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Is Vitamin C Beneficial to Patients with CAP?

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Abstract Community-acquired pneumonia (CAP) is one of the most common causes of morbidity and mortality in elderly and children. Vitamin C is known as a physiological antioxidant, regulating innate immune system in the lung. Vitamin C has been used to prevent and treat CAP. However, the use of vitamin C for preventing and treating CAP has been a subject of controversy. We aim to review the most significant findings about vitamin C supplementation in patients with pneumonia based on literature from the PubMed. First, we reviewed recent advances about the role of oxidative stress in CAP. Oxidative stress is a crucial component of the host defense system and inflammatory response. However, excessive oxidative stress can cause a systemic inflammatory response leading to tissue damage. The degree of oxidative stress has been associated with the severity of CAP. Vitamin C is beneficial to the host defense system by regulating the innate immunity in the lungs. We also discuss the prophylactic use of vitamin C for pneumonia. Vitamin C supplementation decreased the pneumonia risk in patients with vitamin C deficiency. However, it is not beneficial for prophylactic use of vitamin C to prevent pneumonia in the well-nourished population. Finally, we summarize the effect of vitamin C on mechanical ventilation used during respiratory failure. Administration of vitamin C decreases the duration of mechanical ventilation by decreasing oxidative stress.

Keywords Community-acquired pneumonia · Vitamin C · Oxidative stress

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Introduction

Community-acquired pneumonia (CAP) is one of the most common causes of morbidity and mortality in children and the elderly. There were approximately 12 million hospital admissions for severe acute lower respiratory infections (ALRI) in 2010. Of these ALRI cases, 3 million were very severe ALRI in young children; approximately 300,000 resulted in deaths [1••]. The annual incidence of CAP was approximately 2.7 to 10 per 1000 population [2]. CAP exhibits an infectious feature of the lung parenchyma and adjacent organs. The pathogens that cause CAP include respiratory bacteria and respiratory viruses. However, in more than 50 % of cases of CAP, no pathogen is identified [3]. The pneumonia severity index (PSI) and CURB-65 (a modification of the British Thoracic Society rule) have been developed to predict the mortality risk in CAP patients [4], and the increased acute physiology assessment and chronic health evaluation (APACHE) II score has also been found to be related to an increased mortality rate [5]. It has been shown that levels of cytokines and endotoxins in some serum and BAL fluid provide valuable prognostic information for patients with severe CAP. Increased tumor necrosis factor-alpha (TNF-α), IL-6, IL-8, and IL-10 in serum and BAL fluid indicate greater hospital mortality in severe CAP patients [6]. Endotoxin levels in the BAL fluid are higher in patients who survive CAP than in those who do not [6].

With significant tissue damage and a systemic inflammatory response, patients with severe CAP exhibit an increased

mortality rate. Severe CAP with treatment failure has been associated with an excessive inflammatory response and worse outcomes. The acute use of methylprednisolone decreased treatment failure in severe CAP patients with a high initial inflammatory response compared with a placebo [7]. However, evidence is insufficient to determine the effectiveness of corticosteroids for severe CAP. Vitamin C significantly improved the "total respiratory score" in the most severely ill patients without CAP. However, it remains unclear whether vitamin C is beneficial to patients with CAP.

Vitamin C is an enzymatic cofactor for physiological reactions including hormone production, and collagen synthesis, and it plays a key role in the immune response [8]. In the immune system, the major role of vitamin C may protect host cells against excessive oxidative stress caused by infections. Vitamin C also regulates the function of immune cells. Vitamin C increased the function of phagocytes and the proliferation of T lymphocytes related to the increased defense to various viral and bacterial infections [9].

CAP and Oxidative Stress

Oxidative stress is defined as the adverse condition resulting from an imbalance in cellular oxidants and antioxidants. Excessive oxidative stress potentially leads to cellular damage at the respiratory system [10, 11]. However, ***oxidative*** stress is also an important part of the host innate immune response to foreign pathogens. The generation of reactive oxygen species and nitrogen species is a crucial component of the host defense system for the process of pathogen clearance and modulation of immunological response [12]. On the other hand, excessive amounts of oxidative stress cause a systemic inflammatory response and tissue damage [13]. Chen Y et al. reported that severe CAP caused higher oxidative stress, DNA damage and proinflammatory mediator production. CAP patients exhibited increased ROS and DNA damage in peripheral blood mononuclear cells [14]. A macrolide is also used as a modulator of inflammatory response because of antioxidation. Macrolide use did not significantly decrease the levels of IL-6, IL-8, and IFN-γ compared to the non-macrolide use. However, macrolide use showed a trend toward decreased IL-6, IL-8, and IFN-γ levels [15]. The results imply that the degree of oxidative stress may be associated with the severity of CAP.

