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Prevalence of serious bacterial infections and management of febrile infants ≤60 days in Swedish Pediatric Emergency Departments

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BACKGROUND. The reported prevalence of serious bacterial infections (SBI: urinary tract infection (UTI), bacteremia, and meningitis) among febrile infants ≤60 days of age varies from 8% to 23%. There are indications that the prevalence of infections differs between the sexes. Infants with fever at home but afebrile at the pediatric emergency department (PED) might have a lower risk of SBIs. Furthermore, the management of febrile infants and adherence to guidelines varies among PEDs. There is a paucity of knowledge regarding how physicians decide whether to follow management recommendations.

AIM. To describe the age- and sex-specific prevalence of SBIs in infants aged ≤60 days with fever without source (FWS) at four PEDs in Sweden. To evaluate whether there is a difference in the prevalence between infants with reported fever at home who are afebrile at the PED and those who are still febrile. To describe the clinical management and outcomes of febrile infants. To investigate physicians' decision-making process when managing febrile infants aged ≤60 days and to describe the factors that influenced this decision.

METHOD. This thesis is comprised of 2 separate projects. The first is a retrospective cross-sectional study in previously healthy, full-term febrile infants ≤60 days with FWS who presented at 4 PEDs in 2014-2020. The second is a qualitative study with a phenomenographic approach based on focus group discussions with physicians active in 2 of the PEDs.

RESULTS. There were included 2237 febrile infants aged ≤60 days with FWS. The prevalence of SBIs was 12.6% (95% CI, 11.0-14.3), of UTI 11.0% (95% CI, 9.5-12.6), of bacteremia 1.5% (95% CI, 1.0-2.2), and of meningitis 0.5% (95% CI, 0.2–0.9). In infants aged ≤28 days, the prevalence of meningitis did not differ (p=1.000) between girls 0.8% (95% CI, 0.1-2.9) and boys 0.9% (95% CI, 0.2-0.2.7). Similarly, there was no difference in the risk of meningitis between infants aged ≤28 days with reported fever at home who were febrile at the PED and those still febrile, with a risk ratio (RR) of 1.05 (95% CI, 0.18–6.23). In infants aged ≤28 days, lumbar puncture (LP) was performed in 13% (95% CI, 11–16), blood culture in 40% (95% CI, 36–40), broad-spectrum antibiotics were administered in 30% (95% CI, 26–34), and 67% (95% CI,63–71) were hospitalized. Of the infants who did not receive antibiotics at the initial approach, 0.3% (95% CI, 0.1–0.8) were diagnosed with meningitis or bacteremia. Three main factors influenced the decision-making process on whether to perform an LP:1) a possible focus of infection that could explain the origin of the fever; 2) questioning whether the temperature at home reported by the parents was a fever, especially if it was ≤38.2°C; and 3) the infant's general condition and questioning the need for LP in case of well-appearing infants.

CONCLUSIONS. The prevalence of meningitis and bacteremia was low in infants aged ≤60 days with FWS. A different meningitis risk estimation is not justified for infants aged ≤28 days with reported fever at home afebrile at the PED. The management of febrile infants aged ≤28 days did not constitute of routine LP, blood culture, antibiotic treatment, and hospitalization but was not associated with increased adverse outcomes. Such management should be investigated further since it could reduce unnecessary investigations, antibiotic treatments, and hospitalizations. The primary factors that influenced physicians to omit performing LP were general appearance, presence of fever, and possible focus of infection.

Key words: febrile infants, serious bacterial infections, meningitis, bacteremia, management, prevalence, lumbar puncture, blood culture, guidelines, adherence, decision-making process

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To Alma

Never stop questioning

"[in art] less is more''

Ludwig Mies van der Rohe

(often in medicine as well?)

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List of publications

This thesis is based on the following papers, which will be referred to in the text using Roman numerals. The papers are appended at the end of the thesis

I. **Orfanos I**, Alfvén T, Mossberg M, Tenland M, Sotoca Fernandez J, Eklund EA, Elfving K. Age- and sex-specific prevalence of serious bacterial infections in febrile infants ≤60 days, in Sweden. *Acta Paediatrica*; 2021 Nov;110(11):3069-3076.

II. **Orfanos I**, Elfving K, Sotoca Fernandez J, Wennlund L, Weiber S, Eklund EA, Alfvén T. Management and Outcome of Febrile Infants ≤60 days, With Emphasis on Infants ≤21 Days Old, in Swedish Pediatric Emergency Departments. *Pediatric Infect Dis J*; 2022 July;41(7):537-543.

III. **Orfanos I**, Sotoca Fernandez J, Elfving K, Alfvén T, Eklund EA. Paediatric emergency departments should manage young febrile and afebrile infants the same if they have a fever before presenting. *Acta Paediatrica*; 2022 Oct;111(10):2004-2009.

IV. **Ioannis Orfanos**,* Rose-Marie Lindkvist,* Erik A Eklund, Kristina Elfving, Tobias Alfvén, Tom J de Koning, Charlotte Castor. Physician's conceptions of the decision-making process when managing febrile infants ≤60 days old: A phenomenographic qualitative study. Submitted.
* First authors

Abbreviations

AAP	American academy of pediatrics
ANC	Absolute neutrophil count
CFU	Colony forming units
CI	Confidence interval
CRP	C-reactive protein
CSF	Cerebrospinal fluid
E. *coli*	*Escherichia coli*
ED	Emergency department
FWS	Fever without source
HSV	Herpes simplex virus
GBS	Group B *Streptococcus*
IBI	Invasive bacterial infection
LP	Lumbar puncture
NICE	National institute for health and care excellence
NNT	Number needed to treat
PCR	Polymerase chain reaction
PCT	Procalcitonin
PECARN	Pediatric emergency care applied research network
PED	Pediatric emergency department
PROS	Pediatric research in office settings
REDCap	Research Electronic Data Capture
RNA	Ribonucleic acid
RR	Relative risk
RSV	Respiratory syncytial virus
SBI	Serious bacterial infection
OECD	Organisation for Economic Cooperation and Development
US	United States
UTI	Urinary tract infection
WBC	White blood cell

Introduction

Fever is the most common reason for visiting a pediatric emergency department (PED).[1, 2] A study from 12 PEDs in 8 European countries, which included 16 268 febrile children 0-18 years old, showed that no more than 0.8% had a potential life-threatening bacterial infection.[3] Similar results were shown in a similar single-center study from Australia with 15 781 febrile children under 5 years of age.[4] Due to this low risk, immediate contact with a healthcare facility is not recommended for febrile children without alarming symptoms. In contrast, healthcare providers and national advice agencies recommend immediate medical evaluation for febrile infants younger than 60 days of age.[5, 6] The reason is that those febrile infants have a higher risk of serious bacterial infections (SBIs) than older children.[7-9] The term SBI commonly includes urinary tract infections (UTIs), bacteremia, and meningitis.[7] These infections have been associated with increased morbidity and potential mortality.[10-13] Because of the higher risk and the potential severity, most established guidelines for managing febrile infants younger than 60 days of age recommend extensive investigations (e.g., lumbar puncture, urinalysis, cerebrospinal fluid, blood and urine cultures), hospitalization, and treatment with parenteral broad-spectrum antibiotics.[14-16]

