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## RESEARCH ARTICLE

### The Epidemiology and Outcomes of Meningitis among Iranian Children in a Period of 10 Years

Maryam Alizadeh Chamkhaleh<sup>1</sup>, Samileh Noorbakhsh<sup>2</sup>, Mohammad Vafae-Shahi<sup>3,\*</sup>, Aina Riahi<sup>4</sup>, Negar Hajinasab<sup>1</sup>, Alireza Gandomi-Mohammadabadi<sup>1</sup> and Mehrsa Shiasi<sup>1</sup>

<sup>1</sup>Student Research Committee, Iran University of Medical Sciences, Tehran, Iran

<sup>2</sup>Department of Pediatric Infectious Diseases, Rasool Akram Hospital, Iran University of Medical Sciences, Tehran, Iran

<sup>3</sup>Pediatric Growth and Development Research Center, Iran University of Medical Sciences, Tehran, Iran

<sup>4</sup>Pediatric Ward, Rasool Akram Hospital, Iran University of Medical Sciences, Tehran, Iran

#### Abstract:

##### Background:

One of the important causes of childhood febrile illness is meningitis. It causes bacterial, viral, fungal, parasitic, and non-infectious agents. Pediatric bacterial meningitis is one of the most important causes of infant mortality, especially in premature infants. This study aimed to identify the outcome and mortality of children with meningitis.

##### Methods and Materials:

All children with meningitis in the Pediatric Department of Rasool Akram Hospital from December 23, 2007, to December 16, 2017, were included. Signs and symptoms (fever, consciousness, neck rigidity, and seizure) were collected and Cerebrospinal fluid analysis in children was made. Based on these findings, patients were divided into two groups, which include bacterial and non-bacterial meningitis. Then we recalled all families and examined them to discover the child's outcome and complications at least after two years.

##### Results:

During the ten-year study period, 202 children were included in the study. Patients aged less than 12 months were found to be more frequently affected. Fever was the most common presentation (83.4%) followed by seizure (51.5%) and vomiting (49%). 119 (58.9%) of the patients were male and 83 (41.1%) were female. Definite bacterial meningitis was the final diagnosis in 35.6% (72) of patients (mean age 34.1± 48.3 months), and non-bacterial meningitis was diagnosed in 64.4% (130) of cases (mean age 46.3± 52.4 months). The most common organism in bacterial meningitis (by all methods) was *Streptococcus pneumoniae*. Among children, 187 (92.1%) were survivors and 15 (7.9%) were non-survivors. Neurological sequelae such as motor deficit and epilepsy were identified in 9 (4.8%) and 5 (2.6%) subjects, respectively, and that they were all caused by bacterial meningitis. There was no death or neurological sequelae observed during follow-up in children with non-bacterial meningitis. Gender, age, signs and symptoms of patients at the time of admission were not significantly different between the bacterial and non-bacterial meningitis groups ( $p > 0.05$ ). Hydrocephalus, CSF characteristic, morbidity and mortality were significantly different between the bacterial and non-bacterial meningitis groups.

##### Conclusion:

This study showed that elevated LDH and low glucose levels in CSF are characteristic of bacterial meningitis. Increased LDH is significantly related to death in children ( $P$ -value  $> 0.001$ ) with meningitis. Beneficial empirical antibiotics and sufficient follow-up by parents cause good prognosis in children with meningitis. Also in a child with fever and seizure, we should think of meningitis, even though in the absence of positive neurological examinations. It seems that increased CSF LDH, elevated CSF protein and age under one year are significant mortality risk factors in children with meningitis.

**Keywords:** Meningitis, Complications, Epidemiology, Children, Infant, Outcome.

Article History

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## 1. INTRODUCTION

One of the important causes of childhood febrile illness is meningitis. Despite advances in diagnosis, treatment, and vaccine development, meningitis remains a devastating problem in the pediatric age group [1]. It is estimated that about 1.2 million cases of bacterial meningitis occur annually worldwide, causing 135,000 deaths, and many of them consist of children and young adults [2]. There are many different types of meningitis, including bacterial, viral, fungal, parasitic, non-infectious, and aseptic meningitis. Aseptic meningitis includes both confirmed and presumed cases of viral meningitis. Viral meningitis is the most common type of meningitis and it is often less severe than bacterial meningitis, and most people get better without treatment [3, 4]. Pediatric bacterial meningitis is more common in children younger than four years, with a peak incidence in those aged 3–8 months. It is one of the most important causes of infant mortality, especially in premature infants. In general, mortality from bacterial meningitis has been reported to be 20% to 30% in children, which decreases with age up to 25 years old [5, 6].

