Invasive bacterial infection in children with fever and petechial rash in the emergency department: a national prospective observational study

Article *in* Archives of Disease in Childhood · April 2023

DOI: 10.1136/archdischild-2022-325281

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Invasive bacterial infection in children with fever and petechial rash in the emergency department: a national prospective observational study

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Received 27 December 2022
Accepted 28 March 2023

ABSTRACT

Objective To determine the incidence and clinical predictors of invasive bacterial infection (IBI) in well-appearing children who present to the emergency department (ED) with fever and petechiae.
Design A prospective, observational, multicentre study was conducted in 18 hospitals between November 2017 and October 2019.
Patients A total of 688 patients were recruited.
Main outcome measures The primary outcome was the presence of IBI. Clinical features and laboratory test results were described and related to the presence of IBI.
Results Ten IBIs were found (1.5%), comprising eight cases of meningococcal disease and two of occult pneumococcal bacteraemia. Median age was 26.2 months (IQR 15.3–51.2). Blood samples were obtained from 575 patients (83.3%). Patients with an IBI had a shorter time from fever to ED visit (13.5 hours vs 24 hours) and between fever and rash onset (3.5 hours vs 24 hours). Values for absolute leucocyte count, total neutrophil count, C reactive protein and procalcitonin were significantly higher in patients with an IBI. Significantly fewer patients with a favourable clinical status while in the observation unit were found to have an IBI (2/408 patients, 0.5%) than when clinical status was unfavourable (3/18, 16.7%).
Conclusions The incidence of IBI among children with fever and petechial rash is lower than previously reported (1.5%). The time from fever to ED visit and to rash onset was shorter in patients with an IBI. Patients with a favourable clinical course during observation in the ED are at lower risk of IBI.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The presence of fever associated with petechial rash in children may be a sign of invasive bacterial infection (IBI) and therefore requires urgent evaluation by a paediatrician.

WHAT THIS STUDY ADDS

⇒ A shorter history of fever and shorter time between the onset of fever and rash may help to identify children at higher risk of developing an IBI.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The results of this study could help to select children with fever and petechiae in whom further testing would be indicated.

INTRODUCTION

Classically, the presence of a petechial rash associated with fever in children has raised suspicion of an invasive bacterial infection (IBI), especially when *Neisseria meningitidis* is the infective agent. With the introduction of a vaccine against these pathogens, however, petechiae in children with fever is mostly linked to viral infection.[1] Nonetheless, it is still recommended to evaluate these cases in the hospital[2] to allow for testing in the emergency department (ED) and clinical observation. Antibiotics are often administered while waiting for culture results. Most studies that form the basis of current protocols for the management of children with fever and petechiae in the ED were conducted many years ago and are retrospective in nature.[3–5] A recent prospective study has described a lower incidence of bacterial infections in these patients.[6]

This study aimed to determine the incidence of IBI in well-appearing children who present to the ED. Subsequently, we studied the epidemiological and clinical characteristics of these patients to analyse the usefulness of these parameters to predict the presence of IBI.

MATERIALS AND METHODS

Study design and data collection

This prospective, observational, multicentre study was conducted between November 2017 and October 2019. The study, which was endorsed by the Spanish Paediatric Emergency Research Group network, included 18 Spanish paediatric EDs. The attending paediatricians acted in accordance with their own criteria and local protocols for the diagnosis and treatment of children with fever and petechial rash. In each participating ED, a collaborating physician researcher collected epidemiological and clinical data from the medical records of study patients. Follow-up was performed by the same researcher via telephone approximately 30 days

To cite: Storch-De-Gracia P, Fernández JL, Velasco R, *et al*. *Arch Dis Child* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/archdischild-2022-325281

after the ED visit to gather information about the disease course after discharge.

Population

Children were eligible if they were less than 18 years of age, had a measured temperature of ≥38°C, a petechial rash and a normal Paediatric Assessment Triangle (PAT) on arrival to the ED.

Exclusion criteria were the presence of petechiae confined to the area of the superior vena cava, antibiotic treatment in the previous 48 hours, congenital or acquired immunosuppression, pre-existing coagulopathy and refusal to participate.

Variables

The primary outcome was the presence of IBI. The variables recorded were as follows: age, sex, immunisation status (general, *Streptococcus pneumoniae* and *N. meningitidis* serotypes B and C), PAT on arrival to the ED, temperature at ED arrival, maximum temperature, hours with fever when petechial rash appeared, associated signs and symptoms, characteristics of the petechial rash (number and distribution of the lesions), vital signs assessed in the ED (blood pressure and heart rate), and available laboratory results including leucocytes, neutrophils, C reactive protein (CRP) and procalcitonin (PCT). Cultures from urine, blood and cerebrospinal fluid (CSF) samples were also registered when obtained, as well as antigen detection tests and PCR assays for *S. pneumoniae* and *N. meningitidis* from blood and CSF.

