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Fever in infants below 2 months of age: clinical management and outcome

Degree Project in Medicine

Michelle B. Smith

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Supervisor: Kristina Elfving, MD
Department of Infectious Diseases
Institution of Biomedicine
Sahlgrenska Academy
University of Gothenburg

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List of abbreviations

AB	Antibiotics
ANC	Absolute neutrophil count
CFU	Colony forming unit
CoNS	Coagulase-negative staphylococci
CRP	C-reactive protein
CSF	Cerebrospinal fluid
FWS	Fever without source
Hpf	High power field
IBI	Invasive bacterial infection
IL-6	Interleukin-6
LP	Lumbar puncture
PCT	Procalcitonin
PED	Pediatric emergency department
SBI	Serious bacterial infection
UA	Urinalysis
URTI	Upper respiratory tract infection
WBC	White blood cell count

Abstract

Title: Fever in infants below 2 months of age: clinical management and outcome

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Author: Michelle Bäckman Smith, medical student.

Introduction: Fever in the young infant is a common reason for guardians bringing their newborn child to the emergency room. Neonates have a particularly high risk of developing serious bacterial infections (SBI) but classical signs or symptoms are often lacking. This has led to some controversy regarding management, testing and optimal treatment, i.e choosing between treating all or using clinical and laboratory parameters to decide on antibiotic treatment.

Aim: To describe management and physician compliance to existing guidelines of febrile young infants aged ≤60 days attending the pediatric emergency department (PED).

Method: Retrospective observational study based on medical records from patients ≤60 days of age with fever being their main reason for visiting the PED at The Queen Silvia Children´s Hospital in Gothenburg between 1st of January 2015 and 31st of December 2017.

Results: Of 625 infants included in the study 299 (47.8%) were hospitalized. 184 (29.4%) received antibiotics at initial approach, 44.6% in the 0-30 days of age group. 152 (24.3%) had a blood culture done and 86 (13.8%) infants had a lumbar puncture taken, 28.4% in the 0-30-day age group. In total, 10.6% (66/625) of all patients had an SBI. Majority (79%) had a pyelonephritis without an invasive bacterial infection. Leukocyturia was present in 54/65 (83%) of patients with an SBI in comparison with 71/457 (16%) that did not have an SBI (p=0.001). Two infants died.

Conclusion: Outcome for febrile infants at the PED in Gothenburg is favorable although more restricted management. A low frequency of lumbar punctures, antibiotic treatment and admission rate amongst the youngest infants and in the overall group was observed.

Background

Introduction

Fever is one of the most common causes for guardians to bring their child to the pediatric emergency department (PED) (1). This is even more important when it comes to newborn children because of their higher risk of serious bacterial infections (SBI) or invasive bacterial infections (IBI). Parents are therefore advised to bring febrile infants (temperature ≥38°C) to the PED by the child health care centers (2) because fever can be a sign of a serious bacterial infection (SBI) such as meningitis, bacteremia or urinary tract infection. Alternate definitions for SBI also include pneumonia, bone and joint infections, skin and soft tissue as well as bacterial enteritis in the term SBI (3, 4). IBI is defined as an isolated bacterial pathogen found in blood or in Cerebrospinal fluid (CSF) (5).

The clinical assessment of a newborn child can be difficult because of the differences in presentation. Infants with meningitis can present with minimal symptoms and appear well while others present with more typical symptoms like altered status, seizures or bulging fontanelle. Hence, it is difficult for medical personnel to manage these infants which has led to a rather low threshold to do extensive testing e.g. lumbar puncture (LP) and cultures from urine, blood and CSF, give empiric antibiotics (AB) and admit the infant to the ward (3). To assist decide which infant is at low risk for SBI and does not need this extensive evaluation there are several different criteria or guidelines to follow and they all vary with regard to laboratory evaluation and recommendation for administration of antibiotics. E.g. Rochester criteria (6) does not recommend LP or empiric antibiotics for low-risk patients while the NICE-guidelines (7) regards all infants under 3 moths and with a temperature of ≥38C at high risk and recommends LP in all cases for infants under 1 month of age and for 1-3 months of age for those who look unwell(8).

Even though there are a lot of different guidelines and criteria to use when assessing the risk that an infant has an SBI, the adherence has been low (3). The fact that medical personnel neither perform all recommended testing, nor give antibiotics or admit the infant when recommended has lately resulted in the guidelines being questioned because of the good outcomes for these children (9-11). The recommendations from the different criteria and guidelines could also lead to unnecessary and increased risks by invasive procedures, higher costs for medication and inpatient care as well as pain and added stress for the infant and its parents (12).

