Chapter

Modulations in Oxidative Stress of Erythrocytes during Bacterial and Viral Infections

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Abstract

Oxidative stress (OS) occurs when the generation of free radicals and reactive oxygen species (ROS) overwhelms the antioxidant capacity. OS causes storage lesions which can be defined as a series of biochemical and biomechanical changes. Erythrocytes are constantly exposed to OS due to the presence of ROS, which are countered by the endogenous antioxidant system. Various irreversible changes that occur include fragmentation and aggregation of proteins and lipids. The changes in proteins, lipids and antioxidant capacity are used as OS biomarkers to assess the efficacy of the erythrocytes, post oxidative insult. Aging of erythrocytes is also associated with the changes in its physical, biochemical and physiological properties and OS causes its rapid aging. Bacterial and viral infections also cause OS which alters the erythrocytes' antioxidant capacity. These modulations in its microenvironment are both beneficial in terms of protection against invading microorganisms as well as harmful to the erythrocytes, causing damage to surrounding cells and tissues. Thus, OS biomarkers can be used to gain insights into the effects of bacterial and viral infections on the erythrocyte microenvironment.

Keywords: Erythrocytes, Young and Old Erythrocytes, Oxidative stress, Antioxidant capacity

1. Introduction

Oxidative stress is defined as an imbalance between oxidants and antioxidants leading to excessive levels of reactive oxygen species (ROS). Oxidative damage includes oxidative modification of cellular macromolecules, cell death by apoptosis or necrosis, as well as structural tissue damage. DNA, proteins and lipids, are the natural targets of oxidation [1].

In recent years, ROS have gained more attention, because of their central role in the progression of many inflammatory diseases [2]. The radical groups include hydroxyl radical ($OH^{\cdot}$), nitric oxide ($NO^{\cdot}$) and superoxide ($O_2^{\cdot -}$). Non-radical compounds can also be highly reactive, which includes peroxynitrite ($ONOO^{-}$), hydrogen peroxide (H_2O_2) and hypochlorous acid (HOCl) [3]. ROS can be described as oxygen free radicals and other non-radical oxygen derivatives involved in oxygen radical production [4], which are generated by the cells in most tissues and involved in normal cellular metabolism [5].

ROS can react with DNA and cause damage to purines and pyrimidines [6], resulting in the formation of 8-Hydroxy-deoxyguanosine (8-OHdG) [7]. ROS also cause polypeptide chain fragmentation and covalent crosslinking that results in changes in its protein functional activity [8]. The covalent modifications of proteins induced by ROS or by reacting with secondary products of oxidative stress is termed as protein oxidation. These changes lead to many consequences such as, inhibition of enzyme activity, binding activity, aggregation, proteolysis, increased or decreased cell uptake, altered immunogenicity.

Protein oxidation serves as marker for determination of the levels of OS *in vitro*. There are many mechanisms that can induce protein oxidation as all the amino acyl side chains can be oxidatively modified. Cysteine and Methionine are the two amino acids that are most susceptible to oxidative attack due to the presence of sulfur atoms. Oxidation of cysteine leads to the formation of disulfide bonds, mixed disulfides and thiyl radicals, whereas modification of Methionine produces Methionine sulfoxide [8].

Lipids are important constituents of the lipid bilayer of the cellular membrane. Unsaturated fatty acids, which are easily oxidized, initiate the chain reactions, resulting in further oxidative damage. Lipids are susceptible to oxidation and reacts with molecular oxygen to form lipid peroxyl radicals which further oxidizes the neighboring lipids and propagates the oxidative damage [3]. Lipid peroxidation results in the changes of structural integrity and functioning of cell membranes. Lipid peroxidation markers such as malondialdehyde (MDA), 4-hydroxyl-2-nonenal (HNE), and isoprostane are used to evaluate oxidative damage.

