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Oral Zinc as Adjuvant Therapy for Pediatric Recurrent Pneumonia: A Prospective Study in a Tertiary Care Hospital

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Abstract Zinc is an essential element required for the cell metabolism, including immunity. Therefore Zinc deficiency leads to susceptibility to infections and may affect pulmonary epithelial cell integrity. Many investigators have used zinc supplementation to see it's effect on various diseases mainly diarrheal diseases and severe pneumonia. This study aims to evaluate the effect of oral Zinc supplementation in treatment and prevention of recurrent pneumonia. 506 Children aged 2 months to 60 months admitted during September 2011 to August 2014 for recurrent pneumonia with no other underlying illness in the Pediatric department of Manipal Teaching Hospital, Pokhara, Nepal were observed. Along with standard antibiotic treatment one group [Group I] received zinc (10 mg for < 6 months and 20 mg for ≥ 6 months for 10 days) and another group [Group II] did not receive Zinc. The primary outcome like resolution of tachypnea, chest in drawing, hypoxia, starting of oral feeds and hospital stay was noted. All cases were followed up every three monthly for one year to see the recurrence of pneumonia. Data was analyzed using SPSS version 16 and $p < 0.01$ was considered statistically significant. 20.24% of recurrent pneumonia meeting the inclusion criteria was evaluated. Maximum children (65.4%) were of age 2-12 months. Primary as well as secondary outcome was statistically significant ($p<0.001$) in Group I. The mean ± SD for primary outcome in Group I vs. Group II were –tachypnea (2.96±1.12 vs. 4.67 ± 1.61 days), chest in drawings (1.63 ±0.95 vs. 3.35 ±1.55 days), hypoxia (24.61 ±1.77 vs. 41.67 ± 2.11 hours), starting of oral feed (1.22 ±0.95 vs. 2.55 ± 1.23 days) and hospital stay (4.82 ±1.22 vs. 6.45 ± 1.99 days). In Group I 20/253 (7.9%) children lost follow up and 2/253(0.79%) patient died and in group II 1 (0.39%) died and 30 (11.85%) lost follow up. Recurrence of pneumonia was also significantly less ($p<0.001$) in zinc recipients. Determinants in two groups by logistic regression showed earlier resolution in zinc recipients with OR at 99% CI 9.654 (5.605, 16.625) for tachypnea, 14.506 (8.064, 26.095) for chest in drawings, 5.860 (3.415, 10.057) for hypoxia, 13.725 (7.270, 25.912) for starting oral feed and 0.075 (0.040, 0.140) for hospital stay. The recurrence of pneumonia was also less in group I with OR 3.348 at 99% CI (2.009, 5.581). Zinc as an adjuvant therapy is effective in treatment and prevention of recurrent pneumonia in children.

Keywords: *Adjuvant Therapy Zinc, Pediatrics Recurrent Pneumonia*

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1. Introduction

Zinc is an essential trace element required for maintaining intestinal cells, bone growth, and immune function [1]. Children who are living in low-income settings are often undernourished and zinc deficient. Its deficiency is associated with increased risk of infection, particularly diarrhea and pneumonia [2,3]. Pneumonia is a killer disease and it alone kills over two million deaths per year [4]. A subgroup of children with pneumonia suffer from recurrent pneumonia reported to be 8-9% in different studies [5,6]. The lack of epidemiological studies on recurrent pneumonia from developing countries makes it difficult to plan for its prevention and treatment [7]. Recurrent pneumonia pose a significant challenge to the pediatricians especially when no underlying cause is detected. Therefore, we aimed to see if there are beneficial effects of zinc as an adjuvant therapy in treatment and prevention of recurrent pneumonia.

2. Methodology

2.1. Study Setting

This was a prospective, hospital based case control study conducted at Manipal Teaching Hospital from September 2011 to August 2014. Cohort of cases were from 1st September 2011 – 31st August 2013, they were then followed up for one year for each case till 31st August 2014.

2.2. Sample Size Calculation

In a pilot study done prior to original study for power 99% and α error 1% with 99% level of confidence showed proportion of recurrence in zinc supplemented group to be 0.55 and it was 0.30 in non zinc supplemented group. We estimated total sample size of 182 children in each group and we have enrolled 253 children in each group. We expected loss of cases during follow up.

