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Molecular and clinical characterization of *human adenovirus* associated with acute respiratory tract infection in hospitalized children

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ABSTRACT

Background: *Human adenovirus* (*HAdV*) is a common pathogen in children that can cause acute respiratory tract infection (ARTI), but the molecular epidemiological and clinical information relating to *HAdV* among hospitalized children with ARTI are few reported in China.
Objectives: To evaluate the epidemiological, clinical, and molecular characteristics of *HAdV* infections among hospitalized children with ARTI in Hebei, Northern China from June 2017 to May 2018.
Study design: A 12-month longitudinal, retrospective study on *HAdV*, typed by nested polymerase chain reaction targeting the hexon gene's hypervariable region (typing was merely performed by sequencing of the hexon neutralization epitope and thus genotypes could not be identified unequivocally), associated with ARTI was performed. The epidemiological and clinical data of different types of *HAdV* were analyzed using statistical product and service solutions (SPSS) 21.0 software.
Results: *HAdV* was detected in 330 (3.71%) of the 8906 specimens, with most (88.48%, 292/330) *HAdV*-positives cases detected among children < 3 years old. *HAdV* were detected throughout the year with a higher prevalence in spring. 11 types were identified, with *HAdV-2* (33.33%, 110/330) as the predominant type, followed by *HAdV-3* (21.21%, 70/330) and *HAdV-7* (13.94%, 46/330). Of the 330 *HAdV*-positive specimens, 247 (74.85%) were co-detected with other respiratory pathogens, most commonly *rhinovirus* (*HRV*) (58.7%, 145/247). Additionally, patients with *HAdV*-7 positive had longer duration of fever than *HAdV*-2 or -3 positive patients.
Conclusions: During the study period, *HAdV*-2, *HAdV*-3 and *HAdV*-7 were the predominant types identified from children with ARTI in Hebei Province. Pediatric patients with *HAdV*-7 positive may not present more severe clinical outcome except a longer duration of fever.

1. Background

Human adenovirus (*HAdV*) is considered as an important causative agent of acute respiratory tract infection (ARTI) in children [1,2], and accounts for at least 5 to 10% of pediatric ARTI [3]. *HAdV* is a non-enveloped, double-stranded DNA virus belonging to the Mastadenovirus genus (Adenoviridae family). There are currently seven different *HAdV* species (A to G), including 103 *HAdV* types (*HAdV* types up to type number 51 were defined as serotypes and higher type numbers were defined as genotypes) (http://hadvwg.gmu.edu/). *HAdV*-1, 2, 3, 4, 5, 6, 7, 11, 14 and the re-emergent type *HAdV*-55 are known to cause ARTI [4–6]. Although *HAdV* is associated with mild to moderate disease in most cases, types 3 and 7 were increasingly reported [7,8] associated with severe, and even life-threatening infections and outbreaks.

Abbreviations: ARTI, acute respiratory tract infection; *HAdV*, *Human adenovirus*; CAP, community-acquired pneumonia; NPA, nasopharyngeal aspirate; *FluA*, *Influenza A*; *FluB*, *Influenza B*; *09H1*, *Influenza A H1N1 pdm09*; *H3*, *Influenza H3N2*; *HPIV*, *Human parainfluenza virus*; *RSV*, *Respiratory syncytial virus*; *HMPV*, *Human metapneumovirus*; *HRV*, *Rhinovirus*; *HBoV*, *Human bocavirus*; *HCoV*, *Human coronavirus*; *Ch*, *Chlamydia*; *Mp*, *Mycoplasma pneumoniae*

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Therefore, investigating the epidemiological and clinical manifestations of different types of *HAdV* infections is helpful to the prevention and control of *HAdV* circulating.

2. Objectives

Previous studies have reported the adenoviral epidemiology in Beijing and Guangzhou, China [9,10]. However, information on *HAdV* among hospitalized children with ARTI is limited in Hebei, China. To perfect molecular epidemiological and clinical information of *HAdV* infections, we conducted a retrospective study to evaluate the epidemiological, clinical, and molecular characteristics of *HAdV* infections among hospitalized children with ARTI in Hebei, Northern China from June 2017 to May 2018.