Another category of substances called antioxidants exist in the cells and can effectively delay or inhibit ROS-induced oxidation. Antioxidants present in erythrocytes can be broadly classified into enzymatic and non-enzymatic antioxidants. There are three main groups of enzymatic antioxidants that play a significant role in protecting the cells from OS. Superoxide Dismutase (SOD) catalyzes the conversion of superoxides into hydrogen peroxide (H_2O_2) & oxygen (O_2). H_2O_2 is less toxic than compared to superoxides. SOD are metal containing enzymes that depend on a bound Mg, Cu or Zn for their antioxidant activity. There are 3 major families of SOD: Cu/Zn SOD, Fe/Mn SOD and Ni SOD [9–11]. Catalase (CAT) is the most common enzyme that is found in nearly all living organisms. It is found in the peroxisome of eukaryotic cells. It degrades H_2O_2 to H_2O & O_2. Hence it finishes the detoxification reaction started by SOD [12]. Glutathione peroxidase (GPx) contain Selenium, with peroxidase activity whose main activity is to protect the organism against OS. These enzymes like catalase degrade H_2O_2 to H_2O. They also reduce organic peroxides to their corresponding alcohol, thus provides another route for detoxification [13].

The extracellular endogenous antioxidants generally include the transition metal binding proteins i.e. ceruloplasmin, transferrin, hepatoglobin and albumin [14] and Vitamin C, α-tocopherol and Glutathione [15].

a. Glutathione (GSH), a major thiol antioxidant is a multifunctional intracellular antioxidant It is one of the most important cellular antioxidants due to its high concentration and its role in maintaining the redox state of the cell. GSH is a cysteine containing peptide and possesses antioxidant property due to the thiol group that serves as a reducing agent which can be reversibly oxidized and reduced. [16, 17].

b. Vitamin C, also known as L-ascorbic acid or ascorbate, is present naturally in the body and interconverts between each other depending on the pH. Ascorbic acid is well known reducing agent, thus serves as a good antioxidant [18]. Vit C is a water-soluble electron donor vitamin as it donates two of its electrons from

the C-2 and C-3 double bond to act as antioxidants that result in the formation of semi dehydroascorbic acid, an intermediate free radical. This then reduces to a neutral ascorbate molecule [14]. In cells, ascorbic acid is maintained in its reduced form by reacting with glutathione, catalyzed by protein disulfide isomerase and glutaredoxins [17].

c. Vitamin E is a collective name that is given for a set of eight related tocopherols and tocotrienols that are fat soluble. α-tocopherol is the most commonly occurring natural antioxidant and has a phytyl chain that is attached to its chromanol nucleus [14]. It is a lipid soluble antioxidant and acts in the glutathione peroxidase pathway [19]. It protects the cell membranes against lipid peroxidation chain reaction by reacting with the lipid radicals produced due to OS. It removes the free radical intermediates, thus preventing the cascade and further damage [20].

1.1 Bacterial and viral and infections cause OS

Bacterial infections cause OS, which trigger ROS production leading to organ damage by altering the metabolic pathway [21].

1.1.1 Periodontitis-Fusobacterium nucleatum

Periodontitis is a common bacterial infection, caused *Fusobacterium nucleatum*, resulting in the destruction of teeth supporting tissues. Periodontitis is associated with overproduction of ROS by neutrophils. It is characterized by increased metabolites of lipid peroxidation, DNA damage and protein damage.

After pathogen stimulation, neutrophils produce $O_2^{\cdot-}$ via the metabolic pathway called "respiratory burst" catalyzed by NADPH oxidase during phagocytosis [22]. $O_2^{\cdot-}$can be released into phagosome and gets converted to different radical and non-radical derivatives, such as hydrogen peroxide (H_2O_2), hypochlorous acid (HOCl), hydroxyl radical ($OH^{\cdot}$) and singlet oxygen ($_1O_2$). *In vitro* studies have shown that not only neutrophils, but also other phagocytes and cells of periodontal tissues such as monocytes, gingival fibroblast and periodontal ligament cells exhibit enhanced ROS production upon stimulation by periodontal pathogens and their components [23–25]. This was evident in the results of lipid peroxidation and protein oxidation products. Higher levels of TBARS, MDA and 8-isoprostanes were found in blood plasma, erythrocytes, gingival crevicular fluid (GCF) [26], saliva, GCF [27–30] respectively in periodontitis patients compared to healthy controls. Higher levels of protein carbonyl groups (PC) were found in GCF, saliva and serum of periodontitis patients [31–34] and 8-Hydroxy-deoxyguanosine (8-OHdG) in GCF and saliva of periodontitis patients [35–44].

