A Randomised Control Trial to study the effect of Short Course Prophylactic Zinc supplementation on Acute Respiratory Illness among Infants 6-11 months residing in Urban Slums, Hubli, Karnataka

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Abstract

Introduction: Acute respiratory infections (ARIs) are important under-five morbidities. Zinc deficient children are at increased risk of restricted growth and developing diarrhoeal and respiratory tract infections.

Objective: To study the effect of prophylactic zinc supplementation for two weeks on incidence of acute respiratory tract illness in infants aged 6-11 months residing in urban slums.

Methodology: Community Based Randomised Control Trial was conducted on 284 apparently healthy Infants (6-11 months) residing in urban slums. Intervention in the form of oral liquid preparation containing 20mg elemental zinc or placebo respectively were administered to the infants for 14 days, once daily and later followed up for 5 months..

Results: The study shows that there were on an average 2.91 episodes of ARI during the 5 month follow up period in the zinc group which was significantly less when compared to the placebo group (mean= 3.52), ($P<0.05$). The two groups were similar to each other. GEE Analysis showed that short term prophylactic zinc supplementation was effective in reducing the total incidence and number of days with ARI by 20% in infants especially in the 1st two months following administration. On an average, 5.6 infants would have to receive zinc supplementation treatment for one additional infant to NOT have the study outcome i.e acute respiratory infection.

Conclusion: Incidence of respiratory infections cannot be reduced without an overall increase in social and economic development. However implementation of proven and evidence-based interventions, such as zinc supplementation can be one such milestone in reducing the burden of ARI.

Keywords: Acute respiratory infections, prophylactic zinc supplementation, Randomised Control Trial, total incidence and number of days with ARI.

Introduction

Reducing infant and young child mortality is a priority globally and nationally. Millennium developmental goals (goal 4) aimed to reduce the under- five mortality by two thirds by 2015 and Sustainable Development goal aims to end preventable deaths of newborns and children under5 years of age. Realization of these goals requires commitment and reinforced implementation of efforts against pneumonia and diarrhoea (the number 1 childhood killers) and strengthening the nutritional status of mothers and children[1].

Acute respiratory infections (ARIs) are important under-five morbidities causing lots of discomfort, frequent visits to a healthcare provider, admission to an indoor facility and even mortality[2]. According to World Health Organisation, Pneumonia accounts for 15% of all deaths of children under 5 years old, killing an estimated 922000 children in 2015[3]. In spite of its huge toll on human life, relatively few global resources are dedicated to tackling this problem. Mortality due to childhood pneumonia is strongly linked to malnutrition, poverty and inadequate access to health

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care[4]. On an average, children below 5 years of age suffer about 5 episodes of ARI per child per year, thus accounting for about 238 million attacks. Hospital records from states with high infant mortality rate shows that up to 13% of inpatient deaths in pediatric wards are due to ARI. The proportion of death due to ARI in the community is much higher as many children die at home[5].

Zinc is an essential trace element required for maintaining intestinal cells, bone growth and immune function. Its numerous roles in the human body range from structural component of numerous proteins, cofactor for metalloenzymes, nucleic acid and protein metabolism, immunity, cell division and growth. Its deficiency is widely prevalent in the region as reflected in our high child stunting rates. 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 undernutrition may further deplete body stores of zinc[6].

Zinc deficient children are at increased risk of restricted growth and developing diarrhoeal and respiratory tract infections[7]. Supplementation of this micronutrient has already shown impressive benefits in diarrhoea but its effects on acute respiratory illness are unclear.

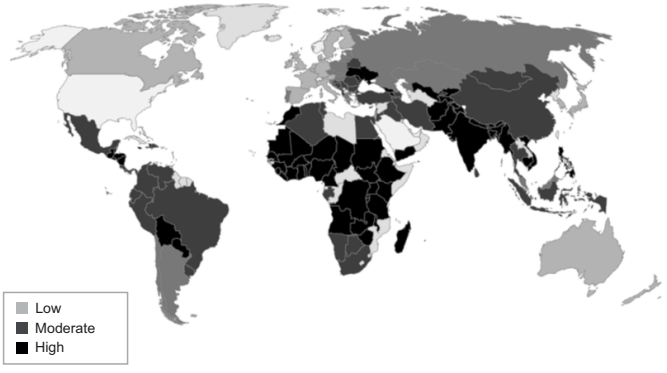

Figure no 1: National risk of zinc deficiency in children under 5 years.

