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ORIGINAL ARTICLE

Role of prophylactic antibiotics in neonates born through meconium-stained amniotic fluid (MSAF)—a randomized controlled trial

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Abstract The objective of the study was to evaluate the effect of administering prophylactic antibiotics on the development of neonatal sepsis in term neonates born through meconium-stained amniotic fluid (MSAF). Two hundred and fifty eligible neonates were randomized to study group (Antibiotic group—receiving first-line antibiotics for 3 days) and control group (No Antibiotic group). Both groups were evaluated clinically and by laboratory parameters (sepsis screen and blood cultures) for development of sepsis. All neonates were monitored for respiratory, neurological, and other systemic complications and received supportive treatment according to standard management protocol of the unit. One hundred and twenty one neonates were randomized to 'Antibiotic' group and 129 to 'No Antibiotic' group. The overall incidence of suspect sepsis was 9.6 % in the study population with no significant difference between 'No Antibiotic' and 'Antibiotic' groups (10.8 vs. 8.2 %, p=0.48, odds ratio (OR) 0.74, 95 % confidence interval (CI) 0.32–1.73). Incidence of culture-proven sepsis was also not significantly different between the two groups (5.42 vs. 4.13 %, p=0.63, OR 0.75, 95 % CI 0.23–2.43). The incidence of mortality, meconium aspiration syndrome, and other complications was comparable amongst the two groups. *Conclusion*: Routine antibiotic prophylaxis in neonates born through MSAF did not reduce the incidence of sepsis in this study population. (Clinicaltrials.gov no. - NCT01290003)

Keywords Prophylactic antibiotics · Neonatal sepsis · Meconium-stained amniotic fluid

Abbreviations

HIE	Hypoxic ischemic encephalopathy
MSAF	Meconium-stained amniotic fluid
MAS	Meconium aspiration syndrome
PPHN	Persistent pulmonary hypertension of newborn
UTI	Urinary tract infection

Introduction

Meconium-stained amniotic fluid (MSAF), as a result of passage of fetal colonic contents into the amniotic cavity, is noted in approximately 13 % of all deliveries [1, 2]. Meconium aspiration syndrome (MAS), a life-threatening neonatal respiratory disorder that results from aspiration of meconium into the lungs during intrauterine gasping or at the time of first breath, develops in 5 % of infants delivered through MSAF. More than 4 % of MAS infants die, accounting for 2 % of all perinatal deaths [1, 3].

Although meconium staining and MAS are common neonatal problems, their delivery room and subsequent nursery management remain debatable. Most newborns with MSAF

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receive antibiotics as part of conventional treatment. Meconium passage in utero has been hypothesized to represent a response to fetal bacterial infection [4]. Experimental work has shown that meconium enhances bacterial growth in vitro [5, 6], and the risk of intraamniotic infection is increased in the presence of MSAF [7]. More recently, specific effects of meconium on host defenses have been demonstrated in vitro, giving credence to the possible role of meconium in inhibition of phagocytic activity and respiratory burst response by alveolar macrophages, rendering patients with MAS more susceptible to infection [8].

However, several studies have shown that empiric use of antibiotics in the routine management of MAS is of no benefit [9–11]. Clinical instances, confirmed by autopsy, in which infection is superimposed on even the most severe forms of MAS, is rare [9]. The incidence of bacterial infection in neonates born through MSAF as well as those developing MAS has not been systematically evaluated till date [12]. Hence, the purpose of this prospective randomized controlled trial is to compare the clinical course, complications, and infection-related outcomes in cases of MSAF and MAS, treated with or without antibiotic therapy.

Methods

This study was an open-label randomized controlled trial conducted from 1 June 2010 to 31 January 2011 in the Neonatal division of Department of Pediatrics of a tertiary care teaching institution. The ethics committee of the institute approved the protocol for conducting the study, and the study was registered with clinical trial registry. (NCT01290003)

All full-term infants born as singleton cephalic presentation through MSAF were eligible for the study. Exclusion criteria were presence of major congenital malformation or refusal of consent by the parents. Parents of the eligible neonates were approached for participation within 1 h of birth, and subjects were enrolled only after obtaining a written informed consent in their own local language.

