Special Article

Low zinc status: a new risk factor for pneumonia in the elderly?

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Low zinc status may be a risk factor for pneumonia in the elderly. This special article reviews the magnitude of the problem of pneumonia (its prevalence, morbidity, and mortality) in the elderly, pneumonia's etiology, and the dysregulation of the immune system associated with increasing age. In addition, recent evidence from the literature is presented demonstrating that low zinc status (commonly reported in the elderly) impairs immune function, decreases resistance to pathogens, and is associated with increased incidence and duration of pneumonia, increased use and duration of antimicrobial treatment, and increased overall mortality in the elderly. Inadequate stores of zinc might, therefore, be a risk factor for pneumonia in the elderly. Randomized, double-blind, controlled studies are needed to determine the efficacy of zinc supplementation as a potential low-cost intervention to reduce morbidity and mortality due to pneumonia in this vulnerable population.

INTRODUCTION

Is low zinc status a risk factor for pneumonia in the elderly? This article reviews the magnitude of the problem of pneumonia (its prevalence, morbidity, and mortality) in the elderly, especially those in nursing homes; the etiology of pneumonia; and dysregulation of the immune system associated with older age along with its implications for pneumonia. In addition, the role of zinc in immune response is discussed, along with the impact of low zinc status on increased morbidity and mortality due to pneumonia and on all-cause mortality in the elderly.

PNEUMONIA IN THE ELDERLY: PREVALENCE, MORBIDITY, AND MORTALITY

Pneumonia is a major public health problem in the elderly in general[1] and in nursing home (NH) residents in particular.[2] The elderly have higher rates of pneumonia-associated morbidity and mortality; in fact, pneumonia is one of the top five leading causes of death among older adults in the United States.[3–5] Recovery from pneumonia takes longer in the elderly, and associated complications and mortality are more frequent than in younger adults.[4,6] Pneumonia is one of the most common causes of hospitalization and decreased activities of daily living (ADL) among the elderly.[7,8] Recent data indicate that both the incidence of pneumonia and its associated mortality are rising in this group.[9] The cost associated with hospitalization due to community-acquired pneumonia (CAP) including NH residents was reported in 2002 to be $4.4 billion[2]; these costs were significantly greater for those admitted from an NH.

Infection is a major reason behind the transfer of NH residents to acute-care hospitals and pneumonia is the leading cause of infection requiring hospitalization.[10–12]

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Pneumonia-related hospitalization rates for NH residents are nearly 30 times higher than those for independently living elderly.[13] Nine to 51% of patients acquiring pneumonia in NHs are reportedly transferred to hospital.[14–18] Death rates from pneumonia in NH residents may reach as high as 57%.[4] Kaplan et al.[19] reported that among elderly persons admitted to hospital, the incidence of death from pneumonia up to 1 year after hospitalization is twice that among the elderly admitted due to other causes. The difference in death rates between pneumonia and other causes could not be attributed to differences in underlying diseases. The cost of treatment in the NH for pneumonia is $480/case, while the cost in the hospital exceeds $7000/case.[20] Given that there are currently 1.6 million NH residents in the USA and the average incidence of pneumonia among them is 0.45 per person per year, this translates into millions of dollars each year in costs associated with pneumonia therapy.

ETIOLOGY OF PNEUMONIA

A wide range of different bacterial and viral pathogens are responsible for CAP in the elderly as well as NH-acquired pneumonia (NHP) in the United States. Foremost among them is *Streptococcus pneumoniae,* which accounts for up to half of all cases.[19] Other commonly encountered bacterial pathogens include *Staphylococcus aureus*, *Haemophilus influenzae*, *Chlamydia pneumoniae*, *Moraxella catarrhalis*, *Legionella pneumophila*, *Mycoplasma pneumoniae*, and gram-negative rods, such as *Klebsiella pneumoniae* and *Escherichia coli*.[5,13] During recent years, the role of viral pathogens in the etiology of acute lower respiratory tract infections (ALRIs) in the institutionalized and non-institutionalized elderly has been described with increasing frequency.[21] While influenza is well recognized as a cause of viral pneumonia in the aged, several studies in recent years have demonstrated the importance of parainfluenza virus (PIV), respiratory syncytial virus (RSV), adenovirus, and human metapneumovirus (hMPV).[22–25] Marrie et al.[26] attributed a viral cause to 11 of 74 patients with NHP and identified etiologic agents including influenza A and B, cytomegalovirus, and PIV. The viruses PIV, hMPV, and coronavirus 229E have also been reported in 33 long-term care facilities in Boston during a 3-year period.[27]

AGE-ASSOCIATED DYSREGULATION OF THE IMMUNE SYSTEM: IMPLICATIONS FOR PNEUMONIA

Many factors such as the presence of certain comorbid medical conditions (e.g., chronic obstructive pulmonary disease), use of certain drugs, changes in physiochemical characteristics of the non-specific host defense system (such as cilia and mucus of the respiratory tract), malnutrition, and mechanical devices contribute to an increased incidence of pneumonia in the elderly. However, an important predisposing factor to the increased incidence of infections is the well-described age-associated decline in immune responsiveness. Changes in immune response not only decrease resistance to pathogens, they also contribute to increased morbidity and mortality due to infections. Adequate functioning of the immune system becomes critical in determining the outcome of infections among elderly persons already compromised by the presence of disease and other physiological changes.