Source (7): Adapted from IZiNCG Technical document no. 1; Assessment of the risk of zinc deficiency in populations and options for its control.

Acute respiratory illnesses (ARIs) pose a substantial morbidity and mortality burden among infants living in urban slums, where environmental exposures and micronutrient deficiencies are prevalent. While several clinical trials have assessed the impact of zinc supplementation on respiratory outcomes in young children, most have involved either continuous or longer-duration regimens or included broader age groups, and yielded mixed results regarding overall ARI morbidity reduction. A few community-based studies have tested short course prophylactic zinc in infants, but these have rarely focused exclusively on the critical 6-11 months age group within the unique context of densely populated urban slums a demographic segment at heightened risk due to weaning, malnutrition, and increased infection exposure

Thus, this article contributes substantially to the existing evidence base by focusing on a particularly vulnerable population, applying a practical and resource-efficient intervention schedule, and rigorously evaluating both immediate and longer-term respiratory health outcomes in a real-world urban slum setting. This may help guide policy implementations for ARI prevention where child health burden is most acute and resources are limited.

Objective: To study the effect of prophylactic zinc supplementation for two weeks on incidence of acute respiratory tract illness in infants aged 6-11 months residing in urban slums.

Materials and Methodology

The study was conducted in urban slum areas of 4 wards of Hubli. Caregivers of Infants aged 6-11 months residing in urban slums of Hubli were the sources of information.

Design of study: Community Based Randomised Control Trial

Inclusion criteria: Infants Age group 6 - 11 months who are apparently healthy, residing in urban slums of Hubli and whose mothers/caregivers give consent to participate in the study.

Exclusion criteria: Infants with severe acute malnourishment, congenital anomalies or malformation, known immunodeficiency or on steroids, suffering from any serious medical/surgical ailments, received zinc supplements in the past 3 months and not willing to participate in the study were excluded from the study.

Size of study sample: For sample size calculation, incidence of ARI was taken as 5.5 episodes (SD = 3.15) per child-year as per previous studies [8]. Thus, for a 20% reduction in the incidence of ARI (α 0.05 and power 80%), we required 258 infants (129 in each group). Taking into account possible 10% attrition, the final sample size was 284.

Method for data collection: A survey was done at the beginning of the study to recruit eligible infants. A total of 15 areas were surveyed and 312 children were found to be eligible. The study purpose was explained to the caregivers/mothers and an informed written consent for participating in the study was taken. Willing participants were then clinically assessed to rule out any exclusion criteria and other information pertaining to child and living conditions were collected using a pre-tested semi-structured questionnaire.

The participants were then randomly allocated to either study group or control group based on lottery method and intervention in the form of oral liquid preparation containing 20 mg elemental zinc or placebo respectively were administered to the infants for 14 days, once daily. Subsequent visits after 2 weeks were made to ensure compliance and note any side effects.

Information was collected from the mother or caregiver on the number and duration of acute respiratory infections after 2 weeks of supplementation of either zinc or placebo on a monthly follow up basis for 5 months after the supplementation.

Case definition used

- Acute upper respiratory infection was diagnosed if a child had cough or cold with or without fever.
- Acute lower respiratory infection if child had symptoms of cough with difficult or/and rapid breathing or chest in drawing as reported by the caregivers.
- Duration was assessed by the number of days with acute respiratory illness and as mean number of days acute respiratory illness episode lasted.
- Recovery from an acute respiratory illness episode was considered when the last day was followed by a 72 hour acute respiratory illness free period. Subsequent episodes were considered to be new episodes.

Ethical consideration: Ethical clearance was obtained from the Institutional Ethical Committee of Karnataka Institute of Medical Sciences. The study is registered with the Clinical Trial Registry and the reference number is REF/2015/02/008414. Written informed consent was taken from the caregivers of the children after explaining the study protocol and the anticipated effects.