Enrolled neonates were randomized into the *study* (n=121) or the *control* group (n=129) based on block randomization, done using random number table generated from computer software by the study statistician. Serially numbered opaque brown sealed envelopes containing group assignment were used for allocation concealment and were opened immediately following enrolment of an eligible neonate, not later than 1 h from birth, by the physician on duty. The treating clinician and nursery personnel were blinded to the study group. A sample size of 112 in each group was shown to have an 80 % power to detect 10 % reduction in the sepsis rate, assuming a baseline value of 15 % (based on past unit records), using a two-group t test with 0.05 two-sided significance.

Neonates randomized to the study (Antibiotic) group received prophylactic intravenous antibiotics (piperacillin-tazobactam 100 mg/kg/day and amikacin 15 mg/kg/day for 3 days) according to first-line antibiotic policy of the unit. The control (No Antibiotic) group did not receive any antibiotics. All babies irrespective of their group allocation were admitted to the nursery and worked up for sepsis using a sepsis screen and blood culture. Sepsis screen consisting of total leukocyte count, absolute neutrophil count and immature to total neutrophil ratio (by Coulter and peripheral smear examination), micro-ESR and C-reactive protein was performed at 2 and 12 h and at 72 h or thereafter if required. Blood culture was performed at 2 h and thereafter if required. Symptomatic babies (presence of respiratory distress, lethargy, abdominal distension, temperature or hemodynamic instability, hypoglycemia, apnea, or any other systemic abnormalities), either from birth or any time during the course of stay, in both groups, were subjected to further investigations such as chest X-ray, arterial blood gas, and lumbar puncture as deemed necessary by the treating physician. Appropriate treatment was started or modified as per the decision of consultant-in-charge taken as one serving the best interest of the baby. All such cases requiring prolongation of antibiotics beyond 3 days in Antibiotic group, or starting of antibiotics in the No Antibiotic group (symptomatic or sepsis screen positive), were noted by the study team, as decided a priori. All babies received supportive care in the form of maintenance of temperature, fluid balance, and blood glucose. Further respiratory, cardiac, or other system support as needed was provided as per standard unit protocol. All these neonates were monitored daily by the study coordinators for vital signs, i.e., heart rate, respiratory rate, blood pressure, oxygen saturation, and signs of respiratory distress or failure till the time of discharge (minimum 72 hours) or death. All neonates were discharged home and were followed up in neonatal follow-up clinic at 2 days, 2 weeks, and 4 weeks post-discharge for signs and symptoms of sepsis.

Data pertaining to various maternal demographic variables like parity, risk factors for sepsis (prolonged rupture of membranes >24 h, intrapartum fever ≥38.0 °C, unclean or frequent per-vaginal examination (≥3), clinical chorioamnionitis, maternal UTI), fetal distress (fetal heart rate abnormalities on auscultation or cardiotocography), meconium consistency (thick pea soup or thin watery), mode of delivery, along with neonatal variables like sex, birth weight, gestational age, APGAR score, incidence of non-vigorous neonates and requirement of endotracheal intubation for positive pressure ventilation was recorded in a pretested proforma. Additional data collected during neonatal hospital stay included duration and severity of respiratory distress (using Downe's score), requirement and total duration of oxygen therapy, need for and duration of CPAP or mechanical ventilation, and incidence of

complications like air leaks or persistent pulmonary hypertension of newborn (PPHN). In addition, any development or progression of hypoxic ischemic encephalopathy (HIE) or involvement of other organ systems and the duration of stay were recorded.

Outcome measures

The primary outcome variable was defined as the incidence of early (within first 72 h of birth) or late onset (after 72 h of birth) suspect sepsis (clinical symptoms or positive sepsis screen defined as ≥2 positive parameters) and confirmed sepsis (positive blood culture). Secondary outcome variables included the incidence and severity of MAS and its complications, HIE, duration of hospital stay, and mortality.

Statistical analysis

Computerized analysis of the data on intention to treat principle was done using SPSS (version 17.A). Continuous data was analyzed by Student's *t* test in normal distribution. Chi-squared test or Fisher's exact test was used for categorical variables. A significance level of 0.05 was used.

