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The adolescent paradox at the ED: teenagers visiting the ED have an increased risk of serious bacterial infections.

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On behalf of PERFORM consortium: Personalised Risk assessment in febrile children to optimise Real-life Management across the European Union.*

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*Membership of the PERFORM Consortium is provided in appendix 1.

Abbreviations

aOR – adjusted odds ratio

AUC – Area under the Curve

ED – Emergency Department

EMS – Emergency Medical Services

IBI – Invasive bacterial infection

ILSI – Immediate life-saving interventions

MOFICHE – Management and Outcome of Fever in children in Europe

NICE - National Institute for Health and Care Excellence

OR – odds ratio

PERFORM - Personalized Risk assessment in Febrile illness to Optimize Real-life Management across the European Union

PEWS - Paediatric Early Warning Score

PICU – Paedatric Intensive Care Unit

SBI – Serious bacterial infection

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The authors declare they have no potential conflicts of interest to disclose.

Data:

An anonymized data set necessary to replicate our study findings will be provided as a public repository with a DOI in case of acceptance of the manuscript.

Abstract

Objective

Most studies regarding febrile children have focused on infants and young children with serious bacterial infections (SBI). Although population studies have described an increased risk of sepsis in adolescents, little is known about febrile adolescents attending the Emergency Department (ED). We aimed to describe patient characteristics and management of febrile adolescents attending the ED.

Design and setting

The MOFICHE/PERFORM, a prospective multicentre study, took place at 12 European EDs. Descriptive and multivariable regression analysis were performed, comparing febrile adolescents (12-18 years) to younger children in terms of patient characteristics, markers of disease severity (vital signs, clinical alarming signs), management (diagnostic tests, therapy, admission) and diagnosis (focus, viral/bacterial infection).

Results

37,420 encounters were included, of which 2,577 (6,9%) were adolescents.

Adolescents were more often triaged as high-urgent (38·9% versus 34·5%) and described as ill-appearing (23·1% versus 15·6%) than younger children.

Increased work of breathing and a non-blanching rash were present less often in adolescents while neurological signs were present more often (1% versus 0%). C-reactive protein was performed more frequently in adolescents and was abnormal more often (aOR 1·7, 95%CI 1·5-1·9). Adolescents were more often diagnosed with SBI (OR 1·8, 95%CI 1·6-2·0) and sepsis/meningitis (OR 2·3, 95%CI 1·1-5·0), more frequently were admitted (aOR 1·3, 95% CI 1·2-1·4) and treated with intravenous antibiotics (aOR 1·7, 95% CI 1·5-2·0).

Conclusions

Although younger children presented to the ED more frequently, adolescents were more often diagnosed with SBI and sepsis/meningitis. Our data emphasize the importance of awareness for severe infections in adolescents.

Keywords

Adolescent health, epidemiology.

Article summary (strengths and limitations of this study)

- Our study provides detailed data on a large number of adolescents attending the ED with fever
- Our data show that although accounting for a relatively small fraction of all ED visits for febrile children, adolescents have an increased risk of serious bacterial infections
- Febrile adolescents are hospitalized more often, are treated with intravenous antibiotics more often and more often required immediate life-saving interventions
- Adolescents with serious bacterial infections present differently than younger children and more research is needed to be able to provide detailed guidelines for this age group

INTRODUCTION

The adolescent age is often described as a health paradox because on the one hand it is a time of enhanced physical and mental capabilities, yet the overall mortality/morbidity rates increase significantly, often due to risk taking behaviour such as substance abuse or injuries.[1]

Although this health paradox has received considerable attention in the international literature, there is a knowledge gap regarding infectious problems in adolescents, as most

studies on adolescents have focused on topics typically associated with adolescence, such as violence or mental health,[2-4] while most studies on infections have focused on younger children.[5]

Case series as well as population studies have shown adolescents to have an increased risk of sepsis in comparison to younger children,[6,7] and several studies showed adolescents with sepsis to have an increased mortality rate.[6-11]

One possible explanation of this increased case-fatality rate might be the atypical presentation of adolescents with sepsis, such as gastro-intestinal complaints.[9,12]

The increased incidence of sepsis and the high case-fatality rates emphasize the importance of awareness for severe infections in adolescents.

Despite this, little is known on the presentation, management and diagnosis of febrile adolescents presenting to the ED.

Our aim was to assess the presentation, management and diagnosis of febrile adolescents attending the ED and explore differences between adolescents and younger children.

METHODS

Study design

This study is part of the MOFICHE study (Management and Outcome of Febrile children in Europe), which is embedded in the PERFORM study (Personalized Risk assessment in Febrile illness to Optimise Real-life Management across the European Union).[13] MOFICHE is an observational multicentre study that evaluates the management and outcome of febrile children in Europe using routinely collected data.[14] 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, ID:28-518ex15/16), Germany (Ethikkommission Bei Der LMU München, ID:699-16), Greece (Ethics committee, ID:9683/18.07.2016), Latvia (Centrala medicinas etikas komiteja, ID:14.07.201.6.No. Il16-07-14), Slovenia (Republic of Slovenia National Medical Ethics Committee, ID:0120-483/2016-3), Spain (Comité Autonómico de Ética de la Investigación de Galicia, ID:2016/331), The Netherlands (Commissie Mensgebonden onderzoek, ID:NL58103.091.16), United Kingdom (Ethics Committee, ID:16/LO/1684, IRAS application no. 209035, Confidentiality advisory group reference: 16/CAG/0136).

In all the participating UK settings, an additional opt-out mechanism was in place.

Patient and public involvement

Patients were not involved in the design of the study.

Study population and setting

Twelve EDs from eight different countries (Austria, Germany, Greece, Latvia, the Netherlands (n=3), Spain, Slovenia, and the United Kingdom (n=3)) participated in the study. Participating hospitals were either tertiary university hospitals or large teaching hospitals (appendix 2). Data were collected for at least one year (January 2017-April 2018).

For this analysis, inclusion criteria were children aged 3 months-18 years presenting to the ED with fever (temperature >=38·0° C) or a history of fever in the previous 72 hours.

Data collection

Data were obtained from patient records and entered into an electronic case report form. Data included general patient characteristics (age, sex, comorbidity, previous medical care,

arrival time, referral (self, primary care physician, Emergency Medical Services (EMS) or other), triage urgency, vital signs, presence of "red traffic light" alarming signs from the National Institute for Health and Care Excellence (NICE) fever guideline,[15] high risk criteria from the NICE sepsis guideline[15] (table 1) and management at the ED. The NICE alarming signs include level of consciousness, ill-appearance, increased work of breathing, age <3 months, non-blanching rash, meningeal signs, status epilepticus and focal neurological signs. High risk criteria from the NICE Sepsis guideline overlap with NICE alarming signs but differ by age-group and include abnormal behaviour, decreased consciousness, low oxygen saturation, abnormal heart rate, respiratory rate or blood pressure, hypothermia, age <3 months, diminished urine output, cyanosis or a non-blanching rash. An overview of the collected alarming signs is provided in table 2.

Data collection ranged from one week per month to the entire month, depending on the number of ED visits per hospital (appendix 2).

Definitions

Adolescents were defined as children aged 12-18 years; younger children were defined as children aged 3 months-12 years.

Previous medical care was defined as medical care for the same complaint in the last 5 days at any facility. Comorbidity was defined as a chronic underlying condition that is expected to last at least 1 year.[16]

Vital signs were classified as abnormal according to APLS reference ranges.[17]

Simplified Paediatric Early Warning Scores (PEWS) were calculated based on the PEWS developed by Parshuram et al. (vital signs, capillary refill time, work of breathing and oxygen therapy, combined into a score).[18,19] Blood pressure was excluded from the PEWS as it was

not routinely performed in our study. A previous study showed that a simplified PEWS without blood pressure showed similar performance in predicting PICU admission in comparison to the original PEWS.[19]

Triage categories were combined into “low urgency” (non-urgent and standard) and “high urgency” (urgent, very urgent and immediate).

Immediate life-saving interventions[20] (ILSI) were categorized into the following categories: airway/breathing support, electrical therapy, emergency procedures, hemodynamic support and emergency medications (appendix 3).

Focus of infection was categorized as: upper respiratory, lower respiratory, gastro-intestinal/surgical abdomen, urinary, skin, musculoskeletal, sepsis, meningitis/central nervous system (CNS), flu-like illness, childhood exanthemas, inflammatory, undifferentiated fever or other.[14]

The consortium developed a consensus-based flowchart[14,21,22] to classify the presumed cause of infection for each visit (appendix 4), depending on clinical signs, CRP and microbiological tests (bacterial cultures, viral or bacterial PCR), into “definite or probable bacterial”, “definite or probable viral”, “unknown” or “other”.

Serious bacterial infection (SBI) was defined as ‘definite/probable bacterial’ with a focus from the gastro-intestinal, lower respiratory, urinary or musculoskeletal tract, CNS or sepsis.

Sepsis/meningitis was defined as ‘definite/probable bacterial’ with a focus from the CNS or sepsis.

Data quality and missing data

Data quality and completeness was improved and standardized by using a digital training module for physicians who assess febrile children at the ED, including clarification of the NICE alarming signs. Data were entered into the patient's record as part of routine care by the treating physician and nurse and were then manually extracted from these records and entered into an electronic case report form by trained research team members.

Missing determinants such as vital signs were handled by multiple imputation (table 1). Imputation was performed by using the MICE package in R, version 3.4. SPSS version 25 was used for the analysis of the data.

Data analysis

We performed descriptive analyses for general patient characteristics, vital signs, PEWS, NICE alarming signs, management (diagnostic tests, intravenous antibiotics, oxygen therapy, ILSI, disposition (discharge, hospital admission, PICU admission) and diagnosis (focus of infection, viral or bacterial disease). Characteristics of adolescents and younger children were compared using chi-squared-tests and Mann-Whitney tests. Results were deemed significant with a p-value <0·05.

We analysed differences in management, disposition and presumed cause of infection by multivariable logistic regression adjusted for general patient characteristics (setting/ED, sex, fever duration, previous medical care, arrival time and comorbidity). We did not adjust for disease severity as our aim was to describe differences in disease severity between young children and adolescents. Subgroup analyses were performed for children and adolescents diagnosed with SBI and for children without comorbidity.

RESULTS

Patient characteristics

37,420 ED encounters were included, of which 2,577 (6·9%) were adolescents (table 1).

Adolescents were less often self-referred (49·4% versus 57·8%) and more often presented by EMS than younger children (17·3% versus 14·8%, p< 0·001).

Adolescents more often had comorbidity (28·5% versus 16·4%, p<0·001, table 1, appendix 5).

Presenting signs and symptoms

Adolescents were more often triaged as high urgent. Tachycardia was present more often (29·6% versus 24·5%, p<0·001) while tachypnoea, increased work of breathing and low oxygen saturation were present less often.

Adolescents more often had a PEWS score of 6 or higher (6·2% versus 4·5%, p<0·001).

Non-blanching rashes were present less often in adolescents while ill-appearance, meningeal signs and focal neurological signs were present more often (table 1).