3. Study design

3.1. Population and definitions

Hospitalized children (< 18 years) with ARTI from Children's Hospital of Hebei Province from May 2017 to April 2018, were retrospectively enrolled in this study. Children with signs and symptoms of respiratory tract infection (such as fever, coughing, nasal obstruction, sneeze), or lower respiratory infection signs (tachypnea, dyspnea, or wheezing/rales upon auscultation etc.) were defined as ARTI. Community-acquired pneumonia (CAP) was diagnosed by radiographic evidence (consolidation, other infiltrate or pleural effusion). Severe CAP was defined as an CAP that presented with one of the following clinical presentations: oxygen saturation < 92%, cyanosis; respiratory rate > 70 (infants) or 50 (older children) breaths/min; significant tachycardia for level of fever; prolonged central capillary refill time > 2 s; difficulty in breathing; intermittent apnoea (infants), grunting; not feeding (infants); chronic conditions (eg, congenital heart disease, chronic lung disease of prematurity, chronic respiratory conditions leading to infection such as cystic fibrosis, bronchiectasis, immune deficiency). This study was approved by the Institutional Review Board of the Children's Hospital of Hebei Province, affiliated to Hebei Medical University. Data records and collected clinical specimens were de-identified and completely anonymous so informed consent was waived.

3.2. Information collection and detection of pathogens

Demographic and clinical data were obtained from the hospital's database. The nasopharyngeal aspirate (NPA) specimens collected from each patient were extracted total nucleic acids using EasyPure Viral DNA/RNA Kit (TransGen Biotech, Beijing, China) according to the manufacturer's instructions. Thirteen common respiratory pathogens and subtypes (*Influenza A* (*Flu A*), *Influenza B* (*Flu B*), *Influenza A H1N1 pdm09* (*09H1*), *influenza H3N2* (*H3*), *human parainfluenza virus* (*HPIV*), *respiratory syncytial virus* (*RSV*), *HAdV, human metapneumovirus* (*HMPV*), *rhinovirus* (*HRV*), *human bocavirus* (*HBoV*), *human coronavirus* (*HCoV*), *Chlamydia* (*Ch*) and *Mycoplasma pneumoniae* (*Mp*)) were detected by using a GeXP-based multiplex reverse transcription PCR assay [11]. *HAdV*-positive samples were molecularly typed by nested PCR amplification and sequencing that targeted hypervariable regions 1-6 of the hexon gene, as described previously [12].

Meanwhile, bronchial alveolar lavage fluids (if available), blood, and pleural effusion (if available) from *HAdV*-positive patients during the entire hospital admission were used to identify any bacteria or fungi.

3.3. Statistical analysis

Epidemiological and clinical data were analyzed using statistical product and service solutions (SPSS) 21.0 software. Categorical variables were evaluated by Chi-square test and Fisher's exact test where appropriate. Continuous variables were compared by a Mann-Whitney test. All tests were two-tailed and the value of $P < 0.05$ was considered to represent a statistically significant difference.

Table 1
HAdV-positive in children of different ages and gender with ARTI.

Variable	total ARIT(N)	*HAdV*-positive (N (%))	*P*
Gender			
Male	5458	209 (3.83)	0.436
Female	3448	121 (3.51)	
Age (years)			
≤1	3787	110 (2.9)	< 0.001
> 1 to ≤2	2054	139 (6.77)	
> 2to≤3	1114	43 (3.86)	
> 3	1951	38 (1.95)	
Total	8906	330 (3.71)	

HAdV: *Human adenovirus*, ARTI: Acute respiratory tract infection.

4. Results

4.1. Characteristics of the children with ARTI

A total of 8906 hospitalized children with ARTI at the Children's Hospital of Hebei Province, affiliated to Hebei Medical University were enrolled, and all children survived. Among those children, 5458 (61.28%) were males and 3448 (38.72%) were females (Table1). The age range was from 1 month to 18 years of age with a median age of 1.5 years. From them, 6955 (78.09%) patients were younger than 3 years old (Table 1).