The most common bacterial causes of acute meningitis in young infants are *Streptococcus pneumoniae* and *Escherichia coli*. These bacteria commonly infect neonates and infants up to the age of three months [5]. Bacterial meningitis in children is usually caused by septicemia, endocarditis, and ear infections [6]. Bacterial meningitis is more common in the autumn and winter seasons, and children under the age of two are more susceptible to complications or mortality due to it. Complications are relatively common and include blindness, hearing loss, neurological disorders, decreased level of consciousness, and paralysis [6, 7]. Many studies have been conducted in Iran regarding meningitis. But little is known about the outcome of meningitis in children. This study aimed to identify epidemiology, outcome, and mortality in children with meningitis.

## 2. METHODS AND MATERIALS

This retrospective study was conducted for 10 years (December 23, 2007, to December 16, 2017) on 202 children (1 month to 18 years) with meningitis referred to the Pediatric Department of Rasool Akram Hospital in Tehran. The study was approved by the Ethics committee of Iran University of Medical Sciences with Ethical number IR.IUMS.REC.1397.117. All project partners adhered to the principles of the Helsinki Declaration. Written informed consent was obtained from the parents of all children enrolled in the study. Preliminary tests and standard examination were requested after initial examinations by a pediatrician for excluding other etiologic causes except for meningitis. A checklist was completed for each case by an authorized physician, covering different aspects, for *e.g.* age, gender, analysis of all CSF samples: Sugar; Protein, WBC count, LDH, gram stain, Latex Particle Agglutination (LPA) and CSF culture (in both conventional and Bactec medium/ or universal bacterial PCR), and Type of meningitis (bacterial, non-bacterial). Latex Particle

Agglutination (LPA) is a very useful tool in the diagnosis of bacterial meningitis with sensitivity and specificity ranging from 95-100%. It is easy to perform and interpret, requires minimum time and the use of antibiotics generally does not alter the results when used for a short interval.

### 2.1. Cases Definition

All children were admitted with documented meningitis. Bacterial meningitis was diagnosed in the presence of clinical signs of meningitis along with positive CSF culture, positive blood culture  $\pm$  CSF culture, or positive universal bacterial PCR of CSF with or without LPA test positive gram stain for bacteria in CSF (Fig. 1).

### 2.2. Exclusion Criteria

First, all cases suspected with other inflammatory processes in CSF (for *e.g.*, ADEM, Guillain Barre syndrome, leukemia, SLE, brain tumor, *etc.*) were excluded.

### 2.3. Lab Test

CSF samples were examined microscopically for total WBC and differential WBC count. Gram stain was performed on all CSF samples. After centrifugation, deposits were cultured on sheep blood agar and incubated in a candle jar at 37°C for 48 h, and then sub-cultured using standard techniques. We used the BACTEC Ped Plus medium (Becton Dickinson company) and automated system (Bio Merieux) for CSF or blood culture. Bacteria isolates were identified using standard techniques. Latex agglutination tests using the BD Directigen Meningitis Combo Test (Becton Dickinson, Maryland, USA) and Wellcogen bacterial antigen kit were performed on CSF samples in patients with negative results of culture and gram stain suggestive of meningitis. A Universal PCR assay for the detection of *N. meningitidis*, *H. influenzae*, and *S. pneumoniae* was used only when CSF samples suggestive of bacterial meningitis showed negative results using other methods (Culture or gram stain for bacteria in CSF or LPA).

### 2.4. Follow-Up of Cases

We recalled all families and examined the patients to find out the outcome and complications. We concentrated on motor, sensation, audition and cognition defects, and also seizure history. Complications after at least two years were evaluated. We excluded patients with data deficits.

