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ACTA PÆDIATRICA NURTURING THE CHILD WILEY

ORIGINAL ARTICLE

European study confirms the combination of fever and petechial rash as an important warning sign for childhood sepsis and meningitis

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Abbreviations: CI, confidence interval; ED, emergency department; ED-PEWS, emergency department paediatric early warning score; OR, odds ratio.

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Abstract

Aim: This study investigated febrile children with petechial rashes who presented to European emergency departments (EDs) and investigated the role that mechanical causes played in diagnoses.

Methods: Consecutive patients with fever presenting to EDs in 11 European emergency departments in 2017–2018 were enrolled. The cause and focus of infection were identified and a detailed analysis was performed on children with petechial rashes. The results are presented as odds ratios (OR) with 95% confidence intervals (CI).

Results: We found that 453/34010 (1.3%) febrile children had petechial rashes. The focus of the infection included sepsis (10/453, 2.2%) and meningitis (14/453, 3.1%). Children with a petechial rash were more likely than other febrile children to have sepsis or meningitis (OR 8.5, 95% CI 5.3–13.1) and bacterial infections (OR 1.4, 95% CI 1.0–1.8) as well as need for immediate life-saving interventions (OR 6.6, 95% CI 4.4–9.5) and intensive care unit admissions (OR 6.5, 95% CI 3.0–12.5).

Conclusion: The combination of fever and petechial rash is still an important warning sign for childhood sepsis and meningitis. Ruling out coughing and/or vomiting was insufficient to safely identify low-risk patients.

KEYWORDS
febrile illness, mechanical cause of petechiae, meningitis, petechial rash, sepsis

1 | INTRODUCTION

The presentation of patients with febrile illness and petechial rash is a diagnostic dilemma for clinicians who treat them. Petechiae might be caused by forceful vomiting/coughing or viral disease, such as Cytomegalovirus or Epstein–Barr virus infection but could also be a sign of potential invasive meningococcal disease or other serious bacterial infections.[1,2] Patients with invasive meningococcal disease often only show unspecific symptoms in the first 4–6 h, but have typical symptoms like petechial rash, meningism and impaired consciousness after 13–22 h.[3] The evaluation of clinical signs and symptoms is of great importance and has been implemented in major clinical guidelines. Accordingly, a petechial rash in a febrile patient is considered a warning sign and further diagnostic work-up and initiation of antibiotic treatment should be considered.[4] However, due to the low incidence of sepsis and meningitis, particularly after meningococcal and pneumococcal vaccination, most patients with petechial rash do not develop a serious disease and will recover within a short time. Despite this, a small proportion of patients suffer from severe bacterial infections with an urgent need for antibiotic treatment and immediate life-saving interventions, such as airway and haemodynamic stabilisation.[5–8] Guidelines are safety-oriented and driven by high mortality and morbidity rates. Accordingly, a relatively high number of patients are investigated or treated unnecessarily, which is time-consuming, costly, uncomfortable and sometimes painful. In order to sharpen the diagnostic yield, further signs and symptoms might be considered, such as clinical appearance and a potential mechanical cause of petechiae, such as coughing and/or vomiting. An observational study from the United Kingdom concluded that clinical practice guidelines, which allowed well-appearing patients with potential mechanical causes of petechiae to be discharged, were as safe as the UK National Institute for Health and Care Excellence guidelines, but more cost-effective.[9] As a consequence, the British Society for Antimicrobial Chemotherapy guidelines defines low-risk patients in two ways. The first is without red flags: unwell appearance or clinically shocked, rash spreading within the department, purpura >2 mm. The second is a clear mechanical cause, such as forceful vomiting, coughing or trauma, which are suitable for management in the community without parenteral antibiotics.[10,11]

Key Notes

- This study provides results from a large-scale observational study of febrile children attending European emergency departments in 11 countries in 2017–2018.
- Children with petechial rashes had a higher risk for sepsis, meningitis and bacterial infections and needed more immediate life-saving interventions and intensive care treatment than other febrile children.
- Coughing and vomiting were common in children with sepsis or meningitis.

This paper reports the findings of febrile patients with petechial rash who presented to paediatric emergency departments. They were prospectively recruited during a large-scale European multicentre study. We also studied the diagnostic value of the petechial rash for bacterial infections, sepsis and meningitis.

