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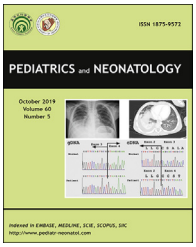

Original Article

Purpuric rash and fever among hospitalized children aged 0—18 years: Comparison between clinical, laboratory, therapeutic and outcome features of patients with bacterial versus viral etiology

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Background: The evaluation of children with purpuric rash and fever (PRF) is controversial. Although many of them have viral infections, on occasion such patients may be infected with *Neisseria meningitidis*. We described all children aged 0—18 years with PRF in southern Israel during the period 2005 2016 and compared their microbiologic, laboratory, clinical and outcome characteristics in relation to various etiologies of this syndrome.
Methods: Data were summarized from electronic patient and microbiology files. Viral diagnoses were made by serology and/or PCR.
Results: Sixty-nine children with PRF were admitted; 30 (43.48%), 9 (13.04%) and 30 (43.48%) had a syndrome of bacterial, viral or non-established etiology, respectively. *N. meningitidis* infection was diagnosed in 16/69 (23.19%) patients and in 16/30 (53.33%) patients with bacterial etiology; 14/30 (46.67%) patients suffered from a non-invasive bacterial disease (9 with Rickettsial disease). Adenovirus and Influenza B (3 and 2 cases, respectively) represented the most frequent etiologic agents among patients with viral etiology. More patients with PRF of bacterial etiology were older, of Bedouin ethnicity, looked ill on admission, had higher

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rates of meningitis and were treated more frequently with antibiotics compared with patients with non-bacterial PRF. Fatality rates among patients with bacterial, viral and non-established etiology were 5/30 (16.7%), 0% and 2/39 (5.1%).
Conclusions: Although PFR was uncommon, high rates of meningococcal infections were recorded in children with PRF, which was associated with high fatality rates. Rickettsial infections were frequent, emphasizing the need for a high index of suspicion for this disease in endemic geographic areas.
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1. Introduction

The occurrence of a purpuric rash in children raises many diagnostic dilemmas related to need of hospitalization and invasive procedures and administration of antibiotic therapy when a suspicion of sepsis and/or meningitis exists, particularly when the infective agent is *Neisseria meningitides*.[1] [5] In the past, when conventional microbiological tests were used for diagnosis, the possibility of bacteremia/septicemia in children with purpuric rash and fever (PRF) was estimated to be around 10 20% when the skin lesions were larger than 2 mm in diameter.[1,2,5] In general, no etiologic agents may be identified in about 72% of the patients with PRF, and a virologic diagnosis could be established in 11 15% of the cases.[2]

Acute meningococcemia may be similar in its initial presentation to viral infections or to non-meningococcal bacterial diseases, and the clinical presentation may be characterized by pharyngitis, fever, weakness, vomiting, diarrhea, and/or headache. An initial maculopapular rash may be present in about 7% of these cases.[6] In patients with fulminant meningococcemia, the disease advances rapidly and within a few hours develops to septic shock, characterized by diffuse petechial rash, hypotension, disseminated intravascular coagulation, metabolic acidosis, adrenal hemorrhage, renal insufficiency, myocardial insufficiency and coma, with or without meningitis.[6] Of 402 patients younger than 21 years with invasive meningococcal disease diagnosed during 1980 2000, 80% were febrile, 40% had hypotension or impaired peripheral infusion and 50% had purpura fulminans.[6]

Viruses, of which Respiratory Syncytial virus (RSV), Epstein Barr virus (EBV), Cytomegalovirus (CMV), enterovirus, adenovirus and parvovirus B19 represent the most common etiologic factors, were also reported in the medical literature as associated with occurrence of purpuric rashes.[7] Furthermore, relatively newly identified viruses, like human metapneumovirus, coronavirus and bocavirus have also been associated with upper respiratory infections and may also cause purpuric rashes.[8–11]

The purpose of the present study is to describe all the cases with PRF occurring in children aged 0 18 years diagnosed and hospitalized at the pediatric departments of the Soroka University Medical Center, Beer-Sheva, Israel, during the period 2005 2016, and to compare their microbiologic laboratory, clinical, therapeutic and outcome characteristics in relation to the various etiologies of this syndrome.

