

Review Article

Oxidative stress markers in infectious respiratory diseases: current clinical practice

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ABSTRACT

Cases of some infectious respiratory diseases are on the increase and aetiology of these diseases is associated with assault from exogenous and endogenous oxidants. This requires constant appraisal on current knowledge hence this review looks at current knowledge on oxidative and nitrosative stresses in selected infectious respiratory diseases and the utility of stress biomarkers. A major metabolic or organic stress is oxidative stress; an imbalance between oxidants and anti-oxidants and it is implicated in aetiology of various diseases including respiratory diseases. Physiologically reactive oxygen and nitrogen species are beneficial since they take part in various cellular processes. During infection, the host produces reactive species to defend against invading pathogens but some microorganisms have mechanisms to defend against the reactive oxygen and nitrosative species produced by host. Hence, there is also the oxidative stress 'pros and cons' paradox in infectious respiratory disease, which makes careful interpretation of laboratory methods necessary. Although most reactive oxygen and nitrosative species are not very stable and cannot be measured directly, there are indirect assessment methods of oxidative stress or oxidants or anti-oxidants. Various biological samples such as exhaled air, exhaled breath condensate, sputum and blood are used in investigation and management of infectious respiratory diseases. Measurement of oxidative stress can be done using various laboratory methods including, chemical, immunoassays and chromatographic thus allowing oxidative stress assessment to be important in infectious respiratory diseases.

Keywords: Oxidative stress, Reactive oxygen species, Reactive nitrogen species, Infectious respiratory diseases, Inflammation, Laboratory methods

INTRODUCTION

Normal aerobic cell metabolism produces reactive oxygen species (ROS), which are the major ones and reactive nitrogen species (RNS). These reactive organic species are produced in organelles such as mitochondria and microsomes; and normally they are beneficial since they are associated with cellular processes such as gene expression, signal transduction, vascular tone, monitoring of O₂ tension and enzyme activation.¹⁻³ In addition to ROS and RNS, aerobic metabolism produces other organic reactive species such as reactive sulphur species (RSS) and reactive chlorine species (RCS), but little is

known about their functions. At high levels, ROS and RNS are detrimental to cells hence they need to be countered by a variety of anti-oxidants.³ The ROS are classified into free radicals, which are molecules with one or more un-paired electrons and non-radicals that are formed as a result of two free radicals sharing un-paired electrons; and examples of ROS are superoxide anion (O₂⁻), hydroxyl radical ([•]OH) and hydrogen peroxide (H₂O₂).^{4,5}

In normal animal metabolism, nitric oxide (NO) is involved in signal transduction, enzyme regulation, immune response and anti-apoptotic responses; and

dilatation of vascular muscles and neural transmission.⁶⁻⁸ In the respiratory system, NO is involved in regulation and modulation of immunity airway tone, pulmonary vascular tone and ciliary beats and stimulation of mucin secretion among others.⁹ Nitric oxide is oxidised by oxygen to nitric dioxide (NO₂), which reacts with NO to give nitrite (NO₂⁻) in aqueous environment.¹⁰

In cellular reactions, NO has dual functions; it can donate an electron hence it is an oxidant and it can also accept electrons making it an anti-oxidant. Although NO is not very reactive and cannot nitrate proteins, it can form reactive intermediates, which affect protein function.⁶ For instance, NO reacts with superoxide (O₂⁻) or sulphhydryl groups to give peroxynitrite (ONOO⁻) and S-nitrosothiols (RSNO), respectively and glutathione.^{6,7} In turn, the peroxynitrite is capable of reacting with tyrosine residues of proteins to form 3-nitrotyrosine; and modification of tyrosine for instance in receptor molecules alters cellular signalling.^{6,11}

