014; Rahal et al. 2014).

Another target of FR are DNA species, which lead to significant structural and functional changes. Following this a number of alterations were outlined in the mechanisms of protein synthesis, which are being directly involved in certain pathologies (Ramos et al. 2012).

In trauma patients with severe burns, a significant amount of superoxide radical is produced by activating macrophages, eosinophils, T-lymphocytes, and B-lymphocytes (Vinha et al. 2013). The biochemical mechanism of superoxide radical release includes reactions produced by NAD(P)H oxidase and xanthine oxidase. Also during the mitochondrial reactions of electron transfer significant amounts of superoxide radical are generated. Subsequently, through the reaction catalyzed by superoxide dismutase (SOD), superoxide radical is transformed into hydrogen peroxide (Miller 2012).

Hydrogen peroxide is enzymatically reduced through catalase enzyme (CAT) in peroxisomes, and through glutathione peroxidase in the cytoplasm or in the mitochondria, forming water and oxygen molecules. By combining hydrogen peroxide with iron ions (II), the so-called Fenton reaction, large amounts of hydroxyl radical are obtained (Yazihan et al. 2008). Hydroxyl radical is a free species with the highest reactivity, being responsible for destroying cell membranes by distorting lipoproteins (Marín-Prida et al. 2012).

Acute endothelial dysfunctions are also present in patients with severe burns in a high percentage. NO is synthesized from L-arginine by nitric oxide synthases (NOS); this reaction is being catalyzed by oxygen, especially in the endothelial cells (Fox et al. 2013). Through the reaction with superoxide radical, nitroperoxide is obtained which is responsible for a number of pathophysiologies in trauma patients with severe burns (Rao et al. 2011; Zapatero-Solana et al. 2014; Duchesne et al. 2015). Endothelial dysfunctions, responsible for disrupting the physiology of the microvascular system, led in many cases to metabolic acidosis, cell apoptosis, sepsis, MODS, and death (Burkhardt et al. 2012). Another syndrome commonly seen in patients with severe burns is the ischemia–reperfusion syndrome, following this large amounts of proinflammatory mediators are released, which include complement fragments, cytokines, or lipid mediators. Han et al. studied a number of aspects of the inflammatory status in patients with severe burns, such as levels of endotoxin, soluble adhesion molecules, and cytokine levels. After the study they reported significantly modified profiles in such patients in terms of inflammatory aspects, due to the significant increase of endotoxins, cytokines, and of proinflammatory mediators (Han et al. 2004). Mühl et al. showed in a similar study, that in critical patients with severe burns, the antioxidant capacity dramatically decreases, being observed increases in proinflammatory marker expressions (Mühl et al. 2011). The endogenous antioxidant system is well represented under physiological conditions by enzymes with antioxidant capacity and by a number of vitamins. Endogenous antioxidant systems. Three types of enzymes were identified: SOD1 (CuZnSOD) in the nucleus and cytosol, SOD2 (MnSOD) identified in the mitochondrial matrix, respectively, SOD3 (EcSOD) located extracellular (Gerbaud et al. 2005; Pilon et al. 2011). During antioxidant mechanism SOD enzymes are involved in converting the superoxide ion into water and oxygen (Miller 2012). Catalase is another enzyme which is able to reduce the oxidative effect of hydrogen peroxide by decomposing it into oxygen and water molecules (Rahman and Adcock 2006; Comar et al. 2013). The antioxidant activity of glutathione (GSH) is represented by maintaining a normal redox balance (Lazzarino et al. 2014). Glutaredoxins (GRXs) are another endogenous antioxidant systems which are

present in human body in two forms, Grx1 present in the cytosol and intermembranous space and Grx2 present in the mitochondrial matrix. Another endogenous antioxidant system responsible for the breakdown of hydrogen peroxide is represented by peroxiredoxins (PRXs) (Elkharaz et al. 2013).

Biomarkers for the Assessment of Oxidative Stress in Burned Patient

A number of specific biomarkers have been described for the assessment and for monitoring the oxidative effects. Some of the most useful markers for the evaluation and optimization of intensive care in patients with severe burns are represented by inflammatory markers, such as interleukin 1 (IL-1), interleukin 6 (IL-6), interleukin 2 (IL-2) interleukin 8 (IL-8), interleukin 17 (IL-17), tumor necrosis factor alpha (TNF-alpha) (Homsi et al. 2009; Trancă et al. 2014). IL-1 has been particularly studied due to its high specificity, being associated with poor outcomes (Abdul-Muneer et al. 2015). Regarding Il-6, numerous studies report the existence of a direct connection between elevated levels of IL-6 and the level of systemic inflammation (Dal-Pizzol et al. 2010; Abdul-Muneer et al. 2015; Kumar et al. 2014). 4-HNE (Ansari et al. 2008) is a specific biomarker for redox reactions in lipid peroxidation. For assessing injuries brought by FR on DNA and RNA 8-hydroxy-2′-deoxyguanosine is used (Abdul-Muneer et al. 2013), which expresses DNA oxidative damage. Regarding the lower immune response in patients with severe burns, a special place is represented by the CD163 receptor (Xie 2013). CD163 expression is particularly highlighted in the surface of macrophages and monocytes (Piatkowski et al. 2011). Piatkowski et al. investigated the expression of CD163 at 120 h postburn. After the study they concluded that dosing, evaluating, and monitoring the expression of CD163 can be a good predictor for inflammation, sepsis, or MODS for this type of patients (Piatkowski et al. 2011). Table 1 presents the most significant biomarkers for assessing and monitoring the OS in burned patient.

