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A case control study on role of zinc levels in acute lower respiratory infections

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Abstract
Pediatric respiratory disease remains an important cause of morbidity in both the developing and the developed world. It has become the most common reason parents cite for taking their children to see the general practitioner, and nutritional factors are a major reasons for ALRI.
Objective: Acute respiratory infection is a leading cause of morbidity and mortality in fewer than five children worldwide especially in developing countries. Hence, the present study was undertaken to identify the serum zinc level in children's hospitalized with acute lower respiratory tract infections (ALRI) in children aged 6 months to 5 yr.
Methods: 100 cases fulfilling WHO criteria for pneumonia, in the age group 6 months to 5 yr were interrogated for potential nutritional risk factors as per a predesigned proforma and serum zinc level was measured. 100 healthy control children in the same age group were also interrogated and zinc level measured.
Results: Significant low serum zinc level (p value <0.05 in all) were identified. Socio demographic factors like low socioeconomic status and partial immunized status were found to be significant.
Conclusion: The present study has identified low levels of zinc in ALRI children's and we focus on role of zinc in the treatment of pneumonia.

Keywords: respiratory infection, zinc, childrens.

Introduction
Zinc is an essential trace element important for almost all biological systems. Zinc nutritive is likely to be suboptimal in many children of developing countries and may contribute to their impaired growth, increased susceptibility to infections and possibly to the high mortality. A large proportion of childhood deaths in developing countries are caused by diarrhea and pneumonia. Impaired zinc nutritive seems to play a role in the increased incidence and severity of these infections [1, 2].
Acute lower respiratory infections (ALRI) predominantly pneumonia cause approximately4 million deaths every year, accounting for one-third of all childhood deaths in developing countries [1]. Various factors have been associated with acute respiratory infections (ARI) in general and pneumonia in particular. These include, among others, nutritional status [2, 3, 4], family characteristics [5] and environmental exposures [7, 8]. Most of environmental risk factors require multispectral coordination for modification. In contrast, some of the childhood risk factors can be modified by simple interventions like vitamin A or zinc supplementation [13]. Recent works have provided conflicting [9, 10, 11] evidence on the role of zinc against ALRI. The study hypothesis was that there is no difference in blood zinc levels in cases of severe pneumonia as compared to controls.
The primary objective of this study was to compare blood zinc levels in cases of severe pneumonia with age, sex and nutritional status matched controls was taken. Secondary objectives were to assess antimicrobial resistance in nasopharyngeal isolates of *S. pneumoniae* and *H. influenzae* and to assess the association of use of biomass fuels with severe pneumonia.

Subject and Methods
Study design
This was a hospital based case control study conducted in Department of Pediatrics Govt Medical College, Nalgonda, and Telangana, India between August 2018 to May 2019.

Included were children between ages of 6 months to 5 years, admitted in the indoor pediatric ward and satisfying the World Health Organization (WHO) case definition of severe pneumonia [14, 15]. Healthy children attending pediatric outdoor for immunization were controls. Informed and written consent of the parents of cases and controls was taken. Excluded were children less than 6 months or more than 5 years, with an associated clinical diagnosis of diarrhea, allergic diseases or asthma, or known zinc supplementation and documented parenteral antibiotic intake prior to indoor admission for current illness.

Sample size

100 cases of severe pneumonia and 100 sex, age and nutritional status matched controls were taken. Age was matched within 6 months. For matching nutritional status weight for height "Z" score were used. This sample size was adequate to assess a difference of 100 µg/dL in mean of blood zinc level in cases and controls with a power of 0.8 and an alpha error of 0.05 with a standard deviation.

Variables for data collection and definitions

Data was collected on age, sex, anthro- pometry, family characteristics, environ-mental exposures and immunization status. Patients were examined clinically. In cases, data on investigations ordered by the treating physician was abstracted. Record of the treatment given and outcome of the disease was also maintained.

Zinc estimation

For this 2 mL of whole blood was collected using 22 gauge steel needle in preheparized Eppendoff's tube through Venepuncture using aseptic precautions. It was sent to the Industrial Toxicology Research Center, Lucknow for analysis. Samples were stored at –20ºC, 1 mL of blood was mixed with 5 mL of deionized water, glass beads and 2 mL of 1:1 mixture of concentrated HN03 and HCIO. Samples were digested at 120-150ºC in a fuming chamber over hot plate for approximately 2 hours, until a clear solution was obtained which was re-diluted to 5 mL with de-ionized water [16]. A sample blank was always prepared with each set of samples in order to control for possible contamination by external zinc. Estimation of zinc levels was done by atomic abosorption spectrophotometry [16].

Results

There were 100 cases, each of severe pneumonia and age, sex and nutritional status matched controls. Seventy four percent of cases and controls were 12 months of age and 26% in each group were between 12 months to 5 years. There were 70% males in cases and controls. Among cases and controls 76% were adequately nourished while 38% were malnourished. Mean weight was 6.06 kg ± 2.54 and 6.18 kg ± 2.25 in cases and controls, respectively (p = 0.63). Mean height was 62.14 cm ± 10.53 and 64.6 cm ± 9.33 in cases and controls, respectively (p = 0.22). Use of biomass fuels emerged as a significant risk factor (Odd's ratio = 1.67; 95% CI: 2.19 - 4.95, p = 0.057) for cases of severe pneumonia. Immunization status, family type, availability of separate cooking space, maternal education and smoking status of father was not significantly associated with case control status (Table I).