Definitions

Fever was defined as a peripheral temperature of 38°C or higher.

Petechial rash consisted of red or purple non-blanching skin lesions of less than 2 mm in size.

PAT was considered normal if its three components were unaltered: appearance, work of breathing and circulation to the skin.

Clinical status during the observation period was considered favourable if the rash did not progress in number or in the size of the lesions, the PAT remained normal, and vital signs were normal while under observation in the ED or observation unit.

Diagnosis of an IBI was determined by a pathogenic bacterium detected in blood or CSF cultures or by antigen tests or PCR for *S. pneumoniae* or *N. meningitidis* in blood or CSF.

Patients were deemed to be well appearing if they had a normal PAT on arrival to the ED.

Statistical analysis

All analyses were conducted using SPSS V.20.0 for Windows. Numerical variables were described using median and IQR when the data were dispersed. Categorical variables were expressed as counts and percentages. Comparisons between groups were performed using the Fisher exact test for categorical variables and the Mann-Whitney U test for numerical variables after it was determined by Kolmogorov-Smirnov goodness-of-fit test that the data did not follow a normal distribution. Statistical significance was set at a p value of <0.05. The sample size was too small to carry out a multivariate analysis. Receiver operating curve analysis was performed for acute-phase reactants. The article was drafted in accordance with the STROBE guidelines for observational research.

RESULTS

During the study period, 1 134 952 children visited the participating EDs. A total of 688 were recruited, 432 of whom (62.8%) were male. Median age was 26 months (IQR 16–54).

Table 1 Associated symptoms

Associated symptoms	n (%) N=686
Pharyngeal/ORL (cough, rhinorrhoea, otalgia)	295 (43)
Respiratory	193 (28)
Gastrointestinal	111 (16)
Skin	16 (2.3)
Neurological	3 (0.4)
Urinary	2 (0.3)
Other	7 (1)

Six hundred seventy-three children (98.1%) had received all vaccinations included in the official immunisation schedule; 593 (86.4%) were also immunised against pneumococcus (two or more doses of the vaccine) and 236 (34.4%) for B meningococcus (with at least two doses). Eighty-three children (12%) had a previous chronic condition.

The median duration of fever was 24 hours (IQR 12–48 hours), and the median time between fever and petechiae appearance was also 24 hours (IQR 7–48 hours). The median maximum temperature was 39°C (IQR 38.5–39.5). Five hundred fifty-two patients (80.5%) had associated symptoms (table 1).

The petechial rash comprised only 1 or 2 lesions in 27 cases (3.9%), 3 to 10 in 343 (50%), and more than 10 in 318 (46.2%). The distribution of petechiae was as follows: 472 patients (68.8%) had lesions above the nipple line, 533 (77.5%) on the trunk and 464 (67.4%) throughout the lower extremities.

A blood sample was obtained from 577 of the 688 patients (84%); of these, a blood culture was performed in 442 (64.2%) and PCR for a bacterial agent in 62 (9%). Five blood cultures (5/442, 1.1%) were positive (three for *N. meningitidis* and two for *S. pneumoniae*). Five of 62 PCR assays (8%) detected *N. meningitidis* in the blood of patients, 3 of whom had a negative blood culture. Lumbar puncture was performed in seven patients (1%). One culture of CSF was positive for *N. meningitidis* and 5 PCR assays in CSF detected *N. meningitidis*. A total of 10/688 children had an IBI (1.5%, 95% CI 0.7 to 2.7). Meningococcal disease (MD) was found in eight children (five with associated meningitis) and two occult bacteraemias caused by *S. pneumoniae*. The characteristics of the patients and comparison between the two groups (patients with and without an IBI) are shown in table 2. The time between development of fever and presentation to the ED and the time from fever to the appearance of petechial rash was significantly shorter in the group of patients with an IBI. The clinical and laboratory data of patients with an IBI are described in table 3.