Over the last period, microRNAs circulating species have been intensively studied, in order to use them as a biomarkers for various diseases. microRNAs species are short noncoding RNAs consisting of 19–24 nucleotides (Kodahl et al. 2014). microRNA formation begins in the nucleus with protein-coding transcription by RNA polymerase II, which represents the primary microRNA (pri-microRNA) (Courts and Madea 2010). Nucleocytoplasmic transporter (Exportin 5) is responsible for the transport into the cytoplasm of the pre-microRNA. Once in the cytoplasm, the pre-miRNA undergoes an additional processing by the Dicer complex, generating double-stranded mature microRNA (19–24 nucleotides in length) and microRNA* (passenger strand) (Kodahl et al. 2014). microRNAs can reach the systemic circulation either with cell death, as apoptotic bodies, or as microvesicles and exosomes. Due to the increased stability and specificity, microRNA circulating species are currently preferred for the assessment and monitoring of various pathologies (Starega-Roslan et al. 2011). In trauma patients with severe burns a series of studies were performed, regarding the expression of microRNAs. Tacke et al. studied the expression of microRNAs in trauma patients

Table 1 Specific biomarkers for molecular changes in the case of severe burns

Biomarker	Characteristics	Reference (s)
IL-1	Proinflammatory cytokine; it is generated by monocytes, macrophages, and endothelial cells; it is responsible for increased capillary permeability; it interferes in the coagulation cascade; it is responsible for lymphocytes activation; it interferes in chain biochemical reactions, generating TNF-alpha	(Chuang et al. 2014; Trancă et al. 2014)
IL-2	Proinflammatory cytokine; it is generated by T-lymphocytes; it is responsible for the production of immunoglobulins; it modulates natural killer cell proliferation	(McLean and El-Omar 2009; Trancă et al. 2014; Mica et al. 2014)
IL-6	Proinflammatory and antiinflammatory cytokine; it is generated particularly by macrophages, monocytes and T-lymphocytes; it modulates lymphocyte differentiation; it is responsible for neutrophils activation; it modulates the activity of NK cells	(Douzinas et al. 2011; Liu et al. 2013)
IL-8	Proinflammatory cytokine; it is generated by macrophages and monocytes; it modulates the activity of immune cells	(Trancă et al. 2014)
IL-12	Proinflammatory cytokine; it is generated by monocytes and macrophages; it modulates lymphocyte differentiation	(Chuang et al. 2014)
IL-17	Proinflammatory cytokine; it is generated by T helper cells; Its biogenesis is modulated by IL-23; it is responsible for increased synthesis of other chemokines; it interferes in neutrophils recruitment in different tissues	(Andruszkow and Fischer 2014; Trancă et al. 2014)
TNF-alpha	Proinflammatory cytokine; it is generated by macrophages, monocytes, and T-lymphocytes; it interferes in NO synthesis; it is a cofactor during the production of other chemokines; it modulates the activity of immune cells	(Erbaş and Taşkiran 2014; Trancă et al. 2014)
4-HNE	Product of lipid oxidative distortion; it assesses the activity of free radicals	(Ansari et al. 2008)
8-hydroxy-2′-deoxyguanosine	Specific marker for DNA and RNA oxidative denaturing reactions	(Abdul-Muneer et al. 2013, 2015)
NT-CNP	It assesses NO oxidative activity; it assesses vascular endothelial dysfunction	(Ferguson et al. 2010; Trancă et al. 2014)
CD163	It is found on the surface of macrophages and monocytes; their expression assess inflammation, sepsis; good predictor for MODS; specific for patients with severe burns	(Piatkowski et al. 2011)

Table 1 continued

Biomarker	Characteristics	Reference (s)
PCR	Proinflammatory activity; it is synthesized in the lungs and liver; it is released in the acute phase of trauma; it is an important marker for assessing inflammation; its expression increases significantly in burns; it modulates the activity of the complement system; it interferes in phagocytosis	(Quoilin et al. 2014; Trancă et al. 2014)
PCT	Proinflammatory activity; specific marker for sepsis	(Trancă et al. 2014)
C3a; C5a	Proinflammatory activity; they are produced by the complement system; they accumulate in tissues; they increase capillary permeability; they are responsible for the increased synthesis of histamine; they activates platelet; they are responsible for bacterial opsonisation	(Coelho and Martins 2012; Rittirsch et al. 2012; Trancă et al. 2014)
microRNAs	They are short noncoding RNAs (19–24 nucleotides); they are markers for inflammation, sepsis, cell and tissue injury; they present high specificity; they present increased stability	(Vasilescu et al. 2009; Moore et al. 2012; Huang et al. 2014; McClure et al. 2014)

IL-1 interleukin 1, *IL-2* interleukin 2, *IL-6* interleukin 6, *IL-8* interleukin 8, *IL-12* interleukin 12, *IL-17* interleukin 17, *IL-23* interleukin 23, *TNF-alpha* tumor necrosis alpha, *CRP* C-reactive protein, *PCT* procalcitonin, *C3a, C5a* complement components, *NT-CNP* N-terminal natriuretic peptide, *microRNAs* micro RNA species, *MODS* multiple organ dysfunction syndrome, *NO* nitric oxide

with sepsis, reporting an increased expression of microRNA-133a in patients with sepsis. Moreover, they concluded that increased expression of microRNA-133a can be a predictor of poor prognosis for sepsis patient (Tacke et al. 2014). Zhao et al. report changes in microRNA 23a-3p expression during ischemia-reperfusion syndrome (Zhao et al. 2014).