2. Patients and methods

We conducted a retrospective study enrolling all the children aged 0 -18 years hospitalized at the pediatric departments of the Soroka University Medical Center, Beer-Sheva, Israel, during the period 01/2005 12/2016, with a diagnosis of purpuric rash accompanied by a fever >38 °C. All patients were seen first at the Pediatric Emergency Department (PED); the diagnosis was made at PED or during the hospitalization. In this retrospective study, the following diagnoses were searched from the medical archives of the hospital (ICD9):

A. Spontaneous ecchymosis (ICD9-7827)
B. Purpura fulminans (ICD9-7827)
C. Meningococcemia (ICD9-0362)
D. Meningococcal meningitis (ICD9-0360)
E. Other Nonthrombocytopenic Purpura (ICD9-2872)
F. Defibrination Syndrome (ICD9-2866)
G. Purpuric Rash (ICD9 7827)
H. Petechial Rash)ICD9 7827)
I. Rickettsial Infection (ICD9-0839)

Exclusion criteria included:

A. Idiopathic Thrombocytopenic Purpura (ICD9-2873)
B. Henoch-Schonlein Purpura (ICD9-2870)

2.1. Study design/Data collection

All data analyzed were collected from the electronic and regular patient files and from additional data from the microbiology laboratory files. The patients of the study were grouped into 3 main categories

2.1.1. Patients with disease of proven bacterial etiology

- Invasive bacterial disease (purpura fulminans) with or without meningitis
- Focal bacterial disease (tonsillopharyngitis, pneumonia, urinary tract infection, bacterial gastroenteritis, etc.)

2.1.2. Patients with disease of proven viral etiology with

- Identification of one single virus
- Identification of more than one virus
- Bacterial/viral co-infection

2.1.3. Patients without a definite microbiological diagnosis (non-established etiology)

The following demographic clinical and laboratory parameters were collected:

- Age, gender, ethnicity, season, medical background
- Fever (highest measured temperature at home or on admission)
- Clinical picture at admission
- Laboratory findings at admission (WBC count, hemoglobin, thrombocytes and coagulation function tests)
- Microbiologic data (blood cultures, urine cultures, throat cultures and any other culture obtained from a sterile source)
- Nasal washes tests performed (by DFA or PCR) for identification of respiratory viruses (RSV, Influenza A,B, H1N1, Parainfluenza 1−3, Adenovirus, Rhinovirus, Human Metapneumovirus, Coronavirus and Bocavirus)
- PCR examination for Enteroviruses from stool samples
- Chest x-rays
- Lumbar puncture results
- Serologic tests for identification of Rickettsia spp. Which is endemic in southern Israel (*R. conorii* and *R. typhi*)
- Antibiotic treatment administered to patients with proven bacterial etiology and also to patients belonging to the other etiologic groups
- Outcome (Alive/Dead)

2.2. Statistical analysis

Database analysis was completed with SPSS software version 23. Missing data were <5%. Descriptive analysis included analyses of distribution of single variable, central tendency and dispersion, graphical or tubular format. We checked normal distribution for all continuous variables. Uni-variable analysis was completed with chi-square or T-test. For ordinal variables, we computed several dichotomous variables preliminary to the analysis. Statistical significance was considered as P value < 0.05.

3. Results

During the study period, 418,693 children aged 0 18 years visited the Pediatric Emergency Department, of whom 108,555 (25.9%) had a body temperature >38 °C. Two hundred and twenty-three patients with Henoch-Schonlein Purpura and 49 with Idiopathic Thrombocytopenic Purpura hospitalized during the study period were excluded from the study. Sixty-nine (0.06% of the febrile children examined at the Pediatric Emergency Department) children with PRF were subsequently admitted to the pediatric departments and represent the study population (Table 1).

Table 1 Etiology: Purpuric rash and fever.