In a sub-analysis of children without comorbidity, results were similar, except triage urgency, PEWS and focal neurological signs, which were then similar in both groups.

Management

After adjusting for general patient characteristics, we found that diagnostic tests were such as CRP were performed more often in adolescents (aOR 1·9, 95% CI 1·7-2·0) and CRP more often reached levels >60 mg/l (aOR 1·7, 95% CI 1·5-1·9).

Hospital admission (aOR 1·3, 95% CI 1·2-1·4), intravenous antibiotics (aOR 1·7, 95% CI 1·5-1·9) and ILSI (aOR 1·5, 95% 1·2-2·0) were more common in adolescents while PICU admission was similar in both age-groups (aOR 1·1, 95% CI 0·6-1·9, figure 1).

Sub-analysis in children without comorbidity showed similar results, except for ILSI, which was similar in both groups (figure 3).

Focus and presumed cause of infection

Upper respiratory tract infection was the most common focus in both age-groups, although this was less common in adolescents than in younger children (41·8% versus 53·9%, figure 2, p<0·001). Gastro-intestinal/surgical abdomen was diagnosed more often in adolescents (16·2%) (10·1%, p<0·001).

Adolescents were more often classified as having bacterial disease (31·0% versus 21·6%, aOR 1·5, 95% CI 1·4-1·7) and SBI (15·8% versus 8·4%, aOR 1·8, 95%CI 1·6-2·0, and less often with probable/definite viral disease. Most common SBI in both adolescents and younger children were lower respiratory tract, urinary tract and gastro-intestinal infections. Bacterial sepsis/meningitis was more common in adolescents (0·6% versus 0·3%, OR 1·9 (1·1-3·3)), although after adjusting for general patient characteristics, this was significant only in children without comorbidity (aOR 2·3, 95% CI 1·1-5·0, figure 3).

Presentation and management of children and adolescents with SBI.

In total 3,347 children presented with SBI. SBI was present in 406 of 2,577 adolescents (15,8%) and 2,941 of 34,843 of younger children (8,4%).

Adolescents with SBI more often had comorbidity (34·0% versus 23·6%, p<0·001), less often presented with tachypnoea and increased work of breathing, while rates of tachycardia and

prolonged capillary refill were similar between adolescents and younger children with SBI. Adolescents with SBI and sepsis/meningitis were more often described as ill-appearing and adolescents that were described as ill-appearing, more often were diagnosed with SBI or sepsis/meningitis. However, high-risk criteria from the NICE sepsis guideline were present less frequently in adolescents with SBI (appendix 6).

No differences were found regarding the frequency of CRP >60mg/l, intravenous antibiotics, admission or PICU admission. Adolescents with SBI more often were treated with ILSI than younger children (aOR 2·2, 95% CI 1·4-3·5), although this difference was not significant after excluding children with comorbidity.

DISCUSSION

Main findings

Our data show that despite accounting for a small fraction of all ED visits for febrile children, adolescents presenting to the ED have an increased risk of SBI such as sepsis/meningitis. Furthermore, adolescents with SBI present differently than younger children. Although adolescents were more often described as ill-appearing, high-risk criteria from the NICE sepsis guideline were present less frequently in adolescents with SBI or sepsis/meningitis. Adolescents were hospitalized more often, and more often received intravenous antibiotics and ILSI. Although adolescents more often had comorbidities, SBI was still more common in adolescents after excluding children with comorbidities.

Findings in relation to previous literature

Previous studies on febrile children have focused on infants and young children,[5] and literature regarding adolescents is scarce. Our data is in line with the few studies that have found an increased incidence of sepsis in adolescents in comparison to younger children[7,9] and emphasize how febrile adolescents form a distinct risk group. Previous studies[23] have suggested that there might be a delay in adolescents presenting to the ED. However, no differences were found in fever duration between adolescents and younger children diagnosed with SBI in our study.

Our data show that the *health paradox* does not only apply to preventable injuries, but also to potentially preventable infectious diseases.

Implications for clinical practice and research

Health care workers evaluating adolescents should be aware of the substantial risk in adolescents for SBI and the potentially different presentation. Diagnostic tests and antibiotic therapy should be considered when SBI cannot be ruled out on clinical grounds and safety netting advice should be given to all febrile adolescents and their caregivers in case of discharge from the ED. Currently, there is a lack of guidelines on the management of febrile adolescents, as, although the NICE sepsis guideline addresses adolescents as well as younger children,[15] its focus is on the recognition of sepsis, while the more general NICE fever guideline is exclusively targeted at children below the age of five.[15] Based on our data, it would be advisable to develop a more general guideline that aids in the management of febrile adolescents and includes (clinical) markers for the recognition of SBI other than sepsis.

As adolescents with SBI less often presented with the classical high-risk criteria cited in the NICE sepsis guideline, future research should focus on identifying alarming signs in the adolescent age-group.

Secondly, empowering caregivers is an important step in the care for their febrile child,[24] as most studies regarding caregivers' knowledge on fever have focused on young children,[25] as do many online information sources for caregivers.[26]

STRENGTHS AND LIMITATIONS

To our knowledge this is the first study looking into patient characteristics, management and diagnosis of febrile adolescents attending the ED.

The main strengths of our study are that detailed information on presenting signs, management and diagnosis was collected on a large number of children and adolescents in different European EDs. Data were collected year-round and included different hospitals with different patient case mixes, which largely increases the generalizability of the results.[14,27]

Furthermore, we included a large number of children with SBI, as determined by a uniformly applied flowchart.

The main limitations include the lack of information regarding outcome after the ED visit, e.g. revisits, 30-day morbidity and mortality and the use of routinely collected data. To ensure data quality, all study sites were extensively trained regarding the accurate documentation of patient characteristics and quality checks were performed regularly. The amount of missing data was limited and its effects were reduced by using multiple imputation.[28]

Another limitation is that blood pressure, cyanosis and diminished urine output were not included in the data collection. A previous study showed that although hypotension is associated with serious illness in children, its sensitivity is limited as routine measurement in *all* children attending the ED.[29,30] and it is a late sign in septic children in comparison to adults. On the other hand, in adolescents, similar to adults, hypotension might present earlier in the disease course, and thus including blood pressure could provide valuable information.

As cases defined as 'probable bacterial' were also included in the definition of sepsis/meningitis, we cannot preclude that some of these cases were not of bacterial origin in either age-groups. However, in the EUCLIDS study on severe sepsis, a pathogen was only found in half of the cases.[11]

Lastly, our data applies to adolescents attending the ED; more research is needed to know whether our results can be applied to adolescents presenting to primary care as well. Furthermore, it is unknown whether a form of "selection bias" exists, as parents might be more inclined to seek help for younger febrile children than for adolescents.

CONCLUSION

Our data show that despite accounting for a relatively small fraction of all ED visits, febrile adolescents have an increased risk of serious bacterial infections including sepsis/meningitis, in comparison to younger children.

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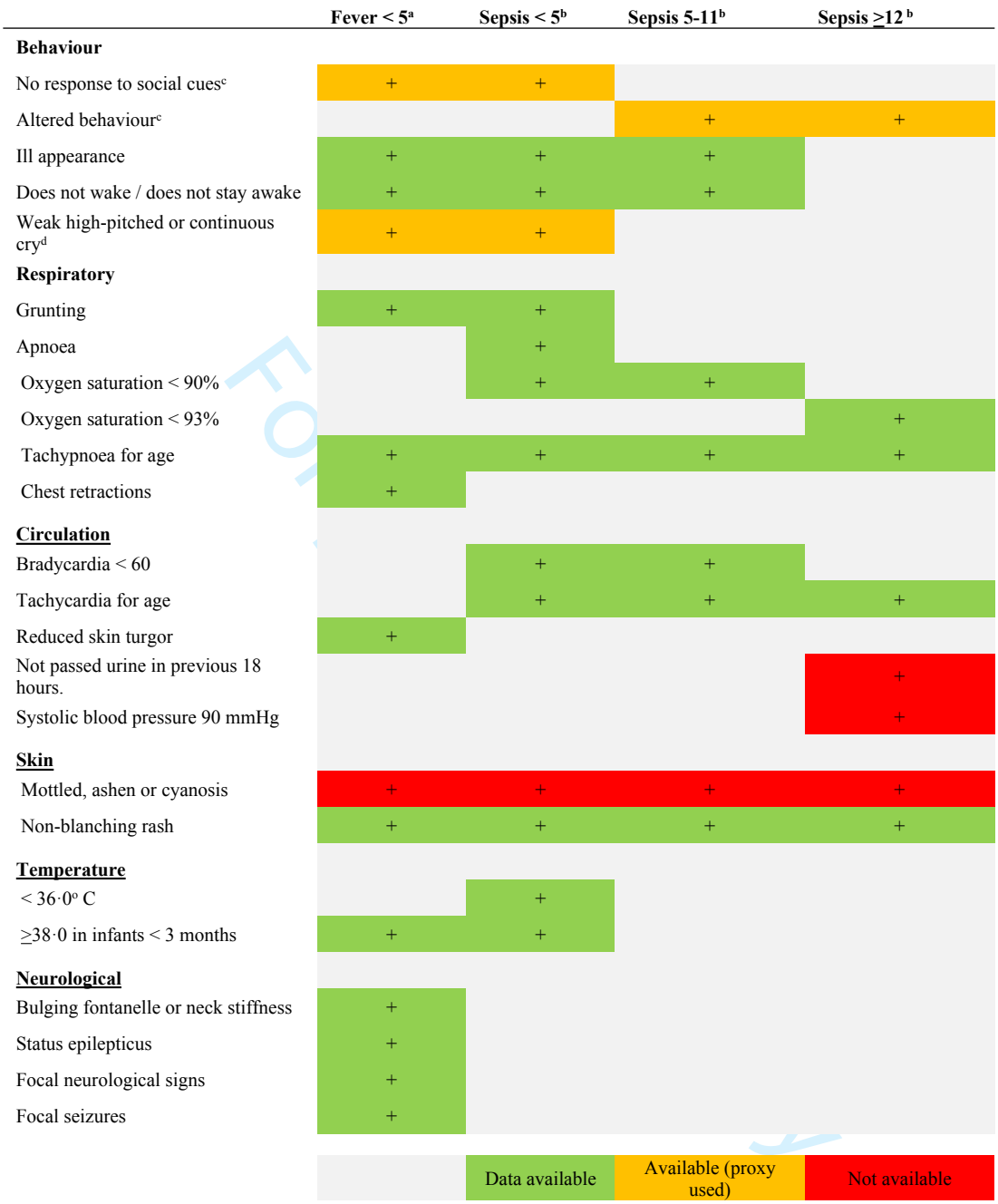
Tables and figures

Table 1: Differences in patient characteristics between young children and adolescents (n=37,420)