Other similar studies, report changes in microRNA-182, microRNA-199a-5p, microRNA-211, microRNA-203, microRNA-222, microRNA-29b, microRNA-150, microRNA-342-5p, and microRNA-122 expression in trauma patients, in patients with severe burns, in severe systemic inflammation, sepsis, and MODS (Vasilescu et al. 2009; Ding et al. 2012; Moore et al. 2012; Xie 2013; Zhao et al. 2014).

Modulation of the Oxidative Response: Antioxidant Therapy Models

The current protocols are focused mainly on the fluid management in such patients, unfortunately fighting against SIRS is not fully approached (Belîi et al. 2014; Mierzewska-schmidt 2015). Studies on experimental animals show a significant decrease of SIRS, sepsis, and MODS incidence associated with high doses of intravenous administration of substances with increased antioxidant capacity (Hu et al. 2015; Preiser et al. 2015) (Table 2). Among these, the most studied as having a

Table 2 Substances with strong antioxidant capacity

The type of research study	Pathologies	The outcome of antioxidant therapy	References
Study in experimental animals	Renal ischemia after hemorrhagic shock ischemia-reperfusion syndrome	It improves renal function; it reduces systemic inflammation; it reduces the catabolites concentration resulted from phospholipid oxidation; Dose: 15 mg/kg/24 h (i.v.) vitamin C	(Lloberas et al. 2002)
Study in experimental animals	Hepatic ischemia after hemorrhagic shock ischemia-reperfusion syndrome	It reduces systemic inflammation; it reduces the serum level of proinflammatory cytokines; it restores liver function; Dose: 30, 100, 300, 1000 mg/kg (i.v.) vitamin C; extremely high doses lead to the loss of liver function	(Seo and Lee 2015)
Study in experimental animals	Sepsis microvascular system dysfunctions	It improves the function of microvascular system; it reduces NO synthesis by inhibiting inducible nitric oxide synthase (iNOS) expression; it reduces edema; it prevents MODS occurrence; it prevents septic dysfunction of capillary blood flow; Dose: 200 mg/kg (i.v.) vitamin C	(Wu et al. 2003)
Study in experimental animals	Sepsis cardiovascular dysfunctions	It protects cardiac function; it restores the functionality of vascular epithelium; it reduces inflammation; it inhibits lipid peroxidation; Dose: 76 mg/kg (i.v.) vitamin C	(Hsu and Wang 2015)
Study in experimental animals	Sepsis; acute kidney injury	It restores renal microcirculation; it reduces inflammation; it reduces the concentration of reactive nitrogen species; it increases the surviving rate; Dose: 100 mg/kg (i.v.) resveratrol	(Wang et al. 2012)
Study in experimental animals	Sepsis; acute lung injury	It enhances Sirtuin 1 (Sirt1) expression, which is responsible for inflammatory status modulation; it decreases pulmonary and systemic inflammation; it reduces acute lung injury syndrome; it reduces the incidence of infection and MODS; Dose: 15, 30 mg/kg resveratrol	(Li et al. 2013)
Study in experimental animals	Severe burns; systemic inflammation; sepsis	It improves cardiovascular function; it reduces tissue inflammation; it inhibits cytokines production by cardiomyocytes; it inhibits nuclear transcription factor-k B (NF-k B); Dose: 38 mg/kg Vitamin C (i.v.); 27 IU/kg vitamin E (i.v.); 41 IU/kg vitamin A (iv)	(Horton 2003)

Table 2 continued

The type of research study	Pathologies	The outcome of antioxidant therapy	References
Study in humans; matched control	Cardiovascular dysfunctions; inflammation	It improves cardiovascular function; it reduces the serum levels of proinflammatory cytokines; it reduces the catabolites concentrations resulted from oxidation reactions; it reduces the length of stay in ICU; it reduces the length of stay in hospital; Dose: 500 mg/daily for 5 days vitamin C (i.v.)	(Carnes et al. 2001)
Study in humans; randomized control trial	Multiple trauma patients; sepsis; respiratory dysfunctions	It reduces lung inflammation; it reduces sepsis; it reduces MODS; It reduces the need for mechanical ventilation; it reduces the length of stay in ICU; Dose: 1 g vitamin C (i.v.) three times daily; 1000 IU vitamin E (enteral), three times daily	(Nathens et al. 2002)
Study in humans; prospective–retrospective cohort study	Multiple trauma patients	It reduces systemic inflammation; it reduces the length of stay in ICU; it reduces the length of stay in hospital; it reduces mortality; Dose: 3 g vitamin C (i.v.) daily; 1000 IU vitamin E (enteral), daily; 200 μg selenium (i.v.)	(Collier et al. 2008)
Study in humans; retrospective controlled trial	Trauma; cardiac surgery; pulmonary dysfunctions; traumatic brain injury	It reduces systemic inflammation; it reduces sepsis; it reduces the length of stay in ICU; statistically significant differences were not observed in the incidence of sepsis or MODS; it lowers PCR serum level; Dose: 540 mg Selenium (i.v.) the first day, 270 mg on days 2–5; 60 mg Zinc (i.v.) in the first day, 30 mg on days 2–5; 305 mg vitamin B1 (i.v.) in the first day, 205 mg on days 2–5; 2.7 g vitamin C (i.v.) the first day, 1.6 g on days 2–5; 600 mg vitamin E (i.v.) the first day, 300 mg on days 2–5	(Berger and Pichard 2014)

