Effect of zinc supplementation on ARI in children with cystic fibrosis & Pneumonia

Dr Seema Mishra, HOD ,Deptt of Clinical Nutrition,
Govt Bilasa Girl's PG Autonomous College & Research Centre, Bilaspur (CG)

Abstract: Acute lower respiratory infection (ALRTI) is the leading cause of death in children below five years of age. Identification of modifiable risk factors of severe ALRTI may help in reducing the burden of disease. A hospital based case control & placebo study was undertaken to determine the effect of Zinc supplementation in ARI affected children up to five to twelve years. A case definition of severe ARI as given by World Health Organization (WHO) was used for cases. Lack of breast-feeding, upper respiratory infection in mother, upper respiratory infection in siblings, severe malnutrition, cooking fuel other than liquid petroleum gas, inappropriate immunization for age and history of LRI in the family were the significant risk factors associated with ARI. The affected children were divided in three groups ,15 demographically matched children in each group –the 1st group was intervention group ,supplemented with Zinc in the form of Zevit for about 3 months , the second group was control group and the 3rd group was placebo group .Before intervention the relevant parameters were estimated in all subjects and after intervention the parameters were analyzed and it was found that the Zn supplemented group had significant improvement in Spirometry and PEFR results also the level of lung infections was low . The blood parameters showed better corrected results after Zn supplementation.

Key words: Acute Respiratory Infections, PEFR, Mucus Plug, Spirometry, PEFR, Zevit .

Introduction: ARIs are the major cause of mortality among children aged less than 5 years especially in developing countries. Worldwide, 20% mortality among children aged less than 5 years is attributed to respiratory tract infections (predominantly pneumonia associated). If we include the neonatal pneumonia also in the pool, the burden comes around to be 35-40% mortality among children aged less than 5 years accounting for 2.04 million deaths/year. Southeast Asia stands first in number for ARI incidence, accounting for more than 80% of all incidences together with sub-Saharan African countries. In India, more than 4 lakh deaths every year are due to pneumonia accounting for 13%-16% of all deaths in the pediatric hospital admissions. Million deaths study based on the register general of India mortality statistics had reported 369,000 deaths due to pneumonia among children 1-59 months at the rate of 13.5/1000 live births. More number of deaths due to pneumonia was reported from central India. Recent estimates suggest 3.5% of the global burden of disease is caused by ARI. In developing countries, on an average every child has five episodes of ARI/year accounting for 30%-50% of the total paediatric outpatient visits and 20%-30% of the paediatric admissions. Recent community-based estimates from prospective study report 70% of the childhood morbidities among children aged less than 5 years are due to ARI. While in developing country, a child is likely to have around 0.3 episodes of pneumonia/year, in developed countries it is 0.03 episodes per child/year. On this basis, India is predicted to have over 700 million episodes of ARI and over 52 million episodes of pneumonia every year. A study from Haryana by Broor *et al*., had reported 2387, 536, and 43 episodes of acute upper respiratory infections, acute lower respiratory infections, and severe acute lower respiratory infections respectively per 1000 child years. Acute lower respiratory tract infection (ALRTI) is a leading cause of mortality in children below five years of age in the developing countries. Behrman in a review of epidemiology of ALRTI in developing countries identified low birth weight, malnutrition, vitamin A deficiency, lack of breastfeeding and passive smoking as risk factors for ALRTI. Recent studies have added other risk factors to the list including poor socioeconomic status, large family size, family history of bronchitis, advanced birth order, crowding, young age, air pollution, and the use of non-allopathic treatment in early stages of illness.

Zinc is an essential trace element required for maintaining intestinal cells, bone growth, and immune function. Children who are living in low-income settings are often undernourished and zinc deficient . Severe zinc deficiency has been associated with stunting of growth, impaired immunity, skin disorders,

learning disabilities and anorexia . Deficiencies may arise from the insufficient intake of foods containing zinc or insufficient absorption. Most foods high in zinc are of animal origin, such as meats, fish and dairy products. These foods may be more difficult to access for low-income populations. Dietary fibre and compounds called phytates, which are often found in foods such as cereals, nuts and legumes, bind to zinc and result in poor absorption. Frequent diarrhoea, that is also associated with chronic under nutrition, may further deplete body stores of zinc .