Fever and difficulty in breathing (*pasli chalna)* were the most common complaints found in 86% and 90% of cases respectively. All cases had intercostals retractions and increased respiratory rate. Mean respiratory rate, in cases, was 83.32 ± 16.38 per minute (range 70-190). 10% had cyanosis. While duration of symptoms among cases from rural areas was more by 2-3 days when compared to those from urban areas, the differences were not statistically significant (data not was not showed). Mean blood zinc levels among cases and controls by place of residence and nutritional status is given in Table II.

Discussion

Childhood pneumonia clearly represents one of the most common infective illnesses in developing countries and is of great importance as a cause of preventable mortality in children. To attack this global problem, WHO shaped strategy for early diagnosis and effective case management that had remarkable impact on mortality due to childhood pneumonia in developing countries? Even after these measures the burden caused by childhood pneumonia in terms of both mortality and morbidity is very high. It is necessary to identify other causes which contribute to the severity of pneumonia. Influence of demographic, socioeconomic and nutritional factors has been a matter of debate for quite few years. Among the nutritional factors, vitamin A deficiency, anaemia, rickets, and zinc level is considered important. Role of zinc in immunity is known to everyone.

In the present study we found lower blood zinc level of cases when compared to age, sex and nutritional status matched controls. One explanation for lower zinc level in severe pneumonia can be pre-existing zinc deficiency, making the child susceptible to pneumonia due to impaired immunity [10]. In addition, respiratory tract infections are also known to result in lower zinc levels [14]. A decline in plasma zinc concentration has been reported after a broad range of febrile illnesses [10]. It has also been suggested that lowered zinc level is mediated by interleukins and tumor necrosis factor alpha (TNFa) and is a part of predictable set of metabolic reactions to infection or tissue injury known as Acute phase reaction [12]. Use of biomass fuels (coal, wood, dung and kerosene) was significantly associated with severe pneumonia. (Tables I & II). Previous studies have also associated use of biomass fuels with respiratory tract infections [11, 12]. This was a hospital based case-control study. We have not used radiological confirmation as an inclusion criteria for cases as this has not been recommended by the WHO and national ARI control programs. We did not perform blood or lung aspirate cultures to confirm invasive bacterial isolates. We conclude that cases of severe pneumonia have a significantly lower blood zinc level as compared to age, sex and nutritional status matched controls. Role of zinc in the treatment of severe pneumonia should be investigated. Use of biomass fuels must be phased out. Incorporation of vaccination against *H. influenzae* in national ARI program can be considered. Since a high resistance to cotrimoxazole has been found in *S. pneumoniae* and *H. influenzae* in the present study, a surveillance system should be instituted to monitor changes in antimicrobial resistance with time and the pattern of bacterial isolates from the community [17].

Table 1: Blood Zinc levels

Blood Zinc levels	Cases		Control		
	N0	Mean Value	No	Mean value	P value
Overall	100	276±245.63	100	438± 348.0	0.0002
Urban subjects	60	337±249.77	70	611±333.35	0.17
Rural subjects	40	276± 151.06	35	502±232.25	0.0001
Malnourished subjects	30	308± 176.03	35	355±184.67	0.02
Adequetly nourished subjects	75	411± 256.03	65	681±252.69	0.06

Table 2: Family characteristics and Environmental conditions of Cases and controls

Characrestics	Cases(N=100)		Control (N=100)		Odd ratio	P value
	N0	% Cases	NO	% Cases		
Un immunized	23	23	17	17	1.58	0.40
Urban Subjects	63	63	70	70	0.79	0.4
Joint Family	60	60	42	42	0.53	0.39
Separate cooking space	42	42	36	36	1.20	0.78
Biomas fuel	65	65	32	32	1.67	0.037
Mother uneducated	43	43	33	33	1.5	0.57
Father nonsmoking	85	85	76	76	1.58	0.64

Conclusion

The present study identified many nutritional risk factors for ALRI. The significant nutritional risk factors were malnutrition, anaemia and low serum zinc level. Socio demographic factors like partial immunization status and SES which were taken into study didn't have any significant association with ALRI. The interesting fact is nutritional factors which were found to be significant in this study are actually either preventable or curable. The above risk factors should be tackled with effective health education of the community and appropriate initiatives should be taken by the government which can lead to a healthy community and a healthy nation as a whole. Limitations of the study should be considered while interpreting the results. The total number of cases taken for the study, ie which satisfied the WHO criteria for ALRI is less compared to the incidence of ALRI. Moreover zinc values were estimated only at the time of admission. A follow up estimation of zinc level at the time of discharge or after 2 weeks of infection would have given more detailed results. A randomized controlled trial study with zinc supplementation would have been an ideal study method.

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Conflict of Interest

None

Source of finding

Nil

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