Are children with prolonged fever at a higher risk for serious illness? A prospective observational study

Ruud G Nijman ,[1,2,3] Chantal D Tan ,[4] Nienke N Hagedoorn ,[4] Daan Nieboer,[5] Jethro Adam Herberg ,[2] Anda Balode,[6] Ulrich von Both ,[7,8] Enitan D Carrol,[9,10] Irini Eleftheriou,[11] Marieke Emonts,[12,13,14] Michiel van der Flier,[15,16,17] Ronald de Groot,[16,17] Benno Kohlmaier ,[18] Emma Lim,[12,19] Federico Martinón-Torres ,[20] Marko Pokorn,[21] Franc Strle,[21] Maria Tsolia,[11] Shunmay Yeung,[22] Joany M Zachariasse ,[4] Dace Zavadska,[6] Werner Zenz,[18] Michael Levin,[2] Clementien L Vermont,[23] Henriette A Moll ,[4] Ian K Maconochie,[1] On behalf of PERFORM consortium

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For numbered affiliations see end of article.

Correspondence to
Dr Ruud G Nijman, Department of Paediatric Emergency Medicine, Imperial College Healthcare NHS Trust, London W2 1NY, UK;
r.nijman@imperial.ac.uk

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ABSTRACT

Objectives To describe the characteristics and clinical outcomes of children with fever ≥5 days presenting to emergency departments (EDs).

Design Prospective observational study.

Setting 12 European EDs.

Patients Consecutive febrile children <18 years between January 2017 and April 2018.

Interventions Children with fever ≥5 days and their risks for serious bacterial infection (SBI) were compared with children with fever <5 days, including diagnostic accuracy of non-specific symptoms, warning signs and C-reactive protein (CRP; mg/L).

Main outcome measures SBI and other non-infectious serious illness.

Results 3778/35 705 (10.6%) of febrile children had fever ≥5 days. Incidence of SBI in children with fever ≥5 days was higher than in those with fever <5 days (8.4% vs 5.7%). Triage urgency, life-saving interventions and intensive care admissions were similar for fever ≥5 days and <5 days. Several warning signs had good rule in value for SBI with specificities >0.90, but were observed infrequently (range: 0.4%–17%). Absence of warning signs was not sufficiently reliable to rule out SBI (sensitivity 0.92 (95% CI 0.87–0.95), negative likelihood ratio (LR) 0.34 (0.22–0.54)). CRP <20 mg/L was useful for ruling out SBI (negative LR 0.16 (0.11–0.24)). There were 66 cases (1.7%) of non-infectious serious illnesses, including 21 cases of Kawasaki disease (0.6%), 28 inflammatory conditions (0.7%) and 4 malignancies.

Conclusion Children with prolonged fever have a higher risk of SBI, warranting a careful clinical assessment and diagnostic workup. Warning signs of SBI occurred infrequently but, if present, increased the likelihood of SBI. Although rare, clinicians should consider important non-infectious causes of prolonged fever.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ A prolonged fever of five days or more is considered a warning sign for serious infection in childhood fever management guidelines.

⇒ Prolonged fever is believed to be associated with serious bacterial infections (SBI) and with non-infectious and inflammatory conditions such as Kawasaki disease.

WHAT THIS STUDY ADDS

⇒ In this multicentre prospective observational study, 10.6% of 35 705 febrile children had a fever ≥5 days, with higher risk of SBI (8.4% vs 5.7%).

⇒ Warning signs of SBI occurred infrequently but, if present, increased the likelihood of SBI in children with prolonged fever.

⇒ Kawasaki disease (0.6%) and other inflammatory conditions were uncommon (1.7%).

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Children with prolonged fever have a higher risk of SBI, warranting a careful clinical assessment and considerate diagnostic work, also with attention for rare but important non-infectious causes.

INTRODUCTION

Guidelines identify prolonged fever, often defined as a duration of fever of 5 days or more, as a risk factor for serious bacterial infections (SBI) in children.[1] Moreover, a prolonged duration of fever could suggest non-infectious causes, such as inflammatory conditions[2–4] and malignancies.[5 6] Hence, a careful diagnostic approach is recommended when these children and young people present to urgent and emergency care facilities. Yet, data scoping how many children present with prolonged fevers or looked at their presenting characteristics and clinical outcomes are scarce. Moreover, little is known about the practice variation of these children in Europe that could inform updated practice strategies to reduce unnecessary diagnostic testing and antimicrobial prescribing. In this prospective, multinational cohort study, we aimed to determine the frequency of children with fever ≥5 days presenting to emergency departments (EDs) across

Europe, and to compare these children with those with a shorter duration of fever. Additionally, we sought to describe the characteristics of children with non-infectious causes of their febrile illness.