Infants younger than 60 days have the highest visit rate to emergency departments (ED) among children.[17, 18] Ramgopal et al. reported that 1,1 million febrile infants ≤60 days old visited an ED in the US during 2007-2017, translating to almost 100 000 visits per year.[19] Febrile infants are also seen in primary and private office health settings and the number of ambulatory visits exceeds that of ED visits.[9, 20, 21] Thus, the actual number of febrile infants ≤60 days old seen annually in US health facilities is likely significanlty higher than 100 000 per year. There are no concrete data in Europe regarding the visits of febrile infants to EDs or primary healthcare facilities. However, in 2021 there were 4.1 million births in Europe versus 3.7 million in the US.[22, 23] Also, most European countries have universal healthcare systems, so access to healthcare is likely at least as easy in Europe as in the US. Therefore, despite the paucity of data for Europe, it could be speculated that the number of febrile infants aged ≤60 days who visit a healthcare facility in Europe could be more than 200 000 per year.

However, despite the higher risk of SBIs, most febrile young infants have benign or self-limiting viral infections.[9, 24] Thus, hundreds of thousands of febrile young infants are subjected to extensive, often unnecessary, investigations,

hospitalizations, and antibiotic treatments every year. Interventions with potentially harmful effects on infants, their families, and the health system. [25, 26]

Due to the potentially harmful effects of investigations, hospitalizations, and antibiotic treatments, researchers have attempted to develop new prediction models in the last few decades. Prediction models that can: a) better identify the febrile infants at low risk of a serious bacterial infection who might not benefit from a medical intervention, b) minimize the complications of excessive investigations on the infants, and c) improve utilization of health resources.[7, 27, 28]

Accurate and updated prevalence data for SBIs are essential for the development of patient-safe and effective prediction models for managing febrile infants. However, no prevalence studies have been conducted in Sweden. Extrapolating prevalence data from countries with different characteristics can result in a significant underestimation or overestimation of risks. Also, it is crucial to study the performance of management guidelines in different settings, particularly in settings with different characteristics from those they were derived. Furthermore, identifying management variations and possible associated differences in outcomes could provide opportunities to improve current guidelines to enhance patient safety and optimize resource utilization. However, no studies in Sweden have described the management and outcomes of febrile infants. Moreover, understanding why physicians follow or do not follow management recommendations is essential for developing new guidelines, improving or adjusting current guidelines, and designing implementation strategies. However, there is a paucity of knowledge on how physicians decide to follow the guidelines when managing febrile infants.

Thus, this thesis investigates the prevalence of serious bacterial infections in febrile infants aged ≤60 days, describes the management of these infants in 4 Swedish PEDs, and describes physicians' decision-making process when managing febrile infants aged ≤60 days.

This thesis aspires to be a comprehensive and in-depth overview of the field of febrile infants. It attempts to present most of what is known and discuss knowledge gaps as I perceive them. The aim is to question commonly accepted beliefs, generate discussions, and raise questions. In trying to achieve the above, this thesis might be perceived as provocative and quite long.

Etiology of fever in young infants

Several studies have investigated the etiology of fever in young febrile infants. Pantell et al. performed a study on febrile infants aged ≤90 days in pediatric office settings in the US between 1995 and 1998. They reported that almost 85% of the final diagnoses were of presumably viral etiology.[9] Similarly, a recent study from

the Pediatric Emergency Care Applied Research Network (PECARN) reported that 40% of febrile infants ≤60 days who were tested for viruses were positive.[29] Other studies have shown a high prevalence of enterovirus,[24, 30-33] respiratory syncytial virus,[24, 33, 34] influenza,[24, 35, 36] rhinovirus,[37] human herpes virus 6, and human parechovirus[31] among febrile infants. The incidence of these viral infections varies seasonally. Enterovirus is identified in up to 50% of febrile infants during summer and fall.[30, 32, 33] Respiratory syncytial virus and influenza are predominant during late fall and winter.[33, 38] Hence, viral infections cause most febrile illnesses in infants.

However, serious bacterial infections (SBI) are not a negligible cause of illness in young febrile infants, because they can cause significant morbidity and mortality in rare cases. The term SBI classically includes urinary tract infections (UTI), bacteremia, and bacterial meningitis.

Serious Bacterial Infections

Studies in the US and Spain have investigated the prevalence of SBIs among young febrile infants. In previous decades, most studies included infants 0-90 days old and separately reported for the ≤1 month age subgroup. Thus, data on infants aged ≤60 days are limited. The reported SBI prevalence in this age group varies greatly from 6% to 26%. It is highest in the first month of life (6-30%) and lower in the second month (5-26%). The lower prevalence data were mostly reported in studies conducted in the US (Table 1).

Table 1. Reported prevalence of serious bacterial infections (SBI) per age group

Author/ Pub Year	Country	Inclusion Criteria	Study Period	≤2 Months (%)	1st Month (%)	2nd Month (%)
Jaskiewicz 1994	USA	Fever, 0-60d	1985-1992	6.1	7.3	5.6
Baker 1993	USA	Fever, 29-56d	1987-1992	–	6.0	–
Schwartz 2008	Israel	Fever, ED, 0-28d	1997-2006	19.4	–	–
Watt 2010	USA	FWS, BC, 0-90d	1997-2006	9.5	8.0	10.6
Ashkenazi 2011	Israel	Fever, Hospitalized, 0-90d	2005-2009	9.7	13.7	7.2
Garcia 2012	Spain	FWS, ED, 0-90d	2003-2010	20.1	26.3	17.7
Bressan 2012	Spain/Italy	FWS, Investigations*, 0-90d	2008-2010	26.2	27.2	25.6
Milcent 2016	France	Fever, Hospitalized, 7-91d	2008-2011	–	7.2	–
Greenhow 2016	USA	Fever, ED, 7-90d	2010-2013	17.9	22.3	15.3
Aronson 2014	USA	Fever, ED, 0-90d	2011-2013	8.6	11.1	7.5
Kuppermann 2019	USA	Fever, BC, ED, No critically ill, 0-60d	2011-2013	9.3	13.0	7.7
Aronson 2015	USA	Fever, ED, 0-56d	2013-2013	8.6	11.9	6.9
Carmon 2017	Israel	Fever, Hospitalized, 0-60d	2013-2014	23.0	30.0	22.0
Yaeger 2018	USA	Fever, ED, 0-90d	2014-2014	14.2	17.0	13.0
Bonilla 2019	Spain	FWS, ED, 0-90d	2003-2017	18.2	21.5	16.6
Velasco 2020	Spain	FWS, PCT, ED, 0-60d	2007-2018	20.7	–	–
Mahajan 2022	USA	Fever, ≥ one culture, 0-60d	2011-2019	10.6	12.2	8.1

FWS, Fever Without source; d, age in days; BC, Blood Culture; ED, Emergency Department; PCT, Procalcitonin;
* Investigations, PCT, CRP, Urine dipstick, and BC

Most studies have used the term SBI to report the prevalence of bacterial infections in febrile infants. However, it is considered problematic to report together UTI and bacterial meningitis, diseases with very different severity and prognosis. Meningitis is associated with significant mortality, morbidity, and short- and long-term sequelae.[10, 11, 39] On the contrary, UTI is rarely the cause of sepsis in otherwise healthy infants and has much lesser short- and long-term sequelae in.[40-43] Thus, the recent American Academy of Pediatrics (AAP) clinical practice guideline for the management of febrile infants ≤60 days old discourages the use of the term SBI.[28]

Invasive Bacterial Infections

In the last decade, the term invasive bacterial infections (IBI) was introduced for infants with bacterial meningitis or bacteremia. The reported IBI prevalence in febrile infants aged ≤60 days varies from 1.6% to 6.4% (Table 2). It is highest in the first month of life (2.2-9.7%) and lower in the second month (1.2-5.0%).

