Journal of Medical and Surgical Practice (JMSP)
ISSN: 2664-1704
Vol. 10, No. 3, July – September, 2024

Role of Zinc Supplementation in the Recovery of Hospitalized Children with Pneumonia

Dr. Muayad salih hamza[1*], Dr. Salah Mahdi Ali[2], Dr. Ahmed Mohemed Aulawy[3]

1. M.B.Ch.B, F.I.C.M.S, Karbala Pediatric Teaching Hospital , Karbala Health Directorate, Holley Karbala, Iraq
2. M.B.Ch.B, C.A.B. Pediatric, F.I.C.M.S.-Subspecialty Endocrinology and Diabetes, Imam Hussein Center of Diabetes and Endocrinology, Karbala Health Directorate , Holy Karbala, Iraq
3. M.B.Ch.B, C.A.B. Pediatric, F.I.C.M.S.-Subspecialty Endocrinology and Diabetes, Imam Hussein Center of Diabetes and Endocrinology, Karbala Health Directorate , Holy Karbala, Iraq

* *Corresponding Author*

Original Article

Abstract

Background: *Pneumonia is a common illness in all parts of the world. It is a major cause of death among all age groups. In children, many of these deaths occur in the newborn period. More cases of pneumonia occur during the winter months than during other times of the year. Pneumonia occurs more commonly in males than females, and more often in Blacks than Caucasians. People who are hospitalized for any reason are also at high risk for pneumonia. Supplemental zinc provides therapeutic benefits in pneumonia.*

Objectives: *To evaluate the role of zinc supplementation in the recovery of hospitalized children with pneumonia*

Patients & Methods: *Randomized control study was conducted at Karbala pediatric teaching hospital during a period of 14 months included inpatient children aged 3 -60 months who presented with pneumonia. Patients were assigned into 2 groups , zinc group included 93 cases to whom zinc supplemetation was given in addition to the traditional treatment they consisted of 51 males and 42 females. The second group received the traditional treatment with no zinc supplementation as control group and they were 82 cases ; 47 males and 35 females Both groups were in good nutritional status. Zinc is given according to WHO guideline, 20mg for children above 6 months of age and 10 mg for those aged below 6 months. For all patient chest X-Ray, complete blood count (CBC) were performed and oxygen saturation and respiratory rate were measured.*

Results: *Our study showed a signifciant improvement within 1st five days of treated children with zinc, the rate of improvement was 89.2% in zinc group versus 56% in control group, (P. value<0.05). There was a good response in breast fed children of zinc group in comparism to control group, the improvement rate was (46.2% versus 34.1%) within 5 days, respectively, while in bottle feeding infant the rates were 24.7% for zinc group and 19.5% for control group. The response to zinc supplementation between male and female in the first 5 days of treatment was 90.4% and 87.8% respectively, with signifciant difference, (P>0.05).*

Conclusions: *Zinc therapy is useful in the management of hospitalized children with pneumonia that lead to decrease the duration and severity of pneumonia, the zinc is more effective in breast feeding than bottle feeding infant.*

Keywords: *Pneumonia, Hospitalization, Treatment, Zinc Supplementation*

Received : May, 2024, **Published**: July, 2024

Citation: Hamza M.S, Ali S.M, Aulawy A.M Role of Zinc Supplementation in the Recovery of Hospitalized Children with Pneumonia. JMSP 2024; 10(3): 135-48