Results

Out of 4,948 hospital deliveries from 1 June 2010 to 31 January 2011, a total of 384 neonates were born through MSAF (7.8 % of all births). Among the 284 eligible neonates, 34 were excluded due to presence of major congenital malformation (6), refusal of consent (12), or logistic reasons such as non-availability of consent within the stipulated time for randomization (16). There were 121 neonates in the Antibiotic group and 129 in the No Antibiotic group. None of the infants discontinued intervention or were lost to follow-up (Fig. 1).

Selected demographic and baseline characteristics for the entire population are represented in Table 1. There was no difference between the groups with regard to gestational age, gender, extent of prenatal care received, consistency of MSAF, or mode of delivery.

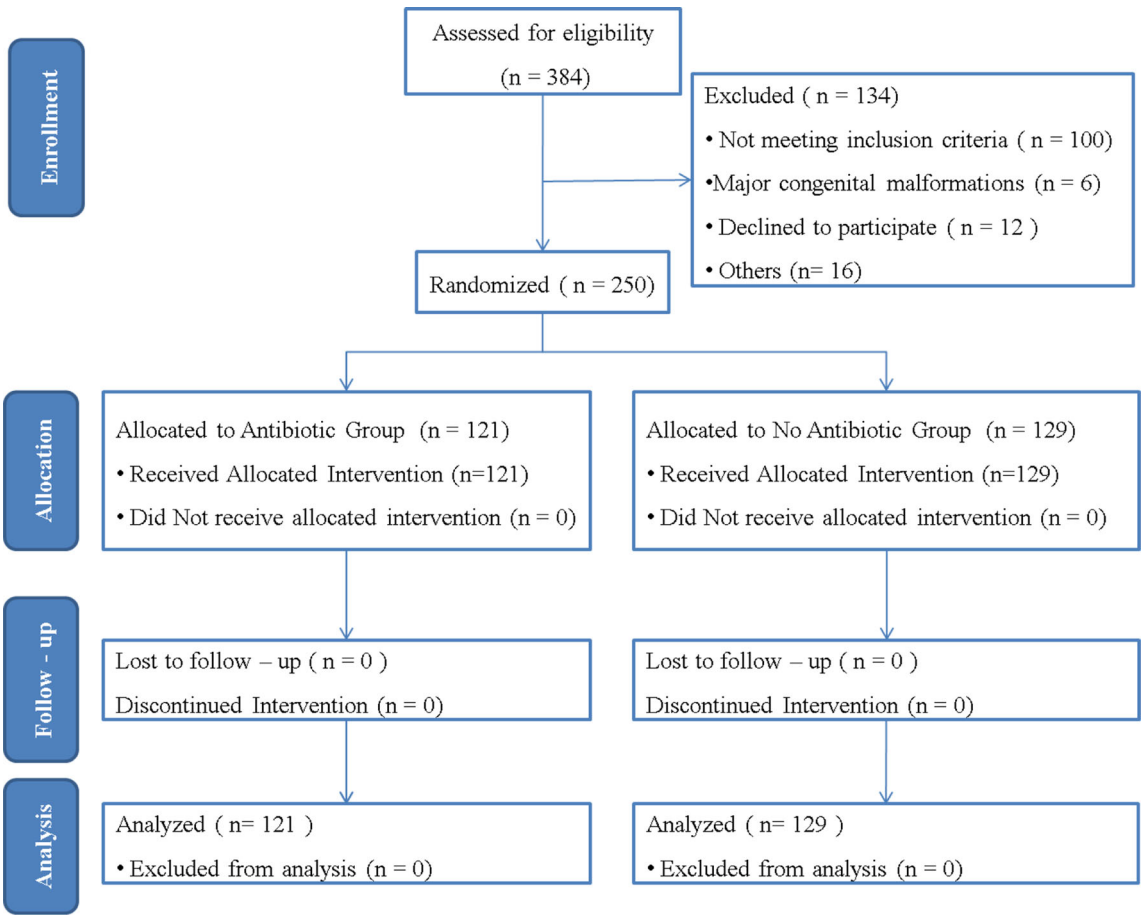

Fig. 1 Trial flow of the study

Table 1 Baseline variables

Parameters	Antibiotic group (n=121)	No Antibiotic group (n=129)	p value
Male sex, n (%)	81 (66.9 %)	74 (57.3 %)	0.12
Gestational age in weeks, median (interquartile range)	39 (38–40)	39 (38–40)	0.72
Birth weight in grams, mean±SD (95 % CI)	2,784.35±447.19 2,703.9–2864.9	2,640.9±427.5 2,567.1–2714.7	0.07
Risk factors for sepsis[a], n (%)	35 (29 %)	34 (26.4 %)	0.65
Use of intrapartum antibiotics, n (%)	21 (17.35 %)	14 (10.86 %)	0.14
Antenatal registration, n (%)	90 (74.4 %)	93(72.1 %)	0.68
Presence of fetal distress	52 (42.9 %)	61 (47.3 %)	0.49
Mode of delivery, n (%)			
Vaginal	66 (54.5 %)	60 (46.5 %)	0.33
Caesarean	54 (44.6 %)	65 (50.4 %)	
Others (forceps/vacuum)	1 (0.8 %)	4 (3.1 %)	
Presence of thick meconium, n (%)	66 (54.6 %)	77 (59.7 %)	0.41
Non-vigorous MSAF, n (%)	50 (41.3 %)	58 (44.9 %)	0.56
Requirement of intratracheal suction, n (%)	50 (41.3 %)	58 (44.9 %)	0.56
Requirement of positive pressure ventilation at birth, n (%)	40 (33.1 %)	44 (34.1 %)	0.86
Respiratory distress at birth, n (%)	39 (32.2 %)	30 (23.4 %)	0.11
Requirement of oxygen at birth, n (%)	14 (11.5 %)	16 (12.4 %)	0.84
APGAR score, median (quartile range)			
1 min	8 (6–8)	7 (5–8)	0.33
5 min	8 (8–9)	8 (8–9)	0.66
10 min	9 (8–9)	9 (8–9)	0.74