Table 2. Reported prevalence of invasive bacterial infections (IBI) per age group

Author/ Pub Year	Country	Inclusion Criteria	Study Period	≤2 Months (%)	1st Month (%)	2nd Month (%)
Jaskiewicz 1994	USA	Fever, 0-60d	1985-1992	–	–	1.2
Baker 1993	USA	Fever, 29-56d	1987-1992	–	–	2.8
Pantell 2004	USA	Fever, 0-90d	1995-1998	2.8	4.1	1.9
Watt 2010	USA	FWS, BC, 0-90d	1997-2006	3.9	4.5	3.5
Schwartz 2008	Israel	Fever, ED, 0-28d	1997-2006	–	3.1	–
Garcia 2012	Spain	FWS, ED, 0-90d	2003-2010	2.2	2.3	2.2
Bonilla 2019	Spain	FWS, ED, 0-90d	2003-2017	3.2	5.1	2.3
Velasco 2020	Spain	FWS, PCT, ED, 0-60d	2007-2018	3.0	–	–
Bressan 2012	Spain/Italy	FWS, Investigations*, 0-90d	2008-2010	2.3	3.7	1.6
Milcent 2016	France	Fever, Hospitalized, 7-91d	2008-2011	–	2.2	–
Greenhow 2016	USA	Fever, ED, 7-90d	2010-2013	3.6	5.3	2.3
Kuppermann 2019	USA	Fever, BC, ED, No critically ill, 0-60d	2011-2013	1.6	2.6	1.3
Aronson 2015	USA	Fever, ED, 0-56d	2013-2013	3.6	5.6	2.5
Carmon 2017	Israel	Fever, Hospitalized, 0-60d	2013-2014	2.4	–	–
Yaeger 2018	USA	Fever, ED, 0-90d	2014-2014	6.4	9.7	5.0
Mahajan 2022	USA	Fever, ≥ one culture, 0-60d	2011-2019	2.4	3.7	1.3

FWS, Fever Without source; d, age in days; BC, Blood Culture; ED, Emergency Department; PCT, Procalcitonin;
* Investigations, PCT, CRP, Urine dipstick, and BC

However, even the term IBI may distort the understanding of the illness panorama among young febrile infants. Studies have investigated the outcome in well-appearing febrile infants with isolated bacteremia who were sent home without antibiotics after their initial encounter at the PED. They did not report any unfavorable outcomes, and 75% of the infants did not have fever on their return visit.[44-46] Similarly, concomitant bacteremia with UTI or meningitis does not worsen the prognosis.[47-49] There is no evidence that bacteremia causes mortality or short- and long-term morbidity to the same extent as meningitis. Therefore, experts in the field recommend reporting prevalence per disease to promote clarity in the nomenclature and to accumulate better data for infrequent infections such as meningitis.[28]

Bacterial Meningitis

The reported prevalence of meningitis among febrile infants aged ≤60 days varies from 0.3% to 1.4% (Table 3). It is highest in the first month of life (0.3-2.4%) and lower in the second month (0.1-1.2%). Biondi et al., in a systematic review and meta-analysis, reported a meningitis prevalence of 1.2% (95% CI, 0.8-1.9) for the first month and 0.4% (95% CI, 0.2-1.0) for the second.[50] The studies included in this review were performed between 1992 and 2010, the majority in the 1990s, and only

one from Europe. Most of the studies presented in Table 3 were performed between 2000 and 2019, and more European studies are included.

Table 3. Reported prevalence of bacterial meningitis per age group

Author/ Pub Year	Country	Inclusion Criteria	Study Period	≤2 Months (%)	1st Month (%)	2nd Month (%)
Baker 1993	USA	Fever, 29-56d	1987-1992	–	–	1.2
Pantell 2004	USA	Fever, 0-90d	1995-1998	0.7	1.2	0.4
Schwartz 2008	Israel	Fever, ED, 0-28d	1997-2006	–	0.7	–
Watt 2010	USA	FWS, BC, 0-90d	1997-2006	0.4	0.4	0.4
Garcia 2012	Spain	FWS, ED, 0-90d	2003-2010	0.5	1.3	0.1
Bonilla 2019	Spain	FWS, ED, 0-90d	2003-2017	0.6	1.6	0.1
Velasco 2020	Spain	FWS, PCT, ED, 0-60d	2007-2008	0.5	–	–
Milcent 2016	France	Fever, Hospitalized, 7-91d	2008-2011	–	1.0	–
Greenhow 2016	USA	Fever, ED, 7-90d	2010-2013	0.3	0.3	0.3
Kuppermann 2019	USA	Fever, BC, ED, No critically ill, 0-60d	2011-2013	0.6	1.2	0.3
Mahajan 2022	USA	Fever, ≥ one culture, 0-60d	2011-2019	0.5	1.2	0.2
Aronson 2015	USA	Fever, ED, 0-56d	2013-2013	0.5	1.0	0.3
Carmon 2017	Israel	Fever, Hospitalized, 0-60d	2013-2014	0.3	–	–
Yaeger 2018	USA	Fever, ED, 0-90d	2014-2014	1.4	2.4	1.0

FWS, Fever Without source; d, age in days; BC, Blood Culture; ED, Emergency Department; PCT, Procalcitonin;

Bacteremia

The reported prevalence of bacteremia among febrile infants ≤60 days varies from 1.3% to 5.7% (Table 4). It is highest in the first month (1-7.3%) and lower in the second month (1.1-5.0%). The same meta-analysis by Biondi et al. reported a bacteremia prevalence of 2.9% (95% CI, 2.3-3.7) for the first month and 1.6% (95% CI, 0.9-2.7) for the second.[50] The prevalence of isolated bacteremia, as reported by a few studies, varies from 0.5% to 4.2%.