In Gothenburg this has not been studied or evaluated. Hence, analysis of management and outcome of febrile young infants in Gothenburg, Sweden is of great value not only for quality assurance but also to serve as base line data for possible future intervention studies

Evolution of clinical management

Previously, it was up to the caring physician of a febrile infant to decide which test and procedures to perform and whether the patient needs hospitalization and antibiotics. The recommendation at that time was often to perform a full work up in all febrile infants independent of laboratory tests and clinical picture. But in the 1990's several studies were made and new protocols were introduced for the management of febrile infants under 90 days of age with a fever without source (FWS): The Rochester- (6), Boston- (13) and Philadelphia criteria (14) were the most common and will be referred to as "the classic criteria" in this report. All three criteria recommend blood and urine test for risk evaluation of febrile children to be able to assign them as "low-risk patients". This means that they are at low risk for having an SBI with no need of further testing, antibiotic treatment or hospitalization and can leave the PED with advice about what their caregivers should be aware of (4, 6, 13, 14).

The criteria that need to be met in order to be classified as a “low risk patient” according to the different criteria are based on appearance at the PED visit, medical history, clinical examination and laboratory testing (table 1). The main differences between the different classic criteria are the need for invasive procedures such as LP and the differences in age. Rochester is the only one that includes infants under the age of 28 days (4) while the majority of the other guidelines recommends a full sepsis work up for these children.

Table 1 Definition of low-risk markers for SBI in classic clinical prediction models. Adapted and inspired by Hui et al (4)

Low-risk markers: Rochester-, Boston- and Philadelphia criteria

Criteria	**Rochester**	**Boston**	**Philadelphia**
Age (d)	≤ 60	28 – 89	29 - 56
Temperature (℃)	≥ 38.0 (rectal T*)	≥ 38.0 (rectal T*)	≥ 38.2 (rectal T*)
Medical history	• ≥37 weeks gestation at birth • No perinatal antibiotics • No treatment for unexplained hyperbilirubinemia • Not received nor receiving antimicrobial agents • No previous hospitalization • No underlying or chronic illness • Not hospitalized longer than mother at birth	• No antimicrobial agents within 48 hours • No immunization within 48 hours • No allergies to β-lactam antimicrobial agents	Not defined
Physical examination at ED	• Well appearing • No sign of skin, soft tissue, bone or ear infection	• Well appearing • No sign of skin, soft tissue, bone or ear infection	• Well appearing • Unremarkable examination
Laboratory values	• Peripheral blood WBC* 5 – 15 x 10^9cells/L • Absolute Band count ≤1.5 x 10^9cells/L • Urine WBC ≤10/hpf* • If diarrhea; stool smear ≤5 WBC*/hpf*	• Peripheral blood WBC* <20 x 10^9cells/L • UA* < 10 WBC*/hpf* • CSF* < 10 x 10^6 cells/L • Chest x-ray: no infiltrate (if obtained)	• Peripheral blood WBC* <15 x 10^9cells/L • UA* < 10 WBC*/hpf* • CSF* < 8 x 10^6 cells/L • Band-neutrophil ratio < 0.2 • CSF*: Gram stain negative • Urine: Gram stain negative • Stool: no blood, few or no WBCs on smear (if indicated) • Chest x-ray: no infiltrate
Management for low risk patients	Home or outpatient care No antibiotics Follow-up required	Home or outpatient care Empiric antibiotics Follow-up required	Home or outpatient care No antibiotics Follow-up required

** T =Temperature; WBC = white blood count; hpf = high power field; UA= urinalysis; CSF = cerebrospinal fluid*

After Rochester, Boston and Philadelphia criteria there have been a lot of studies on the management of the febrile infant with few new inputs on the management protocol. One of the more validated is the "Step-by-step" approach (15, 16). Newer studies have also evaluated the accuracy of new diagnostic tests like Procalcitonin (PCT) or C-reactive protein (CRP) that can be combined with parts of the classic protocols to help identify SBI in febrile infants and avoid excessive antibiotic treatment, hospitalization or invasive procedures like LP (9).

The "Step-by-step"-approach (15, 16) is one of the newer protocols that has been introduced in several PEDs. The purpose is to identify the infants at risk for IBI and select those who safely can be sent home from the PED without AB or LP (16).

It is, like the classic criteria, based on appearance at PED and age but also takes into account the following laboratory parameters; urinalysis (UA), CRP, PCT and absolute neutrophil count (ANC). Limits for age and laboratory values are shown in the flowchart displayed in figure 1.