Although nitration of proteins is a feature in normal cells, nitration of tyrosine is associated with various diseases including lung infections.^{9,12} The synthesis of ROS is catalysed by NADPH-oxidase complex, while the synthesis of NO involves oxidation of L-arginine by nitric oxide synthase (NOS).^{13,14} Although ROS have been viewed in some cases as a harmful consequences of aerobic metabolism, it is now accepted that ROS have other roles including regulation of growth as mentioned hence enzymes such as NAD oxidase (NOX) and dual oxidase (DUOX) specifically produce ROS in a regulated manner in response to e.g. calcium and growth factors¹

Oxidative stress and disease

In 1997, Sies pointed out that oxidative stress was a result of an imbalance of between oxidants and anti-oxidants in favour of oxidants and this potentially leads to damage. This imbalance can be a result of depletion of anti-oxidants or accumulation of oxidants.⁴ Although oxidants are normal products of aerobic metabolism when O₂ is reduced to water H₂O this production is increased in some pathophysiological states.¹⁵ About 2% of inhaled O₂ is made up of ROS and it is probable that half of this portion is responsible for damage to proteins and a quarter damages DNA.¹⁶ This therefore means that besides stress brought about by diseases of the respiratory system there is possibly an inherent oxidative stress as a result on breathed-in gases.

Oxidants and anti-oxidants are diverse.¹⁶ An anti-oxidant is a substance that, when present at low level compared to that of an oxidisable substrate, significantly delays or inhibits the oxidation of that substrate.¹⁵ This definition encompasses enzymatic and non-enzymatic compounds; and the various anti-oxidants can be lipid or aqueous soluble.^{15,16} Enzymatic anti-oxidant defences include superoxide dismutase (SOD), catalase, haeme oxygenase-1, glutathione peroxidase and glutathione transferase and

redox proteins such as thioredoxin, peroxiredoxin and glutaredoxins. On the other hand, non-enzymatic anti-oxidant defences encompass ascorbic acid (vitamin C), all trans retinol 2 (vitamin A), α -tocopherol (vitamin E), β -carotene, and glutathione (Table 1). The functions of anti-oxidants include prevention of the formation of the oxidants, interception of the activity of oxidants and also repair the damage caused by oxidants.^{4,15} Hence, the various enzymes and non-enzymatic anti-oxidants and radical scavengers work to limit the damage caused by oxidants.

Table 1: Examples of anti-oxidants.

Enzymes	Proteins	Non-protein
Superoxide dismutase (SOD)	Thioredoxin, peroxiredoxin	Ascorbic acid (vitamin C)
Catalase haeme oxygenase-1, glutathione peroxidase	Glutaredoxins	All trans retinol 2 (vitamin A)
glutathione transferase	Ferritin	A-tocopherol (vitamin E)
	Albumin	B-carotene, and glutathione
	Ceroloplasmin	Uric acid bilirubin

Reactive oxygen and nitrogen species in disease: overview

Studies show that oxidative stress contributes to pathogenesis of various diseases including respiratory diseases; since it results in; metabolic derangements, damage to proteins, lipids, carbohydrates and membrane lipids as well as damage to DNA, RNA and mtDNA, all which are implicated in pathogenesis of diseases. ROS react non-specifically and rapidly with DNA, lipids, proteins, carbohydrates and other biomolecules and such reactions give rise to DNA mutation, lipid peroxidation and protein oxidation, which are the bases of the harm that they cause.^{3-5,13,17}

Further, elevated levels of ROS produce pro-inflammatory and anti-inflammatory cytokines; as well as in aerobic organisms, inflammatory cells generate oxidative states and inflammation also contributes to e.g. carcinogenesis and studies show that cancers can arise from sites of infection, irritation and inflammation, which is why it is important to limit infections, thus oxidative stress, especially in the respiratory system that is prone to infection.^{3,4} It is noteworthy that sources of ROS, RNS as well as other reactive organic species are varied and they include infections, this means the inputs into oxidative stress are varied and many thus creating challenges to counter.¹⁸

For instance, peroxidation of membrane lipids in oxidative stress is implicated to cause various diseases; and the process of lipid peroxidation also synthesises conjugated dienes and malondialdehyde, which can be measured as an index of oxidative stress. Protein nitration and oxidation by ROS and RNS *in vitro* have been

associated with reduction in function in a number of proteins in alveolar space.^{4,19,20}