4.2. Epidemiology of HAdV

Among the 8906 children, 330 (3.71%) *HAdV*-positive cases were detected. And most (88.48%, 292/330) *HAdV*-positives cases detected among children < 3 years old. No significant differences were observed in males 209 (63.33%) and females 121 (36.67%) in the rate of *HAdV*-positive ($P = 0.436$). Children at age groups > 1 to ≤ 2 years had higher *HAdV*-positive rates than other age groups ($P < 0.001$) (Table 1). Low *HAdV*-positive rates were detected in October 2017 (2.28%) and January 2018 (2.39 %), while a peak positive rate occurred during March-April 2018 (Fig.1).

4.3. Typing of HAdV

We identified 11 *HAdV* types in 330 samples. *HAdV*-2 [33.33% (110/330)] was the most prevalent type, followed by *HAdV*-3 [21.52% (70/330)] and *HAdV*-7 [13.94% (46/330)] (Table 2). Beside, 2 cases with multiple *HAdV* types (*HAdV*-2 and *HAdV*-3) were identified. *HAdV*-1 and 2 positive cases were more detected during February to Apirl, 2018; *HAdV*-3 was more prevalent during July to August, 2017 and November to December, 2017; *HAdV*-5 was more frequent in March, 2018 and *HAdV*-7 in November 2017. In contrast, *HAdV*-4, 6, 31, 41, 55 and 57 were sporadic detected during the study period (Fig. 1).

4.4. Co-detected with other respiratory pathogens

Of the 330 *HAdV*-positive cases, 247 (74.85%) were co-detected with other respiratory pathogens including 163 (65.99%, 163/247) with one other pathogens, 74 (29.96%, 74/247) with two other pathogens, and 10 (4.05%, 10/247) with three other pathogens. The most frequently identified mixed infection was *HRV* (58.7%, 145/247), as shown in Table 3. The median age of children with co-detection was 1.25 years and younger than children with single-detection (median age was 1.75 years, $P = 0.032$). Compared with *HAdV-B* positive cases, the

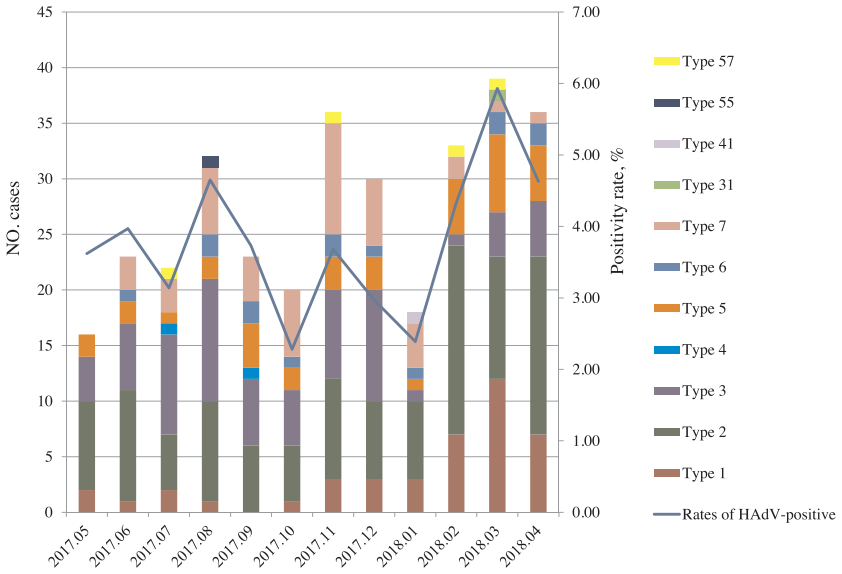

Fig. 1. Seasonal distribution of *HAdV* and diffenert *HAdV* types in children with ARTI from May 2017 to April 2018. *HAdV*: *Human adenovirus*, ARTI: acute respiratory tract infection.

Table 2
Molecular types of *HAdV* in single-detection and co-detection groups.