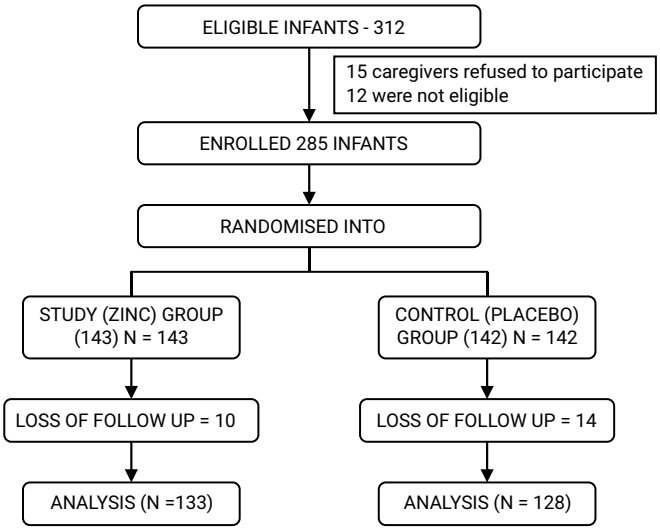

Figure no. 2: CONSORT DIAGRAM

Statistical analysis: The data was collected and checked for accuracy and entered in SPSS version 20. The baseline characteristics were assessed for comparability between the two groups and identify possible confounders. The incidence is expressed as episodes per child per year. The counts are expressed by Mean and standard deviation. Difference between means is tested using unpaired student t test.

Generalized Estimating Equations (GEE) are used to obtain relative risk (RR) with 95% confidence intervals, in order to compare month-wise number of episodes and duration of ARIs using Poisson log linear distribution, by intention to treat analysis. The exchangeable working correlation matrix was selected for all the outcomes. We included all children who had taken at least two doses of the intervention for the analyses.

Results

Among the total 261 study participants, infants are distributed almost equally in all age groups (6-11 months). The gender distribution of the infants is 1:1.

Majority of the study families belonged to Muslim community (78.5%). Hindus contributed 21.5% to the study population. Of the study families, majority (67%) fall under poor socio-economic classes (class IV & V) as per Modified B.G Prasad classification. 7.3% belong to class II, 25.7% to class III, 41.4% to Class IV and 25.7% to class V.

35.6% of the study infants are 1st child of their parents, 36% are 2nd child, 24.1% are 3rd child and 4% are of birth order 4th or above. Analysis of gestational age at birth reveals that 88% were born at term (between 37-42 weeks of pregnancy). 6.9% were preterm (less than 37 weeks) and 5% were post term (born after 42 weeks of gestation).

In the present study only 54.4% had birth weight more than 2.5 kg. Proportion of low birth weight is 37.9%. 7.6% infants had birth weight more than 4 kgs. Among the study infants, neonatal complications occurred in 10.7%. Relatively more infants in study group had such neonatal complications.

Timely onset of breastfeeding was seen in 66.67% infants (35.2% within 1 hr and 31.4% within 1-4 hours of delivery). 11.9% started breastfeeding in the later parts of the 1st day and in 19.2% breastfeeding was delayed by 3 days. NICU feeds were given to 6 infants. The study shows that the practice of pre-lacteal feeds was widely prevalent in the area and similar practices were seen in both groups. Of the total infants 60% received pre-lacteal feeds in form of sugar water or honey. 53.2% infants were started on complementary feeds on time after 6 months of age. Delayed feeds were noted in 35.2% infants and 11.5% infants were started on complementary feeds early. There is no significant difference between the groups with regard to onset of complementary feeds.

The practice of exclusive breast feeding was seen in only 33.7% families. 66.3% families had some fallacy in child feeding practice. Similar child feeding practices was seen in both the study groups with no statistical difference between them. Timely immunisation was seen in 73.2% study infants. 26.8% infants were due for some vaccines. No statistical difference was found between the groups with reference to immunisation coverage.

The total proportion of underweight infants in the study was 29.1%. 29.3% infants were underweight in zinc group and 28.9% in control group. No significant difference was noted in the distribution of underweight children in the two groups. The proportion of stunted children was high in the study population with almost 50% infants demonstrating stunted growth. The proportions of stunted infants in zinc and placebo groups are 54.1% and 45.3% respectively. This difference was found to be statistically insignificant.

