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Serious Bacterial Infections in Febrile Infants Below Two Months of Age, in Gothenburg, Sweden

Degree Project in Medicine

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Abstract

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Background: Fever is a common reason for pediatric emergency department visits. The frequency of serious bacterial infections (SBI) in febrile infants is estimated, in international studies, to 6.8 – 22.4%. Recent studies have reported a shift in the epidemiology over the last decades with an increased incidence of pyelonephritis caused by *Escherichia Coli* and a decrease of bacteremia and meningitis. Other common causes of fever are otitis and upper respiratory tract infections, while it is common that no obvious cause is identified.

Aim: To describe etiologies and prevalence of SBIs in febrile infants \leq 2 months of age presenting to the pediatric emergency department in Gothenburg, Sweden.

Method: Medical records of infants \leq 60 days from 2015, 2016 and 2017, with fever as main complaint, were retrospectively examined. SBI was defined as pyelonephritis, bacteremia, meningitis.

Results: Out of 625 included patients, 66 (10.6%) had an SBI. Pyelonephritis was found in 52 (78.8%), bacteremia in six (9.1%), meningitis in two (3.0%) of the 66 SBI cases respectively and in six (9.1%) cases were a combination of SBIs found. *E. Coli* was identified in 49 (94.2%) cases of pyelonephritis, in one (16.7%) case of bacteremia and in five (83.3%) of combined cases. Other commonly identified causes were upper respiratory tract infections (168; 26.8%) and otitis (49; 7.8%). No focus of infection was identified in 297 (47.5%) cases.

Conclusion: The SBI prevalence of 10.6% corresponds well with what is previously seen in international studies. E. Coli was the most dominant pathogen. Benign causes were found in three quarters of cases.

Key words: Serious bacterial infection, infant, fever, etiology

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List of abbreviations

CSF – cerebrospinal fluid

GAS – Group A *Streptococcus*; *Streptococcus pyogenes*

GBS – Group B *Streptococcus*; *Streptococcus agalactiae*

HiB – Hemophilus Influenzae type B

IAP – Intrapartum antibiotic prophylaxis

LP – Lumbar puncture

N – Number of observations

PED – Pediatric emergency department

SBI – serious bacterial infection

SD – Standard deviation

PCR – polymerase chain reaction

URT – upper respiratory tract

Introduction

Fever is a common reason for pediatric emergency department (PED) visits among young infants and may be a symptom of a variety of different conditions [1] but elevated temperatures may also be caused by daytime activities such as feeding or playing [2]. Bacterial infections is a known cause of fever and occurs when macrophages, as a response to different bacterial structures, release interleukin 1 into the bloodstream which stimulate the temperature regulating center in the hypothalamus [3, 4]. In Sweden, the national medical information center (1177 Vårdguiden) [5] recommends that all febrile infants (temperature above 38.0 °C) should contact a primary care center or a PED.

Bacteremia, meningitis and pyelonephritis are the most feared causes of fever and are usually referred to as serious bacterial infections (SBI) [6]. SBI is commonly defined as bacteremia, meningitis or pyelonephritis. The identification of infants with SBI is a highly debated subject and several different protocols to detect SBI have been presented. Most of these protocols focus on identifying infants with a low risk of SBI [7]. Other reasons for fever among infants are viral infections such as bronchiolitis, influenza and viral meningitis but also pneumonia, gastroenteritis and otitis. Many infants though, present to the PED with no focus of infection and the fever is self-limiting without any intervention.

Several studies report that the etiology of SBIs have changed over the last decades [7-9] with *Escherichia coli* being the most dominant pathogen. The overall SBI prevalence has not changed though. The reason for this is not fully understood but vaccinations against *Streptococcus pneumoniae* and *Hemophilus influenzae* type B (HiB) together with intrapartum antibiotic prophylaxis (IAP) against *Streptococcus agalactiae* (Group B streptococcus; GBS) is thought to have contributed to this change [7].

Serious bacterial infections

During the last forty years several studies have been published with the focus on SBIs in infants, mostly in the US, where the first sets of diagnostic criteria for identification of SBIs were published. Early diagnostic criteria were the Rochester [10], the Philadelphia [11] and the Boston [12] criteria which all focused on identifying young infants with a low risk of having SBIs. These protocols focused on febrile infants although the age span for which they were designed for varied. The Rochester criteria were the least invasive of these protocols and relied mostly on peripheral white blood cell count and a urine analysis, while the other two required a lumbar puncture. Moreover, the Boston criteria required a chest radiograph and intra muscular antibiotic treatment for the low-risk group.

Data on the prevalence and etiology of SBIs from this period is well summarized by Baskin [13] in a review article, published 1993. A total of 11 reports studying SBIs in infants below 90 days of age, were included in this review. The total prevalence of SBI in the included studies was 7.2% and the prevalence of bacteremia or meningitis was 2.5%. GBS were the leading cause of bacteremia and meningitis, followed by *E. Coli*, *Salmonella* spp. and *streptococcus pneumoniae*. In pyelonephritis cases *E. Coli* was the dominant pathogen followed by *Klebsiella* spp., GBS and *Enterococcus* spp.

A study conducted by Watt et al [9], which included all infants < 90 days old who had a blood culture performed during 1997 – 2006 showed an overall SBI prevalence of 10.8%. The study results were also presented in two five-year periods (1997 – 2001 and 2002 – 2006) with a prevalence of 6.5% and 14.4% respectively. During 1997 – 2001, 4.2% of the included infants had a pyelonephritis (84.6% caused by *E. Coli*) whereas during 2002 – 2006 12.2% had a pyelonephritis (91.5% caused by *E. Coli*). The authors were surprised by these results and did not have a clear explanation for this observed epidemiological change but speculated in if this

were either caused by IAP against GBS or a new strain of *E. Coli* with more uro-pathological properties.