The negative predictive value(NPV) and the sensitivity of the Step-by-step approach, Rochester-, Boston- as well as the Philadelphia criteria to identify SBIs have been shown to be quite high (NPV 89.7-100.0%, sensitivity 93.7-100.0%) but specificity and positive predictive value are generally in the lower range (4, 9, 14, 15). This means that

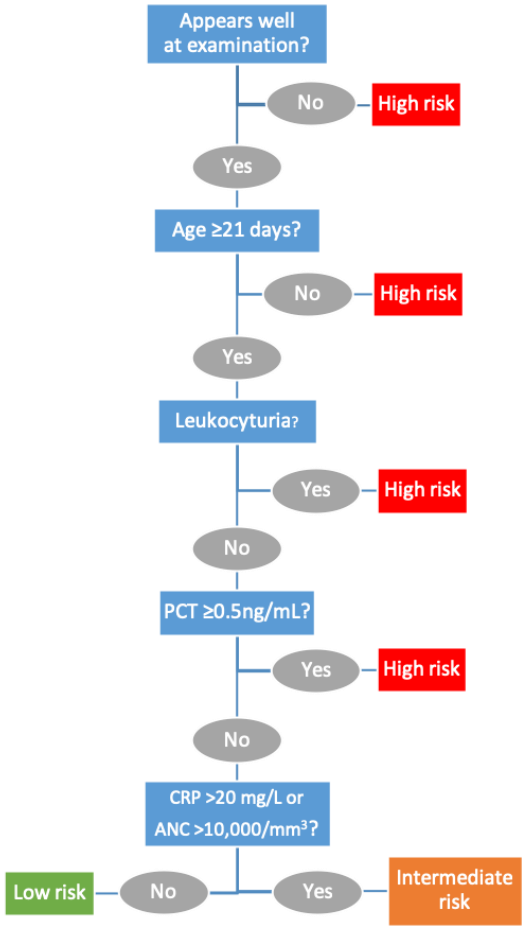

Figure 1 - The Step-by-step approach.
Image inspired from Mintegi et al (16)
PCT=procalcitonin; CRP= c-reactive protein; ANC=absolute neutrophil count

majority of the ill infants are in fact detected as ill upon testing as well as the healthy infants are detected as low risk infants by the different guidelines.

Role of diagnostic markers in ruling out SBI in febrile infants

CRP, PCT and Interleukin-6 (IL-6) are newer laboratory markers that have made their way into the evaluation of the risk of SBI in febrile infants, more specifically predicting if the infant has an SBI rather than identifying them as a low-risk patient (9). Neither of them are recommended as a single test for predicting SBI and an exact cut-off limit has not been determined for predicting the risk of an SBI in any of them. However, when they are combined with other markers and test like in the "Step-by-step" approach they might help to identify febrile infants with SBI (17-21).

CRP is an acute phase reactant that can be found in serum in a majority of bacterial-, viral- and other inflammatory illnesses (22). It is synthesized in the liver after 4-6h as a response to tissue injury or inflammation somewhere in the body and has its peak somewhere within 36-50h after first stimulus (23).

PCT is a precursor of calcitonin and it can be found in high levels in patents with bacterial infections. It has its peak at 12h and starts to rise already after 6-8h after the first sign of infection. This makes it easier to detect in higher concentrations earlier than CRP which has its peak several hours later (24, 25).

IL-6 is one of the markers that also might help with early detection of infectious disease in febrile infants (20). Being one of the proinflammatory cytokines that contributes to the production of CRP from the liver. It can also be detected in high levels in serum before CRP with a mean peak time of around 12h (19, 26).

Aim

The aim of this study is to describe the management and outcome of febrile infants visiting the pediatric emergency department in Gothenburg and further to compare it with international guidelines for febrile infants under 2 months of age.

Material and Methods

Study design and study population

This is a retrospective observational study which was performed at the Sahlgrenska Academy, University of Gothenburg with medical records collected from patients at the PED at The Queen Silvia Children´s Hospital in Gothenburg between 1st of January 2015 to 31st of December 2017. The total number of visits for infants ≤60 days during these years were 6381 and out of these there were 825 who had a fever as the main complaint when visiting the PED.

All included patients were ≤60 days of age and with a documented temperature of 38°C or above measured either at home (guardian report) or/and at the PED.

Exclusion criteria were: gestational age <35 weeks; severe congenital or acquired medical condition; hospital admission or antibiotic treatment in the proceeding ten days; temperature below 38.0°C; incomplete medical records (no registered or measured temperature); no encounter with a medical doctor