METHODS

Design, setting and participants

This is a secondary analysis of data collected as part of a prospective, multinational cohort study called the Management and Outcome of Fever in Children in Europe study.[7] This study was an observational study embedded in the Personalised Risk Assessment in Febrile Illness to Optimise Real-life Management across the European Union study. Routine clinical data of consecutive febrile children aged 0–18 years were collected between January 2017 and April 2018. Fever was defined as a temperature measure of ≥38.0°C at triage, or a history of fever at home in the preceding 72 hours. At each of the 12 participating institutions, data collection varied from 1 week/month to the whole month, as reported previously. These institutions represented eight European countries (Austria, Germany, Greece, Latvia, the Netherlands (3), Spain, Slovenia and the UK (3)), of which nine were tertiary university hospitals and three teaching hospitals, and with nine having dedicated paediatric EDs and three being mixed adults and paediatric EDs.[8] Data were extracted from clinical notes and the deidentified data were then entered into a prespecified digital data entry form using the REDCap online platform by trained members of the research teams.[9]

Definitions of variables of interest

A previous visit included visits to a healthcare provider during this disease episode within 7 days prior to ED visit. Comorbidity was defined as a chronic underlying condition that is expected to last at least 1 year.[10] Triage urgency was categorised into three levels (ie, emergent–very urgent, urgent, standard–non-urgent), transformed from the five-level Manchester Triage System or locally adapted triage systems.[11] Warning signs of fever were defined as per the National Institute for Health and Care Excellence guidelines for the management of children with fever.[1] We combined chest wall retractions, nasal flaring, grunting and apnoea to define increased work of breathing. Neurological symptoms included meningeal signs (ie, Kernig, Brudzinski, tripod phenomenon, neck stiffness, bulging fontanelle for <1 year) and focal neurological signs. Tachycardia and tachypnoea were defined according to the age-adjusted advanced paediatric life support threshold values for respiratory rate and heart rate.[1 12] Decreased level of consciousness was defined as any other than A(lert), meaning any of V(erbal), P(ain) or U(nresponsive), on the AVPU scale. We analysed non-specific respiratory signs and symptoms defined as coughing, runny nose, sore throat, sneezing; non-specific gastrointestinal symptoms defined as vomiting or diarrhoea; and non-specific rash as any rash or viral exanthema other than a non-blanching rash. Immediate life-saving interventions (ILSI) in the ED were defined as airway and breathing support, emergency procedures, haemodynamic support or emergency medication.[13] Acuity of presentations was determined by (1) triage urgency, (2) need for ILSI or (3) intensive care admission.

Outcome measures

The primary outcome was SBI, defined as patients with 'definite bacterial' or 'probable bacterial' with focus of infection from the gastrointestinal tract, lower respiratory tract, urinary tract, bone and joints, central nervous system or sepsis. Next, we evaluated the characteristics of children with a non-infectious cause for their fever. The outcomes were allocated following a classification flow chart (online supplemental file 2), based on presenting signs and symptoms, inflammatory markers, virology, microbiology and imaging, by independent trained members of the research staff.[7 14] When needed, consensus diagnoses were obtained by an expert panel. Invasive bacterial infections were those with a positive bacterial pathogen isolated in blood or cerebral spinal fluid.

Data analyses

First, comparative analyses between children with ≥5 days vs <5 days of fever were performed. Variables were expressed in absolute numbers and relative frequencies, or medians with the IQR where appropriate. X^2 analyses were used for categorical and dichotomous variables, and Fisher's exact test was used when ≤5 cases present; non-parametric Wilcoxon rank-sum test was used for non-parametrically distributed continuous variables. Second, children with a prolonged fever with and without SBI were compared and, third, diagnostic accuracy (ie, sensitivity, specificity, positive predictive value, negative predictive value, diagnostic OR (dOR) and positive and negative likelihood ratios (LR)) was calculated for the presence of SBI for (1) non-specific signs and symptoms, (2) duration of fever at cut-offs of ≥7 and ≥10 days, (3) warning signs of fever and (4) C-reactive protein (CRP) at various cut-offs.

RESULTS

Comparing children with prolonged fever with those with a shorter duration of fever

A total of 3778/35 705 (10.6%) febrile children had fever ≥5 days, with differing seasonal patterns for each site (online supplemental file 3). These children were older than those with a shorter duration of fever (3.0 years (IQR 1.5–6.0 years) vs 2.7 years (IQR 1.3–5.4 years), p<0.001). They had more prior visits to healthcare providers within the same disease episode (1929 (55%) vs 7062 (23%), p<0.001) and were more frequently referred for ED assessment (1759 (48%) vs 13 225 (43%), p<0.001) (table 1). Children with fever ≥5 days were prescribed antibiotics prior to attending ED more frequently (n=1014 (27%) vs n=2879 (9%), p<0.001).

Children with fever ≥5 days had more non-specific respiratory symptoms (1560 (50%) vs 9927 (37%), p<0.001), and presented with tachycardia less frequently (993 (33%) vs 10 524 (42%), p<0.001). Children with fever ≥5 days had similar levels of acuity as by 'emergent' or 'very urgent' triage urgency (<5 days: n=3190 (10%), ≥5 days: n=241 (6%), p<0.001), ILSI (<5 days: n=513 (2%), ≥5 days: n=50 (1%), NS) and intensive care admission (<5 days: n=125 (0.4%), ≥5 days: n=18 (0.5%), NS). Children with fever ≥5 days had more laboratory testing (dOR 2.08 (95% CI 1.93–2.25)) and imaging (dOR 1.69 (95% CI 1.58–1.81)). They were prescribed more antibiotics as part of this ED presentation (dOR 1.59 (95% CI 1.49–1.71)), with antibiotic prescribing in children with fever ≥5 days ranging from 27% to 63% between study sites.