Four hundred twenty-six patients (62%) remained under observation in the ED. The median time of observation was 7 hours (IQR 6.3–7.7). After this, 46 patients were admitted (including all 5 patients presenting an IBI who stayed under observation), and 380 were discharged. Antibiotic treatment was administered to 93 patients (33 in the admitted group and 60 of those discharged). Patients with an impairment while in the observation unit were significantly more likely to have an IBI (3/18, 16.7%) than those who remained well appearing (2/408, 0.5%) (p<0.01). Patients having both a favourable clinical status in the observation unit and an IBI were eventually admitted and received parenteral antibiotics. Two hundred sixty patients required no observation in the ED: 6 were admitted directly and 254 were discharged following initial assessment. One of these 254 patients (0.4%) was diagnosed with an IBI, namely, an occult *S. pneumoniae* bacteraemia with normal biomarkers.

Table 2 Baseline characteristics of children with and without IBI and comparison between them

	Non-bacterial aetiology (n=678)	IBI (n=10)	P value
Male, n (%)	426 (62.8)	6 (60)	1
Age (months), median (IQR)	26.5 (15.4–51.2)	13.8 (5.1–50.4)	0.14
Previous illness, n (%)	83/678 (12.2)	0	0.61
Vaccination, n (%)			
General (includes *Neisseria meningitidis* A and C)	665 (98.1)	10 (100)	1
≥2 doses against *Streptococcus pneumoniae*	586 (87.2)	7 (70)	1
≥2 doses against *N. meningitidis* B	235 (38.3)	2 (20)	0.26
Maximum temperature (°C), median (IQR)	39 (38.5–39.5)	39.3 (39–40)	0.095
Time of evolution of fever until ED presentation (hours), median (IQR)	24 (12–49)	13.5 (8.25–24.0)	0.03
Time of evolution of fever to petechiae (hours), median (IQR)	24 (8–48)	3.5 (1.75–12.0)	0.03
Number of petechiae, n (%)			
1–2	27 (4)	0	0.8
3–10	338 (50)	5 (62.5)	
>10	313 (46)	3 (37.5)	
Localisations of petechiae (several possible), n (%)			
Above nipple line	468 (69)	5 (50)	0.3
Trunk	524 (77.3)	10 (100)	0.13
Lower extremities	456 (67.3)	7 (70)	1
Heart rate >p95 percentile for age (APLS),* n (%)	152 (22.4)	3 (30)	0.72
Systolic blood pressure <p5 percentile for age (APLS),* n (%)	2 (0.7)	0	1
Laboratory tests median (IQR)			
Total leucocyte count (x10^9/L)	9.98 (6.69–13.82)	27.64 (17.26–28.66)	<0.01
Total neutrophil count (x10^9/L)	5.3 (3.15–8.19)	20.15 (14.25–22)	<0.01
C reactive protein (mg/L)	19.6 (6.2–46.0)	65 (22–290)	0.009
Procalcitonin (ng/mL)	0.16 (0.1–0.4)	19.4 (2.8–27.7)	<0.01
Antibiotic treatment prescribed at any time, n (%)	113 (16.7)	9 (90)	<0.01
Evolution in observation unit, n (%)			0.01
Favourable	405 (59.7)	5 (50)	
Unfavourable	15 (2.2)	3 (30)	
Non-observed in ED	258 (38.1)	2 (20)	
Time of observation in ED (hours), median (IQR)	4 (3–7)	3 (2.5–24.0)	0.55
Destiny at discharge, n (%)			
Home	632 (93.2)	1 (10)	<0.01
Hospital admission	46 (6.8)	3 (30)	<0.01
ICU admission	0	6 (60)	<0.01

ED, emergency department; IBI, invasive bacterial infection; ICU, intensive care unit.

The area under the curve for total leucocyte count was 0.89 (95% CI 0.72 to 1.0), for total neutrophil count was 0.94 (95% CI 0.85 to 1.0), for CRP was 0.77 (95% CI 0.54 to 1.0) and for PCT was 0.87 (95% CI 0.16 to 1.0).

DISCUSSION

This research reports on one of the largest series of children with fever and petechiae collected to date, particularly after the introduction of the meningococcal B vaccine. As ours is the only study performed exclusively in well-appearing patients, its findings could be applied to patients in whom decisions concerning the diagnostic approach are still challenging. We found a shorter time periods between both fever onset and ED presentation and between fever and exanthema in patients with an IBI, which may guide paediatricians in making decisions regarding the need for a blood test.

In our study, the incidence of IBI in patients with fever and petechial rash was 1.5%. This value is markedly lower than those previously published (15%, Nielsen *et al* in 2001[7]; 18%, Dumitrascu-Biris *et al* in 2016[8]; 23%, Riordan *et al* in 2016[9]; and 23%, Gawie-Rotman *et al* in 2019[10]). However, the recent study by Waterfield *et al*[6] in the UK has described an incidence of MD of 1% in patients with fever and petechiae in the ED, which is consistent with the 1.1% rate in our population if only meningococcal infections are taken into account (8/688).