Table 4. Reported prevalence of bacteremia per age group

Author/ Pub Year	Country	Inclusion Criteria	Study Period	≤2 Months (%)	1st Month (%)	2nd Month (%)
Jaskiewicz 1994	USA	Fever, 0-60d	1985-1992	1.3	1.4	1.2
Baker 1993	USA	Fever, 29-56d	1987-1992	–	–	2.5
Schwartz 2008	Israel	Fever, ED, 0-28d	1997-2006	–	3.1	–
Watt 2010	USA	FWS, BC, 0-90d	1997-2006	3.2	4.0	3.5
Gomez 2010	Spain	FWS, BC, 0-90d	2003-2008	3.3	3.3	2.1
Garcia 2012	Spain	FWS, ED, 0-90d	2003-2010	1.7	1.0	2.0
Bonilla 2019	Spain	FWS, ED, 0-90d	2003-2017	2.3	2.9	2.0
Velasco 2020	Spain	FWS, PCT, ED, 0-60d	2007-2018	2.8	–	–
Milcent 2016	France	Fever, Hospitalized, 7-91d	2008-2011	–	1.2	–
Powel 2018	USA	Fever, BC, 0-60d	2008-2011	1.8	3.1	1.1
Greenhow 2016	USA	Fever, ED, 7-90d	2010-2013	3.2	5.5	2.0
Kuppermann 2019	USA	Fever, BC, ED, No critically ill, 0-60d	2011-2013	1.6	2.1	1.2
Mahajan 2022	USA	Fever, ≥ one culture, 0-60d	2011-2019	1.8	3.0	1.3
Aronson 2015	USA	Fever, ED, 0-56d	2013-2013	3.1	4.7	2.2
Carmon 2017	Israel	Fever, Hospitalized, 0-60d	2013-2014	2.2	–	–
Yaeger 2018	USA	Fever, ED, 0-90d	2014-2014	5.7	7.3	5.0

FWS, Fever Without source; d, agen in days; BC, Blood Culture; ED, Emergency Department; PCT, Procalcitonin;

Urinary Tract Infection

The reported prevalence of UTI among febrile infants aged ≤60 days varies from 4.7% to 21.3% (Table 4). It is highest in the first month of life (5.5-27%) and lower in the second month (3.2-18%). Shaikh et al., in a meta-analysis, reported a prevalence ranging from 3% to 14% in febrile infants ≤2 months. Uncircumcised boys ≤2 months had the highest prevalence of all groups.[51]

Table 5. Reported prevalence of urinary tract infection (UTI) per age group

Author/ Pub Year	Country	Inclusion Criteria	Study Period	≤2 Months (%)	1st Month (%)	2nd Month (%)
Jaskiewicz 1994	USA	Fever, 0-60d	1985-1992	4.7	5.7	4.5
Baker 1993	USA	Fever, 29-56d	1987-1992	–	–	3.2
Schwartz 2008	Israel	Fever, ED, 0-28d	1997-2006	–	18.3	–
Watt 2010	USA	FWS, BC, 0-90d	1997-2006	7.0	5.5	10.2
Garcia 2012	Spain	FWS, ED, 0-90d	2003-2010	18.4	24	15.6
Bonilla 2019	Spain	FWS, ED, 0-90d	2003-2017	14.6	16.0	13.9
Velasco 2020	Spain	FWS, PCT, ED, 0-60d	2007-2018	17.5	–	–
Milcent 2016	France	Fever, Hospitalized, 7-91d	2008-2011	–	17.6	–
Greenhow 2016	USA	Fever, ED, 7-90d	2010-2013	14.3	17.3	12.8
Kuppermann 2019	USA	Fever, BC, ED, No critically ill, 0-60d	2011-2013	7.7	10.3	6.6
Mahajan 2022	USA	Fever, ≥ one culture, 0-60d	2011-2019	8.2	9.8	7.4
Aronson 2015	USA	Fever, ED, 0-56d	2013-2013	5.2	7.2	4.1
Carmon 2017	Israel	Fever, Hospitalized, 0-60d	2013-2014	21.3	27.0	17.9
Yaeger 2018	USA	Fever, ED, 0-90d	2014-2014	7.8	7.3	8.0

FWS, Fever Without source; d, age in days; BC, Blood Culture; ED, Emergency Department; PCT, Procalcitonin;

However, there is significant heterogeneity in the diagnosis of UTI among the studies. The urine collection methods varied from suprapubic aspiration to bladder catheterization, urine bags, or ‘‘clean catch.” In addition, the definition of UTI has changed, and inflammation, defined as leukocyturia or the presence of nitrate on urinalysis, has been endorsed as a component of the definition. Older studies did not have urinalysis as a prerequisite for the diagnosis, and growth of bacteria, even without signs of inflammation, was considered diagnostic of UTI.[52, 53]

Another point of interest is that there seems to be an increase in the reported prevalence of UTIs over time.[51] The reasons behind this are unclear, but there are concerns that the UTI prevalence might have been systematically and increasingly overestimated. In recent decades, many influential articles and institutional guidelines have highlighted the importance of early identification and treatment of UTIs to prevent renal scarring and long-term complications.[14, 27, 54-56] This has led to aggressive testing in pursuit of the diagnosis of UTIs. However, studies have shown considerable contamination rates of urine samples, even when collected with suprapubic aspiration or catheterization, which have been considered the gold standard.[57] Also, the entity of asymptomatic bacteriuria has recently been recognized and accepted for children as well as for adults, opposed to the ‘‘traditional belief’’ that the urine bladder is ‘‘sterile’’.[58] Finally, urinalysis has low specificity and positive predictive value.[59, 60] Thus, the aggressive pursuit might have resulted in an overdiagnosis and misdiagnosis of UTIs.[40] Considering that UTIs account for up to 90% of SBIs,[8, 61, 62] a likely overestimation of the UTI prevalence might have resulted in an overestimation of SBIs in general. However,

the increase in the reported prevalence of UTI might be partially true due to a decrease in the rates of circumcision.[63, 64] Furthermore, it has been hypothesized that intrapartum antibiotic prophylaxis for Group B *Streptococcus* might be leading to a selection for gram negative bacteria, like *E. coli*, which are common causes of UTI.[65-67]

Prevalence per week of age

Several studies have reported the prevalence of infections per week of age. Garcia et al.[68] from Spain, Aronson et al.[69] from the US, and Schwartz et al.[70] from Israel reported that the prevalence of SBIs was highest during the second and third week of life and declined after that. Similar results have been shown for the prevalence of IBIs.[68, 69, 71, 72] Also, Ladhani et al., in an analysis of prospective national surveillance data in England, reported that the incidence of IBIs was highest during the first week of life and declined rapidly afterward.[73] Similarly, Okike et al., in a national population-based surveillance study in the United Kingdom and Ireland, reported the highest incidence of meningitis during the first weeks of life.[74]

Epidemiology and etiology of bacterial infections

In medical textbooks, Group B *Streptococcus* (GBS), *Escherichia coli* (*E. coli*), and *Listeria monocytogenes* have traditionally been mentioned as the leading causes of bacterial infections in young febrile infants. This is true for GBS and *E. coli*. Recent studies have shown that these 2 bacteria account for approximately 60–80% of bacterial infections during the 2 first months of life.[61, 65, 71, 75-78] The prevalence of *E. coli* has increased in the last decades and has become the predominant pathogen according to many studies.[65, 79] This shift might reflect the increase in the prevalence of UTIs, as previously mentioned, which now accounts for approximately 90% of all SBIs. The implementation of intrapartum antibiotic prophylaxis has been implicated as a cause for the decrease in GBS incidence. However, most studies have shown a decrease in early onset disease (e.g., <72 h), but not in late-onset.[78, 80-82] *Staphylococcus aureus* is an increasing cause of infections, and other pathogens, such as *Klebsiella spp., Enterococcus spp.*, *Enterobacter spp.*, *Salmonella spp.,* and Group A *Streptococcus* are also detected in febrile infants with bacterial infections. *Listeria monocytogenes,* once considered a common pathogen in neonates, is only rarely reported, a significant decrease which might reflect improved food safety standards.[9, 61, 71, 75, 77, 83, 84] Similarly, *Haemophilus influenzae, Streptococcus pneumoniae,* and *Neisseria meningitidis* have also become very rare, likely due to herd immunity induced by widespread vaccination.[85-87]