2 | METHODS

2.1 | Study design

This study formed a part of the Management and Outcome of Fever in Children in Europe, which is embedded in the Personalized Risk assessment in Febrile illness to Optimize Real-life Management across the European Union project.[12] This study is an observational, multicentre study that assessed the management and outcome of febrile children attending 12 European emergency departments using routine data. Various groups were analysed to study the diagnostic value of petechial rashes for bacterial infections, sepsis or meningitis. We described the clinical characteristics of patients with petechial rash compared to patients with other rashes or no rash. The characteristics and findings of all patients with a petechial rash were analysed, as well as patients in this group with sepsis or meningitis and with bacterial and non-bacterial infections. Furthermore, we stratified patients with petechial rash by the potential mechanical cause of petechiae, such as coughing and/or vomiting in patients with or without bacterial infection, sepsis or meningitis. In addition, we stratified patients according to their age and the presence of comorbidities for bacterial infections, sepsis or meningitis.

2.2 | Study population and setting

The study comprised 12 emergency departments from eight different countries: one in Austria, Germany, Greece, Latvia, Spain and Slovenia and three each in the Netherlands and the United Kingdom. All the study sites were either tertiary university hospitals or large teaching hospitals.[13] Consecutive patient recruitment was performed for at least 1 year in the study period from 1 January 2017 to 30 April 2018. The periods of active data collection per month differed in the participating hospitals, ranging from 1 week per month to the entire month. We included children and adolescents aged 0–18 years with fever, defined as a temperature ≥38°C measured in the ED or a history of fever in the 72 h before visiting the ED. We excluded patients without documented rash status.

2.3 | Data collection

The data collected included basic patient characteristics, clinical signs and symptoms, immediate life-saving interventions, investigations performed and the treatment and disposition of the patients.

Clinical signs and symptoms were assessed by the treating clinician. The focus and cause of the infection were determined by a research team using a modified flowchart (Figure S1). For this analysis, we used the following categories for the cause of infection: definitive and probable bacterial infections, definitive and probable viral infections, unknown inflammatory infections and others. If the patients had both bacterial and viral infections, they were classified as bacterial. Patients without documented rash status or contradicting rash status were excluded. The Emergency Department Paediatric Early Warning System (ED-PEWS) tool, developed by Zachariasse et al., was used to assess disease severity.[14,15]

2.4 | Data quality

Data quality and completeness were improved and standardised using a digital training module for physicians who assessed febrile children in the ED. Data were entered into the patient's record as part of routine care by the treating physician and nurse. They were then manually extracted from these records and entered into an electronic case report form by trained research team members. Data completeness was overall good but not complete in all patients, caused by the observational study design. Missing values are reported in the table's footnotes. Numbers in the text are reported as numbers/available observations and percentages (*n*/*n*, %).

2.5 | Statistical analysis

The data were analysed using descriptive statistics. Groups were compared using chi-square tests, Fisher's exact test, one-way-analysis of variances or the Mann–Whitney *U* test. Fisher's exact test was used if more than 20% of cells had an expected count of less than five. Odds ratios (ORs) were computed by dividing the odds of one group (e.g. children with fever and petechiae) by the odds in the other group (e.g. children with fever and no/other rash). 95% confidence intervals were calculated using the following formula, where the letters a, b, c and d represent the cell counts of a 2×2 contingency table:

$$\text{Upper 95\% CI} = e\{\left[\ln(\text{OR}) + 1.96 \times \text{sqrt}(1/a + 1/b + 1/c + 1/d)\right].$$

$$\text{Lower 95\% CI} = e\{\left[\ln(\text{OR}) - 1.96 \times \text{sqrt}(1/a + 1/b + 1/c + 1/d)\right].$$

The *p*-value was computed for the Chi-square statistic, indicating a possible relationship between two categorical variables. Missing values for individual items for the ED-PEWS were imputed using the MICE package in R. The imputation model included hospital, general patient characteristics, clinical signs and symptoms, treatment, disposition and cause and focus of infection. The multiple imputation resulted in 20 imputation sets and results for the ED-PEWS were pooled. Data sets were analysed using SPSS version 27.0 (IBM Corp.) and R (R Foundation).