	No. Cases (%)
1.**Bacterial etiology**	**30/69 (43.48%)**
A.**Invasive bacterial disease**	**16/30 (53.33%)**
Neisseria meningitidis	16/16
a.Bacteremia with meningitis	2/16 (12.5%)
b.Bacteremia w/o meningitis	13/16 (81.25%)
c.Meningitis only	1/16 (6.25%)
B.**Non-invasive bacterial disease**	**14/30 (46.67%)**
a.Tonsillopharyngitis	3/14 (21.43%)
Group A Streptococcus	3/3
b.Acute bacterial gastroenteritis	2/14 (14.28%)
Campylobacter spp.	1/2
Salmonella spp.	1/2
c.Rickettsial disease (positive serology)	9/14 (64.3%)
2.**Viral/Mixed etiology**	**9/69 (13.04%)**
a.Adenovirus	3/9 (3.33%)
b.Influenza B	2/9 (2.22%)
c.Parainfluenza	1/9 (1.11%)
d.CMV	1/9 (1.11%)
e.Rickettsia + EBV	1/9 (1.11%)
f.hMPV + Enterovirus	1/9 (1.11%)
3.**Etiology non-established**	**30/69 (43.48%)**
Total Cases	**69 (100%)**

Of the 69 children with PRF, 30 (43.48%) and 9 (13.04%) suffered from a syndrome of bacterial or viral etiology, respectively. The remaining 30 (43.48%) had a syndrome where the final microbiological diagnosis could not be established. Viral PCR examination (from nasal washes and stool samples) was performed in all 9 patients diagnosed with a syndrome of probable viral etiology, and in 2/30 (6.66%) and 8/30 (26.66%) patients with bacterial and non-established etiology, respectively. Overall, 16/69 (23.2%) patients received antibiotics in the community prior to admission (6 [20%], 2 [22.2%] and 8 [20.5%] of the patients with bacterial, viral or non-established etiology).

Sixteen (53.33%) of the 30 patients with PRF with bacterial etiology suffered from an invasive bacterial disease, caused in all cases by *Neisseria meningitidis* (13/16, 81.25%, diagnosed with meningococcemia only and 3 with meningitis). Overall, *N. meningitidis* infection was diagnosed in 16/69 (23.19%) patients hospitalized with PRF. Fourteen (46.67%) patients suffered from a non-invasive bacterial disease (3, 2 and 9 cases of tonsillopharyngitis, acute bacterial gastroenteritis and Rickettsial disease, respectively). One patient had Group A streptococcus tonsillopharyngitis and a strong clinical suspicion of Rickettsial disease (negative serology). There were 9 cases of PRF with appropriate clinical picture and positive serology (IgG and IgM) for *Rickettsia* spp.

Adenovirus, influenza B, parainfluenza, EBV, CMV, human metapneumovirus and enterovirus (3, 2, 1, 1, 1, 1

and 1 cases, respectively) represented the etiologic agents identified in the patients with viral etiology. One patient had a mixed infection caused by EBV together with serologically-proven *Rickettsia* spp.

Of the 30 patients with PRF without a definitive microbiological diagnosis, 12 (40%) were discharged with a diagnosis of viral syndrome, 3 (10%) with acute otitis media, 4 (13.3%) with possible Rickettsial disease (negative serology) and 2 (6.67%) had a discharge diagnosis of "post-vaccination reaction". Seven (23.33%) of these patients received antibiotics in the community prior to hospitalization and had a discharge diagnosis of culture-negative septicemia without meningitis. Two (6.67%) of these patients were diagnosed with pneumonia and suspicion of scarlet fever, respectively. One patient was diagnosed during hospitalization with acute leukemia.

Table 2 describes the clinical and laboratory characteristics of the patients with PRF in relation to their bacterial or proven viral etiology. The patients with bacterial etiology were older than those with viral etiology ($p = 0.02$). No differences were recorded between the group with bacterial etiology and the group with viral etiology in patient distribution among the three age subgroups (0–1, 1–3 and >3 years) and seasonal distribution of cases. No differences were recorded between the patients with bacterial etiology *vs.* those with viral etiology in terms of gender, ethnicity and diagnoses at discharge. Two (12.5%) of the patients with proven meningococcal disease received prior antibiotic treatment in the community. Fifteen (50%) of the patients in the group with bacterial etiology and 2 (22.2%) from the group with viral etiology had a fever >39 °C at admission. Twenty (66.7%) of the 30 patients with bacterial etiology looked ill at admission, compared with only 2/9 (22.2%) of those with viral etiology ($p = 0.03$). More patients with viral etiology had rhinorrhea compared with those with bacterial etiology. Of a total of 18 patients who

Table 2 Purpuric rash and fever: comparison of the clinical picture of patients with bacterial etiology and of patients with viral etiology.