1. INTRODUCTION

Pneumonia is a common illness in all parts of the world. It is a major cause of death among all age groups. In children, many of these deaths occur in the newborn period. The World Health Organization estimates that one in three newborn infant deaths are due to pneumonia (1). Over two million children under five die each year worldwide. WHO also estimates that up to 1 million of these (vaccine preventable) deaths are caused by the bacteria Streptococcus pneumoniae, and over 90% of these deaths take place in developing countries (2). Mortality from pneumonia generally decreases with age until late adulthood. Elderly individuals, however, are at particular risk for pneumonia and associated mortality. Because of the very high burden of disease in developing countries and because of a relatively low awareness of the disease in industrialized countries, the global health community has declared November 2 to be World Pneumonia Day, a day for concerned citizens and policy makers to take action against the disease (2,3) . More cases of pneumonia occur during the winter months than during other times of the year. Pneumonia occurs more commonly in males than females, and more often in Blacks than Caucasians due to differences in synthesizing Vitamin D from sunlight. Individuals with underlying illnesses such as cystic fibrosis, emphysema, or immune system problems are at increased risk for pneumonia. These individuals are also more likely to have repeated episodes of pneumonia. People who are hospitalized for any reason are also at high risk for pneumonia (4). The term "community-acquired pneumonia" (CAP) refers to a pneumonia in a previously healthy person who acquired the infection outside a hospital. CAP is one of the most common serious infections in children, with an incidence of 34 to 40 cases per 1,000 children in Europe and North America (5–7) . Although death from CAP is rare in industrialized countries, lower respiratory tract infection is one of the leading causes of childhood mortality in developing countries (8,9) . Group B streptococcus and gram-negative enteric bacteria are the most common pathogens in neonates (i.e., birth to 20 days) and are obtained via vertical transmission from the mother during birth. Anaerobic organisms may be acquired from chorioamnionitis. Pneumonia in infants aged three weeks to three months is most often bacterial; Streptococcus pneumoniae is the most common pathogen. In infants older than four months and in preschool-aged children, viruses are the most frequent cause of CAP; respiratory syncytial virus (RSV) is the most common. Viral pneumonia occurs more often in

the fall and winter than in the spring and summer. Bacterial infections can occur at any time of the year in preschool- and school-aged children and in adolescents. S. pneumoniae is the most common bacterial cause of CAP after the neonatal period. Less common bacterial etiologies include Haemophilus influenzae type B, Moraxella catarrhalis, and Staphylococcus aureus. Mycoplasma pneumoniae and Chlamydia pneumoniae frequently are associated with CAP in preschool-aged children and are common causes of CAP in older children and adolescents (10,11).Pertussis should be considered in all children with CAP, especially if immunizations are not current. Mycobacterium tuberculosis also may cause CAP in children at risk for exposure. Coinfection with two or more microbial agents is more common than previously thought, with a rate of up to 41 percent in hospitalized patients (10,12) . The commonest presentation of pneumonia in children are fever, cyanosis, and signs of respiratory distress; tachypnea, cough, nasal flaring, retractions, rales, and decreased breath sounds (9,13,14). Pneumonia is diagnosed according to the patient history, clinical assessment and Physical examination, Laboratory and imaging studies (9,15). Sometimes pneumonia can lead to additional complications, particularly in bacterial pneumonia. The most important complications are respiratory and circulatory failure, Sepsis and septic shock; Sepsis most often occurs with bacterial pneumonia; Streptococcus pneumoniae is the most common cause. Pleural effusion, empyema, and abscess (16). Childhood immunizations have helped greatly in the prevention of pneumonia in children (17). However, treatment decisions are based on the child's age, clinical and epidemiologic factors (5,12). Antibiotic therapy should be initiated promptly in children who are thought to have bacterial CAP. Because definitive information about the causative organism is usually unknown, the choice of antibiotic is empiric (18).

The role of zinc in human health and functioning has primarily focused on dietary supplementation for the promotion of health and disease prevention. Aside from dietary zinc supplementation, zinc has been studied for therapeutic use in the common cold, atopic eczema, psoriasis, acne vulgaris, degenerative retinal lesions, age-related macular degeneration, inflammatory bowel disease, and various other disorders (19–24). Therefore, the aim of this study is to evaluate the therapeutic response to zinc supplementation in patients with pneumonia.

2. PATIENTS and METHODS

A randomized control study was conducted at Karbala pediatric teaching hospital during a period of 14 months included 175 inpatient children aged 3 -60 months who presented with pneumonia.