Zinc deficient children are at increased risk of restricted growth and developing diarrhoeal diseases, as well as respiratory tract infections such as acute lower respiratory tract infections . Diarrhoeal disorders and acute lower respiratory tract infections, especially pneumonia are the two most common causes of infant and child death in low-income countries. Under nutrition is considered the underlying cause of approximately half of these fatal acute lower respiratory tract infections. Pneumonia alone kills more children each year than AIDS, malaria or measles combined, with over two million deaths per year . Some research studies have suggested that zinc supplementation may reduce the number of episodes and severity of bronchiolitis and pneumonia cases in children. Zinc supplementation in combination with oral rehydration solution has already formed the basis of the WHO/UNICEF recommendation for use in the management of children with diarrhoea

Zinc is thought to help decrease susceptibility to acute lower respiratory tract infections by regulating various immune functions, including protecting the health and integrity of the respiratory cells during lung inflammation or injury. Studies of zinc supplementation for the treatment or improved management of acute lower respiratory tract infections, including pneumonia have had mixed results . A recent review and meta-analysis of existing studies, for example found that the beneficial effects of zinc supplementation have been most clearly demonstrated in south Asia, when children were given at least 70 milligrams of zinc per week. Another systematic review has demonstrated that zinc supplementation was significantly associated with reducing rates of pneumonia, and recommended supplementing zinc intake in deficient populations.

A range of supplementation doses have also been assessed, from 15 mg to 140 mg per week, with the upper range exceeding the recommended daily intake (RDI) for children of 2 mg per day for children less than one year of age and up to 7 mg per day for children between 1 to 3 years . It is important to better understand optimal supplementation doses, especially because high dosages of zinc and long-term supplementation have been shown to be associated with the inhibition of absorption of other nutrients such as copper and iron as well as poorer survival rates for children with HIV. Dietary impacts on micronutrient absorption should also be considered, as it has been suggested that the bioavailability of zinc is greater in more refined urban diets. In addition, supplementation is not the only route to decrease nutrient deficiencies that may make children more susceptible to infection. Decreasing the consumption of absorption-inhibiting foods, dietary diversification and food fortification should also be investigated as possible alternatives. The review by Lassi et al. considered preventive zinc supplementation among children 2-59 months of age .The study by Srinivasan et al. demonstrated that zinc supplementation was associated with reduced pneumonia case fatality rate. In that report, 11% of the children who had bacteraemia complicating their pneumonia died. Children who were receiving zinc supplementation also developed bacteraemia as a complication of their LRTI, but none of them died . Finally, a 2012 report on a study performed in India showed that zinc supplementation in infants 7 days to 120 days with probable serious bacterial infection decreased their risk for treatment failure .

Immuno-nutrition is a recognized scientific sub discipline interrelating different fields of Immunity and Nutrition, but despite their apparent independence, it is proved that the condition of malnutrition adversely affect on antigenically non specific host defence. Clinical and public health importance of nutritional immunology is receiving attention now. Immunity related dysfunctions that result from malnutrition is in fact nutritionally Acquired Deficiency Syndromes [NAIDA]. With increasing longevity, to maintain the health status of elderly is also a public issue. With advancing age there is increased susceptibility for many diseases, including maximally infective diseases. They include urinary tract infections, pneumonia, and skin/soft tissue infections. Aging alters both humoral and cell-mediated immunity. However cell mediated immunity is dis-proportionally affected.. Across species, immune parameters that decline include thymic tissue mass, antibody production, delayed hypersensitivity tests (DHST) and T-cell responsiveness to polyclonal activators. Immune parameters that increase include heterogeneity of immune response between individuals, monoclonal immunoglobulin

