



# Fever Etiology in Infants Aged 1-12 Months with No Apparent Focus at Onset

Başlangıçta Ateş Odağı Saptanamayan 1-12 Ay Arası İnfantlarda Ateş Etiyolojisi

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## Abstract

**Objective:** Fever without a source (FWS) is common in infants. Although viral infection is the most common in etiology, the risk of serious bacterial infection (SBI) cannot be ignored. The aim of our study was to detect viral agents by nasopharyngeal PCR method and to investigate the relationship with SBI in infants aged 1-12 months hospitalized with the diagnosis of FWS.

**Material and Methods:** Electronic medical charts of the patients who were hospitalized in İzmir Tepecik Training and Research Hospital between January 2016 and January 2019 with the diagnosis of FWS were analyzed retrospectively. Demographic and clinical data of the patients, the presence of viral agents was evaluated with complete blood count, acute phase reactants and nasopharyngeal viral swab sample. In addition, the frequency of SBI was analyzed according to blood and urine cultures from all patients, cerebrospinal fluid culture was obtained in necessary cases.

**Results:** A total of 100 patients, 44 (44%) of whom were girls, were included in the study. Fifty percent of the cases were in the 1-2 months age group, 18% were in the 2-3 months age group, and 32% were in the 3-12 months age group. SBI was detected in 34 (34%) of the cases. Considering the distribution of SBI, 28 (82.3%) of the cases were diagnosed with urinary tract infection, four (11.8%) cases with occult bacteremia, and two (5.9%) cases with bacterial meningitis. In regard to nasopharyngeal viral PCR test, at least one virus was detected in 53 patients. Rhinovirus was the most frequently isolated virus. It was observed that the presence of a nasopharyngeal viral agent did not reduce the possibility of SBI ( $p=0.402$ ). However, when only rhinovirus detected cases were compared with other viruses, rhinovirus was found to increase the probability of SBI by 2.18 times ( $p=0.024$ ). It was observed that the focus of fever could not be detected in the final diagnosis among 30% of the cases.

## Öz

**Giriş:** Akut odağı olmayan ateş infantlarda sık görülür. Etiyolojide daha çok viral enfeksiyonlar suçlansa da ciddi bakteriyel enfeksiyon (CBE) riski göz ardı edilemez. Çalışmamızın amacı akut odağı olmayan ateş tanısıyla hastaneye yatırılan 1-12 ay arası infantlarda nazofarengeal PCR yöntemiyle viral etkenlerin saptanması ve CBE ile ilişkisinin araştırılmasıdır.

**Gereç ve Yöntemler:** Ocak 2016 ve Ocak 2019 tarihleri arasında İzmir Tepecik Eğitim ve Araştırma Hastanesine akut odağı olmayan ateş tanısıyla yatırılarak izlenen hastaların elektronik tıbbi kayıtları geriye dönük olarak incelendi. Hastaların demografik, klinik verilerinin yanında tam kan sayımı, akut faz reaktantları ve nazofarengeal viral sürüntü örneği ile viral etken varlığı değerlendirildi. Ayrıca tüm hastalardan kan ve idrar kültürü, gerekli olgulardan alınmış beyin omurilik sıvısı kültürüne göre CBE sıklığı incelendi.

**Bulgular:** Çalışmaya 44 (%44)'ü kız olmak üzere toplam 100 hasta alındı. Olguların %50'si 1-2 ay, %18'i 2-3 ay, %32'si ise 3-12 ay yaş grubu aralığındaydı. CBE, olguların 34 (%34)'ünde saptandı. CBE dağılımına bakıldığında ise 28 (%82.3) olgu idrar yolu enfeksiyonu (İYE), dört (%11.8) olgu gizli bakteriyemi, iki (%5.9) olgu bakteriyel menenjit tanısı almıştır. Nazofarengeal viral PCR test değerlendirilmesinde 53 hastada en az bir virüs saptanmıştır. Rinovirüs en sık izole edilen virüs olmuştur. Nazofarengeal viral etken varlığının ciddi bakteriyel enfeksiyon olasılığını azaltmadığı görülmüştür ( $p=0.402$ ). Bununla birlikte sadece rinovirüs saptanan olgularla diğer virüsler karşılaştırıldığında rinovirüsün CBE olasılığını 2.18 kat arttırdığı saptanmıştır ( $p=0.024$ ). Olguların %30'unda sonuç tanısında halen ateş odağının saptanamadığı görülmüştür.