### 2.5. Statistical Analysis

Data analysis was performed using SPSS software for Windows (statistical product and service solutions, version 20.0. SPSS Inc., Chicago, IL, USA). Categorical (discrete) groups were compared by Chi-square ( $\chi^2$ ) test. Continuous variables were analyzed by Student's t-test or *Mann-Whitney U test*. Data were summarized as Mean  $\pm$  SD (standard deviation). A p-value less than 0.05 was defined as statistically significant.

## 3. RESULTS

During the ten-year study period, 202 children admitted to the hospital due to meningitis were included. Gender and age

\* Address correspondence to this author at the Pediatric Growth and Development Research Center, Iran University of Medical Sciences, Iran; E-mail: dr.vafaeshahi@gmail.com

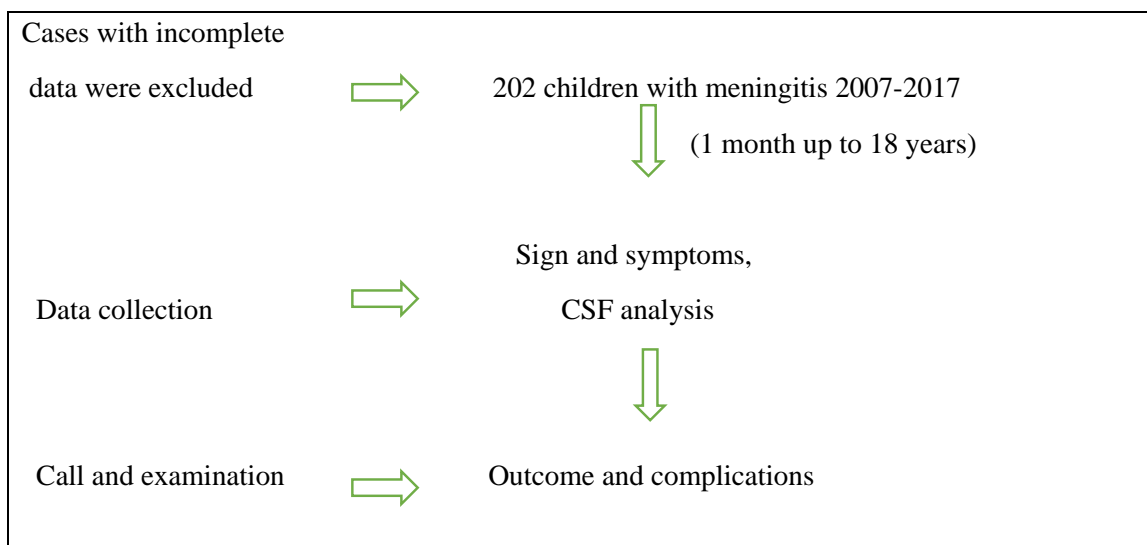


Fig. (1). Study design and the process of patient’s selection.

of the studied cases are shown in Table 1. Most patients were male, with a mean age of 40.8±52.2 months. 46% of children aged under 12 months old Table 1, 29.2% aged one to five, and 24.8% aged above five years old. Patients aged less than 12 months were found to be more frequently affected; 28.2% of the children were under six months old, and 18.3% were under three months old. Since 46% of the children were less than 12 months old, we decided to split them into two groups: those younger than 12 months and those older than 12 months. Fever was the most common presentation (83.4%), followed by seizure (51.5%) and vomiting (49%) Tables 2 and 3 present the characteristics of the patients and biochemical analysis of patients' CSF at ward admission. The mean levels of lactate dehydrogenase, protein, and glucose of the patients were 74.7 ± 102.2 U/L, 61.8 ± 58.4 mg/dl, and 52.4 ± 37.3 mg/dl, respectively. Most of the patients had CSF glucose level 40-60 mg/dl (41.2%), protein level less than 45 mg/dl (55.2%), and LDH level more than 70 U/L (64.9%).