Inclusion criteria:

1. Iraqi child patients with proved diagnosed pneumonia
2. Age between 3 and 60 months
3. Both genders

Exclusion criteria:

Child was excluded if he/she had

1. Currently using zinc supplementation
2. Active measles
3. Systemic illness (e.g. sepsis, acute meningitis, hemodynamic instability).
4. Congenital or chronic heart or renal diseases
5. Pneumonia is severe enough that required ventilation or complicated with lung abscess, pleural effusion, pneumatocele, atelectasis.
6. Severe malnutrition which requires micronutrient supplementation including zinc or any other sign of severe malnutrition.
7. Severe anemia (HGB.<8g/dl)
8. Pneumonia due to aspiration of foreign body.

Study protocol:

1. The physician diagnosed pneumonia on the basis of the presence of fever, cough and fast breathing (respiratory rate >50/min for children aged 2-11 months and >40/min for children aged 12-24 months and > 30/min for children aged >24 months) or lower chest indrawing. The severity of pneumonia is depend on the presence of chest indrawing, subcostal retraction, grunting and decrease O2 saturation.
2. The collected data were age, sex, body weight, type of feeding (breast fed, bottle fed, mixed, or weaned food). History of previous admission due to pneumonia and recently receive antibiotics . Duration of illness prior to enrollment, temperature, respiratory rate and O2 saturation. Laboratory and imaging studies' findings

3. A full-history was taken and a thorough clinical examination was performed to all children to determine if they had any exclusion criteria, then oatients were assigned into 2 groups , Zinc group included 93 cases to whom zinc supplemetation was given in addition to the traditional treatment and they consisted of 51 males and 42 females. The second group received the traditional treatment with no zinc supplementation as control group and they were 82 cases; 47 males and 35 females. Both groups were in good nutritional status.
4. In both groups chest X-ray and CBC were performed and oxygen saturation and respiratory rates were measured.
5. All patients receive other required treatment according to their clinical assessment and decision of the pediatrician such as antibiotic, bronchodilator, antipyretic and oxygen and according to patient condition.
6. Zinc sulfate tablet available in 2 forms, 10mg and 20mg, zinc supplementation was given according to WHO guideline; 10mg for children aged less than 6 months and 20mg for those older than 6 months for 14 days. If vomiting or regurge occur within 1hr after introduced zinc another dose given (by dividing dose regime) and the patient was excluded from the study when did not tolerate the dose or presence of persistent vomiting.
7. The children were followed up daily and we measured the temperature, respiratory rate, and O2 saturation.

Data analysis

was performed using the statistical package for social sciences (SPSS) version 24, data were summarized as frequencies , percentage, mean and standard deviation accordingly. Statistical tests were applied according to the type of variable at a level of significance of 0.05 or less to be significant

3. RESULTS

A total of 182 children were enrolled in the study. Secven cases were excluded and the remaining 175 child cases were randomized into two groups to receive Zinc supplementation (Zinc group) or not (control group). Zinc group consisted of 93 patients; 51 (55 %) males and 42 (45.0%) females. The control group included 82 patients; 47 (57%) males and 35 (43%) females. The mean age in zinc group was 11.4 months compared to 13.1 months in control group, moreover, most patients in both groups aged between 3-11 months. Breast feeding was the more frequent type of feeding in both groups. Duration of pneumonia prior to hospitalization was 2 – 4 days in most cases, Previous hospitalization for a cause other than pneumonia was reported in 27 (29%) and 32 (39%) cases of zinc and control groups, respectively, (**Table 1**). Radiological findings of the studied groups are shown in (**Table 2**); Non-homogenous infiltration was the more frequent findings; 32.2% in zinc group and 38.9% in control group. Followed by hilar shadow, right upper zone consolidation, Hyperinflation, right middle zone consolidation and right lower zone consolidation. The mean duration of admission in zinc group was 4.2 days compared to 5.2 days in the control group (**Figure 1**). Furthermore, the duration of admission after initiation of zinc for ≤ 5 days reported in majority of cases (89.2%) of zinc group compared to 56% in controls with a statistically signifciant difference that patients in zinc group had shorter duration of admission after initiation of zinc supplementation compared to controls, (P. value < 0.05), (**Table 3**). Comparison of duration of admission was performed across the type of feeding in both groups, it had been observed that the mean duration of admission of breast feeding infant 3.7 days in zinc group and it was 4.6 days in control group, for those who were bottle fed, the mean duration of admission was 3.6 days and 4.9 days in zinc and control groups, respectively, as shown in (**Table 4**). Response to treatment in the 1st 5 days according to sex and type of feeding in both groups are summarized in (**Table 5**), in zinc group , response to treatment reported in 83 cases of them 47 males and 36 females, in control group lower responses were reported where response reported in 46 cases only of the 26 males and 20 females. With regards to the type of feeding, among responders in zinc group, 43 were breast fed and 23 were bottle fed while in controls, 28 were breast fed and 18 on bottle feeding, (**Table 5**).