Studies report that ROS such as superoxide, H₂O₂, and perhaps hydroxyl radicals contribute to inflammation in pulmonary airways; as well as the major sources of ROS in the lungs include neutrophils, eosinophils, alveolar macrophages, alveolar epithelial cells, bronchial epithelial cells and endothelial cells.^{9,21-24} Phagocytic cells in response to infection produce increased levels of NO, which is cytotoxic to micro-organisms. Further, NO can react with superoxide (O₂⁻), produced also by inflammatory and phagocytic cells to give reactive nitrogen oxide intermediates such as peroxynitrite (ONOO⁻), which are strong oxidants and nitrants on proteins, lipids, thiols and nucleic acids. The result is oxidative and nitrate stresses, which are observed in various viral infections.^{8,25-29}

Nitrate stress is as important as oxidative stress in that it can be beneficial or pathogenic to tissues and cellular processes. For instance, NO inactivates enzymes involved in growth and metabolism in protozoan and helminth parasites both *in vivo* and in animals thus conferring protection against infection.³⁰ However, NO can react with superoxide to form peroxynitrite, which is a strong oxidant; and studies show that NO is produced in abnormal levels in pneumonic lung infected with *Influenza A virus*, exemplifying its pathologic effects.^{8,25,31}

Nitric oxide is produced by various cells in the immune system and during the early phase of inflammation, L-arginine is converted to NO by NOS and because NO is highly diffusible it acts on local and distant cells to exert anti-microbial activity.^{32,33} Nitric oxide (NO) is synthesised as a result of macrophage activation by cytokines or microorganisms and it kills or reduces replication on viruses, bacteria, protozoa, fungi and helminths.¹⁴ At elevated levels, NO acts via reactive nitrogen oxide species (RNOS) that are produced by the reaction of NO with O₂ or superoxide (O₂⁻). Further increased levels of RNOS can lead to DNA damage, lipid peroxidation as well as oxidation of thiols and nitration of tyrosine.^{33,34}

NO has been reported to protect against inflammation and immunity and to reduce the effects of inflammatory responses in various diseases and high levels of NO are reported have anti-inflammatory effects in asthma hence suggested as supplementation in inflammatory diseases, but such beneficial effects are not clear in respiratory infections.³³

Oxidative stress and the respiratory system

A healthy lung is protected by non-enzymatic anti-oxidants and radical scavengers and these include uric acid, ferritin and α-tocopherol, vitamins C and E, β-carotene, and enzymatic anti-oxidants that include

superoxide dismutase (SOD), catalase and peroxidases.^{16,24} Glutathione level is reported to be hundred times more in epithelial lining fluid of respiratory tract by comparison to plasma and this glutathione is mostly reduced.³⁵ This possibly makes glutathione an important anti-oxidant for defence in respiratory diseases. Further lungs possess specialised proteins such as peroxiredoxins, thiodoxins, glutaredoxins, haeme oxygenases and reductases that also protect against oxidative damage.¹⁶

The airways are prone to oxidative assault and the extent depends on the ability of the body to counter or up-regulate the protective ROS scavenging mechanisms. There are intracellular and extracellular anti-oxidants e.g. catalase and SOD and glutathione peroxidase in the lungs that protect against inhaled ROS but these mechanisms can be over-whelmed.³⁶ Synthesis of ROS and RNS is a very effective host-defence system against intracellular pathogens, and the synthesis of NO is therefore important in inflammatory and infection responses.^{13,14,33,37} Studies have shown that ROS products such as superoxide anion and hydrogen peroxide alone in low levels are not very effective in killing *Mycobacterium tuberculosis* in culture.³⁸ However, inducible NO at low level has been reported to cytotoxic to *M. tuberculosis* but it is acknowledged that this could be strain-dependent.³⁹ Thus, oxidative stress in infectious respiratory disease has pros and cons (Figure 1).