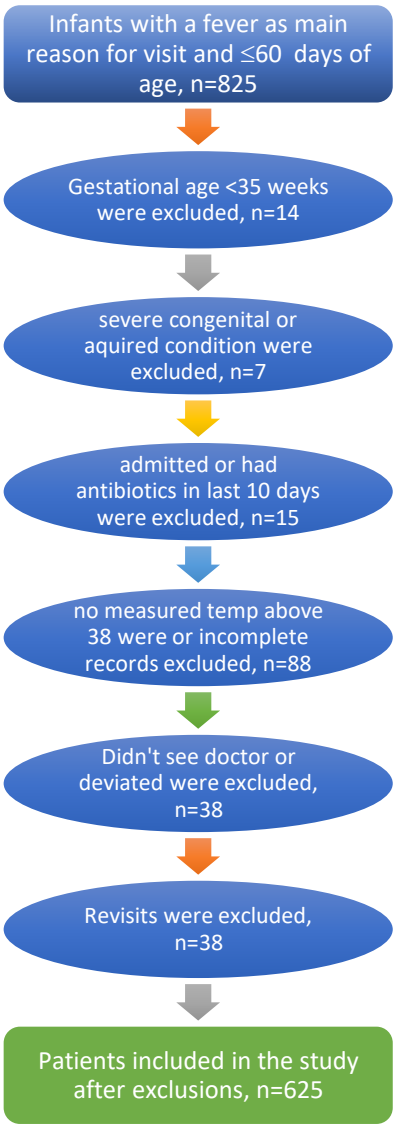

Figure 2 – Flow chart of the inclusion and exclusion process of patients in this study

before leaving the PED. Revisits were also excluded and registered as a follow up of the initial visit to the PED if visit took place in the previous 10 days.

Table 2 Definitions of terms and their meaning used during the collection of medical records of participants in this study

Study definitions	
Fever	Measured body temperature ≥ 38°C at home or at the PED
Fever without source (FWS)	Temperature ≥38.0°C measured at home or at the PED in well appearing patients with a normal physical examination without signs or symptoms from respiratory tract or skin.
Well appearing	Defined as physician not describing infants' condition as "not well" or "irritable" in analyzed medical records.
SBI:	Serous bacterial infection such as bacteremia, pyelonephritis or meningitis, also in combinations with each other.
Bacteremia	Isolated bacteria in blood culture (coagulase-negative staphylococci (CoNS) was considered contamination if not stated otherwise)
Pyelonephritis	Significant growth in a urine culture (E. Coli requires growth of ≥10,000 colony forming unit (CFU)/ml and a CRP ≥20 for diagnosis).
Meningitis	Elevated white blood cell count (WBC) in CSF or positive CSF culture.
Delayed SBI diagnosis	If SBI diagnosis was made after the initial approach i.e. at ward, at revisit or if the patient were sent home before diagnosis and treatment. This meant that the physician did not consider SBI as a possible diagnosis at first approach.
Final study diagnosis	Final diagnosis when discharged from the hospital as interpreted by author in analyzed medical records, mainly referring to FWS diagnoses. SBI assigned as written in medical journals if equivalent to the study definitions above.

Data collection

The patients in this study were all collected through a program called Cognos analytics. It uses the information from ELVIS (a patient registration program used by Sahlgrenska Hospitals) to collect and sort out a group of patient visits to the PED that match the study inclusion criteria; i.e. patient age ≤60 days of age and with a fever as the main complaint during 1st of January 2015 to 31st of December 2017. The patient visits matching these screening criteria were listed with social security number, date of visit and also date of discharge from ward if admitted.

The patient visits collected through our Cognos screening were all analyzed based on our inclusion and exclusion criteria listed above. All were anonymized and replaced with a study ID when the final group of included patient visits were completed.

The retrospective information collected systematically after inclusion was age, gender, vital signs and RETTS (rapid emergency triage and treatment system) assessment. Additionally, symptoms described by guardian, findings from physician's examination, laboratory values and initial- as well as final diagnosis and treatment were collected from medical records and registered in REDCap.

Statistical methods

To calculate and analyze results in this report SPSS version 25 (IBM Corp., Armonk, New York) was used. To calculate the significance for each variable Mann-Whitney U for non-parametric variables and Chi-square test were used for variations in laboratory testing, treatment, outcome and revisits. For other results like Gender, age or SBI descriptive and frequency statistics were used.

Ethics

The study was conducted according to the Helsinki Declaration and approved by the central ethical review board in Lund, Sweden (Dnr 2017/967 and 2018/831), since it is part of a larger national study. Because the study is retrospective the management and the information has already been collected and the author have no part in or need for information about future treatment of the patients. Each patient visit received a study ID upon inclusion which means the identity of the infant will not be registered by their social security number and will therefore be anonymous and unable to trace. This means that the main ethical problem that can be faced and need to consider is data mismanagement.

Results

Study group characteristics

Out of the 625 included infants 0-60 days of age, 44.3% (n=277) were female and 55.7% (n=348) were male. The median age of patients was 38 days and with a mean age of 37.4 days. Mean temperature at the PED was 38.3°C and 86.7% of the patients had a fever duration <24h and 69.4% <12h as shown in table 3.

Table 3 Fever duration before first examination in total study population, as described by parents.