		Total	Single-detection	Co-detection	*P*
***HAdV* -positive**		330	81 (24.55)	247 (74.85)	-
Gender, male		209 (63.33)	55 (67.9)	153 (61.94)	0.334
Age, median (IQR) (y)		1.33 (1.17)	1.75 (2)	1.25 (1.17)	0.032
Genotypes					
HAdV -A	31	1 (0.3)	1 (100)	-	
HAdV -B		117 (35.45)	41 (35.04)	76 (64.96)	0.001[b]
	3	70 (21.21)	22 (31.43)	48 (68.57)	
	7	46 (13.94)	18 (39.13)	28 (60.87)	
	55	1 (0.3)	1 (100)	-	
HAdV -C		207 (62.73)	38 (18.36)	169 (81.64)	
	1	42 (12.73)	10 (23.81)	32 (76.19)	
	2	110 (33.33)	19 (17.276)	91 (82.73)	
	5	37 (11.21)	7 (18.92)	30 (81.08)	
	6	14 (4.24)	1 (7.14)	13 (92.86)	
	57	4 (1.21)	1 (25)	3 (75)	
HAdV -E	4	2 (0.61)	1 (50)	1 (50)	
HAdV -F	41	1 (0.3)	-	1 (100)	
HAdV -2&3[a]		2 (0.61)	-	-	

Data are presented as No. (%) unless otherwise indicated. IQR: interquartile range. [a] *HAdV* -2&3: *HAdV* -2 co-infection with *HAdV* -3. [b] The mixed detection rate of *HAdV -B* was compared with those of *HAdV-C*.

mixed detection rate of *HAdV-C* was significantly higher ($P = 0.001$). Detailed co-detection distribution of different types was shown in Table 2.

4.5. Demographic and clinical data of different types of HAdV

After excluding 247 cases with co-detection, 2 cases with multiple types, 1 case diagnosed with bronchial foreign body and 1 case diagnosed with herpangina, demographic and clinical data of 79 cases were collected and shown in supplementary material S1. Fever, cough, and sore throat were the most common clinical features among different types. CAP was the most common diagnoses of the patients. 2 patients with *HAdV*-2 positive were admitted to PICU, 2 patients (1 with *HAdV*-1 positive and 1 with *HAdV*-3 positive) required respiratory support with mechanical ventilation, and 5 patients (2 with *HAdV*-2 positive, 1 with *HAdV*-3 positive and 2 with *HAdV*-7 positive) underwent immunoglobulin therapy. All *HAdV*-positive patients recovered fully from respiratory infections.

Because *HAdV*-2, *HAdV*-3 and *HAdV*-7 were the most predominant types among patients with *HAdV* positive, the age and gender distribution, clinical characteristics, and laboratory findings of patients with single *HAdV*-2, *HAdV*-3 and *HAdV*-7 positive were further compared to exclude the possible effect of other respiratory pathogens infection. The *HAdV-7* positive patients had a longer median duration of fever, followed the *HAdV*-3 positive patients and the *HAdV*-2 positive patients were shortest ($P = 0.006$). Runny nose was observed in 33.33% of *HAdV*-2 positive patients, 22.73% of *HAdV*-3 positive patients and only 5.56% of *HAdV*-7 positive patients ($P = 0.008$). *HAdV*-3 and *HAdV*-7 positive patients were more likely to experience sore throat ($P = 0.015$) and had higher leukocyte count ($P = 0.048$) than *HAdV*-2 positive patients. Underlying respiratory diseases were more frequently observed with the *HAdV*-3 positive patients (27.27%) and the *HAdV*-7 positive patients (11.11%) compared to *HAdV*-2 positive patients (0%) ($P = 0.044$). No significant differences were found in the age and gender distribution, complications and clinical outcomes when compared among the three *HAdV* types.

5. Discussion

HAdV is a common pathogen associated with ARTI in hospitalized children. Among our studied cohort, 3.71% of paediatric patients with ARTI exhibited *HAdV* positive, which is lower than the finding (5.64%) in Beijing [9] during the same period. Such discrepant *HAdV* detection rates were easy to be explained by different regions. Previous studies from Beijing and Guangzhou [9,10] revealed that *HAdV* infections occurred throughout the year with the highest prevalence in the summer. However, a peak positive rate occurred during March-April in the present study, which is consistent with another study that has reported seasonal peak for *HAdV* infections in spring in Northern China [13]. We found that *HAdV*-positives cases detected predominantly (88.48%) in children under 3 years of age, with a peaking in children aged 1-2 years ($P < 0.001$), demonstrating that most children become infected by *HAdV* at an early age. A recent repeated cross sectional study [14] drew similar findings that the *HAdV* positive rate of children at the age of < 3 years was 63.51% and the rate of *HAdV* infection peaking in children aged l-3 years in Northern China ($P = 0.021$).