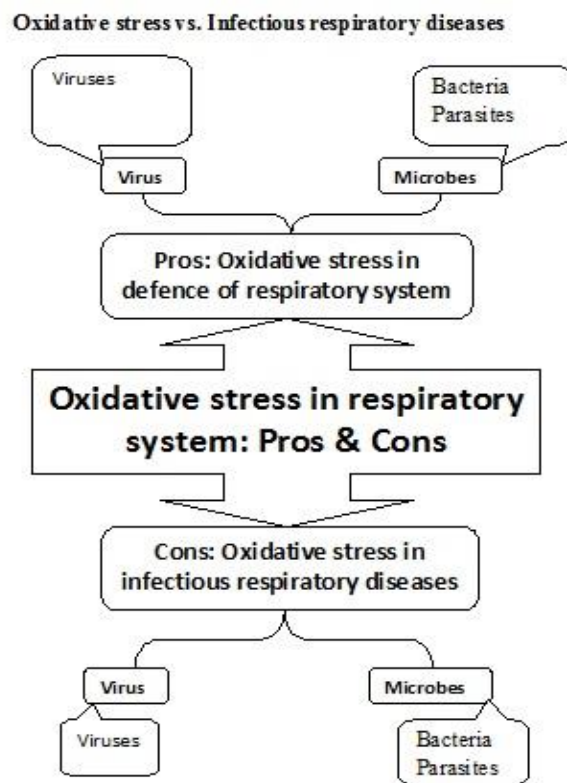


Figure 1: Pros and cons of oxidative stress in respiratory infections and in defense.

Oxidative stress as a defence mechanism against infections in the respiratory system

Reactive organic species are required for host defence against infections and inflammatory cells release as well as utilise these oxidising agents. Neutrophils and macrophages have high O₂ demand for phagocytosis and in this regard, NADH oxidase is activated to oxidise NADH. The reaction releases electrons that reduce oxygen to superoxide radicals, which dismutate to

hydrogen peroxide and oxygen with the latter generating superoxide radical ([•]OH), which damage bacterial cell walls. Phagocytic vacuoles possess myeloperoxidase and in the presence of H₂O₂ and Cl⁻ give hypochlorous (HOCl), which is also a very reactive species hence, ROS and RNS are important in inflammatory processes.¹⁶ It is worth pointing out that microorganisms counter the destructive effects of oxidative stress directed to them by various mechanisms and some are reviewed below and summarised in Table 2.

Table 2: Some of the mechanisms that microorganisms use to counter destructive effects of oxidative stress from host.

Tool	Mechanism
Reactive nitrogen intermediates	Use of immunosuppressive macrophages that suppress T-cell proliferation of host ⁴⁰
Superoxide dismutase in exosporium	Regulation of the levels of reactive oxygen intermediates in the host ⁴¹
Cytochrome <i>bd</i> oxidase	Increase resistance of microbial cells to oxidative and nitrosative stress thus enabling the bacteria to evade the immune defences of the host ⁴²
Production of homologs of mammalian cytokine such as transforming growth factor-beta (TGF-β) and macrophage migration inhibitory factor (MIF)	Immune evasion: suppression, diversion and conversion of host defences to benefit the pathogen ⁴³
Haem- and thiol-based mechanisms	Sensing of redox signals such as O ₂ and NO from ROS and RNS ⁴⁴
Genes for catalase, superoxide dismutase, alkyl peroxide reductase, thioredoxin, and thioredoxin reductase	Break down and neutralise oxidative species ^{45,46}
Lipoarabinomannan (LAM) and cyclopropanated mycolic acids as well as phenolic glycolipid 1 (PGL-1)	Scavenge of oxygen radicals ⁴⁷
Mycothiols	Protects against oxidants by maintaining a reduced environment thus offering resistance to oxidative stress ⁴⁸
Flavo-haemoglobin	Detoxification of NO ⁴⁹
Sulphoxide reductase	Methionine sulphoxide, a product of reaction of reactive oxidative intermediates with methionine is converted back to methionine by sulphoxide reductase ^{45,50,52}