Table 1. Baseline characteristics of the studied groups

Variable		Zinc group (n=93)		Control group (n=82)	
		No.	%	No.	%
Age (month)	3 - 11	67	72.0	46	56.1
	12 - 60	26	28.0	36	43.9
Sex	Male	51	54.8	47	57.3
	Female	42	45.2	35	42.7
Types of feeding	Breast feeding	43	46.2	37	45.1
	Bottle feeding	24	25.8	23	28.0
	Mixed feeding	13	14.0	12	14.6
	Weaned food	13	14.0	10	12.2
Duration of pneumonia prior to hospitalization	2 - 4 day	53	57.0	56	68.3
	≥ 5 day	40	43.0	27	32.9
Previous hospitalization for a cause other than pneumonia		27	29.0	32	39.0

Table 2. The radiological finding in zinc and control group.

Radiological finding	Zinc group (N=93)		Control group (N=82)	
	No.	%	No.	%
Non-homogenous infiltration	30	32.2	28	38.9
Hilar shadow	18	19.4	15	20.9
Right upper zone consolidation	18	19.4	16	13.4
Hyperinflation	13	14.0	11	6.0
Right middle zone consolidation	11	11.8	9	13.4
Right lower zone consolidation	3	3.2	6	7.4

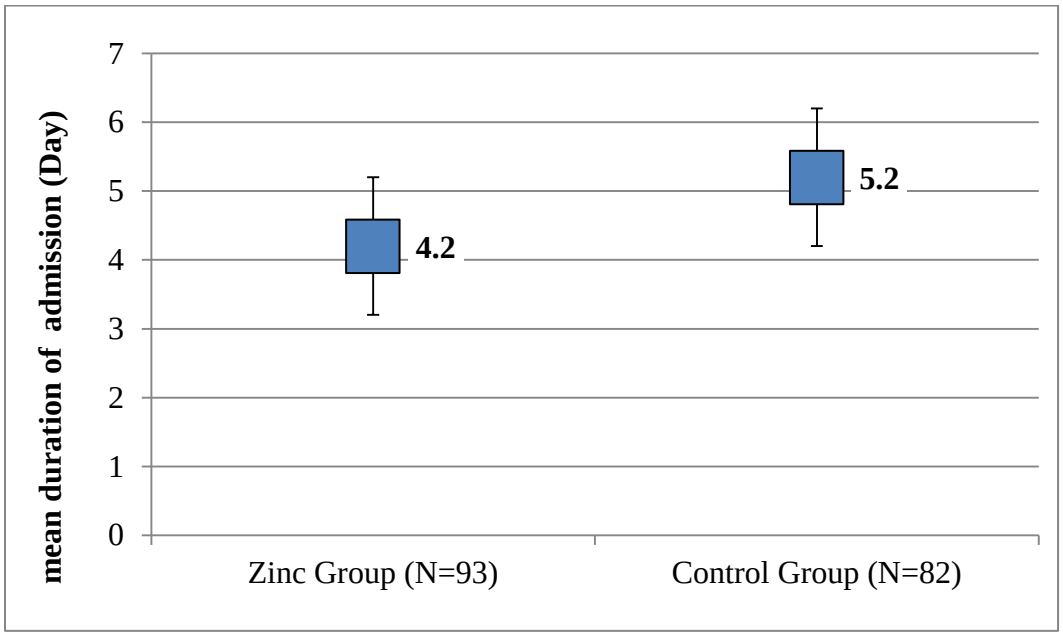

Figure 1. Line-Marker Plot for the mean duration of hospitalization in both studied groups