Incidence of SBI was significantly higher in those with fever ≥5 days (n=319, 8.4%) than in those with shorter duration of fever (n=1812, 5.7%) (dOR 1.53 (95% CI 1.35–1.74), p<0.001). Children with fever ≥5 days and SBI had a focus of lower respiratory tract infections more often (n=172 (54%) vs n=628 (35%)); urinary tract infections were seen commonly (≥5 days: n=111 (35%) vs <5 days:

Table 1 Characteristics of children with prolonged fever and their outcomes compared with children with shorter duration of fever

		All children with fever <5 days n=31 927 (89.4%)*	All children with fever ≥5 days n=3778 (10.6%)*	P value
General characteristics				
Age	Median (IQR)	2.7 (1.3–5.5)	3.0 (1.5–6.0)	<0.001
Sex	Female, n (%)	14 416 (45)	1720 (46)	0.68
Previous visit to any healthcare provider in the last 7 days	n (%)	7062 (23)	1929 (55)	<0.001
Referral	n (%)	13 225 (43)	1759 (48)	<0.001
Comorbidity	n (%)	5240 (17)	583 (16)	0.13
Triage urgency classification	Emergent–very urgent	3190 (10%)	241 (6%)	<0.001
	Urgent	7931 (25%)	903 (24%)	
	Standard–non-urgent	19 960 (63%)	2527 (67%)	
Duration of fever	Days, median (IQR)	3 (3–4)	6 (5–7)	<0.001
Non-specific signs and symptoms				
Respiratory signs and symptoms	Any	9927 (37%)	1560 (50%)	<0.001
Gastrointestinal signs and symptoms	Any	9677 (34%)	1133 (34%)	0.61
Other type of rash†	Any	2806 (10%)	479 (14%)	<0.001
Warning signs and symptoms				
Ill appearance	n (%)	5101 (17)	599 (17)	0.97
Tachypnoea (breaths/min)	APLS thresholds, n (%)	6139 (33)	644 (32)	0.19
Tachycardia (beats/min)	APLS thresholds, n (%)	10 524 (42)	993 (33)	<0.001
Prolonged capillary refill	≥3 s, n (%)	354 (1)	53 (2)	0.07
Oxygen saturations (%O_2)	<94%O_2, n (%)	636 (3)	126 (4)	<0.001
Level of consciousness	Decreased (verbal, pain, unresponsive), n (%)	166 (1)	14 (0.4)	0.27
Increased work of breathing	n (%)	4768 (17)	481 (15)	0.005
Non-blanching rash	n (%)	926 (3)	90 (3)	0.09
Neurological signs	n (%)	210 (1)	24 (1)	1.00
Seizures	n (%)	1261 (4)	42 (1)	<0.001
Diagnostics				
C-reactive protein	mg/L, median (IQR)	17 (5–48)	23 (6–64)	<0.001
Laboratory testing at ED	Any, n (%)	14 412 (45)	2200 (58)	<0.001
Imaging at ED	Any, n (%)	5375 (17)	1121 (30)	<0.001
Treatment and outcomes				
Immediate life-saving interventions‡	Any, n (%)	513 (2)	50 (1)	0.21
Antibiotics prescribed this attendance	Any, n (%)	9857 (31)	1560 (42)	<0.001
Diagnosis—focus of infection	Upper respiratory tract	17 157 (54%)	1861 (49%)	<0.001
	Lower respiratory tract	4295 (13%)	838 (22%)	
	Gastrointestinal	3417 (11%)	191 (5%)	
	Urinary tract	1104 (3%)	152 (4%)	
	Childhood exanthema	1511 (5%)	221 (6%)	
	Soft tissue or musculoskeletal	748 (2%)	92 (2%)	
	Sepsis or meningitis	236 (1%)	22 (1%)	
	Undifferentiated fever	2559 (8%)	247 (7%)	
	Inflammatory, other	877 (3%)	151 (4%)	
Diagnosis	Serious bacterial infection	1812 (5.7%)	319 (8.4%)	<0.001
	Invasive bacterial infection	129 (0.4%)	15 (0.4%)	1.00
Disposition	Discharge without follow-up	11 393 (36%)	1307 (35%)	0.04
	Discharge with follow-up	12 288 (38%)	1410 (37%)	
	Admission <24 hours	1546 (5%)	189 (5%)	
	Admission 24 hours or more	5974 (19%)	787 (21%)	
	Admission, duration unknown	370 (1%)	45 (1%)	
	PICU or death§	125 (0.4%)	18 (0.5%)	
	Left without being seen	190 (1%)	15 (0%)	

*The MOFICHE study included a total of 38 480 febrile children[7]; n=2775 (7%) were excluded because of missing data on duration of fever.
†This excludes any non-blanching rash including petechiae and purpura.
‡Immediate life-saving interventions (ILSI): airway and breathing support (non-rebreathing mask, (non-invasive) ventilation, intubation), emergency procedures (chest needle decompression, pericardiocentesis or open thoracotomy), haemodynamic support (fluid bolus (>10 mL/kg) or blood administration) or emergency medication (naloxone, dextrose, atropine, adenosine, epinephrine or vasopressors).
§In total, 1 death was recorded in the MOFICHE study, which had a duration of fever <5 days.
APLS, advanced paediatric life support; ED, emergency department; MOFICHE, Management and Outcome of Fever in Children in Europe; PICU, paediatric intensive care unit.