No. cases	Bacterial etiology	Viral etiology	Total	P value
	30 (43.5%)	9 (13.0%)	39 (56.5%)	
Age				
Years	6.24 ± 5.47	2.71 ± 2.88	4.4 ± 4.3	
Months (mean ± SD)	72.38 ± 65.35	32.56 ± 34.52	51.14 ± 55.4	0.02
0–1	5 (16.7%)	4 (44.4%)	9 (23.1%)	
1–3	6 (20.0%)	3 (33.3%)	9 (23.1%)	0.09
>3	19 (63.3%)	2 (22.2%)	21 (53.8%)	
Male	20 (66.7%)	5 (55.6%)	25 (64.1%)	0.54
Female	10 (33.3%)	4 (44.4%)	14 (35.9%)	
Jewish	10 (33.3%)	5 (55.5%)	15 (38.5%)	0.24
Bedouin	20 (66.7%)	4 (44.5%)	24 (61.5%)	
Season				
Winter	8 (26.7%)	4 (44.4%)	12 (30.8%)	0.31
Spring	9 (30%)	2 (22.2%)	11 (28.2%)	0.65
Summer	10 (33.3%)	2 (22.2%)	12 (30.8%)	0.53
Fall	3 (10%)	1 (11.1%)	4 (10.2%)	0.92
Main symptoms				
Rhinorrhea	2 (6.7%)	3 (33.3%)	5 (12.8%)	0.04
Cough	2 (6.7%)	1 (11.1%)	3 (7.7%)	0.73
Vomiting	14 (46.7%)	1 (11.1%)	15 (38.5%)	0.11
Diarrhea	6 (20.0%)	1 (11.1%)	7 (18.0%)	0.51
Meningeal signs	5 (16.7%)	0 (0.0%)	5 (12.8%)	0.18
Joint swelling	2 (6.7%)	0 (0.0%)	2 (5.1%)	0.30
Maximal temperature (°C) at admission				
38.0 39.0	15 (50%)	7 (77.8%)	22 (56.4%)	0.14
>39.0	15 (50%)	2 (22.2%)	17 (43.6%)	
Ill appearance at admission	20 (66.7%)	2 (22.2%)	22 (56.4%)	0.03
Diagnosis at discharge[a]				
Meningococcemia	15 (50.0%)	0 (0.0%)	15 (38.5%)	
Rickettsiosis	9 (30.3%)	1 (11.1%)	10 (25.6%)	0.26
Septic shock	5 (16.7%)	0 (0.0%)	5 (12.8%)	0.19
Fever & purpura (only)	0 (0.0%)	4 (44.5%)	4 (10.2%)	0.001
Meningitis	3 (10.0%)	0 (0.0%)	3 (7.7%)	0.3
Tonsillopharyngitis	3 (10.0%)	0 (0.0%)	3 (7.7%)	1.0
Other	6 (20%)	3 (33.3%)	9 (23.1%)	0.4
Positive lumbar puncture	3/11 (27.3%)	0/1 (0.0%)	3 (7.7%)	1.0

[a] Some patients had more than 1 diagnosis.

underwent a lumbar puncture, the procedure was performed in 11 of the patients with a bacterial etiology and 1 of those with viral etiology. Four (13.3%) of the patients with bacterial etiology had neck stiffness at admission and 3 of them underwent a lumbar puncture (negative in all 3). None of the patients with viral etiology had neck stiffness at admission. Twenty-nine (96.7%) of the 30 patients with PRF of bacterial etiology received antibiotic treatment at admission. Ceftriaxone was administered in 20/29 (69.0%) patients with bacterial etiology (single therapy in 16 patients, together with Vancomycin in 3 patients and together with Doxycycline in 1 patient). In the group of patients with proven Rickettsial disease, Doxycycline alone was administered in 7 patients and in combination with other antibiotics in 2 additional patients. Seven (77.8%) of the 9 patients with PRF of viral etiology received antibiotic treatment at admission (Ceftriaxone and Doxycycline in 6 and 1 of them, respectively).