NO nitric oxide, *iNOS* inducible nitric oxide synthase, *Sirt1* sirtuin 1, *PCR C*-reactive protein, *MODS* multiple organ dysfunction syndrome, *NF-k B* nuclear transcription factor-k B, *ICU* intensive care unit

strong antioxidant potential are *N*-acetylcysteine (Csontos et al. 2012), vitamin C (Biesalski and McGregor 2007), vitamin E (Oudemans-van Straaten et al. 2014), vitamin A (Aschauer et al. 2014), selenium (Sakr et al. 2014), and resveratrol (Lagouge et al. 2006). Atabak Najafi et al. studied the influence of *N*-acetylcysteine administration in patients with ventilator support. As a result of this prospective

study, which included 44 patients with multiple trauma, they showed a reduction of systemic inflammation and of complications caused by this (Najafi et al. 2014). In a similar study, Al-Jawad et al. (2011) confirm the benefic effects of *N*-acetylcysteine on the inflammatory status, reporting a decrease in the mortality in such patients. Csontos et al. studied the effects induced by the antioxidant therapy with *N*-acetylcysteine in patients with severe burns, reporting a considerable decrease in plasma levels for proinflammatory cytokines, such as IL-6, IL-8, IL-10. Moreover, patients who received antioxidant therapy showed low serum levels of malondialdehyde and a lower necessary for catecholamine (Csontos et al. 2012). Other studies also revealed low plasma levels for MDA and myeloperoxidase activity, where *N*-acetylcysteine was given in trauma patients with severe burns (Heyland et al. 2005; Hall et al. 2012). Studies performed in humans regarding the administration of high doses of vitamin C, given intravenously, reported an increase in the survival rate for this type of patients (Lira and Pinsky 2014; Tompkins and Hospital 2015). Moreover, various studies associate the administration of intravenous vitamin C with a decrease in oxidative reactions given by neutrophils, systemic inflammation, sepsis, mechanical ventilation, as well as in the length of stay in intensive care unit (ICU) (Dubick et al. 2005; Oudemans-van Straaten et al. 2014).

Tanaka et al. studied the effects of vitamin C administration in trauma patients with severe burns. They administered high doses of vitamin C (66 mg/kg/h) in the first 24 h posttrauma, in patients who had burns on more than 30 % of the body surface area. After the study, they concluded that the antioxidant therapy implemented in the first 24 h posttrauma reduced the need for fluids during fluid management in this type of patients, it also reduced the wound edema and the incidence of respiratory disorders (Tanaka et al. 2000). Juretic et al. studied the effects of vitamins A, C, and E administration on nuclear transcription factor-kappa B (NF-kB), inflammatory status, and cardiac function in patients with severe burns. The antioxidant therapy was achieved by coadministration of 38 mg/kg vitamin C (i.v.), 27 U/kg vitamin E (i.v.), and 41 U/kg vitamin A (i.v.). The animal group who received antioxidant therapy, showed significant improvements in heart function. Also, the study reported a reduction of the inflammatory response. Regarding NF-kB, a decrease of proinflammatory cytokines biogenesis was observed, due to the inhibition of NF-kB nuclear migration (Horton 2003).

Conclusions

In this review we resumed the biochemical and physiological implications of FR in trauma patients with severe burns. Available clinical and preclinical studies report a series of pathologies induced by OS in critically ill patient, such as microvascular system dysfunction, severe systemic inflammation, vulnerability to infection, metabolic disorders until in the end when multiple organ dysfunction or death occur.

In order to minimize the destructive effects induced by OS, a series of studies were performed regarding the administration of antioxidant substances, such as vitamins C, E, A, selenium, *N*-acetylcysteine, and resveratrol. These protective

effects against FR refer to protection against inflammation, organ injury, and dysfunction, as well as to a more rapid recovery of patients with severe burns. Finally, we can conclude that the administration of vitamin C, associated or not with other antioxidants, brings beneficial effects in critically ill patient, by reducing particularly the systemic inflammation and the microvascular system dysfunctions. However, there still are a series of questions that need to be answered, including the optimal dose, the time of antioxidant substances administration, and the antioxidant combinations.

Compliance with ethical standards

Conflict of interest The authors declare that there is no conflict of interests regarding the publication of this paper.