	N (%)
<6 h	245 (39.2)
6-12 h	189 (30.2)
12-24 h	108 (17.3)
24-48 h	31 (5.0)
>48 h	18 (2.9)
Unknown	34 (5.4)
Total	625(100.0)

The majority, 77.9% (n=487) had a gestational age of 37-42 weeks, 3.7% (n=23) were born at 35-36 weeks and 3.5% (n=22) were born at >42 weeks. Also, 14.9% (n=93) were categorized as presumably term because lack of information in collected medical records and nothing else stated that the infant was premature.

Exclusive breastfeeding was the most common with 57.3% (n=358) of 625 infants, 23.4% (n=146) were partially breast fed, 11.4% (n=71) only using formula and lastly 8% (n=50) unknown.

Final study diagnosis

The three most common final study diagnoses were FWS, upper respiratory tract infection (URTI) and SBI. A total of 47.5% (n=297) of the study population were diagnosed as having a FWS, followed by 26.9% (n=168) having a URTI and 10.6% (n=66) diagnosed with SBIs, as shown in table 4. Pyelonephritis was the most common accounting for 78.8% of the SBIs, and the most frequent pathogen was *Escherichia coli.*

Table 4 Final study diagnoses in total population and percentage of each diagnosis amongst SBI group.

	N (%)	% of SBI
SBI: *	66 (10.6)	100.0
Pyelonephritis	52 (8.3)	78.8
Meningitis	2 (0.3)	3.0
Bacteremia	6 (1.0)	9.1
Pyelonephritis + Bacteremia	4 (0.6)	6.1
Meningitis + Bacteremia	1 (0.2)	1.5
Pyelonephritis + Meningitis + Bacteremia	1 (0.2)	1.5
FWS*	297 (47.5)	
URTI*	168 (26.9)	
Otitis	49 (7.8)	
Bronchiolitis	14 (2.2)	
Viral meningitis	11 (1.8)	
Pneumonia	5 (0.8)	
Influenza	4 (0.6)	
Gastroenteritis	2 (0.3)	
Skin infection	1 (0.2)	
Other [a]	8 (1.3)	
Total	625 (100)	

** SBI= Serious bacterial infection; FWS= fever without source; URTI = Upper respiratory tract infection*
[a]= viral infections, fever triggered by vaccination and transferred patients

The last group of patients mentioned as "other" referring to patients with conditions like varicella zoster, viral encephalitis, fever triggered by vaccinations, hand, foot and mouth disease or roseola infantum. Additionally, patients being transferred to other hospitals without proper final diagnosis in reviewed medical journals were also identified as other diagnosis.

17.6% (n=110) infants out of 625 were initially treated as an SBI with empirical antibiotics, but only 51.8% (57/110) out of these had an SBI as final study diagnosis at discharge from the hospital. 30/62 in the younger age group (0-30 days) and 27/48 in the older age group (31-60 days).

Nine out of the 66 patients who received an SBI diagnosis as final study diagnosis were not considered as having an SBI at initial approach. On the other hand, 64 out of 66 SBI patients received AB at initial approach. 64 had no clinical focus and 2 had upper respiratory tract focus at physical examination at first visit.

Four out of 66 (6.1%) received their diagnosis and the appropriate treatment after initial approach. Two bacteremia, both got empirical antibiotics from the ED but were sent home without AB the morning after because they were well-appearing. They were both later admitted and treated with AB because of positive blood cultures (GBS and GAS). Also, there were one meningitis where AB first was initiated after admission. Lastly, one pyelonephritis who had visited the ED the day before admission but was sent home without treatment. All four were well at discharge from the hospital.

There were two deaths (0.3%), of whom one patient had a sepsis and meningitis and one a pneumonia. One of them was later found to be born with asplenia. The patient who had sepsis and meningitis was given meropenem upon initial approach. The patient with pneumonia received antibiotic treatment upon revisit to the PED.

SBI vs Non-SBI patients

There was a significant difference in mean as well as median temperature (p-value <0.001) and pulse at first examination (p-value <0.008), first CRP (p-value <0.001), first IL-6 (p-value <0.001), as well as WBC (p-value <0.001) (table 4).

Also, leukocyturia was present in 54/65 (83%) of patients with an SBI and in 71/457 (16%) that did not have an SBI (p=0.001).

The non-SBI patients with leukocyturia (n=71) were diagnosed and distributed as 43 patients with FWS, 16 URTI, 1 gastroenteritis, 1 skin infection, 9 otitis as well as 1 roseola infantum.

Table 5 Difference in mean temperature, CRP, IL-6, WBC, pulse, respiratory rate and saturation between the SBI and non-SBI group at first examination at PED.