**Sonuç:** Büyük çoğunluğunu 1-3 ay arası infantların oluşturduğu çalışmamızda, nazal viral PCR yöntemiyle saptanan etkenlerin CBE olasılığını dışlayamadığı görülmüştür. Olguların önemli bir kısmında sonuç tanı-

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**Conclusion:** In our study, the majority of which consisted of infants aged 1-3 months, it was observed that the factors detected by nasal viral PCR method could not exclude the possibility of SBI. Considering that the fever focus could not be detected in the final diagnosis in a significant part of the cases, it was observed that viral and bacterial PCR tests that can be examined in the blood are also necessary in order to maximize the effectiveness. Since the detection of viral agents will prevent unnecessary antibiotic use, studies on this subject should continue.

**Keywords:** Fever, infant, fever without a source, virus

## Introduction

In 20% of the patients admitted to hospital due to fever, the focus of fever cannot be identified. The aim in evaluating these patients is to determine the risk of serious bacterial infection (SBI) (1,2). Although self-limiting viral infections are usually the cause of fever in well-appearing infants in whom no focus of fever can be identified, SBIs such as bacteremia, meningitis, urinary tract infection, pneumonia, septic arthritis, osteomyelitis and enteritis may also occur. Especially in infants younger than three months, the incidence of SBI has been reported to be 9-18% (3-6). Studies have shown a decrease in bacteremia rates in older children as a result of the use of conjugated vaccines (7,8).

When a bacterial source cannot be demonstrated as the probable etiology of fever, a virus is probably considered (9,10). Most children with fever without a focus require diagnostic laboratory tests to exclude SBI, which is usually followed by hospitalization and empirically initiated antibiotics (11).

The aim of our study was to determine the etiology of fever in infants aged 1-12 months hospitalized with a diagnosis of fever of unknown origin, to determine the frequency of viral agents by nasopharyngeal viral polymerase chain reaction (PCR), and to investigate the place of the detected agents in the etiology of fever and the possibility of excluding SBI.

## Materials and Methods

The study population consisted of patients admitted to İzmir Tepecik Training and Research Hospital between January 2016 and January 2019. The study population consisted of patients between the ages of 1-12 months who were admitted to the hospital and diagnosed with non-focal fever and hospitalized. The study was retrospective and record-based. Criteria for patients to be included or excluded from the study were determined. Patients aged 1-12 months (calendar age), with a measured rectal temperature  $>38^{\circ}\text{C}$ , without a focus of fever on detailed physical examination, and with nasopharyngeal viral PCR in their examinations were included in the study. Patients with underlying diseases predisposing to infection (cancer, immunodeficiency, immunosuppressive therapy, cystic fibrosis, sickle cell anemia, presence of venous catheter),

ında ateş odağının saptanamadığı düşünülürse etkinliği en üst düzeye çıkarmak için kanda bakılabilecek viral ve bakteriyel PCR testlerinin de gerekli olduğu görülmüştür. Viral etkenlerin saptanması gereksiz antibiyotik kullanımını önleyeceği için bu konuda çalışmalar devam etmelidir.

**Anahtar Kelimeler:** Ateş, infant, odağı bilinmeyen ateş, virüs

positive rapid antigen test for influenza, significant fever/infection focus at the beginning (upper respiratory tract infection, lower respiratory tract infection, urinary tract infection, soft tissue infection, etc.), antibiotic use in the last seven days at hospital admission, fever lasting longer than five days were excluded.