18.8% mothers were in the age group of 18-21 years and 52.1% in 22-25 years age group. 24.1% were 26-30 years and proportion of more than 30years mothers was hardly 5% in the study population. The education profile of the mothers in the sample population was poor with 44% women having schooling less than 7% and 10% being uneducated. High school was completed by 40% mothers and higher education (PUC & Degree obtained by 16% mothers. There was no statistical difference in the groups in this regard. Majority of the women in the study population were homemakers (97.3%).

34.5% of mothers gave history of frequent respiratory ailments in family members and risk of infections to infant. There was no statistical difference found between the groups.In the study population it is observed that the living conditions of the families were unsatisfactory with almost all families living in overcrowded houses(100%), 75% families are using smoke producing fuel like wood chulla for cooking with inadequate ventilation(92%). 98.5% families also complained of water scarcity as water was supplied once in 3-4 days.

The intervention in the form of oral supplementation was well tolerated by most infants (88.89%). Adverse effects in the form of diarrhoea only and diarrhoea with vomiting was noted in 6.9% and 4.2% respectively. A significant difference in the proportion of adverse effects was found between zinc (8.8%) and placebo (2.9%) groups with higher incidence in zinc supplemented children.

Table no 1: Table showing baseline characteristics of the infants

	Study group	Control group	P value
Age (in months) (Mean ± S.D)	9.46±2.073	8.79±2.014	0.075
Gender (M:F)	1:1.29	1:0.77	0.041
Mother education (Above 7th std)	59.4%	52.3%	0.2511
Practice of exclusive breastfeeding	30%	37.5%	0.205
Weight for age (% wasting)	29.3%	28.9%	0.941
Length for age (% stunted)	54.1%	45.3%	0.154
Socio-economic status (% Class IV &V)	70.7%	63.3%	0.545
Immunisation status- Up to date	73.7%	72.7%	0.851
Presence of Overcrowding	100%	100%	NA
Indoor pollution	75.2%	75.8%	0.911

The above table shows that the infants in both the groups were comparable and similar to each other in most aspects. This is supported by the non significant statistical P values obtained.

Table 2 showing the total number of acute respiratory illness episodes during the study period

	Study group (Mean ± S.D)	Control group (Mean ± S.D)	P value
Total no. of ARI episodes	2.91±1081	3.52±1.87	0.008*
Incidence of ARI per child year	6.984	8.448	
Total no. of days with ARI	8.56±5.55	10.70±6.09	0.003*

*Significant at P<0.05

The study shows that there were on an average 2.91 episodes of ARI during the 5 month follow up period in the zinc group which was significantly less when compared to the placebo group(mean= 3.52), (P<0.05). This gives an incidence rate of 6.98 episodes of ARI/ child/ year in the zinc group and 8.45 episodes of ARI/ child/ year in the control group.

Our study revealed that zinc supplementation reduced the total number of days with ARI (Mean=8.56) when compared to control group (Mean=10.7). This was found to be statistically significant.

In the intervention study it was found that zinc supplementation f or 14 days reduced the incidence of acute upper respiratory infections for the 1st two months significantly. When compared to the incidence of URTI in the placebo group. Zinc supplementation significantly reduced the duration of the individual episodes of URTI in the first two months following the supplementation.(P<0.001)

In our study it was observed that short course prophylactic zinc supplementation did not have any beneficial effect in reducing the incidence or duration of LRTI as compared to the placebo group.

On applying GEE Logistic regression model, we found a significant decreases in the ARI Incidence of 20% in the zinc group as compared to the control.

When the types of ARIs were analyzed separately, it was found that there was a significant reduction of 20% in occurrence of upper respiratory illness. However a non-significant increase of 39% was noted in occurrence of LRTI.

On GEE logistic regression analysis a statistically significant reduction of 21% was found in the zinc group with respect to total days with ARI. Furthermore zinc supplementation led to a significant 24% decrease in the days with URTI. However the no. of days with LRTI showed a non significant increase of 16%.