2.3. Ethical Committee Approval

Approval was obtained from the Ethics committee of the Manipal Teaching Hospital and written consent in the local Nepali language was obtained from the parents of the children before the commencement of the study. For those parents who were unable to read or write, consent statement was verbally read out to them if they agreed their thumb impressions were obtained in the presence of a witness. Study was done according to the latest declaration of Helsinki [8].

2.4. Enrollment of Cases

Children aged 2 months to 60 months with recurrent pneumonia, [pneumonia 2 or more episodes in a single year or 3 or more episodes ever] [9] were enrolled. We considered diagnosis of pneumonia in the following ways:

1. Reported fever, cough and difficulty breathing with a respiratory rate (RR) above the WHO defined age-specific values (RR ≥ 50 breaths per minute for children aged two to 11 months, or RR ≥ 40 breaths per minute for children aged 12 to 59 months [10], with or without chest in drawings.
2. A diagnosis of pneumonia based on chest examination by a physician.
3. A diagnosis of pneumonia based on a chest radiograph (CXR) by using the WHO standardized tool for interpretation of CXR [11]. CXR taken for each child was interpreted by a radiologist blinded to clinical data.

All children were assessed for hypoxemia according to WHO guidelines, SpO2 of 90% [12] by using a pulse oximeter, [Trusatoximeter, GE Healthcare *Finland Oy*. Kuortaneenkatu 2, FI-0051010, Helsinki, Finland]with a pediatric sensor [Trusatoximeter, TruSignal Integrated Finger sensor GE, TS-F4-MC] Oxygen saturation (SpO2) was recorded after stabilization of the reading for 1 minute. Children with SpO2 of ≤ 90%, oxygen was provided before further evaluation. Nutritional status was assessed by detailed anthropometry. Height: Measured in nearest centimeter by infantometer in children till 2 years and beyond 2 years standing height was measured by using a standard wooden height measuring board. Weight: Measured in nearest 100 grams with the help of standardized weighing machine (Krups Empress Manual Weighing Scale). Grading of nutritional status was done by using classification by Indian Academy of Pediatrics [13].

2.5. Inclusion Criteria

1. Age 2 month to 60 months presenting with recurrent pneumonia with no other underlying illness.
2. Mild and moderate Malnutrition was included.