Table 3. Duration of admission in zinc and control group after initiation of zinc supplementation

Duration	Zinc group		Control group		P. value
	No.	%	No.	%	
≤5days	83	89.2	46	56	**0.003**
>5 days	10	10.8	36	44	

Table 4. Comparison of mean duration of admission between groups according to the type of feeding of infants

Type of feeding	Duration of admission (days)			
	Zinc group		Control group	
	Mean	SD	Mean	SD
Breast feeding infant	3.7	0.90	4.6	1.11
Bottle feeding infants	3.6	0.88	4.9	1.19

SD: standard deviation

Table 5. Response to treatment in the 1st 5 days according to sex and type of feeding in both groups

Variable		Zinc group		Control group	
		No.	%	No.	%
Sex	Male	47	90.4	26	55.3
	Female	36	87.8	20	57.1
Type of feeding	Breast feeding	43	46.2	28	34.1
	Bottle feeding	23	24.7	18	22.0

4. DISCUSSION

In this study we assess the effect of zinc administration during a severe episode of pneumonia on the course of illness. The study show clinically and statistically reduction in recovery time from severe pneumonia and overall hospital stay in children from 3 months to 5 years whom given zinc sulphate with standard antimicrobial therapy. The total days of admission for zinc group was (397 days and mean of 4.2) versus (429 days and the mean of 5.2 days) of control group this indicate that zinc treatment has a direct effect to decrease duration of admission which supported by the Meta analysis studies (25) which show the mean reduction is equivalent to 1 hospital day for both severe pneumonia and time in hospital. In our study population, children who received zinc supplementation during pneumonia episode who had improvement within 5 days is (89.2%) versus (56%) improvement of control group , This result is supported by other 2 trials done one in India (26), and Bangladesh (25). After 5 days of treatment, the patient who need more time to recovery was (10.8%) zinc group patient versus (44%) of control group. This indicates that the patient response was more prolong in control group and more severe cases were related to this group compared with zinc group. In the other hand, our study shows that there is a good response in breast feed zinc group in comparison to breast feed control group which had improvement of (46.2% versus 34.1%) within 5 days. this probably attributed to the role of breast milk in enhancing the efficacy of zinc absorption from the intestine (27). The difference in response to zinc in bottle feeding infant and the result was 24.7% for zinc group and 19.5 for control group and the small difference in response may be attributed to that the presence of calcium in milk in high

concentration is known to decrease zinc absorption from intestine by competition (27) therefore those infant responses to more zinc added to milk. that the same response to zinc supplementation between male and female in the first 5 days of treatment and the result was (90.4% and 87.8% respectively), and this result not agree with other study done in India (the recovery rate was (1.39) (26) that show the response was more in male than female, this difference may be related to small sample size.

Our study reported some limitations; firstly, we could not measure the plasma level of zinc before and after zinc supplementation due to unavailability of plasma zinc test in our hospital Secondly, it was difficult assess the effect of zinc in cases suspected to have viral infection. However, future studies can take into account these limitations for more precise conclusions

5. CONCLUSIONS

The use of zinc sulfate supplemetation in the management of acute lower respiratory tract infection is effective to decrease both severity and duration of illness. Zinc therapy was more effective in breast than bottle feeding infant and was effective in both male and female. Therefore we recommend to evaluate the effect of zinc when mixed with other micronutrient like copper, vitamin A, assessment of the effect of zinc in chronic lung diseases, recurrent chest infection and to encourage the mother to continue breast feeding additionally we highly suggest conducting further studies with larger sample size including multiple centers for further evaluation.