In our study, the age and time of birth of the patients were recorded in the case report form. The presence of concomitant chronic diseases, vaccination status in accordance with the vaccination calendar of the Ministry of Health and the season in which the patient was admitted to the hospital were examined. Hemogram, C-reactive protein (CRP), procalcitonin (PCT), blood culture, complete urinalysis and urine culture were evaluated. Cerebrospinal fluid (CSF) examinations (cell count, glucose, protein level, CSF culture and viral PCR in necessary cases) of patients who underwent lumbar puncture were evaluated. The results of nasopharyngeal viral PCR were analyzed. Stool examination and viral agents in stool (rotavirus, adenovirus) were evaluated in patients with watery stools. Nasopharyngeal swabs were analyzed for 16 respiratory viruses (respiratory syncytial virus A and B, human rhinovirus, parainfluenza virus 1, 2, 3 and 4, adenovirus, 'coronavirus' OC43, 229E and NL63, influenza A and B, human bocavirus, parecovirus, human metapneumovirus and enterovirus) by "multiplex polymerase chain reaction" (M-PCR) (Anyplex II RV 16 Detection; Seegene, Seoul, South Korea) method.

SPSS for Windows, version 22.0, was used for statistical analysis of the data. Pearson's chi-square test and Fisher's exact test were used for the evaluation of categorical variables, Student's t-test was used for group comparisons of normally distributed continuous variables, and Mann-Whitney U test was used for group comparisons of non-normally distributed variables.  $p < 0.05$  was considered significant.

On 14.09.2020, approval was obtained from the Ethics Committee of İzmir Tepecik Training and Research Hospital (Decision No: 2020/11-60).

## Results

A total of 100 infants hospitalized between the ages of 1-12 months who presented with fever and whose foci could not be identified by history and physical examination were included in the study. When the cases were divided according to age

**Table 1.** Demographic and clinical characteristics of the cases included in the study

Demographics	Patient number, n (%)
Sex	
Female	44 (44)
Male	56 (56)
Birth	
Preterm	18 (18)
Term	82 (82)
Vaccination status	
Vaccinated	91 (91)
Unvaccinated	9 (9)
Admission time (season)	
Spring	36 (36)
Summer	7 (7)
Autumn	32 (32)
Winter	25 (25)
Final diagnoses	
Viral infection	36 (36)
Those without a focus	30 (30)
Urinary tract infection	28 (2)
Bacteremia	4 (4)
Acute bacterial meningitis	2 (2)
Empirical antibiotic use	
Yes	39 (39)
No	61 (61)

groups, it was observed that 50% were in the 1-2 months, 18% in the 2-3 months and 32% in the 3-12 months age group. Median age (IQR) was 70 (73) days. It was observed that 44 (44%) of the patients were girls and 18 (18%) had a history of preterm birth. When the vaccination status was considered

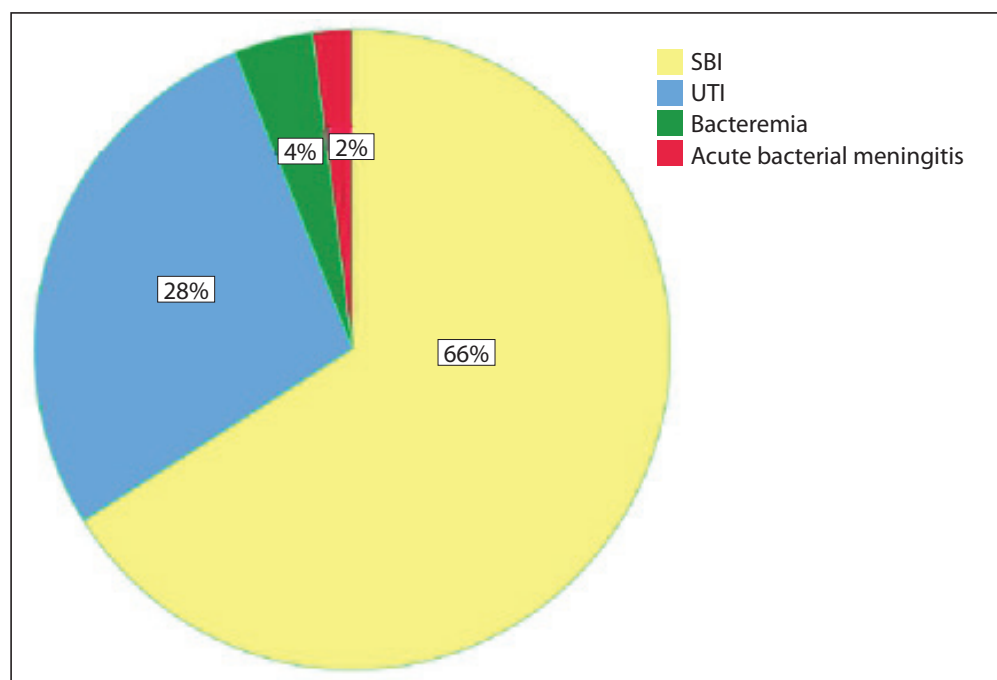
as complete if the necessary vaccines were administered according to the current month and incomplete if not administered according to the current month, it was observed that 91 (91%) patients had complete vaccines. It was observed that the most common season of hospital admissions with the complaint of fever was the spring season with the highest rate of 36%. Demographic and some clinical data of the patients are presented in Table 1. When these demographic and clinical characteristics of the patients were evaluated in terms of the presence of SBI, no significant difference was observed.