Table 2 Characteristics of children with fever for 5 days or more with and without serious bacterial infection

		Non-SBI n=3459 (91.6%)	SBI n=319 (8.4%)	P value
General characteristics				
Age	Median (IQR)	3.1 (1.6–6.1)	2.4 (1.3–5.6)	0.004
Sex	Female, n (%)	1545 (45)	175 (55)	<0.001
Previous visit to any healthcare provider in the last 7 days	n (%)	1742 (54)	187 (60)	0.046
Referral	n (%)	1557 (46)	202 (65)	<0.001
Comorbidity	n (%)	527 (15)	56 (18)	0.34
Triage urgency classification	Emergent–very urgent	217 (6%)	24 (8%)	0.12
	Urgent	820 (24%)	83 (26%)	
	Standard–non-urgent	2340 (68%)	187 (59%)	
Duration of fever	Days, median (IQR)	6 (5–7)	6 (5–8)	<0.001
Non-specific signs and symptoms				
Respiratory signs and symptoms	Any	1458 (51%)	102 (38%)	<0.001
Gastrointestinal signs and symptoms	Any	1024 (34%)	109 (38%)	0.18
Other type of rash*	Any	455 (15%)	24 (8%)	0.003
Warning signs and symptoms				
Ill appearance	n (%)	502 (17)	97 (31)	<0.001
Tachypnoea (breaths/min)	APLS thresholds, n (%)	590 (31)	54 (41)	0.03
Tachycardia (beats/min)	APLS thresholds, n (%)	881 (32)	112 (43)	<0.001
Prolonged capillary refill	≥3 s, n (%)	43 (1)	10 (4)	0.006
Oxygen saturations (%O_2)	<94%O_2, n (%)	111 (4)	15 (6)	0.20
Level of consciousness	Decreased (verbal, pain, unresponsive), n (%)	10 (0)	4 (1)	0.03
Increased work of breathing	n (%)	410 (14)	71 (27)	<0.001
Non-blanching rash	n (%)	84 (3)	6 (2)	0.61
Neurological signs	n (%)	21 (1)	3 (1)	0.64
Seizures	n (%)	33 (1)	9 (3)	0.003
Diagnostics				
C-reactive protein	mg/L, median (IQR)	18 (5–46)	111 (71–174)	<0.001
Laboratory testing at ED	Any, n (%)	1946 (56)	254 (80)	<0.001
Imaging at ED	Any, n (%)	900 (26)	221 (69)	<0.001
Treatment and outcomes				
Immediate life-saving interventions	Any, n (%)	42 (1)	8 (3)	0.09
Antibiotics prescribed this attendance	Any, n (%)	1268 (37)	292 (92)	<0.001
Diagnosis—focus of infection	Upper respiratory tract	1861 (54%)	0 (0%)	<0.001
	Lower respiratory tract	665 (19%)	173 (54%)	
	Gastrointestinal	172 (5%)	19 (6%)	
	Urinary tract	41 (1%)	111 (35%)	
	Childhood exanthema	221 (6%)	0 (0%)	
	Soft tissue or musculoskeletal	88 (3%)	4 (1%)	
	Sepsis or meningitis	10 (0%)	12 (4%)	
	Undifferentiated fever	247 (7%)	0 (0%)	
	Inflammatory or other	151 (1%)	0 (0%)	
Disposition	Discharge without follow-up	1288 (37%)	19 (6%)	<0.001
	Discharge with follow-up	1302 (38%)	108 (34%)	
	Admission <24 hours	176 (5%)	13 (4%)	
	Admission 24 hours or more	614 (18%)	173 (54%)	
	Admission, duration unknown	41 (1%)	4 (1%)	
	PICU	16 (0%)	2 (1%)	
	Left without being seen	15 (0%)	0 (0%)	

*This excludes any non-blanching rash including petechiae and purpura.
APLS, advanced paediatric life support; ED, emergency department; PICU, paediatric intensive care unit; SBI, serious bacterial infection.

n=769 (42%)) (online supplemental file 4). Invasive bacterial infections were rare in both fever duration groups (≥5 days: n=15 (0.4%) vs <5 days: n=129 (0.4%), NS). Rates of SBI were similar between those with a measured fever ≥38.0°C at triage (n=1161 (33%), 9%) and those without (n=2335 (67%), 8%, NS).

Characteristics of children with fever ≥5 days with and without SBI

Children with fever ≥5 days and SBI were younger than those without SBI (2.4 years (IQR 1.3–5.6 years) vs 3.1 years (IQR 1.6–6.1 years), p<0.01) and were more often female (175 (55%) vs 1545 (45%), p<0.001) (table 2). Warning signs such as ill

Table 3 Diagnostic accuracy of clinical signs and symptoms and C-reactive protein and their risk of having serious bacterial infection in children with fever of 5 days or more