	SBI group, mean/median (n)	Non-SBI group, mean/median (n)	P-value [a]
Mean/median temperature at PED (℃)	38.8 / 38.9 (66)	38.2 / 38.2 (557)	< .001
Mean/median CRP	51.3 / 45.5 (66)	7.2 / 0.0 (476)	< .001
Mean/median IL-6	684.3 / 98.5 (46)	276.7 / 31.9 (365)	< .001
Mean/median WBC	13.8 / 14.0 (52)	9.1 / 8.3 (377)	< .001
Mean/median pulse	170.2 / 171.0 (60)	163.5 / 163.0 (537)	0.008
Mean/median respiratory rate	54.8 / 55.5 (30)	52.6 / 52.0 (295)	0.468
Mean/median saturation	97.6 / 98.0 (61)	97.9 / 98.0 (539)	0.212

[a]= P value determined by Mann-Whitney U test

CRP=c-reactive protein; IL-6=interleukin-6; WBC= white blood cell count; PED=pediatric emergency department

Variations in management

Variations in management of febrile young infants 0-60 days of age divided into age-groups are listed in table 6. The majority in both age groups had only urine analysis (urine dipstick by clean catch or suprapubic puncture) performed with 49.3% in the ≤30 days group and 68.8% in the 31-60 days group. The difference in proportions in admission between the two age groups were almost inverted with 66.5% in the ≤30 days group being admitted while it was only 38% in the 31-60 days group.

29.4% (184/625) of the infants were treated with AB at first approach and 33.4% (209/625) got AB sometime during their stay at the hospital regardless if they were sent home or admitted. 44.7% (96/215) of the younger infants got AB at first approach.

The most prescribed or used antibiotics amongst the 625 patient visits was cefotaxime at 7.2%, penicillin V at 6.2%, followed by Ceftibuten at 5.9% and Meropenem at 4.2%. Antibiotics used

in hospitalized patients are shown in table 5. Most prescribed antibiotics in the group sent home from PED (n=33) were penicillin V (n=30) followed by ceftibuten (n=2) and erythromycin (n=1)

In the total population, 13.8% (86/625) had a lumbar puncture taken, 28.4% in the younger age group. 24.3% (152/625) had a blood culture done, 83.5% (522/625) had a urine dipstick and 24.2% (151/625) of the patients had a urine culture done.

Table 6 Patient-level variation in management and outcome of patients ≤ 60 days with fever at The Queen Silvia Children´s Hospital.

	Total (n=625), n (%)	*≤30 days (n=215), n (%)*	*31-60 days (n=410), n (%)*	*P-value* [h]
Laboratory testing [a,d]				
Urine + Blood + CSF	69(11.0)	50(23.3)	19(4.6)	<.001
Urine + Blood	62(9.9)	30(14.0)	32(7.8)	0.015
Urine Only	388(62.1)	106(49.3)	282(68.8)	<.001
Other combinations of urine, blood, CSF	24(3.8)	14(6.5)	10(2.4)	0.012
None	82(13.1)	15(7.0)	67(16.3)	0.001
Treatment [a]				
AB at first approach	183(29.3)	95(44.2)	88(21.5)	0.018
Hospitalized: [f]				
AB at first approach	150(50.2)	86(60.1)	64(41.0)	<.001
AB at ward	25(8.4)	14(9.8)	11(7.1)	0.20
No AB	124(41.5)	43(30.1)	81(51.9)	0.947
Type of antibiotic: [i]				
Cefotaxime	52(29.7)	27(27.0)	25(33.3)	
Ceftibuten	37(21.1)	12(12.0)	25(33.3)	
Meropenem	27(15.4)	22(22.0)	5(6.7)	
Cefotaxime + Gentamycin	13(7.4)	10(10.0)	3(4.0)	
Cefotaxime + Ampicillin	13(7.4)	11(11.0)	2(2.7)	
Other PO or IV combinations	33(18.9)	18(18.0)	15(20.0)	
Discharged from PED: [e]				
AB at first approach	33(10.1)	9(12.5)	24(9.4)	0.529
No AB	293(89.9)	63(87.5)	230(90.6)	<.001
Acyclovir [g]	12(1.9)	9(4.2)	3(0.7)	0.003
Outcome [b]				
Hospitalized	299(47.8)	143(66.5)	156(38.0)	<.001
Home	326(52.2)	72(33.5)	254(62.0)	<.001
Revisits [c]				
10-d revisit [e]	56(17.2)	13(18.1)	43(16.9)	0.353
10-d revisit resulting in hospitalization [e]	19(5.8)	5(6.9)	14(5.5)	0.427

[a]= *testing or treatment performed at PED, ward or revisit*
[b]= *outcome of first initial PED-visit*
[c]= *revisits within 10 days, planned or not planned.*
[d]=*urine testing defined as urine dipstick, urine culture or UriCult; blood testing as blood culture; CSF as cell count, culture or lumbar puncture.*
[e]=*Percentage among discharged patients after first PED-visit.*
[f]= *Percentage among hospitalized patients after first PED-visit.*
[g]= *Percentage among total study population*
[h]= *P-value determined by Chi-square test*
[i]= *Percentage among hospitalized patient that received antibiotic treatment.*
PED=pediatric emergency department; AB=antibiotics