Infections including bacterial produce ROS and RNS, but microorganisms have evolved strategies that include NO and L-arginine metabolism to counter effects of macrophages allowing persistent infections.^{33,53-55} Mycobacterium infections in murine model have been observed to suppress T-cell proliferation thus reducing host immunity and these processes are mediated by reactive nitrogen intermediates.⁴⁰

B. anthracis have superoxide dismutase in the outer surface layer i.e. exosporium, which possibly is involved in regulation of the levels of reactive oxygen intermediates in the host.^{33,41} Removal of the outmost layer of the spores increases NO production hence it is suggested that the exosporium protects from antimicrobial activity by regulating the synthesis of free radicals.⁵³ Such similar protective mechanisms possibly

also apply to bacterial respiratory infections. Cytochrome *bd* oxidase found in various bacteria has been observed to increase resistance of microbial cells to oxidative and nitrosative stress thus enabling the bacteria to evade the immune defences.⁴²

As with other infections, parasites induce release of pro-inflammatory molecules and production of NO in the host to which parasites are sensitive, but parasites have also evolved mechanisms that include suppression, diversion and conversion of host defences to benefit the pathogen e.g. an immune evasion strategy is production of homologs of mammalian cytokine such as transforming growth factor-beta (TGF-β) and macrophage migration inhibitory factor (MIF).^{33,43} Defence mechanisms of macrophages is in part through secretion of NO, which perhaps suppresses viral replication.^{26,33,36} Although the exact role of NO in pathogenesis of viral infections is not

clear, it has been suggested that NO also oxidises cell membranes.⁵⁶ Some studies also report that accumulation of NO as a result of macrophage response to infection is perhaps immunosuppressant and also toxic to tissues.⁵⁷ Viruses e.g. vaccinia and avian are reported to suppress NO release perhaps to evade the immune responses by the host while others such as rabies and coxsackie B3 induce NO synthesis, such mechanisms perhaps exist in viral infections in the lungs for reasons that are not clear.³³

Oxidative stress in infectious respiratory diseases

Airways epithelium is subjected to oxidants from the outside and endogenous from reactions of free radicals and ROS and such reactions damage cells; and since lungs have a large surface area and daily breathing volume, they are susceptible to damage by reactive species.^{16,58,59} RNS and ROS are reactive due unpaired electrons they possess and these mechanisms are defences against e.g. invading pathogens.²⁴

ROS have direct effects on the respiratory airways and also activate signal transduction pathways and transcription factors via formation of oxidised mediators such as isoprostanes and hydroxyl-nonenal.^{60,61} The unique structure and function of lungs makes them susceptible to attack and the resultant inflammation and oxidative and nitrosative molecules that are produced further contribute to inflammation.^{20,61}

Oxidants in excess of anti-oxidant defences lead to lung inflammation that result in acute lung injury (ALI) or acute respiratory distress syndrome (ARDS). Nitric oxide synthesis is increased in inflammation and may be beneficial since it is anti-microbial but it also has tissue damaging effects. Oxidant induced inflammatory responses in the lung result in induction of expression of cytokines e.g. tumour necrosis factor-alpha (TNF- α), which activates endothelial cells and macrophages and also recruits neutrophils and eosinophils.^{20,62}

The lungs persistently inhale pathogens and toxins and this leads to production of ROS, which initiate inflammation and other pathogenic mechanisms that trigger or worsen airway diseases.⁶³ Most respiratory diseases are associated with inflammatory processes, which generate ROS and RNS. ROS contribute to the inflammation in airways and NO react with oxygen and ROS to give nitrite, nitrate and RNS species such as peroxynitrite, which nitrate proteins and this is linked to lung infections.⁹