	Children 3 months- 12 years N = 34,843 N (%)	Children ≥ 12 years N = 2,577 N (%)
Male	19,182 (55·1)	1,307 (50·7)
Age in years, median (IQR)	2·6 (1·3-4·9)	14·5 (13·2-16·1)
Comorbidity[a]		
Simple	4,302 (12·5)	489 (19·1)
Complex	1,332 (3·9)	241 (9·4)
Duration of fever *		
< 24 hours	11,410 (35·1)	854 (37,3)
24-48 hours	10,622 (32,7)	682 (29,8)
> 48 hours	10,433 (31,1)	755 (33,0)
Referral		
Self	19,537 (57·8)	1,231 (49·4)
GP/private paediatrician	5,654 (16·7)	493 (19·8)
Emergency medical service	5,010 (14·8)	430 (17·3)
Other	3,574 (10·6)	337 (13·5)
Triage urgency		
High: immediate, very urgent, intermediate	11,664 (34·5)	967 (38·9)
Vital signs[b] and PEWS		
Tachycardia APLS	8,552 (24·5)	764 (29·6)
Tachypnoea APLS	5,282 (15·2)	189 (7)
Hypoxia, oxygen saturation <95% APLS	805 (2·3)	30 (1)
Prolonged capillary refill >=3 seconds[ns]	343 (1·1)	25 (1)
Simplified PEWS 6 or higher	782 (4·5)	81 (6)
Nice "red traffic lights" (alarming signs)		
Ill appearance	5,203 (15·6)	559 (23·1)
Increased work of breathing	3,050 (10·0)	67 (3)
Rash: petechiae/non-blanching	1,040 (3·4)	53 (2)
Decreased consciousness[ns]	178 (1)	16 (1)
Meningeal signs	97 (0)	23 (1)
Status epilepticus[ns]	58 (0)	8 (0)
Focal neurology	110 (0)	19 (1)

Missing values: general patient characteristics: < 7%. Vital signs: 9-23%. NICE alarming signs 1-18%.
[a]. Comorbidity: a chronic underlying condition that is expected to last at least 1 year. Complex comorbidity: a chronic condition in ≥2 body systems or malignancy or immunocompromised patients.
[b]. According to APLS cut-off values by age.
All comparisons p<0·001, except * = <0·05 and [ns] = not significant.

Table 2. "Red traffic light" symptoms (alarming signs) from the NICE guideline on fever and high-risk criteria from the NICE sepsis guideline.



[a] NICE fever guideline
[b] NICE sepsis guideline
[c] Defined as reduced consciousness
[d] defined as ill appearance

Figure 1: Adjusted odds ratios for younger children versus adolescents for diagnostic tests, therapy, disposition and final diagnosis. [a]

[a] Younger children used as reference. Adjusted for hospital, sex, duration of fever, previous medical care, time of arrival and comorbidity.

To convert CRP values to nmol/L, multiply by 0·9524

Figure 2: focus of infection in young children and adolescents

Data shown as percentages within the groups of young children and adolescents.
LRTI=lower respiratory tract infection; gastro-intestinal=gastro-intestinal and surgical abdomen; UTI=urinary tract infection, exanthems=exanthems and flulike illness; musculoskeletal=soft-tissue, skin and musculoskeletal infection.
LRTI (not shown in graphic) = lower respiratory tract infection: young children 54%, adolescents 42%.

Figure 3: Adjusted odds ratios for younger children versus adolescents for diagnostic tests, therapy, disposition and final diagnosis, patients with comorbidity excluded.[a]

[a] Younger children used as reference. Adjusted for hospital, sex, duration of fever, previous medical care and time of arrival.

To convert CRP values to nmol/L, multiply by 0·9524

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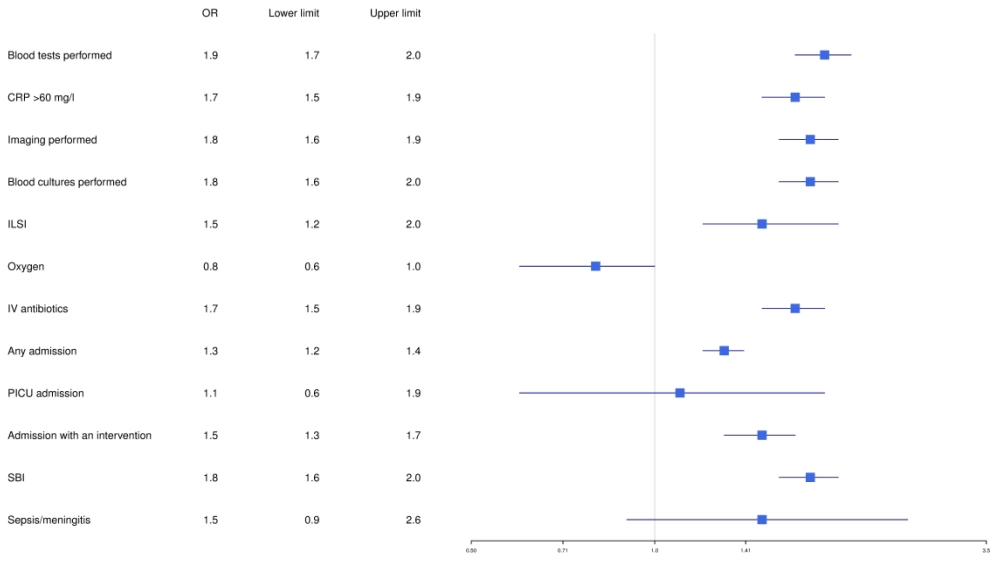

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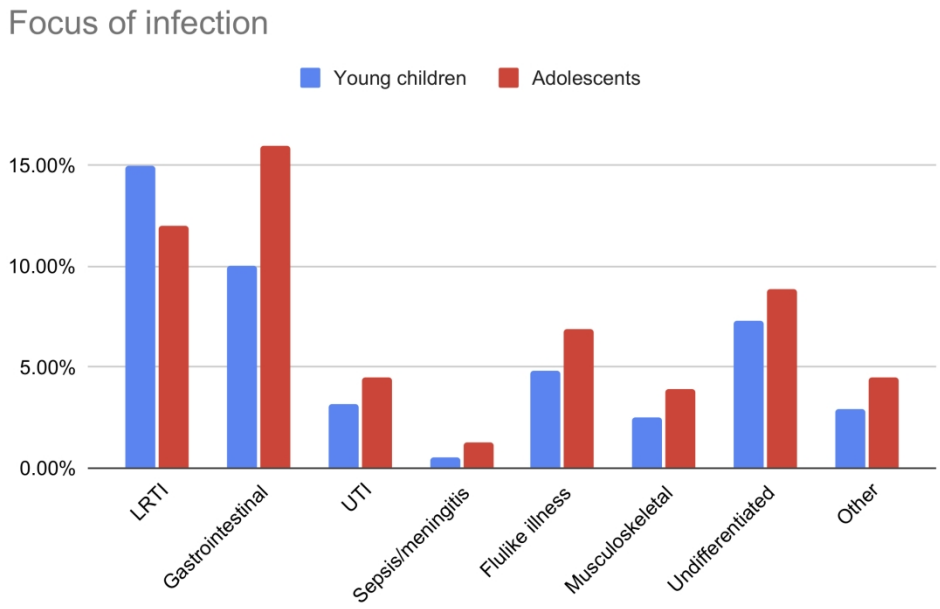

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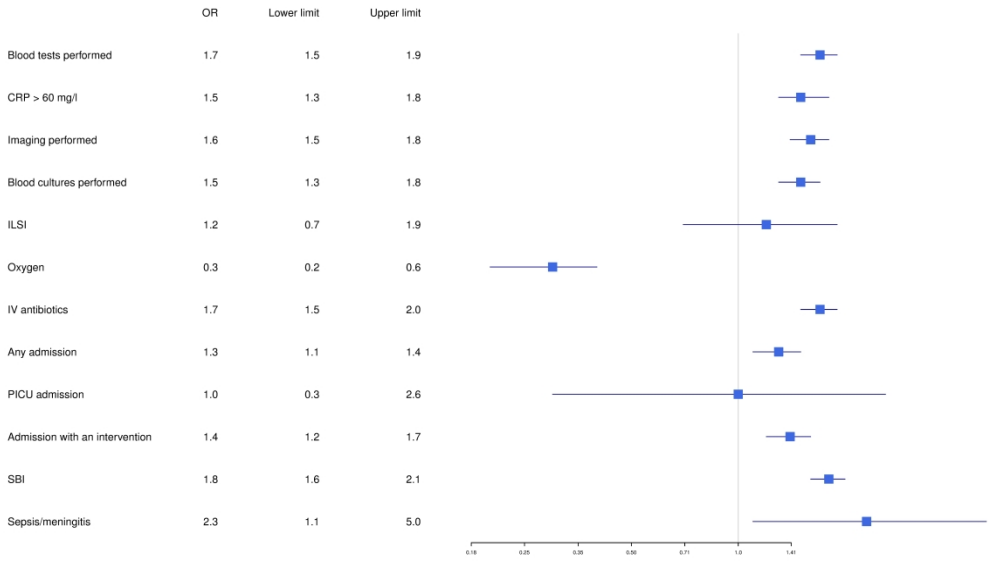

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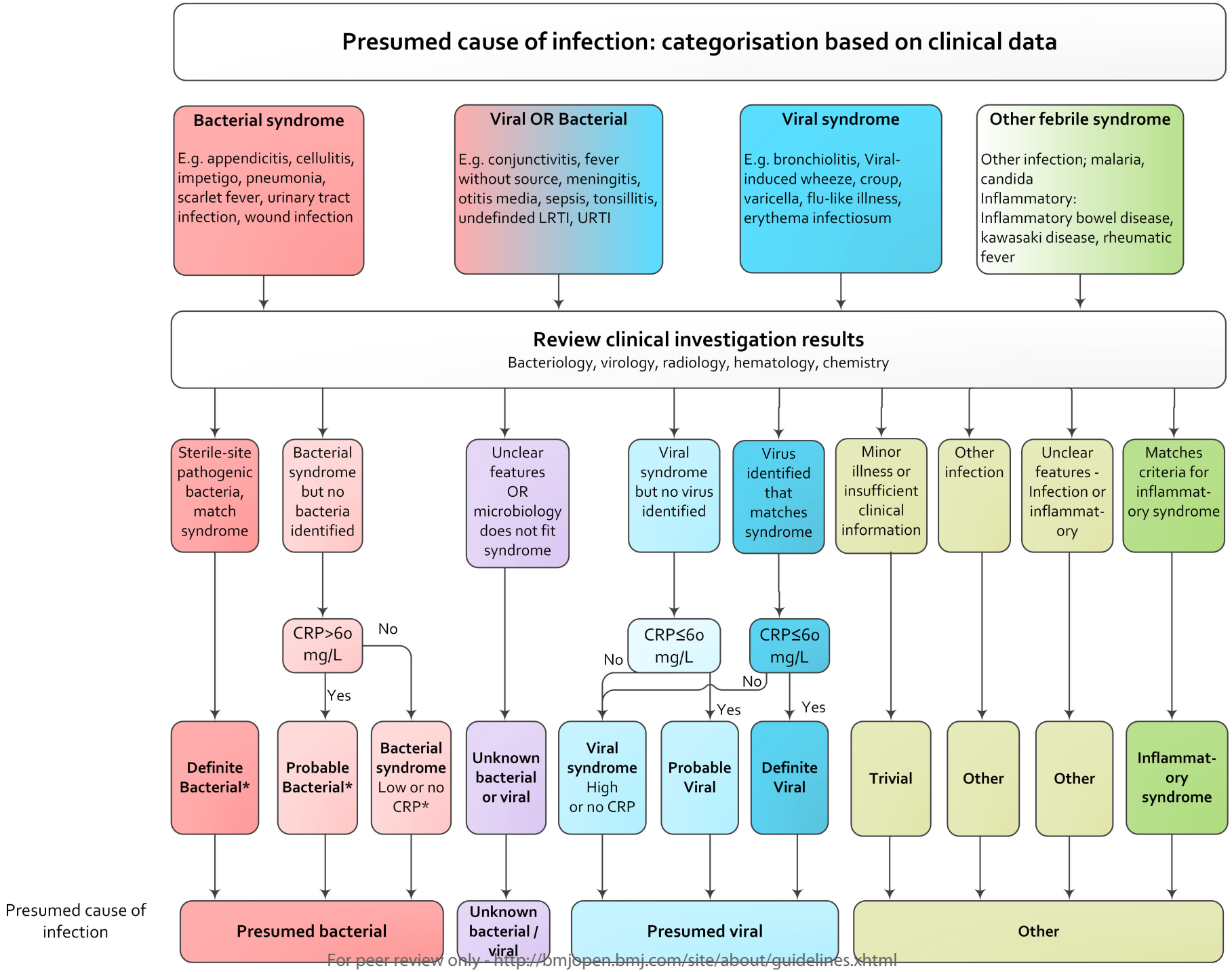
Appendix 2: Participating EDs