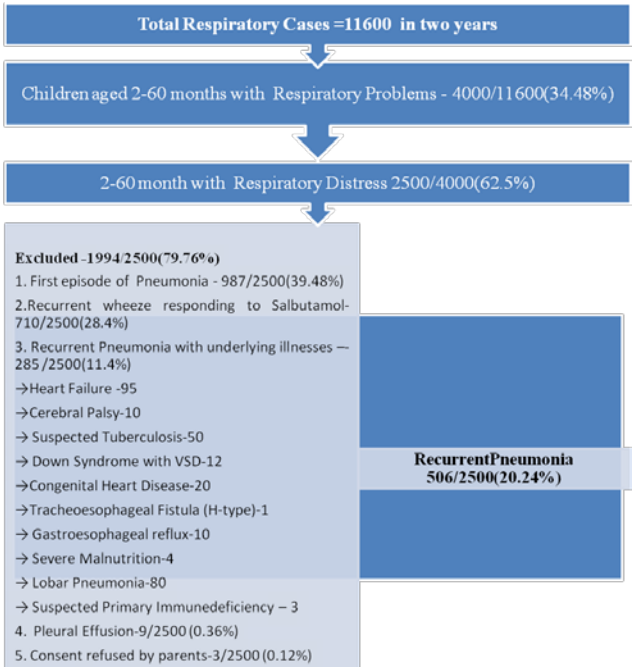

Figure 1. Enrollment of cases

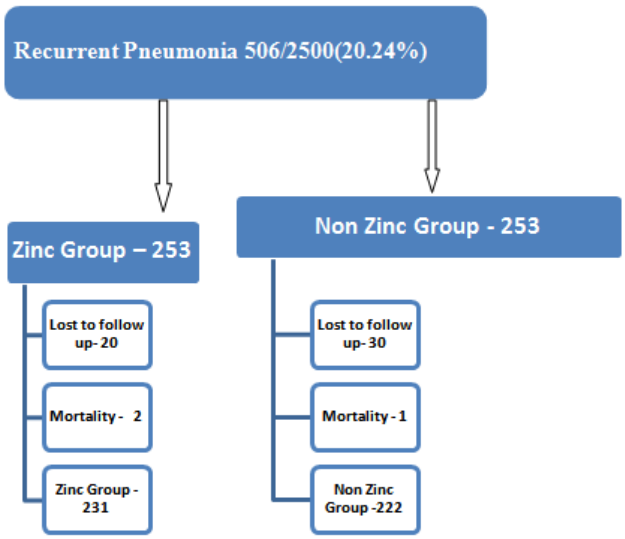

Figure 2. Recurrent Pneumonia selected – 506 (20.24%)

2.6. Exclusion Criteria

1. Recurrent pneumonia with underlying illnesses like - congenital heart diseases, tracheoesophageal fistula, gastro esophageal reflux, pulmonary tuberculosis, AIDS, severe malnutrition, bronchiectasis, pneumonia in cerebral palsy, suspected immune deficiency or any genetic disorders.
2. Lobar pneumonia.
3. Respiratory distress due to other causes like heart failure or metabolic acidosis, pleural effusion,

pneumothorax, Congenital anomalies of the respiratory tract, interstitial lung diseases.
4. Refusal of Consent.
5. Children presenting with recurrent wheezing (defined as 3 episodes over the past 6 months and on treatment with bronchodilators) [14] and who responded to 3 doses of nebulized Salbutamol given 20 minutes apart.

Then the whole population was divided into two groups.
Group I - received zinc with standard antibiotics.
Group II –received only standard antibiotics.
These cases were followed up every three monthly for one year to see the recurrence.

2.6. Dependent Variable/Exposure Variable

Zinc supplementation.

2.7. Independent Variables/Outcome Variables

Definitions of Outcome Measures:

1. **Primary outcome:** The admitted children were monitored by study physicians at ~6 hourly intervals from time of admission to clinical recovery until discharge
   Primary outcome is defined as follows:
   a) Resolution of tachypnea – within 2 days or > 2 days
   b) Resolution of chest in drawings – within 2 days or > 2 days
   c) Hypoxia – Discontinuation of oxygen – within 48 hours or >48 hours. The absence of hypoxia was confirmed after a second reading taken 30 minutes later.
   C) Starting of feed - within 2 days or > 2 days
   D) Time to Hospital discharge: 5 days or > 5 days
2. **Secondary Outcome:** These children were followed up every three monthly for one year after discharge.
   1. Re-admission/re-diagnosis with pneumonia – yes / no

2.8. Dose of Zinc Used

Dispersible zinc tablets containing 10 mg of elemental zinc sulfate was used in the study. Children alternately falling under even number were given zinc and odd numbers were not given zinc. As per the guidelines by World Health Organization and UNICEF [15], children till 6 months were given 1 tablet (10 mg) and children more than 6 months were given 2 tablets (20 mg) dissolved in 5 mL of clean water or breast milk. This was given for 10 days. All children were observed for vomiting. For children who vomited within the first 15 minutes, a repeat dose was given.

2.9. Statistical Analysis

Data was collected, tabulated and analyzed using statistical package SPSS 16.0 version. Chi-square test was used to compare the parameters and P value <0.01 was considered statistically significant. Logistic regression analysis was done for primary and secondary outcome after zinc supplementation.

3. Results

Out of 2500 total case admitted the study period, only 506 (20.24%) cases met the criteria and were included in the cohort. [Table 1], out of them 322 (63.63%) were males and 184 (36.36%) females with male: female ratio of 1.75:1.65.4% children belonged to age 2-12 months. (Table 1).

Table 1. Sample Variables:

Variables	Number	Percentage	Total
			506
Sex: Male Female	 322 184	 63.6 36.4	
Age: 2-12 months 13-60 months	 331 175	 65.4 34.6	
Birth weight: LBW: Normal weight: Wt unknown	 63 415 28	 12.5 82 5.5	
Gestation at birth: Term Preterm	 469 37	 92.7 7.3	
Mode of delivery Normal LSCS	 445 61	 87.9 12.1	

The baseline demographic and clinical variables like age, gender, gestation age at birth, Ethnic group, mode of delivery, birth weight, immunization, socioeconomic status and nutritional status were similar in the two groups with no statistical differences (Table 2).