Because acute lung injury (ALI) with concomitant systemic release of inflammatory mediators causes an inflammation response and hypoxemia, acute respiratory distress syndrome (ARDS) is recognized as the most serious form of CAP [16]. The generation of ROS by enzymatic and nonenzymatic mechanisms, including activation of the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase enzymes, may contribute to the pathobiology of ALI/ARDS. This oxidative stress-induced ALI involves activation of the C-Jun N-terminal kinase and extracellular signal-regulated kinase pathways [17]. Recent evidence suggests that chronic alcohol ingestion induced severe oxidative stress and was associated with increasing consequences of ARDS. A history of alcohol abuse was an independent risk factor that increased the risk of developing ARDS [18]. Reactive oxygen species is also associated with the inflammatory process. Changes in thiol homestasis and redox signaling decisively contribute to amplification of the inflammatory cascade through mitogen-activated protein kinase (MAP kinase) pathways [19]. Thioredoxin-1 is a redox-active defensive protein that exhibits potent antioxidative and anti-inflammatory actions. Exogenous administration of recombinant human thioredoxin-1 significantly improved the survival rate and attenuated lung histological changes in the murine model of influenza pneumonia associated with potent antioxidative and anti-inflammatory actions [20]. Taken together, oxidative stress has a dual function. The generation of reactive oxygen species and reactive nitrogen species kills microbial pathogens directly. On the other side, excess production of reactive oxygen species contributes to inflammatory tissue injury. Severe oxidative stress may be associated with ARDS. However, antioxidative therapy was not fully elucidated to be useful for severe CAP or ARDS.

Oxidative Stress and Vitamin C

Oxidative stress has long been associated with cellular inflammation. Reactive oxygen species are regarded as second messenger that activate redox-sensitive transcription factors nuclear erythroid-2 like factor-2, nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB), O_2-responsive transcription factors, apoptosis signaling, including C-Jun N-terminal kinase pathways, p38 mitogen-activated protein kinases, extracellular signal-regulated kinase pathways, phosphatidylinositol 3-kinase (PI_3K/Akt), protein kinase C, Src family kinases, and growth factor tyrosine kinase receptor pathways [21, 22]. NADPH oxidase enzyme activation and reactive oxygen species overproduction in response to proinflammatory mediators regulated the expression of matrix metalloproteinase-9, intercellular adhesion molecule-1, vascular cell adhesion molecule-1, cyclooxygenase-2 (COX-2), and cytosolic phospholipase A2 [23]. Nrf2 is a key transcription factor that modulates cellular defense mechanisms against the key stress response [24]. Vitamin C exhibits anti-inflammatory activity through modulation of the redox-sensitive transcription factors Nrf2 and NF-kB [25]. Vitamin C compound mixtures significantly reduced ozone (O_3) induced-oxidative damage and abolished the nuclear translocation of NF-kB and Nrf2 in human keratinocytes [26]. Vitamin C inhibits p53-induced senescence by preventing ROS generation and reducing the activation of p38 mitogen-activated protein kinase [27]. Dietary vitamin C modulates monocyte intercellular adhesion molecule-1 gene expression in vivo, where regulation of gene expression represents

a key mechanism of the benefit from dietary antioxidants [28]. The above results indicated that vitamin C ameliorates oxidative stress and inflammatory response and exerts the potential to affect prevention and clinical treatment of CAP.

Innate Immunity and Vitamin C

The innate immune system of the lungs is comprised of the airway epithelial barrier, alveolar macrophages, dendritic cells, neutrophils, and natural killer cells [29]. The lung's innate immune systems play an important role in the host defense system. Vitamin C regulated the innate and adaptive immune system, influencing both cellular and humoral immune responses. Normal differentiated airway epithelium plays a key role in bacterial defense. Airway epithelium is one of the frontline defense systems against pathogens by providing both a physical barrier as well as immunological substances, including antimicrobial molecules and proinflammatory factors against a variety of pathogens [30]. Reactive oxygen species damages the integrity of the epithelial barrier by induced airway epithelium apoptosis [31]. The antioxidant effect of vitamin C provides an important defense against inhaled oxidants and limits cell damage by inflammatory-derived oxidants at the air-lung interface [32]. A portion of the bacteria likely cross a barrier of epithelium in reactive oxygen species-induced barrier dysfunction in enteric epithelium. Vitamin C quenched reactive oxygen species and prevented *Escherichia coli* internalization and translocation evoked by indomethacin [33]. However, the effect of vitamin C on bacteria internalization and translocation in airway epithelia remains unclear.