Hospital	Country, city	Hospital type	Total annual paediatric ED visits	Total period of inclusion	Period of inclusion per month	Number of patients included
Medizinische Universität Graz	Austria, Graz	University	10,000-30,000	1-1-2017 – 31-12-2018	10 days	2243
Dr. von Hauner Children's Hospital	Germany, Munich	Teaching	10,000-30,000	1-1-2017 – 31-12-2018	1 week	1175
P. and A. Kyriakou Children's Hospital	Greece, Athens	University	>30,000	1-1-2017 – 1-5-2018	1-2 weeks	4549
Children clinical university hospital	Latvia, Riga	Teaching	>30,000	1-1-2017 – 31-12-2018	All	9000
Univerzitetni Klinični Center	Slovenia, Ljubljana	University	<10,000	1-1-2017 – 31-12-2018	All	3659
Hospital Clínico Universitario	Spain, Santiago de Compostela	University	>30,000	1-1-2017 – 1-5-2018	1-2 weeks	3877
Erasmus MC-Sophia Children's Hospital	The Netherlands, Rotterdam	University	<10,000	1-1-2017 – 1-4-2018	All	1681
RadboudUMC	The Netherlands, Nijmegen	University	<10,000	1-1-2017 – 1-4-2018	All	676
Canisius Wilhelmina Ziekenhuis	The Netherlands, Nijmegen	Teaching	<10,000	1-1-2017 – 31-12-2018	2 weeks	415
Alder Hey Children's Hospital	United Kingdom, Liverpool	Teaching	>30,000	1-1-2017 – 31-12-2018	1 week	1624
St. Mary's Hospital	United Kingdom, London	University	10,000-30,000	1-1-2017 – 31-12-2018	All	5714
Great North Children's Hospital	United Kingdom, Newcastle upon Tyne	University	>30,000	1-4-2017 – 1-4-2018	2 weeks	3870

Appendix 3. Immediate life-saving interventions

1. Airway and breathing support, including intubation or emergent noninvasive positive pressure ventilation.
2. Electrical therapy, including defibrillation, emergent cardioversion, or external pacing.
3. Procedures, including chest needle decompression, pericardiocentesis, or open thoracotomy.
4. Hemodynamic support, including significant intravenous fluid resuscitation in the setting of hypotension, blood administration, or control of major bleeding.
5. Emergency medications, including naloxone, dextrose, atropine, adenosine, epinephrine, or vasopressors



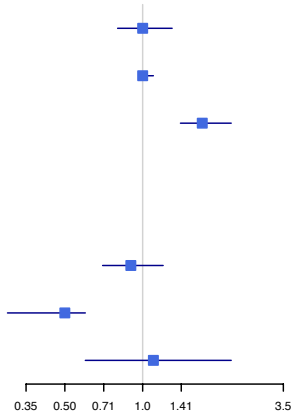
Appendix 5: Comorbidity.

	Children 3 months- 12 years N = 34,843 N (%)	Children > 12 years N = 2,577 N (%)
No comorbidity	28,881 (83·7)	1,833 (71·5)
Non-complex comorbidity	4,302 (12·5)	489 (19·1)
Complex comorbidity	1,332 (3·9)	241 (9·4)
Type of comorbidity		
Neurological & psychomotor delay	1,604 (28·5)	298 (40·8)
Pulmonary	1,224 (21·7)	182 (24·9)
Prematurity	945 (16·8)	20 (2·7)
Urological/nephrological	634 (11·3)	57 (7·8)
Malignancy & immunodeficiency	583 (10·4)	162 (22·2)
Cardiac	557 (9·9)	58 (7·9)
Gastro-intestinal	422 (7·5)	81 (11·1)
Musculoskeletal	171 (3·0)	55 (7·5)
Metabolic	165 (2·9)	53 (7·3)
Endocrine	63 (1·1)	27 (3·7)
Other comorbidity	729 (12·9)	83 (11·3)

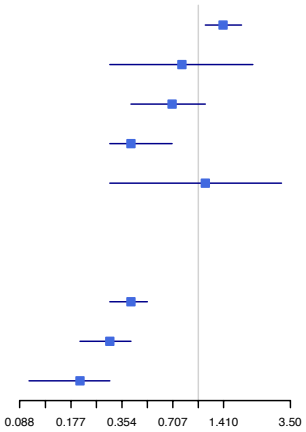
Type of comorbidity displayed as percentage of children with comorbidity.

Appendix 6: Differences in patient characteristics between young children and adolescents with a final diagnosis of SBI. [a]

	OR	Lower limit	Upper limit
General patient characteristics			
Triage urgency high	1.0	0.8	1.3
Referral by EMS	1.0	1.0	1.1
Comorbidity	1.7	1.4	2.2
Vital signs			
Tachycardia	0.9	0.7	1.2
Tachypnoea	0.5	0.3	0.6
Prolonged capillary refill	1.1	0.6	2.2



	OR	Lower limit	Upper limit
NICE fever guideline alarming signs			
Ill appearance	1.4	1.1	1.8
Non–blanching rash	0.8	0.3	2.1
Blanching rash	0.7	0.4	1.1
Increased work of breathing	0.4	0.3	0.7
Neurological signs	1.1	0.3	3.1
NICE sepsis guideline high risk criteria			
1 or more	0.4	0.3	0.5
2 or more	0.3	0.2	0.4
3 or more	0.2	0.1	0.3



[a] Younger children used as reference. Adjusted for hospital, sex, duration of fever, previous medical care, time of arrival and comorbidity. * According to APLS cut-off values by age.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
5Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	5
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	5
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	7
Objectives	3	State specific objectives, including any prespecified hypotheses	7
Methods			
Study design	4	Present key elements of study design early in the paper	8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	8
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	9,10
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	9,10
Bias	9	Describe any efforts to address potential sources of bias	11
Study size	10	Explain how the study size was arrived at	9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9,10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	11,12
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	12
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	12,13, 24
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	Report numbers of outcome events or summary measures over time	12,13

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	11-13 27
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	13,14
Discussion			
Key results	18	Summarise key results with reference to study objectives	14,15
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	16,17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14-17
Generalisability	21	Discuss the generalisability (external validity) of the study results	16,17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Author statement form

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Characteristics and management of adolescents attending the ED with fever: a prospective multicentre study.

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On behalf of PERFORM consortium: Personalised Risk assessment in febrile children to optimise Real-life Management across the European Union.*

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*Membership of the PERFORM Consortium is provided in appendix 1.

Abbreviations

aOR – adjusted odds ratio

CRP – C-reactive protein

ED – Emergency Department

EMS – Emergency Medical Services

ILSI – Immediate life-saving interventions

MOFICHE – Management and Outcome of Fever in children in Europe

NICE - National Institute for Health and Care Excellence

OR – odds ratio

PERFORM - Personalized Risk assessment in Febrile illness to Optimize Real-life Management across the European Union

PCR – Polymerase Chain Reaction

PEWS - Paediatric Early Warning Score

PICU – Paedatric Intensive Care Unit

SBI – Serious bacterial infections

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The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. This publication is the work of the authors who will serve as guarantors for the contents of this paper.

Competing interest:

The authors declare they have no potential conflicts of interest to disclose.

Abstract

Objective

Most studies regarding febrile children have focused on infants and young children with serious bacterial infections (SBI). Although population studies have described an increased risk of sepsis in adolescents, little is known about febrile adolescents attending the Emergency Department (ED). We aimed to describe patient characteristics and management of febrile adolescents attending the ED.

Design and setting

The MOFICHE/PERFORM, a prospective multicentre study, took place at 12 European EDs. Descriptive and multivariable regression analysis were performed, comparing febrile adolescents (12-18 years) to younger children in terms of patient characteristics, markers of disease severity (vital signs, clinical alarming signs), management (diagnostic tests, therapy, admission) and diagnosis (focus, viral/bacterial infection).

Results

37,420 encounters were included, of which 2,577 (6·9%) were adolescents.

Adolescents were more often triaged as high-urgent (38·9% versus 34·5%) and described as ill-appearing (23·1% versus 15·6%) than younger children.

Increased work of breathing and a non-blanching rash were present less often in adolescents while neurological signs were present more often (1% versus 0%). C-reactive protein was performed more frequently in adolescents and was abnormal more often (aOR 1·7, 95%CI 1·5-1·9). Adolescents were more often diagnosed with SBI (OR 1·8, 95%CI 1·6-2·0) and sepsis/meningitis (OR 2·3, 95%CI 1·1-5·0), more frequently were admitted (aOR 1·3, 95% CI 1·2-1·4) and treated with intravenous antibiotics (aOR 1·7, 95% CI 1·5-2·0).

Conclusions

Although younger children presented to the ED more frequently, adolescents were more often diagnosed with SBI and sepsis/meningitis. Our data emphasize the importance of awareness for severe infections in adolescents.

Keywords

Adolescent health, epidemiology.