Variation of the reported prevalence

The reported prevalence of SBIs varies almost 5-fold. This variation likely reflects the differences in the methodology and heterogeneity of the studies. One significant difference is that European studies reported prevalence in infants with fever without a source (FWS). In contrast, US studies included infants with fever in general, such as febrile infants with signs or symptoms of respiratory infections predominantly of viral origin. Numerous studies have investigated the prevalence of SBIs in febrile infants with positive viral test results. They reported an overall SBI prevalence ranging from 2.3% to 7.0% among infants who tested positive for respiratory syncytial virus (RSV), influenza, or had clinical signs of bronchiolitis. Infants who tested negative had a 2- to 7-fold higher prevalence.[24, 34-36, 88] Among febrile infants with clinical signs of respiratory viral infection or a positive viral test, more than 90% of the SBIs were UTIs. McDaniel et al., in a recent meta-analysis, showed that in infants with suspected bronchiolitis, the overall reported UTI prevalence of 3.1% (95% CI, 1.8-4.6) would drop to 0.8% (95% CI, 0.3-1.4) if a positive urinalysis result, defined as the presence of pyuria or nitrates, was added as a prerequisite in the definition of UTI.[89] It is essential to highlight that none of the studies mentioned above reported any case of meningitis in infants with respiratory symptoms or with a positive test for RSV or influenza. Thus, it could be safely speculated that in the US, the prevalence of SBIs, particularly meningitis, among febrile infants with FWS is likely much higher than the reported prevalence in febrile infants in general.

Other methodological differences may have contributed to the wide variation in the reported prevalence data. Most studies included febrile infants seen in the emergency department, while others included only hospitalized infants.[90, 91] In addition, a few studies included febrile infants only if blood cultures were performed[7, 62, 65] or procalcitonin was measured.[8] Other studies excluded critically ill infants.[7] The prevalence of SBI is likely higher in hospitalized infants or those who underwent investigations than in those discharged home or those whom the treating physician chose not to perform investigations.

However, the reported variation in the prevalence of SBIs might reflect real differences between countries or even between different settings within countries, and not only methodological heterogeneity. Yaeger et al., in a study performed in an urban setting in the US, reported a 3-fold higher SBI prevalence among infants from neighborhoods with high rates of childhood poverty.[92] Similarly, a study from New Zealand reported a higher incidence of severe infectious diseases in children from the most socioeconomically deprived quintile.[93] In line with socioeconomic status, low maternal education and maternal smoking during pregnancy and after birth are also associated with a higher incidence of bacterial infections.[94-97] Additionally, the mode of delivery has been shown to have a strong association with infections in infants, with higher rates in children born with cesarean section than those with vaginal delivery.[98, 99] Furthermore, low birth weight for gestational age

(SGA) is also associated with a higher incidence of infections.[94, 100] Finally, breastfeeding is one more factor associated with a lower risk of infections in infants.[101]

Most prevalence studies have been conducted in the US and Spain. Of the high income countries, the US and Spain are among the ones with the higher rates of childhood poverty,[102, 103] lower rates of maternal employment and high education,[104] higher rates of maternal smoking during pregnancy,[105] higher rates of cesarean sections,[106, 107] higher rates of newborns with low birth weight,[108, 109] and lower rates of breastfeeding.[110] On the contrary, according to the Organisation for Economic Co-operation and Development (OECD) metrics, Sweden is among the countries with the most favorable rates of all the previously mentioned factors associated with a lower incidence of infection in infants.

Sex-specific prevalence data

Studies on febrile infants have reported differences in the incidence of bacterial infections between the sexes. Almost 40 years ago, Dagan et al., in the paper presenting the Rochester criteria, mentioned that ‘‘being a male is associated with bacterial infections’’.[33] Milcent et al.[91] and Schwartz et al.[70] mentioned a higher prevalence of SBIs among boys, while Gomez et al.[83] mentioned that the prevalence of bacteremia was higher in boys. However, detailed sex-specific prevalence data were not presented in either of these studies. Thus, these reports can be attributed to the significantly higher prevalence of UTI in boys during the first 2 months of life.[51] Videholm et al., in a population-based cohort study, reported a higher incidence of sepsis and bacterial meningitis in boys than in girls in early childhood.[94] Similar sex differences in the incidence and severity of bacterial infections have also been reported in other studies.[111-114] Despite the indications of different risk profiles between boys and girls, detailed sex-specific prevalence data for febrile infants have not been presented in any of the prevalence studies.

Importance of prevalence data

When managing febrile infants, accurate disease prevalence data, particularly for meningitis, are essential for estimating risks, choosing investigations, interpreting test results, selecting optimal antibiotic treatment, and undertaking risk-appropriate decisions on whether to discharge home or hospitalize. In addition, knowledge of the national and local prevalence data is vital for developing management guidelines to enhance patient safety and optimize resource utilization. Furthermore, age- and sex-specific prevalence data might allow for more patient-centered and individualized risk assessments. However, extrapolating SBI and IBI prevalence data from heterogeneous studies and settings with different characteristics could result in significant underestimation or overestimation of risks.

Thus, there is a need for prevalence studies in diverse settings and across several countries. Sweden has different population characteristics compared to the countries where most studies have been conducted. This leads to the first aim of this thesis, which is to investigate the age- and sex-specific prevalence of SBIs in infants ≤60 days old with FWS who presented at the Pediatric Emergency Department in four urban areas in Sweden.