	Sensitivity	Specificity	PPV	NPV	dOR
Clinical warning signs					
Tachypnoea	0.41 (0.32–0.50)	0.69 (0.67–0.71)	0.08 (0.06–0.11)	0.94 (0.93–0.95)	1.52 (1.06–2.18)
Tachycardia	0.43 (0.37–0.50)	0.68 (0.67–0.70)	0.11 (0.09–0.13)	0.93 (0.92–0.94)	1.64 (1.27–2.13)
Ill appearance	0.31 (0.26–0.37)	0.85 (0.84–0.86)	0.16 (0.13–0.19)	0.93 (0.92–0.94)	2.57 (1.98–3.33)
Increased work of breathing	0.17 (0.13–0.22)	0.91 (0.90–0.92)	0.15 (0.11–0.20)	0.92 (0.91–0.93)	2.18 (1.54–3.08)
Prolonged capillary refill	0.04 (0.02–0.07)	0.99 (0.98–0.99)	0.19 (0.09–0.32)	0.92 (0.91–0.93)	2.79 (1.38–5.62)
Oxygen saturations <94%	0.06 (0.03–0.09)	0.96 (0.95–0.97)	0.12 (0.07–0.19)	0.92 (0.91–0.93)	1.50 (0.86–2.62)
Non-blanching rash	0.02 (0.01–0.04)	0.97 (0.97–0.98)	0.07 (0.02–0.14)	0.91 (0.90–0.92)	0.74 (0.32–1.71)
Seizure	0.03 (0.01–0.06)	0.99 (0.99–0.99)	0.21 (0.10–0.37)	0.92 (0.91–0.93)	3.24 (1.54–6.84)
Neurological signs	0.01 (0.00–0.03)	0.99 (0.99–1.00)	0.13 (0.03–0.32)	0.92 (0.91–0.93)	1.68 (0.50–5.66)
Any warning sign	0.92 (0.87–0.95)	0.24 (0.22–0.26)	0.11 (0.09–0.12)	0.97 (0.95–0.98)	3.52 (2.12–5.84)
Duration of fever (days)					
7	0.47 (0.42–0.53)	0.62 (0.60–0.63)	0.10 (0.09–0.12)	0.93 (0.92–0.94)	1.45 (1.16–1.83)
10	0.21 (0.17–0.26)	0.85 (0.84–0.86)	0.12 (0.09–0.15)	0.92 (0.91–0.93)	1.54 (1.16–2.05)
Non-specific signs and symptoms					
Other type of rash*	0.08 (0.05–0.12)	0.85 (0.84–0.86)	0.05 (0.03–0.07)	0.91 (0.90–0.92)	0.51 (0.33–0.79)
Gastrointestinal symptoms	0.38 (0.33–0.44)	0.66 (0.64–0.68)	0.10 (0.08–0.11)	0.92 (0.91–0.93)	1.20 (0.93–1.54)
Respiratory symptoms	0.38 (0.32–0.44)	0.49 (0.47–0.51)	0.07 (0.05–0.08)	0.90 (0.88–0.91)	0.60 (0.46–0.77)
Biomarkers					
C-reactive protein ≥10 mg/L	0.94 (0.90–0.96)	0.36 (0.34–0.39)	0.16 (0.14–0.18)	0.98 (0.96–0.99)	8.40 (5.02–14.06)
C-reactive protein ≥20 mg/L	0.92 (0.87–0.95)	0.52 (0.50–0.54)	0.20 (0.18–0.23)	0.98 (0.97–0.99)	11.84 (7.50–18.67)
C-reactive protein ≥60 mg/L	0.82 (0.76–0.86)	0.81 (0.79–0.82)	0.36 (0.32–0.40)	0.97 (0.96–0.98)	18.42 (13.12–25.87)
C-reactive protein ≥80 mg/L	0.66 (0.60–0.72)	0.86 (0.85–0.88)	0.39 (0.34–0.44)	0.95 (0.94–0.96)	12.20 (9.11–16.35)

*This excludes any non-blanching rash including petechiae and purpura.
dOR, diagnostic OR; NPV, negative predictive value; PPV, positive predictive value.

appearance, tachypnoea, tachycardia and increased work of breathing occurred more frequently in those with SBI than in those without; prolonged central capillary refill, abnormal level of consciousness and seizures, although present more frequently in those with SBI, were seen in few children. CRP was higher in children with SBI (111 mg/L (IQR 71–174 mg/L) vs 18 mg/L (IQR 5–46 mg/L), p<0.001). Antibiotic prescribing (292 (92%) vs 1268 (37%), p<0.001) and hospital admission >24 hours (173 (54%) vs 614 (18%), p<0.001) were higher in children with SBI.

Several warning signs, such as prolonged capillary refill, increased work of breathing, non-blanching rash, seizures and neurological signs, had specificities >0.90 (table 3). Presence of a non-specific rash (dOR 0.51 (95% CI 0.33–0.79)) and non-specific respiratory symptoms (dOR 0.60 (95% CI 0.46–0.77)) was associated with the absence of SBI. Having fevers for ≥7 or