SBI was detected in 34% of the total 100 patients. Bacterial pneumonia was not observed in any of the cases. The causes of SBI subsets are shown in Figure 1.

In the nasopharyngeal viral PCR evaluation, at least one virus was detected in 53 patients, two viruses in seven patients and three viruses in four patients. In the evaluation of nasopharyngeal viral PCR results, rhinovirus was the most common virus (Table 2).

SBI was detected in 20 (58.8%) patients in whom virus was detected in nasopharyngeal viral PCR. Severe bacterial infection was detected in 14 (41.2%) patients in whom virus was not detected in nasopharyngeal viral PCR. In general, it was observed that the presence of nasal viral agent did not reduce the likelihood of SBI ( $p=0.402$ ).

When this evaluation was performed with rhinovirus, which constituted the majority of cases, it was found to be significant in increasing the likelihood of SBI, while other viruses other than rhinovirus, including influenza A, which was

**Figure 1.** Serious bacterial infection rates in cases.

**Table 2.** Nasopharyngeal viral PCR results in febrile cases without focus

Nasal viral agents	Number of patients detected, n (%)
<b>Single agents</b>	<b>42 (42)</b>
Rhinovirus	19 (19)
Adenovirus	0 (0)
Enterovirus	1 (1)
Parechovirus	2 (2)
Bocavirus	0 (0)
Metapneumovirus	1 (1)
Parainfluenza virus	5 (5)
Influenza A virus	8 (8)
Coronavirus	3 (3)
RSV	3 (3)
Influenza B virus	0 (0)
<b>Multiple agents</b>	<b>11 (11)</b>
Enterovirus + Coronavirus	1 (1)
Influenza B virus + RSV	2 (2)
Enterovirus + Rhinovirus	3 (3)
Enterovirus + Metapneumovirus	1 (1)
Rhinovirus + Influenza A virus + Coronavirus	1 (1)
Influenza B virus + Adenovirus + Coronavirus	1 (1)
Bocavirus + Rhinovirus + RSV	1 (1)
Bocavirus + Rhinovirus + Influenza A virus	1 (1)

**Table 3.** Possibility of SBI incidence in cases detected with only rhinovirus out of all viruses detected in nasopharyngeal viral PCR

	SBI (+), n (%)	SBI (-), n (%)	p
Rhinovirus (+), n (%)	11 (11)	8 (8)	<b>0.024</b>
(-), n (%)	9 (9)	25 (25)	

the other common agent, did not change the likelihood of SBI ( $p=0.744$ ) (Table 3). At the same time, it was observed that the probability of SBI increased in cases with only rhinovirus detection compared to cases with no virus detection ( $p=0.033$ ), [OR= 1.94 (1.08-3.48)].

