

Oxidative Stress in Host-Pathogen Interactions: Molecular Mechanisms, Biomarkers, and Therapeutic Strategies

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Abstract

Oxidative stress is now thought to be one of the major factors regulating the course of host-pathogen interactions and the evolution of infectious illnesses. When infected, the immune cells generate reactive oxygen species (ROS) and reactive nitrogen species (RNS) as part of the body's defense against invading microbes. These compounds are important in the control of microbial growth, but their overproduction may cause disturbances of redox equilibrium and oxidative damage to lipids, proteins and DNA. Simultaneously, many infections have evolved complex defense strategies to survive oxidative stress, increase their virulence and thwart antimicrobial therapy. This review summarizes current knowledge on oxidative stress in bacterial, viral, fungal and parasitic infections with a focus on biochemical pathways of ROS and RNS generation, main sources of oxidative stress during infection and microbial adaptive strategies to counteract oxidative damage. It talks about the clinical value of oxidative stress biomarkers such as malondialdehyde (MDA), total oxidant status (TOS), total antioxidant capacity (TAC), glutathione (GSH), superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), 8-hydroxy-2'-deoxyguanosine (8-OHdG) and protein carbonyls in assessing disease severity and therapeutic response. Emerging therapeutic techniques are also discussed, including antioxidant therapy, nanotechnology-based approaches, suppression of microbial antioxidant defense mechanisms, and biomarker-guided personalized medicine. A greater knowledge of redox regulation in infection may help in the development of novel diagnostic tools and tailored therapeutics to improve infection management, while maintaining the balance between efficient antimicrobial immunity and protection of host tissue.

Keywords: Oxidative stress, Host-pathogen interactions, Reactive oxygen species (ROS), Reactive nitrogen species (RNS), Infectious diseases.

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Introduction

Infectious diseases remain a primary source of illness and death around the world, despite great breakthroughs in medicine[1]. The evolution of antimicrobial resistance continuously, in conjunction with the introduction of new and re-emerging pathogens, has made the control of infectious diseases increasingly difficult. This is the reason why the molecular and biochemical interactions between infections and their hosts have become a prominent field of modern biomedical research[2].

Production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) is one of the most critical events that occurs during infection[3]. These extremely reactive chemicals are produced by the host immune cells as part of the natural defense system to kill invading germs[4]. In moderate levels, they are crucial in suppressing microbial development and modulating immunological responses. However, overproduction of these chemicals can damage host tissue by oxidation of lipids, proteins and nucleic acids, leading to oxidative stress[5].

Oxidative stress occurs when there is an imbalance between the synthesis of reactive molecules and the antioxidant defense system[6]. This imbalance may be associated with the immunological response of the host and the metabolic activities of invading microorganisms during infection[7]. Many pathogens have developed complex antioxidant defense systems to survive in oxidative circumstances. Such microbial methods not only promote survival but also virulence, persistence and resistance to antimicrobial therapy[8]. Recent investigations have shown that oxidative stress is implicated in the pathogenesis of a wide variety of bacterial, viral, fungal and parasitic illnesses[9]. At the same time, markers of oxidative stress such as malondialdehyde (MDA), total oxidant status (TOS), total antioxidant capacity (TAC), glutathione (GSH), superoxide dismutase (SOD), and catalase (CAT) have been helpful in assessing disease severity, tracking response to treatment, and gaining insights into host–pathogen interactions[10].

This review summarizes the existing knowledge of the function of oxidative stress in host-pathogen interactions. It reviews the molecular pathways involved for the formation of reactive oxygen species, antioxidant defense systems of both hosts and microbes, oxidative stress indicators and the relevance of oxidative stress to diverse infectious illnesses. In addition, emerging therapeutic techniques against oxidative stress are presented in order to propose future options for improvement of infection management.

Reactive Oxygen Species and Reactive Nitrogen Species

Living cells continuously generate reactive oxygen species (ROS) and reactive nitrogen species (RNS) which are extremely reactive chemicals[11]. These molecules are involved in a number of important biological processes under normal physiological settings, such as cell signaling, regulation of gene expression and maintenance of immunological function. Their creation is thus a natural aspect of cellular metabolism and not a sign of sickness[12].

ROS encompass several oxygen-derived compounds such as the superoxide anion ($O_2^{\bullet-}$), hydrogen peroxide (H_2O_2), hydroxyl radical ($\bullet OH$) and singlet oxygen. These compounds have different chemical stability and biological activity[13]. The most reactive of these is thought to be the hydroxyl radical which is capable of causing serious damage to biological components in a very short period[14].

Reactive nitrogen species are derived mostly from nitric oxide (NO), which is created by nitric oxide synthase enzymes[15]. Nitric oxide interacts swiftly with superoxide anions to give peroxynitrite ($ONOO^-$) which is a highly reactive molecule capable of oxidising proteins, lipids and DNA. RNS are involved in anti-microbial response but their overproduction can also cause damage to host tissue[16].

The mitochondrial electron transport chain is the main intracellular generator of ROS[17]. During oxidative phosphorylation a few electrons escape from the respiratory complexes and react with molecular oxygen to generate superoxide radicals. Under normal conditions, antioxidant enzymes transform these molecules into less hazardous compounds quickly enough that severe oxidative damage does not occur[18].

Upon recognizing pathogens, the generation of ROS is greatly enhanced in immune cells including neutrophils and macrophages[19]. This process, called the oxidative burst or respiratory burst, starts with the activation of the NADPH oxidase enzyme complex. The rapid production of ROS enables immune cells to kill invading microbes by oxidising cellular membranes, proteins, and nucleic acids[20].