Discussion and conclusion

This study included 625 febrile newborns under the age of 60 days visiting the pediatric emergency department in Gothenburg. The study presented a low frequency (13.8%) of LP as well as a low frequency (29.4%) of AB treatment in the overall group. Moreover, the frequency of LP among the younger infants (0-30 days) were 28.4% and barely 60.1% of the hospitalized 0-30-day patients got treated with AB. Despite the low frequency of LP in this study there were no missed cases of meningitis, which may imply that excessive testing like LP for all 0-30-day febrile infants might be unnecessary when well-appearing and without other clinical signs.

The most frequent final study diagnosis was fever without source with 47.4%, followed by upper respiratory tract infections at 26.9%. In other words, the majority of the patients visiting the PED with fever as main complaint had no SBI. SBI were only diagnosed in 10.6% of the population. These 10.6% were distributed as 8.3% pyelonephritis, 1.0% bacteremia and 0.3% meningitis and 1% consisting of different combinations of the three. The percentage of SBIs in this study were in the lower range compared to other big studies with similar inclusion criteria who had SBI frequencies between 8.4 - 22.4%. The main difference seen in frequency of pyelonephritis patients and the different definitions of SBI can be because this study included all febrile infants from the PED not just the ones diagnosed as FWS (10, 14, 16, 27-29).

Pyelonephritis represented the majority of SBI diagnoses in all analyzed age groups. The higher percentage in this study compared to other studies (10) can be explained by the definition for urinary tract infection or pyelonephritis. Our study included infants with a CFU above 10,000 and a CRP ≥20 when *Escherichia coli* was found in positive urine cultures whereas other studies have a limit of >100,000 CFU or 50,000 CFU together with an abnormal urine analysis (30). The different limits regarding culture results therefore might be a reason for the difference in results but the main reason might also be the limit for CRP in this study.

Nonetheless, pyelonephritis represented the vast majority of the SBI diagnoses, 83% of the SBI patients had leukocyturia compared to 16% amongst the non-SBI patients. This should imply the importance of urine analysis, i.e. a negative result reduces the risk of the infant having an SBI. Importantly, it also helps the treating physician make a correct diagnosis with a simple and sometimes non-invasive test, since most of our urine analyses are performed by clean catch urine samples. The recommendation for some type of urine test is also concluded and recommended by Jaskiewicz et al(6), Baker et al(14) as well as the NICE-guideline (8).

Furthermore, the overall hospitalization rate for this study was 47.8%. Though, it was 66.5% in the younger age group and 38.0% in the older age group. The more frequent hospitalization of infants up to 30 days of age may stem from the majority of the international guidelines, except the Step-by-step approach, recommending hospitalization for all infants in this age group as well as AB treatment or that the perceived risk of SBI is higher than in the 31-60-day group. This probably also explains the difference in antibiotic treatment amongst the hospitalized patients (29).

Variation in laboratory testing also shows that physicians are more prone to do a full work up with urine-, blood- and CSF cultures on the younger population. Still the frequency of hospitalization and AB treatment among 0-30 day of age hospitalized infants is lower in this study than in other international studies with a frequency between 79.4-96.1% in AB treatment and a 78.3-83.6% hospitalization rate (3, 10, 29).

Overall, the study shows that infants with SBI are found and treated at the PED in Gothenburg regardless the lack of a set guideline to follow for febrile infants under 60 days of age. The majority of the patients had their vitals taken: temperature, pulse and saturation. As well as WBC, CRP and IL-6 analyzed at first approach. In comparison to the classical criteria introduced earlier in this report the results show that when it comes to medical evaluation the

only criteria that are in some way followed are the Rochester criteria because the lack of invasive procedures while Boston- and Philadelphia criteria recommend LP.

The "Step-by-step" approach recommends urine test, PCT, CRP or ANC which are done for a high number of patients at the PED in Gothenburg except for the PCT test which was done in 1 out of the 625 patients. PCT (24, 25) and IL-6 (19) has similar peak time and are both recommended as tests for predicating infectious disease making them comparable and in this study IL-6 seems to be the test of choice.

Consequently, making it clear that when PCT are replaced by IL-6 testing the "step-by-step" approach are the guideline closest to the type of evaluation used at the PED in Gothenburg for febrile children under 60 days of age with fever as main complaint. If IL-6- or CRP levels are high physicians may continue with SBI evaluation as cultures and other testing as well as antibiotic treatment. While if IL-6- or CRP levels are low in otherwise well-appearing infants they are usually discharge from the PED with parental advice and a low threshold for revisits.