The lungs can up-regulate protective ROS and RNS defence mechanisms and the epithelial lining fluid in alveolar space contains anti-oxidants as well as catalase, superoxide dismutase, glutathione, glutathione peroxidase, vitamin E and bilirubin.^{9,64} Even though NO is associated with tissue injury, studies have also demonstrated that NO administered exogenously protects

against lung injury, thus NO has anti-oxidant role [65]. In response to infection, phagocytes such as neutrophils, macrophages and monocytes go through respiratory burst, a process that generates ROS and RNS with the intention to destroy the ingested pathogens but this oxidative burst also contributes to inflammatory injury of the host tissue.¹⁹

Chronic obstructive pulmonary disease (COPD) has various causes including infections and features of this disease are progressive irreversible narrowing of bronchi and loss of elasticity as well as inflammation and oxidative stress.^{66,67} Studies have linked increased endogenous oxidants in macrophages and neutrophils to possibly account for acute exacerbations of COPD due to bacterial and viral infections.¹⁶ Oxidative stress is associated with pathogenesis of lung fibrosis; and increased levels of by-products of free radicals as well as reduction in anti-oxidants that include ascorbic acid, vitamin E and glutathione.^{18,19,68-70}

The oxidative stress in the pathogenesis of COPD possibly starts with activation of processes that include redox-sensitive transcription factors.^{16,71,72} In addition to increased oxidative stress there is elevated inflammatory response, which results in destruction and re-modelling of lung tissue leading to airflow restrictions in COPD.^{60,73} Increased oxidative stress in pathways of COPD may also potentiate the inflammatory responses and this is reflected in the activation of NF- κ B and activator protein-1 (AP-1) that induce neutrophilic inflammation as a result of elevated expression of interleukin 8 (IL-8) and other CXC chemokines.⁶⁰

It is also possible that oxidative stress increases the breakdown of elastin in lung parenchyma by impairing the activity of anti-proteases such as α_1 -antitrypsin.⁷⁴ Indeed, increased expression of pro-inflammatory cytokines resulting in elevated activity of xanthine oxidase that gives rise to high levels of superoxide radical ($O_2^{\cdot -}$) and H_2O_2 has been reported in COPD patients.^{67,75} These ROS react with nucleic acids, lipids and proteins and interfere with tissue repair as well as compromise surfactant and anti-protease protection.^{67,76}

Chlamydia pneumoniae, is responsible for respiratory infections and the infection disseminates to extra-pulmonary sites, such as vascular wall and this has led to the hypothesis that inflammation due to *C. pneumoniae* contributes atherosclerosis since there is increased secretion of inflammatory cytokines and chemokines in vascular cells; and there are elevated inflammatory markers in patients with CVDs and *C. pneumoniae*.⁷⁷⁻⁷⁹ It has also been suggested that increased ROS in vascular cells as a result of *C. pneumoniae* infection contributes to atherosclerosis and ROS in *C. pneumoniae* infected macrophages have been reported to result in LDL oxidation and foam cell formation.^{77,80} Studies report that during infection with *M. tuberculosis*, the host produces

ROS and RNS from antibacterial macrophages.^{46,81} It has been shown that children with defective oxidative burst have a high incidence of tuberculosis emphasising the importance of reactive oxygen intermediates in the protection from *M. tuberculosis*.⁸² During infection, *M. tuberculosis* is assaulted by a range of host-mediated stresses, which include antibacterial properties of macrophages that produce antimicrobial ROS and RNS.^{45,46}

The macrophages produce cytokines such as tumour necrosis factor alpha (TNF- α) and interleukin beta (IL- β), which together with interferon gamma (INF- γ) from T lymphocytes induce NO synthesis, which in association with reactive nitrogen intermediates have antibactericidal properties.⁸¹⁻⁸⁴ Suppression of mycobacterial growth by human macrophages at least in the early phase is possibly independent of NO; and it has been shown that macrophages from subjects infected with *M. tuberculosis* produce NO that correlate with intracellular inhibition of the bacterium.^{85,86}