Management of febrile infants

Identifying febrile infants with IBI or SBI is of paramount importance for initiating appropriate antibiotic treatment. However, identification is challenging. Meningitis, bacteremia, and UTI often present only with fever, and disease-specific signs are usually lacking, particularly at the beginning of the illness course. This is even more prominent in young infants, where typical meningeal signs such as nuchal rigidity, headache, photophobia, or UTI symptoms such as sychnuria and dysuria are absent or cannot be recognized. Therefore, in febrile infants, clinical evaluation is based more on non-specific clinical features such as the quality of the cry, skin color, alertness, and symptoms such as lethargy, irritability, and refusal to feed. Risk assessment becomes even more difficult because most febrile infants are brought to the emergency department soon after the parents have identified the fever. In this case, even non-specific symptoms have not yet been developed.[7, 8] Consequently, physicians' clinical assessment of febrile infants has shown to be of low sensitivity in identifying infants with IBI. In a study by Nigrovic et al., almost 50% of infants with bacterial meningitis were evaluated as having a lower than 5% risk of meningitis.[115] Private office practitioners, in a study by Pantell et al., missed 2 IBI cases out of 63 when they relied on their clinical judgment.[9] Clinical scores also have limitations. In the study by Nigrovic et al., only 10 of the 24 infants with bacterial meningitis had a high Yale Observation Scale score.[115]

Because of these challenges in identifying infants with IBI, several management strategies have been employed. During the 70s-80s, the commonly accepted practice for all febrile infants younger than 3 months of age consisted of urinalysis, blood tests, urine, blood, and cerebrospinal fluid (CSF) cultures. This set of investigations is usually referred to as ''sepsis evaluation''. In addition, all infants were hospitalized and treated with parenteral broad-spectrum antibiotics.[116] DeAngelis et al., in a landmark paper published in 1983, highlighted the possible complications of hospitalization on infants and the economic burden on the families.[25] This prompted the first attempts to develop management strategies to identify infants at low risk that could be managed without antibiotics and hospitalization.

Management guidelines

The first strategy to identify infants at low risk was published in 1985 by Dagan et al.[33] They developed a set of low-risk criteria based on physical findings, peripheral white blood cell (WBC) count, and urinalysis by retrospectively analyzing a cohort of hospitalized febrile infants aged ≤3 months during 1982-1984 (Table 6). They suggested that it could be safe to hospitalize and observe without antibiotics febrile infants who met all the low-risk criteria. This set of criteria did not include lumbar puncture, which was quite radical at that time. These low-risk criteria were tested in a prospective study of 237 febrile infants aged ≤60 days in 1985-1986. The conclusion was that "managing fever in selected infants younger than 2 months as outpatients is feasible, although not simple" and that adequate follow-up should be ensued.[117] This set of criteria, known as the Rochester criteria, was studied again a few years later.[118] It was once more concluded that low-risk febrile infants ≤60 days could be managed as outpatients with the condition of an adequate safety net. Furthermore, modifications to expand the low-risk criteria should be considered.

A new set of low-risk criteria for febrile infants 28-90 days old was tested prospectively in Boston during 1987-1990.[16] The Boston criteria consisted of WBC count, urinalysis, and cerebrospinal fluid (CSF) testing (Table 6). Routine management included ''sepsis evaluation'' for all infants. The researchers concluded that "after a full evaluation for sepsis, outpatient treatment of febrile infants with intramuscular administration of ceftriaxone pending culture results and adherence to a strict follow-up protocol is a successful alternative to hospital admission."[16] According to the Boston criteria, febrile infants aged <28 days should be considered high risk, hospitalized, and treated with antibiotics.

Another set of criteria, the Philadelphia criteria, was published in 1993. These criteria were similar to the Boston criteria, only with different thresholds (Table 6).[15] They were based on a prospective study of febrile infants 29-56 days old from 1987 through 1992. The researchers concluded that "it is possible to identify a group of febrile infants older than 28 days of age who are at low risk for serious bacterial illness and who can be safely and effectively cared for at home without antibiotics".[15] As in the Boston criteria, the standard management included ''sepsis evaluation'' for all infants, and infants ≤28 days were considered high-risk. A prospective study was performed to validate the efficacy of the Philadelphia criteria from 1994 to 1996.[119] It was concluded that outpatient management of low-risk febrile infants without antibiotics is reliable and safe.

Several studies have assessed the accuracy of the Rochester, Boston, and Philadelphia criteria. Most recently, Lyons et al. modified the Boston and Philadelphia criteria and performed a secondary analysis in a cohort of 10 928 infants 29-60 days of age evaluated for meningitis in 23 EDs in the US and Canada.[85] They reported that the modified Philadelphia and Boston criteria misclassified as low risk 23-32% of infants with bacterial meningitis. Similarly,

Aronson et al. modified the Philadelphia criteria by excluding routine CSF testing. They performed a secondary analysis in a cohort of febrile infants ≤60 days with IBI seen in 11 PEDs in the US.[120] They reported that the modified Philadelphia criteria without routine CSF testing had high sensitivity for IBI and could be used for infants >28 days. However, they recommended caution and further studies on infants aged ≤28 days.

It took almost 20 years for a new management approach to be suggested. Mintegi et al., published a risk stratification protocol based on urinalysis, absolute neutrophil count (ANC), C-reactive protein (CRP), and procalcitonin (PCT) in 2014.[27] Low-risk infants could be discharged without antibiotics (Table 6). The major difference from the Boston and Philadelphia criteria was that the age cutoff point to be considered high-risk was lowered to 21 days. Additionally, CSF analysis was not necessary for the stratification of infants aged >21 days. These low-risk criteria, known as the ''step by step'' approach, were retrospectively derived from a cohort of infants ≤90 days old with FWS seen in 5 Spanish and 2 Italian PEDs from 2008 to 2010. Gomez et al., retrospectively validated this new approach in a cohort of febrile infants seen in 11 European PEDs.[121] A similar validation was performed in a Spanish PED.[122] Both validation studies concluded that evaluating well-appearing febrile infants aged >21 days without routine lumbar puncture (LP) and discharge home without antibiotics the low-risk infants is appropriate.

In 2019, Kuppermann et al. from the PECARN febrile infants working group published a set of low-risk criteria based on urinalysis, ANC, and PCT.[7] This set, known as the PECARN rule, was retrospectively developed from a cohort of 1896 febrile infants ≤60 days old who were recruited in a prospective multicenter study to evaluate RNA microarray analysis for detecting bacterial infections.[123] All previous prediction models used pre-existing test cutoff points based solely on expert opinion or established praxis. The PECARN researchers statistically derived the new set of low-risk criteria (Table 6). However, the authors recommended further validation before implementing the new rule. Furthermore, they suggested caution in managing infants aged ≤28 days without routine LP due to the high risk of bacterial meningitis and herpes encephalitis. Velasco et al., validated the PECARN rule in a cohort of 1247 febrile children seen in a Spanish PED between 2007 and 2018.[8] They reported that the rule performed less well than in the original study since it stratified 5 infants with IBI as low-risk with 2 cases of bacterial meningitis among them.

The Boston and Philadelphia criteria have been the most influential and have shaped the management of febrile infants in most parts of the world over the last 3 decades. The United Kingdom's National Institute for Health and Care Excellence (NICE) recommends routine ''sepsis evaluation'' for all febrile infants ≤3 months of age. For febrile infants younger than one month additionally recommends LP, hospitalization, and treatment with parenteral antibiotics.[14] Similar management is

recommended at the major university children's hospitals in Australia and Canada.[124, 125]

Table 6. Most common management guidelines for young febrile infants.