Out of 202 patients admitted with meningitis, 119 (58.9%) of the patients were male and 83 (41.1%) were female. Definite bacterial meningitis was the final diagnosis in 35.6% (72) of patients (mean age 34.1± 48.3 months), while non-bacterial meningitis was diagnosed in 64.4% (130) of cases (mean age 46.3± 52.4 months). In patients with bacterial meningitis, 11.1% (8 patients) of cases showed positive gram stain for bacteria in CSF. Positive CSF culture was proved in 25% (18 patients) of cases. Positive universal bacterial PCR in CSF was 44.5% (32 patients). Positive LPA test was detected in 19.4% (14 patients) of cases. The most common organisms in bacterial meningitis (by all methods), respectively, were *S. pneumoniae*, *H. influenzae*, *N. meningitides*, *GBS*, *E. coli*, *S.*

*Aureus*, *Acinetobacter*, *P. aeruginosa*, *Enterococcus*, and *Klebsiella*.

Among children, 187 (92.6%) were survivors and 15 (7.4%) were non-survivors. The mean age of the survived group was 41.1 ± 52.4 months and 36.1 ± 51.3 in the un-survived group. There was no significant relationship observed between age and mortality rate (p>0.05). There were 78 girls and 110 boys in the survived group and 5 girls and 9 boys in the non-survivors. Gender was not significantly different between the survived and non-survivor groups (p>0.05).

In patients with bacterial meningitis, eight deaths occurred in children aged under 12 months, mostly in children at the age of under six months (5 patients), and in 4 patients under the third month of life. Neurological sequelae in patients with meningitis including motor deficit and epilepsy were identified in 9 (4.8%) and 5 (2.6%) subjects, respectively, during clinical follow-up, and that they were all caused by bacterial meningitis. Hearing impairment, sensory defect, and cognitive defect were not identified during follow-up in children with meningitis (Table 4). There was no death or neurological sequelae observed during follow-up in children with non-bacterial meningitis (Table 5). Table 5 reveals differences in signs and symptoms of patients at the time of admission, CSF characteristics, gender, age, morbidity and mortality between bacterial and non-bacterial meningitis. Gender, age, signs and symptoms of patients at the time of admission were not significantly different between the bacterial and non-bacterial meningitis groups (p>0.05). However, Hydrocephalus, CSF characteristic, morbidity and mortality were significantly different between the bacterial and non-bacterial meningitis groups.

Table 1. Gender and age of the study population.

Characteristic	Total, n=202
Gender	
Boy, n (%)	139 (69.2%)
Girl, n (%)	63 (30.8%)

(Table 1) contd.....

Age ≤ 12 months, n (%)	93 (46%)
Age > 12 months, n (%)	109 (54%)

Table 2. General clinical and CSF characteristics in patients at hospital admission (n = 202).

Characteristic	Total n = 202	Survivors n = 187	Un-Survivors n = 15	P-Value
Age, month	40.8 ± 52.2	41.1 ± 52.4	36.1 ± 51.3	> 0.05
<b>Signs and symptoms at admission</b>				
Fever, n (%)	161 (83.4%)	151 (80.3%)	10 (71.4%)	> 0.05
Seizure, n (%)	101 (51.5%)	91 (49.7%)	10 (71.4%)	> 0.05
Nausea and vomiting, n (%)	97 (49%)	97 (52.7%)	10 (71.4%)	> 0.05
Neck rigidity, n (%)	15 (7.7%)	15 (8.3%)	0(0.0%)	> 0.05
Hydrocephalus, n (%)	21 (10.6%)	19 (10.3%)	2 (14.3%)	> 0.05
LDH/Csf* (U/L)	74.7 ± 102.2	67.7 ± 82.4	605 ± 161.6	< 0.001
Glucose/Csf* (mg/dl)	52.4 ± 37.3	59.7 ± 37.3	39.3 ± 45.7	> 0.05
Protein/Csf* (mg/dl)	61.8 ± 58.4	57.7 ± 51	187.7 ± 133.2	0.02

<sup>a</sup> Continuous variables were analyzed by Student's t-test or Mann-Whitney U test, and categorical data by Chi-square test.

<sup>c</sup> Variables are expressed as mean (standard deviation) and categorical data are expressed as number (percentage).

Table 3. Biochemical cerebrospinal analysis of patients at admission.