Article summary (strengths and limitations of this study)

- Our study provides detailed data on a large number of adolescents attending the Emergency Department with fever
- Our data show that although accounting for a relatively small fraction of all Emergency Department visits for febrile children, adolescents have an increased risk of serious bacterial infections
- Febrile adolescents are hospitalized more often, are treated with intravenous antibiotics more often and more often required immediate life-saving interventions
- Adolescents with serious bacterial infections present differently than younger children and more research is needed to be able to provide detailed guidelines for this age group

INTRODUCTION

The adolescent age is often described as a health paradox because on the one hand it is a time of enhanced physical and mental capabilities, yet the overall mortality/morbidity rates increase significantly, often due to risk taking behaviour such as substance abuse or injuries. [1]

Although this health paradox has received considerable attention in the international literature, there is a knowledge gap regarding infectious problems in adolescents, as most studies on adolescents have focused on topics typically associated with adolescence, such as violence or mental health,[2] [3] [4] while most studies on infections have focused on younger children.[5]

Case series as well as population studies have shown adolescents to have an increased risk of sepsis in comparison to younger children [6, 7] and several studies showed adolescents with sepsis to have an increased mortality rate. [6–11]

One possible explanation of this increased case-fatality rate might be the atypical presentation of adolescents with sepsis, such as gastro-intestinal complaints. [9, 12] The increased incidence of sepsis and the high case-fatality rates emphasize the importance of awareness for severe infections in adolescents.

Despite this, little is known on the presentation, management and diagnosis of febrile adolescents presenting to the Emergency Department (ED). Our aim was to assess the presentation, management and diagnosis of febrile adolescents attending the ED and explore differences between adolescents and younger children.

METHODS

Study design

This study is part of the MOFICHE study (Management and Outcome of Febrile children in Europe), which is embedded in the PERFORM study (Personalized Risk assessment in Febrile illness to Optimise Real-life Management across the European Union).[13] MOFICHE is an observational multicentre study that evaluates the management and outcome of febrile children in Europe using routinely collected data.[14] In this sub-study we specifically assessed patient characteristics, diagnosis and management of febrile adolescents and compared it to the characteristics and management of younger children.

Patient and Public Involvement

Patients were not involved in the design of the study.

Study population and setting

Twelve EDs from eight different countries (Austria, Germany, Greece, Latvia, the Netherlands (n=3), Spain, Slovenia, and the United Kingdom (n=3)) participated in the study (appendix 1). Participating hospitals were either tertiary university hospitals or large teaching hospitals (appendix 2). Data were collected for at least one year (January 2017-April 2018).

For this analysis, inclusion criteria were children aged 3 months-18 years presenting to the ED with fever (temperature >=38·0° C) or a history of fever in the previous 72 hours.

Data collection

Data were obtained from patient records and entered into an electronic case report form. Data included general patient characteristics (age, sex, comorbidity, previous medical care, arrival time, referral (self, primary care physician, Emergency Medical Services (EMS) or

other), triage urgency, vital signs, presence of “red traffic light” alarming signs from the National Institute for Health and Care Excellence (NICE) fever guideline,[15] high risk criteria from the NICE sepsis guideline[15] (table 1) and management at the ED. The NICE alarming signs include level of consciousness, ill-appearance, increased work of breathing, age <3 months, non-blanching rash, meningeal signs, status epilepticus and focal neurological signs. High risk criteria from the NICE Sepsis guideline overlap with NICE alarming signs but differ by age-group and include abnormal behaviour, decreased consciousness, low oxygen saturation, abnormal heart rate, respiratory rate or blood pressure, hypothermia, age <3 months, diminished urine output, cyanosis or a non-blanching rash. An overview of the collected alarming signs is provided in table 2.

Data collection ranged from one week per month to the entire month, depending on the number of ED visits per hospital (appendix 2).

Management comprised diagnostic tests (performance of blood tests, imaging, blood cultures and CRP test results), treatment (intravenous antibiotics, oxygen, Immediate Life Saving Interventions (ILSI)) and disposition (discharge, general ward admission or Paediatric Intensive Care unit (PICU) admission).

Definitions

Adolescents were defined as children aged 12-18 years; younger children were defined as children aged 3 months-12 years.

Previous medical care was defined as medical care for the same complaint in the last 5 days at any facility, including a general practitioner. A previous ED visit was defined as a visit to either the same or a different ED in the previous five days. Comorbidity was defined as a chronic underlying condition that is expected to last at least 1 year.[16]

Vital signs were classified as abnormal according to Advanced Paediatric Life Support (APLS) reference ranges.

Simplified Paediatric Early Warning Scores (PEWS) were calculated based on the PEWS developed by Parshuram et al. (vital signs, capillary refill time, work of breathing and oxygen therapy, combined into a score).[17, 18] Blood pressure was excluded from the PEWS as it was not routinely performed in our study. A previous study showed that a simplified PEWS without blood pressure showed similar performance in predicting PICU admission in comparison to the original PEWS.[18]

Triage categories were combined into "low urgency" (non-urgent and standard) and "high urgency" (urgent, very urgent and immediate).

ILSI[19] were categorized into the following categories: airway/breathing support, electrical therapy, emergency procedures, hemodynamic support and emergency medications (appendix 3).

Focus of infection was categorized as: upper respiratory, lower respiratory, gastro-intestinal/surgical abdomen, urinary, skin, musculoskeletal, sepsis, meningitis/central nervous system (CNS), flu-like illness, childhood exanthemas, inflammatory, undifferentiated fever or other.[14]

The consortium developed a consensus-based flowchart [14] [20] [21] to classify the presumed cause of infection for each visit (appendix 4), depending on clinical signs, C-reactive protein (CRP) and microbiological tests (bacterial cultures, viral or bacterial polymerase chain reaction (PCR)), into "definite or probable bacterial", "definite or probable viral", "unknown" or "other".

Serious bacterial infections (SBI) were defined as 'definite/probable bacterial' with a focus from the gastro-intestinal, lower respiratory, urinary or musculoskeletal tract, CNS or sepsis.

Sepsis/meningitis was defined as 'definite/probable bacterial' with a focus from the CNS or sepsis.

Data quality and missing data

Data quality and completeness was improved and standardized by using a digital training module for physicians who assess febrile children at the ED, including clarification of the NICE alarming signs. Data were entered into the patient's record as part of routine care by the treating physician and nurse and were then manually extracted from these records and entered into an electronic case report form by trained research team members.

Missing determinants such as vital signs were handled by multiple imputation (table 1). Imputation was performed by using the MICE package in R, version 3.4. SPSS version 25 was used for the analysis of the data.

Data analysis

We performed descriptive analyses for general patient characteristics, vital signs, NICE alarming signs, management, disposition and diagnosis. Characteristics of adolescents and younger children were compared using chi-squared-tests and Mann-Whitney tests. Results were deemed significant with a p-value <0·05.

We analysed differences in management, disposition and presumed cause of infection by multivariable logistic regression, displayed as odds ratios (OR), and adjusted for general patient characteristics (setting/ED, sex, fever duration, previous medical care, arrival time and comorbidity), displayed as adjusted odds ratios (aOR). We did not adjust for disease severity as our aim was to describe differences in disease severity between young children and

adolescents. Subgroup analyses were performed for children and adolescents diagnosed with SBI and for children without comorbidity.

RESULTS

Patient characteristics

37,420 ED encounters were included, of which 2,577 (6·9%) were adolescents (table 1). Adolescents were less often self-referred (49·4% versus 57·8%) and more often presented by EMS than younger children (17·3% versus 14·8%, p< 0·001). 2,816 (8·1%) younger children and 239 adolescents (9·3%) had attended an ED in the previous five days. Adolescents more often had comorbidity (28·5% versus 16·4%, p<0·001, table 1, appendix 5).

Presenting signs and symptoms

Adolescents were more often triaged as high urgent. Tachycardia was present more often (29·6% versus 24·5%, p<0·001) while tachypnoea, increased work of breathing and low oxygen saturation were present less often.

Adolescents more often had a PEWS score of 6 or higher (6·2% versus 4·5%, p<0·001).

Non-blanching rashes were present less often in adolescents while ill-appearance, meningeal signs and focal neurological signs were present more often (table 1).

In a sub-analysis of children without comorbidity, results were similar, except triage urgency, PEWS and focal neurological signs, which were then similar in both groups.

Management

After adjusting for general patient characteristics, we found that diagnostic tests were such as CRP were performed more often in adolescents (aOR 1·9, 95% CI 1·7-2·0) and CRP more often reached levels >60 mg/l (aOR 1·7, 95% CI 1·5-1·9).

Hospital admission (aOR 1·3, 95% CI 1·2-1·4), intravenous antibiotics (aOR 1·7, 95% CI 1·5-1·9) and ILSI (aOR 1·5, 95% 1·2-2·0) were more common in adolescents while PICU admission was similar in both age-groups (aOR 1·1, 95% CI 0·6-1·9, figure 1, figure 2).

Of those children that had attended the ED previously, 36·1% of younger children and 49·0% of adolescents were admitted (p<0·001). ICU admission was similar for younger children (0·9%) and adolescents (0·8%).

Sub-analysis in children without comorbidity showed similar results, except for ILSI, which was similar in both groups (figure 3, figure 4).

Focus and presumed cause of infection

Upper respiratory tract infection was the most common focus in both age-groups, although this was less common in adolescents than in younger children (41·8% versus 53·9%, figure 5, p<0·001). Gastro-intestinal/surgical abdomen was diagnosed more often in adolescents (16·2%) (10·1%, p<0·001). Adolescents were more often classified as having bacterial disease (31·0% versus 21·6%, aOR 1·5, 95% CI 1·4-1·7) and SBI (15·8% versus 8·4%, aOR 1·8, 95%CI 1·6-2·0), and less often with probable/definite viral disease. Most common SBI in both adolescents and younger children were lower respiratory tract, urinary tract and gastro-intestinal infections. Bacterial sepsis/meningitis was more common in adolescents (0·6% versus 0·3%, OR 1·9 (1·1-3·3)), although after adjusting for general patient characteristics, this was significant only in children without comorbidity (aOR 2·3, 95% CI 1·1-5·0, figure 4).

Of those children that had attended the ED previously, 13·8% of younger children and 21·8 of adolescents were diagnosed with SBI (p<0·001).

Presentation and management of children and adolescents with SBI.

In total 3,347 children presented with SBI. SBI were present in 406 of 2,577 adolescents (15·8%) and 2,941 of 34,843 of younger children (8·4%).

Adolescents with SBI more often had comorbidity (34·0% versus 23·6%, p<0·001), less often presented with tachypnoea and increased work of breathing, while rates of tachycardia and prolonged capillary refill were similar between adolescents and younger children with SBI.

Adolescents with SBI and sepsis/meningitis were more often described as ill-appearing and adolescents that were described as ill-appearing, more often were diagnosed with SBI or sepsis/meningitis. However, high-risk criteria from the NICE sepsis guideline were present less frequently in adolescents with SBI (appendix 6).

No differences were found regarding the frequency of CRP >60mg/l, intravenous antibiotics, admission or PICU admission. Adolescents with SBI more often were treated with ILSI than younger children (aOR 2·2, 95% CI 1·4-3·5), although this difference was not significant after excluding children with comorbidity.

DISCUSSION

Main findings

A well-known-statement emphasizes how "children are not small adults", [22] [23] however, our data show that adolescents are not large children either.