Strengths and limitations

Retrospective studies such as this one has a couple of disadvantages, one being that it is impossible to control the assessment and outcome that was done for each patient. Only trusting notes from medical records, which can vary in quality and can easily be misinterpreted. Also, the fact that the same patient could be evaluated differently by two different medical doctors.

Another disadvantage is that the reviewing of medical records can be colored by the reviewer and when this is done by several people, in this case two different persons, some factors can be interpreted in different ways.

Thirdly, our inclusions criteria of only including patients with fever being their main complaint when visiting the PED makes it possible for SBI patients being missed because they were registered under other complaints in ELVIS when visiting the PED.

Strengths of this study are that all included patients visited the same PED which makes it easier to assume that the evaluation of each patient were more consistent than if it were several different PEDs, which also was seen in the results showing significant difference in treatment between the different age groups but similar management amongst them.

Secondly, the number of included patients is a strength because we could see trends and differences amongst the whole population as well as between the age groups.

More strengths are that this is, to our knowledge, one of the first studies of its kind in Sweden and Gothenburg showing significant trends of management. It can be used when composing the necessary prospective studies needed in this field in the future, hopefully resulting in new guidelines for febrile infants under 60 days of age.

Conclusion

Outcome for febrile infants at the PED in Gothenburg is favorable although more restricted management with low frequency of lumbar punctures, antibiotic treatment and admission rate amongst the youngest infants as well as in the overall group was observed compared to other international studies.

Populärvetenskaplig sammanfattning

Feber hos barn under 2 månaders ålder: klinisk handläggning och utfall

Feber är en utav de vanligaste anledningarna till att småbarn besöker akutmottagningen. Rekommendationer från BVC och annan vårdpersonal ser ut på detta sätt då spädbarn har en hög risk för svåra bakteriella infektioner, ett begrepp som innefattar potentiellt livshotande tillstånd. Detta innefattar bland annat sjukdomar där dåliga bakterier till exempel har tagit sig till hinnorna som omger hjärnan, till njurarna eller att de går att hitta i blodet och därmed gör oss sjuka.

Läkare har idag en stor utmaning i att urskilja dessa sjuka barn och bestämma vilka som är säkra att skicka hem utan fler undersökningar och vilka som bör genomgå fler tester. Svårigheten i att ta emot dessa barn ligger i att barnen inte alltid visar upp typiska tecken eller visar väldigt vaga sådana trots allvarlig sjukdom.

För att underlätta denna utmaning finns det diverse riktlinjer som läkarna kan följa. Vissa rekommenderar ryggvätskeprov och antibiotikabehandling medan andra riktlinjer ser att barn som ej uppvisar avvikelser på blodprover eller fysisk undersökning bör skickas hem utan antibiotika men med uppföljning samt råd till föräldrarna.

Även fast det finns olika riktlinjer som ska underlätta för läkarna så följs dem inte i de flesta fall. Trotts det har det inte varit något större antal ”missade” barn med dessa allvarliga tillstånd vilket har lett till att riktlinjerna har börjat ifrågasättas.

Vårt syfte med denna studie var därför att undersöka handläggningen och diagnoserna hos spädbarn med feber under två månaders ålder vid Göteborgs barnakut.

Studien bestod av 625 spädbarn med sökorsak feber som besökt barnakuten mellan 1 januari 2015 och 31 december 2017. Faktorer som undersöktes var bland annat: ålder, temperatur,

prover, inläggningsfrekvens, antibiotikabehandling, diagnos och om det skedde något återbesök samt resultatet av detta. Analyser genomfördes både genom att jämföra handläggning mellan barn i 0-30- samt 31-60 dagars ålder samt de med slutdiagnos svår bakteriell infektion mot de med andra diagnoser.

Av de 625 inkluderade barnen så lades 48% in på avdelning och 29% fick antibiotika efter första besöket på akuten. 14% av hela gruppen genomgick ett ryggvätskeprov, motsvarande siffra i den yngre gruppen var 28%. 11% hade en svår bakteriell infektion, vanligast var infektion i njurarna som stod för 79% av dessa. Vi såg också betydande skillnader i genomförda undersökningar mellan de yngre och de äldre barnen i både provtagning, inläggningar och antibiotikabehandling.

Slutsatsen av denna studie är att läkarna vid barnakuten i Göteborg följer de internationella riktlinjerna med viss modifikation. Också att de handlägger spädbarn med feber på ett sådant sätt som ändå gör att de svåra infektionerna upptäcks och att barnen får rätt behandling. En annan sak var även att det genomförs betydligt färre ryggvätskeprov samt att Göteborgs barnakut har en lägre frekvens av antibiotikabehandling jämfört med annan internationell barnakutsjukvård.

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