Variable	n (%)
<b>Protein (mg/dl)</b>	
<45	114 (55.2)
45-100	52 (26)
100-500	36 (18)
<b>Glucose (mg/dl)</b>	
<40	40 (19.6)
40-60	83 (41.2)
>60	79 (39.2)
<b>Lactate dehydrogenase(units/L)</b>	
<70	70(35.1)
≥70	132(64.9)

Table 4. Clinical evolution comparing patients aged under 12 months and above 12 months in terms of prognosis.

	Total n=202	Age>12 month n= 109	Age <12 month n= 93	Age <6 month n= 57	Age <3 month n= 37
Mortality	14 (6.9%)	6 (5.5%)	8 (8.6%)	5 (8.8%)	4 (10.8%)
Neurological sequelae	14 (7.4%)	0 (0%)	14 (15%)	12(22.7%)	5 (12.5%)
Motor deficit	9 (4.8%)	0 (0%)	9 (10%)	9 (15%)	5 (12.5%)
Auditory defect	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Sensory defect	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Cognitive defect	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Epilepsy	5 (2.6%)	0 (0%)	5(6.7%)	3 (7.7%)	0 (0%)

Table 5. Gender, age, general clinical CSF characteristics, morbidity and mortality in patients with bacterial vs. non-bacterial meningitis (n = 202).

Characteristic	Total n = 202	Bacterial n = 72	Non-bacterial n = 130	P-Value
Age, month	40.8 ± 52.2	41.1 ± 52.4	36.1 ± 51.3	> 0.05
Signs and symptoms at admission				

(Table 5) contd....

Fever, n (%)	161 (83.4%)	62 (86.1%)	99 (76.1%)	> 0.05
Seizure, n (%)	101 (51.5%)	42 (58.7%)	59 (45.3%)	> 0.05
Nausea and vomiting, n (%)	97 (49%)	40 (55.5%)	57 (43.8%)	>0.05
Neck rigidity, n (%)	15 (7.7%)	9 (12.5%)	6(4.6%)	>0.05
Hydrocephalus, n (%) CSF characteristic	21 (10.6%)	21 (29.1%)	0(0.0%)	< 0.001
LDH/Csf* (U/L)	74.7 ± 102.2	121.3 ± 62.7	48.7 ± 67.4	< 0.001
Glucose/Csf* (mg/dl)	52.4 ± 37.3	35.9 ± 43.2	62.8 ± 45.7	< 0.05
Protein/Csf* (mg/dl)	61.8 ± 58.4	102.1 ± 61.5	46.4 ± 32.8	< 0.05
<b>Gender and age</b>				
<b>Boy, n (%)</b>	119 (58.9%)	44 (61%)	75 (57%)	> 0.05
<b>Girl, n (%)</b>	83 (41.1%)	28 (39%)	55 (43%)	> 0.05
<b>Age ≤ 12 months, n (%)</b>	93 (46%)	37 (51%)	56 (43%)	> 0.05
<b>Age &gt; 12 months, n (%)</b>	109 (54%)	35 (49%)	74 (57%)	> 0.05
<b>Morbidity</b>				
<b>Neurological sequelae</b>	14 (7.4%)	14 (7.4%)	0	<0.001
<b>Motor deficit</b>	9 (4.8%)	9 (4.8%)	0	<0.05
<b>Auditory defect</b>	0 (0%)	0 (0%)	0	-
<b>Sensory defect</b>	0 (0%)	0 (0%)	0	-
<b>Cognitive defect</b>	0 (0%)	0 (0%)	0	-
<b>Epilepsy</b>	5 (2.6%)	5 (2.6%)	0	< 0.05
<b>Mortality</b>	14 (6.9%)	14 (6.9%)	0	< 0.001
<i><sup>a</sup> Continuous variables were analyzed by Student's t-test or Mann-Whitney U test, and categorical data by Chi-square test</i>				
<i><sup>c</sup> Variables are expressed as mean (standard deviation) and categorical data are expressed as number (percentage)</i>				

#### 4. DISCUSSION

Meningitis is inflammation of the brain membrane caused by a virus, bacteria, or other microorganisms, and in some cases, it is drug-induced [8]. Early diagnosis and treatment can prevent severe complications such as brain damage, hearing loss, learning disabilities, and death [9, 10]. Viral meningitis is mostly self-limited but bacterial ones need antibiotic therapy. It has been noted that 1.2 million cases of bacterial meningitis are diagnosed every year annually which causes about 135000 deaths [11, 12].