Our data show that despite accounting for a small fraction of all ED visits for febrile children,

adolescents presenting to the ED have an increased risk of SBI such as sepsis/meningitis. Furthermore, adolescents with SBI present differently than younger children. Although adolescents were more often described as ill-appearing, high-risk criteria from the NICE sepsis guideline were present less frequently in adolescents with SBI or sepsis/meningitis. Adolescents were hospitalized more often, and more often received intravenous antibiotics and ILSI.

Findings in relation to previous literature

Previous studies on febrile children have mainly focused on infants and young children, [5] and literature regarding febrile adolescents is scarce. A recent study by Brockhus et al. on adolescents attending the ED, showed that adolescents present with complaints different from those in children as well as adults and infectious problems were far less common than trauma or mental health issues. [23]

However, as stated above, although adolescents present with infectious problems less common than younger children, adolescents that *do* present to the ED, have an increased risk of suffering from a severe infection. Our data is in line with the few studies that have found an increased incidence of sepsis in adolescents in comparison to younger children [7] [9] and emphasize how febrile adolescents form a distinct risk group. In line with this, a study by Glynn et al [24] showed the severity of several infectious diseases (e.g. varicella, mononucleosis, meningococcal infections and scarlet fever) to be high in infancy, lower in school-aged children and then again increasing from the adolescent age, following a J-shaped pattern.

To date it is unclear why adolescents have an increased risk for serious infections. Possible explanations include immunological deterioration with age, so-called “immune senescence”, the influence of sex hormones on the immune system or the increase of comorbidity with age. [24] Regarding immune senescence, Glynn et al suggest that this process starts earlier

than previously believed, with optimal immune function being reached at age 5-14, and a decrease in immune function starting form adolescence. [24] Evidence supporting this theory comes from data on vaccine response by age, showing a decreased vaccine response in adolescents. [24] Regarding puberty and hormonal influences, data seems to be inconsistent as the increased mortality rates in infectious diseases seen in males in comparison to females is not seen in adolescence. [24] Regarding comorbidity, although in our study adolescents more often had comorbidity, SBI were still more common in adolescents after excluding children with comorbidity and sepsis/meningitis was more common in adolescents only in the subgroup of children without comorbidity, showing that comorbidity does not offer a clear-cut explanation for these trends.

In addition to presenting with different rates of the same diseases, adolescents with the same disease can present differently as well. [12] As stated before, although not "small adults", adolescents are not "large children" either, differing from both adults and children with regards to physiology, the immune system and the endocrine system. [25] Further differences might be explained by differences in health seeking behavior, lack of parental supervision or a delayed presentation [12] [10] [26] although the latter was not the case in our study. Regarding parental supervision, this was shown to be related to treatment adherence in adolescents with cystic fibrosis [27] or diabetes, [28] but there is a paucity of data regarding parental supervision in adolescents with infectious diseases and its impact on presentation or disease course.

Our data show that the *health paradox* does not only apply to preventable injuries, but also to potentially vaccine-preventable infections, such as meningococcal disease, or treatable infectious diseases, such as sepsis, where early recognition has the potential to improve outcome. [10] [29]

Implications for clinical practice and research

Our data highlight a gap in clinical guidelines addressing the presentation and management of febrile adolescents. While the NICE sepsis guideline addresses adolescents as well as younger children, [15] its focus is on the recognition of sepsis, while the more general NICE fever guideline is exclusively targeted at children below the age of five and our data show how the alarming signs for this age group cannot be extrapolated unambiguously to adolescents. [15] Furthermore, as most studies on adolescents focus on mental health issues, there's a paucity of literature on febrile adolescents.

As adolescents with infectious problems form only a small fraction of ED visits [23] exposure for each individual health care provider is expected to be low, [30] making the management of this group even more challenging. Therefore, there's an urgent need for future studies directed at identifying clinical criteria that can help improve the identification of SBI in the febrile adolescent age group.

While awaiting future studies, health care workers evaluating adolescents should have an increased level of awareness regarding the substantial risk in adolescents for SBI and the potentially different presentation.

Diagnostic tests and antibiotic therapy should be considered at a low threshold when SBI cannot be ruled out on clinical grounds. In addition to ordering routine tests such as C-reactive protein and white blood count, clinicians should consider performing additional

tests such as lactate and procalcitonin, as these offer improved diagnostic performance when it comes to differentiating sepsis from other causes of fever. [31] [32] [33] [34] [15]

Secondly, safety netting advice should be given to all febrile adolescents and their caregivers in case of discharge from the ED. Empowering adolescents on when to seek help and when and how to self-care at home is an important step in the management of febrile illnesses in adolescents. Most studies regarding patient's knowledge on fever have focused on caregivers of young children, [35] [36] as do many online information sources.[37] Previous research on how to improve empowerment in adolescents with medical problems can aid in optimally addressing this specific population as this requires a different approach than addressing adults or parents of younger children. [38] [39]

STRENGTHS AND LIMITATIONS

To our knowledge this is the first study looking into patient characteristics, management and diagnosis of febrile adolescents attending the ED.

The main strengths of our study are that detailed information on presenting signs, management and diagnosis was collected on a large number of children and adolescents in different European EDs. Data were collected year-round and included different hospitals with different patient case mixes, which largely increases the generalizability of the results.[14] [40] Furthermore, we included a large number of children with SBI, as determined by a uniformly applied flowchart.

The main limitations include the lack of information regarding outcome after the ED visit, e.g. 30-day morbidity and mortality in the use of routinely collected data. To ensure data quality, all study sites were extensively trained regarding the accurate documentation of

patient characteristics and quality checks were performed regularly. The amount of missing data was limited and its effects were reduced by using multiple imputation.[41] Another limitation is that blood pressure, cyanosis and diminished urine output were not included in the data collection. A previous study showed that although hypotension is associated with serious illness in children, its sensitivity is limited as routine measurement in *all* children attending the ED. [42, 43] and it is a late sign in septic children in comparison to adults. On the other hand, in adolescents, similar to adults, hypotension might present earlier in the disease course, and thus including blood pressure could provide valuable information.

As cases defined as 'probable bacterial' were also included in the definition of sepsis/meningitis, we cannot preclude that some of these cases were not of bacterial origin in either age-groups. However, in the EUCLIDS study on severe sepsis, a pathogen was only found in half of the cases.[11] Lastly, our data applies to adolescents attending the ED; more research is needed to know whether our results can be applied to adolescents presenting to primary care as well. Furthermore, it is unknown whether a form of "selection bias" exists, as parents might be more inclined to seek help for younger febrile children than for adolescents.

CONCLUSION

Our data show that despite accounting for a relatively small fraction of all ED visits, febrile adolescents have an increased risk of serious bacterial infections including sepsis/meningitis, in comparison to younger children.

Data availability

Individual participant data that underlie the results reported in this article, including a data dictionary, will be made available after de-identification to researchers who provide a methodologically sound proposal. Proposals should be directed to d.borensztajn@erasmusmc.nl. To gain access, data requestors will need to sign a data access agreement.

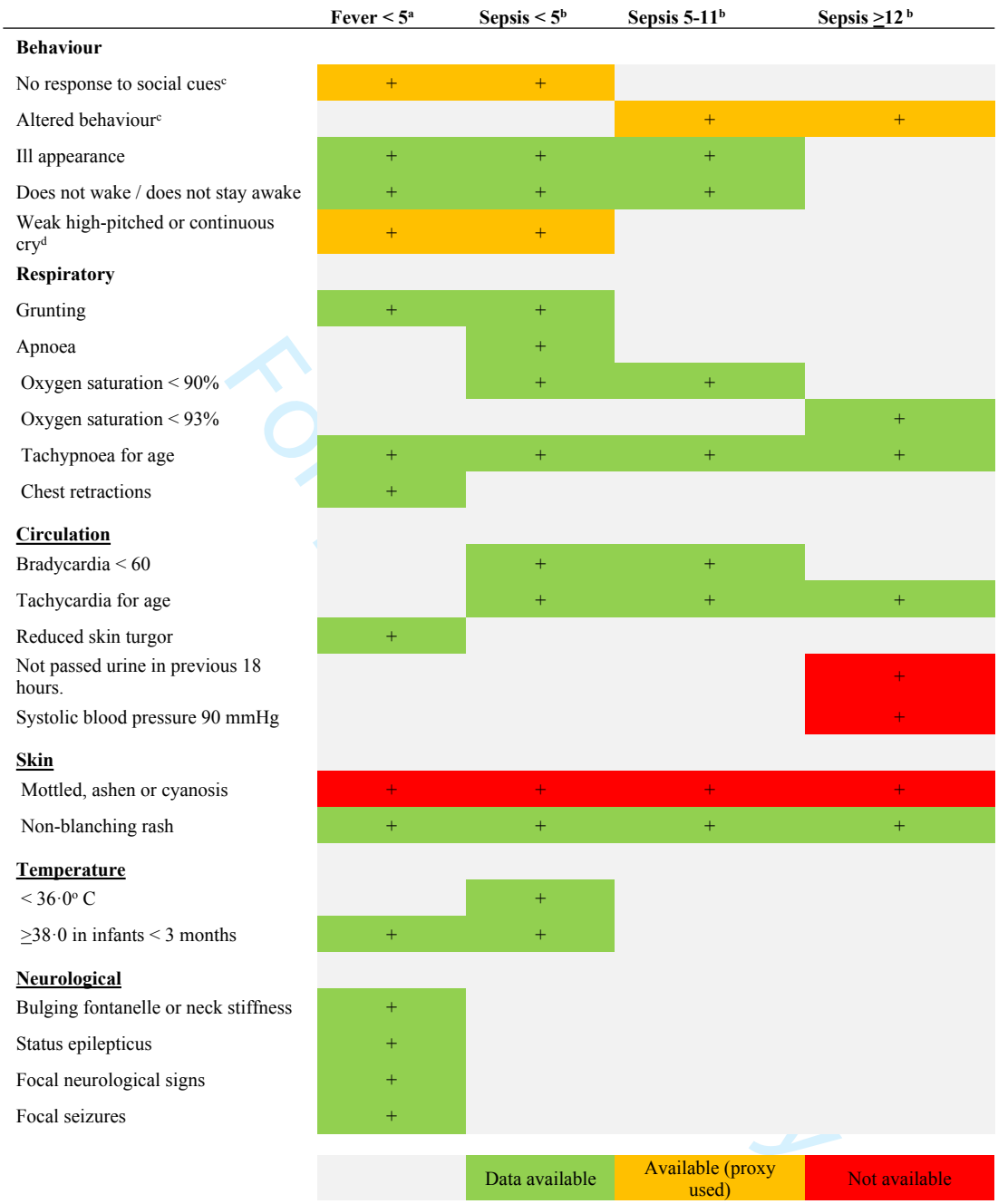
Tables and figures

Table 1: Differences in patient characteristics between young children and adolescents (n=37,420)