As mentioned, *M. tuberculosis* infection is associated with increased oxidative stress; and macrophages and granulocytes generate free radicals during inflammatory responses.^{67,87,88} In guinea pigs infected with *M. tuberculosis*, malondialdehyde was reported elevated in lung lesions as the infection progressed while total serum anti-oxidant capacity was reduced early, confirming occurrence of oxidative stress early in infection before lesions. Other observations consistent with reduced anti-oxidant capacity were decreased reduced glutathione levels.⁶⁹

Studies report that mycobacteria infection induces synthesis of ROS, which contribute to immunosuppression, especially in HIV infection where anti-oxidant capacity is already impaired.⁸⁹⁻⁹¹ Although synthesis of ROS and RNS by the host is a mechanism to counter the growth, microorganisms as mentioned have developed mechanisms to counter as shown in Table 2.

Komaravelli et al have shown that in *Respiratory syncytial virus* infection, there is virus-induced inhibition of antioxidant enzyme expression with decreased expression and/or activities of superoxide dismutase (SOD), catalase, glutathione peroxidase (GPx) and glutathione S-transferase (GST) in human airway epithelial cells and this is suggestive of oxidative damage.⁹²

Respiratory syncytial virus infection has been reported to increase release of superoxide, hydrogen peroxide and myeloperoxidase (MPO) from epithelial cells of airways.⁵ In regards to infection with *Rhinovirus*, it has been demonstrated that markers of oxidative and nitrosative stress are elevated and they correlated with viral load and inflammatory markers.⁹³ In eosinophilic pneumonia, which can be due to parasitic infection, the accumulation of eosinophils in the lungs results in inflammation and

this infiltration is induced by eosinophil chemotactic factors such as interleukin-5 (IL-5), interleukin-18 (IL-18) and granulocyte-macrophage colony-stimulating factor (GM-CSF). Eosinophils release superoxide ion, leukotrienes and cytokines, which inflame and injure tissues hence are crucial in development of eosinophilic lung disease.⁹⁴⁻⁹⁶

Dietary supplements as defence

Dietary supplements that attenuate oxidative stress have been tried in management of respiratory infections and a brief consideration is important since such supplements can be viewed as part of natural defence because they are components of natural diet. Uchide and Toyoda reported that a combination of antioxidants such as ascorbic acid, glutathione, *N*-acetyl-L-cysteine with antiviral drugs synergistically reduced complications of influenza viral infections.⁹⁷

Dietary antioxidants such as resveratrol and quercetin have also been suggested to be effective in modulating human metapneumovirus infection.⁹⁸ Seyedrezazadeh et al reported in pulmonary tuberculosis patients that malondialdehyde, was elevated and it decreased after treatment with a combination of supplementary vitamin E and selenium and anti-tuberculosis medication by comparison with pre-treatment.⁹⁹ Whey protein has antioxidant, anti-inflammatory and anti-microbial properties and when subjected to hyperbaric pressure treatment to facilitate unfolding of the protein it has been found in a murine model infected with non-lethal *P. aeruginosa* to attenuate airway protein oxidation and oxidative burst in response to the bacteria was also increased.¹⁰⁰ Zinc an essential metal, when supplemented is reported beneficial in management of various diseases. For instance it is reported to decrease incidences of respiratory infections in children, it is not clear if this is via modulation of oxidative stress since zinc is reported to decrease oxidative stress.¹⁰¹

Markers of oxidative stress: laboratory measurements

The various species of oxidants and anti-oxidants require that their analyses are varied. It is worthy pointing out that oxidants are also products of other processes such as radiation and sheer-stress.¹⁵ This possibly has implications in assessment of oxidative stress since the contribution of the various sources may qualitatively or quantitatively be unknown.

There are a variety of samples also utilised in assessing oxidative burden in respiratory diseases including exhaled air, exhaled breath condensate, sputum, serum/plasma, endo-bronchial biopsies, sputum, platelets, leucocytes and lung secretions.^{16,102}

This is unique in the sense that in addition to use of blood which can suffer from dilution effects, samples such as biopsies, sputum and exhaled air can be used and are thus

perhaps more informative from a local perspective. Table 3 gives examples of laboratory samples and

measurements of oxidative stress and in respiratory infections oxidants are elevated and antioxidants reduced.