production, autoantibody production and a higher production of memory T-cells subsets with a compensatory disease in the number of native T-cells. Overall, T-cells in many elderly individuals are anergic and calcium resistant.There is an interest in the potential for micronutrient supplementation, especially Zinc to enhance immune functions and decrease the incidence of infections in all age groups. Many world wide studies found generalized micronutrient deficiency in all age groups. In many double blind, placebo controlled, randomized studies the immunological importance of Zinc was proved. The association between Zinc and immunity was first documented with the discovery of human Zn deficiency by Prasad et al. Along with the characteristic hypogonadism and dwarfism; Zn deficient person experienced increased susceptibility to infections. Later a lethal mutation to Holstein-Fresian Cattle was found responsible for the failure to both absorb Zn and to develop thymus. These immuno-deficient cattle could be treated with Zn and symptoms could be prevented. Further evidence for Zn's role in immunity came from the discovery that the inborn error in human metabolism, acrodermatitis enteropathica, was caused by defective absorption of Zn. This was prevented by only Zn supplementation. The first report of Zn deficiency with thymic atrophy and loss of T helper cell was published by Fraker et al .The affected person was other wise normal with normal food intake, with normal growth parameters, but with severe Zn deficiency, that damaged thymus and spleen. The affected spleen and thymus started reduced production of SRBC- a T- dependent antigen. Additional manifestations include disturbed serum immunoglobulin profile due to the deficiency. This specific deficiency also causes reduced antibody production. Repletion with Zn resulted in normalization of plaque response and even an elevation of the response.

Based on role of Zinc for preventing/curing ARI a Hypothesis is designed to assess the role for Zn for treating/ reducing severity of ARI in children-

Study design-The children suffering from ARI were contacted personally in various clinics, Chhattisgarh Institute of Medical Sciences and Dr Deorus Clinic , Bilaspur . Under supervision of Dr Deorus the study group was divided into three groups –

(1) Zn intervention Group-15 children

(2) Placebo Group-15 children

(3) control group-15 Children

All the studied subject are in age range of 5-12 years with demographic matched data ,specially all subjects are from low socioeconomic group and most of them are having moderate degree of malnourishment as per WHO criteria. The Zn Intervention group was given supplementation of Zn in the form of Zevit , in which Zn is present as Zinc Sulfate Monohydrate (41.1 mg in each capsule) [supplementation-2/3 RDA/week] . The control group was not given any Zn supplementation and the Placebo group was given empty capsules which were similar to the Zevit Capsules. The antibiotic treatment was same for all otherwise.

Study Duration-June 2014- December 2018

They all have had common symptoms of -

- nasal congestion,
- runny nose (rhinorrhea),
- nasal discharge (may change from clear to white to green)
- nasal breathing,
- sneezing,
- sore or scratchy throat,
- painful swallowing (odynophagia),
- cough (from laryngeal swelling and post nasal drip)

Materials & Methods- [1] Measurement of capacities of Upper Respiratory Tract- For the measurements of narrowing due to repeated infections and reduced immunity –Spirometry and Peak Flow Analysis methods [PEFR] were used in subjects. The results were compared with the healthy controls.

[2] Biochemical Testing- As it is proved fact that the resultant anorexia and hypoxia due to ARI is the cause of increased RBCs and increased Lymphocytes and Eosinophils in blood. Also serum Hemoglobin level was said to be increased due to severe hypoxia. So the biochemical testing of the above data's was done. Serum Hemoglobin gm% value was measured by Sahil's hemoglobinometer. The Serum values of Eosionophils and Lymphocytes were measured by using Neubar's chamber of Differential Counting. The WBC count of the blood samples of all the subjects are calculated by Neubauer Hemocytometer, by using WBC diluting fluid, made up of Glacial Acetic Acid-1.5 ml, 1% solution of Gentian Violet in water, distilled water up to 98 ml. A small quantity of Thymol was added to prevent mould growth.