Table 3 compares the clinical and laboratory characteristics of the 30 patients with bacterial etiology and those

Table 3 Purpuric rash and fever: comparison of the clinical picture of patients with bacterial etiology and of patients with non-bacterial etiology.

No. cases	All patients	Bacterial etiology	Non-bacterial etiology	P value
	69	30 (43.5%)	39 (56.5%)	
Age (months)		72.38	39.87	0.77
Years	4.6 ± 4.7	6.24 ± 5.47	3.32 ± 3.67	
Months (mean ± SD)	53.94 ± 56.24	72.38 ± 65.35	32.56 ± 34.52	
0—1	22 (31.9%)	5 (16.7%)	17 (43.6%)	
1—3	14 (20.3%)	6 (20.0%)	8 (20.5%)	0.02
>3	33 (47.8%)	19 (63.3%)	14 (35.9%)	
Male	69	20 (66.7%)	23 (59.0%)	0.51
Female		10 (33.3%)	16 (41.0%)	
Jewish	69	10 (33.3%)	24 (61.5%)	0.02
Bedouin		20 (66.7%)	15 (38.5%)	
Season				
Winter	24 (34.8%)	8 (26.7%)	16 (41.0%)	0.21
Spring	18 (26.1%)	9 (30%)	9 (23.1%)	0.52
Summer	20 (29%)	10 (33.3%)	10 (25.6%)	0.48
fall	7 (10.1%)	3 (10%)	4 (10.3%)	0.97
Main symptoms				
Rhinorrhea	9 (13.0%)	2 (6.7%)	7 (17.9%)	0.17
Cough	9 (13.0%)	2 (6.7%)	7 (17.9%)	0.17
Vomiting	27 (39.1%)	14 (46.7%)	13 (33.3%)	0.26
Diarrhea	10 (14.5%)	6 (20.0%)	4 (10.3%)	0.25
Meningeal signs	8 (11.6%)	5[a] (16.7%)	3 (7.7%)	0.25
Joint swelling	2 (2.9%)	2 (6.7%0	0 (0.0%)	0.1
Maximal temperature (°C) at admission				
38.0 39.0	34 (49.3%)	15 (50%)	19 (48.7%)	0.92
>39.0	35 (50.7%)	15 (50%)	20 (51.3%)	
Ill appearance at admission	34 (49.3%)	20 (66.7%)	14 (35.9%)	0.01
Diagnosis[c] at discharge				
Meningococcemia	15 (21.7%)	15 (50.0%)	0 (0.0%)	
Fever & purpura (only)	13 (18.8%)	0 (0.0%)	13 (33.3%)	<0.001
Rickettsiosis	10 (14.5%)	9 (30.3%)	1 (2.6%)	0.001
Septic shock	7 (10.1%)	5 (16.7%)	2 (5.1%)	0.12
Gastroenteritis	6 (8.7%)	2 (6.7%)	4 (10.3%)	0.69
Susp. Rickettsiosis	4 (5.8%)	1 (3.3%)	3 (7.7%)	0.71
Meningitis	3 (4.3%)	3 (10.0%)	0 (0.0%)	0.04
Tonsillopharyngitis	3 (4.3%)	3 (10.0%)	0 (0.0%)	0.08
Otitis media	3 (4.3%)	0 (0.0%)	3 (7.7%)	0.12
LRTI	2 (2.9%)	0 (0.0%)	2 (5.1%)	0.21
Pneumonia	2 (2.9%)	0 (0.0%)	2 (5.1%)	0.5
Limping	2 (2.9%)	0 (0.0%)	2 (5.1%)	0.2
Other	12 (17.4%)	4 (13.3%)	8 (20.5%)	0.3
Positive lumbar puncture	3/18 (16.7%)	3/11 (27.3%)[b]	0/7 (0.0%)[b]	0.24