ROS and RNS are important for antimicrobial defense and their beneficial effects depend substantially on optimum balance[21]. At low and moderate concentrations, ROS are involved in pathogen killing and

immunological control, but overproduction or prolonged production of ROS leads to oxidative stress, inflammation, tissue damage and organ dysfunction[22]. Conversely, poor production can impair the capacity of immune cells to remove pathogenic germs, allowing the pathogens to live and reproduce. Due to these dual biological activities, ROS and RNS are now recognized as the primary mediators connecting biochemistry with microbiology[23]. They are important components of host-pathogen interactions as they regulate host immune response and microbial survival, and are prospective targets for future therapeutic therapies[24].

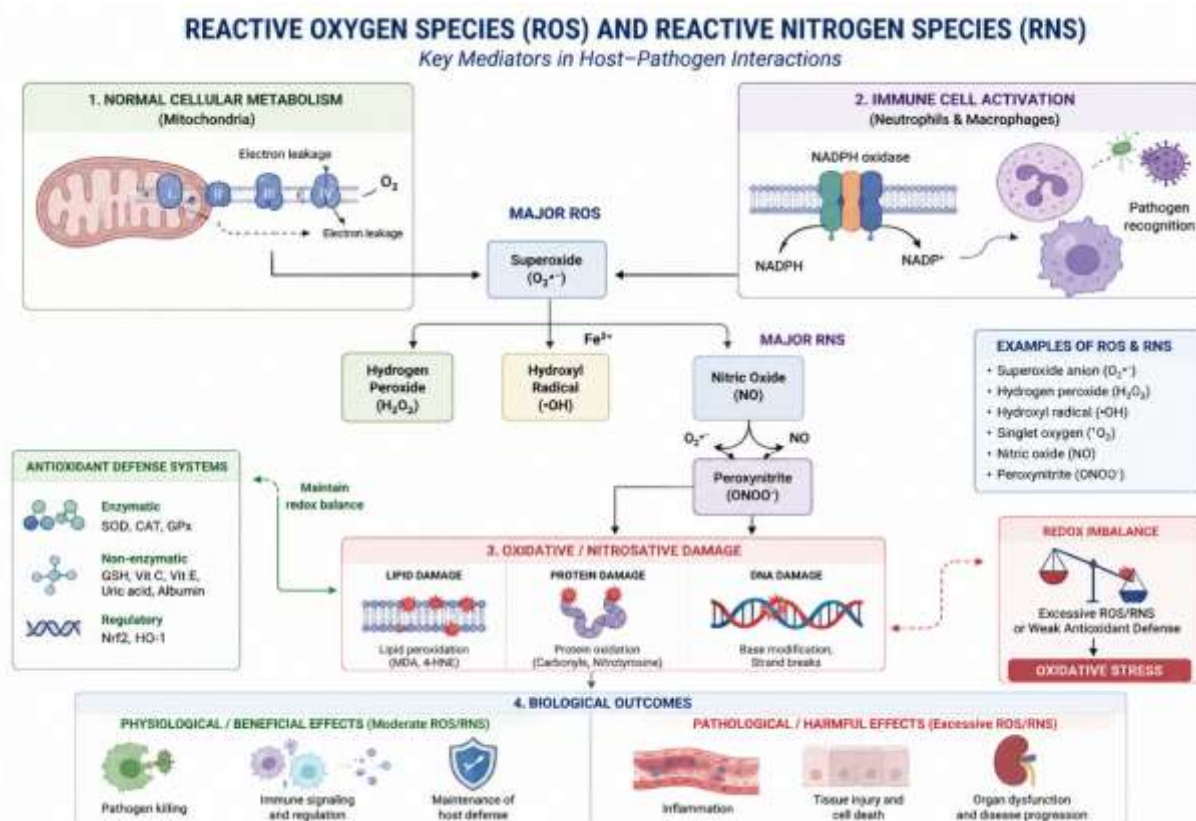


Figure 1. Generation of Reactive Oxygen and Nitrogen Species During Host-Pathogen Interactions and Their Biological Consequences.

Sources of Oxidative Stress During Infection

Oxidative stress occurs when the synthesis of reactive oxygen species (ROS) and reactive nitrogen species (RNS) surpasses the capability of the antioxidant defense system. In infection this imbalance is due to the joint activity of both the host immune response and the invading pathogen[25]. While oxidative stress is a crucial component of antimicrobial defense, dysregulated synthesis of reactive molecules may also contribute to tissue injury and disease development[26].

Activation of immune cells is one of the main causes of ROS during infection. Neutrophils and macrophages are activated upon detection by pattern recognition receptors (PRRs) and rapidly generate substantial levels of ROS by the enzyme complex NADPH oxidase[27]. This procedure is called the respiratory burst. It is one of the first defense systems exerted by the innate immune system to kill invading bacteria. The superoxide radicals that are produced are then transformed to hydrogen peroxide and other very reactive compounds that have great antibacterial action[28].

Inflammatory cytokines further amplify oxidative stress by promoting immune cell activation and raising the expression of enzymes responsible for ROS and RNS generation[29]. Cytokines such as tumour necrosis factor- α (TNF- α), interleukin-1 beta (IL-1 β), and interferon-gamma (IFN- γ) play essential roles in macrophage activation and in the promotion of antimicrobial responses. However, chronic cytokine production can maintain a persistent inflammatory state that continuously creates reactive molecules and aggravates oxidative damage[30].