Variations in antioxidant enzymes were also observed in many studies. SOD, CAT, GPx and glutathione reductase activities decreased in saliva of periodontitis patients [36, 45]. However, SOD and CAT in plasma, erythrocytes and gingival tissues were elevated, whereas activities of non-enzymatic antioxidants (vitamins E, vitamin C, and reduced glutathione) decreased in periodontitis [26]. Periodontitis is associated with decreased Total antioxidant capacity (TAC) [46–52].

1.1.2 Tuberculosis- mycobacterium tuberculosis

Mycobacteria initiate infection at oxygen rich lung microenvironments, generating oxidative radicals. These toxic radicals kill the pathogens by causing

disintegration of bacterial cell membrane, DNA damage, deactivation of metabolic enzymes or proteins [53–56]. After invasion into the host, mycobacteria induce NADPH oxidase 2 (NOX2) expression to generate superoxide radicals ($O_2^{\cdot -}$), which are then converted to more toxic hydrogen peroxide (H_2O_2) by superoxide dismutase (SOD) and subsequently reduced to water and molecular oxygen by catalase [57, 58]. NADPH oxidase 2 (NOX2) is the key enzyme responsible for the cellular ROS production by using superoxide radicals (O_2-) as precursor molecule [59]. Alterations in regulatory components of NOX2 results in generation of phagocytic oxidative stress and phagocytic burst to eliminate enclosed pathogen [58].

However, pathogenic mycobacteria can inhibit oxidative stress mechanisms by modulation of cell signaling mechanisms, up-regulation of antioxidant enzymes and redox buffering systems [59–62].

1.1.3 Pneumococcal meningitis- streptococcus pneumoniae

Pneumococcal meningitis is a life-threatening disease characterized by acute infection affecting the pia mater, arachnoid, and subarachnoid spaces [63]. *Streptococcus pneumoniae* crosses the blood–brain barrier (BBB) and disrupts the intraepithelial tight junctions. Host polymorphonuclear leukocytes produce nitric oxide, superoxide radicals, and hydrogen peroxide in response to bacterial infection. $O_2 - \bullet$ and NO• can lead to the formation of peroxynitrite (ONOO), a strong oxidant [64–66]. $ONOO^-$ can damage neurons and glial cells by lipid peroxidation and cell membrane destabilization, resulting in DNA disintegration and subsequent poly (ADP-ribose) polymerase (PARP) activation. Elevated 4-HNE and MDA levels are found in bacterial meningitis patients [67]. Thus, ROS/ RNS can be considered key players of immune activation, blood–brain barrier disruption, vascular failure, neuronal injury, and cochlear damage during pneumococcal meningitis.

1.1.4 Gastritis/gastric cancer- Helicobacter pylori

Helicobacter pylori is the causative pathogen for human gastritis or gastric cancer, which is characterized with inflammation and ulceration of the stomach and duodenum. Gastric cancer arises from oxidative stress and environmental toxins, which increase DNA mutation rates [68]. The possible sources of ROS/ RNS in *H. pylori* infected stomach, include neutrophils, vascular endothelial cells and gastric mucosal cells. Neutrophils are believed to be the main source of ROS/ RNS [69] and their production is catalyzed by NADPH oxidase on the cell membrane [59]. These highly reactive ROS (HOCl and $^{\cdot}OH$) are used by the phagocyte to kill pathogenic bacteria. *H. pylori* infected gastric mucosal phagocytes produce greater amounts of ROS, which is believed to be the major cause of gastric mucosal damage.