2.6 | Ethical statement

The study was approved by the ethical committees of all the participating hospitals and no informed consent was needed for this study. Austria: Ethikkommission Medizinische Universitat Graz (28-518ex15/16). Germany: Ethikkommission LMU München (699-16). Greece: Ethics Committee (9683/18.07.2016). Latvia: Centrala medicinas etikas komiteja (14.07.201.6. No. II16-07-14). Slovenia: Republic of Slovenia National Medical Ethics Committee (0120-483/2016-3). Spain: Comité Autonómico de Ética de la Investigación de Galicia (2016/331). The Netherlands: Commissie Mensgebonden Onderzoek (NL58103.091.16). UK: Ethics Committee (16/LO/1684, Integrated Research Application System number 209035, Confidentiality Advisory Group reference 16/CAG/0136). The UK has an opt-out mechanism for people who do not want their data to be used for research, and this was in place in all the participating UK settings.

3 | RESULTS

3.1 | All febrile patients

There were 38480 febrile patients in the Management and Outcome of Fever in Children in Europe cohort and the rash status was recorded for 34010 (88.4%) patients. Of those, 453 (1.3%) had a petechial rash, 4270 (12.6%) had other rashes and 29287 (86.1%) had no rashes.

The focus of infection was recorded in 33995 patients. In the petechial rash group, 10/453 (2.2%) had sepsis and 14/453 (3.1%) had meningitis. In patients with other rashes, 35/4269 (0.8%) had sepsis and 21/4269 (0.5%) had meningitis, while in patients without a rash, 82/29273 (0.3%) had sepsis and 82/29273 (0.3%) had meningitis.

Cause of infection was recorded in 33752 patients, revealing 67/447 (15.0%) bacterial infections in patients with petechial rash, 504/4256 (11.8%) bacterial infections in patients with other rashes and 3306/29049 (11.4%) bacterial infections in patients without a rash.

We compared the 453 patients with a petechial rash to the 33557 other patients. Patients with petechial rashes had higher rates of sepsis and meningitis (OR 8.5, 95% CI 5.3–13.1, $p < 0.001$) and bacterial infections (OR 1.4, 95% CI 1.0–1.8, $p = 0.023$). They were also more likely to need immediate life-saving interventions (OR 6.6, 95% CI 4.4–9.5, $p < 0.001$) and intensive care unit admissions (OR 6.5, 95% CI 3.0–12.5, $p < 0.001$). (Figures 1 and 2, Table S1).

3.2 | Febrile patients with petechial rashes

All further analyses were performed on the 453 patients (60.9% male) with petechial rashes (Tables 1 and 2). The patients' median age was 3.8 years, with an interquartile range of 1.6–6.3 years. Most children had coughing (219/372, 58.9%) and/or vomiting (195/406, 48.0%). The mean ED-PEWS (emergency department paediatric early warning score) was two, but 42 (9.2%) of the patients scored six or more. The focus of the infection was mainly upper respiratory infections (189/453, 41.7%) and undifferentiated fever (91/453, 20.1%). We found that 14 (3.1%) had meningitis and 10 (2.2%) had sepsis.

In 447 patients, the cause of infection was assigned. In the majority, the cause of the infection was unknown bacterial or viral (195/447, 43.6%), followed by viral infections (159/447, 35.6%). The data showed that 67/447 (15.0%) patients had a bacterial infection, 6/447 (1.3%) had an inflammatory disease and 20/447 (4.5%) had other diagnoses.

We analysed the children with petechial rash according to the focus of their infection, namely meningitis or sepsis versus others. Our results showed that children with meningitis or sepsis were more likely to look ill (OR 23.1, 95% CI 6.7–124.3, $p < 0.001$), had prolonged capillary refill time (OR 16.5, 95% CI 3.6–66.8, $p < 0.001$)