Oxidative stress can also be caused by the pathogens themselves. Many bacteria secrete toxins and virulence factors that harm host cells, impair mitochondrial function, and activate inflammatory pathways[20]. Viral infections often change cellular metabolism and enhance the formation of mitochondrial ROS, and fungal pathogens may cause oxidative damage via sustained inflammation and immunological activation[31]. Thus, oxidative stress is not solely generated by host defenses but also arises from the biological activity of invading microbes[32].

Additional host and environmental factors influence oxidative stress during infection. Ageing, starvation, diabetes mellitus, obesity, smoking, environmental pollution and exposure to harmful chemicals, all lower antioxidant capacity and increase vulnerability to oxidative damage. Patients with chronic conditions usually have increased initial oxidative stress and so are more susceptible to serious infection consequences[32].

The interaction between these multiple sources leads to a complicated redox environment during infection[33]. Initially, increased ROS production promotes germ death and immunological activation[34]. However, when oxidative stress becomes extreme or protracted, antioxidant defenses become depleted, resulting in lipid peroxidation, protein oxidation, DNA damage and impairment of tissue function. So, an optimum balance between oxidant generation and antioxidant protection is necessary for an effective immune response and to minimize host tissue harm[35].

Microbial Strategies to Resist Oxidative Stress

During infection, microorganisms are exposed to oxidative stress as part of the host immunological response[36]. To survive in this hostile environment, bacteria, viruses, fungi and parasites have evolved a wide spectrum of defensive mechanisms to decrease oxidative damage and sustain cellular function[7]. These adaptation techniques are critical for microbial survival, persistence and pathogenicity.

Production of antioxidant enzymes is one of the most powerful defense strategies. Many bacteria produce superoxide dismutase (SOD), catalase (CAT) and a variety of peroxidases that detoxify reactive oxygen species before they harm vital biological components. Superoxide dismutase transforms superoxide radicals into hydrogen peroxide which is then converted by catalase into water and oxygen[37]. These enzymes dramatically reduce intracellular oxidative stress and enhance bacterial survival in host tissues.

In addition to enzyme antioxidants, microbes create tiny antioxidant molecules as well to protect cellular structures from oxidation[38]. Glutathione is one of the most essential intracellular antioxidants in many bacteria, as it maintains redox balance and repairs oxidized proteins. Other bacteria employ other low molecular weight thiols with similar protective properties to survive in highly oxidative conditions[38].

Another key strategy for survival is to repair oxidative damage once it has occurred. Reactive oxygen species can alter proteins, harm DNA, and interfere with membrane lipids[39]. To counteract these consequences, efficient DNA repair systems, protein repair enzymes and mechanisms of membrane remodeling are present in microbes. These repair processes enable the pathogen to survive oxidative damage and continue to replicate[40].

Another efficient strategy for resistance to oxidative stress is biofilm development. Microorganisms within a biofilm are embedded in an extracellular polymeric matrix that forms a physical barrier to immune cells and antibacterial chemicals[41]. This protective environment limits the entrance of reactive oxygen species and enables microorganisms to survive for lengthy periods of time. Biofilm-associated illnesses are thus generally more resistant to both immune clearance and antimicrobial treatment[42].

Some infections also influence the expression of genes involved in resistance to oxidative stress[43]. Exposure to high levels of ROS triggers the activation of specialized transcriptional regulators that activate antioxidant genes and repress nonessential metabolic pathways. This coordinated reaction helps bacteria to rapidly adapt to changing environmental conditions and enhances their ability to live within host cells[44]. Several intracellular infections have evolved additional methods to escape oxidative death[45]. They do not directly neutralize ROS but interfere with immune cell function by blocking phagosome maturation, impeding lysosomal fusion, or decreasing activation of the NADPH oxidase complex[46]. These techniques reduce the generation of reactive chemicals in the vicinity of the pathogen, resulting in intracellular survival and long-term persistence[47].

Viruses use several strategies to deal with oxidative stress. Viruses do not have bacterial antioxidant enzymes that are free-living, but many viral proteins modulate signalling pathways of the host cell to limit oxidative damage or to control cellular antioxidant systems[48]. Some viruses also induce oxidative stress to enhance viral replication while simultaneously sparing infected cells from premature death until viral production is complete[49].

Fungal infections also possess very efficient antioxidant defense systems[49]. These enzymes are catalase, superoxide dismutase and glutathione peroxidase that assist the fungi to survive oxidative attack from immune cells. These defense mechanisms are involved in fungal pathogenicity, particularly in immunocompromised patients, where chronic fungal infections are frequent[50].

Overall, oxidative stress resistance is a key driver of microbial pathogenicity. Pathogens' ability to detoxify reactive chemicals, repair oxidative damage, control antioxidant genes and escape host immune defense underpins their capacity to initiate infection, persist inside host tissues and resist antimicrobial therapy. Insights into these microbial adaptations may aid the development of new therapeutic techniques targeting pathogen antioxidant systems and improving the effectiveness of existing antimicrobial medications.