1.1.5 HIV and Hepatitis

Oxidative Stress has always played a major pathogenic role in HIV and hepatitis infections. HIV causes decrements in glutathione (GSH), cystine, vitamin C and SOD levels, and increments in lipid peroxidation [70–73]. A decline in the antioxidant capacity represents a weakened immune system, thus requiring more antioxidants to maintain normal functionality [74]. Hepatitis, similar to HIV, also increases the lipid peroxidation (malondialdehyde (MDA) and 4-hydroxynonenal (HNE)) and activity of caspases, whereas reduces zinc [75–77] (**Table 1**).

OS Markers	Bacterial diseases	Viral diseases	References
TBARS	Periodontitis- Increased Tuberculosis- Increased Sepsis- Increased		[26] [78] [79]
MDA	Periodontitis- Increased Meningitis- Increased	HBV- Increased HCV- Increased HIV- Increased JEV- Increased RSV- Increased	[26] [80] [81]
8-IP	Periodontitis- Increased		[26]
4-HNE	Meningitis- Increased		[80]
PC	Periodontitis- Increased Sepsis- Increased		[31] [79]
8-OHdG	Periodontitis- Increased	HCV- Increased	[35] [81]
NO	Tuberculosis- Decreased Sepsis- Increased	RSV- Increased	[78] [82] [81]
NT	Meningitis- Increased Sepsis- Increased		[80] [82]
SOD	Periodontitis- Decreased Gastritis- Decreased	HBV- Decreased HIV- Decreased JEV- Increased DENV-Decreased RSV- Decreased	[36, 45] [83] [81]
CAT	Periodontitis- Decreased Tuberculosis- Decreased	Paramyxovirus-Decreased DENV-Decreased RSV- Decreased	[36, 45] [78] [81]
GPx	Periodontitis- Decreased Gastritis- Decreased	HBV- Decreased Paramyxovirus-Decreased DENV-Decreased RSV- Decreased	[36, 45] [83] [81]
GSH	Sepsis- Decreased	HIV- Decreased JEV- Increased Influenza virus-Decreased	[82] [81]
GR	Periodontitis- Decreased		[36, 45]
GST		Paramyxovirus-Decreased RSV- Decreased	[81]
Vit-C	Sepsis- Increased Meningitis- Decreased	Influenza virus-Decreased HIV- Decreased Covid-19- Decreased	[79] [80] [81] [84]
Vit-E		Covid-19- Decreased Influenza virus-Decreased	[81] [84]
β-Carotene		Covid-19- Decreased	[84]
Bilurubin, UA, FRAP, TRAP	Sepsis- Increased		[79]

HBV- Hepatitis B virus; HCV- Hepatitis C virus; HIV- Human immunodeficiency virus; JEV- Japanese encephalitis virus; DENV- Dengue virus; RSV- Respiratory syncytial virus; Covid-19-Coronavirus Disease 2019.
TBARS- Thiobarbituric acid reactive substances; MDA- Malondialdehyde; 8-IP- 8-isoprostanes; 4-HNE- 4-hydroxynonenal; PC- Protein Carbonyls; 8-OHdG- 8-Hydroxy-deoxyguanosine; NO- nitric oxide; NT- Nitrotyrosine; SOD- Superoxide dismutase; CAT- Catalase; GPx- Glutathione Peroxidase; GSH- Glutathione; GR- Glutathione Reductase, GST- Glutathione S-Transferase; UA- Uric acid; Vit-C- Vitamin C; Vit-E- Vitamin E; FRAP- ferric reducing antioxidant power; TRAP- Total-trapping radical antioxidant potential.

Table 1.
Oxidative stress (OS) in bacterial and viral diseases.

2. OS has dual role in diseases

OS offers protection against invading microorganisms, and on the other hand can cause damage to cells/tissues.