Urinary tract infections were detected in 28 patients. *Escherichia coli* (*E. coli*) was the most common causative agent [19 cases (67.8%)]. Lumbar puncture was performed in 57 patients without fever focus and bacterial meningitis was found in two patients and viral meningitis in one patient. The patients diagnosed with bacterial meningitis were three and six months old and *Streptococcus agalactiae* and *Haemophilus influenzae* were found in CSF; the patient diagnosed with viral meningitis was two months old and enterovirus was found in CSF PCR. Seven of the blood cultures were evaluated as contamination, and no growth was detected in the control blood culture tests. Growth was found in the blood cultures of

four patients with occult bacteremia [*Streptococcus pneumoniae* (2), *Citrobacter freundii*, *Klebsiella pneumoniae*]. When blood, CSF and urine cultures of the patients were analyzed, it was observed that the same agent was not detected at the same time.

Complete blood count parameters and acute phase reactant results were compared between patients with and without SBI. Significant differences were found in white blood cell count, absolute lymphocyte count, platelet count and CRP values. The results are shown in Table 4.

In 30 patients, no foci, including viral infections, could be identified, and a fever focus could be demonstrated in 70 patients.

### Discussion

In this study in which viral agents were studied by nasopharyngeal viral PCR in children hospitalized between 1-12 months with a diagnosis of fever without a focus, it was shown that the detected viral agents were not effective in excluding the risk of SBI. Our data showed that the risk of SBI was higher in cases in which only rhinovirus was detected by nasopharyngeal viral PCR compared to other viruses. SBI was seen in 1/3 of the cases, and UTI was the most common cause in this group, as expected. With the nasopharyngeal viral PCR techniques studied in recent years, it has been predicted that most cases diagnosed with fever without a focus are actually viral infections and studies in this direction have become widespread. In our study, one or more viruses were detected in 53% of the cases. This rate was similar to other studies conducted under one year of age depending on the specific pathogen and the type of diagnostic test (9,12,13). In studies, rhinovirus usually ranks first, followed by RSV (9). The dominant viruses detected in our data were rhinovirus and influenza A. RSV was seen at lower rates. In a study in which outpatients with fever without a focus between 2-36 months were followed up, viral agents detected by nasal and blood viral PCR methods were found significantly higher in children without evidence of bacterial infection compared to those without (14). This study suggested that viral PCR in blood should be added to the nasopharyngeal viral PCR method and indicated that the etiology could be further explained. In our study, the fact that a significant rate of virus was detected in SBI cases did not show the effectiveness of nasal viral agents in excluding SBI.

In our study, the 2-fold increase in the rate of CBE in rhinovirus cases compared to other viruses drew attention. A similar study supports our data. In this study, the presence of rhinovirus in 1-3-month-old infants increased the likelihood of CBE 2.2-fold (9), which may be explained by the fact that rhinovirus may alter the innate immune response and lead to more severe outcomes as shown in previous studies (15,16).

**Table 4.** Relation between SBI and complete blood count and acute phase reactants

	<b>SBI (-), (n= 66) Median (IQR) (min-max) Mean ± SD</b>	<b>SBI (+), (n= 34) Median (IQR) (min-max) Mean ± SD</b>	<b>p</b>
WBC (mm <sup>3</sup> )	8850 (10925) (3200-32000) 11255 ± 6993	11100 (11150) (4200-50800) 14400 ± 9414	<b>0.036</b>
ANC (mm <sup>3</sup> )	3950 (8150) (400-21100) 5973 ± 5104	4400 (68000) (400-18600) 6232 ± 5149	0.522
ALC (mm <sup>3</sup> )	2750 (3450) (700-14500) 3817 ± 3074	5000 (3050) (1100-7700) 4730 ± 2035	<b>0.009</b>
AMC (mm <sup>3</sup> )	1200 (700) (100-2600) 1258 ± 576	1400 (12000) (200-46200) 2984 ± 792	0.071
AEC (mm <sup>3</sup> )	100 (177) (0-800) 143 ± 176	100 (141) (0-700) 148 ± 161	0.452
PLT (x1000)	339.5 (186.5) (112-631) 348625 ± 123046	449.0 (126.5) (197-701) 434000 ± 125733	<b>0.002</b>
CRP (mg/L)	8.9 (19.63) (0.6-169.7) 28.09 ± 45.98	34.1 (80.95) (0.2-278.1) 65.55 ± 77.63	<b>0.017</b>
PCT (µg/L)	0.17 (0.42) (0.03-47.43) 2.74 ± 7.74	0.23 (2.05) (0.03-55.07) 3.91 ± 10.57	0.412