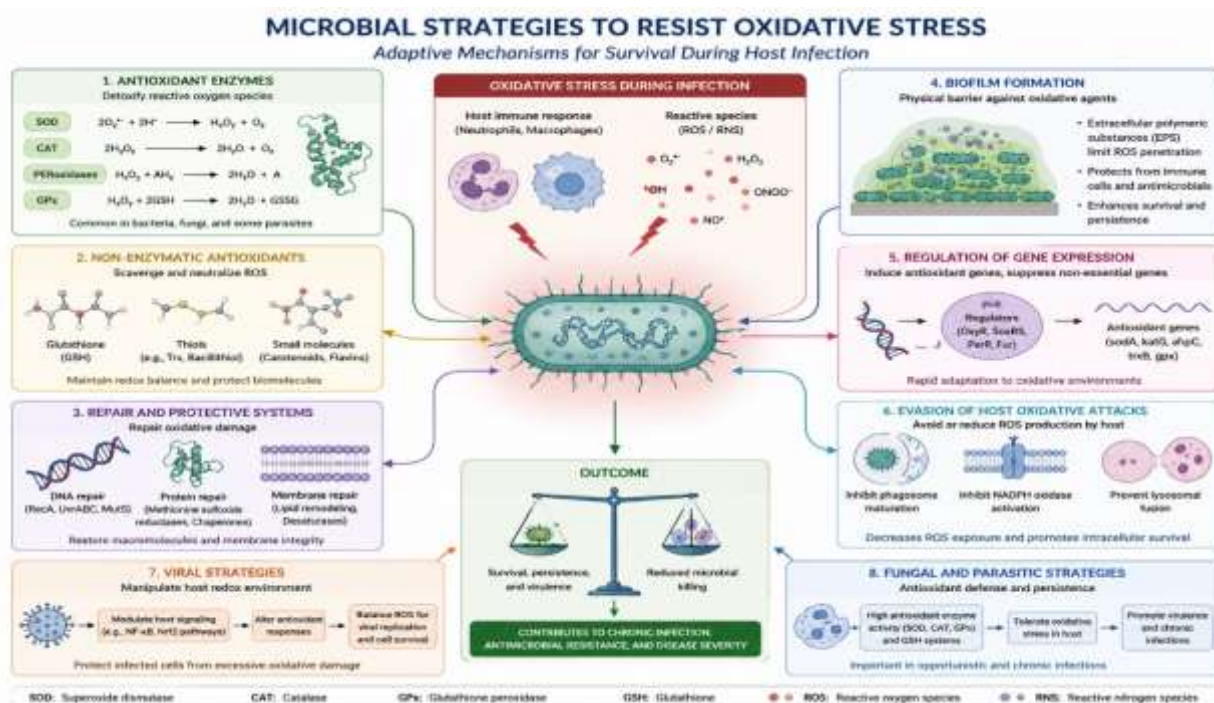


Figure 2. Major microbial strategies that protect pathogens against oxidative stress during infection, including antioxidant defenses, repair systems, biofilm formation, gene regulation, immune evasion, and metabolic adaptation, which collectively enhance microbial survival and persistence.

Oxidative Stress Biomarkers in Infectious Diseases

Biomarkers of oxidative stress are excellent tools to evaluate the balance between oxidant production and antioxidant defense in viral illnesses[51]. The measurement of reactive oxygen species (ROS) and reactive nitrogen species (RNS) in biological samples is problematic due to their very short half-lives. Instead, researchers rely on persistent biochemical indicators that indicate oxidative damage or antioxidant capacity[52]. These biomarkers give essential information regarding the severity of the disease, immune activation, therapy response, and prognosis.

Table 1. Major Oxidative Stress Biomarkers Used in Infectious Diseases

Biomarker	Biological Significance	Sample Type	Clinical Interpretation	Common Detection Methods
Malondialdehyde (MDA)	End product of lipid peroxidation caused by ROS attack on cell membranes	Serum, plasma, tissue	Increased levels indicate enhanced lipid peroxidation and oxidative damage	TBARS assay, HPLC, ELISA
Total Oxidant Status (TOS)	Reflects the overall oxidizing capacity of biological samples	Serum, plasma	Elevated levels indicate increased systemic oxidative stress	Colorimetric assay (Erel method)
Total Antioxidant Capacity (TAC)	Represents the combined activity of enzymatic and non-enzymatic antioxidants	Serum, plasma	Reduced levels indicate depletion of antioxidant defenses	Colorimetric assay (Erel method), FRAP, ABTS
Reduced Glutathione (GSH)	Major intracellular antioxidant that maintains redox homeostasis	Whole blood, erythrocytes, tissues	Decreased levels reflect impaired antioxidant capacity and increased oxidative stress	Spectrophotometry, HPLC
Superoxide Dismutase (SOD)	Converts superoxide radicals into hydrogen peroxide	Serum, erythrocytes, tissues	Altered activity reflects changes in antioxidant enzyme defense	Enzyme activity assay
Catalase (CAT)	Converts hydrogen peroxide into water and oxygen	Serum, erythrocytes, tissues	Reduced activity suggests impaired detoxification of hydrogen peroxide	Spectrophotometric enzyme assay
Glutathione Peroxidase (GPx)	Detoxifies hydrogen peroxide and lipid hydroperoxides using glutathione	Whole blood, plasma	Lower activity indicates weakened antioxidant protection	Enzyme activity assay

8-Hydroxy-2'-deoxyguanosine (8-OHdG)	Marker of oxidative DNA damage	Serum, urine, tissues	Elevated concentrations indicate oxidative DNA injury	ELISA, HPLC, LC-MS/MS
Protein Carbonyls (PC)	Indicator of irreversible protein oxidation	Serum, plasma	Increased levels reflect oxidative modification of proteins	DNPH assay, ELISA

One of the most common biomarkers is malondialdehyde (MDA) which is a persistent end product of lipid peroxidation[52]. MDA is generated through assault of polyunsaturated fatty acids in cellular membrane by reactive oxygen species[53]. Elevated levels of MDA imply greater membrane damage and oxidative stress. Several clinical studies have revealed considerably greater levels of MDA in patients with bacterial, viral, fungal and parasite diseases when compared with healthy subjects. MDA levels generally related to severity of disease and activity of inflammation[54].