	Children 3 months- 12 years N = 34,843 N (%)	Children ≥ 12 years N = 2,577 N (%)
Male	19,182 (55·1)	1,307 (50·7)
Age in years, median (IQR)	2·6 (1·3-4·9)	14·5 (13·2-16·1)
Comorbidity[a]		
Simple	4,302 (12·5)	489 (19·1)
Complex	1,332 (3·9)	241 (9·4)
Duration of fever *		
< 24 hours	11,410 (35·1)	854 (37·3)
24-48 hours	10,622 (32·7)	682 (29·8)
> 48 hours	10,433 (31·1)	755 (33·0)
Referral		
Self	19,537 (57·8)	1,231 (49·4)
GP/private paediatrician	5,654 (16·7)	493 (19·8)
Emergency medical service	5,010 (14·8)	430 (17·3)
Other	3,574 (10·6)	337 (13·5)
Triage urgency		
High: immediate, very urgent, intermediate	11,664 (34·5)	967 (38·9)
Vital signs[b] and PEWS		
Tachycardia APLS	8,552 (24·5)	764 (29·6)
Tachypnoea APLS	5,282 (15·2)	189 (7)
Hypoxia, oxygen saturation <95% APLS	805 (2·3)	30 (1)
Prolonged capillary refill >=3 seconds[ns]	343 (1·1)	25 (1)
Simplified PEWS 6 or higher	782 (4·5)	81 (6)
Nice "red traffic lights" (alarming signs)		
Ill appearance	5,203 (15·6)	559 (23·1)
Increased work of breathing	3,050 (10·0)	67 (3)
Rash: petechiae/non-blanching	1,040 (3·4)	53 (2)
Decreased consciousness[ns]	178 (1)	16 (1)
Meningeal signs	97 (0)	23 (1)
Status epilepticus[ns]	58 (0)	8 (0)
Focal neurology	110 (0)	19 (1)

Missing values: general patient characteristics: < 7%. Vital signs: 9-23%. NICE alarming signs 1-18%.
[a]. Comorbidity: a chronic underlying condition that is expected to last at least 1 year. Complex comorbidity: a chronic condition in ≥2 body systems or malignancy or immunocompromised patients.
[b]. According to APLS cut-off values by age.
All comparisons p<0·001, except * = <0·05 and [ns] = not significant.

Table 2. "Red traffic light" symptoms (alarming signs) from the NICE guideline on fever and high-risk criteria from the NICE sepsis guideline.



[a] NICE fever guideline
[b] NICE sepsis guideline
[c] Defined as reduced consciousness
[d] defined as ill appearance

Figure 1: Adjusted odds ratios for younger children versus adolescents for diagnostic tests and therapy. [a]

[a] Younger children used as reference. Adjusted for hospital, sex, duration of fever, previous medical care, time of arrival and comorbidity.

To convert CRP values to nmol/L, multiply by 0·9524

Figure 2: Adjusted odds ratios for younger children versus adolescents for disposition and final diagnosis.[a]

[a] Younger children used as reference. Adjusted for hospital, sex, duration of fever, previous medical care, time of arrival and comorbidity.

Figure 3: Adjusted odds ratios for younger children versus adolescents for diagnostic tests and therapy, patients with comorbidity excluded.[a]

[a] Younger children used as reference. Adjusted for hospital, sex, duration of fever, previous medical care and time of arrival.

To convert CRP values to nmol/L, multiply by 0·9524

Figure 4: Adjusted odds ratios for younger children versus adolescents for disposition and final diagnosis, patients with comorbidity excluded.[a]

[a] Younger children used as reference. Adjusted for hospital, sex, duration of fever, previous medical care and time of arrival.

Figure 5: focus of infection in young children and adolescents

Data shown as percentages within the groups of young children and adolescents.
LRTI=lower respiratory tract infection; gastro-intestinal=gastro-intestinal and surgical abdomen; UTI=urinary tract infection, exanthems=exanthems and flulike illness; musculoskeletal=soft-tissue, skin and musculoskeletal infection.
LRTI (not shown in graphic) = lower respiratory tract infection: young children 54%, adolescents 42%.

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Ethics 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, ID:28-518ex15/16), Germany (Ethikkommission Bei Der LMU München, ID:699-16), Greece (Ethics committee, ID:9683/18.07.2016), Latvia (Centrala medicinas etikas komiteja, ID:14.07.201.6.No. Il16-07-14), Slovenia (Republic of Slovenia National Medical Ethics Committee, ID:0120-483/2016-3), Spain (Comité Autonómico de Ética de la Investigación de Galicia, ID:2016/331), The Netherlands (Commissie Mensgebonden onderzoek, ID:NL58103.091.16), United Kingdom (Ethics Committee, ID:16/LO/1684, IRAS application no. 209035, Confidentiality advisory group reference: 16/CAG/0136).

In all the participating UK settings, an additional opt-out mechanism was in place.

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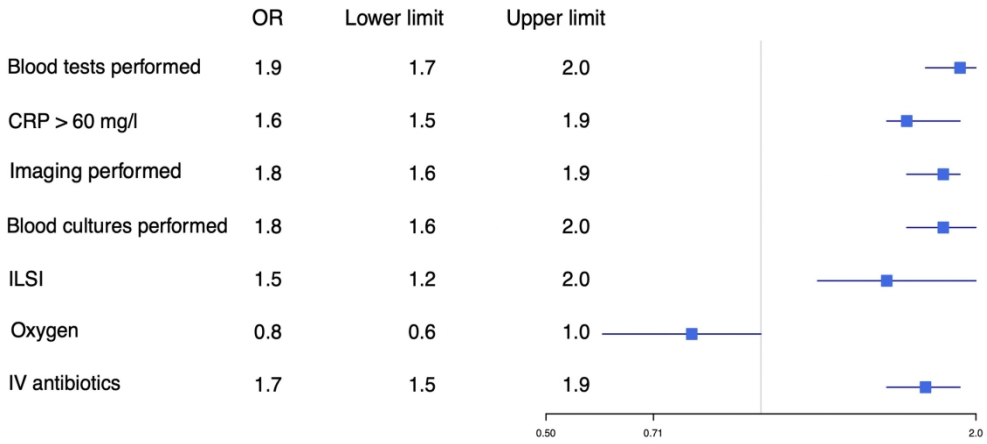

Figure 1

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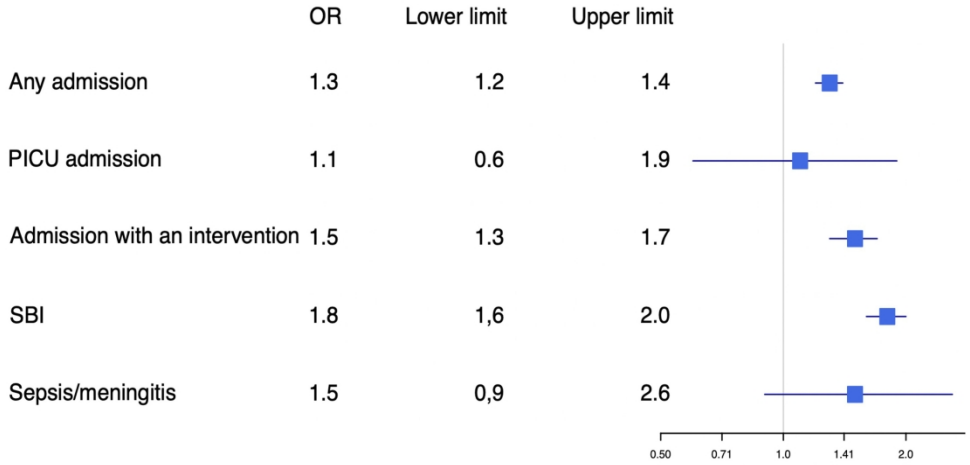

Figure 2

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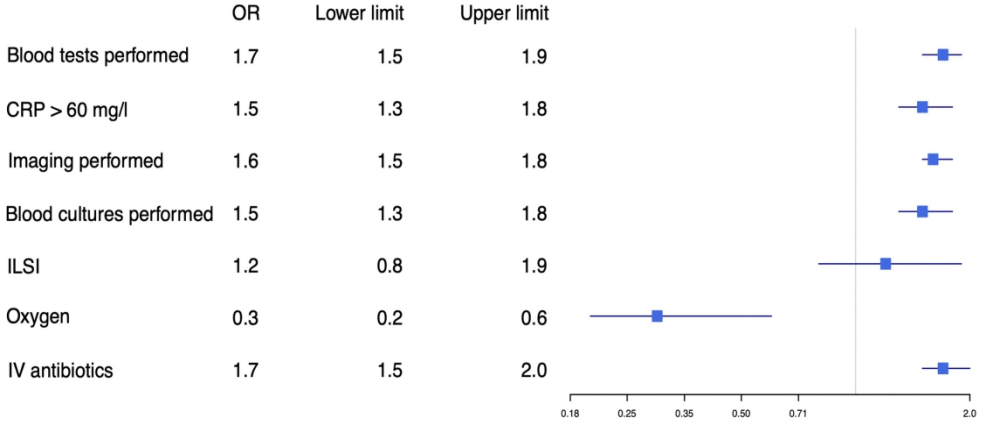

Figure 3

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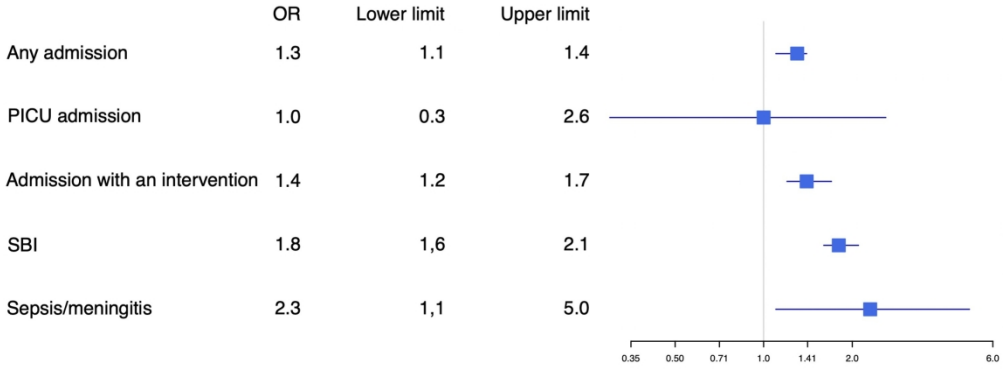