In the last two decades several new biomarkers for infections have been identified such as C-reactive protein, procalcitonin and interleukin 6 which are all equal or superior to white blood cell count and absolute neutrophilic cell count in the identification of SBIs [14-18]. Implementation of these in different sets of criteria have been made. Such criteria are the Lab-score [19-21] and the Step-by-step method [22, 23]. Both systems relay on results of C-reactive protein, procalcitonin and urine dipsticks while the Step-by-step method also consider age and absolute neutrophilic count.

Table 1. SBI prevalence in published studies conducted on mostly febrile infants.

<i>Authors</i>	<i>Country</i>	<i>Studied period</i>	<i>Age of infants</i>	<i>Number of infants</i>	<i>Prevalence of SBIs, %</i>
<i>Nicholson et al [24]</i>	USA	2015 – 2016	0 – 90	104	16
<i>Carmon et al [25]^c</i>	Israel	2013 – 2014	2 – 60	623	25.2
<i>Zarkesh et al [18]</i>	Iran	2012 – 2013	0 – 90	195	14.9
<i>Milcent et al [26]^c</i>	France	2011 – 2014	0 – 90	2,047	6.8
<i>Aronson et al [27]</i>	USA	2011 – 2013	0 – 89	35,070	8.4
<i>Gomez et al [22]^b</i>	Italy, Spain & Switzerland	2008 – 2017	0 – 90	2,185	23.1
<i>Mintegi et al [23]</i>	Italy & Spain	2008 – 2010	0 – 90	1,123	22.4
<i>Greenhow et al [8]^a</i>	USA	2005 – 2011	7 – 90	6,232	13.5
<i>Bilavsky et al [14]^c</i>	Israel	2005 – 2008	0 – 90	892	11.4
<i>Mintegi et al [28]</i>	Spain	2003 – 2016	0 – 90	2,470	18.8
<i>Garcia et al [6]^b</i>	Spain	2003 – 2010	0 – 90	1,575	19.7
<i>Watt et al [9]^b</i>	USA	1997 – 2006	0 – 90	668	10.8
<i>Byington et al [29]</i>	USA	1996 – 2002	1 – 90	1,385	9.5
<i>Baker et al [11]</i>	USA	1987 – 1992	29 – 56	747	8.7
<i>Jaskiewicz et al [30]</i>	USA	1984 – 1992	0 – 60	931	8.5

^a – included non-febrile infants; ^b – only results for infants with no focus of infection after examination; ^c – only included hospitalized infants; SBI – serious bacterial infection.

As seen in *Table 1* the prevalence of SBIs has been extensively studied during the last two decades with reports from Israel, Iran, Italy, Spain, France and the US. The prevalence of SBIs span from 6.8 to 25.2% in the more recent studies but the study designs varies. Regarding the etiology of SBI several studies [8, 14, 24-26] report that pyelonephritis is the most common

SBI type and *E. Coli* is the most commonly found pathogen. The rate of isolated pyelonephritis and of isolated bacteremia is 75 – 85% and 5 – 25%, respectively. *E. Coli* is found in approximately 90% of urine cultures and 60% of blood cultures in studies from the US [8, 24] and France [26]. Compared with data from Israel [14, 25] is this remarkably high, as *Enterobacter* spp. and *Klebsiella* spp. is found in almost 20% of positive urine cultures, each, while *E. Coli* is found in 60 – 75% of urine cultures.

Serious bacterial infections in Sweden

There are very few published studies regarding SBI in Swedish populations, one of the few was published in 1990 by Tessin et al. [31] and conducted in 1975 to 1986 in the Gothenburg area. The study included all patients younger than 28 days who had a blood culture performed. GBS was the most common pathogen. Other common pathogens were *S. Aureus*, *E. Coli* and *Klebsiella pneumoniae*.

Changing epidemiology

As previously mentioned several different strategies have been used to decrease some of the most common and dangerous pathogens, like HiB and *S. pneumoniae* vaccination [32-36], as well as intrapartum antibiotic prophylaxis against GBS in mothers [9, 35, 37-39].

Vaccinations

Immediately after vaccination against HiB was introduced 1992 in Sweden [36], the incidence of HiB infections dramatically decreased in children younger than 4 years [34]. The decrease was somewhat more pronounced in cases of meningitis than bacteremia cases, 92% and 83%, respectively, when compared to a period prior to the introduction. Similar reductions of HiB incidence, in the same age group, were seen in both the UK and US [40, 41].

Vaccination against *S. pneumoniae* were, in Sweden, introduced nationwide 2009 [36]. In both Sweden and the US, a decrease of invasive *S. pneumoniae* cases were seen among vaccinated infants after the first introduction [33, 42]. The effects of both vaccination against HiB and *S.*

pneumoniae, with data from Umeå in northern Sweden, was published in 2019 [43]. This study found that the effects of both vaccines were sustained several years after introduction. The decrease in all cause HiB and *S. pneumoniae* infections were 89.1% and 84.7% respectively, among infants 0 – 4 years old.

Intrapartum antibiotic prophylaxis

Risk factor based (previous pregnancy with GBS infection, GBS in urine during the pregnancy, premature birth, prolonged membrane rupture or fever during delivery) IAP were nationally introduced, in Sweden, 2008 [39]. The introduction almost immediately decreased the incidence of early onset (infection within the first week after birth) GBS infections with approximately 50% amongst the infants to mothers with risk factors [39]. The effects of IAP have been questioned in a recent Cochrane review [38]. This review concluded that IAP should be studied in double blinded clinical trials. The opportunity to conduct such study is however probably lost, according to the authors, due to the widespread usage of IAP nowadays.

