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Original Article

Respiratory morbidity in newborns with a gestational age at or above 32 weeks

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ABSTRACT

INTRODUCTION. This study aimed to investigate the reasons for early admissions to two neonatal intensive care units (NICU) for respiratory morbidity, defined as any disease presenting with respiratory symptoms in moderate to late preterm and term infants.

METHODS. This retrospective cohort study included all infants with gestational age (GA) ≥ 32 weeks admitted to the NICUs in 2021 in two hospitals covering almost 20% of all births in Denmark.

RESULTS. In total, 921 infants (8% of all liveborn with a GA ≥ 32 weeks) were admitted to the NICUs within the first 24 hours of life. Among these, 60% were diagnosed with respiratory morbidity, with a corresponding incidence of 35% and 3.2% in preterm and term infants, respectively. In the term group, the median duration of respiratory support was five hours, with 73% being treated for less than 12 hours. In the preterm group, respiratory support was also brief (19 hours median), and 30 (15%) infants developed respiratory distress syndrome (RDS) (5.3% incidence of liveborn with a GA of 32-36 weeks).

CONCLUSIONS. In term newborns, mild respiratory morbidity is the most frequent cause for early admission, and the duration of treatment is often short. In moderate to late preterm infants, respiratory morbidity also tends to be mild, though 15% of the admitted infants developed RDS.

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Approximately 8% of newborns in Denmark are admitted to a neonatal intensive care unit (NICU) within 24 hours of life. Respiratory morbidity is a common and possibly major cause of these admissions [1, 2]. Respiratory morbidity is defined as any disease presenting with respiratory symptoms. In term infants, early admissions are often brief, indicating mild symptoms. Still, early mother-infant bonding is impaired, and recent years have brought a growing interest in reducing these early separations [3]. In infants born moderate to late preterm (gestational age (GA) 32-36 weeks), respiratory symptoms are also common, and some infants progress to respiratory distress syndrome (RDS). Uncomplicated RDS symptoms progress during the first 48-72 hours, followed by recovery, during which endogen surfactant production increases and lung function improves. RDS usually resolves completely within seven days. The clinical course can be altered by treatment with surfactant, leading to immediate resolution of symptoms [4]. The indication for surfactant treatment is well investigated in very preterm infants (GA below 32 weeks), with treatment recommended when oxygen requirements exceed 30%. However, there are no evidence-based guidelines for moderately and late preterm infants [5, 6].

Few studies have described the extent of respiratory morbidity in moderate to late preterm and term infants

admitted to the NICU, and no data are available from Denmark. This study aimed to address this gap by investigating the early NICU admissions in moderately to late preterm and term infants with respiratory morbidity. We aimed to characterise respiratory morbidity and duration of treatment in the NICU, including the incidence of RDS and surfactant use.

Methods

In Denmark, 97% of newborns are delivered in hospitals, all registered in the Danish Newborn Quality database (DNQ) [7]. Infants born with a GA below 34-35 weeks or deemed "not healthy" are typically admitted to the neonatal ward, while other infants may either be admitted to a maternity ward or discharged home [8, 9].

This observational cohort study was based on data collected retrospectively from two level-2 NICUs in Denmark. In East Denmark, there are seven level-2 NICUs, local units that provide medical care for infants with a GA above 28 weeks, and one central level-3 NICU. Infants are transferred from the local NICU to the level-3 facility if intensive care, including mechanical ventilation, is required. Prenatal transfer to the level-3 facility is standard if intensive care is expected after delivery. The present study encompassed two hospitals (North Zealand Hospital, Hilleroed and Hvidovre Hospital), accounting for almost 20% of all deliveries in Denmark [10].

The participants were identified by the shared electronic healthcare platform Epic. All neonates born in either hospital and admitted to the NICU in 2021 were included if they met the inclusion criteria: at least one respiratory diagnosis (identified by diagnosis codes) or treatment with nasal continuous positive airway pressure (NCPAP) or surfactant (identified by procedure codes). All the infants' medical records were retrieved, and prespecified data were collected retrospectively. Moreover, the DNQ database was used to calculate the admission rate of all liveborn infants at the two hospitals.

The study was designed as a quality improvement study and was approved by the local administration at the participating hospitals.