Cord gases			
Cord pH, mean±SD (95 % CI)	7.18+0.14 (7.155–7.204)	7.19+0.15 (7.164–7.215)	0.58
Base excess, median (interquartile range)	8.6 (6.2–11.9)	10.4 (7.2–15.2)	0.26

[a] Risk factors for sepsis (≥2 parameters positive)—prolonged rupture of membranes >24 h, intrapartum fever ≥38.0 °C, unclean or frequent per-vaginal examination (PVE ≥3), clinical chorio-amnionitis, maternal UTI, and presence of perinatal asphyxia (pH<7.0 with base excess>−16 with neonatal depression at birth)

Primary outcome All the babies were assessed for development of suspect and confirmed sepsis. The incidence of suspected sepsis was found to be 10.8 % (n=14) in the No Antibiotic group and 8.2 % (n=10) in the Antibiotic group. Overall incidence of suspect sepsis in the study population was 9.6 %. The difference however was not found to be statistically significant (p=0.48, odds ratio (OR)=0.74, 95 % confidence interval (CI)=0.31–1.73).

Total number of neonates who developed confirmed sepsis in both the groups were very few and were comparable, being five (4 %) and seven (5.5 %), respectively, in the Antibiotic and No Antibiotic group. There was no statistically significant difference between the two groups (p=0.63, OR=0.75, 95 % CI=0.23–2.43) (Table 2). The predominant bacterial flora cultured included *Staphylococcus aureus* in two patients and Gram-negative organisms like *Escherichia coli* in three, *Pseudomonas* in three, *Acinetobacter* in three, and *Klebsiella* in one patient. The incidence of late onset sepsis defined as development of sepsis after 72 h of life was also found to be comparable in both groups (n=3 and 5, respectively, p=0.72, OR=0.63, 95 % CI=0.15–2.7). Antibiotics were continued beyond 3 days/changed in the study group or added in the control group subjects, based on clinical judgement or sensitivity pattern, as per decision of the treating clinical team. In

Table 2 Primary outcome measures—incidence of sepsis

Outcome	Antibiotic group	No Antibiotic group	p value	Odds ratio	95 % CI
Suspect sepsis, n (%)	10 (8.2 %)	14 (10.8 %)	0.48	0.74	0.31–1.73
Confirmed sepsis, n (%)	5 (4.17 %)	7 (5.42 %)	0.63	0.75	0.23–2.43