Aim

To accurately, and safely, diagnose and treat febrile young infants it is important to know the cause of fever. The lack of recent studies, conducted on Swedish infants, led to the design of this retrospective study with the overall aim to describe the etiology of SBIs. The material may also be used to create a new set of clinical guidelines and/or an intervention study for febrile infants.

As part of this study, this degree project aims to analyze the febrile infants < 2 months of age at The Queen Silvia Children's Hospital regarding infectious disease etiology, and prevalence, of serious bacterial infections and other causes of fever.

Specific research questions

This report aims to answer three specific research questions regarding febrile infants up to two months old (≤ 60 days) presenting at the pediatric emergency department in Gothenburg, Sweden; what is the frequency of serious bacterial infections? What is the infectious etiology of serious bacterial infections? What is the cause of fever in infants that do not have a serious bacterial infection?

Materials and Methods

Study design and setting

This study was conducted as a retrospective observational study with a studied period of three years, from January 1st, 2015 to December 31st, 2017, and was conducted at The Queen Silvia Children's Hospital, in Gothenburg, Sweden. The Queen Silvia Children's Hospital is a tertiary university hospital completely dedicated to pediatric care and it is the only pediatric hospital in the Gothenburg area.

Study population

The studied population were all infants 60 days old or younger who had fever as their main reason for contact and visited the PED at The Queen Silvia Children's Hospital during the studied period.

Inclusion and exclusion criteria

Inclusion criteria were fever as main reason for contact and age ≤ 60 days.

Exclusion criteria were measured temperature less than 38°C both at home and in the PED; no record of exact temperature at home when less than 38°C at the PED; severe congenital or acquired conditions; gestational age less than 35 weeks; no evaluation by a physician; revisit within ten days from previously visit; (see definitions for how revisits were defined) and antibiotic treatment or hospitalization within the previous 10 days.

Data collection, validation and definitions

Data collection

Through Cognos Analytics a list of patients, of the correct age, who had "fever" registered as their main complaint, identified by Swedish social security number, was acquired. The same patient could be registered several times if several visits were made with fever as main complaint. If these visits were more than ten days apart were they classified as new cases, otherwise were they classified as revisits. All patients were assigned an anonymous study ID

which was used for registration in REDCap. REDCap is a secure database acquired through Lund University. The list with social security numbers and corresponding study IDs was kept in a locked safe when not used for data collection.

Data was collected from the electronic medical record system. All data collection was done by two medical students and anonymously gathered in REDCap. Data collection was assisted by the project supervisor. Reviewed parameters were basic parameters such as age, sex and breast-feeding status, number of revisits and days of admission as well as findings in the physical examination, results from blood and urine tests, results from microbiological diagnostics, initial and final diagnosis and if any microbiological treatment was given.

Definitions

Clinical focus of infection was defined as suspected focus after physical exam and before blood test results and initial diagnosis was defined as either the reason for admission or the diagnosis from the first PED visit. The final diagnosis was defined as the diagnosis at discharge or the latest diagnosis at the PED. All included infants could only be assigned one diagnosis as the final diagnosis, if the infant presented with multiple diagnoses the most severe was assigned. Due to the retrospective study design was the assignment of different final diagnoses made from interpretations of what the physicians had written. This were primarily relevant for upper respiratory tract (URT) infections and fever without focus since there are no clear guidelines among physicians how these infants should be classified using the International Statistical Classification of Diseases and Related Health Problems - Tenth Revision.

Revisits were defined as all relevant visits in the proceeding ten days and if there were more than one revisit all revisits that occurred within ten days from each other was counted as revisits.

Bacterial meningitis was defined as either growth in cerebrospinal fluid (CSF) cultures or elevated cell count in CSF, if deemed to be of bacterial origin by the treating physician. Viral

meningitis was defined as findings of viral DNA and/or RNA in CSF or elevated cell count together with a clinical assessment.

Bacteremia was defined as growth of known pathogens in a blood culture. All growth of coagulase negative *streptococci* was defined as contaminations.

Pyelonephritis was defined as growth of a known urine pathogen in a culture and CRP ≥ 20 mg/L during the stay. Cultures with *E. Coli* had to contain at least 10,000 colony forming units to be considered pathological. International studies often use 10,000 colony forming units as well as cut off for pyelonephritis, although this is often combined with an added criterion of finding leucocytes during analysis of the urine [9, 23, 26]. Since urine analysis is not routinely used in our PED and CRP were deemed to be the test most likely to be used in our population were this added to the definition in accordance with what Xu et al have suggested [44].

SBI was defined as pyelonephritis, bacteremia or meningitis alone or in any combination and all SBIs that was discovered at a revisit or after admission was considered delayed if the treating physician at the initial approach did not consider SBI as a plausible diagnosis.

Statistical method and analysis

Since this study is descriptive in its nature and were designed to analyze all infants who met inclusion and exclusion criteria were no power analysis deemed necessary. Data was processed using SPSS (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp). All categorial variables was presented with number of observation (N) and percentages. Quantitative variables were either assumed to be normally distributed and presented as mean and standard deviation (SD) or assumed not to be normally distributed and in those cases presented as median and range.

Ethics

The Helsinki Declaration states that all research should consider the dignity, integrity and privacy of all research subjects and that all subjects should give their informed consent before being included in any study. If it is impossible or impractical to gain this from the subjects and if the research is made on previously recorded data may the study continue after consideration and approval of an ethical committee. The International Bill of Human Rights also state that no one should be exposed to medical experiments without informed consent.

This study is retrospective in design and research subjects are not exposed to any risk by being enrolled nor is any participant exposed to tests or procedures outside of the normal healthcare. Gaining informed consent from all guardians were not deemed possible and everybody have the right to hinder access to their own journal by medical staff if they desire.