Outcome measures, classification of respiratory morbidity and background data

The criterion for respiratory morbidity was met if the infant was given one of the following ICD-10 diagnoses: P22.0 RDS, P22.1 transient tachypnea of the newborn (TTN), P24.0 meconium aspiration syndrome (MAS) or P22.8 other respiratory distress in newborn. Additionally, the criterion was fulfilled if the infant required non-invasive continuous positive airway pressure (NCPAP) (BGFC 32) or was treated with surfactant (BGHF 1). The extent of respiratory morbidity was described by the duration of respiratory support, the fraction of inspired oxygen (FiO_2) at admission, the highest FiO_2 required during admission, the need for surfactant treatment and complications such as the presence of pneumothorax, the need for mechanical ventilation and transfer to a level-3 NICU. The duration of admission to the NICU was used as a marker of disease severity. The medical records were retrieved, and in some cases, the diagnoses were reclassified for this study. The diagnoses were classified based on commonly accepted descriptions of the diseases [11]. RDS and all alternative classifications in cases of uncertainty were resolved through consensus within the research group. When available, classifications were corroborated by X-ray findings.

The classification of RDS was based on the following criteria: need for NCPAP for more than four days and a maximum oxygen requirement exceeding 0.3 FiO_2. Additionally, RDS was classified if the infant received exogenous surfactant with an immediate improvement in respiratory symptoms and a reduced need for supplemental oxygen without immediate relapse. This was characterised by an initial reduction in oxygen requirements followed by a subsequent increase shortly after administration.

To differentiate RDS from infection, we classified the diagnosis as infection if the infant received antibiotics for

at least five days. In newborns, infection is treated with at least five days of antibiotics according to guidelines [12]. If antibiotics are initiated due to clinical symptoms, treatment is discontinued after 2-3 days if blood cultures and repetitive measurements of c-reactive protein (CRP) do not support the diagnosis of infection (not exceeding 50 mg/l).

To differentiate RDS from TTN, respiratory disease was classified as TTN if the infants were treated with NCPAP for less than four days or had a maximum oxygen requirement below 30%.

MAS was considered in infants born in meconium-stained amniotic fluid, particularly in cases where it could not be clearly differentiated from TTN,

Persistent pulmonary hypertension (PPHN) of the newborn is characterised by increased pulmonary vascular resistance after delivery, resulting in hypoxia. The severe form of this disease requires intensive treatment. In most cases, PPHN is due to various pulmonary diseases, and the diagnosis was not included in the inclusion criteria [13].