Considerable evidence indicates that aging is associated with impaired regulation of the immune system.[28–32] This decline in immune function contributes to the increased incidence of infectious, inflammatory, and neoplastic diseases observed in elderly subjects, as well as their prolonged post-illness recovery periods. Prospective studies indicate a higher incidence of morbidity and mortality in elderly subjects with low delayed-type hypersensitivity (DTH) responses, an in vivo measure of cell-mediated immune response.[33–37]

Different cells of the immune system contribute to the impaired immunity associated with old age, but T cells have been shown to be the major contributor.[38–40] In vivo, T cell-dependent functions, such as DTH,[35,41] resistance to viral and bacterial challenge,[39] and response to T cell-dependent vaccines,[31,42] have been shown to be depressed with age. In vitro, the proliferative responses of lymphocytes to phytohemagglutinin (PHA), concanavalin A (Con A), and anti-CD3 (T cell receptor) have been shown to be depressed with age.[40,43–46] Antigen- and mitogen-stimulated interleukin-2 (IL-2) accumulation declines with age and contributes to the T cell-mediated defects observed with aging.[45,47–53]

The observed alterations in T cell function have been attributed to intrinsic changes in the T cells themselves and include the following: shifts in the distribution of functionally distinct T cell subsets,[54] increases in the accumulation of memory T cells and decreases in naïve T cells,[55,56] diminished ability of naïve cells to produce IL-2 and progress through cell cycle division,[53] changes in the efficiency of early signal transduction events,[30,45,57–60] and the ability of T cells to produce and respond to IL-2 (T cell growth factor) and to express the IL-2 receptor,[45,47–53,61] as well as increases in prostaglandin E2 (PGE2) production.[41,62–64]

Reports on the age-associated changes in the production of other cytokines are less consistent. For example, decreases, increases, or no change in the production of IL-6, tumor necrosis factor-α (TNF-α), IL-1, and interferon-γ (IFN-γ) have been noted.[65–73] Looney et al.[74] showed that peripheral blood mononuclear cells (PBMC) from elderly subjects produced significantly less IFN-γ

compared to young subjects when stimulated with autologous dendritic cells (DC) infected with RSV, suggesting that aging may be associated with a defect in the T cell response to RSV. Humoral response to RSV tested in different adult age groups have shown that older and frail elderly adults have a lower neutralizing antibody titer than young adults and that neutralizing antibody titer declines with age.[75–77] These findings suggest potential mechanisms for the increased morbidity observed with RSV infection in the elderly.

The ability of antigen presenting cells [macrophages (Mϕ) and DC] to process and present antigen to T cells is, for the most part, maintained in older individuals.[78] Innate immunity, which consists of phagocytic cells and natural killer (NK) cells, continues to function reasonably well.[79] Most studies indicate that the chemotaxis, adherence, and phagocytic ability of monocytes, Mϕ, and polymorphonuclear cells (PMNs) are not affected by aging,[38] although a decrease in the respiratory burst of monocytes, PMN production of reactive oxygen species, and chemotaxis have been reported in elderly subjects compared to young subjects.[80]

ZINC, IMMUNE RESPONSE, AND PNEUMONIA

Zinc, in addition to being a cofactor to more than 300 enzymes,[81,82] is essential for membrane integrity, DNA synthesis, and cell proliferation, and thus is needed for all highly proliferating cells, especially the immune cells.[83] Zinc has been shown to play an important role in the regulation of the immune response, particularly T cell-mediated function.[82,84,85] Similar to changes observed in the immune response of the elderly, zinc deficiency is associated with thymus involution and reductions in lymphocyte proliferation, DTH, and antibody response to vaccines.[86] Zinc deficiency is also associated with reductions in the ratio of naïve to memory CD4 T cells and Th1/Th2 ratios, as indicated by lower IL-2 and IFN-γ production.[86,87] Reports on the effect of zinc on other cells of the innate immune system are less consistent. Decreases,[88,89] increases, or no changes in Mϕ and PMN functions have been reported due to changes in zinc status.[83,90–93] Like the elderly, zinc-deficient subjects have greater susceptibility to a variety of pathogens.[94]