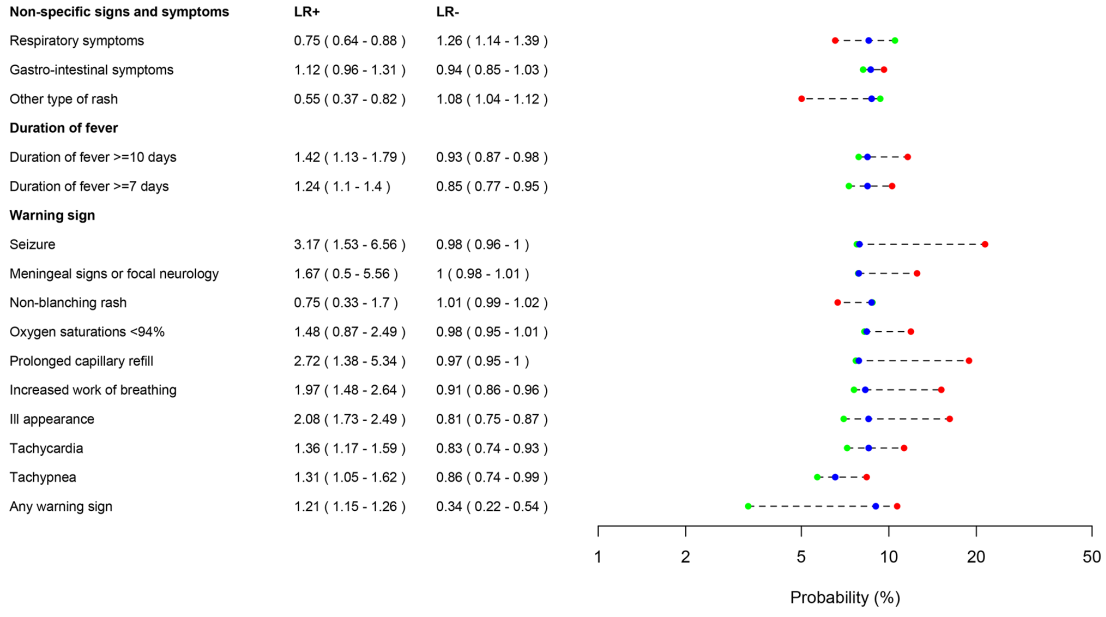

Figure 1 Likelihood ratio (LR) and dumbbell plots of the probabilities of having serious bacterial infection (SBI) for clinical warning signs. The change from pretest probabilities (blue dots) to post-test probabilities using negative LRs (green dots; rule out value) and positive LRs (red dots; rule in value) for non-specific signs and symptoms, duration of fever and clinical warning signs. Please note the incidence of SBI varies based on number of available data for each of the predictor variables. The x-axis is depicted on a logarithmic scale.

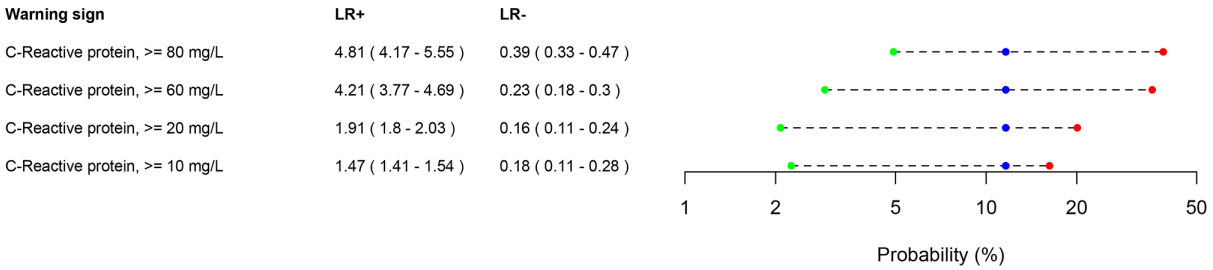

Figure 2 Likelihood ratio (LR) and dumbbell plots of the probabilities of having serious bacterial infection (SBI) for different cut-offs of C-reactive protein (CRP; mg/L). The change from pretest probabilities (blue dots) to post-test probabilities using negative LRs (green dots; rule out value) and positive LRs (red dots; rule in value) for different cut-offs of CRP (mg/L). Please note the incidence of SBI in those with CRP performed (11.6% in n=2152 children) was higher than in the overall cohort of children with fever ≥5 days. The x-axis is depicted on a logarithmic scale.

≥10 days did not change the probabilities of SBI (figure 1). Several clinical warning signs changed pretest probabilities considerably, with the limitation of broad CIs due to their sparse occurrence. Absence of warning signs (sensitivity 0.92 (95% CI 0.87–0.95), negative LR 0.34 (95% CI 0.22–0.54)) did not alter post-test probabilities sufficiently to reliably rule out SBI. Positive and negative LRs of clinical warning signs in children with fever <5 days were similar to those in children with fever ≥5 days (online supplemental file 5). CRP <20 mg/L was a good marker for ruling out SBI (negative LR 0.16 (0.11–0.24)) (figure 2). One child with CRP <20 mg/L and no warning signs (out of 2448 with data available (online supplemental file 6)) had an SBI.

Diagnostic management of children with fever ≥5 days

The diagnostic management for children with fever ≥5 days varied between EDs, with inflammatory markers in blood (white cell count 56%, CRP 57%), urinalysis (27%), chest X-ray (26%) and respiratory tests (21%) done most frequently; many children (26%) did not undergo additional diagnostic tests (table 4).