Ethical Clearance:

Ethical issues were taken from the research ethics committee. Informed consent was obtained from each participant. Data collection was in accordance with the World Medical Association (WMA) declaration of Helsinki for the Ethical Principles for Medical Research Involving Human Subjects, 2013 and all information and privacy of participants were kept confidentially.

Conflict of interest: Authors declared none

Funding: None, self-funded by the authors

6. *REFERENCES*

1. Garenne M, Ronsmans C, Campbell H. "The magnitude of mortality from acute respiratory infections in children under 5 years in developing countries". World Health Stat (1992) Q 45 (2-3): 180–91.
2. WHO. "Pneumococcal vaccines. WHO position paper". Wkly. Epidemiol. (1999)Rec. 74 (23): 177–83.
3. Hoare Z, Lim WS. "Pneumonia: update on diagnosis and management". (2006)BMJ 332: 1077–9.
4. Almirall J, Bolíbar I, Balanzó X, González CA. "Risk factors for community-acquired pneumonia in adults: a population-based case-control study". (February 1999)Eur. Respir. J. 13 (2): 349–55.
5. British Thoracic Society Standards of Care Committee. British Thoracic Society guidelines for the management of community acquired pneumonia in childhood. Thorax 2002;57(suppl 1):i1-24.
6. Murphy TF, Henderson FW, Clyde WA Jr, Collier AM, Denny FW. Pneumonia: an eleven-year study in a pediatric practice. Am J Epidemiol 1981;113:12-21.
7. Jokinen C, Heiskanen L, Juvonen H, Kallinen S, Karkola K, Korppi M, et al. Incidence of community-acquired pneumonia in the population of four municipalities in eastern Finland. Am J Epidemiol 1993;137:977-88.
8. Boschi-Pinto C, Debay M. Informal consultation on epidemiologic estimates for child health. 11-12 June 2001. Accessed online February 27, 2004.
9. Redd SC, Vreuls R, Metsing M, Mohobane PH, Patrick E, Moteetee M. Clinical signs of pneumonia in children attending a hospital outpatient department in Lesotho. Bull World Health Organ 1994;72:113-8.
10. Juven T, Mertsola J, Waris M, Leinonen M, Meurman O, Roivainen M, et al. Etiology of community-acquired pneumonia in 254 hospitalized children. Pediatr Infect Dis J 2000;19:293-8.
11. Gaston B. Pneumonia. Pediatr Rev 2002;23:132-40.
12. McIntosh K. Community-acquired pneumonia in children. N Engl J Med 2002; 346:429-37.

13. Margolis P, Gadomski A. The rational clinical examination. Does this infant have pneumonia? JAMA 1998;279:308-13.
14. Cincinnati Children's Hospital Medical Center Health Policy and Clinical Effectiveness Program. Evidence based clinical practice guideline. Community acquired pneumonia in children 60 days to 17 years of age. Accessed online February 27, 2004.
15. World Health Organization. Essential drugs and medicines policy. Drugs used in bacterial infections. Accessed online February 27, 2004.
16. Odeyemi AO, Oyedeji AO, Adebami OJ, Odeyemi AO, Agelebe E. Complications of pneumonia and its associated factors in a pediatric population in Osogbo, Nigeria. Niger J Paediatr. 2020;47(4):318–23
17. . Mandell GL, Douglas RG, Bennett JE, Dolin R. Mandell, Douglas, and Bennett's principles of practice of infectious diseases. 5th ed. Philadelphia: Churchill Livingstone, 2000:2416-7.
18. McCracken GH Jr. Diagnosis and management of pneumonia in children. Pediatr Infect Dis J 2000;19:924-8.
19. Alberta Clinical Practice Guidelines Steering Committee. Guideline for the diagnosis and management of community acquired pneumonia: pediatric. 2002. Accessed online June 1, 2004.
20. Bradley JS. Management of community-acquired pediatric pneumonia in an era of increasing antibiotic resistance and conjugate vaccines. Pediatr Infect Dis J 2002;21:592-8, 613-4.
21. Korppi M, Heiskanen-Kosma T, Leinonen M, Halonen P. Antigen and antibody assays in the aetiological diagnosis of respiratory infection in children. Acta Paediatr 1993;82:137-41.
22. Korppi M, Leinonen M. Pneumococcal immune complexes in the diagnosis of lower respiratory infections in children. Pediatr Infect Dis J1998;17:992-5.
23. Nohynek H, Valkeila E, Leinonen M, Eskola J. Erythrocyte sedimentation rate, white blood cell count and serum C-reactive protein in assessing etiologic diagnosis of acute lower respiratory infections in children. Pediatr Infect Dis J 1995;14:484-90.