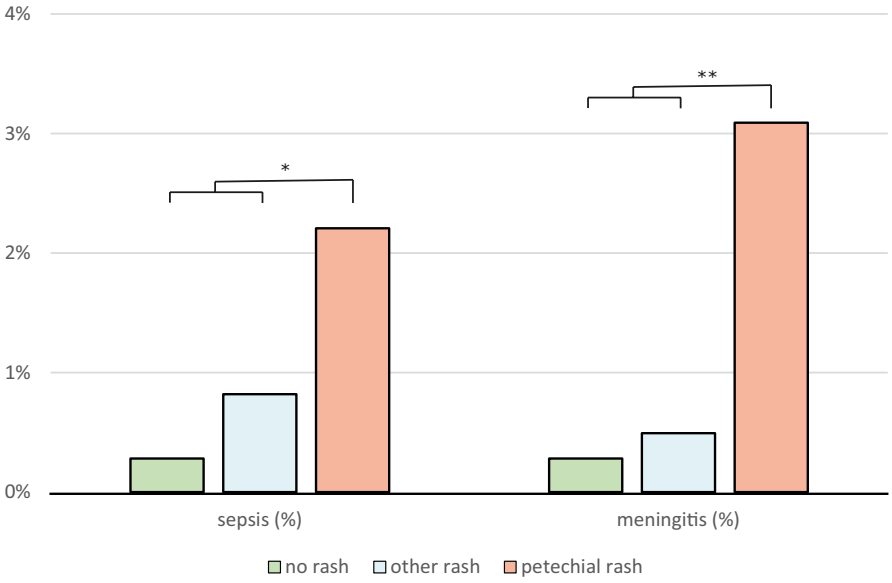

FIGURE 1 Proportion of sepsis and meningitis in febrile patients according to rash status. *OR 6.5 [3.4–12.4], $p < 0.001$; **OR 10.4 [5.9–18.3], $p < 0.001$.

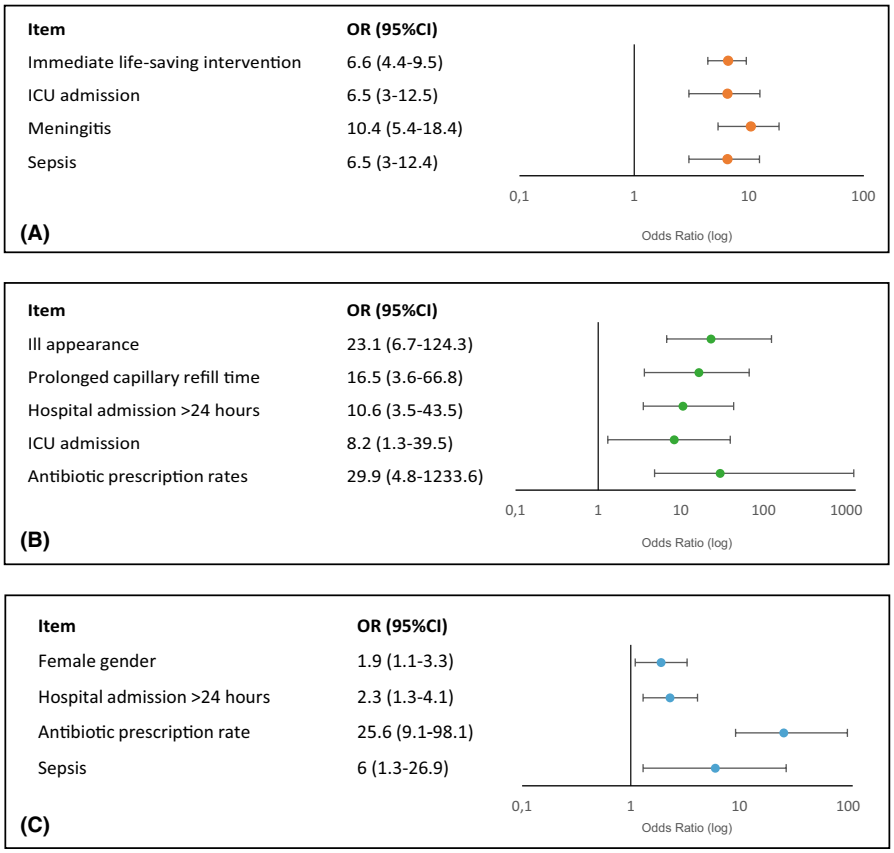

FIGURE 2 (A) Febrile patients, findings in patients with petechial rash ($n = 453$) compared to patients without a rash or other rashes ($n = 33\,557$). (B) Febrile patients with petechial rash, findings in patients with sepsis or meningitis ($n = 24$) compared to patients with other focus of infection ($n = 429$). (C) Febrile patients with petechial rash, findings in patients with bacterial infection ($n = 67$) compared to patients with other cause of infection ($n = 380$).

and higher C-reactive protein ($p = 0.003$). They were more likely to be admitted to the hospital for more than 24 h (OR 10.6, 95% CI 3.5–43.5, $p < 0.001$), be admitted to intensive care (OR 8.2, 95% CI 1.3–39.5, $p = 0.013$) and had higher antibiotic prescription rates (OR 29.9, 95% CI 4.8–1233.6, $p < 0.001$).