References

Abdul-Muneer PM, Schuetz H, Wang F et al (2013) Induction of oxidative and nitrosative damage leads to cerebrovascular inflammation in an animal model of mild traumatic brain injury induced by primary blast. Free Radic Biol Med 60:282–291. doi:10.1016/j.freeradbiomed.2013.02.029

Abdul-Muneer PM, Chandra N, Haorah J (2015) Interactions of oxidative stress and neurovascular inflammation in the pathogenesis of traumatic brain injury. Mol Neurobiol 51:966–979. doi:10.1007/s12035-014-8752-3

Alencar de Castro RJ, Leal PC, Sakata RK (2013) Pain management in burn patients. Rev Bras Anestesiol 63:149–158. doi:10.1016/S0034-7094(13)70206-X

Al-jawad FH, Ph D, Sahib AS et al (2011) Effect of *N*-acetylcysteine on wound healing in burned patients. Mustansiyria Med J 10:28–31

Andruszkow H, Fischer J (2014) Interleukin-6 as inflammatory marker referring to multiple organ dysfunction syndrome in severely injured children. Scand J Trauma Resusc Emerg Med 22:16. doi:10.1186/1757-7241-22-16

Ansari MA, Roberts KN, Scheff SW (2008) Oxidative stress and modification of synaptic proteins in hippocampus after traumatic brain injury. Free Radic Biol Med 45:443–452. doi:10.1016/j.freeradbiomed.2008.04.038

Arlati S, Storti E, Pradella V et al (2007) Decreased fluid volume to reduce organ damage: a new approach to burn shock resuscitation? A preliminary study. Resuscitation 72:371–378. doi:10.1016/j.resuscitation.2006.07.010

Aschauer S, Gouya G, Klickovic U et al (2014) Effect of systemic high dose vitamin C therapy on forearm blood flow reactivity during endotoxemia in healthy human subjects. Vasc Pharmacol 61:25–29. doi:10.1016/j.vph.2014.01.007

Belîi N, Moghildea V, Şandru S et al (2014) Anxiety, but not pain catastrophizing, represents a risk factor for severe acute postoperative pain: a prospective, observational, cohort study. J Rom Anest Terap Int 21:19–26

Berger MM, Pichard C (2014) Development and current use of parenteral nutrition in critical care—an opinion paper. Crit Care 18:478. doi:10.1186/s13054-014-0478-0

Biesalski HK, McGregor GP (2007) Antioxidant therapy in critical care—is the microcirculation the primary target? Crit Care Med 35:S577–S583. doi:10.1097/01.CCM.0000278598.95294.C5

Burkhardt M, Nienaber U, Pizanis A et al (2012) Acute management and outcome of multiple trauma patients with pelvic disruptions. Crit Care 16:R163. doi:10.1186/cc11487

Carnes CA, Chung MK, Nakayama T et al (2001) Ascorbate attenuates atrial pacing-induced peroxynitrite formation and electrical remodeling and decreases the incidence of postoperative atrial fibrillation. Circ Res 89:E32–E38

Chaturvedi RK, Beal MF (2013) Mitochondrial diseases of the brain. Free Radic Biol Med 63:1–29. doi:10.1016/j.freeradbiomed.2013.03.018

Chuang T-Y, Chang H-T, Chung K-P et al (2014) High levels of serum macrophage migration inhibitory factor and interleukin 10 are associated with a rapidly fatal outcome in patients with severe sepsis. Int J Infect Dis 20:13–17. doi:10.1016/j.ijid.2013.12.006

Coelho FR, Martins JO (2012) Diagnostic methods in sepsis: the need of speed. Rev Assoc Med Bras 58:498–504. doi:10.1590/S0104-42302012000400024

Collier BR, Giladi A, Dossett LA et al (2008) Impact of high-dose antioxidants on outcomes in acutely injured patients. J Parenter Enter Nutr 32:384–388

Comar JF, Babeto De Sá-Nakanishi A, De Oliveira AL et al (2013) Oxidative state of the liver of rats with adjuvant-induced arthritis. Free Radic Biol Med 58:144–153. doi:10.1016/j.freeradbiomed.2012.12.003

Courts C, Madea B (2010) Micro-RNA—a potential for forensic science? Forensic Sci Int 203:106–111. doi:10.1016/j.forsciint.2010.07.002

Csontos C, Rezman B, Foldi V et al (2012) Effect of *N*-acetylcysteine treatment on oxidative stress and inflammation after severe burn. Burns 38:428–437. doi:10.1016/j.burns.2011.09.011

Dal-Pizzol F, Ritter C, Cassol-Jr OJ et al (2010) Oxidative mechanisms of brain dysfunction during sepsis. Neurochem Res 35:1–12. doi:10.1007/s11064-009-0043-4

Ding X, Ding J, Ning J et al (2012) Circulating microRNA-122 as a potential biomarker for liver injury. Mol Med Rep 5:1428–1432. doi:10.3892/mmr.2012.838

Douzinas EE, Betrosian A, Giamarellos-Bourboulis EJ et al (2011) Hypoxemic resuscitation from hemorrhagic shock prevents lung injury and attenuates oxidative response and IL-8 overexpression. Free Radic Biol Med 50:245–253. doi:10.1016/j.freeradbiomed.2010.10.712

Dubick MA, Williams C, Elgjo GI, Kramer GC (2005) High-dose vitamin c infusion reduces fluid requirements in the resuscitation of burn-injured sheep. Shock 24:139–144

Duchesne JC, Kaplan LJ, Balogh ZJ et al (2015) Role of permissive hypotension, hypertonic resuscitation and the global increased permeability syndrome in patients with severe haemorrhage: adjuncts to damage control resuscitation to prevent intra-abdominal hypertension. Anaesthesiol Intensive Ther 47:143–155