[a] 4 patients with neck stiffness, 1 patient with bulging fontanella.
[b] Total no. of patients who underwent lumbar puncture.
[c] Some patients had more than 1 diagnosis.

the 39 patients with non-bacterial etiology (including the 9 patients with proven viral etiology). Significantly more patients with bacterial etiology were recorded in the group aged >1 year. No differences were recorded between the two groups in respect to gender, seasonal occurrence, maximal temperature at admission and symptoms. Twenty (66.7%) of the 30 patients with bacterial etiology looked ill at admission compared with only 14/39 (35.9%) of those with non-bacterial etiology ($p = 0.01$). More patients among the group with non-bacterial etiology were of Jewish ethnicity. Three (7.7%) patients with non-bacterial etiology presented with neck stiffness. More patients in the group with bacterial etiology had meningitis. All 7 lumbar punctures performed in patients with non-bacterial etiology were negative. More patients in the non-bacterial etiology group (compared with patients with bacterial etiology) were not treated with antibiotics at admission (11/39, 28.2% vs. 1/30, 3.3%, $p = 0.02$). Of the antibiotic-treated patients, 12, 10, and 6 were initially treated with Ceftriaxone, Amoxycillin and Doxycycline, respectively.

No differences were recorded in the peripheral blood hemoglobin, white blood cells and thrombocytes counts and PTT values between patients with bacterial etiology and those with viral etiology (Table 4). Higher young neutrophil forms (bands) counts and prolonged INR were more common in patients with bacterial etiology compared with those with viral etiology. Monocytes percentages were higher among patients with viral etiology compared with those with bacterial etiology.

Similar laboratory findings were recorded when comparing between patients with bacterial etiology and the group of 39 patients with non-bacterial etiology, except for the band count, which was not different between the 2 groups ($4.5 \pm .8$ vs. 2.6 ± 4.3, $p = 0.3$).

3.1. Outcome

Seven (10.2%) of all 69 patients died on admission or during hospitalization, 5 (7.2%) diagnosed with a bacterial etiology (4 with meningococcemia and 1 with acute gastroenteritis, hypovolemic shock and growth of *C. jejunii* from stool culture) and 2 (2.9%) with non-established etiology (both with septic shock on admission and prior antibiotic treatment in the community). The fatality rates among patients with proven bacterial etiology, proven viral etiology and non-established etiology were 5/30 (16.7%), 0/9 (0%) and 2/39 (5.1%).

4. Discussion

The aim of the present study was to determine the etiology of all cases of PRF occurring in children aged 0 18 years hospitalized in southern Israel during the period 2005 2016, and compare their microbiologic, laboratory, clinical, therapeutic and outcome characteristics in relation to the various etiologies of this syndrome. The study was completed at the Soroka University Medical Center, a primary and tertiary referral hospital which is the only hospital in the Negev area of southern Israel and provides medical services for around 250,000 children. The Pediatric Emergency Department of the hospital receives around 36,000 visits/year. The study enrolled all the children presenting at the Pediatric Emergency Department and hospitalized due to occurrence of a new purpuric rash accompanied by fever >38 °C, after exclusion of Idiopathic Thrombocytopenic Purpura and Henoch-Schonlein Purpura. The patients with PRF were grouped and analyzed according to their inclusion in one of the following 3 etiologic entities: patients with disease of bacterial, viral or non-established (microbiologically) etiology.

Our present study showed the following: 1. PRF was uncommon. 2. A bacterial etiology of PRF was established in 43.48% of the patients while the rest of 43.48% and 13.04% had a syndrome of non-established or viral etiology, respectively. 3. *N. meningitidis* infection was diagnosed in 23.19% patients hospitalized with PRF. 4. Rickettsial disease was diagnosed in a considerable number of patients (14.5%). 5. More patients were recorded in the group aged >1 year among the patients with bacterial etiology than in those with non-bacterial etiology. 6. Higher bands counts and prolonged INR were more common in patients with bacterial etiology compared with those with viral etiology. 7. The fatality rate in PRF of a bacterial etiology patients was high (16.7%) and *N. meningitidis* infection was reported in 80% of the fatal cases with established etiology.