Statistics

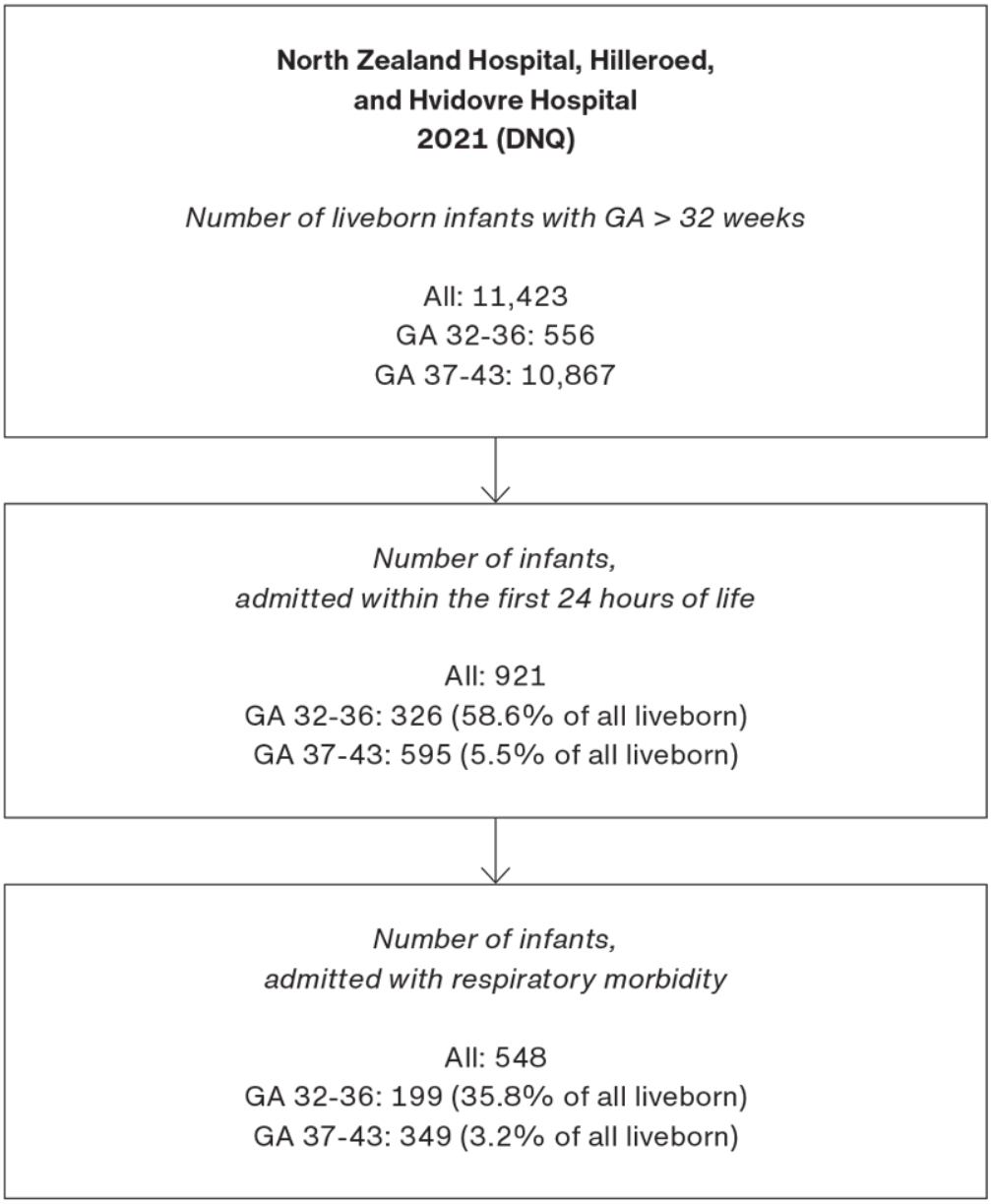
Categorical variables were presented as frequencies in counts with corresponding percentages; continuous variables as medians with interquartile range. Incidences were presented as cases per 100 liveborn infants within a similar GA range. Baseline data from the two hospitals were compared with the χ^2 or Fisher's exact test for categorical variables. Results were considered statistically significant if $p < 0.05$. Data management and statistical analyses were performed using Redcap and IBM SPSS Statistic (version 28.0.0.0).

Trial registration: not relevant.

Results

In total, 11,423 infants with a GA at or above 32 weeks were liveborn at the two hospitals in 2021. Among these infants, 8% were admitted to the NICU within the first 24 hours of life, corresponding to 5.5% of all full-term live births and 58.6% of all moderate to late preterm infants. Among these early NICU admissions, approximately 60% had respiratory morbidity (**Figure 1**). In the entire cohort, more than half of the infants admitted to NICUs with respiratory morbidity were delivered by Caesarean section, and more than 60% were boys (**Table 1**). The baseline characteristics between the two hospitals were similar (data not shown in Table 1) – except for more women with gestational diabetes at Hvidovre Hospital ($p = 0.012$).

FIGURE 1 Trial diagram showing the study population.



DQN = The Danish Newborn Quality database; GA = gestational age.

TABLE 1 Baseline characteristics of the study population divided into two groups based on gestational age.