	Rochester	Boston	Philadelphia	Step by Step	PECARN[1]
Study Period	1982-1984	1987-1990	1987-1992	2008-2010	2011-2013
Design	Retrospective	Prospective	Prospective	Retrospective	Retrospective
Cohort size	233	553	747	1123	1821
Age (days)	≤90	28-89	29-56	0-90	≤60 days
Fever (˚C)	≥38.0	≥38.0	≥38.2	≥38.0	≥38.0
History	Term, Previously healthy, No prior antibiotics	No prior antibiotics or immunization	Not defined	Not defined	Term, Previously healthy, No prior antibiotics
Physical Examination	Well-appearing, No focal signs	Well-appearing, No focal signs	Well-appearing, No focal signs	No focal signs	Well-appearing, No soft-tissue infection
Laboratory Low-Risk Criteria	WBC[2] >5000 & <15000 ABC <1500 UA ≤10 WBC/hpf Stool ≤5 WBC/hpf (if diarrhea/bloody stools) Normal CXR (if respiratory symptoms)	WBC[2] <20000 UA <10 WBC/hpf CSF <10 WBC[2] Normal CXR if respiratory symptoms	WBC[2]<15000 UA <10 WBC/hpf Negative urine microscopy CSF <8 WBC[2] Negative CSF Gram stain Stool with minimal WBC and no blood if diarrhea Normal CXR if respiratory symptoms	ANC <10000 Urine dipstick without leukocyturia PCT <0.5 CRP <20	Urine dipstick without leucocyte esterase or nitrite UA <5 WBC/hpf ANC <4090 PCT <1.71
High Risk	Ill-appearing, Abnormal laboratory results	All <28 days, Ill-appearing, Abnormal laboratory results	All ≤28 days, Ill-appearing, Abnormal laboratory results	All ≤21 days, Ill-appearing, Abnormal laboratory results	Ill-appearing, Abnormal laboratory results
Management for Low-risk	No antibiotics, Inpatient observation or discharge home if adequate follow up	Intramuscular Ceftriaxone Outpatient if adequate follow up, Sepsis evaluation	No antibiotics, Inpatient observation or discharge home if adequate follow up	No antibiotics, Inpatient observation or discharge home if adequate follow up	No specific recommendation, Cautiousness for ≤28 days

[1]Not endorsed at the time; [2]WBC, white blood cells per mm^3; ABC, absolute band count per mm^3; UA, urinalysis; hpf, high power field; CXR, chest X-ray; CSF, cerebrospinal fluid; ANC, absolute neutrophil count per mm^3; PCT, procalcitonin, ng/ml; CRP, C reactive protein, mg/ml; sepsis evaluation, blood, urine, and CSF culture

The variation of recommendations for managing febrile infants recently led the AAP to perform an extensive review of the literature and develop a recommendation for evaluating and managing well-appearing infants aged 8 to 60 days old.[28] One key statement is that the 21 days age threshold could be considered to stratify well-appearing febrile infants as high-risk. Another statement is that newer inflammatory

markers, such as CRP and PCT, should be incorporated into management. However, the authors underscored that these recommendations ‘‘do not indicate an exclusive course of treatment or serve as a standard of medical care.” Local circumstances, individual differences, and parental preferences should be considered. This statement reflects a lack of consensus and ongoing debate regarding the management of febrile infants.

The debate about the management

In 1993 Baker et al. opened the paper presenting the Philadelphia criteria by stating: ‘‘What the management of fever should be in an infant less than two months of age has been strongly debated in the pediatric literature’’.[15] Since then, modifications of the Rochester, Boston, and Philadelphia criteria or new prediction rules have been suggested every few years. These suggestions were initially met with criticism to later become common ground and eventually be adopted by health associations. Thus, 30 years after the Philadelphia criteria were published, the debate is not only on but also involves more aspects and is more geographically spread.

Differences in prevalence

First, it is questioned whether management strategies can have universal applicability. All protocols were developed in the US, except the ‘‘step by step’’ approach. The derivation and the validation studies were performed in university pediatric hospitals in large urban centers, hence they were based on local epidemiological data. However, as described in previous chapters, the prevalence of SBI and IBI might differ significantly between countries, and even between different settings within countries. Furthermore, the Boston and Philadelphia criteria, which constitute the basis for managing febrile infants, were developed almost 30 years ago. Since then, the epidemiology of bacterial infections has changed, with an increase in the proportion of UTIs and *E. coli* becoming the predominant causative organism.[61, 65]

Small cohorts and lack of external validation

The second aspect of the debate is the accuracy of protocols derived from relatively small patient cohorts. The Rochester, Boston, and Philadelphia criteria were derived from single-center studies that included 233–747 febrile infants. Even the subsequent validation studies were mostly single-center, and none included more than 1053 infants. The ‘‘step by step’’ approach was retrospectively derived from a study performed in 7 PEDs which included 1123 febrile infants. Two years later it was validated in a study that included 4 additional PEDs in a cohort of 2185 infants. External validation is essential before implementing prediction models in clinical practice because prediction models tend to perform better on the data on which the model was constructed than on new data.[126, 127] However, most of these prediction

models have not been externally validated in diverse settings and in several countries.

New biomarkers

The third aspect of the debate is the utility of WBC count in identifying an IBI in infants and the emergence of new biomarkers. The WBC cutoffs used in the Rochester, Boston, and Philadelphia criteria were based on preexisting values and were not statistically derived. Furthermore, numerous studies have shown that the WBC count has a low sensitivity and a low positive predictive value to rule in or rule out an IBI.[128, 129] Thus, the new AAP practice guideline does not recommend using WBC for risk stratification.[28] The absolute neutrophil count (ANC) has been shown to have better characteristics and has replaced the WBC count in the recent prediction models (i.e., ''step by step'' and PECARN rule).[7, 27]

C-reactive protein (CRP) is an acute-phase protein produced in the liver in response to inflammation, which rises in the blood within 6 hours and peaks within 24-48 hours.[130] It has been shown to have better sensitivity and specificity than WBC and ANC in identifying an IBI.[91, 131-133] However, Gomez et al. in a study evaluating the performance of CRP concluded that they could not identify any reliable cutoff value to rule out an IBI in febrile infants ≤21 days.[134] Several studies reported similar conclusions that CRP could not serve as a stand-alone test to identify or exclude IBIs.[91, 132, 135]

Procalcitonin (PCT) is a relatively new biomarker that is becoming available in more hospitals. It is the precursor of the hormone calcitonin and is released into circulation due to systemic infection.[136] Its levels start to rise 4 hours after the onset of inflammation and peak between 12-24 hours. It is shown to have better sensitivity and specificity, in identifying IBIs, than CRP, WBC count, and ANC.[91, 133, 134, 137, 138] Thus, it has become central in all newer prediction models (i.e., ''step by step'' and PECARN). Although PCT is probably the best biomarker, its sensitivity and specificity are far from sufficient to be used alone for the identification of febrile infants with IBI, according to the above studies.

RNA biosignatures is a novel diagnostic tool that has shown promising results for discriminating bacterial from viral infections. Microarray analyses of blood leucocytes can identify specific host responses induced by microbial pathogens. This host responses, called "RNA biosignatures," have the potential to translate into a simple bedside diagnostic test. However, further studies with larger cohorts are needed to validate the test accuracy and assess the utility of RNA biosignatures in clinical practice.[123, 139, 140]

The utility of Lumbar Puncture

The fourth aspect of the debate is the age threshold for routinely performing LP in well-appearing febrile infants, or even whether LP should be routinely performed.