[3] Serum C –reactive Protein – This protein was assessed by using kit of Span Diagnostics, reagent kit, Surat [code 25934] used for in vitro detection of C - reactive protein (CRP) in human sera in auto-analyser by agglutination method.50 micro ml serum was mixed with 1 ml reagent, clumping was indication of positive test. This parameter is indicator of organ/tissue damage due to any reason.

[4] Also ESR was estimated as it is also bio-indicator of infection by using disposable ESR tube.

[3] Spirometry Analysis- For the measurement of pulmonary function tests Spirometry was done. The analysis was done on some selected samples-42 only. Through Spirometry –FVC (Forced Vital Capacity) and FEV (Forced Expiratory Volume in one second) were measured.

FEV_1/ FVC (80-120 %) : Normal

FEV_1/ FVC (60-80 %) : Mild Obstruction

FEV_1/ FVC (40-59 %) : Moderate Obstruction

FEV_1/ FVC (< 40 %) : Severe Obstruction

[4] Peak Expiratory Flow Rate (PEFR) -It was measured by Peak Flow-meter. PEFR is the maximum flow rate attainable anytime during FEV from the position of maximum inspiration. It was recorded Liters /Second. The patient had to take a deep breath and then blow the air in a peak flow meter as fast as possible. Probably the most important innovation to aid in diagnosis and subsequent treatment of ARI is the PEFR.

The Calculation was based on the following formula-

Daily Variability =

$$\frac{\text{PEFR Evening - PEFR Morning}}{{}^1/_2\ (\text{PEFR Evening + PEFR Morning})} \times 100$$

1] If variability is > 20% for at least two weeks –ARI is present.

2] If variability is > 40% ARI condition is severe.

3] If variability is > 60% it's an urgent condition.

Apart from these observations ,the anterior-posterior diameter of the patients were also taken , because the diameter is increased in ARI patients.

[5] Pulse Measurement-The pulse is measured because "Pulsus Paradoxus" is common symptom in an asthmatic patient.

[6] Personal Interview- The case history related to Upper Respiratory Tract Disorders was collected by interview method and also the information related to top feed of the affected child patient's been collected.

The subjects (patients) were undergone tests of Spirometry, for the measurement of Vital Capacity (VC) of the patients. The ratio between FVC (Forced Vital Capacity) and FEV (Forced Expiratory Volume in one second) are taken for grading degree of obstruction in Asthma, during different seasons.

[7] Measurement of Vital Capacity- To assess the Respiratory capacities in all studied subjects in all groups this was measured by Doglus Bag Method.

[8] The serum Zinc status of all the selected patients was analyzed by Nitro-PAPS method developed by Akita Abe. Nitro-PAPS react with Zinc in alkaline solution to form a purple colored complex. The color absorbance was read at 575 nm in spectrophotometer. The diagnostic kit from the 'Chema' (Glaxo} company was used for estimation, the kit contained Reagent-A, which had borate buffer 370mM, pH 8.20, Salicyladoxime 12.5mM, Dimethylgloxime 1.25mM, Surfactants and preservatives. The Reagent-B contained Nitro-PAPS buffer 0-. 40ml. The standard solution was Zinc in diluted acid 200 µg/dl. This assay is linear up to 500 µg/dl. The estimations were done in local patho – lab of Dr Mehta with pathologist Mr Tamrakar.

[9] The Zinc was supplemented as 'Zavit' to the patients for about a three months , in which Zn is present as Zinc Sulfate Monohydrate (41.1 mg in each capsule) [supplementation-2/3 RDA/week]

[10] Blood tests and Mucus culture. Blood test was done not in all studied subjects. This was done in Dr Aggrawal,s Patholab Lab, Mumbai only for 6 subjects (3 from each group) and the results were collected. Blood tests helped to tell whether antibodies to a specific organism that can cause ARI are present are not and also what is the effect of supplementing Zn on the population of microbs causing ARI.