Ethical approval was first granted by the Regional Ethics Committee in Lund for implementation in Lund and Malmo (DNR 2017/967). Later the committee granted the study ethical approval for additional data collection in Gothenburg (DNR 2018/236). All patient data was anonymized after to collection.

Results

Population

During the studied period a total of 6381 visits were made by infants 60 days old, or younger at the PED at The Queen Silvia Children's Hospital and 825 (12.9%) of these cases had fever listed as the main complaint. Of the examined cases 200 (24.2%) were excluded, yielding a total of 625 included cases. Reasons for exclusion, by year, are presented in *Table 2*.

Table 2. Reason for exclusion presented by year

<i>Reasons for exclusion</i>	<i>2015</i>	<i>2016</i>	<i>2017</i>	<i>Total</i>
<i>Temperature below 38°C</i>	17	28	25	70
<i>Revisit</i>	18	11	9	38
<i>Not evaluated by a physician</i>	11	12	13	36
<i>Issues with retrieving correct medical records</i>	11	6	1	18
<i>Gestation age less than 35 weeks</i>	11	2	1	14
<i>Antibiotic treatment within 10 days</i>	5	3	4	12
<i>Severe comorbidities</i>	1	2	4	7
<i>Hospitalized within 10 days</i>	1	0	2	3
<i>Deviated from PED without full examination</i>	1	1	0	2
<i>Total</i>	76	65	59	200

PED – pediatric emergency department.

Of the included infants 348 (55.7%) were males and 277 (44.3%) were females. All had documented fever either at home or in the PED, fever characteristics are presented in *Table 3*.

Twenty-three (3.7%) infants were mildly premature (born between gestation week 35 and 37), 487 (77.9%) infants were term and 22 (3.5%) infants were post term. Additionally, 93 (14.9%) infants were presumed to be term because their gestational age was not included in the reviewed records. Median age was 38 days (range: 3 – 60 days) and 10 infants were seven days old or younger. Breastfeeding was common, 57.3% were exclusively breastfed while 11.4% received formula.

Table 3. Description of fever characteristics

Temperature at home (n=545 cases), mean (SD)	38.5°C (0.51)
Temperature at the PED (n=623), mean (SD)	38.3°C (0.71)
Temperature duration	
- < 6 hours, N (%)	245 (39.2)
- 6 – 12 hours, N (%)	189 (30.2)
- 12 – 24 hours, N (%)	108 (17.3)
- 24 – 48 hours, N (%)	31 (5.0)
- > 48 hours, N (%)	18 (2.9)
- Unknown, N (%)	34 (5.4)

PED – pediatric emergency department; SD – standard deviation

Outcome

A total of 326 (52.2%) patients were sent home from the PED and 299 (47.8%) were hospitalized for further investigation and treatment. Two infants died, one of pneumonia and one from *S. pneumoniae* meningitis. Of the infants that were sent home, 56 (17.2%) came back and were registered as revisits out of which 3 (5.4%) were planned and 19 (33.9%) were hospitalized for further care. Among the identified SBI cases were four classified as delayed diagnoses. Two were found at revisits and two were found after admission.

Microbiological diagnostics

Urine samples were analyzed by dip-stick in 522 (83.5%) of included cases and sent for culture in 151 (28.9%) of these cases. The method of choice was ‘clean catch’ in 482 (90.9%) cases and suprapubic aspiration in 44 (8.3%) cases. One-hundred-twenty-four (23.8) of all dip-sticks were positive for leukocytes and 30 (5.7%) were positive for nitrate. *E. Coli* was the isolated pathogen in 65 cases and in 54 (83.1%) cases were the growth >100,000 colony forming units and in five (7.7%) cases were it <10,000 colony forming units.

One-hundred-fifty-one infants had blood sent for cultures. In 110 (72.3%) of these cases were the culture negative and the remaining were deemed positive. In total were 29 cultures (70.7% of positive cultures) deemed to be contaminations and 16 out of these were positive for coagulase negative *streptococci*. Only 12 cultures were positive for a known pathogen and thus deemed as true positive cultures.

Table 4. Results of 151 blood cultures, 78 CSF cultures and 151 urine cultures.

	Negative, N (%)	Positive, N (%)	Contamination, N (%)
Blood culture	110 (72.8)	12 (7.0)	29 (19.2)
CSF culture	73 (93.6)	2 (2.6)	3 (3.8)
Urine culture	62 (41.1)	69 (45.7)	20 (13.2)

CSF – cerebrospinal fluid

A lumbar puncture was done in 86 (13.8% of all cases) cases and of these, cultures were performed in 78 (90.7%) cases. Only two (2.6%) of the cultures were positive. In addition to the growth of cultures, detection through polymerase chain reaction (PCR) was used for a variety of neurotropic viruses and bacteria in 44 (51.2%) cases. The result from CSF PCR was positive in 11 (25.0%) cases, of unclear relevance in two (4.5%) cases and negative in 31 (70.4%) cases. Positive results from all types of microbiological diagnostics are reported in Table 5 by isolated pathogen.