HAdV -2, -3 and -7 are the most prevalent species in China [15,16], but the type distribution of *HAdV* varies for different regions and periods of studies. *HAdV*-7 was the most prevalent types from 2007 to 2012

Table 3
Co-detection of *HAdV* with other respiratory pathogens.

2 pathogens (N = 163)		3 pathogens (N = 74)		4 pathogens (N = 10)	
Etiologic agents (*HAdV*+)	Proportion	Etiologic agents (*HAdV*+)	Proportion	Etiologic agents (*HAdV*+)	Proportion
HRV	80	*HRV*+*HPIV*	23	*HRV* + *Mp*+*HPIV*	2
RSV	25	*HRV* + *RSV*	13	*HRV* + *Mp*+*HBoV*	2
HPIV	16	*HRV*+*HMPV*	7	*HRV* + *Mp*+*HMPV*	1
HMPV	13	*HRV*+*HCoV*	7	*HRV* + *Mp* + *FluB*	1
HBoV	8	*HRV* + *Mp*	3	*HRV*+*HPIV*+*HCoV*	1
Mp	8	*HRV*+*HBoV*	3	*HRV* + *RSV*+*09H1*	1
09H1	6	*HPIV*+*HCoV*	3	*HRV*+*HCoV*+*H. influenzae*	1
S. Pneumoniae	3	*HCoV* + *RSV*	3	*HBoV* + *Mp* + *RSV*	1
FluB	2	*RSV*+*09H1*	2		
HCoV	1	*HPIV*+*HMPV*	2		
H3	1	*HPIV* + *RSV*	1		
		HPIV+*09H1*	1		
		HBoV+*HCoV*	1		
		HBoV+*H. influenzae*	1		
		HMPV + *FluB*	1		
		09H1+*FluB*	1		
		RSV + *S. Pneumoniae*	1		
		H. influenzae + *S. aureus*	1		

HAdV: Human adenovirus, HRV: Rhinovirus, RSV: Respiratory syncytial virus, HPIV: Human parainfluenza virus, HMPV: Human metapneumovirus, HBoV: Human bocavirus, Mp: Mycoplasma pneumoniae, 09H1: Influenza A H1N1 pdm09, S. pneumoniae: Streptococcus pneumoniae, FluB: Influenza B, HCoV: Human coronavirus, H3: Influenza H3N2, H. influenzae: Haemophilus influenza, S. aureus: Staphylococcus aureus.

in Beijing [17], *HAdV*-3 dominated from 2017 to 2018 in Beijing [9] and from 2012 to 2013 in Guangzhou [8]. While throughout the present study period, *HAdV*-2 was the most prevalent type, followed by *HAdV*-3 and -7.

HAdV-55 is a recombinant virus which has a genomic backbone of type 14 and a neutralization epitope of type 11, and once caused an outbreak of respiratory tract infection in Shanxi Province, China, in 2006 [18]. In the present study, a hexon sequence identical to type 55 was detected from a boy aged eight months. This boy diagnosed with CAP and presented with a ten-days of fever (Maximum temperature = 40 °C), cough and sore throat, but no PICU admission, mechanical ventilation and immunoglobulin therapy required during the hospitalization period. Although this hexon sequence is also almost identical to type 11 which is not closely related to respiratory infections, it was thought as type 55 according to clinical feature of this boy. This is the first report of mono-detection of *HAdV*-55 in children with ARTI in Hebei Province, though *HAdV*-55 infection has been reported in other provinces in China [17,19].