[11] Oximetry. This was done to assess the amount of Oxygen in blood as ARI causes lesser oxygenation of Blood . The effect of Zn supplementation is also assessed on this parameter. Your "Normal" SpO_2 Range. According to the Mayo Clinic, normal pulse oximeter readings usually range from 95 to 100 percent. Values under 90 percent are considered low, and indicate the need for supplemental oxygen. Normal arterial oxygen is approximately 75 to 100 millimeters of mercury (mm Hg). Values under 60 mm Hg usually indicate the need for supplemental oxygen.Normal pulse oximeter readings usually range from 95 to 100 percent. Values under 90 percent are considered low.

[12] Arterial blood gases. An arterial blood gas test can measure the levels of oxygen in a sample of blood drawn from your artery. Doctors use this test to find out whether enough oxygen is getting into your bloodstream from your lungs.

- partial pressure of oxygen (PaO2): 80–100 millimeters of mercury (mmHg)
- partial pressure of carbon dioxide: 35–45 mmHg.
- bicarbonate: 22–26 milliequivalents per liter.
- oxygen saturation: 95 percent.

[13] Computed tomography (CT) scan. A CT scan uses X-rays to produce detailed pictures of structures inside your body. It may be used in people who are not responding to their treatment.

[14] Sweat Chloride-A positive sweat chloride test indicates that it is likely that the infant or person tested has cystic fibrosis (CF).

[15] Alpha-1 antitrypsin – to determine if a person has AAT deficiency, this is strong cause and Indicator of ARI.

Observations-

The following observations were made and analyzed-

Table-1

Sr No	**Parameters**	**Initial Values**		
		Subjects (N-15)	**Controls (N-15)**	**Placebo (N-15)**
1.	RBC Count	4.9 million/cubic mm	4.89 million/cubic mm	4.94 million/cubic mm
2.	WBC Count	12.0×10^9/L	11.0×10^9/L	14.0×10^8/L
3.	Arterial O_2 level	66 mm Hg	67 mm Hg	67 mm Hg
4.	Blood Microbes Cont	+ + +	+ + +	+ + +
5.	Mucus Plug Microbial Count	+ + +	+ + +	+ + +

6.	Sweat Chlorine Amount	60 millimoles per liter	60 millimoles per liter	60 millimoles per liter
7.	Alpha 1 Anti Tripsin Count	71 mg/dl	68 mg/dl	77 mg/dl
8.	Bicarbonate Content	18–20 milliequivalents / liter.	17–21 milliequivalents / liter.	18–22 milliequivalents / liter.
9.	Hg gm % value	13.4 gm %	14.1 gm %	12.9 gm %
10.	Vital Capacity	1670 ml	1730 ml	1590 ml
11.	Pulse Rate	92	96	89
12.	Spirometry Results	50.554	52.561	55.122
13.	PEFR Results	45.007	43.223	47.089
14.	CT Results	Broncho-Contraction 28 % and spasms	Broncho-Contraction and 31% spasms	Broncho-Contraction 34 % and spasms
15.	Partial Pressure of CO2	56 mm of Hg	54 mmof Hg	58 mmohg
16.	O2 saturation %	74 %	71%	73%
17.	Serum Zn Level	34 .23 µg/dl.	36.1 µg/dl.	31.45 µg/dl.
18.	C –Reactive Protein	8.33 mg/dl	9.12 mg/dl	9.56 mg/dl
19.	ESR	22 mm/ Hour	23 mm /Hour	23mm/Hour
20.	Eosinophil Count	18 %	19 %	18 %