Macrophages are essential for innate immunity and the host defense in the lung and alveolar spaces [34]. Vitamin C deficiency significantly delayed resolution of inflammation and generated an exaggerated proinflammatory response to LPS stimulation in macrophages [35]. Neutrophils provide the first line of defense of the innate immune system by phagocytosing, killing, and digesting bacteria and fungi [36]. Neutrophils contain high concentrations of vitamin C and this is thought to be essential for their function [37]. Vitamin C treatment exerts an anti-apoptotic effect on peripheral blood neutrophils by reducing caspase-3 and poly ADP-ribose polymerase levels and increasing B cell lymphoma-2 (Bcl-2) levels [38]. Dendritic cells are regarded as potent antigen-presenting cells enhancing antigen-specific immune responses. The expression of CD80 and CD86 on dendritic cells is a crucial secondary signal for the generation of effector T cells. Vitamin C could enhance the activity of dendritic cells through the increasing expression of CD80, CD86, and major histocompatibility complex molecules and the activation of p38 mitogen-activated protein kinases [16]. Red ginseng and vitamin C enhanced the activation of T cell and natural killer cell by the upregulation of expression of CD25 and CD69 in peripheral blood mononuclear cells and natural killer cells, and repressing the progress of the viral lytic cycle. Vitamin C also reduced the lung inflammatory response caused by viral infection, and thereby increasing survival rates [39]. Taken together, these studies identified an important role by which vitamin C affected by regulating lung innate immune system.

The Prophylactic Use of Vitamin C and Pneumonia Risk

The confounding variables of human vitamin C intervention studies include diet, vitamin C status, genetic polymorphisms, and heavy physical stress. With high dietary intakes (>500 mg/day), the plasma vitamin C levels will reach a plateau at 70 to 80 μmol/L, and overt vitamin C deficiency is rare [9, 40]. However, surveys indicate that low vitamin C levels are not rare. Ugwa et al. reported in a prospective study of 400 pregnant women that vitamin C deficiency was found in 79.5 % of the participants [41]. The possible effect of vitamin C deficiency on the risk of respiratory infections in physically stressed people is also highly relevant [9]. There is strong evidence that several genetic alterations, including a single-nucleotide polymorphisms, gene duplications, or gene deletions, affect ascorbate levels in the human body. Human genetic variation of regulation of vitamin C homeostasis was involved in the direct transport and regulation of vitamin C concentrations by the sodium-dependent vitamin C transporter family—SLC23 (encoded by the *SLC23A1* and *SLC23A2* genes). The second category of genes is related to the antioxidant and redox activities of vitamin C and involves genetic variants affecting iron homeostasis and oxidative stress such as manganese superoxide dismutase (*SOD2*) and glucose transport proteins (*SLC2* family) [42].

Whether vitamin C is beneficial for pneumonia patients, however, remains controversial. Current evidence is too weak to advocate prophylactic using vitamin C to prevent pneumonia in the general population [43•]. Hemilä et al. identified three prophylactic trials that recorded 37 cases of CAP in 2335 people. Data showed a statistically significant (80 % or greater) reduction in pneumonia incidence because of vitamin C supplementation among elderly patients in the UK. Vitamin C was also associated with lower mortality and reduced severity in the vitamin C supplementation; however, the benefit was restricted to the most ill patients [43•]. Hunt et al. reported in a randomized double-blind trial involving vitamin C or placebo supplementation in 57 elderly patients admitted to the hospital with acute respiratory infections that patients supplemented with vitamin C had a significantly better cell response than those administered a placebo [44]. Specifically, vitamin C supplementation decreased the acute lung inflammatory response; expression of metalloprotease-12, TNF-α, and NFkB activation in animals exposed short-term to cigarette smoke [45]. Marrie et al. reported that antibiotic therapy

with nutritional supplements and vitamin C may improve outcomes in elderly pneumonia patients [46].

However, Neuman et al. reported that in 925 CAP patients, after adjusting for age, cigarette smoking, body mass index, physical activity, total energy intake, and alcohol consumption, there were no associations between dietary or total intake of any individual vitamin and risk of CAP. Vitamin C supplements did not decrease the risk of pneumonia in well-nourished women [47]. Merchant et al. reported in a prospective study conducted between 1990 and 2000 among 38,378 males, after adjustment for age, smoking, BMI, alcohol use, physical activity, diabetes, and total energy intake that there were no associations between total intakes of antioxidants or vitamins and pneumonia risk. Vitamin supplements are unlikely to reduce pneumonia risk in well-nourished, middle-aged, and older men [48]. Bjelakovic et al. assessed the beneficial and harmful effects of antioxidant supplements for the prevention of mortality in 78 randomized trials with 296,707 participants. The results found no evidence to support antioxidant supplements for primary or secondary prevention for infection [49]. These differences are probably due to the action of the genetic polymorphisms and/or heavy physical stress differences. Taken together, these results indicated that dietary intakes, genetic polymorphisms, and heavy physical stress impact vitamin C status. The ill patients with vitamin C deficiency are highly relevant to the risk of respiratory infections. Current studies also support that vitamin C supplementation significantly reduced the pneumonia incidence in patients with vitamin C deficiency or low levels. However, it is not benefitful to advocate prophylactic use of vitamin C to prevent the incidence of pneumonia in the general population.