Table 5. Isolated pathogens by site and method

Pathogen	Urine culture	Blood culture	CSF culture	CSF PCR	URT PCR	RSV-RT
Bocavirus	-	-	-	-	1	-
Coronavirus	-	-	-	-	2	-
<i>E. Coli</i>	65	6	1	-	-	-
<i>Enterobacter</i>	1	-	-	-	-	-
<i>Enterococcus</i>	2	-	-	-	-	-
<i>Enterovirus</i>	-	-	-	7	22	-
GAS	-	2	-	-	-	-
GBS	-	2	-	-	-	-
<i>Influenza A</i>	-	-	-	-	2	-
<i>Influenza B</i>	-	-	-	-	2	-
<i>Parainfluenza</i>	-	-	-	-	4	-
<i>Parechovirus</i>	-	-	-	3	-	-
<i>Rhinovirus</i>	-	-	-	-	37	-
RSV	-	-	-	-	11	22
<i>S. Aureus</i>	1	1	-	-	-	-
<i>S. Pneumoniae</i>	-	1	1	1	-	-
Total	69	12	2	11	79	22

CSF – cerebrospinal fluid, GAS – group A streptococcus (*Streptococcus pyogenes*), GBS – group B streptococcus (*Streptococcus agalactiae*), RT – rapid testing, RSV – respiratory syncytial virus, URT – upper respiratory tract. In 18 cases the URT PCR identified two pathogens in varying combinations.

PCR was also used on secrete from the URT in 112 cases of which 43 (38.4%) were positive for one pathogen, 18 (16.1%) positive for two pathogens and 50 (44.6%) were negative. Rapid testing for respiratory syncytial virus (RSV) were routinely used in the PED as well and 22 infants were positive for RSV using this test.

Final diagnosis

In this study no obvious focus of infection was found in 431 (69.0%) cases after clinical examination and before initial testing. Physicians suspected SBI in 110 (17.6%) cases after initial testing and no focus was identified in 324 (51.8%) cases, even after initial testing.

Fever without focus was the final diagnosis in 297 (47.5%) cases and URT infection was diagnosed in additionally 168 cases (26.9%). The third most common diagnosis at discharge was SBI with 66 (10.6%) cases. Other fever causes diagnoses were: 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%), and skin infection (1; 0.2%). The eight cases labeled as other constituted of: varicella zoster cases, fever caused by vaccination, roseola infantum, viral encephalitis, hand-foot-mouth disease and infants who was transferred out of the region before any diagnosis were made. Final diagnoses are presented in *Figure 1*.

In the 11 cases of viral meningitis the pathogen was identified in eight cases. Isolated pathogens were enteroviruses in six cases and parechoviruses in two. Three cases were clinically diagnosed after lumbar puncture, one of these patients was positive for enterovirus/rhinovirus in the URT. A co-infection of pyelonephritis and viral meningitis caused by enterovirus was found as well although this case is only reported as a pyelonephritis case in this study. Additionally, parechovirus was found in one case of viral encephalitis.

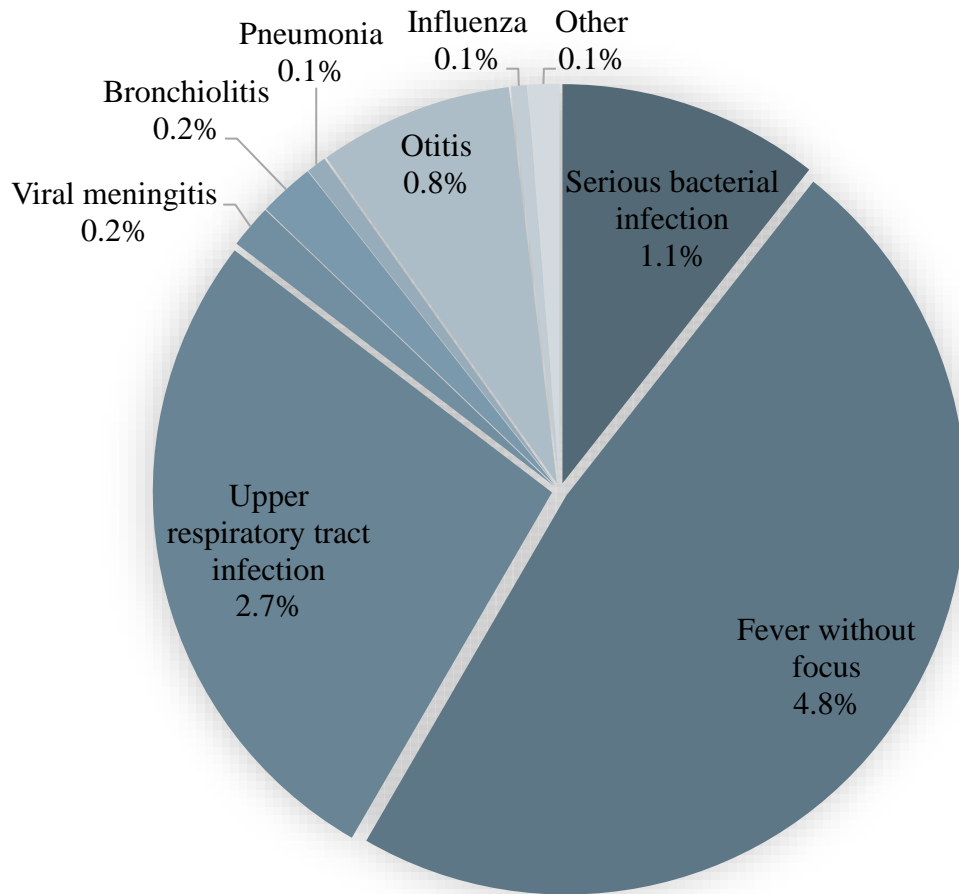


Figure 1. All included (625 cases) presented by final diagnosis.

Pies are not shown for final diagnoses composing less 0.5% of diagnosed cases (gastroenteritis: 0.3% and skin infection: 0.2%)

In the 14 cases of bronchiolitis were the rapid testing for RSV positive in nine cases and additional PCR testing isolated the pathogen in five cases. Among those with positive rapid testing were PCR performed on two, one negative and one positive for RSV. PCR found RSV alone in two cases (one in combination with positive rapid testing) and in combination with rhinoviruses in three cases.