Other serious illness in children with fever ≥5 days

There were 66 children (1.7%) with other serious conditions (online supplemental file 7), including 21 cases (0.6%) of Kawasaki disease and 28 cases (0.7%) of inflammatory conditions. Children with Kawasaki disease presented with a rash commonly (86%) and were more often described as ill appearing (43%) compared with other groups of febrile children. In both the Kawasaki disease (25%) and other inflammatory condition groups (18%) antibiotics were prescribed less. New diagnoses of malignancies were rare (n=4 (0.1%)).

Table 4 Details of diagnostics performed in children with fever of 5 days or more

Type of test	n (%)	Range per hospital
C-reactive protein	2152 (57)	17%–98%
White cell count	2133 (56)	17%–98%
Urinalysis	1010 (27)	10%–37%
Chest X-ray	979 (26)	9%–46%
Any type of respiratory test (virology and/or microbiology)	781 (21)	5%–35%
Blood culture	494 (13)	1%–38%
Ultrasound	299 (8)	0%–21%
Urine culture	328 (9)	1%–32%
Faeces culture	103 (3)	0%–4%
CT	32 (1)	0%–5%
Cerebral spinal fluid	25 (1)	0%–2%
No diagnostic test performed	969 (26)	5%–56%

DISCUSSION

Principal findings

A considerable percentage of febrile children presenting to EDs will have a prolonged fever ≥5 days (10.6%). Warning signs of fever were observed equally between those with a prolonged and a shorter duration of fever, and they had similar acuity of presentations as reflected by triage urgency, need for ILSI or paediatric intensive care unit admissions. However, incidence of SBI in children with fever ≥5 days was higher than for those with duration <5 days (8.4% vs 5.7%). Most children with fever ≥5 days and SBI had either a urinary tract or a lower respiratory tract focus, with invasive bacterial infections being rare (0.4%). Other serious causes for prolonged fever, including Kawasaki disease, inflammatory conditions and malignancies, were infrequent (1.7%).

Comparison with literature

Studies previously showed an association between SBI, and in particular pneumonia, and the duration of fever.[15 16] However, two systematic reviews found inconclusive and contradicting evidence.[17 18] Most studies used continuous duration of fever, whereas we looked at children with duration of fever at a cut-off of 5 days. Our data suggest a reassuring narrative that a prolonged fever by itself is not a convincing warning sign for bacterial infections leading to critical illness, as illustrated by similar rates of warning signs and measures of acuity between children with a prolonged and shorter duration of fever. However, the large proportion of children with prolonged fever and SBI having a lower respiratory tract focus is in line with reports of secondary bacterial infection following initial viral illness and translocation of nasopharyngeal microbiome.[19] Importantly, our targeted population differs from the population of children with fever of unknown origin, which typically requires fevers for at least 2 weeks, and which reportedly has higher rates of non-infectious causes.[20 21]

Implications for clinical practice

The observed higher rate of SBI in children with fever ≥5 days signals a need for a careful yet balanced diagnostic workup. A blanket approach for extensive diagnostic testing appears unwarranted, supported by low rates of other causes of serious illness and current practice showing many of these children undergoing no additional testing. However, the history taking and clinical examination should reflect the broad differential diagnostic possibilities, both infectious and

non-infectious, and which include rare, but serious, underlying pathologies, sometimes requiring time critical recognition and treatment,[22] and in our study the rates of these were not negligible. The presence of warning signs, though some were infrequently encountered, should lead to senior clinical review and a low threshold for additional testing. The absence of these warning signs does not reliably rule out SBI. The presence of non-specific clinical signs and symptoms should be evaluated in the context of other possible warning signs. Our results show an important diagnostic role for CRP, arguing for its inclusion in the diagnostic management, in particular in unwell-appearing children, in those with additional warning signs and in those without a clear focus of bacterial infection. Similarly, with many having a urinary tract focus, our results reiterate the need for targeted urinalysis testing. Previous work showed a limited role for routine viral respiratory tests for ruling out of SBI in febrile children, while recognising the difficulties of defining true bacterial lower respiratory tract infections.[23] As no single clinical sign, symptom or currently available biomarker can reliably identify those with a prolonged fever caused by SBI or inflammatory conditions, future research should focus on next generation biomarkers.[14] How the COVID-19 pandemic changed the current and future epidemiology of infectious and inflammatory diseases in childhood is unclear, particularly given the emergence of the multisystem inflammatory syndrome in children,[24] and additional studies are needed. Even before the COVID-19 pandemic inflammatory conditions, such as Kawasaki disease, appeared to be increasing.[2]

Strengths and limitations

The main strength is the use of data from consecutive children with a prolonged fever attending a diverse range of paediatric EDs across Europe, underlining the validity and generalisability of our findings. Despite many children presenting to healthcare earlier in the disease episode, we do not have those data and thus unable to assess disease evolution. Unsurprisingly, CRP was an important predicting variable for SBI, and although allocation of SBI for some children (ie, those with a 'definite bacterial infection', online supplemental file 2) was independent of CRP level, assigning SBI was dependent on CRP level for others (those with 'probable bacterial infection'). Another limitation was the amount of missing clinical data introducing selection bias (online supplemental file 6). Additionally, many children did not undergo additional investigations despite a fever ≥5 days causing verification bias. Finally, the work will have to consider the variable prevalences of infectious pathogens given the impact of seasonality.