Table 4 Laboratory findings: bacterial versus viral etiology.

	All patients	Bacterial etiology	Viral etiology	P value
Total number				
Hemoglobin (g/dL)	11.49 ± 1.56	11.7 ± 1.8	11 ± 1.1	0.27
Thrombocytes (/μL)	226.42 ± 154.36	292.7 ± 158.9	261.8 ± 172.1	0.3
Leukocytes (/μL)	13.33 ± 8.32	13.2 ± 10.1	14.9 ± 7.4	0.58
Segmented Neutrophils[a]	7.73 ± 7.27	8.1 ± 7.1	5.5 ± 4.7	0.23
Banded Neutrophils[a]	3.43 ± 4.56	4.5 ± 4.8	0.8 ± 0.5	0.02
Lymphocytes[a]	3.81 ± 3.83	2.9 ± 3.6	4.9 ± 3.6	0.15
Monocytes[a]	0.95 ± 0.78	0.7 ± 0.5	1.5 ± 1.2	0.009
CRP (mg/L)	55.52 ± 80.98	60.3 ± 44.5	33.3 ± 50.3	0.46
INR[b]	1.45 ± 0.59	1.7 ± 0.7	1.1 ± 0.1	0.04
PTT (s)[b]	32.94 ± 10.05	34.1 ± 11.2	31.5 ± 3.6	0.43

[a] % of total leukocytes.
[b] Expressed as % of abnormal tests.

We showed that 23.19% of all enrolled children and 53.33% of all children with an established bacterial etiology who presented with PRF had meningococcal infection. The rate of meningococcal infection in our study was higher than previously described, both among all patients with PRF enrolled (0.5% 11%)[1–4] and also among all patients with proven bacterial etiology (4.2 24%).[2,3] The overall mortality rate in our series was 10.2% and reached 16.7%% among the patients with PRF associated with a bacterial infection. Four of the 5 fatalities recorded in our series were due to proven meningococcal invasive disease and two additional fatalities were recorded in patients without recovery of any pathogen and a high suspicion of meningococcal disease, based on their clinical presentation and possible masking of the etiology by previous antibiotic therapy. In a study from 1989 enrolling 190 patients with PRF, 13 (7%) had meningococcal disease, but the most common bacterial association was with *Streptococcus pyogenes* (19 patients).[2] Viral infections were documented in 28 patients. Patients with invasive bacterial disease appeared more ill, were more likely to have neck stiffness and were more likely to have petechiae on the lower extremities than those with no bacteremic disease. A higher peripheral white blood count and absolute band form count was found in the patient with invasive bacterial disease.[2] Nguyen et al. reported in 1984 on 129 patients hospitalized with PRF in Syracuse, NY, and they found that 26 patients (20.2%) had culture-proven bacterial infection (13 and 8 had N. *meningitidis* and *Haemophilus influenzae* type B, respectively).[1] As in our study, the authors could not document any single laboratory test as sensitive enough to detect all patients with life-threatening bacterial infections. Mandl et al. reported in 1997 on 411 patients with PRF examined at the emergency department of the Pediatric Teaching Hospital in Boston.[3] Eight (1.9%) patients had bacteremia or clinical sepsis and 6 of them had serious invasive bacteremia (*N. meningitidis* recovered in 2 patients). None of the 357 well-appearing patients had serious invasive bacteremia. This study, by reporting invasive bacteremia less frequently than in previous series and being able to identify this condition by clinical criteria, supported the concept of the treatment of selected well-appearing children with PRF as outpatients.[3] In a study examining 233 infants and children younger than 15 years presenting with a non-blanching rash during the period 1998–1999 in the UK, 11% had proven meningococcal infection.[4] The authors showed that most children with meningococcal infection were ill at presentation, had a purpuric rash, were febrile and had a delayed capillary refill. None of the children with a non-blanching rash confined to the distribution of the superior vena cava had meningococcal infection. In Israel, Ben-Shimol et al.[12] described the dynamics of childhood invasive meningococcal disease during a 22-year period (1989 2010). The authors reported on a total of 743 cases, 69.2% of them with meningitis and 30.8 with meningococcemia only. The mean annual incidence was 2 cases/100,000 children aged 0 15 years, an incidence similar to those reported from other developed countries.[12] The mean mortality incidence was 0.2 $\pm$ 0.1 cases/100,000 children and this was higher in children without meningitis (14.9%) compared to children with meningitis (7.9%). In Israel, meningococcal vaccine was not introduced in the national immunization program and it is administered only to high-risk patients. It is understandable that preventive, rather than therapeutic strategies will have a major contribution to the decrease of the serious morbidity and mortality associated with invasive meningococcal disease.