Another notable finding of this study was the identifying of *HAdV*-57 in 4 respiratory samples. *HAdV*-57 was first isolated from the feces of a healthy child as part of an acute flaccid paralysis surveillance program. The detection of *HAdV*-57 in respiratory samples collected from pediatric patients with ARTI was first reported by a study from 2007 to 2012 in Beijing [17]. However, all the three *HAdV*-57-infected cases were co-infected with other respiratory viruses in their study. In this present study, *HAdV*-57 alone was identified in a previously healthy 10-months girl who diagnosed with bronchitis requiring hospitalization. The girl not only presented with signs and symptoms of respiratory tract infection, including fever (Maximum temperature = 37.5 °C), cough, runny nose, nasal congestion, sore throat and dyspnea, but also accompanied by vomiting. Unfortunately, the further *HAdV* detection on her stool sample was not performed.

Similar to the report from Beijing (69.6%), Nouthern China [17], results here showed that 74.85% of *HAdV* were co-detected with one or more other respiratory tract pathogens and that coinfections were more frequently observed in younger children. Moreover, co-detection rates of different *HAdV* types varied, especially the co-detection rate of *HAdV-C* was significant higher than those of *HAdV-B* ($P = 0.001$). Nested PCR with a low limit of detection was used for typing of *HAdV* in the present study. Thus low level *HAdV* DNA shedding of latent *HAdV* infections could be detected, which may be explain the high rate of co-detection of *HAdV-C* with other pathogens.

In a recent study in Taiwan [15], clinical features of *HAdV*- 2, -3, and -7 mono-infections in children were investigated in an outbreak, and drawn a conclusion that childhood *HAdV*-2, *HAdV*-3 and *HAdV*-7 infections may exhibit different clinical manifestations and *HAdV*-7 caused more severe disease characteristics and outcomes. Similarly, through a comprehensive series of assays in vitro and in vivo as well as clinical correlates, a study in Chongqing [20] shown that *HAdV*-7 replicates more robustly than *HAdV*-3, and promotes an exacerbated cytokine response, causing a more severe airway inflammation. Our results revealed that patients with *HAdV*-7 positive experienced longer durations of fever than *HAdV*-2 or *HAdV*-3 positive patients, which was consistent with the results reported by Taiwan [15]. However, although patients with *HAdV*-7 positive had a higher rate of severe CAP and tended to require longer hospital stays in our study, no significant difference was found. Meanwhile, no patients with *HAdV*-7 positive needed PICU admission and mechanical ventilation in our study. These results may not support the conclusion from previous investigations [15,20] that *HAdV*-7 positive patients may have more severe clinical consequence.

One potential weakness of our data is that there was small sample size, since we have excluded the possible interference by any other co-infected respiratory pathogens. So, a larger sample size of case-control study is needed to illustrate the effectiveness of our results. Another limitation of this study is that typing of *HAdV* was merely performed by sequencing of the hexon neutralization epitope. However, some genotypes share their neutralization epitope with one of the (sero-)types. Thus we cannot exclude completely that the hexon sequence though as type 55 was truly type 11 in this study.

6. Conclusions

Our study reported the molecular epidemiology and clinical characterization of among the *HAdV*-positive pediatric hospitalized patients with ARTI in Hebei, Northern China in 2017-2018, providing reliable scientific basis for diagnosis, prevention and control for the future of *HAdV* infection in Hebei region.

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of the

Children's Hospital of Hebei Province, affiliated to Hebei Medical University. Data records and collected clinical specimens were de-identified and completely anonymous so informed consent was waived.

Availability of data and materials

The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.

Declaration of Competing Interest

The authors declare that there are no competing interests.

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Authors' contributions

MCZ, GXL and ZSF conceived the study. MCZ, YHG and FZQ performed the experiments. YHG, FZQ, LW and SY conducted the clinical work. MCZ, YHG and FZQ wrote this article, ZSF revised it. All the authors have read and approved the final version of this manuscript.

CRediT authorship contribution statement

Meng-chuan Zhao: Conceptualization, Methodology, Writing - original draft, Funding acquisition. **Ying-hui Guo:** Methodology, Investigation, Writing - original draft. **Fang-zhou Qiu:** Methodology, Investigation, Writing - original draft. **Le Wang:** Formal analysis, Resources. **Shuo Yang:** Investigation, Resources. **Zhi-shan Feng:** Conceptualization, Writing - review & editing, Funding acquisition. **Gui-xia Li:** Conceptualization, Writing - review & editing, Supervision.

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Not applicable.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jcv.2019.104254.

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