URT cases had a pathogen diagnosed in 35 cases and in 11 of these cases two pathogens was isolated. The most commonly isolated pathogen was rhinoviruses (n=18), followed by enteroviruses (n=12), parainfluenza (n=3) and RSV (n=1). In the cases with two pathogens

isolated, rhinoviruses were isolated in additionally seven cases, RSV in two cases and enterovirus in two cases.

Serious bacterial infections

Of the 66 cases of SBI identified in this study, were 52 (78.8% of total SBIs) pyelonephritis. All but three pyelonephritis cases were caused by *E. Coli* (94.2% of pyelonephritis cases) and the other three were caused by *Enterococcus* spp. and by *Enterobacter* spp. Isolated bacteremia was found in six cases (9.1% of the total SBIs). The bacteremia cases were caused by *Streptococcus pyogenes* (Group A streptococcus; GAS) and GBS in two cases each, by *S. pneumoniae* in one case and by *E. coli* in one case. Two cases of isolated meningitis (3.0% of the total SBIs) were found during the studied period. One case was caused by *S. pneumoniae* and in the other the infant had signs of bacterial meningitis and the lumbar puncture (LP) showed elevated cell count, but no pathogen was not isolated in any culture.

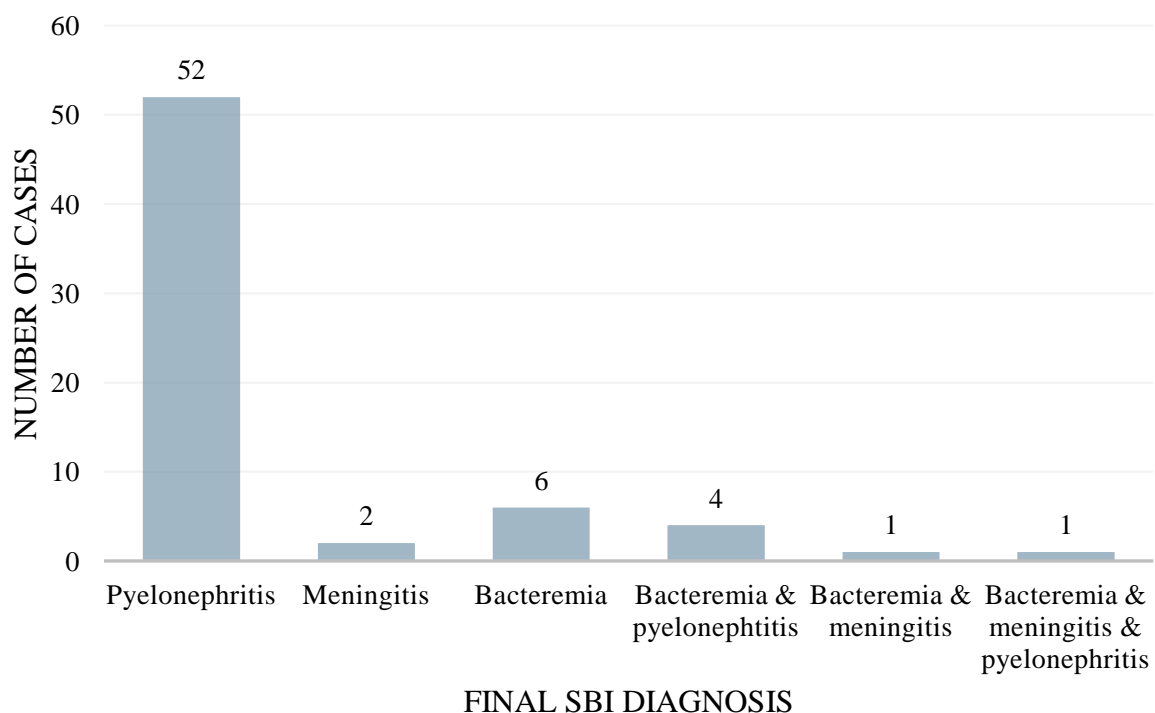


Figure 2. The 66 cases of SBIs presented by type.
SBI – Serious bacterial infection

Additionally, six (9.1%) cases of combined SBIs were seen. Five of these were caused by *E. Coli* while the last case, a combination of bacteremia and pyelonephritis, were caused by *S. Aureus*. In the case with bacteremia, meningitis and pyelonephritis showed both the infant and the lumbar puncture signs of meningitis and the case was classified a combination of all three types, despite no positive CSF culture. *Figure 2* shows the number of cases with SBI divided by type.

Discussion

SBI frequency

The main finding in this report is the SBI frequency of 10.6% and this matches quite well other reported frequencies. Some studies exclude all cases with a suspected focus of infection (e.g. infants with coughs, runny noses or rashes) as done by Garcia et al [6]. If this is done to our data (64 cases of SBI among 431 cases with no focus of infection after clinical exam) the SBI frequency increases to 14.8%. Another difference is that almost all studies, with whom comparison is made in this report, are conducted with infants up to three months. Aronson et al [27] demonstrate that SBI frequency do not differ remarkably between the group aged 29-56 days (7.5% SBIs) and those aged 57-89 days (7.7% SBIs). Garcia et al [6] could also demonstrate a similar pattern but with a slightly lower incidence in the older group, instead.

A third difference between our study and others, is the definition of SBI. In this study bacteremia, meningitis and pyelonephritis, in any combination were used and this is the same definition as in several other studies [6, 8, 9, 12] while a broader definition including pneumonia, cellulitis and enteritis have been used by other studies [10, 11, 26, 27, 29]. If the five cases of pneumonia and two cases of gastroenteritis are included as SBIs as well, the number increases to 73 cases and yields a frequency of 11.7%. If this broader definition of SBI is applied to the group with no focus of infection this yields an SBI frequency of 15.5% (64 true SBIs, two pneumonia and one gastroenteritis). This is still lower than the reported frequencies around 20% seen in southern Europe [6, 23, 28].