We also analysed children with petechial rash according to the cause of their infection, namely bacterial versus non-bacterial and this showed that patients with bacterial infections were more likely to be female (OR 1.9, 95% CI 1.1–3.3, $p = 0.022$). They had higher leucocytes counts, neutrophil counts, C-reactive protein (all $p < 0.001$), rates of hospital admissions for more than 24 h (OR 2.3, 95% CI 1.3–4.1, $p = 0.002$), antibiotic prescription rates (OR 25.6, 95% CI 9.1–98.1, $p > 0.001$) and higher rates of urinary tract infections (OR 15.1, 95% CI 2.4–161.6, $p = 0.001$). Children with bacterial infections were also more likely to have sepsis (OR 6.0, 95% CI 1.3–26.9, $p = 0.009$) (Table 2, Figure 2).

3.3 | Clinical signs in patients with petechial rash

Out of 453 patients with petechial rash, 411 patients were included for the analysis of the clinical signs vomiting and/or coughing. Forty-two patients were excluded because of missing information. We concluded that coughing and/or vomiting was common in patients with petechial rash (327/411, 79.6%), with comparable rates in patients with sepsis/meningitis (17/23, 73.9%) as in patients with other focus of disease (310/388, 79.9%) and comparable rates in patients with bacterial infection (48/61, 78.7%) and non-bacterial infection (275/344, 79.9%).

Vice versa, rates of sepsis or meningitis as well as bacterial and viral infections were not different in patients with or without coughing and/or vomiting (Table 3).

Further analyses showed that 7/10 (70%) patients with sepsis had coughing and/or vomiting, but two appeared well. We also found that 10/13 (76.9%) patients with meningitis had coughing and/or vomiting, but one appeared well.

Body temperature and duration of fever did not differ according to the focus and cause of the infection.

3.4 | Age stratification for bacterial infections, sepsis or meningitis

Age stratification showed that the highest odds ratio for sepsis or meningitis was in children aged 3–5 years (OR 18.3, 95% CI 7.0–42.3, $p < 0.001$) followed by children aged 6–9 years (OR 12.9, 95% CI 3.1–40.6, $p = 0.001$). No differences were seen in the rates of bacterial infections (Table S2, Figure S2).

4 | DISCUSSION

This study describes the findings from a large-scale European multicentre observational study that investigated the combination of

TABLE 1 Characteristics and findings of 453 patients with fever and petechial rash, by the focus and cause of the infection.

	All ($n = 453$)	Focus: sepsis ($n = 10$)	Focus: meningitis ($n = 14$)	Cause: bacterial ($n = 67$)	Cause: non-bacterial ($n = 380$)
General characteristics					
Age in years, median (IQR)	3.8 (1.6–6.3)	4.0 (2.6–7.0)	3.7 (0.4–6.6)	4.3 (2.5–6.6)	3.7 (1.5–6.3)
Male sex, *n* (%)	276 (60.9)	50.0	57.1	52.2	36.6
Symptoms					
Ill appearance, *n* (%)	103 (24.8)	7 (77.8)	12 (92.3)	19 (29.7)	83 (24.1)
Vomiting, *n* (%)	195 (48.0)	4 (50.0)	9 (69.2)	27 (44.3)	165 (48.7)
Coughing, *n* (%)	219 (58.9)	4 (50.0)	3 (30)	34 (59.6)	182 (58.9)
Signs of resp. infection, *n* (%)	229 (63.4)	4 (57.1)	3 (30.0)	39 (70.9)	186 (62.0)
Diarrhoea, *n* (%)	61 (16.2)	3 (30.0)	2 (20.0)	8 (14.5)	53 (16.8)
Seizures, *n* (%)	20 (4.6)	0 (0.0)	2 (15.4)	0 (0.0)	20 (5.4)
Vital signs					
Prolonged capillary refill (<3 s), *n* (%)	12 (3.0)	3 (33.3)	2 (16.7)	1 (1.7)	11 (3.3)
Oxygen saturation, median (IQR)	98 (97–100)	99 (96–100)	99 (97–99)	98 (97–99.5)	98 (97–100)
Temperature in °C, median (IQR)	37.8 (37.0–38.6)	38.1 (37.2–38.9)	38 (37.6–39.0)	37.7 (36.8–39.1)	37.8 (37–38.5)
Fever duration, median days (IQR)	4 (3–5)	3 (3–22)	n.a.	3 (3–4)	4 (3–5)
ED-PEWS[a], median (IQR)	8 (6–12)	13 (7–24)	13 (9–20)	9 (6–13)	8 (6–12)
Blood findings					
Leucocytes G/L, median (IQR)	9.7 (6.8–14.8)	7.5 (1.5–13.1)	10.8 (7.0–24.5)	15.1 (7.4–20.2)	9.4 (6.7–13.5)
Neutrophiles G/L, median (IQR)	6.2 (3.1–9.7)	6.4 (0.7–11.6)	6.3 (2.6–18.9)	11.5 (5.2–16.3)	5.8 (2.8–9.0)
CRP mg/L, median (IQR)	19.6 (5.5–53.6)	56.9 (9.1–210.8)	40.5 (17.6–200.5)	87.7 (52.2–166.3)	13.0 (4.6–37.9)