In contrast to the studies published to date, ours included only those who were well appearing. Classically, ill appearance has been used as a criterion for high risk of MD in patients with fever and purpuric rash,[5] together with other signs such as prolonged capillary refill time or an altered neurological state (which makes up the 'ILL criteria': irritabilty, lethargy, low capillary refill and also leukocytosis and elevatde CPR, proposed by Brogan and Raffles in 2000).[4] Given the robustness of this association, we chose to include only well-appearing patients, as the need for further testing or antibiotic treatment in these cases is usually less clear-cut. The PAT was used as an indicator of the patient's general condition, since it has been previously validated for this purpose.[11–14] Additionally, our investigation focused on patients who visited the ED. Several studies used to develop current diagnostic criteria were conducted in admitted patients (Baker *et al*,[15] Soult Rubio *et al*,[16] Nielsen *et al*,[7] Gawie-Rotman *et al*[10]), which may explain why the incidence of MD and IBI

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Table 3 Description of patients with an invasive bacterial infection

Age	Duration of fever (hours)	Time between fever and rash (hours)	Maximum temperature (°C)	Skin lesions (n)	Location of skin lesions	Vaccine doses (meningococcus B/C)	Leucocytes $x10^9/L$	Neutrophils $x10^9/L$	CRP (mg/L)	Procalcitonin (ng/mL)	Evolution in observation unit	Destination	Blood culture	Blood PCR	CSF (culture/PCR)
10 months	12	0	40	>10	Trunk Lower limbs	0/1	28.8	21.6	69.1	8.9	Unfavourable	ICU	Negative	*Neisseria meningitidis*	–/–
3 months	24	1	40	>10	Trunk Lower limbs	0/0	28.4	19	321	71.5	–	ICU	Negative	*N. meningitidis*	Negative/*N. meningitidis*
2 months	72	5	39.5	3–10	Above nipple line Trunk	0/0	20.22	16.4	279.9	28.8	Favourable	Admitted	Negative	–	Negative/*N. meningitidis*
15 months	9	5	41	3–10	Trunk	3/2	28.4	21.3	14	0.74	–	Discharged	*Streptococcus pneumoniae*	–	–/–
19 months	24	24	39	3–10	Above nipple line Trunk Lower limbs	3/2	26.87	22.8	202.6	24.3	Favourable	Admitted	*N. meningitidis*	Negative	–/–
2 years	2	2	39	3–10	Above nipple line Trunk	4/2	22.75	19	3.8	0.16	Favourable	Admitted	*S. penumoniae*	–	–/–
3 years	12	8	39	>10	Above nipple line Trunk Lower limbs	0/2	8.4	7.78	61	4.4	Unfavourable	ICU	*N. meningitidis*	–	*N. meningitidis/N. meningitidis*
21 months	24	24	38	3–10	Trunk Lower limbs	0	28.61	21.74	396.9	10.9	Unfavourable	ICU	Negative	*N. meningitidis*	Negative/*N. meningitidis*
6 months	6	2	40	> 10	Above nipple line Trunk Lower limbs	0/1	1.52	0.88	29.5	29.5	–	ICU	*N. meningitidis*	*N. meningitidis*	–/–
3 years	15	2	39	> 10	Above nipple line Trunk Lower limbs	0/2	39.7	35.3	24	16.4	–	ICU	Negative	*N. meningitidis*	Negative/*N. meningitidis*

CRP, C reactive protein; CSF, cerebrospinal fluid; WBC, white blood cell.

was clearly higher in these other studies. Riordan *et al*[9] included several retrospective cohorts and one prospective. He included among the MD cases patients in whom tests were negative but clinical suspicion was high, which is likely to have overestimated the incidence of MD. The introduction of meningococcal vaccination in many countries has led to a decrease in the incidence of MD in recent years, which is another factor explaining the lower incidence found in our population compared with previous research.[17–1920]In Spain, meningococcal A and C vaccines are offered to the entire population, but vaccinations against meningococcal B, W and Y are not included in the nationwide vaccination schedule. Only 34% of the study population was vaccinated against meningococcal B. Therefore, the progressive increase in the rate of vaccination is expected to have a considerable effect on the incidence of IBI in patients presenting to the ED with fever and petechial rash in the coming years. Among the MD cases, there were two infants younger than 4 months (who had not received two doses of meningococcal B or C vaccine). In the study population, there were only four infants under 4 months of age. Decision making in young infants with fever and petechiae differs from that in older children.