CONCLUSION

In children with prolonged fever, there is a higher risk of SBI, warranting a careful clinical assessment and considerate diagnostic workup. In this cohort, warning signs of SBI occurred infrequently; however, if present, they increase the likelihood of SBI. Although rare, clinicians should consider the possibility of important non-infectious causes of prolonged fever.

Author affiliations
[1]Department of Paediatric Emergency Medicine, Division of Medicine, St. Mary's hospital - Imperial College NHS Healthcare Trust, London, UK
[2]Faculty of Medicine, Department of Infectious Diseases, Section of Paediatric Infectious Diseases, Imperial College London, London, UK
[3]Centre for Paediatrics and Child Health, Imperial College London, London, UK
[4]Department of General Paediatrics, Erasmus MC-Sophia Children's Hospital, Rotterdam, Netherlands
[5]Department of Public Health, Erasmus University Medical Centre, Rotterdam, Netherlands
[6]Department of Pediatrics, Children's Clinical University Hospital, Rīgas Stradiņa Universitāte, Riga, Latvia
[7]Division of Paediatric Infectious Diseases, Dr. von Hauner Children's Hospital, University Hospital, Ludwig-Maximilian-University, Munich, Germany
[8]Partner site Munich, German Centre for Infection Research, Munich, Germany
[9]Institute of Infection and Global Health, University of Liverpool, Liverpool, UK
[10]Alder Hey Children's NHS Foundation Trust, Liverpool, UK
[11]Second Department of Paediatrics, P & A Kyriakou Children's Hospital, National and Kapodistrian University of Athens, Athens, Greece
[12]Paediatric Immunology, Infectious Diseases & Allergy, Great North Children's Hospital, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, UK
[13]Translational and Clinical Research Institute, Newcastle University, Newcastle upon Tyne, UK
[14]NIHR Newcastle Biomedical Research Centre, Newcastle upon Tyne Hospitals NHS Trust and Newcastle University, Newcastle upon Tyne, UK
[15]Paediatric Infectious Diseases and Immunology, Wilhelmina Children's Hospital, University Medical Centre Utrecht, Utrecht, Netherlands
[16]Paediatric Infectious Diseases and Immunology, Amalia Children's Hospital, Radboud University Medical Centre, Nijmegen, Netherlands
[17]Section Paediatric Infectious Diseases, Laboratory of Medical Immunology, Radboud Institute for Molecular Life Sciences, Nijmegen, Netherlands
[18]Department of General Paediatrics, Medical University of Graz, Graz, Austria
[19]Population Health Sciences Institute, Newcastle University, Newcastle upon Tyne, UK
[20]Genetics, Vaccines, Infections and Paediatrics Research group (GENVIP), Hospital Clinico Universitario de Santiago, Santiago de Compostela, Spain
[21]Department of Infectious Diseases, University Medical Centre Ljubljana, Ljubljana, Slovenia
[22]Clinical Research Department, Faculty of Tropical and Infectious Disease, London School of Hygiene and Tropical Medicine, London, UK
[23]Department of Paediatric Infectious Diseases and Immunology, Erasmus MC-Sophia Children's Hospital, Rotterdam, Netherlands

Twitter Ruud G Nijman @rgnijman, Enitan D Carrol @CarrolEnitan and Benno Kohlmaier @BennoKohlmaier

Collaborators Members of the Personalised Risk Assessment in Febrile Illness to Optimise Real-life Management across the European Union (PERFORM) consortium are provided in online supplemental file 1.

Contributors Conceptualisation, design, funding: RGN, CDT, NNH, JMZ, DN, JAH, AB, UvB, EC, IE, ME, MvdF, RdG, BK, EL, IM, FM-T, MP, FS, MT, SY, DZ, WZ, ML, CV, HAM, IKM. Data curation: RGN, CDT, NNH, JMZ, DN, JAH, AB, UvB, EC, IE, ME, MvdF, RdG, BK, EL, FM-T, MP, FS, MT, SY, DZ, WZ, ML, CV, HAM, IKM. Formal analysis: RGN, CDT. Methodology: RGN, CDT, NNH, JMZ, DN, JAH, AB, UvB, EC, IE, ME, MvdF, RdG, BK, EL, FM-T, MP, FS, MT, SY, DZ, WZ, ML, CV, HAM, IKM. Supervision: RGN, HAM, IKM, CDT. Writing—original draft: RGN, HAM, IKM, CDT. Writing—review and editing: RGN, CDT, NNH, JMZ, DN, JAH, AB, UvB, EC, IE, ME, MvdF, RdG, BK, EL, FM-T, MP, FS, MT, SY, DZ, WZ, ML, CV, HAM, IKM. Guarantor: RGN.

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ORCID iDs
Ruud G Nijman http://orcid.org/0000-0001-9671-8161
Chantal D Tan http://orcid.org/0000-0002-1148-9716
Nienke N Hagedoorn http://orcid.org/0000-0001-9237-4904
Jethro Adam Herberg http://orcid.org/0000-0001-6941-6491
Ulrich von Both http://orcid.org/0000-0001-8411-1071
Benno Kohlmaier http://orcid.org/0000-0003-0685-689X
Federico Martinón-Torres http://orcid.org/0000-0002-9023-581X
Joany M Zachariasse http://orcid.org/0000-0002-4093-8509
Henriette A Moll http://orcid.org/0000-0001-9304-3322

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