Elkharaz J, Ugun-Klusek A, Constantin-Teodosiu D et al (2013) Implications for oxidative stress and astrocytes following 26S proteasomal depletion in mouse forebrain neurones. Biochim Biophys Acta 1832:1959–1968. doi:10.1016/j.bbadis.2013.07.002

Erbaş O, Taşkiran D (2014) Sepsis-induced changes in behavioral stereotypy in rats; involvement of tumor necrosis factor-alpha, oxidative stress, and dopamine turnover. J Surg Res 186:262–268. doi:10.1016/j.jss.2013.08.001

Farina J, Rosique MJ, Rosique RG (2013) Curbing inflammation in burn patients. Int J Inflam 2013:715645. doi:10.1155/2013/715645

Ferguson S, Mouzon B, Kayihan G et al (2010) Apolipoprotein E genotype and oxidative stress response to traumatic brain injury. Neuroscience 168:811–819. doi:10.1016/j.neuroscience.2010.01.031

Fox ED, Heffernan DS, Cioffi WG, Reichner JS (2013) Neutrophils from critically ill septic patients mediate profound loss of endothelial barrier integrity. Crit Care 17:R226. doi:10.1186/cc13049

Gerbaud P, Petzold L, Thérond P et al (2005) Differential regulation of Cu, Zn- and Mn-superoxide dismutases by retinoic acid in normal and psoriatic human fibroblasts. J Autoimmun 24:69–78. doi:10.1016/j.jaut.2004.10.003

Hall KL, Shahrokhi S, Jeschke MG (2012) Enteral nutrition support in burn care: a review of current recommendations as instituted in the ross tilley burn centre. Nutrients 4:1554–1565. doi:10.1155/2012/539426

Halliwell B (2007) Biochemistry of oxidative stress. Biochem Soc Trans 35:1147–1150. doi:10.1042/BST0351147

Han T-H, Lee S-Y, Kwon J-E et al (2004) The limited immunomodulatory effects of escharectomy on the kinetics of endotoxin, cytokines, and adhesion molecules in major burns. Mediators Inflamm 13:241–246. doi:10.1080/09629350400003191

Heyland DK, Dhaliwal R, Suchner U, Berger MM (2005) Antioxidant nutrients: a systematic review of trace elements and vitamins in the critically ill patient. Intensive Care Med 31:327–337. doi:10.1007/s00134-004-2522-z

Homsi S, Federico F, Croci N et al (2009) Minocycline effects on cerebral edema: relations with inflammatory and oxidative stress markers following traumatic brain injury in mice. Brain Res 1291:122–132. doi:10.1016/j.brainres.2009.07.031

Horton JW (2003) Free radicals and lipid peroxidation mediated injury in burn trauma: the role of antioxidant therapy. Toxicology 189:75–88. doi:10.1016/S0300-483X(03)00154-9

Hsu C-C, Wang J-J (2015) L-Ascorbic acid and alpha-tocopherol attenuates liver ischemia-reperfusion induced of cardiac function impairment. Transplant Proc 44:933–936. doi:10.1016/j.transproceed.2012.01.098

Hu D, Yu Y, Wang C et al (2015) microRNA-98 mediated microvascular hyperpermeability during burn shock phase via inhibiting FIH-1. Eur J Med Res 20:1–10. doi:10.1186/s40001-015-0141-5

Huang J, Sun Z, Yan W et al (2014) Identification of MicroRNA as sepsis biomarker based on miRNAs regulatory network analysis. Biomed Res Int 2014:594350. doi:10.1155/2014/594350

Kodahl AR, Lyng MB, Binder H et al (2014) Novel circulating microRNA signature as a potential non-invasive multi-marker test in ER-positive early-stage breast cancer: a case control study. Mol Oncol 8:874–883. doi:10.1016/j.molonc.2014.03.002

Kumar RG, Diamond ML, Boles JA et al (2014) Acute CSF interleukin-6 trajectories after TBI: associations with neuroinflammation, polytrauma, and outcome. Brain Behav Immun 45:253–262. doi:10.1016/j.bbi.2014.12.021

Lagouge M, Argmann C, Gerhart-Hines Z et al (2006) Resveratrol improves mitochondrial function and protects against metabolic disease by activating SIRT1 and PGC-1α. Cell 127:1109–1122. doi:10.1016/j.cell.2006.11.013

Lazarus RC, Buonora JE, Jacobowitz DM, Mueller GP (2015) Free radical biology and medicine protein carbonylation after traumatic brain injury: cell speci fi city, regional susceptibility, and gender differences. Free Radic Biol Med 78:89–100. doi:10.1016/j.freeradbiomed.2014.10.507

Lazzarino G, Di Pietro V, Lazzarino G et al (2014) Neuroglobin expression and oxidant/antioxidant balance after graded traumatic brain injury in the rat. Free Radic Biol Med 69:258–264. doi:10.1016/j.freeradbiomed.2014.01.032

Le Lay S, Simard G, Martinez MC, Andriantsitohaina R (2014) Oxidative stress and metabolic pathologies: from an adipocentric point of view. Oxid Med Cell Longev 2014:908539. doi:10.1155/2014/908539