Table 2. Comparison of Sample Variables and Risk Factors for Pneumonia in Two Groups

Variables	Zinc Yes (n=253)	Zinc No (n=253)	Chi – square Test	P value
Sex: Male Female	 153(60.5%) 100(39.5%)	 169(66.8%) 84(33.2%)	0.166	0.083
Age: 2 – 12 months 13-60 months	 159(68%) 94(37.2%)	 172(68%) 81(32%)	1.476	0.262
Mode of delivery Normal LSCS	 222(87.7%) 31(12.3%)	 223(88.1%) 30(11.9%)	0.019	1.000
LBW Yes No Weight unknown	 27(10.7%) 215(85%) 11(4.3%)	 36(14.2%) 200(79.1%) 17(6.7%)	3.114	0.211
Gestation age at birth Term Preterm	 237(93.7%) 16(6.3%)	 232(91.7%) 21(8.3%)	0.729	0.495
Ethnic group: Brahmin Chhettri Dalit Mongol Newar Others	 80(31.6%) 56(22.1%) 42(16.6%) 48(19%) 15(5.9%) 12(4.7%)	 66(26.1%) 61(24.1%) 31(12.3%) 52(20.6%) 33(13%) 10(4%)	10.30	0.067
Socioeconomic status Good Average Low	 66(26.1%) 141(55.7%) 46(18.2%)	 57(22.5%) 148(58.5%) 48(19%)	0.871	0.647
Immunization Complete Incomplete None	 227(89.7%) 16(6.3%) 10(4%)	 221(87.4%) 21(8.3%) 11(4.3%)	0.804	0.669
Malnutrition Yes No	 136(53.8%) 117(46.2%)	 118(46.6%) 135(53.4%)	2.561	0.131

Outcome of Pneumonia with Zinc Supplementation:

Time to resolution of pneumonia – tachypnea, chest in drawings, hypoxia, nil per oral days and hospital stay was significantly (p<0.001) shorter in Group I [Table 3]. The mean ± SD for resolution of pneumonia in Group I Vs Group II were - tachypnea (2.96±1.128 vs. 4.67± 1.613 days), chest in drawings (1.632±0.952 Vs 3.359±1.558 days), hypoxia (24.616±1.778 vs. 41.675±2.11 hours), starting of oral feed (1.217±0.957 vs. 2.553±1.238 days) [Table 3].

Table 3. Early Outcome Variables with Mean ±SD Of Pneumonia in Two Groups:

Early outcome Variables	Zinc group(n=253)	Placebo group (n=253)	Chi – square Test	P value	Zinc group Mean± SD	Placebo group Mean ± SD
Resolution of tachypnea 2 days >2 days	206(81.4%) 47(18.6%)	79(31.2%) 174(68.8%)	1.29	0.001	2.96±1.128	4.67± 1.613
Chest in drawings: -no chest in drawings -improved in 2 days - improved after >2 days	10(4%) 208(82.2%) 35(13.8%)	10(4%) 66(26.1%) 177(70%)	1.687	0.001	1.632±0.952	3.359±1.558
Feed started: -Feed not stopped Feed started in 2 days Feed started in > 2 days	50(19.8%) 178(70.4%) 25(9.9%)	14(5.5%) 85(33.6%) 154(60.9%)	1.461	0.001	1.217±0.957	2.553±1.238
Duration of hypoxemia: -(O_2) not required - O_2) <48 hours - (O_2) ≥ 48 hours	51(20.2%) 159(62.8%) 43(17%)	15(5.9%) 100(39.5%) 138(54.5%)	53.785	0.001	24.616±1.778	41.675±2.11
Hospital stay 5 days > 5 days	227(89.7%) 26(10.3%)	100(39.5%) 153(60.5%)	1.394	0.001	4.826±1.225	6.450±1.990

In Group I 20/253 (7.9%) children were lost during follow up and 2/253 (0.79%) patient died and in group II 1 (0.39%) died and 30 (11.85%) were lost during follow up period. Hence, recurrence of pneumonia was assessed in 232 (506-22) /45.8% cases in Group I and 222 (506-31) /43.87% cases in Group II. This was also significantly less (p<0.001) in zinc recipients. [Table 4]