As described above, our study suggests that the prevalence of severe bacterial infections among febrile young infants attending the ER in the Gothenburg region might be lower than in southern Europe [6, 23, 28] and Israel [14, 25, 45] while it quite well match the frequencies seen in the US and northern Europe [8, 9, 26, 27]. Environmental and cultural differences between Sweden and the countries around the Mediterranean Sea may influence the differences. This is

somewhat supported by the fact that the prevalence in the US and France is more similar to our prevalence than from the Mediterranean countries.

Etiology

E. Coli was the most commonly isolated pathogen in pyelonephritis cases (49 of 52 cases; 94.2%). The dominance of *E. Coli* as seen in other studies [8, 9, 26] is thus confirmed in Gothenburg as well. Compared with these studies the amount of *E. Coli* positive urine cultures is somewhat higher than expected as *E. Coli* is found in 60 – 90% [9, 25, 26] of urine cultures, internationally. More surprising is that *Klebsiella* spp was not found in a single urine culture, although it is a rather common pathogen in other studies [8, 9, 16, 45]. It is important to notice that most urine cultures were grown on urine captured by a clean catch instead of via catheterization which the method of choice is abroad [8, 26, 28]. Since clean catch is not a sterile testing method the risk of contaminations or false positive results is increased.

Of the 12 cases of positive blood cultures six were isolated bacteremia cases and six were cases of combined SBIs. Here was the spectrum of pathogens, as expected, much more diverse. Half of all blood cultures (50%) were positive for *E. Coli* and five of these were combined with either pyelonephritis or meningitis. This is somewhat lower than previously seen with approximately 60% of blood cultures being positive for *E. Coli* [8, 26]. The findings of two cases of GAS is quite remarkable as almost no identified study [8, 9, 26, 45] have found a single case of this pathogen. The reason behind the findings of GAS bacteremia is not known.

Among meningitis cases pathogens were isolated in two cases, one case of *E. Coli* meningitis and one case of *S. pneumoniae* meningitis. In addition, a case of bacteremia and pyelonephritis caused by *E. Coli* also showed clear signs of meningitis and the LP was performed after antibiotic treatment had begun. It is highly probable that *E. Coli* caused meningitis as well. This means that *E. Coli* was, most likely, the pathogen in half of all cases with involvement of the

meninges (four cases in total). Compared with results by Greenhow et al (34% *E. Coli* meningitis) and Mah et al (29%) this is uncommon. The reason for *E. Coli* being more dominant in meningitis as well as pyelonephritis cases is unknown, but it is noteworthy that GBS which is a common pathogen, internationally, is missing in this study.

The dominance of *E. Coli* is, as previously mentioned, not fully understood. In our study is the high prevalence of *E. Coli* possibly an effect of that other pathogens was not identified in the expected extent. Why *Klebsiella* spp. was not identified is unclear and highly surprising but this may be due to environmental factors. Regarding the lack of GBS cases may this be an effect of a working IAP program. IAP may also contribute to the increasing amount of *E. Coli* SBIs as some studies [7] speculate that *E. Coli* is quite commonly resistant to ampicillin which is the antibiotic of choice abroad for IAP. This may select for *E. Coli* strains that is resistant and maybe more pathogenic. Since antibiotic resistance was not examined in our study and benzylpenicillin is the antibiotic of choice in Sweden is it impossible to conclude if IAP may influence which *E. Coli* strains cause SBI in our PED.

Other causes of fever

In this study we choose to study other infectious causes of fever in addition to SBIs which is not usually done. The amount of URT infections and cases with no focus, 27% and 48%, respectively, may be compared with Baker et al [11] who found a viral infection in 60% of included cases. Compared with the same study is it remarkable that only 1.8% of all infants had viral meningitis, in our study, as this were much more common with a prevalence of 13.5%. Why the difference in viral meningitis differ this much is unclear but the fact that all infants received an LP in the study by Baker et al while only 13.8% received an LP in our study, may influence this. The amount of viral meningitis cases may also be influenced by the fact that PCR against Parechoviruses was put into clinical use during the spring of 2017 and thus cases with this pathogen may have been dismissed as fever without focus before this date.

Regarding the etiology of identified viral infections in this study is it clear that enteroviruses and rhinoviruses that are the most common. RSV were also identified in quite a few cases and this were expected if the results is compared with Byington et al [29] who, in a prospective study, performed viral testing on all included infants. A total of 35% had a viral infection, which is higher than seen in our study and lower than seen by Baker et al. This implicates that the difference between URT infections and fever without focus is narrow and that without viral testing is it objectively difficult to identify which patients have a viral infection. The differentiation between these two groups is how ever academical as no difference in treatment exists between URT infections and fever without focus, when other causes have been ruled out.

All in all, do not the data regarding other causes of fever seem to cause any concern for physicians as most infants have a benign cause of fever. Regarding detection of SBIs is it important to recognize as there are other potentially sever infections that is not classified as SBIs and remain a threat to some infants. This might be shown by the fact that one infant died from pneumonia in our study, which is not classified as an SBI. Thus, is it important that any protocol regarding SBI detection gives room for detection of other infections such as pneumonia, bronchiolitis and viral meningitis and not classify all infants who do not have an SBI as healthy.

Strengths and weaknesses

Among the biggest strengths in this study are that fact there is only one PED in the immediate area and the number of included infants. Although some infants with fever may have visited a primary care physician is it highly likely that all infants with an SBI or other infectious diagnosis was evaluated at our PED during some part of the febrile episode. Among strengths in study is it also important to mention the high accessibility and completeness of the reviewed medical records. In some cases, there were problems with retrieving the medical records, in most cases the infant was not found at all in the system at all, this were probably due to that the

infant did not receive an evaluation by a physician or that the parents deviated from the PED, although it is impossible to be sure of this.