Figure 4

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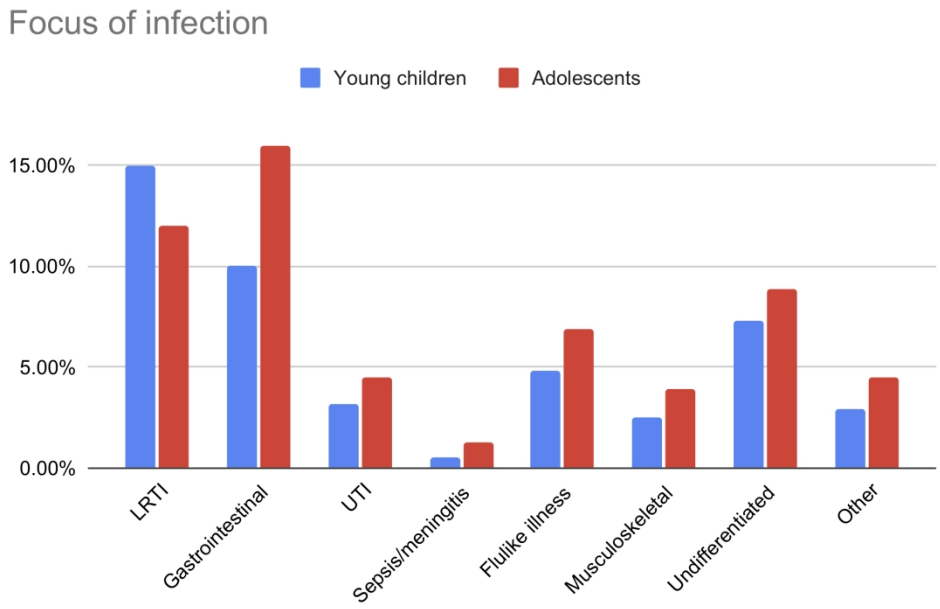

Figure 5

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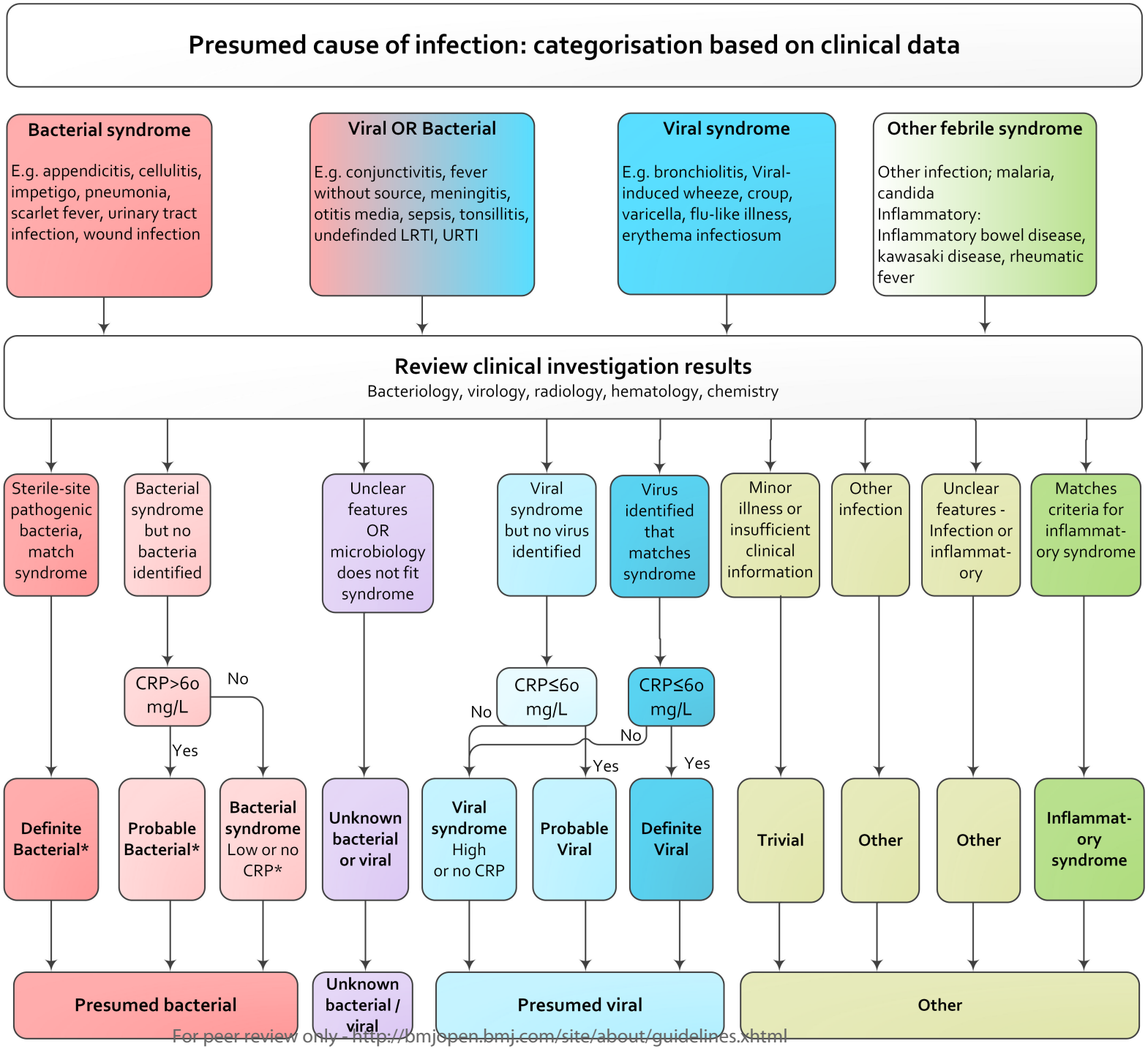
Appendix 2: Participating EDs

Hospital	Country, city	Hospital type	Total annual paediatric ED visits	Total period of inclusion	Period of inclusion per month	Number of patients included
Medizinische Universität Graz	Austria, Graz	University	10,000-30,000	1-1-2017 – 31-12-2018	10 days	2243
Dr. von Hauner Children's Hospital	Germany, Munich	Teaching	10,000-30,000	1-1-2017 – 31-12-2018	1 week	1175
P. and A. Kyriakou Children's Hospital	Greece, Athens	University	>30,000	1-1-2017 – 1-5-2018	1-2 weeks	4549
Children clinical university hospital	Latvia, Riga	Teaching	>30,000	1-1-2017 – 31-12-2018	All	9000
Univerzitetni Klinični Center	Slovenia, Ljubljana	University	<10,000	1-1-2017 – 31-12-2018	All	3659
Hospital Clínico Universitario	Spain, Santiago de Compostela	University	>30,000	1-1-2017 – 1-5-2018	1-2 weeks	3877
Erasmus MC-Sophia Children's Hospital	The Netherlands, Rotterdam	University	<10,000	1-1-2017 – 1-4-2018	All	1681
RadboudUMC	The Netherlands, Nijmegen	University	<10,000	1-1-2017 – 1-4-2018	All	676
Canisius Wilhelmina Ziekenhuis	The Netherlands, Nijmegen	Teaching	<10,000	1-1-2017 – 31-12-2018	2 weeks	415
Alder Hey Children's Hospital	United Kingdom, Liverpool	Teaching	>30,000	1-1-2017 – 31-12-2018	1 week	1624
St. Mary's Hospital	United Kingdom, London	University	10,000-30,000	1-1-2017 – 31-12-2018	All	5714
Great North Children's Hospital	United Kingdom, Newcastle upon Tyne	University	>30,000	1-4-2017 – 1-4-2018	2 weeks	3870

Appendix 3. Immediate life-saving interventions

1. Airway and breathing support, including intubation or emergent noninvasive positive pressure ventilation.
2. Electrical therapy, including defibrillation, emergent cardioversion, or external pacing.
3. Procedures, including chest needle decompression, pericardiocentesis, or open thoracotomy.
4. Hemodynamic support, including significant intravenous fluid resuscitation in the setting of hypotension, blood administration, or control of major bleeding.
5. Emergency medications, including naloxone, dextrose, atropine, adenosine, epinephrine, or vasopressors



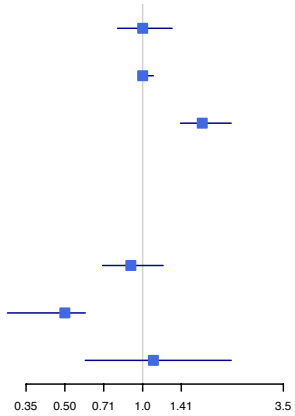
Appendix 5: Comorbidity.

	Children 3 months- 12 years N = 34,843 N (%)	Children > 12 years N = 2,577 N (%)
No comorbidity	28,881 (83·7)	1,833 (71·5)
Non-complex comorbidity	4,302 (12·5)	489 (19·1)
Complex comorbidity	1,332 (3·9)	241 (9·4)
Type of comorbidity		
Neurological & psychomotor delay	1,604 (28·5)	298 (40·8)
Pulmonary	1,224 (21·7)	182 (24·9)
Prematurity	945 (16·8)	20 (2·7)
Urological/nephrological	634 (11·3)	57 (7·8)
Malignancy & immunodeficiency	583 (10·4)	162 (22·2)
Cardiac	557 (9·9)	58 (7·9)
Gastro-intestinal	422 (7·5)	81 (11·1)
Musculoskeletal	171 (3·0)	55 (7·5)
Metabolic	165 (2·9)	53 (7·3)
Endocrine	63 (1·1)	27 (3·7)
Other comorbidity	729 (12·9)	83 (11·3)

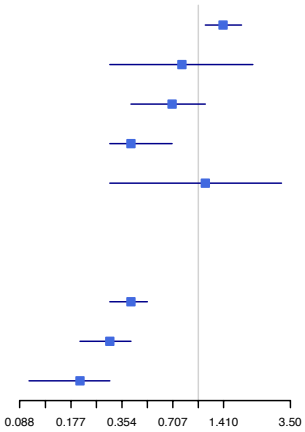
Type of comorbidity displayed as percentage of children with comorbidity.

Appendix 6: Differences in patient characteristics between young children and adolescents with a final diagnosis of SBI. [a]

	OR	Lower limit	Upper limit
General patient characteristics			
Triage urgency high	1.0	0.8	1.3
Referral by EMS	1.0	1.0	1.1
Comorbidity	1.7	1.4	2.2
Vital signs			
Tachycardia	0.9	0.7	1.2
Tachypnoea	0.5	0.3	0.6
Prolonged capillary refill	1.1	0.6	2.2



	OR	Lower limit	Upper limit
NICE fever guideline alarming signs			
Ill appearance	1.4	1.1	1.8
Non–blanching rash	0.8	0.3	2.1
Blanching rash	0.7	0.4	1.1
Increased work of breathing	0.4	0.3	0.7
Neurological signs	1.1	0.3	3.1
NICE sepsis guideline high risk criteria			
1 or more	0.4	0.3	0.5
2 or more	0.3	0.2	0.4
3 or more	0.2	0.1	0.3



[a] Younger children used as reference. Adjusted for hospital, sex, duration of fever, previous medical care, time of arrival and comorbidity. * According to APLS cut-off values by age.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
5Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	5 5
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	7
Objectives	3	State specific objectives, including any prespecified hypotheses	7
Methods			
Study design	4	Present key elements of study design early in the paper	8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	8
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	9,10
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	9,10
Bias	9	Describe any efforts to address potential sources of bias	11
Study size	10	Explain how the study size was arrived at	9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9,10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	11,12
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	12
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	12,13, 24
Outcome data	15*	Report numbers of outcome events or summary measures over time	12,13

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	11-13 27
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	13,14
Discussion			
Key results	18	Summarise key results with reference to study objectives	14,15
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	16,17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14-17
Generalisability	21	Discuss the generalisability (external validity) of the study results	16,17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Author statement form

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.