Table 3: Examples of laboratory samples and measurements of oxidative stress.

Disease	Sample	Oxidant	Anti-oxidant
<i>M. tuberculosis</i>	Plasma	Lipid peroxidation i.e. Malondialdehyde	Superoxide dismutase Glutathione Catalase ⁹¹
	Serum	Conjugated dienes Malondialdehyde ¹⁹	
	Plasma		Vitamin C and E Glutathione ¹⁸
	Red blood cells		Glutathione ¹⁸
COPD	Exhaled breath condensate	H ₂ O ₂ ¹⁰³⁻¹⁰⁵	
	Sputum	8-isoprostane ^{1106,107}	
	Exhaled breathe condensate Bronchoalveolar lavage fluid	Thiobarbituric acid reactive substances Isoprostanes ^{04,108-110}	
Community acquired pneumonia	Plasma	8-isoprostane ¹¹¹	
	Red blood cells	Malondialdehyde	Glutathione Glutathione peroxidase Superoxide dismutase Catalase ¹¹¹

It has been shown that in respiratory diseases several oxidative stress markers are measured in exhaled breath condensate, a technique that is simple and non-invasive.^{104,112,113} It has been mentioned that some of the samples e.g. sputum, exhaled breath condensate and biopsies are local and as in measurement of metabolites, blood distributes oxidants and anti-oxidants in the body hence blood samples are useful as this is indicative of the body status in general.

Although blood collection is evasive it is routinely done in laboratory analysis and measurement of oxidant status is carried out in most laboratories. For instance, H₂O₂ is widely used in assessing oxidative stress and its⁷ level is elevated in plasma.^{16,114,115} Reddy et al demonstrated low anti-oxidant potential (superoxide dismutase, glutathione and catalase) and increased lipid peroxidation i.e. malondialdehyde in serum in *M. tuberculosis* patients by comparison with healthy people.⁹¹

Nitration reactions give stable products and thus indicators of RNS-mediated reactions and are easily detected but various ROS and RNS have short half-lives hence can be difficult to measure directly and it is also important to be mindful that it is possibly the cooperation among the various anti-oxidants that provides greater protection and perhaps more informative against attack by ROS than an individual anti-oxidant.^{20,69,102} Equally, it may be the synergistic effects of reactive species that is more harmful rather than their individual contributions

hence assessment of total oxidant assault instead of individual oxidants or anti-oxidants may be more useful. Although many biomarkers have been investigated for clinical usefulness in oxidative stress, it appears that there is no ideal marker since none of the investigated markers are able to discriminate between the various diseases such as asthma or pneumonia.¹⁶ A problem with direct measurement of oxidants such as superoxide, hydroxyl radicals and hydrogen peroxide is their highly reactive and short-life properties as mentioned. This has necessitated measurement of oxidative damage on lipids e.g. isoprostanes, aldehydes and ethane, proteins e.g. carbonyls and nitrotyrosine, and DNA e.g. 8-hydroxy-2-deoxyguanosine, in some cases. The measurement of oxidant status is a challenge not only because of short biological half-lives but also of the fact that the levels of oxidants may fluctuate during the course of a disease.¹⁸

CONCLUSION

The contribution of metabolic or organic stress in respiratory infections is not in doubt however the relative quantitative contributions of the various stresses; oxidative and nitrosative as well as forms of stress from reactive chloride and reactive sulphur species are not clear. Equally, microorganisms have mechanisms to defend against the host defend mechanisms. In part this is the basis of resistance at least in some microorganism. Of interest in management of respiratory infections are perhaps dietary supplements that target to alter stress in

the host and in the microorganism. Again, dietary supplements that have anti-oxidant activities could be useful in attenuating stress and inflammation in respiratory infections and this is an area that needs close attention. The availability of various samples and biomarkers makes oxidative stress and its markers ideal in management of respiratory infections.

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