Another relevant biomarker is the total oxidant status (TOS), which is an indicator of the total oxidizing capacity of biological fluids. Instead of assessing different oxidants independently, TOS is an integrated measure of the entire oxidative burden. High TOS levels have been observed in numerous viral illnesses and are generally related with systemic inflammation, tissue damage and bad clinical outcomes[10]. As several oxidants are involved at the same time in pathogenesis of a disease, TOS is accepted as a useful indication of global oxidative stress.

However, the total antioxidant capacity (TAC) reflects the additive activity of enzymatic and non-enzymatic antioxidants in serum or plasma. TAC represents the body's capacity to neutralise reactive chemicals before they damage cells[55]. In severe infections, antioxidant reserves are typically used up quicker than they can be replenished, resulting to lower TAC values. Together, TAC and TOS give a fuller view of redox balance than either metric alone[56].

Glutathione (GSH) is the principal intracellular antioxidant, which maintains cellular redox equilibrium[57]. It directly scavenges free radicals and is also a substrate for various antioxidant enzymes. Excessive ROS production during infection promotes glutathione consumption, leading to a drop in intracellular GSH levels in many cases[58]. Reduced glutathione levels have been linked to compromised immune function, elevated oxidative damage, and prolonged recovery in certain infectious illnesses[59].

Several antioxidant enzymes are also widely utilized as indicators of oxidative stress. Superoxide dismutase (SOD) is an enzyme that transforms superoxide radicals to hydrogen peroxide, and catalase (CAT) is an enzyme that rapidly decomposes hydrogen peroxide to water and oxygen[60]. Glutathione peroxidase (GPx) also detoxifies hydrogen peroxide and lipid hydroperoxides with glutathione as reductant[60]. Changes in the activity of these enzymes indicate changes in the antioxidant defense mechanisms during infection. The enzyme activity may go up at first, as a defensive reaction, depending on the stage and severity of the disease, and then fall off when oxidative stress is sustained or overwhelming[61].

In the last years, more and more emphasis is paid to other biomarkers. 8-Hydroxy-2'-deoxyguanosine (8-OHdG) is often used to evaluate oxidative DNA damage, and protein carbonyls are indicative of irreversible oxidation of proteins[62]. Both markers have been related with chronic inflammation, chronic infections and tissue injury. Their measurement complements classical markers of oxidative stress by providing information on specific biochemical targets that undergo alterations during infection.

In this context, new studies are in favor of using many oxidative stress markers rather than a single biomarker in order to better evaluate the redox status[63]. The combination of TOS, TAC, MDA, GSH, SOD, CAT, GPx and DNA oxidation indicators provide a comprehensive view of oxidative damage and antioxidant defense[64]. The integrated method also enhances disease monitoring, and may help to identify individuals at increased risk for severe infection or poor therapy response.

In general, oxidative stress biomarkers have become important instruments in the research of the infectious diseases[51]. In addition to increasing our understanding of host-pathogen interactions, they could also be promising for the diagnosis, prognosis, and monitoring of therapy of diseases, as well as for the development

of antioxidant-based therapeutic techniques.