Erythrocytes being heme rich, provides the invading bacteria a rich source of iron for its metabolism. Bacteria have evolved mechanisms to scavenge the iron through hemolytic toxins and heme scavenging systems [85–87]. Erythrocytes counteract the bacteria through the production of ROS. The α and β sub units of hemoglobin possess high affinity binding sites for lipopolysaccharides (LPS), and leads to macrophage cytokine production and enhances the macrophage binding to LPS. Hemoglobin in μM concentrations have shown to inhibit yeast and bacterial growth through the production of ROS [88–90].

The protection conferred by hemoglobin against invading organisms have a detrimental effect in case of pathological states. Elevations in free hemoglobin is associated with increased mortality. Globin is associated with the protective properties, whereas heme triggers the proinflammatory response. During endotoxemia, the protective effects of hemoglobin is attributed to globin scavenging free heme, which has the property of activating a host of proinflammatory proteins and ROS generation. It has also been shown to increase the transcription of proinflammatory genes by 100-fold [91–93].

3. Modulations in erythrocytes due to OS

3.1 ROS cascade

The ROS cascade in erythrocytes begins with the autooxidation of hemoglobin (Hb) into methemoglobin (MetHb). Oxidation of MetHb results in the formation of sulfhemoglobin (SulfHb) along with superoxide anion (O_2). Erythrocytes have an innate antioxidant system that detoxifies the cells. The superoxide generated is detoxified by superoxide dismutase into H_2O and H_2O_2, which is further detoxified by catalase and glutathione peroxidase (with the help of glutathione) into H_2O and O_2. Erythrocytes also contain non-enzymatic antioxidants such as glutathione, ascorbic acid (Vit C), and α-tocopherol (Vit E). This antioxidant mechanism helps the erythrocyte's survival in an oxygen-rich environment. Glutathione redox system: reduced glutathione (GSH), glutathione disulfide (GSSG), glutathione reductase (GR), glutathione peroxidase plays an important role in inactivating the ROS [94, 95].

3.2 Erythrocyte aging

The lifespan of erythrocytes *in vivo* is around 120 days. About 1% of the erythrocytes are cleared or phagocytized from circulation every day in humans. The membrane of erythrocytes comprises of proteins (50%), lipids (40%), and carbohydrates (10%). Hb comprises about 95% of the total cytoplasmic proteins. The membrane-associated proteins include band 3 (anion exchanger), band 4.1, spectrin, ankyrin, and glycophorin C which are responsible for maintaining the structure of the cell [94].

As the reticulocyte ages and transforms into erythrocyte, various changes occur in its membrane, composition, appearance and catalytic functions [96]. Aging of erythrocytes is associated with the changes in physical, biochemical and physiological properties. Thus, aged cells are more prone to be trapped and ultimately

destroyed during microcirculation [97]. During aging, a decrease in the cell volume and hemoglobin is observed. The old erythrocytes also increase in density as they bind to autologous IgG (immunoglobulin G), that serves as an initiator for the removal of senescent erythrocytes. The binding of antibodies is also associated and triggered by changes to the anion exchanger, Band 3. There is a decline in sulphate transport with age, thus hampering the binding of ankyrin to Glyceraldehyde 3-phosphate dehydrogenase (GAPDH), a key enzyme in glycolysis [98]. The N- and C- terminal regions of Band 3 are conformationally changed during aging that results in the formation of neoantigens, which serve as a senesce marker. It is also observed that damaged hemoglobin (Hb) bind to band 3 resulting in cluster formations [99–102]. There is also an increase in the amount of glycated Hb.

Aging erythrocytes also lose water, 2,3-BPG, ATP, proteins, Hb and vesicles that cause the cell volume and surface charge to decrease. There is also loss of some of the surface materials such as sialic acids that alter the structure and function of the membrane. These sialic acids are 90% *N*-acetylneuraminic acid (NANA) which accords the electrical charge to the cells [103]. These senescent RBCs also expose membrane phosphatidylserine. An increase in erythrocyte OS causes accelerated aging, resulting in decreased function and survival [97].

The study of Igbokwe *et al*., 1994 reported the effects of *Trypanosoma brucei* infection in mice. They concluded that a lowered ability to prevent lipid peroxidation in infected mice may increase aging of erythrocytes [104].