Several investigators have reported low zinc status or decreased zinc intake in elderly subjects.[95–97] Furthermore, low zinc status in the elderly contributes to age-associated dysregulation of the immune response[98,99] and zinc supplementation has been shown to improve T cell function in the elderly.[95,99–102] Thus, zinc deficiency is indicated as a risk factor for immune deficiency and susceptibility to infection in the elderly.[99,103,104] Zinc supplementation may therefore play an important role in the prevention of infectious diseases in this group.[95,98,101,104] Various studies on zinc supplementation in the elderly have observed increased circulating zinc concentrations[100,101] as well as enhanced immune status, including improved cell-mediated immune response, IL-2 production, and increased response to DTH.[99,102,105]

In a randomized, double-blind, placebo-controlled clinical trial ($n = 81$), institutionalized elderly (>65 years) had a significant decrease in the mean number of respiratory infections during a 2-year period of supplementation with micronutrients containing 20 mg of zinc and 100 μg of selenium (as zinc sulfate and selenium sulfide, respectively), but not vitamins.[106] In another, larger ($n = 725$), randomized, double-blind, placebo-controlled intervention study, low-dose zinc and selenium supplementation (20 mg as zinc sulfate and 100 μg as selenium sulfide) significantly increased the humoral response in institutionalized elderly subjects (aged 65–103 years) after vaccination.[107] The number of subjects without respiratory infections during the study period was also found to be higher in the group that received trace elements over a 2-year period.[107] While these studies suggest zinc may have a protective effect against respiratory tract infections, contributions from other nutrients in the administered mixture cannot be ruled out. A recent study by Prasad et al.[108] showed that supplementation with 45 mg/day of elemental zinc in the gluconate form for 12 months in a small number (24–25/group) of elderly (aged 55–87 years) subjects significantly reduced the incidence of all infections, including respiratory infections. The effect on pneumonia could not be evaluated due to the low incidence of infections. The authors concluded that while these results are encouraging, they need to be repeated with a larger number of participants. The decreased incidence of infection in subjects receiving zinc supplementation was suggested to be due to improvements in T cell-mediated function, as shown by an increase in IL-2 mRNA levels. In addition, in this study, zinc supplementation was associated with decreased production of the pro-inflammatory cytokine, TNF-α, and DNA and lipid oxidation.

In an observational study, we recently showed that 29% of NH residents (≥65 years) had low serum zinc levels (<70 μg/dL) despite supplementation with 7 mg/day of zinc (in the sulfate form) over a period of 1 year.[109] All-cause mortality was 39% lower (RR, 0.61; 95% CI, 0.37–1) in those with normal (≥70 μg/dL) versus low (<70 μg/dL) preintervention or baseline serum zinc concentrations ($P = 0.049$) (Table 1). Controlling for comorbidities, other risk factors for pneumonia, and other variables found to be significantly different between those with low and normal baseline serum zinc concentrations did not materially change the statistical significance of the difference observed in the model. Our findings suggest zinc may play a crucial role in influencing all-cause mortality in the elderly. Similarly, the risk of mortality was

Table 1 **Pneumonia, antibiotic use, and overall mortality by serum zinc concentration.**

Outcome measures	Serum zinc group*		Rate ratio or mean difference (95% CI)†	*P* value
	≥70 μg/dL (*n* = 310)	<70 μg/dL (*n* = 110)		
Incidence of pneumonia (no. per person-year)	0.25	0.46	0.52 (0.36, 0.76)	<0.001
Duration of pneumonia (days per person-year)	3.19	6.82	−3.9 (−6.2,−1.6)	<0.001
Antibiotic prescriptions for pneumonia (no. per person-year)	0.26	0.48	0.52 (0.36, 0.75)	<0.001
Duration of antibiotic use for pneumonia (days per person-year)	2.50	4.85	−2.6 (−4.4,−0.9)	0.004
Overall deaths (no. per person-year)‡	0.12	0.19	0.61 (0.37, 1.00)	0.049

* Crude values: data for overall deaths analyzed using baseline serum zinc levels (*n* = 379 for ≥70 μg/dL serum zinc group and *n* = 174 for <70 μg/dL serum zinc group); all other data were analyzed using final serum zinc levels.

† Poisson regression analyses were used for incidence of pneumonia and number of antibiotic prescriptions. Least squares regression analyses were used for duration of pneumonia and of antibiotic use. All analyses controlled for treatment [supplementation with 200 IU/day vitamin E or not (placebo) over a period of 1 year; both vitamin E and placebo groups also received a capsule that contained 50% of the recommended dietary allowance for essential micronutrients, including 7 mg/day of zinc (in the sulfate form)], age, sex, chronic obstructive lung disease, current smoking, diabetes mellitus, year of enrollment (1998–2000) and baseline and change in BMI between baseline and follow-up; additional controlling for coronary artery disease and, in separate models, baseline serum albumin and change in serum albumin concentrations between baseline and follow-up, did not affect the observed associations. *P*-values derived from Poisson and least squares regression analyses.