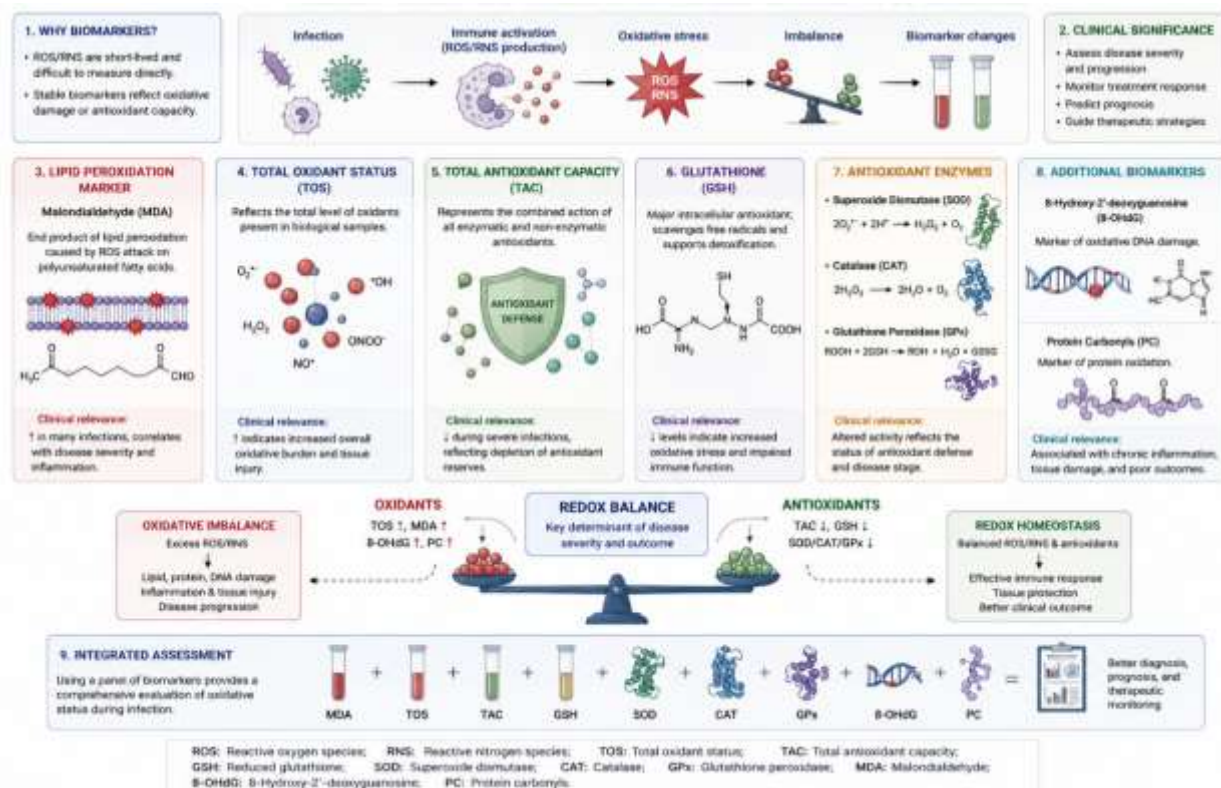


Figure 3. Schematic overview of oxidative stress biomarkers and their clinical applications in infectious diseases.

Oxidative Stress in Bacterial, Viral, Fungal, and Parasitic Infections

Infectious disorders produced by bacteria, viruses, fungi and parasites are linked with oxidative stress in their genesis and progression[9]. But the processes underlying these pathogens are different. One common aspect affecting both pathogen survival and damage to host tissues is the excessive production of reactive oxygen species (ROS) and reactive nitrogen species (RNS)[64]. Understanding these pathways provides vital insight into disease aetiology and may suggest novel treatment targets.

Oxidative Stress in Bacterial Infections

One of the strongest inducers of bacterial infections is oxidative stress. Neutrophils and macrophages are rapidly attracted to the site of infection following bacterial invasion of host tissues[65]. These immune cells produce enormous amounts of ROS by means of respiratory burst in an attempt to kill the invading bacteria. This response is quite efficient against many bacterial species, but the excess production of ROS may also damage neighbouring healthy tissue[3].

Gram-positive and Gram-negative bacteria have different interactions with oxidative stress[66]. Many dangerous bacteria like *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa* and *Mycobacterium TB* possess antioxidant enzymes like superoxide dismutase and catalase that enable them to survive inside the host[67]. Some bacteria also create pigments, biofilms or antioxidant compounds that minimize oxidative harm and contribute to antimicrobial resistance[26].

In clinical trials, increased levels of MDA and TOS are reported in individuals with severe bacterial infections together with decreasing TAC and Glutathione. These metabolic alterations are frequently associated with raised inflammatory cytokines, disease severity and extended hospitalizations[68].

Oxidative Stress in Viral Infections

Viral infections also generate significant oxidative stress, however the mechanism differs from that of bacterial diseases[49]. Viruses depend fully on host cells for replication and often affect cellular metabolism to create an environment conducive to viral replication. Such metabolic alterations stimulate mitochondrial ROS generation and activate inflammatory signalling pathways[31].

Oxidative stress has been linked to the increase of several viruses including influenza virus, hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV) and SARS-CoV-2[69]. The increased generation of ROS is involved in viral propagation, inflammation, apoptosis, and tissue injury. Many viruses also modulate host antioxidant pathways to delay cell death until viral replication is complete, which enhances viral survival[69].

In patients with severe viral infections, MDA, protein carbonyls, 8-OHdG are usually raised and the activity of antioxidant enzymes is decreased. Such changes are generally linked to poor clinical outcomes and ongoing inflammation[70].

Oxidative Stress in Fungal Infections

Fungal pathogens are continually faced with oxidative assaults from host immune cells, particularly during phagocytosis by neutrophils and macrophages[50]. In response, fungi have evolved very efficient antioxidant defense systems to defend themselves from ROS-mediated death[8].

Antioxidant enzymes like catalase, superoxide dismutase, and glutathione peroxidase are expressed by species such as *Candida albicans*, *Aspergillus fumigatus*, and *Cryptococcus neoformans*[71]. These enzymes minimize intracellular oxidative damage and improve fungal survival in host tissues. Moreover, biofilm development increases resistance by restricting the entry of reactive chemicals and antifungal medicines[72].

Chronic inflammation and tissue death are consequences of ongoing oxidative stress in fungal infections. Fungal infections are generally more severe and difficult to cure in immunocompromised patients[73].

Oxidative Stress in Parasitic Infections

Parasitic infections are also associated with complicated relationships between oxidative stress and host immunity[7]. During infection immune cells create ROS and RNS which are used to limit parasite development and kill infected cells. However, many parasites have efficient anti-oxidant system to survive in these adverse settings[74].

Parasites including *Plasmodium*, *Leishmania*, *Trypanosoma* and *Toxoplasma gondii* synthesize antioxidant enzymes and specialized metabolic pathways for neutralizing free radicals. Some parasites also modulate host immune responses to minimize oxidative damage and ensure long-term infection[75].