Table 4. Secondary outcome variable of pneumonia in two groups

Improvement Variables (N=453)	Zinc Yes (n=231)	Zinc No (n=222)	Chi – square Test	P value	Zinc Yes Mean± SD	Zinc No Mean ± SD
Recurrence of pneumonia - No - Yes	136(53.8%) 96(37.9%)	66(26.1%) 156(61.7%)	38.341	0.001	0.97±1.529	2.61±2.124
Mortality (n=3)	2(0.79%)	1(0.39%)				
Lost during follow up Period (n=50)	20(7.9%)	30(11.85%)	-	-		

Determinants in Two Groups by Logistic Regression:

There was earlier resolution of respiratory distress in zinc recipients with OR at 99% CI was 9.654 (5.605, 16.625) for tachypnea, 14.506 (8.064, 26,095) for chest in drawings, 5.860 (3.415, 10.057)for hypoxia, 13.725 (7.270, 25.912) for oral feed, 0.075 (0.040, 0.140) for hospital stay respectively. The recurrence of pneumonia was also less in group I with OR 3.348 at 99% CI (2.009, 5.581) [Table 5].

Table 5. Relation of Variables in Zinc and Non Zinc Groups

Variables Total (N=454)	Zinc		P value	Odds ratio (99% CI)
	Yes (n=231)	No (n=222)		
Secondary outcome (N=453)	22 –lost during follow up	31- lost during follow up		
Recurrence of Pneumonia: No recurrence Recurrence	136 96	66 156	0.001	3.348(2.009,5.581) 1
Primary outcome (N=506)				
Resolution of Tachypnea: Within 2 days >2 days	206 47	79 174	0.001	9.654(5.605,16.625) 1
No Chest in drawings: Within 2 days** >2 days	218 35	76 177	0.001	14.506(8.064,26.095) 1
Oxygen use for Hypoxia: <48 hours ## ≥ 48 hours	210 43	115 138	0.001	5.860(3.415,10.057) 1
Oral Feed: -within 2 days*** - >2 days	228 25	99 154	0.001	13.725(7.270,25.912) 1
Hospital stay: 5 days >5days	227 26	100 153	0.001	0.075(0.040,0.140) 1

[** No chest in drawing + chest in drawing improved in 2 days], [##No hypoxia + hypoxia improved in <48 hours] [***Oral feed not stopped + feed started in two days]

4. Discussion

There exists conflicting information regarding the efficacy of zinc as an adjunct to treatment for pneumonia in children. Results from Bangladesh [16] and Kolkata, India [17], showed that zinc supplemented children had a shorter duration of recovery from severe pneumonia. However, a trial conducted in South India found zinc to have no effect on recovery status [18]. Out of two studies done in Nepal, one showed no beneficial effect [19] and other showed marginal benefit [14] on short term clinical recovery of severe pneumonia. Unlike our study, all these above mentioned studies were done in severe pneumonia with no follow ups. This study has evaluated the effect of zinc in primary (short term clinical recovery) as well as secondary (recurrence of pneumonia) outcomes of recurrent pneumonia and found a significant beneficial role of zinc.

Severe pneumonia includes a wide spectrum of causes and does not define the specific etiology [20], hence this may be the reason why cases have responded differently to zinc administration in different studies. We evaluated a specific etiology that was bronchopneumonia and have excluded lobar or interstitial pneumonia and maybe Zinc has beneficial role in bronchopneumonia. The differences in study population and methods between studies may also have affected, thus the heterogeneity in the results. Another reason for the difference in results may be differences in the prevalence of zinc deficiency in the different study populations. Therefore a serum zinc levels would have given additional information but unfortunately serum zinc level was not done in any of the studies mentioned.

Recurrent wheezing (28.4%) in this study, which responded to Salbutamol were excluded from the study which decreased the chances of overlapping of diseased conditions. Compared to other studies [5,6], this study showed a high incidence of recurrent pneumonia which was 20.4%. The reason for this may be that mild and moderate malnutrition was included in this study where child maybe zinc deficient, hence immune deficiency leading to increased incidence of recurrent pneumonia.