WBC: White blood count, ANC: Absolute neutrophil count, ALC: Absolute leucocyte count, AMC: Absolute monocyte count, AEC: Absolute eosinophil count.

The epidemiology of SBIs has changed in recent years. In publications until the 1990s, CBE was reported with rates of 20-30% bacteremia, 30-55% UTI and 0-14% meningitis (17,18). In recent studies, UTI has been found to be very dominant with a rate of 84%. A significant decrease has been observed in the rates of isolated bacteremia and isolated bacterial meningitis. It has been reported that the reason for this shift is multifactorial and that the decrease in bacteremia and meningitis may be due to a decrease in *Haemophilus influenzae* type b, *Streptococcus pneumoniae* infections due to social immunity and a significant decrease in *Listeria* infections (19,20). In our data, blood and urine cultures were obtained from all cases, and CSF culture was obtained from 57% of the cases. The most common cause of SBI in our cases was UTI with 82%. This was similar to studies conducted with larger populations in febrile children without a focus (19). In our study in which *E. coli* bacteria were predominant as the causative agent of UTI, the fact that we did not see *E. coli* bacteremia was different from previous studies. In our patients with SBI, no growth was detected in the culture in other areas at the same time. In a study in which febrile infants between one week and three months of age were evaluated, CBE was found in 842 cases, and in 78 of these, growth was found with the same causative bacteria in at least two of the blood, urine or CSF at the same time (19).

Our study has several limitations. First of all, in this retrospective study, in cases with fever without a focus, cases in which nasopharyngeal viral PCR was performed were taken as the basis. This limited the number of cases included in the

study. Our second limitation is that in the study investigating viral causes in febrile children with fever without foci, only nasopharyngeal viral PCR methods were used to investigate viral agents rather than extended viral agents including blood and feces. This may limit the generalizability of our results and makes it important to repeat this study prospectively with other studies. Third, the detection of a virus in a febrile child, especially using very sensitive molecular methods, does not prove that it is responsible for the child's illness. Because these viruses may reflect previous asymptomatic disease as well as the etiologic cause (9,21). Although it is not clear that the viruses detected are always clinically significant, it has been reported that viruses that are well recognized as pathogens are detected much more frequently in children with fever without a focus compared to children without fever (22). The important aspect is that nasopharyngeal viral PCR does not play an effective role in excluding SBI in febrile patients with fever without a focus who are only hospitalized rather than outpatients.

In conclusion, in our study, in which the majority of febrile children aged 1-3 months with fever without a focus, it was observed that the agents detected by nasopharyngeal viral PCR method could not exclude the possibility of SBI. Considering that the focus of fever cannot be detected in the final diagnosis in 1/3 of the cases, viral and bacterial PCR tests that can be detected in the blood are also necessary to maximize the efficiency. These studies should be continued as better recognition of viral etiologies may help to avoid unnecessary antibiotic use.



**Ethics Committee Approval:** This study was approved by İzmir Tepecik Training and Research Hospital Clinical Research Ethics Committee (Decision no: 2020/11-60, Date: 14.09.2020).

**Informed Consent:** Patient consent was obtained.

**Peer-review:** Externally peer-reviewed.

**Author Contributions:** Concept- DCE, AK; Design- DCE, AK; Supervision- AK; Resource- AK; Data Collection and/or Processing- DCE, AK; Analysis and/or Interpretation- DCE, AK; Literature Search - DCE, AK; Writing- DCE, AK; Critical Review- DCE, AK.

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