

## EDITORIAL

# Antioxidant therapy in sepsis and multi-organ dysfunction: From bench to bedside?

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**Abstract.** Oxidative stress derived from activated neutrophils is considered important in the development of multi-organ dysfunction syndrome during sepsis. However, so far, trials investigating the putative beneficial effects of antioxidant therapy have yielded conflicting results and have been subject to debate because of heterogenous patient populations and differences in the dosage and types of antioxidant administered. Therefore, a well-designed placebo-controlled trial should be carried out before antioxidant therapy can be considered standard treatment of septic patients.

**Keywords:** sepsis, multi-organ dysfunction syndrome, oxidative stress, antioxidant

The formation of oxygen radicals and the resultant oxidative stress has been at the centre of attention for researchers in all fields in medicine. The production of oxidizing species is essential in the first phase of the immune response. Phagocytic cells activated by an inflammatory stimulus produce reactive oxygen and nitrogen species (ROS and RNOS). These highly reactive substances damage the invading pathogen and are therefore vital in the first line of defence against infection. Furthermore, they are of pivotal importance in redox signalling and carefully orchestrate the immune response via activation of nuclear factor- $\kappa$ B (NF- $\kappa$ B) [1].

Apart from these beneficial effects, the highly reactive nature of ROS and RNOS may damage the host by destroying the lipid layer of cells and mutating DNA. A role in oncogenesis has therefore been implied. The endothelial damage caused by oxidative stress is considered important in a multitude of diseases including adult respiratory distress syndrome, atherosclerosis, microangiopathic haemolytic anaemia, vasculitis, ischaemia-reperfusion injury and sepsis.

Attempting to change the pro- to anti-oxidative balance by the administration of antioxidants is a logical step in research for this plethora of diseases. However, trials performed in the past trying to lower cancer incidence using beta-carotene and vitamin A have yielded no beneficial effects and even demonstrated a higher incidence of lung cancer in the patients treated [2]. Therefore, antioxidant treatment cannot be regarded completely harmless.

In the present issue of NJCC, Spapen and Jacobs [3] present an interesting review of the literature concerning anti-oxidant therapy in sepsis. In septic patients, neutrophils are considered a main source of oxidative stress and a relation with the development of multiple organ dysfunction syndrome (MODS) has been implied. Also, septic patients are known to have a lowered antioxidant potential and this correlates with outcome [4]. Nevertheless, it is unclear if a high level of oxidative stress and low antioxidant potential is causally related to the development of MODS or can be considered as epiphenomena during severe sepsis. Interestingly, in human endotoxaemia experiments, vascular hyporeactivity was attenuated after the administration of high dose vitamin C or N-acetylcysteine [5,6]. Therefore anti-oxidant

therapy may represent a promising intervention in septic patients. However, as presented in this review, the results of administration of different antioxidants in septic patients have yielded conflicting results and data from the different studies remain difficult to interpret due to heterogenous patient populations, different antioxidants (or combinations) supplied and different dosage regimens. Furthermore, the studies described are not sufficiently powered to determine an effect on mortality. As discussed by Spapen and Jacobs in their review, a recent study performed by Angstwurm et al [7], one of the most promising agents from animal studies, selenium (in the form of sodium selenite), decreased mortality in his study of 249 systemic inflammatory response syndrome or sepsis patients. However, the study has been the subject of debate because of a high rate of protocol violations and a possible selection bias. Therefore, convincing evidence is still lacking and the need for a new randomized, double-blind, placebo-controlled trial persists [8].

N-acetylcysteine, another well-known antioxidant which is widely clinically applied in pulmonary medicine, has been tested in septic patients and administered in the late phase of sepsis, has surprisingly increased mortality [9]. This indicates that, as in the previous beta-carotene study, antioxidant administration is potentially harmful.

As discussed by Spapen and Jacobs, vitamin C and E have demonstrated promising effects in rodent studies but their precise effects in human sepsis remain unclear because they have mainly been administered in combination with other antioxidative or anti-inflammatory agents. Other anti-oxidants such as glutathione and zinc have shown promising effects, but well-designed clinical trials proving their benefit are lacking.

Another point of interest is the timing of administration. Studies have demonstrated different kinetics for different factors in oxidative stress [10]. Combined with the data from the clinical trials, this suggests that the timing of antioxidant administration is of utmost importance and needs further elucidation.

In conclusion, restoring the pro- to antioxidant balance is a promising target to prevent sepsis-induced MODS. However data on which antioxidant to use, at what dosage and at what point in time are insufficient to draw unifying conclusions. Future studies, in a blinded, placebo-controlled fashion and sufficiently powered to show an effect on mortality should be performed to elucidate the role of anti-oxidant therapy in the treatment of septic patients.

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