Leipnitz G, Amaral AU, Fernandes CG et al (2011) Pristanic acid promotes oxidative stress in brain cortex of young rats: a possible pathophysiological mechanism for brain damage in peroxisomal disorders. Brain Res 1382:259–265. doi:10.1016/j.brainres.2011.01.014

Li T, Zhang J, Feng J et al (2013) Resveratrol reduces acute lung injury in a LPS-induced sepsis mouse model via activation of Sirt1. Mol Med Rep 7:1889–1895. doi:10.3892/mmr.2013.1444

Liberati A, Moja L, Moschetti I et al (2006) Human albumin solution for resuscitation and volume expansion in critically ill patients. Intern Emerg Med 1:243–245. doi:10.1007/BF02934748

Lindahl AE, Low A, Stridsberg M et al (2013) Plasma chromogranin A after severe burn trauma. Neuropeptides 47:207–212. doi:10.1016/j.npep.2012.10.004

Lira A, Pinsky MR (2014) Choices in fluid type and volume during resuscitation: impact on patient outcomes. Ann Intensive Care 4:38. doi:10.1186/s13613-014-0038-4

Liu T, Fei Z, Gangavarapu KJ et al (2013) Interleukin-6 and JAK2/STAT3 signaling mediate the reversion of dexamethasone resistance after dexamethasone withdrawal in 7TD1 multiple myeloma cells. Leuk Res 37:1322–1328. doi:10.1016/j.leukres.2013.06.026

Lloberas N, Torras J, Herrero-Fresneda I et al (2002) Postischemic renal oxidative stress induces inflammatory response through PAF and oxidized phospholipids. Prevention by antioxidant treatment. FASEB J 16:908–910. doi:10.1096/fj.01-0880fje

Marín-Prida J, Pentón-Rol G, Rodrigues FP et al (2012) C-Phycocyanin protects SH-SY5Y cells from oxidative injury, rat retina from transient ischemia and rat brain mitochondria from Ca^{2+}/phosphate-induced impairment. Brain Res Bull 89:159–167. doi:10.1016/j.brainresbull.2012.08.011

McClure C, Brudecki L, Ferguson DA et al (2014) MicroRNA 21 (miR-21) and miR-181b couple with NFI-A to generate myeloid-derived suppressor cells and promote immunosuppression in late sepsis. Infect Immun 82:3816–3825. doi:10.1128/IAI.01495-14

McLean MH, El-Omar EM (2009) Genetic aspects of inflammation. Curr Opin Pharmacol 9:370–374. doi:10.1016/j.coph.2009.06.003

Mica L, Vomela J, Keel M, Trentz O (2014) The impact of body mass index on the development of systemic inflammatory response syndrome and sepsis in patients with polytrauma. Injury 45:253–258. doi:10.1016/j.injury.2012.11.015

Mierzewska-Schmidt M (2015) Intraoperative fluid management in children—a comparison of three fluid regimens. Anaesthesiol Intensive Ther 47:125–130

Miller A-F (2012) Superoxide dismutases: ancient enzymes and new insights. FEBS Lett 586:585–595. doi:10.1016/j.febslet.2011.10.048