In this study, we grouped all cases with proven viral etiology together with those with a non-established etiology and obtained a group of patients with non-bacterial etiology, which was further compared with the group of patients with PRF of bacterial etiology. We found that more patients with PRF of bacterial etiology were older, of Bedouin ethnicity, looked ill on admission, had more meningitis and received more antibiotic treatments compared to the patients with PRF of non-bacterial etiology. These findings may be useful, at least in part, in the management of the patients with PRF at the emergency room and during their hospitalization.

Israel is considered endemic for 2 types of spotted fevers, caused by *Rickettsia conorii* and *Rickettsia typhi*.[13–15] The diagnosis is based on nonspecific clinical findings (fever, weakness, myalgia) and a specific petechial rash; it has a benign course in the majority of cases but sometimes can be severe and may reach mortality rates of 1.4 5.6%.[13,16,17] In the present study, we treated with Doxycycline 10 (14.5%) patients with PRF caused by a proven Rickettsial infection and 4 (5.8%) additional patients with a clinical picture appropriate for Rickettsial infection. Therefore, taking into consideration the high rates of Rickettsial infections reported in Israel and particularly in the southern area of the country and into the Bedouin population, we consider that Rickettsial infection should be highly suspected, in our geographic area, in the initial investigation of patients presenting with PRF and empiric treatment has to be administered to the patients with a high index of suspicion for this disease.

We found a definitive viral etiology in a minority (13%) of the patients with PRF, with Adenovirus and Influenza B identified as the most commonly isolated viruses in these patients. In a prospective study completed in Germany during 2009 2012, Schneider et al.[7] described 58 febrile and afebrile children aged 0 -18 years examined at the emergency room with a purpuric rash $<$2 mm in diameter, symptoms of viral disease and exclusion of meningococcal disease. The authors reported that a viral pathogen was found in 67% of the PCR examinations performed from the nasopharynx.[7] The most frequent pathogens associated with PRF were CMV and EBV (18% each of all patients) followed by enteroviruses and rotavirus (14% each) and H1N1 and human bocavirus (9% each); 41% of the patients were diagnosed with more than one viral pathogen. This study emphasizes that novel viral rapid detection methods (like multiplex q-PCR) are available and should be used in determining the possible viral etiology in a considerable number of patients with PRF and thereby avoiding unnecessary treatments and hospitalizations.

Our study had some limitations, derived mainly from its retrospective nature, which could have caused to some missing or inexact information in the data collection from the medical and laboratory charts. We were not able to determine, after a thorough search of the patient files, valuable data on the number, location and diameter of the lesions of the enrolled patients. Another limitation is

related to the relatively small number of patients enrolled and of virologic investigations performed, particularly in the group of patients with non-established microbiological diagnosis, making it possible that the number of infectious etiologies among our study population was even higher.

In conclusion, we report in this study that PRF is an uncommon occurrence in hospitalized febrile children. We showed high rates of meningococcal infections in the etiology of PRF in children, associated with higher fatality rates than in the published medical literature. Rickettsial infections were also frequently diagnosed in our study population, emphasizing the need for a high index of suspicion for this disease in endemic geographic areas.

Compliance with Ethical Standards: The study was conducted in accordance with the ethical standards of the Soroka University Medical Center.

Conflict of interest

No potential conflict of interest was reported by the authors.

Ethical approval

The study was conducted following the approval of the Helsinki committee of the Soroka University Medical Center.

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