Mechanical Ventilation and Vitamin C

Mechanical ventilation is an important therapeutic measure for severe CAP with respiratory failure. Oxidative stress is a key mechanism contributing to mechanical ventilation-induced respiratory muscle dysfunction. Blood markers of oxidative stress predict weaning failure from mechanical ventilation [50•]. Kahn et al. showed that resuscitation of burn victims with high-dose vitamin C (66 mg/kg/h) administration decreased fluid requirements and increased urine output, and these patients also suffered less respiratory impairment and reduced requirement for mechanical ventilation [51]. Howe et al. showed that antioxidant supplementation decreased the duration of mechanical ventilation, although antioxidant supplementation did not affect the all-cause mortality during hospitalization or the length of stay in the intensive care unit or hospital. Administration of antioxidants was a safe and effective intervention that decreased the duration of mechanical ventilation in critically ill adults [52]. Nathens et al. found that days of mechanical ventilation were significantly reduced in the antioxidant administration. Patients with antioxidant supplementation also required a shorter duration of mechanical ventilation [53]. These findings suggest that antioxidant supplementation may reduce the respiratory injury following mechanical ventilation in ICU patients.

Verona et al. showed that mechanical ventilation in weaning failure patients had very low levels of vitamin C. Weaning failure patients were less able to obtain vitamin C from plasma because of the downregulation of SLC23 family of sodium-dependent vitamin C transporters in the diaphragm. The lack of transport of vitamin C from plasma into muscle could result in weakness of the diaphragm [50•, 54]. We revealed that severe CAP exhibited significantly increased oxidative stress and proinflammatory mediators (such as TNF-α and IL-6) in the lung and peripheral blood. The production of reactive oxygen species, TNF-α, and IL-6 as well as DNA damage in the cells from severe CAP was significantly increased compared with that in non-severe CAP. Vitamin C also reduced the reactive oxygen species, DNA damage, and TNF-α production in lipopolysaccharide-stimulated macrophages [14]. Thus, administration of antioxidants including vitamin C is effective intervention that decreases the duration of mechanical ventilation in severe CAP patients with respiratory failure.

Conclusions and Future Challenges

CAP is one of the most common causes of morbidity and mortality. Severe CAP with treatment failure was associated with excessive inflammatory response and oxidative stress. The degree of oxidative stress may be associated with the severity of CAP. ARDS is caused by acute lung injury with concomitant systemic release of inflammatory mediators causing inflammation and hypoxemia. Oxidative stress may contribute to the pathobiology of ALI/ARDS. However, current evidence is too insufficient to determine the effectiveness of antioxidative therapy for severe CAP.

Vitamin C is an enzymatic cofactor for physiological reactions, protecting host against oxidative stress. Vitamin C regulates lung innate immune system and affects host defense. Vitamin C affects the function of airway epithelial barrier, and enhances the activity of neutrophils, and natural killer cells. However, the effect of vitamin C on bacteria internalization and translocation in airway epithelial needs to be futurely studied. Vitamin C status is associated with genetic polymorphisms, heavy physical stress, and diet.

The SLC23 family of sodium-dependent vitamin C transporters encoded by *SLC23A1* and *SLC23A2* are genetic alterations that affect vitamin C levels in the human body. The genetic variation of manganese superoxide dismutase and *SLC2* family impact antioxidant and redox activities of vitamin C. Pregnant women and ill patients often exhibit vitamin C deficiency, which are highly relevant to the risk of respiratory infections. Vitamin C supplementation decrease pneumonia

incidence in patients with vitamin C deficiency or low vitamin C levels. However, it is not beneficial to prescribe prophylactic vitamin C in order to prevent the incidence of CAP in a well-nourished population or patients. Oxidative stress is a key mechanism contributing to mechanical ventilation-induced respiratory muscle dysfunction. Blood markers of oxidative stress predict weaning failure from mechanical ventilation. Administration of antioxidants including vitamin C may have some effects on alleviation of mechanical ventilation-associated side effects in severe CAP with respiratory failure. However, clinical trials need to be performed to warrant further consideration of the effect of vitamin C on mechanical ventilation-induced respiratory muscle dysfunction.

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Compliance with Ethical Standards

Conflict of Interest Yin Li & Guoping Li declare no conflicts of interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the author.

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