A comparison of the clinical characteristics of patients who had an IBI and those who did not revealed that the history of fever on ED presentation and the time between the onset of fever and petechial rash were significantly shorter in the former group. We believe this finding is of great significance in as much as it could inform decisions as to which patients should undergo blood testing and which should be kept under observation in the ED. Thompson *et al*[21] described a rapid disease progression in a large cohort of children with MD. In most cases, petechiae appeared within 18 hours of disease onset and this time was even shorter in infants; almost none of the patients developed new symptoms more than 24 hours after illness onset. We found that only 27% of patients without an IBI had fever for less than 13 hours, and in 14%, the time between onset of fever and rash was less than 3.5 hours. The PiC study (Petechiae in Children)[6], which was carried out in the UK in 2021, compared eight existing guidelines for ED management of paediatric patients with fever and petechiae; of note, the time between the onset of fever and petechial rash tended towards statistical significance on univariate comparison, though this association was not confirmed by a multivariate analysis. The authors concluded that all the guidelines had a sensitivity of 100% but a very low specificity, the lowest of which reported specificities of 36% and 35%, respectively. Most of the patients underwent a blood test for determination of biomarkers and blood culture, following current recommendations. However, in 16% of the cases in our study, the attending physician decided not to obtain a blood sample. Of these 111 patients, 38 were discharged from the ED with no observation whatever, and none had an IBI. This could indicate a tendency towards less invasiveness in the management of these patients, especially when they are well appearing and the exanthema consists of a few small lesions. In the light of current findings, the same author in a later article[22] argues in favour of a less invasive approach in which testing of acute phase reactants would not always be indicated, improving the specificity of clinical scales while maintaining excellent sensitivity for IBI. However, the two patients with S. *pneumoniae* infection with a normal CPR and normal or slightly elevated PCT, merit commentary. One patient was discharged without observation and the other was admitted. Antibiotic treatment was prescribed for both. We did not find invasive infections due to bacteria other than meningococcus and pneumococcus, but group A and B *Streptococcus*, acute bacterial gastroenteritis or rickettsial disease have been associated with petechial rashes.[10]

More than half of the patients in this study spent several hours under observation in the ED. This approach could be a valid alternative to blood testing in patients with a low probability of IBI based on their clinical characteristics given the rapid progression of the disease. We observed that the likelihood of IBI was significantly lower in patients with a favourable clinical status during ED observation.

Limitations

Inclusion bias likely influenced patient selection, as some patients with fever and petechiae were not recruited, and therefore we cannot determine the frequency of fever together with petechial rash as a reason for presentation to the paediatric ED. We believe it is likely that most of these missed patients had few lesions or underwent no complementary tests, which would imply that the real incidence of IBI could be even lower than the one found. Failure to include patients without fever may have resulted in missed cases of bacterial infection. To assess this, all cases of MD seen in the participating hospitals were reviewed. All of them had fever, but not all had petechiae. No child with MD who met the inclusion criteria was left out. Due to the small number of patients with an IBI, multivariate analysis could not be performed.

In conclusion, we have found that the incidence of IBI among patients with fever, petechial exanthema and a normal PAT is lower than previously reported (1.5%). The duration of fever before ED presentation and between the onset of fever and petechial rash is significantly shorter in patients with an IBI, indicating that these factors could help in making decisions for these patients. In addition, patients who evolve favourably during the observation period in the ED have a lower risk of IBI.

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Contributors PS-D-G contributed to the study conception and design, material preparation and analysis, wrote the first draft of the manuscript and act as the guarantor. JLF conceptualised and designed the study, coordinated and supervised the data collection, and critically reviewed the manuscript. RV contributed to the study conception and design, carried out the initial analyses and critically reviewed the manuscript. The following doctors revised the data collection form, collected data and critically reviewed the manuscript: IS, RR, SY, EC, EG, PdR, EG, AC, AJPD, MC, MH,

JJP, MJdlT, GN, JM and VS-T. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects contained.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by Comité de Ética de la Investigación con Medicamentos del Hospital Infantil Universitario Niño Jesús (internal code R-0052/16). The participants gave informed consent to participate in the study before taking part. Ethical approval was obtained from the ethics committees of all participating hospitals. The study was conducted in accordance with the tenets of the Declaration of Helsinki regarding confidentiality of the data collected. Parents or legal guardians of children under age 12 years as well as those patients aged 12 years or older who agreed to participate signed a written informed consent form.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

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