Table-2

Observation after Zinc Intervention for three Months -

Sr No	**Parameters**	**Values after Intervention**			**t test values**
		Subjects (N-15)	**Controls (N-15)**	**Placebo (N-15)**	
1.	RBC Count	4.1 million/cubic mm	4.89 million/cubic mm	4.94 million/cubic mm	0.00498*,**
2.	WBC Count	9.0×10^5/L	11.0×10^9/L	14.0×10^8 /L	0.1983*,**
3.	Arterial O_2 level	82 mm Hg	67 mm Hg	67 mm Hg	0.348*
4.	Blood Microbes Cont	+	+ + +	+ + +	--
5.	Mucus Plug Microbial Count	+	+ + +	+ + +	--
6.	Sweat Chlorine Amount	39 millimoles /liter	60 millimoles / liter	60 millimoles /liter	5.48*,**
7.	Alpha 1 Anti Tripsin Count	118 mg/dl	68 mg/dl	79 mg/dl	3.76*,**
8.	Bicarbonate Content	26 milli equivalents / liter.	17milli equivalents / liter.	22 milli equivalents / liter.	9.86*,**
9.	Hg gm % value	13.6 gm %	14.1 gm %	12.9 gm %	0.242*,**
10.	Vital Capacity	2026 ml	1730 ml	1590 ml	2.01*
11.	Pulse Rate	81	96	89	2.9*,**
12.	Spirometry Results	39.123	52.561	55.122	5.07*,**
13.	PEFR Results	23.178	43.223	47.089	4.445*,**
14.	CT Results	Broncho-	Broncho-Contraction	Broncho-	---

		Contraction and spasms	and spasms	Contraction and spasms	
15.	Partial Pressure of CO2	37 mm of Hg	54 mm of Hg	58 mm of Hg	6.029*,**
16.	O2 saturation %	82 %	71%	73%	2.032*,**
17.	Serum Zn Level	57 .47 µg/dl.	36.1 µg/dl.	31.45 µg/dl.	5.217*,**
18.	C –Reactive Protein	4.17 mg/dl	9.12 mg/dl	9.56 mg/dl	3.59*,**
19.	ESR	17 mm/ Hour	23 mm /Hour	23mm/Hour	5.09*,**
20.	Eosinophil Count	11 %	19 %	18 %	4.42*,**

Significant at * P<0.05 level, **P<0.01 level

Discussion- A significant difference has been observed between subjects, who received Zn supplementation than in Controls and Placebo group ,especially in parameters of the O2 saturation percentage , co2 content of blood, c-protein, Eosinophil count, ESR values, Spirometic and PEFR results showed better respiratory conditions in Zn receivers group. A significant difference is seen in Vital Capacity among all groups, maximum in Zn receivers group. A significant drop was observed in bold and mucus plug of Intervention group. As Zn is powerful anti-infective element along with it's antioxidant capacity, these results are strongly reflected in the Zn receiver group of this study.

Conclusion- Providing children younger than 12 years of age with zinc supplementation for longer than 3 months has been shown to be effective for correcting ARI as evidenced by decreasing number of WBCS, serum C-protein level, ERS values, specially sweat chlorine amount ,which is clear indicator for ARI . Also decreased level of Co2 amount in blood, increased o2 level and saturation level of Arterial blood. Decreased Eosinophil count is strongly negatively associated with increased serum level of Zn as evidenced by this study. Adjunctive zinc supplementation (with antibiotics) for treatment of pneumonia is currently not recommended. Current evidence supports zinc supplementation for prevention in developing countries where the nutritional status of children is suboptimal compared with children in developed countries. There is an additional unfinished research agenda that must also be perused without holding Zn interactions back. It is also important to unravel several unanswered questions such as interactions with Iron and multiple micronutrient deficiencies in susceptible populations, optimal delivery systems for Zinc and frequency of administrations as well as potential adverse effects . However given the overwhelming evidence of the potential benefit of Zn for treatments of at-risk children in susceptible populations, it is important to introduce this intervention in public health system as soon as possible. Taken together, such observations are promising that zinc supplementation may play a role in decreasing mortality associated with LRTIs. Large scale randomized trials across multiple populations are needed before a robust conclusion can be made.

References-_

1. Rasmussen Z, Pio A, Enarson P. Case management of childhood pneumonia in developing countries: Relevant research and current initiatives. Int J Tuber Lung Dis 2000; 4: 807-826.

2. Behrman S. Epidemiology of acute respiratory infection in children of developing countries. Rev Infect Dis 1991; (Suppl 6): S454-S462.