Note: Due to missing cases in the respective characteristics, the percentages are referring to the data available for a specific characteristic or variable, and not necessarily to the total number of individuals in a group. In addition, as the variables 'focus of disease' and 'cause of infection' represent separate variables, the sum of the different groups does not coincide with the total number of children with fever and petechial rash. Number of observations: All patients $n = 453$, except for ill appearance $n = 415$, vomiting $n = 406$, diarrhoea $n = 376$, coughing $n = 372$, signs of resp. infection, $n = 361$, seizures $n = 437$, prolonged capillary refill $n = 397$, oxygen saturation $n = 360$, temperature $n = 422$, fever duration $n = 408$, leucocytes $n = 297$, neutrophiles $n = 297$, CRP $n = 297$.

Abbreviations: CRP, C-reactive protein; ED-PEWS, emergency department paediatric early warning score; n.a., not available.

[a]Based on multiple imputation: missing values for individual items for the PEWS were imputed using the MICE package in R.

fever and petechial rashes in children and adolescents presenting to paediatric EDs. Rates of sepsis (10/453, 2.2%) and meningitis (14/453, 3.1%) were low in febrile children with petechial rash but significantly higher than in other febrile patients (220/33 557, 0.7%). These findings point to the importance of petechial rash as a warning sign in all patients with potentially life-threatening diseases.

The focus of infection was most commonly a viral upper respiratory infection, which has already been reported in previous studies, and only a few patients were diagnosed with serious diseases.[2,16] Rates of bacterial infection were comparable with previous studies and considerably lower than historical cohorts analysed before the broad introduction of vaccines against *Neisseria meningitidis* and *Streptococcus pneumoniae*.[2,9,16–19]

Admission rates in patients with petechial rash were higher compared to other febrile patients (214/451, 47.5% vs. 11 897/33 548, 35.5%) and so were rates of intravenous antibiotic treatment (142/444, 32.0% vs. 3212/32 879, 9.8%). This might have been due to clinicians being more aware of serious diseases and the need for precautions.[20]

Most, but not all, of the patients with sepsis (7/9, 77.8%) and meningitis (12/13, 92.3%) appeared ill and so did about a third of patients with bacterial infection (19/64, 29.7%) and just under a quarter of the patients with non-bacterial infections (83/345, 24.1%). We concluded that clinical appearance was not an indisputable way to exclude sepsis or meningitis in all patients. Furthermore, appearing ill was not a suitable way of discriminating bacterial infections from other causes of infection. In conclusion,

TABLE 2 Outcome of 453 patients with fever and petechial rash, by the focus and cause of the infection.