4. Bacterial and viral infections causing variations in erythrocytes

Erythrocytes were assumed to only function as innate oxygen carriers. However, recent studies have shown them to be important in modulating the innate immune response [105–107]. Mammalian erythrocytes, unlike the erythrocytes of birds, amphibians and fishes, are enucleate and lack major cell organelles. The organelles of the latter modulate the immune response through production of cytokine like factors, upregulating viral response genes and pathogen sequestering through phagocytosis. Mammalian erythrocytes on the other hand modulate the innate immune response through generation of reactive oxygen species (ROS) to promote inflammatory and autoimmune response against invading microorganisms [108].

Minasyan, 2014 highlighted the role of erythrocytes in conferring bacterial immunity, which is comparable to phagocytic leukocytes as: (i) they are more numerous in number; (ii) fend off microorganisms repeatedly without injury; and (iii) resistant to infection. Erythrocytes have a longer lifespan when compared with leukocytes as well as being produced at a faster rate. The cytosol of erythrocytes is unfavorable to parasitic organisms such as chlamidiae, mycoplasmas, rickettsiae, viruses, etc. Erythrocytes elevate to the primary line of defense against bacterial infections when: (i) there is a presence of massive microbial load; (ii) ineffective recruitment of phagocytes; (iii) faster proliferation and spread of the microorganisms than the phagocytes' capacity; and (iv) ineffectiveness of the phagocytes against the invading microorganisms [109].

4.1 Bacterial infections

Sepsis is one of the most recognized life-threatening dysfunctions that is caused due to infections and is the leading cause for mortality in non-cardiac ICUs (intensive care units) around the world. Sepsis may be caused by gram-positive,

gram-negative and poly microbial infection. It results in elevated OS caused due to inflammatory response, which alters erythrocytes leading to phagocytosis by macrophages and polymorphonuclear leukocytes (PMN). This activation of the macrophages and PMN results in a positive feedback mechanism, as the modified erythrocytes trigger its continuous activation with the generation of ROS. This mechanism may further lead to septic shock, even if the blood-derived bacteria have been cleared off the system [110].

Sepsis develops when bacteria in the bloodstream survive oxidation on the surface of erythrocytes [109]. The changes in erythrocytes can be caused due to several reasons, one of them being OS, and these interactions seem to be interconnected. The levels of antioxidants and oxidants are inversely proportional in septic patients. Decrements in Vitamin E, ascorbate, β-carotene and retinol, while increments in lipid peroxidation were observed. Antioxidant supplementation improved the outcome of patients. Thus, erythrocytes can be model cells for the management of sepsis/septic shock to improve the outcome of patients [111]. Larsen *et al*., 2010, have reported that one of the major causes for sepsis is the increasing levels of free heme released due to hemolysis. It can be sequestered and cleared off using hemopexin, as its administration reduced tissue damage and lethality [112].

4.2 Viral infections

Studies have shown that viruses cause cell death by generating OS within infected cells [113–115]. The influenza virus and parmovirus activates monocytes to generate ROS *in vitro* [113]. The influenza virus also possesses hemagglutinin glycoprotein on its surface, which helps the virus in binding to cells rich in sialic acids like erythrocytes. Influenza carries hemagglutinin in its inactive form (HOA), which is activated by proteases by cleaving HOA into hemagglutinin 1 and hemagglutinin 2 (HA1 and HA2). HOA can be activated by ROS resulting in a non-infectious virus getting converted into an infectious one [116, 117]. Thus, an increase in ROS levels is beneficial for the invading influenza virus.

COVID-19, caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) was believed to interact with Hb, facilitating the removal of heme, which was proposed by Liu and Li as likely pathway for the loss of function of hemoglobin (Hb) and the accumulation of free heme resulting in elevated OS. De Martino *et al*., 2020, reported that COVID-19 did not exhibit any hemolytic anemia. The levels of Hb, bilirubin, lactate dehydrogenase, iron, ferritin and haptoglobin in COVID-19 patients were similar to those with acute respiratory distress syndrome (ARDS) not infected with COVID-19, suggesting that the oxygen delivery impairment was not due to red cell hemolysis and removal of iron from heme. [118].