One factor that should be considered regarding the study method is that only infants with fever listed as the main reason for contact was included and it is probable that not all infants who had an SBI was registered with this as the main reason for contact. It is also possible that not all infants with fever were registered as this if they showed other symptoms as well. The aim with study was not however to describe the total frequency of SBIs but to describe the prevalence among those who only have fever, because it is this group of patients who is the biggest challenge for physicians.

Another important factor to consider regarding this study is the retrospective design that have some obvious limitations. Such limitations may be that some information may have been left out of the records due to human nature or that information was misinterpreted by the reviewer. Data collection was made by two persons and this may influence the result as well, since different persons may have interpreted the information in different ways.

Conclusion and implication

This study's aim was mainly to describe the frequency and etiology of SBIs and the secondary objective was to also describe other causes of fever in our population. The frequency of SBIs was 10.6% and this is comparable with results from similar studies from the US and remarkably lower than reported from southern Europe and Israel. The dominance of *E. Coli*. Seen internationally, was confirmed and somewhat more prominent when compared to previous studies. Other causes of fever were mostly benign and since very few studies are published regarding other causes no conclusions can be made with a high level of certainty but nothing in this data seems to be out of normal and should not cause any alarm among clinicians.

Based on this study there we identify two possible paths to follow regarding future research. One path is to use current epidemiological data to construct a new set of clinical guidelines in order to tailor these to the population in Gothenburg. Since this project is part of a bigger study with this as goal, this is a highly feasible way. The other path for future research is to develop ways to prevent future infections, nowadays mostly *E. Coli* infections, in different ways. This study gives no clear insights in how this should be done but given the results presented here both vaccination and antibiotic prophylaxis have had effect on other pathogens. If prophylaxis or vaccination against *E. Coli* is a feasible way is although quite unclear as very few studies regarding this is published and most of the published articles are focused on preventing *E. Coli* caused diarrhea.

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Populärvetenskaplig sammanfattning

Svåra infektioner hos spädbarn under två månader gamla med feber

Feber är en vanlig orsak för besök på en akutmottagning för spädbarn. En ansevärd mängd av besöken är svår, sjukhusvårdskrävande, infektion orsakad av bakterier. Flertalet internationella studier, från bl.a. USA och medelhavsområdet (Israel, Italien och Spanien framför allt), har undersökt hur stor andel som har en allvarlig infektion. I USA har frekvensen varit mellan 8,6 och 16,3 procent medan den i medelhavsområdet ligger på 22,4 procent. I Sverige har det genomförts få studier inom området och det är oklart hur stor frekvensen är här. En svår bakteriell infektion brukar definieras som blodförgiftning (s.k. bakteremi; ”bakterier i blodet”), hjärnhinneinflammation eller urinvägsinfektion, ensamma eller i kombination. Oftast diagnosticeras dessa genom att odla fram bakterier från vätskor från dess respektive plats (blod, urin eller ryggmärgsvätska). I tidigare genomförda studier har urinvägsinfektioner utgjort ungefär 90 procent av alla allvarliga infektioner, blodförgiftning har varit den näst vanligaste och hjärnhinneinflammation har enbart utgjort någon enstaka procent. *E. Coli* brukar vara den i särklass vanligaste bakterien i alla genomförda studier.

Internationellt finns det ett flertal riktlinjer framarbetade för att minska risken att missa svåra bakteriella infektioner, i Sverige används dock inga av dessa.

Den här studien har haft som mål att undersöka alla barn, yngre än två månader (≤ 60 dagar), som har sökt för feber på akutmottagningen på Drottning Silvias barn- och ungdomssjukhus i Göteborg under åren 2015, 2016 och 2017. Syftet med detta var att ta reda på frekvensen av svåra infektioner, vilka bakterier som orsakat dessa och vilka andra orsaker till feber som fanns. Studien baseras på en journalgenomgång av aktuella patienter.

Totalt gjordes 6381 besök på akutmottagningen av spädbarn som var yngre än två månader under de aktuella åren. Av dessa hade 825 spädbarn feber som besöksorsak, 200 sorterades bort

under genomläsningen på grund av olika orsaker så som: ingen feber (feber definierades som temperatur över 38 °C hemma eller på akuten), återbesök av en patient som tidigare registrerats eller på grund av komplicerande sjukdomar som kan påverka risken för infektion. Totalt analyserades 625 fall av feber och 66 (10,6%) av dessa hade en svår bakteriell infektion, 168 (26,8%) hade en förkylning, 49 (7,8%) hade en öroninflammation, 11 (1,8%) hade en hjärnhinneinflammation orsakad av virus och i 297 (47,5%) fall hittades ingen orsak till febern. Av de allvarliga infektionerna var 52 (78,8%) urinvägsinfektioner, sex (9,1%) var blodförgiftningar, två (3,0%) var hjärnhinneinflammationer och sex (9,1%) fall bestod av en kombination av allvarliga infektioner. *E. Coli* var den vanligaste bakterien i både urinvägsinfektionerna och i de kombinerade fallen medan förvånansvärt få fall av blodförgiftning orsakades av denna bakterie.

Frekvensen av allvarliga infektioner på 10,6 procent ligger i linje med vad som rapporterats från USA. Med tanke på att ett av tio febriga barn har en allvarlig bakteriell infektion krävs det mer forskning för att på ett effektivt sätt kunna upptäcka dessa utan att övriga barn utsätts för stora risker eller onödiga behandlingar.

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