	North Zealand Hospital, Hilleroed, and Hvidovre Hospital, n (%) (N_{tot} = 548)	
	GA 32-36 wks (N_{32-36} = 199)	GA 37-43 wks (N_{37-43} = 349)
Gender		
Male	126 (63.3)	212 (60.7)
Delivery mode		
Vaginal	66 (33.2)	135 (38.8)
Instrumental vaginal delivery	6 (3.0)	65 (18.7)
Emergency Caesarean section	112 (56.3)	89 (25.6)
Elective Caesarean section	15 (7.5)	59 (17)
Maternal factors		
Risk for infection[a]	55 (27.6)	150 (43.1)
Maternal antibiotic	57 (28.6)	42 (12.1)
Multiple pregnancy	55 (27.6)	14 (4.0)
Maternal diabetes	21 (10.6)	29 (8.3)
Maternal smoking	2 (1.0)	6 (1.7)
Pre-pregnancy BMI		
< 18.5 kg/m²	5 (2.5)	8 (2.3)
18.5-24.9 kg/m²	105 (52.8)	196 (56.2)
25.0-29.9 kg/m²	45 (22.6)	83 (23.9)
≥ 30 kg/m²	38 (19.1)	56 (16.1)
Missing	6 (3.0)	6 (1.7)
Betamethasone use		
GA < 34 wks	37 (18.6)	
GA 34-36 wks	4 (2.0)	
Subtotal	41 (20.6)	-
Apgar 5 score		
7-10	190 (95.5)	309 (88.5)
4-6	8 (4.0)	28 (8.0)
< 4	1 (0.5)	11 (3.2)
Missing	0	1 (0.3)
pH, umbilical artery		
≥ 7.20	166 (83.4)	192 (55)
< 7.20	29 (14.6)	153 (44)
Missing	4 (2.0)	4 (1.1)

GA = gestational age.
a) Maternal risk factors for infection include maternal Group B Streptococcus infection, fever during birth, prolonged rupture of the membranes and meconium-stained fluid.

The incidence of early respiratory morbidity was 3.2% among all liveborn term infants and 35.8% among moderate to late preterm infants, with no significant differences between the two hospitals (p = 0.5).

In the term group, 81.6% (n = 284) were classified as TTN; 76% of these infants never required supplemental oxygen, and respiratory support was provided for median five hours (with a median nine-hour admission time). Infections and MAS were the most frequent alternative diagnoses. Six of the term infants were treated with surfactant (two infants without clinical effect, one with RDS and three with MAS). Among the infants with respiratory morbidity, 11 infants (3.2%) were transferred to the level-3 NICU, and all were treated with mechanical ventilation. A total of six infants developed pneumothorax, and hereof three were treated with

mechanical ventilation (**Table 2**).

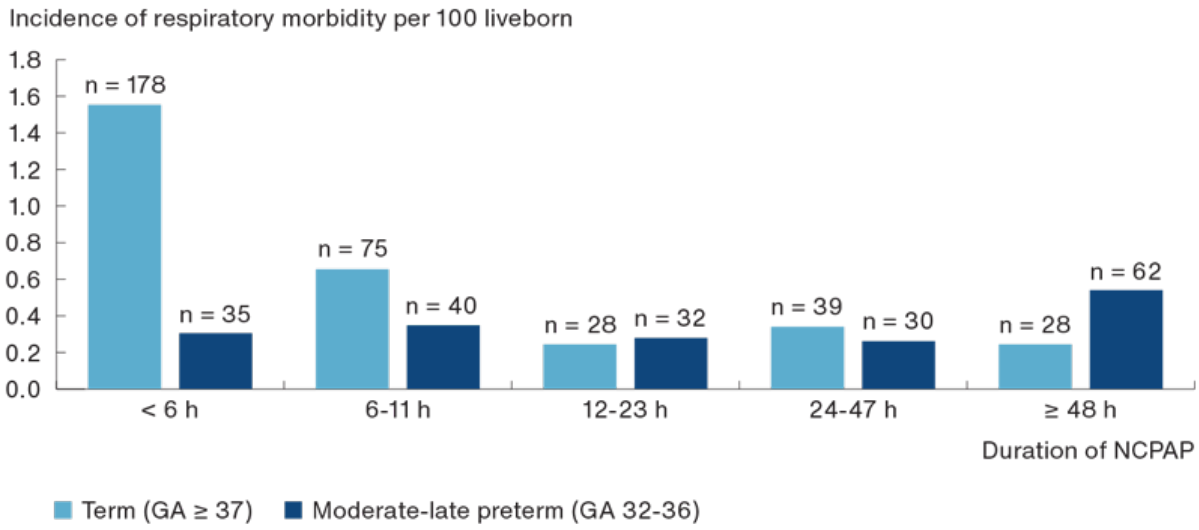
TABLE 2 Respiratory data for term and moderate-late preterm infants.