4.3 Bacterial v/s viral infections

Trefler et al., 2014 compared the patterns of OS in bacterial origin community acquired pneumonia [BCAP] and 2009 A/H1N1 virus community acquired pneumonia [VCAP], revealing the distinct responses between bacterial and viral infections. Erythrocyte GR activity was significantly higher in patients with VCAP in respect of BCAP patients. Lower TBARS levels were observed in VCAP patients in comparison to BCAP, suggesting an increase of antioxidant activity related to the redox glutathione system. GR, GSSG, GSSG/GSH and GPx levels were more elevated in patients with viral pneumonia. A higher antioxidant activity in patients with 2009 A/H1N1 viral pneumonia was observed (**Figure 1**) [119].

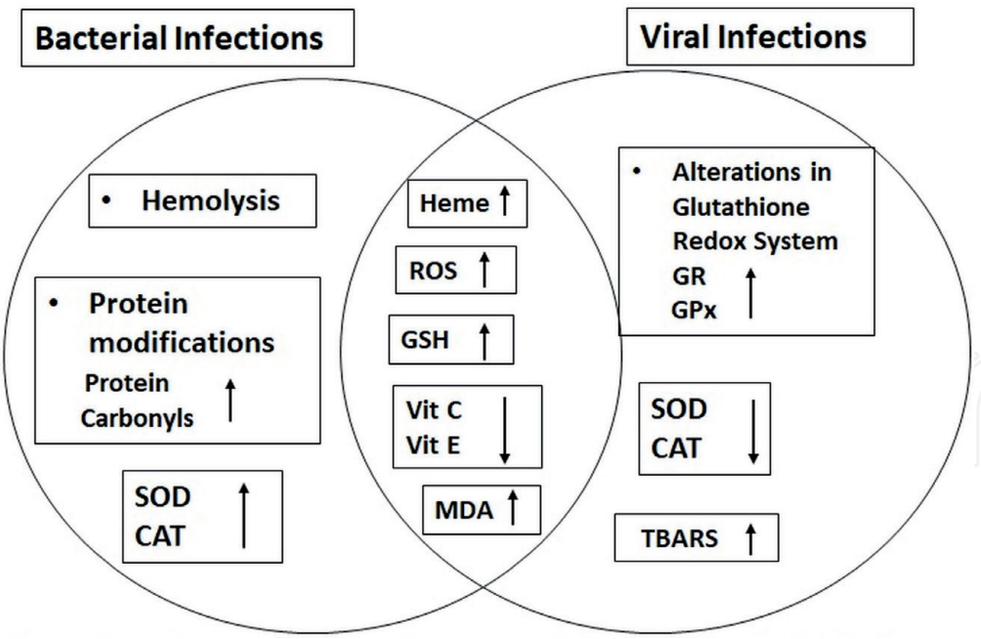

Figure 1.
Oxidative modifications in Erythrocytes during Bacterial and Viral infections [109, 112, 118–120]. SOD – Superoxide dismutase; CAT – Catalase; ROS – Reactive oxygen species; GSH – Glutathione; Vit C – Vitamin C; Vit E – Vitamin E; MDA – Malondialdehyde; GR – Glutathione reductase; GPx – Glutathione peroxidase; TBARS – Thiobarbituric acid reactive substances.

5. Conclusion

ROS levels increase rapidly leading to lipid peroxidation and protein oxidation in erythrocytes during infections. Generally, there is a decline in the antioxidant capacity of erythrocytes. Nevertheless, some microbes evade their destruction by altering the antioxidant enzymes of erythrocytes. Thus, OS biomarkers can be used to gain insights into the effects of bacterial and viral infections on the erythrocyte microenvironment. Therefore, erythrocytes act as good indicators and can be promising candidates as peripheral biomarkers during bacterial and viral infections.

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Conflict of interest

The authors have no conflict of interest to disclose.

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