Recurrent pneumonia was more prevalent in age group of 4-12 months (65.5%). This is the time when children are gradually weaned off from breast milk and additional supplementary food is added. Plus by this is time they grow and the nutritional requirement is more hence they may be deficient of many micronutrients including zinc.

4.1. Zinc Supplementation

Severe zinc deficiency depresses immune function [21], and even mild to moderate degrees of zinc deficiency can impair macrophage and neutrophil functions, natural killer cell activity, and complement activity [22]. These alterations in immune function might explain why low zinc status has been associated with increased susceptibility to pneumonia and other infections in children in developing countries [23,24]. The World Health Organization and UNICEF now recommend short-term zinc supplementation (20 mg of zinc per day, or 10 mg for infants under 6 months, for 10–14 days) to treat acute childhood diarrhea [15]. But there is no universal recommendation for zinc supplementation in pneumonia. As mentioned above many researches have been done in severe pneumonia with mixed results. The dose of zinc used in this study was same as per the WHO recommendation for diarrhea cases and was given for only 10 days.

4.2. Primary Outcome after Zinc Supplementation

Primary outcome in this study was evaluated on the basis of resolution of tachypnea, hypoxia, improvement on chest in drawings, starting of oral feeds, hospital stay. All these parameters showed statistically significant results. Similar findings were also noted by Ehsan Valavi et al [25]. Shorter duration of recovery with similar parameters in severe pneumonia was also observed in other studies [16,17] but again another study showed no effect of Zinc on the recovery status [18]. Yet in another study time for resolution of respiratory distress, tachypnea, dangers signs and hypoxia were similar in two groups but duration of hospital stay was shorter by 9 hrs. in the zinc group [26]. In this study also hospital stay was significantly shorter in zinc supplemented group. Beneficial effect of zinc on hospital stay can reduce the financial burden and sufferings of the patient so also the hospital load will be less as pneumonia is the most common cause in less than 5 years old for admission in the Pediatric Ward of the hospitals.

4.3. Secondary outcome after Zinc Supplementation

Recurrence of pneumonia episodes was significantly less in zinc supplemented group. Beneficial effect of Zinc for reduction in the incidence and prevalence of pneumonia was also reported in a Cochrane database of Systematic reviews in 2010 [27]. Zinc supplemented children had an OR of 0.59 (95% CI 0.41 to 0.83) for pneumonia [1] and in this study the OR was 3.348 (99% CI 2.009 to 5.581).

4.4. Limitations

This being a hospital based study, inferences cannot be generalized. There was no facility in the laboratory to measure zinc level of individual patients . If this could be done, more accurate information would have been obtained. During follow up period 53 cases were lost which might have an effect on the accuracy of the outcome result.

5. Conclusion

Zinc supplementation is beneficial in treatment as well as prevention of recurrent pneumonia. Possibly children having recurrent pneumonia have deficiency in zinc. Appropriate facilities in the laboratory for measurement of zinc levels should be made available. Other possible approaches and remedial measures should include food fortification, dietary diversification, and inclusion of zinc rich vegetables in the food.

List of Abbreviations

SD: Standard deviation
SPSS: Statistical Package for the Social Sciences
OR: Odds Ratio
AIDS: Acquired Immunodeficiency Syndrome
WHO: World Health Organization
RR: Respiratory Rate
CXR: X-ray Chest
SpO2: Peripheral capillary oxygen saturation
VSD: Ventricular septal defect
UNICEF: United Nations Children's Fund
>: More than
>: Less than
≤: Equal and less than
≥: Equal and more than

What this Study Adds

Maximum studies with zinc supplementation have been done in cases of severe pneumonia but this study was done in recurrent pneumonia. This study also gives information on beneficial effect of zinc supplementation in primary as well as secondary outcome of recurrent pneumonia.

Authors' Contributions

TM responsible for article concept, designing, data collection and analysis, literature review and write up of manuscript. KM responsible for article concept, designing, critical analysis of manuscript writing. BS responsible for statistical analysis and write up of manuscript. PP, EG and SB responsible for literature review and revision of the manuscript. All the authors approved the final document.

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Declaration of Conflicting Interests

The authors declare that there is no potential conflicts of interest with respect to the research, authorship and /or publication of this article.

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