	Moderate-late preterm (N_{pre} = 199)			Term (N_{term} = 349)		
	RDS	TTN	other: infection, MAS	RDS	TTN	other: infection, MAS
Infants, n (%)	30 (15)	156 (78.4)	13 (6.5)	5 (1.4)	284 (81.6)	60 (17.2)
GA, n (%)						
32-34 wks	18 (60)	71 (45.5)	7 (53.8)	-	-	-
35-46 wks	12 (40)	85 (54.5)	6 (46.2)	-	-	-
37-38 wks	-	-	-	2 (40)	82 (28.9)	3 (5)
39-43 wks	-	-	-	3 (60)	202 (71.1)	57 (95)
NCPAP, median (min.-max), hrs						
GA 32-34 wks	120.5 (74-312)	23 (2-189)	35 (0-128)	-	-	-
GA 35-36 wks	100 (7-154)	11.5 (0-114)	18 (0-46)	-	-	-
GA 37-38 wks	-	-	-	122 (93-151)	5 (0-111)	0 (0-6)
GA 39-43 wks	-	-	-	97 (16-264)	5 (0-192)	15 (0-120)
FiO_2, n (%)						
At admission:						
21%	2 (6.7)	126 (80.8)	7 (53.8)	0	219 (77.1)	27 (45.0)
22-29%	7 (23.3)	9 (5.8)	3 (23.1)	0	19 (6.7)	5 (8.3)
30-39%	13 (43.3)	13 (8.3)	3 (23.1	3 (60)	24 (8.5)	6 (10.0)
≥ 40%	8 (26.7)	8 (5.1)	0	2 (40)	22 (7.7)	22 (36.7)
Maximum						
21%	0	108 (69.2)	8 (61.5)	0	217 (76.4)	27 (45.0)
22-29%	0	19 (12.2)	2 (15.4)	0	21 (7.4)	5 (8.3)
30-39%	7 (23.3)	20 (12.8)	2 (15.)	0	26 (9.2)	5 (8.3)
≥ 40%	23 (76.7)	9 (5.8)	1 (7.7)	5 (100)	20 (7)	23 (38.4)
Surfactant, n (%)						
GA 32-34 wks	10 (33.3)	0	0			
GA 35-36 wks	4 (13.3)	0	0			
GA 37-38 wks				0	2 (0.7)	0
GA 39-43 wks				1 (20)	0	3 (5.1)
Complications, n (%)		0				
Transferred to level 3 unit	4 (13.3)		3 (23.1)	1 (20)	2 (0.7)	8 (13.6)
Of the transferred:						
Treated with mechanical ventilation	2 (6.7)		1 (7.7)	1 (20)	2 (0.7)	8 (13.6)
Developed pneumothorax	1 (3.3)		0	1 (20)	2 (0.7)	3 (5.1)
Antibiotics duration[a], n (%)						
< 5 days: suspected infection	13 (43.3)	9 (5.8)	2 (15.4)	3 (60)	12 (4.2)	18 (30.5)
≥ 5 days: probable infection	3 (10)	2 (1.3)	2 (15.4)	2 (40)	30 (10.6)	27 (45.8)

FiO_2 = fraction of inspired O_2; GA = gestational age; MAS = meconium aspiration syndrome; NCPAP = nasal continuous positive airway pressure; RDS = respiratory distress syndrome; TTN = transient tachypnoea of the newborn.
a) The likelihood of infection was based on the duration of antibiotic treatment: infection was suspected if the infant was treated for < 5 days, and if the infant was treated for ≥ 5 days, infection was probable.

In the moderate to late preterm group, respiratory support was provided for a median of 19 hours. Among these infants, 78% were classified as TTN. Of these, 69% never required supplemental oxygen, whereas 18% had a peak oxygen requirement exceeding 30%. The incidence of RDS was 5.4 per 100 liveborn infants, 10.5% (n = 18) and 3% (n = 12) of infants with GA 32-34 and 35-36 weeks, respectively. Among the infants with RDS, 47% (n = 14) were treated with surfactant by the INSURE procedure (intubate, surfactant, extubate). Among all the moderate to late preterm infants with respiratory morbidity, seven infants (3.5%) were transferred to the regional level-3 NICU, three required mechanical ventilation and one of these infants had a pneumothorax (Table 2). The duration of respiratory support in the moderate to late preterm and term is shown in **Figure 2.** Admissions were generally of short duration for term infants, at a median of 22 hours.