	All ($n = 453$)	Focus: sepsis ($n = 10$)	Focus: meningitis ($n = 14$)	Cause: bacterial ($n = 67$)	Cause: non-bacterial ($n = 380$)
Immediate life-saving interventions					
Yes, *n* (%)	34 (7.5)	3 (30.0)	6 (42.9)	8 (11.9)	26 (6.8)
Progression/disposition					
Discharged home, *n* (%)	222 (49.2)	0 (0.0)	0 (0.0)	24 (35.8)	194 (51.1)
Admission to ward, *n* (%)	214 (47.5)	8 (80.0)	13 (92.9)	39 (58.2)	167 (43.9)
Admission ICU, *n* (%)	10 (2.2)	2 (20.0)	1 (7.1)	2 (3.1)	8 (2.1)
Antibiotics prescribed					
Yes, *n* (%)	207 (46.2)	10 (100.0)	13 (92.9)	63 (94.0)	143 (38.1)
Oral, *n* (%), i.v, *n*. (%)	61 (30), 142 (70)	0 (0), 10 (100)	0 (0), 13 (93)	21 (35), 39 (65)	39 (27), 103 (73)
Focus of disease					
Sepsis, *n* (%)	10 (2.2)	—	—	5 (7.5)	5 (1.3)
Meningitis, *n* (%)	14 (3.1)	—	—	5 (7.5)	9 (2.4)
Undifferentiated fever, *n* (%)	91 (20.1)	—	—	7 (10.4)	83 (21.8)
URTI, *n* (%)	189 (41.7)	—	—	27 (40.3)	161 (42.4)
LRTI, *n* (%)	40 (8.8)	—	—	12 (17.9)	28 (7.4)
GIT, *n* (%)	38 (8.4)	—	—	1 (1.5)	36 (9.5)
Flu-like illness, *n* (%)	19 (4.2)	—	—	1 (1.5)	17 (4.7)
UTI, *n* (%)	7 (1.5)	—	—	5 (7.5)	2 (0.5)
Inflammatory illness, *n* (%)	3 (0.7)	—	—	0 (0.0)	3 (0.8)
Others, *n* (%)	42 (9.3)	—	—	4 (6.0)	36 (9.5)
Cause of infection					
Bacterial, *n* (%)	67 (15.0)	5 (50.0)	5 (35.7)	67 (100.0)	0 (0.0)
Viral, *n* (%)	159 (35.6)	1 (10.0)	6 (42.9)	—	159 (41.8)
Unknown bacterial or viral, *n* (%)	195 (43.6)	4 (40.0)	3 (21.4)	—	195 (51.3)
Inflammatory, *n* (%)	6 (1.3)	0 (0.0)	0 (0.0)	—	6 (1.6)
Others, *n* (%)	20 (4.5)	0 (0.0)	0 (0.0)	—	20 (5.3)

Note: Due to possible missing cases in the respective characteristics, the percentages are referring to the data available for a specific characteristic or variable, and not necessarily to the total number of individuals in a group. In addition, as the variables 'focus of disease' and 'cause of infection' represent separate variables, the sum of the different groups does not coincide with the total number of children with fever and petechial rash. Number of observations: all patients $n = 453$, except progression/disposition $n = 451$, antibiotics prescribed $n = 448$, route of prescription $n = 203$, cause of infection $n = 447$.

Abbreviations: GIT, gastrointestinal infection; ICU, intensive care unit; LRTI, lower respiratory tract infection; URTI, upper respiratory tract infection; UTI, urinary tract infection.

appearance was an insufficient discriminative sign and clinicians should be careful of using it as a criterion to ultimately rule out non-serious infections.

Vomiting and/or coughing were reported in most patients with petechial rash (327/411, 79.6%). These are known causes of petechiae of the upper half of the body, due to elevated intravascular pressure. Interestingly, high rates of at least one or both signs were observed in patients with petechial rash diagnosed with sepsis (7/10, 70.0%) or meningitis (10/13, 76.9%). This means that vomiting and coughing are a non-specific feature in sepsis and meningitis and cannot be used to rule these out in low-risk patient groups.

Measured temperature and fever duration in patients with petechial rash were comparable in all groups. They did not differ significantly with respect to the focus of infection (sepsis or meningitis vs. others) or the cause of infection (bacterial vs. non-bacterial infection). Fever characteristics did not qualify as a discriminative marker in this study, while other studies showed that a higher rate of serious bacterial infections was likely in infants under 3 months of age with hyperpyrexia >40°C.[21,22]

Centralisation, defined as a capillary refill time of more than 2 seconds, has been described as being likely to be discriminative for sepsis or meningitis,[2,17–20] and this was confirmed in our study. Prolonged capillary refill time was seen in 3/9 (33.3%) patients with sepsis and 2/12 (16.7%) patients with meningitis, whereas only 7/376 patients (1.9%) with other diagnoses had a prolonged capillary refill time.