Parasitic infections often show increased levels of oxidative stress indicators, which are a consequence of immune activation and tissue harm[76]. Increased lipid peroxidation, DNA oxidation and depletion of antioxidant defenses have been described in several parasite diseases, suggesting that oxidative stress plays an important role in disease progression[77].

In summary, oxidative stress is a common biological route that is shared by bacterial, viral, fungal and parasite illnesses. Although each pathogen interacts uniquely with the host, the disruption of redox equilibrium is a common occurrence that determines microbial survival, immunological responses, tissue damage and clinical outcome. These findings underscore the importance of oxidative stress as a possible diagnostic marker and treatment target in a wide range of viral illnesses.

Table 2. Oxidative Stress in Different Types of Infectious Diseases

Type of Infection	Major Sources of Oxidative Stress	Common Oxidative Stress Biomarkers	Microbial Defense Mechanisms	Clinical Consequences
Bacterial infections	Respiratory burst, NADPH oxidase activation, inflammatory cytokines	↑ MDA, ↑ TOS, ↓ TAC, ↓ GSH	SOD, CAT, peroxidases, biofilm formation	Tissue injury, inflammation, antimicrobial resistance
Viral infections	Mitochondrial dysfunction, chronic inflammation, altered cellular metabolism	↑ MDA, ↑ Protein carbonyls, ↑ 8-OHdG, ↓ Antioxidant enzymes	Manipulation of host antioxidant pathways, modulation of apoptosis	Persistent inflammation, organ damage, enhanced viral replication
Fungal infections	Phagocytic oxidative burst, inflammatory mediators	↑ MDA, ↓ GSH, altered SOD/CAT activity	Catalase, SOD, GPx, biofilm formation	Chronic inflammation, tissue destruction, persistent infection
Parasitic infections	Activated macrophages, nitric oxide production, inflammatory responses	↑ MDA, ↑ TOS, ↓ TAC, oxidative DNA damage	Antioxidant enzymes, redox metabolism, immune modulation	Chronic infection, oxidative tissue damage, disease progression

Therapeutic Strategies Targeting Oxidative Stress During Infection

Growing awareness of the role of oxidative stress in infectious diseases has spurred researchers to develop novel treatment approaches aimed at re-establishing redox homeostasis and sustaining robust antimicrobial immunity. Oxidative stress contributes to the destruction of pathogens as well as host tissue[43]. Therefore, current therapeutic techniques try to diminish excess oxidative damage without fully blocking the beneficial effects of reactive oxygen and nitrogen species.

Antioxidant Therapy

Antioxidants are one of the most studied techniques for lowering oxidative stress during infection. These chemicals scavenge reactive oxygen species, protect cellular components from oxidative injury and assist in the restoration of antioxidant defense systems[78]. Experimental and clinical research has proven that a number of natural and synthetic antioxidants have positive benefits.

Vitamin C is a powerful water-soluble antioxidant that removes free radicals and regenerates other antioxidant molecules[79]. It also helps immune cells to carry out their tasks and may lessen inflammatory reactions in severe infections[80]. Vitamin E prevents lipid peroxidation of cell membranes and N-acetylcysteine (NAC) restores intracellular glutathione levels, thus increasing the cellular antioxidant capability[81].

Antioxidant supplements may prevent oxidative damage, however excessive use should be avoided as total suppression of ROS production may impede the ability of immune cells to eradicate invading pathogens[82]. Therefore, an antioxidant therapy should focus at recovering the natural redox balance instead than eradicating reactive species[38].

Nanotechnology-Based Therapeutic Approaches

Nanotechnology is one of the most promising approaches to decrease oxidative stress in infection[83]. The metal nanoparticles such as silver, gold, zinc oxide and copper oxide and iron oxide nanoparticles have unique physicochemical features that improve the antibacterial action and influence the oxidative pathways.[84]

Many nanoparticles kill bacteria by boosting intracellular ROS generation, destroying microbial membranes, interrupting DNA replication, and interfering with critical metabolic activities. Nanoparticles could be a good candidate against multidrug resistant germs as these mechanisms are different from the standard antibiotics[85].

Special focus has been paid to green synthesis of nanoparticles, because phytochemicals from plants increase stability of the nanoparticles and reduce toxicity[86]. Besides antibacterial action, certain green nanoparticles also possess antioxidant and anti-inflammatory activity, which can protect host tissues from excess oxidative damage[87].

Targeting Microbial Antioxidant Defense Systems

A therapeutic strategy could be to suppress the antioxidant defense s of infections, rather than to increase ROS generation. Many bacteria resist the oxidative attacks of host immune cells by means of enzymes such as superoxide dismutase, catalase and peroxidases[88].

The inhibition of these protective enzymes leads to increased sensitivity of microbes to oxidative stress and potentiation of both immune responses and antimicrobial medicines[26]. While numerous experimental inhibitors have showed promise, further study is needed to increase their selectivity and clinical safety.

Combination Therapy

Recent studies have suggested that the combination of traditional antibacterial medicines with antioxidants or nanomaterials may enhance therapeutic effects[89]. The combination therapy could minimize microbial load, restrict excessive inflammation, decrease oxidative tissue damage and inhibit the development of antimicrobial resistance simultaneously[90].

For instance, nanoparticles can increase the permeability of bacterial membranes, allowing drugs to get into microbial cells more efficiently[91]. Similarly, moderate antioxidant intake may protect host tissues from damage without severely affecting antimicrobial immunity[92]. These combination techniques are increasingly being explored in both experimental models and clinical trials.