3. Hussey GD, Apolles P, Arendse Z, Yeates J, Robertson A, Swingler G *et al*. Respiratory syncytial virus infection in children hospitalized with acute lower respiratory tract infection. S Afr Med J 2000; 90: 509-512.

4. Banajeh SM. Outcome for children under 5 years hospitalized with severe acute lower respiratory tract infection in Yemen: A 5-year experience. J Trop Pediatr 1998; 44: 342-346.

5. Hamid M, Qazi SA, Khan MA. Clinical, nutritional and radiological features of pneumonia. J Pak Med Assoc 1996; 46: 95-99.

6. Shah N, Ramankutty V, Premila PG, Sathy N. Risk factors for severe pneumonia in children in south Kerala, a hospital based case control study. J Trop Pediatr 1994; 40: 201-206.

7. Suwanjuth S, Ruangkanchanasetr S, Chantarojanasiri T, Hotrakitya S. Risk factors associated with morbidity and mortality of pneumonia in Thai children under 5 years. Southeast Asian J Trop Med Public Health 1994; 25: 60-66.

8. Murtagh P, Cerqueiro C, Halac A, Avita M, Salomon H, Weissenbacher M. Acute lower respiratory infection in Argentanian children - A 40 month clinical and epidemiological study. Pediatr Pulmonology 1993; 16: 1-8.

9. Campbell H, Armstrong JR, Byass P. Indoor air pollution in developing countries and acute respiratory infection in children. Lancet 1989; 1: 1012.

10. Collings DA, Sithole SD, Martin KS. Indoor wood smoke pollution causing lower respira-tory disease in children. Trop Doctor 1990; 20: 151-155.

11. Deb SK. Acute respiratory disease survey in Tripura in case of children below five years of age. J Indian Med Assoc 1998; 96: 111-116.

12. Sharma S, Sethi GR, Rohtagi A, Chaudhary A, Shankar R, Bapna JS, *et al*. Indoor air quality and acute lower respiratory infection in Indian urban slums. Environ Health Perspect 1998; 106: 291-297.

13. Agrawal PB, Shendurnikar N, Shastri NJ. Host factors and pneumonia in hospitalized children. J Indian Med Assoc 1995; 93: 271-272.

14. Bruce N, Perez-Padilla R, Albalak R. Indoor air pollution in developing countries: A major environmental and public health challenge. Bull WHO 2000; 78: 1078-1092.

15. Smith KR, Sarnet JM, Romieu I, Bruce N. Indoor air pollution in developing countries and acute lower respiratory infection in children. Thorax 2000; 55: 518-532.

16. Technical Basis for WHO Recommendations on the Management of Pneumonia in Children at First Level Health Facilities. WHO/ARI/91.20 Geneva, World Health Organization, 1991.

17. Park K. Immunization schedule. Principles of epidemiology and epidemologic methods. *In:*Textbook of Preventive and Social Medicine. 14th edn. Ed. Park K, Jabalpur, Banarasidas Bhanot Publishers, 1991; pp 125-128.

18. Bun HF, Anemia. *In:* Harrisons Principles of Internal Medicine, 11th edn. Eds. Brounwald E, Isselbacher KJ, Petersdorf RG, Wilson JD, Maston JB, Fauci AS, New York, McGraw Hill Book Company, 1987; pp 262-266.

19. Rao KV, Singh D. An evaluation of the relationship between nutritional status and anthropometric measurements. Am J Clin Nutr 1970; 23: 83-93.

20. Morrow PW. Toxicological data on NO: An overview. J Toxicol Environ Health 1984; 13: 205-227.

21. Lippmann M. Effects of respiratory function and structure. Ann Rev Public Health 1989; 10: 49-67.

22. O'Brian KL, Valters ML, Selbnan J, Quinlisk H, Schwartz B, Dovell SF. Severe pneumococcal pneumonia in previously healthy children: Role of preceding influenza infection. Clin Infect Dis 2000; 30: 784-789.

==========