Table 3 showing effect of zinc supplementation on number of ARI Incidence on study group compared to control group

Generalized Linear Models for	Relative risk (Exp B)	95% confidence levels		Significance
		Lower	Upper	
Total number of ARI episodes	0.828	0.723	0.948	0.006*
Total URTI episodes between the two groups.	0.804	0.699	0.925	0.002*
Total LRTI episodes between the two groups.	1.390	0.762	2.535	0.283

*Significant at P<0.05

Table 4 showing effect of zinc supplementation on duration of ARI on study group compared to control group.

Generalized Linear Models	Relative risk (Exp B)	95% confidence levels		Significance
		Lower	Upper	
Total ARI duration	0.799	0.739	0.865	0.000*
Total URTI duration	0.767	0.706	0.834	0.000*
Total LRTI duration	1.162	0.903	1.494	0.243

*Significant at P<0.001

Number Needed to Treat (NNT) represents the number of patients over a given time period that one would need to treat to achieve one additional study endpoint. In our study NNT was 5.6, this implies that on an average, 5.6 patients would have to receive zinc supplementation treatment for one additional patient to NOT have the study outcome i.e acute respiratory infection.

Discussion

The present study was a community based RCT conducted in infants 6-12 months of age to evaluate the protective effect of prophylactic short course oral zinc supplementation on incidence and duration of acute respiratory illness during the 5 month follow-up period. We recruited 261 infants (133 in zinc group &128 as controls) who were similar to each other at baseline and then administered the intervention.

At the end of the study period we found that the number of ARI episodes reported in the zinc group were significantly lesser than those in the control group. Zinc supplementation demonstrated a 20%

protective effect in reducing ARI. But this held true mostly with regard to upper respiratory tract illness, which were more common. LRTI were not affected significantly.

The duration of the individual episodes when analysed was significantly shorter in the zinc group. URTI showed a mean reduction of 2.29 days, with respect to the duration of URTI in control group. LRTI duration was however not much affected. This may be due to the fact that there is severe zinc deficiency in the population (stunting almost 50%) which requires long term supplementation for improvement along with better feeding practices.

A study conducted by Nitu Bhandari et al in 6 months to 3 years old children in a slum community in New Delhi to evaluate the effect of daily zinc supplementation on incidence of acute LRTI and pneumonia found that at the end of four months follow up there was no difference in the proportion of children who had ALRI in the two groups[9]. This study supports our findings. Even in our study, zinc supplementation did not significantly prevent or reduce the LRTI episodes.

The study done by Vakili et al, on effects of zinc supplementation in occurrence and duration of common cold in school aged children during cold season found that among the zinc-supplemented group common cold incidence of 1.37±0.86 episodes per child during the study period was recorded in comparison to 3.15±0.55 cold episodes per child among the placebo group (P<0.001). Mean overall missing days from school was 0.55±1.09 days and 1.35±1.79 days for zinc-supplemented and placebo groups, respectively. The need for administration of antibiotics for bacterial infections (pharyngitis, acute otitis media, sinusitis, pneumonia) were 20 and 47 courses for zinc-supplemented and placebo groups, respectively (P<0.01)[10].Their results were in support of our findings of reduced URTI episodes post supplementation.

A study was conducted by Malik et al, in an urban resettlement area of Delhi in 2014. They found that zinc supplementation had no effect on incidence of ARI. However a decrease of 15% in days and 12% in duration of episodes in ARI was observed. Incidence of ALRI decreased by 62% and the effect was observed for full five months of follow up[8]. These observations although dissimilar to our findings, they demonstrate the protective effect of zinc supplementation.

A study done by Chandya et al, on Nepalese children found that short-course zinc supplementation did not reduce the incidence and prevalence of respiratory or diarrheal illness during 6 month of follow-up among young Nepalese children diagnosed with pneumonia at enrollment. Hence they concluded that Short-course zinc administration during pneumonia may not be effective in preventing childhood infections[11]. In our study there was no significant preventive effect found in lower respiratory illness. However a major reduction in incidence and duration of upper respiratory illness was noted.