24. Esposito S, Bosis S, Cavagna R, Faelli N, Begliatti E, Marchisio P, et al. Characteristics of Streptococcus pneumoniae and atypical bacterial infections in children 2-5 years of age with community-acquired pneumonia. Clin Infect Dis 2002;35:1345-52.
25. . Korppi M, Kiekara O, Heiskanen-Kosma T, Soimakallio S. Comparison of radiological findings and microbial aetiology of childhood pneumonia. Acta Paediatr 1993;82:360-3.
26. Peter G. Pneumonia. In: Burg FD, Gellis SS, Kagan BM. Gellis & Kagan's current pediatric therapy. 16th ed. Philadelphia: Saunders;1999:32-5.
27. Heffelfinger JD, Dowell SF, Jorgensen JH, Klugman KP, Mabry LR, Musher DM, et al. Management of community-acquired pneumonia in the era of pneumococcal resistance: a report from the Drug-Resistant Streptococcus pneumoniae Therapeutic Working Group. Arch Intern Med 2000;160:1399-408.
28. Nelson JD. Community-acquired pneumonia in children: guidelines for treatment. Pediatr Infect Dis J 2000;19:251-3.
29. McCracken GH Jr. Etiology and treatment of pneumonia. Pediatr Infect Dis J 2000;19:373-7.
30. Göransson K, Lidén S, Odsell L. Oral zinc in acne vulgaris: a clinical and methodological study. Acta Derm Venereol . 1978;58(5):443-448.
31. Ewing CI, Gibbs AC, Ashcroft C, David TJ. Failure of oral zinc supplementation in atopic eczema. Eur J Clin Nutr . 1991;45(10):507-510.
32. Leibovici V, Statter M, Weinrauch L, Tzfoni E, Matzner Y. Effect of zinc therapy on neutrophil chemotaxis in psoriasis. Isr J Med Sci . 1990;26(6):306-309.
33. Faure P, Benhamou PY, Perard A, Halimi S, Roussel AM. Lipid peroxidation in insulin-dependent diabetic patients with early retina degenerative lesions: effects of an oral zinc supplementation. Eur J Clin Nutr . 1995;49(4):282-288.
34. VandenLangenberg GM, Mares-Perlman JA, Klein R, Klein BE, Brady WE, Palta M. Associations between antioxidant and zinc intake and the 5-year incidence of early age-related maculopathy in the Beaver Dam Eye Study. Am J Epidemiol . 1998;148(2):204-214.

35. Mulder TP, van der Sluys Veer A, Verspaget HW, et al. Effect of oral zinc supplementation on metallothionein and superoxide dismutase concentrations in patients with inflammatory bowel disease. J Gastroenterol Hepatol . 1994;9(5):472-477
36. Brook WA, Yunus M, Santoshan M, et al. Zinc for severe pneumonia in very young children; double-blind placebo-controlled trial.Lancet 2004;363:1983-8.
37. Mahalanabis D,Lahiri M, Paul D, et al. Randomized, double-blind, placebo-controlled clinical trial of the efficacy of treatment with zinc or vitamine A in infant and young children with severe acute lower respiratory infection. Am J Clin Nutr 2006;83:1089-96.
38. Larry K P, John DS. Gastroenteritis . In Beherman RE, Kligman RM, Jonson HB (eds): Nelson text book of pediatrics, 17th Ed. Philadelphia, WB Saunders, 2004 ; 1272 - 6.