Moore CC, McKillop IH, Huynh T (2012) MicroRNA expression following activated protein C treatment during septic shock. J Surg Res 182:116–126. doi:10.1016/j.jss.2012.07.063
Mühl D, Woth G, Drenkovics L et al (2011) Comparison of oxidative stress and leukocyte activation in patients with severe sepsis and burn injury. Indian J Med Res 134:69–78
Najafi A, Mojtahedzadeh M, Ahmadi K et al (2014) The immunological benefit of higher dose *N*-acetyl cysteine following mechanical ventilation in critically ill patients. DARU J Pharm Sci 22:57. doi:10.1186/2008-2231-22-57
Nathens AB, Neff MJ, Jurkovich GJ et al (2002) Randomized, prospective trial of antioxidant supplementation in critically ill surgical patients. Ann Surg 236:814–822. doi:10.1097/00000658-200212000-00014
Oudemans-van Straaten HM, Man A, de Waard MC (2014) Vitamin C revisited. Crit Care 18:460. doi:10.1186/s13054-014-0460-x
Piatkowski A, Grieb G, Das R et al (2011) Soluble CD163: a novel biomarker for the susceptibility to sepsis in severe burn injuries. Indian J Plast Surg 44:118–124. doi:10.4103/0970-0358.81454
Pilon M, Ravet K, Tapken W (2011) The biogenesis and physiological function of chloroplast superoxide dismutases. Biochim Biophys Acta 1807:989–998. doi:10.1016/j.bbabio.2010.11.002
Preiser J-C, van Zanten AR, Berger MM et al (2015) Metabolic and nutritional support of critically ill patients: consensus and controversies. Crit Care 19:1–11. doi:10.1186/s13054-015-0737-8
Quoilin C, Mouithys-Mickalad A, Lécart S et al (2014) Evidence of oxidative stress and mitochondrial respiratory chain dysfunction in an in vitro model of sepsis-induced kidney injury. Biochim Biophys Acta 1837:1790–1800. doi:10.1016/j.bbabio.2014.07.005
Rahal A, Kumar A, Singh V et al (2014) Oxidative stress, prooxidants, and antioxidants: the interplay. Biomed Res Int 2014:761264. doi:10.1155/2014/761264
Rahman I, Adcock IM (2006) Oxidative stress and redox regulation of lung inflammation in COPD. Eur Respir J 28:219–242. doi:10.1183/09031936.06.00053805
Ramos SF, Mendonça BP, Leffa DD et al (2012) Effects of neuropeptide S on seizures and oxidative damage induced by pentylenetetrazole in mice. Pharmacol Biochem Behav 103:197–203. doi:10.1016/j.pbb.2012.09.001
Rao S, Sireesha K, Aparna Y, Sadanandam M (2011) Free radicals and tissue damage: role of antioxidants. Free Radicals Antioxidants 1:2–7. doi:10.5530/ax.2011.4.2
Rittirsch D, Redl H, Huber-Lang M (2012) Role of complement in multiorgan failure. Clin Dev Immunol. doi:10.1155/2012/962927
Rosanova MT, Stamboulian D, Lede R (2014) Risk factors for mortality in burn children. Brazilian J Infect Dis 18:144–149. doi:10.1016/j.bjid.2013.08.004
Rosenfeldt F, Wilson M, Lee G et al (2013) Oxidative stress in surgery in an ageing population: pathophysiology and therapy. Exp Gerontol 48:45–54. doi:10.1016/j.exger.2012.03.010
Sakr Y, Maia VP, Santos C et al (2014) Adjuvant selenium supplementation in the form of sodium selenite in postoperative critically ill patients with severe sepsis. Crit Care 18:R68. doi:10.1186/cc13825
Scheibmeir HD, Christensen K, Whitaker SH et al (2005) A review of free radicals and antioxidants for critical care nurses. Intensive Crit Care Nurs 21:24–28. doi:10.1016/j.iccn.2004.07.007
Seo MY, Lee SM (2015) Protective effect of low dose of ascorbic acid on hepatobiliary function in hepatic ischemia/reperfusion in rats. J Hepatol 36:72–77. doi:10.1016/S0168-8278(01)00236-7
Starega-Roslan J, Krol J, Koscianska E et al (2011) Structural basis of microRNA length variety. Nucleic Acids Res 39:257–268. doi:10.1093/nar/gkq727
Tacke F, Roderburg C, Benz F et al (2014) Levels of circulating miR-133a are elevated in sepsis and predict mortality in critically ill patients. Crit Care Med 42:1096–1104
Tanaka H, Matsuda T, Miyagantani Y et al (2000) Reduction of resuscitation fluid volumes in severely burned patients using ascorbic acid administration: a randomized, prospective study. Arch Surg 135:326–331
Tompkins RG, Hospital MG (2015) Survival from burns in the new millennium: 70 years experience from a single institution. Ann Surg 261:263–268
Trancă SD, Laura C, Hagă N (2014) Biomarkers in polytrauma induced systemic inflammatory response syndrome and sepsis—a narrative review. J Rom Anesth Terap Int 21:118–122
Tsakiridis K, Mpakas A, Kesisis G et al (2014) Lung inflammatory response syndrome after cardiac-operations and treatment of lornoxicam. J Thorac Dis 6:S78–S98. doi:10.3978/j.issn.2072-1439.2013.12.07

Vasilescu C, Rossi S, Shimizu M et al (2009) MicroRNA fingerprints identify miR-150 as a plasma prognostic marker in patients with sepsis. PLoS One. doi:10.1371/journal.pone.0007405

Vf E, Kosoko A, Sb A et al (2012) Plasma antioxidant enzymes, lipid peroxidation and hydrogen peroxide in wistar rats exposed to dichlorvos insecticide. Arch Appl Sci Res 4:1778–1781

Vinha PP, Martinez EZ, Vannucchi H et al (2013) Effect of acute thermal injury in status of serum vitamins, inflammatory markers, and oxidative stress markers: preliminary data. J Burn Care Res 34(2):e87–e91

Wang Z, Holthoff JH, Seely KA et al (2012) Development of oxidative stress in the peritubular capillary microenvironment mediates sepsis-induced renal microcirculatory failure and acute kidney injury. Am J Pathol 180:505–516. doi:10.1016/j.ajpath.2011.10.011

Wu F, Wilson JX, Tyml K (2003) Ascorbate inhibits iNOS expression and preserves vasoconstrictor responsiveness in skeletal muscle of septic mice. Am J Physiol Regul Integr Comp Physiol 285:R50–R56. doi:10.1152/ajpregu.00564.2002

Xie LX (2013) New biomarkers for sepsis. Med J Chin People's Lib Army 38:6–9

Yazihan N, Uzuner K, Salman B et al (2008) Erythropoietin improves oxidative stress following spinal cord trauma in rats. Injury 39:1408–1413. doi:10.1016/j.injury.2008.03.010

Zapatero-Solana E, García-Giménez JL, Guerrero-Aspizua S et al (2014) Oxidative stress and mitochondrial dysfunction in Kindler syndrome. Orphanet J Rare Dis 9:1–10. doi:10.1186/s13023-014-0211-8

Zhao H, Tao Z, Wang R et al (2014) MicroRNA-23a-3p attenuates oxidative stress injury in a mouse model of focal cerebral. Brain Res 1592:65–72. doi:10.1016/j.brainres.2014.09.055