A Systematic Review on Acute Respiratory Infection and Pneumonia in India was conducted in 2011 to identify, synthesize and summarize current evidence to guide scaling up of management of childhood acute respiratory infection/pneumonia in India, and identify existing knowledge gaps. Among the various findings it was found that Pneumonia affects children irrespective of socioeconomic status; with higher risk among young infants, malnourished children, non-exclusively breastfed children and those with exposure to solid fuel use. They also concluded that Zinc supplementation for at least three months duration could be useful to prevent pneumonia (defined by specific criteria). But Zinc does not have therapeutic value in childhood pneumonia[12]. Our study supports their results.

A meta-analysis and meta-regression of randomised control trials on zinc supplementation for prevention of acute lower respiratory infections in children in developing countries done by Roth et al. Revealed that routine zinc supplementation reduced the incidence of childhood ALRI defined by relatively specific clinical criteria, but the effect was null if lower specificity case definitions were applied and by meta-regression, the effect of zinc was associated with ALRI case definition, but not with mean baseline age, geographic location, nutritional status or zinc dose[13].

Michelle Science et al studied the efficacy of zinc for the treatment of the common cold by performing a systematic review and meta-analysis of randomized controlled trials. They included 17 trials involving a total of 2121 participants, compared with patients given placebo. Those receiving zinc had a shorter duration of cold symptoms (mean difference -1.65 days, 95% confidence interval [CI] -2.50 to -0.81). Zinc shortened the duration of cold symptoms in adults (mean difference -2.63, 95% CI -3.69 to -1.58), but no significant effect was seen among children (mean difference -0.26, 95% CI -0.78 to 0.25). Heterogeneity remained high in all subgroup analyses, including by age, dose of ionized zinc and zinc formulation. The occurrences of any adverse events (risk ratio [RR] 1.24, 95% CI 1.05 to 1.46) like bad taste (RR 1.65, 95% CI 1.27 to 2.16) and nausea (RR 1.64, 95% CI 1.19 to 2.27) was more common in the zinc group than in the placebo group. The results of the meta-analysis showed that oral zinc formulations may shorten the

duration of symptoms of the common cold[14]. Our study also yielded similar results; adverse effects were more in zinc group but not significantly. The incidence and duration of URTI was lesser in study group.

A Cochrane review was undertaken by Lassi et al, on Zinc supplementation for the prevention of pneumonia in children aged 2 months to 59 months, they included six trials and 7850 participants in the meta-analysis. Analysis showed that, zinc supplementation reduced the incidence of pneumonia by 13% (risk ratio (RR) 0.87; 95% confidence interval (CI) 0.81 to 0.94, fixed-effect, six studies) and prevalence of pneumonia by 41% (RR 0.59; 95% CI 0.35 to 0.99, random-effects, one study). On subgroup analysis, they found that zinc reduced the incidence of pneumonia defined by specific clinical criteria by 21% (i.e. confirmation by chest examination or chest radiograph) (RR 0.79; 95% CI 0.0.71 to 0.88, fixed-effect, four studies, n = 4591) but had no effect on lower specificity pneumonia case definition (i.e. age specific fast breathing with or without lower chest indrawing) (RR 0.95; 95% CI 0.86 to 1.06, fixed-effect, four studies, n = 3259).Thus analysis of the studies concluded that zinc supplementation was significantly associated with reducing the incidence and prevalence of pneumonia among children of two to 59 months of age and Evidence provided so far from randomised controlled trials is sufficient to recommend zinc intake in deficient populations through supplementation, dietary improvements, or fortification, for enhancing child survival[15].

Recommendations

Considering the high burden of ARI, vulnerability to zinc deficiency and frequent diarrheal diseases, regular zinc supplementation offers a feasible strategy to tackle the top two childhood diseases. Further research into the feasibility and effectiveness of prophylactic zinc supplements can improve comprehensive child health programs.

Conclusion

By this study it can be concluded that prophylactic zinc supplementation has preventive effect of approximately 20 % on the overall prevalence of ARI. However, the incidence of respiratory infections cannot be reduced without broader improvements in social and economic development. Substantial evidence indicated that several interventions ca effectively reduce ARI-related morbidity and mortality. Every reduction in deaths due to ARI contributes incrementally toward achieving Sustainable Development Goal 3 (SDG3). A committed approach to implementing proven, evidence based interventions is essential for the control of ARI.

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