FIGURE 2 Duration of nasal continuous positive airway pressure treatment by intervals, and number of newborn infants requiring nasal continuous positive airway pressure within those time intervals.



GA = gestational age; NCPAP = nasal continuous positive airway pressure.

Discussion

Among infants born at term, respiratory morbidity was the most common reason for early NICU admissions. Treatment was often required only for a short period, and the stay in the NICU was short in most cases. Among the moderate to late preterm infants, the course of respiratory morbidity also tended to be mild, though 15% of those with respiratory morbidity developed RDS, and only half of these cases were treated with surfactant. Postnatal transfers of infants with early respiratory morbidity to the level-3 NICU were 3.2% among term infants and 3.5% among moderate to late preterm infants.

Other studies also found that respiratory morbidity was a common reason for NICU admission of term newborns to the NICU [1]. The British National Health Service Improvement Group has also shown interest in avoiding early separation of newborns from their mothers. They reported that 25% of term infants admitted to the NICU had respiratory symptoms as their primary problem, two-thirds were discharged within two days and 10% never required oxygen [3]. In our study, we found a significantly higher proportion of term infants not requiring supplementary oxygen, which may be related to the strategy of NCPAP as the first approach to respiratory support. We speculate that regardless of GA, in many cases, effective treatment for respiratory morbidity could be initiated in the delivery room with skin-to-skin contact with one of the parents. The importance of such an approach and of avoiding early separation is supported by evidence indicating health benefits for mother and infant, including promoting successful breastfeeding, reducing stress and helping the infants' transition into postnatal life [14, 15].

A strategy of early treatment of the infants at the delivery ward should be safe, and it may potentially be costly because the neonatal nurse only cares for a single infant at the delivery ward, which is often not the case in the NICU. However, because treatment duration was short for many newborns, this strategy may also potentially reduce the number of admissions. In our cohort, approximately 40% of the term infants were delivered by Caesarean section compared to approximately 20% in the background population [10]. This is expected because

Caesarean section is a risk for respiratory morbidity. This consideration is essential when planning a new approach to the treatment of newborns immediately after delivery.

Among the moderate to late preterm infants, RDS incidence was 5.4%. Even though the sample size was small, our results are similar to those presented in a Swedish study reporting RDS incidences [16]. A systematic review, which included 17 studies, found that surfactant was used in almost half of the late preterm and term infants with RDS [17]. At the time of the study, it was recommended to treat RDS with surfactant when the oxygen requirement exceeded an FiO_2 of 0.3, regardless of GA, and our data showed deviations from this [5]. Using surfactant might reduce complications in infants with RDS [17]. However, the overall complications seemed low in our cohort. Similarly, a study from India showed no significant difference in complications with NCPAP alone versus NCPAP and surfactant but found that the duration of respiratory support was shorter in infants treated with surfactant [18]. Establishing an RDS diagnosis early in the course is challenging. We suspect that a proportion of the infants retrospectively classified with TTN would have been treated with surfactant if a 30% oxygen requirement threshold had been used as the indication for surfactant treatment. Thus, in moderate to late preterm infants, improved diagnostic modalities in the early course are needed, together with evidence of the benefits of treatment with surfactant [19, 20].

Our study provided data based on all liveborn infants at the two hospitals, accounting for 20% of all deliveries in Denmark. The respiratory morbidity and treatment patterns were similar at both sites and may indicate that our results are representative of other Danish level-2 NICUs. Our study had limitations. The records of all newborns admitted to a NICU in the first 24 hours were not reviewed, which might lead to misclassification in those classified without respiratory morbidity. The retrospective study design depended on the validity of registered data, and we were unable to describe the duration of elevated oxygen at different levels of FiO_2. Furthermore, specific information regarding the treatment and time spent in the delivery room was incomplete.

Conclusions

Among term-born infants, respiratory morbidity is common in newborns admitted to the NICU within the first 24 hours, and the duration of treatment is often short. Among moderate to late preterm infants, respiratory morbidity also tends to be mild, although RDS may develop. Evidence-based guidelines for surfactants in these infants are warranted.

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