Table 3 Secondary outcome measures—respiratory outcomes

Outcome	Antibiotic group	No Antibiotic group	*p* value	Odds ratio	95 % CI
Respiratory distress					
Present, *n* (%)	40 (33 %)	36 (27.9 %)	0.37	1.27	0.74–2.19
Duration (h), median (range)	24 (6–72)	12 (4–66)	0.90		
Oxygen therapy					
Received oxygen, *n* (%)	19 (15.7 %)	20 (15.5 %)	0.96	1.02	0.51–2.01
Duration (h), median(range)	52 (12–88)	30 (12–90)	0.86		
Requirement ≥48 h, *n* (%)	7 (5.7 %)	12 (9.3 %)	0.15	2.57	0.70–9.23
Mechanical ventilation					
Received, *n* (%)	6 (4.95 %)	3 (2.32 %)	0.32	2.19	0.54–8.96
Duration (h), median (range)	43 (14–56)	26 (1–78)	0.75		
Incidence of MAS[a], *n* (%)	22 (18.18 %)	20 (15.5 %)	0.57	1.21	0.62–2.35
Severity of MAS[b], *n* (%)					
Mild	12 (9.9 %)	12 (9.3 %)	0.72		
Moderate	4 (3.3 %)	5 (3.8 %)			
Severe	6 (4. 9 %)	3 (2.3 %)			
Duration of stay (days), median (range)	3 (3–3)	3 (3–3)	0.36		

Respiratory outcomes include symptoms developing anytime during the course of stay

[a] MAS—respiratory distress in a neonate born through MSAF with compatible radiological findings

[b] Severity of MAS—mild, disease requiring <40 % oxygen for <48 h; moderate, requiring >40 % oxygen or for >48 h or need for CPAP without air leak; severe, disease requiring assisted ventilation or presence of complications like PPHN or air leaks

the study group, seven (5.7 %) patients received antibiotics beyond 3 days and antibiotics were changed in two (1.6 %) patients. In the controls, antibiotics were added in 17 patients (13 %). The reasons were positive blood culture (n=7), lumbar puncture suggestive of meningitis (n=2), positive sepsis screen with symptoms (n=2), and clinical condition suggestive of infection like diarrhea and skin pustules (n=6). On performing a per protocol sensitivity analysis on these crossovers, the incidence of suspect sepsis between the two groups was found to be significant (p=0.03); however, no significant difference was observed in confirmed sepsis (p=0.06). Suspect sepsis was a diagnosis based on clinician's assessment of the neonate deemed to require prompt treatment to prevent apparent deterioration, which might not have been confirmed on blood culture reports later. On doing a subgroup analysis on incidence of sepsis in symptomatic babies (presenting with respiratory distress), both groups were found to have comparable incidence of suspect sepsis (p=0.084). The incidence of confirmed sepsis was more in symptomatic babies, although the total numbers was very few (p=0.01).

Secondary outcomes Respiratory distress at birth was noted in 40 and 36 babies in Antibiotic and No Antibiotic groups, respectively, which settled within first 48 h in majority of the subjects irrespective of the group. The requirement of oxygen therapy (monitored by pulse oximetry and instituted if SpO_2<90 %) was also comparable between both groups (19 vs. 20, p=0.96). No significant difference was detected between the two groups as regards the duration and severity of respiratory distress, incidence and severity of MAS, requirement and duration of oxygen therapy or ventilation, development of HIE, and duration of stay (Table 3).

Six patients died during hospitalization, three in each group. The causes included respiratory failure with hypoxic ischemic encephalopathy with PPHN (n=3) and respiratory failure with hypoxic ischemic encephalopathy with septic shock (n=3). The incidence of complications was also similar in the two groups. One patient in the Antibiotic group developed pneumothorax while one patient in the

Table 4 Complications

Complications	Antibiotic group, *n*	No Antibiotic group, *n*	*p* value
Pneumothorax	1	0	0.48
PPHN	1	2	1.0
Intracranial hemorrhage	0	1	1.0
Oliguria	1	0	0.48
Azotemia	1	0	0.48
Diarrhea	0	4	0.12
Mortality	3	3	1.0
HIE			
Stage I/II	14	14	1.0
Stage III	1	2	

Antibiotic group and two in the No Antibiotic group suffered from PPHN (Table 4).