TABLE 3 Analysis of 411 patients with petechial rash by the presence or absence of vomiting and/or coughing.

	No vomiting, no coughing ($n = 84$)	Vomiting and/or coughing ($n = 327$)
Age in years, median (IQR)	3.2 (1.3–6.3)	3.9 (1.7–6.3)
Male gender (%)	65.5	61.8
Progression		
Discharged home, *n* (%)	40 (50)	158 (49.7)
ICU admission, *n* (%)	3 (3.75)	6 (1.9)
Antibiotics prescribed, *n* (%)	37 (44.6)	151 (46.7)
Focus of infection		
Sepsis or meningitis, *n* (%)	6 (7.1)	17 (5.2)
Cause of infection		
Bacterial infection, *n* (%)	13 (15.9)	48 (14.9)
Viral infection, *n* (%)	25 (30.5)	124 (38.4)
Inflammatory, *n* (%)	2 (2.4)	3 (0.9)
Unknown, *n* (%)	37 (45.1)	136 (42.1)
Other, *n* (%)	5 (6.1)	12 (3.7)

Note: All tested *p*-values were > 0.05.

Abbreviations: ICU, intensive care unit; IQR, interquartile range.

Blood findings revealed significantly elevated CRP in patients with sepsis (Mdn = 57 mg/L, IQR 9–211) and meningitis (Mdn = 41 mg/L, IQR 18–201) compared to patients with another focus of infection (Mdn = 18 mg/L, IQR 5–52). Despite this, clinicians should be careful when they interpret blood results, because some patients with meningococcal sepsis might present with low CRP caused by the rapid course of their disease.[23] Previous studies showed the superiority of additional testing for procalcitonin to detect early meningococcal disease.[24–26] Furthermore, IL-6 proved high diagnostic sensitivity and direct comparison with PCT stated better kinetics for monitoring the effectiveness of antibiotic treatment.[27] This should be considered in future diagnostic algorithms for febrile children with a petechial rash. In addition, it is essential to search for novel biomarkers to improve diagnostic accuracy.[28]

One previously mentioned UK study validated clinical practice guidelines for managing children with non-blanching rashes. It concluded that tailored clinical practice guidelines, which allowed well-appearing patients with potential mechanical causes of petechiae to be discharged, were as safe as the National Institute for Health and Care Excellence guidelines but more cost-effective.[9] It found that 1251 of 1329 children with suspected meningococcal disease had petechiae, but only 19 of them had a confirmed diagnosis. Our study could not fully assess the British Society for Antimicrobial Chemotherapy guideline criteria, which resulted from this study, because we had no information about the location, size and spread of the rashes. However, we could conclude that a potential mechanical cause of a rash, such as coughing and/or vomiting, is not a sufficient criterion to exclude sepsis or meningitis.

Encouragingly, all the patients with sepsis and meningitis in our study were admitted and none were discharged home, although three patients were described as appearing well and several patients were reported to have vomiting and coughing.

4.1 | Strengths and limitations

This study had a number of strengths. To our knowledge, it was the largest international study investigating children with fever and petechial rash presenting to European paediatric emergency departments. It provides detailed information on clinical signs, management, diagnosis and the progression of patients. The consecutive patient recruitment provides a representative cohort of the general population.

Some potential limitations should also be considered. For example, the vaccination strategies, number of vaccinated individuals and clinical practice guidelines differed among the countries that took part.[29] However, investigating an international multicentre cohort, as we have done here, does provide the most reliable information. This study was planned and performed with greatest accuracy, but further interpretations should be made carefully, since this study was limited by missing information about the size, location and further progression of the petechial rashes.[11] Furthermore, we had no information about return visits and no data on individual immunisation status.

5 | CONCLUSION

Our results show that fever and petechial rashes are still essential warning signs associated with higher rates of sepsis and meningitis than in other febrile children. Rates of vomiting and/or coughing were similar in patients with sepsis, meningitis and other febrile causes and did not qualify as a discriminative marker. Identifying all patients with serious diseases remains difficult and requires careful clinical examinations and blood tests, including C reactive protein. Depending on the complete clinical picture, further elaborated diagnostics may be required and safety advice should be provided if patients are discharged.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to disclose.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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