The result of our study reveals that the most common agent that causes meningitis in children admitted in hospital is a viral infection (64.4%). Elevated LDH, low glucose, and high protein levels were seen in bacterial meningitis. On the other hand, only a few positive CSF cultures (25%) were found in a patient with bacterial meningitis. Due to multiple problems (low technical instrument and expert persons for culture) in some developing countries like Iran, there are not enough criteria for treating bacterial meningitis [13, 14]. So, it seems that we cannot rely only on cultures to manage patients. Signs and symptoms have an important role in diagnosis. Streptococcus pneumonia was the most positive bacteria (by all methods) in our study, which is similar to other pediatric results that showed S. pneumonia and N. meningitides as the most common agents [14 - 17].

Fever, seizure, nausea, and vomiting were the most common characteristics found in children. So it is necessary to think of meningitis in children even with no neurological sign. Well-designed studies are needed to distinguish the clinical and laboratory features of meningitis [4, 18]. We should not miss the diagnosis of meningitis in the absence of typical features in infants, thus early lumbar puncture leads us to diagnose it as soon as possible. Also, we should conduct CSF analysis in children with fever and seizure, because only 7.7% of them had neck rigidity as a significant sign which has also been noticed in other researches.

Most children survived (92.5%); it might be due to early diagnosis and early empirical treatments as shown in other studies [19]. Also, neurologic sequelae were few (7.4%); it may be because of better socioeconomic care and rehabilitation courses. Un-survived children had upper LDH and protein levels with p-value < 0.001 and 0.02, respectively. These results prompt us to notice bacterial meningitis in infants more because it significantly may cause death.

In the end, the mortality range was more in children less than one year than other children 1 to 18 years old with meningitis. 10.8% under three months and 8.8 under six months have died. So we should care for infants more and more, as they are more susceptible to sequelae.

The most commonly reported meningitis sequelae are hearing loss, cognitive impairment, epilepsy, and sensory or motor deficits [20, 21]. Survived ones had motor defects and epilepsy as the most common neurological complications in our study as well. There was no death or neurological sequelae observed during follow-up in children with non-bacterial meningitis. Gender, age, signs and symptoms of patients at the time of admission were not significantly different between the bacterial and non-bacterial meningitis groups (p>0.05). Hydrocephalus, CSF characteristic, morbidity and mortality were significantly different between the bacterial and non-bacterial meningitis groups.

#### CONCLUSION

This study revealed that most patients have had non-bacterial meningitis. Elevated LDH, elevated protein and low glucose level in CSF analysis are characteristic of bacterial meningitis, and this type of meningitis also causes more death and morbidity among children. Increased LDH was significantly related to death in children (P-value < 0.001). Although we had limitations related to bacteriology culture, beneficial empirical antibiotics and sufficient follow-up by parents caused good prognosis in children with meningitis.

Also, in a child with fever and seizure, we should think of meningitis, even though in the absence of positive neurological examinations. So that it may lead to rapid diagnosis and beneficial treatment, thereby reducing disease complications.

It seems that increased CSF LDH, elevated CSF protein and age under one year are significant mortality risk factors in children with meningitis.

#### AUTHORS' CONTRIBUTIONS

AM, VM and NS designed and managed the study. RA and GA analyzed and interpreted the patients' data and performed follow-up of patients. AM, HN and SHM were major contributors in the writing of the manuscript. All the authors read and approved the final manuscript.

#### ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the Ethics Committee of Iran University of Medical Sciences, with ethical approval number IR.IUMS.REC.1397.117.

#### HUMAN AND ANIMAL RIGHTS

No Animals were used in this research. All human research procedures were followed in accordance with the ethical standards of the committee responsible for human experimentation (institutional and national), and with the Helsinki Declaration of 1975, as revised in 2013.

#### CONSENT FOR PUBLICATION

Written informed consent was obtained from the parents of all children enrolled in the study.

#### AVAILABILITY OF DATA AND MATERIALS

The datasets used during the current retrospective study are available in the text of the manuscript.

#### FUNDING

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#### CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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