Discussion

This trial shows that routine administration of prophylactic antibiotics has no demonstrable benefit in the management of neonates born through MSAF, especially in asymptomatic neonates. The incidence of infectious and respiratory complications is not altered by antibiotic use, and the overall mortality or morbidity of such neonates is also not affected by this intervention. In both groups, incidence of sepsis, severity of MAS, mortality, and duration of stay are comparable.

Presence of meconium in the amniotic fluid has long been speculated to increase the susceptibility of neonates to sepsis. Studies in the past have shown the likelihood of fetal bacterial infection as a causative factor for passage of meconium [4, 13]. Moreover in vitro studies done by Florman et al. [6], Bryan et al. [5], and Schimmel et al. [14] have demonstrated that meconium alters the bacteriostatic properties of amniotic fluid predisposing the fetus to infection. This increased susceptibility to infection has been believed to result from decreased host immune response as demonstrated by Craig et al. [8]. The difficulty in differentiating bacterial pneumonia from MAS on the basis of clinical and radiographic findings prompts physicians globally to have a low threshold for starting antibiotics in infants with MSAF [15].

Recent studies have however challenged this concept both in terms of overall incidence of sepsis and the role of antibiotics in reducing or preventing infectious morbidity in neonates born through MSAF. Wiswell et al. examined the incidence of culture-proven bacteremia in 741 meconium-stained neonates and demonstrated the incidence of culture-proven bacteremia to be 0.7 % in MSAF population compared with 0.8 % in babies born through clear liquor [12]. In a retrospective analysis by Singh et al., positive blood culture was obtained only in 2.5 % of neonates born with MAS [16]. Similarly, Krishnan et al., in their retrospective review, found no significant difference in the incidence of septicemia, between infants intubated for intratracheal suctioning of meconium compared to non-intubated infants [17]. These three studies reveal that incidence of sepsis is not significantly high in meconium-stained neonates.

Studies evaluating the role of antibiotics found no difference in infectious morbidity in babies with MAS, treated with or without antibiotics, in the studies by Lin et al. [10] and Shankar et al. [11]. Similarly, the incidence of sepsis in MAS reported by Basu et al. [9] was 4 % in the antibiotic and 2.7 % in No Antibiotic group. In the present study, the incidence of culture-proven sepsis was 4 and 5 %, respectively, in the two groups. Further, no difference in the duration of tachypnea, oxygen supplementation, mean duration and severity of respiratory distress, duration of stay, and mortality was noted between the two groups in any of these trials [9, 10, 11], similar to the results obtained in our study.

However, most of the previous studies have focused on the effect of prophylactic antibiotics in preventing sepsis in a select group of neonates with MAS. Further, they differ from our study in terms of inclusion criteria, measurement of outcome parameter, and sample size. The study by Shankar et al. [11] had a very small sample size, excluded neonates with maternal risk factors for neonatal sepsis, and did not define sepsis based on blood culture positivity. Basu et al. [9], in their study of infants with MAS, excluded all infants with any risk factor for sepsis and those who developed early onset sepsis within first 24 h of life. Moreover, they randomized the subjects at 24 h of life thus compromising the generalizability of the study. No follow-up was done in both of these studies. A more extensive study by Lin et al. [10] though comparable in sample size to our study included only non-ventilated cases of MAS with no perinatal risk factor for sepsis. All these studies have included neonates without risk factors for sepsis and have reported no benefit of antibiotic administration for management of MAS. Our study has comprehensively included all meconium-stained neonates irrespective of risk status for sepsis, and yet the results reveal no role of antibiotics in their management. In babies with high suspicion or with presence of risk factors for sepsis, sepsis screen can be used to avoid unnecessary use of antibiotics and intravenous access and at the same time prevent missing of cases requiring treatment. The limitations of the study include practical limitations in ensuring blinding due to presence or absence of intravenous line which could have introduced some clinician bias. Further, sample size calculation for this study was based on incidence of sepsis in our unit in the past year (2008–2009). With steady improvement in clinical practices, the same has decreased over the following years as reflected in the sepsis outcome in both study groups.

Conclusion

Our study concludes that there is no difference in the incidence of infection in neonates with meconium-stained amniotic fluid treated with or without antibiotics. Hence, we recommend the avoidance of empirical

use of antibiotics in such infants without documented evidence of infection.

Conflict of interest None

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