‡ Cox proportional hazard regression analysis was used for mortality data. Analyses controlled for treatment (see above), age, sex, chronic obstructive lung disease, current smoking, diabetes mellitus, year of enrollment (1998–2000), and baseline BMI; additional controlling for coronary artery disease and, in separate models, baseline serum albumin concentrations, did not affect the observed associations. *P*-value derived from Cox proportional hazard regression analysis.

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reduced by 27% in participants (aged 55–81 years) in the Age-Related Eye-Disease Study (AREDS) who received high-dose zinc (80 mg/day of zinc oxide) during a median follow-up period of 6.5 years (RR, 0.73; 95% CI, 0.61–0.89).[110] However, the authors also noted increased hospital admissions due to genitourinary complications among those who received the high-dose zinc.[111]

In our observational study, subjects with normal post-intervention or final serum zinc concentrations had a lower incidence of pneumonia, reduced total antibiotic use (by almost 50%), and shorter duration of pneumonia and antibiotic use (by 3.9 and 2.6 days, respectively) (all *P*-values ≤ 0.004) relative to those with low final zinc concentrations (Table 1).[109] Controlling for known pneumonia risk factors and other variables found to be significantly different between those with low and normal final serum zinc concentrations such as age, percent lymphocyte, serum albumin concentration, coronary artery disease,[1,112,113] or statin use[114] in a multiple regression analyses model did not materially change the statistical significance of the differences observed.

In that study, we were not able to show significant differences in susceptibility to pneumonia using pre-intervention or baseline serum zinc concentrations as a measure of zinc status. It is likely that the higher risk of death among subjects with low baseline zinc concentrations or due to loss of subjects from serious illnesses and/or hospitalizations may have attenuated these findings. Additionally, the baseline zinc concentrations may not reflect zinc status during much of the study period because all study participants, i.e., those in both the treatment (200 IU/day vitamin E) or placebo (4 IU/day vitamin E) groups, were provided with half of the RDA supplement that included, as mentioned above, 7 mg/day of zinc (as zinc sulfate). The effects observed were specific to zinc, but not with other micronutrients. Additionally, the lower incidence of pneumonia and associated morbidity observed in subjects with normal final zinc concentrations compared to those with low final zinc concentrations were not due to differences between the two groups in changes in weight, BMI, or other micronutrient levels[115] during the study period. The low final serum zinc levels were also not due to higher incidence of pneumonia in the last few months of the study, nor to higher C-reactive protein (CRP) or lower albumin levels.

In some of the studies performed to date on the role of supplemental zinc on immune parameters and infections in the elderly, other micronutrients were given in addition to zinc. While all of the improvements in immune response and infections in these studies cannot be attributed to zinc alone, a number of studies have been done in children and the elderly that have clearly demonstrated the beneficial impact of supplementation with zinc alone on immune function and the prevention of infections.[102,105,108,116–118]

In a previous study, we detected several viruses in 157 NH residents in the Boston area.[27] These viruses were detected with significantly higher frequency in those with ALRIs, including pneumonia. Our data indicate that multiple viral pathogens circulate in NHs and are likely

associated with clinically significant illnesses. Furthermore, significantly more RSV infections [11% versus 5% ($P = 0.04$)] were noted in those with low zinc levels (Falsey et al. unpublished data). A similar trend was noted for PIV infections, although it did not reach statistical significance.

CONCLUSION

Results from our observational study,[109] in addition to findings by other studies described above, suggest that inadequate stores of zinc might be a risk factor for pneumonia in the elderly. Elderly persons with low serum zinc concentrations might therefore benefit from zinc supplementation. Such a measure has the potential to reduce not only the number and duration of pneumonia episodes and the total amount and duration of antibiotic use due to pneumonia, but also all-cause mortality in the elderly. Based on our careful review of the literature and given the upper safe limit of zinc, a dose of 30 mg elemental zinc per day might be adequate to improve immune function and to reduce the risk of infections. However, it needs to be emphasized that in order to provide conclusive evidence to support this recommendation, and to substantiate the findings described above, randomized, double-blind, controlled studies, with adequate numbers of participants, are needed to determine the efficacy of zinc supplementation as a potential low-cost intervention to reduce morbidity and mortality due to pneumonia in this vulnerable population. Such studies have the potential to significantly improve the health and quality of life of the elderly, particularly those residing in NHs, leading to healthcare savings on the order of millions of dollars.

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Declaration of interest. The authors have no relevant interests to declare.

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