Future Therapeutic Perspectives

Oxidative stress biomarkers will provide more personalized therapies in the future. Measurement of biomarkers such as MDA, TOS, TAC, GSH, SOD and CAT can help in identifying patients with severe oxidative imbalance and guide in individualized therapy options.

Development of nanomedicine, targeted drug delivery systems, artificial intelligence and biomarker-guided therapy are expected to bring improvements in infection management and reduction of unwanted effects. Moreover, a greater knowledge of redox interactions between the host and pathogens should help to develop new medications that selectively target microbial oxidative defense systems without affecting host tissues. In conclusion, the therapies targeting oxidative stress should focus on restoring physiological redox equilibrium rather than just decreasing reactive oxygen species. This balance is crucial to antimicrobial immunity without causing too much inflammation and tissue damage.

Table 3. Therapeutic Strategies Targeting Oxidative Stress During Infection

Therapeutic Strategy	Mechanism of Action	Advantages	Current Limitations
Antioxidants (Vitamin C, Vitamin E, NAC)	Neutralize ROS and restore antioxidant capacity	Reduce oxidative damage and inflammation	Excessive use may suppress beneficial immune ROS
Metal nanoparticles	Increase microbial ROS production, membrane disruption, DNA damage	Broad-spectrum antimicrobial activity, effective against MDR pathogens	Potential toxicity and limited long-term clinical data
Green-synthesized nanoparticles	Combined antimicrobial, antioxidant, and anti-inflammatory activities	Improved biocompatibility and lower toxicity	Need for standardized synthesis and clinical validation
Microbial antioxidant enzyme inhibitors	Inhibit SOD, CAT, GPx, and related enzymes	Enhance microbial susceptibility to oxidative killing	Mostly experimental; limited clinical application
Combination therapy	Combines antibiotics with antioxidants or nanoparticles	Improved treatment efficacy and reduced resistance	Optimal dosage and treatment protocols remain unclear
Biomarker-guided personalized therapy	Uses oxidative stress biomarkers to guide treatment decisions	Personalized management and prognosis prediction	Requires further clinical validation and standardized protocols

Future Perspectives

The last decade has witnessed tremendous growth of research on oxidative stress in infectious diseases, bringing new insights into the intricate interplay between host immunity and germ survival. Much of redox biology during infection, however, is poorly known. Future investigations should be aimed at elucidating the precise mechanisms that govern oxidative balance at different phases of infection and the consequences of these mechanisms on disease progression and treatment outcome.

One possible avenue is the identification of more sensitive and specific oxidative stress biomarker. The intricacy of redox alterations during infection cannot be fully captured by commonly used markers such as MDA, TOS, TAC, GSH, SOD and CAT. Using various biomarkers along with genomic, proteomic and metabolomic approaches may enhance the understanding of host–pathogen interactions and improve disease monitoring.

Furthermore, nanotechnology is foreseen to assume an even more prominent function in future anti-microbial medicines. Smart nanoparticles capable of selectively targeting sick areas, delivering therapeutic drugs, or controlling oxidative stress may improve therapy efficacy while sparing healthy cells from injury. Further studies are necessary to optimise their safety, biocompatibility and long-term clinical performance. Artificial intelligence and machine learning could improve the interpretation of oxidative stress biomarkers by merging laboratory data with clinical characteristics. Such technologies can aid in the early identification of disease, prediction of disease severity, and help clinicians to pick individual therapeutic methods depending on the redox profile of the patient.

Another significant research objective is the development of treatments that can selectively target microbial antioxidant defense mechanisms. Rather than directly enhancing ROS generation, such strategies might reduce resistance of pathogens to oxidative stress and preserve normal function of host cells. Such techniques may be especially beneficial in the treatment of multidrug resistant illnesses.

Future progress will likely come from the integration of biochemistry, microbiology, immunology, nanotechnology and clinical medicine. A multidisciplinary approach will be required to translate laboratory

data into effective diagnostic tools and therapeutic strategies.

Conclusion

Oxidative stress has a dual role in infectious diseases and is a key component of host-pathogen interactions. The controlled synthesis of reactive oxygen and nitrogen species is a prerequisite for removal of invading microbes and for appropriate immune responses. However, excessive or sustained generation of these reactive molecules alters the redox balance resulting in oxidative damage, inflammation, and tissue injury. This review discusses the biochemical pathways involved in the formation of ROS and RNS, the principal causes of oxidative stress during infection, microbial defense tactics against oxidative damage and clinical implications of oxidative stress indicators. We also debated the role of oxidative stress in bacterial, viral, fungal and parasite illnesses and summarized novel therapeutic options to restore redox homeostasis.

Current research indicates that oxidative stress biomarkers such as MDA, TOS, TAC, GSH, SOD, CAT, and GPx are useful for disease severity, treatment response and prognosis. Incorporating them into ordinary clinical research may improve understanding of infectious diseases and contribute to the development of personalized therapy strategies.

Promising potential for the improvement of infection control are offered by recent advances in antioxidant therapy, nanotechnology and tailored antibacterial methods. However, further experimental and clinical research are needed to elucidate the appropriate balance between antimicrobial oxidative responses and protection of host tissues.

In summary, oxidative stress is a major relationship between biochemistry and microbiology. Enhanced understanding of redox regulation during infection would facilitate our understanding of the pathophysiology of diseases as well as help in the creation of novel diagnostic and therapeutic strategies to treat infectious diseases.

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Conflict of Interest

The authors declare that they have no conflicts of interest related to this study.

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