Bacterial meningitis is a devastating disease with significant mortality, morbidity, and short- and long-term sequelae.[10, 11, 39, 141] Therefore, early identification and treatment are of utmost importance.

The main argument in favor of routine LP is the perception that young febrile infants, especially early in the trajectory of the illness, can appear well despite having bacterial meningitis. Martinez et al. demonstrated that out of 11 febrile infants ≤90 days with meningitis, 6 were evaluated as well appearing during the initial encounter, and all were younger than 21 days.[142] Therefore, routine LP is recommended for all febrile infants ≤21 days, even when they appear well. However, several studies have shown that in most meningitis cases, lethargy, seizures, irritability, coma, bulging fontanel, respiratory distress, signs of shock or circulatory failure often are present at the presentation or develop within several hours after the onset of the fever.[11, 143-145] Thus, the likelihood of meningitis in infants with no alarming symptoms is probably very low. Clinical observation can identify alarming signs or symptoms in infants who present too early in the trajectory of the illness.

Furthermore, the utility of routine LP is questionable because of the reported low sensitivity and specificity of routine CSF testing. A study by Ouchenir et al. showed that 5% of infants with proven bacterial meningitis had no pleocytosis at admission, and an additional 6% had CSF WBC count within the normal references.[141] Lyons et al. reported that despite routine CSF testing, the modified Philadelphia criteria misclassified 23% of the infants with meningitis and the modified Boston criteria misclassified 32%.[85] A recent systematic review also concluded that the absence of pleocytosis does not reliably exclude bacterial meningitis, particularly in cases with short fever duration.[146] Furthermore, Scarfone et al. demonstrated that among febrile infants 29-60 days who underwent an LP, only 3.4% had a positive CSF culture, but in none of them the bacteria identified were considered as true pathogens.[147] Similarly, Greenhow et al. demonstrated that of 1796 CSF cultures, 73 (4%) were positive, but 57 of 73 (78%) were considered contaminants.[79] Leazer et al. also reported an 87% CSF contamination rate.[148] Thus, routine CSF testing has low specificity and, if performed very early in the course of the disease, low sensitivity as well.

Another argument for routinely performing LP is the perceived considerable risk of Herpes Simplex Virus (HSV) infection. Kuppermann et al., recommended cautiousness with applying any protocol without routine LP in febrile infants younger than 28 days due to the risk of HSV meningitis or encephalitis.[7] The incidence of neonatal herpes is estimated to be around 9 per 100 000 live births in Europe and 19.9 per 100 000 in North America.[149] However, several studies have demonstrated that around 30% of HSV cases are identified in premature neonates. In addition, most infants have skin lesions or symptoms such as seizures, lethargy, apnea, irritability, poor feeding, temperature instability, or maternal history of HSV infection or fever.[150-153] Thus, the prevalence of HSV infection among term, well-

appearing infants without risk factors is likely very low. Furthermore, studies have shown that approximately 20-40% of neonates with confirmed HSV central nervous system infection had no CSF pleocytosis at the initial investigation, and around 30% had negative CSF PCR results.[151, 153, 154] Hence, routine CSF testing has also been shown to have low sensitivity in identifying an HSV infection.

In conclusion, the prevalence of bacterial and HSV meningitis is likely extremely low in term, well-appearing infants without risk factors. In addition, CSF testing may have low sensitivity and specificity, especially in the early stages of the illness. Thus, in patients with low pre-test probabilities, such as well-appearing infants who present very early, routine CSF testing may have low positive and negative predictive values and may result in high rates of ''false positives'' and ''false negatives.

The notion that clinical appearance is not reliable

The fifth aspect of the debate is whether physicians can rely on their clinical judgment when evaluating young febrile infants. It has been shown that the Yale Observational Score is not accurate for febrile infants ≤60 days.[115, 155] In another study by Martinez et al., 18 febrile infants ≤21 days who were evaluated as well-appearing were subsequently diagnosed with an IBI.[142] However, studies performed in office settings in the US showed uniformly reassuring outcomes without an alarming rate of missed IBIs, although pediatricians relied more on their clinical judgment and performed fewer investigations.[9, 156, 157]

Altered healthcare-seeking behavior

The sixth aspect of the debate is the utility of management guidelines after an observed change in parents' healthcare-seeking behavior. Pediatric healthcare visits due to fever have been steadily increasing in the recent decades both in Europe and in the US,[17, 158] despite the fact that the pediatric population has not increased.[159, 160] It has been reported that parents increasingly believe that fever is a disease that can cause harmful effects, such as brain damage and death, rather than just a sign of illness. The term ''fever phobia'' has been introduced to describe such exaggerated concerns about the consequences of childhood fever.[161, 162] The combination of ''fever phobia'' and the perceived high risk of serious bacterial infections may have resulted in febrile infants being brought to the PED earlier than before. The PECARN study from the US reported a fever duration of less than 12 hours for 63% of the infants seen at the PED.[7] Studies from Spain reported that for almost 80% of the infants, the duration was less than 12 hours, and for 50-70% fewer than 6 hours.[8, 27, 134] There are concerns that early presentation may hamper the ability of physicians to spot febrile infants with an IBI, since alarming symptoms and signs may not have developed. It also undermines the sensitivity of biomarkers, such as CRP and PCT, which start to rise after 4–12 hours.

The measured outcome of ''failure''

The seventh aspect of the debate is whether a missed SBI or IBI should a priori be considered an adverse outcome. All prediction rules and validation studies have reported as ''failure'' the proportion of SBIs or IBIs that were not identified at the index visit. However, it is questionable whether a delay of a few hours in the identification of disease should always equal ''harm."

For many years, UTI has been classified alongside bacteremia and meningitis as an SBI. Physicians commonly believe that early treatment prevents sepsis, renal scarring, and chronic kidney disease. However, studies have shown that UTI is seldom the cause of sepsis in infants without urinary tract abnormalities.[163, 164] Furthermore, data on whether early treatment prevents renal scarring are conflicting. Some studies have shown that delayed treatment of more than 72 hours from the debut of the fever increases the risk of renal scarring,[41, 165] while other studies have shown that early treatment does not decrease the risk of renal scarring development.[40, 166] Additionally, there is no convincing evidence that renal scarring causes long-term consequences, such as chronic kidney disease and hypertension.[42, 167, 168]

Similarly, bacteremia is classified alongside meningitis as an IBI. Bacteremia has long been feared to lead to sepsis or meningitis with potentially dire short- and long-term consequences. This belief probably originates from the pre-vaccine era, when *Neisseria meningitidis*, *Haemophilus influenzae*, and *Streptococcus pneumoniae* were common causes of occult bacteremia.[169, 170] These three bacteria are specifically associated with the progression of bacteremia to meningitis.[13] The widespread vaccination programs have substantially decreased their prevalence among the general pediatric population and subsequently among young infants through herd immunity. As a result, as discussed in the previous chapter, *Neisseria meningitidis*, *Haemophilus influenzae*, and *Streptococcus pneumoniae* are currently extremely rare causes of bacteremia in febrile infants aged ≤60 days. Thus, the notion that occult bacteremia can cause significant morbidity and mortality in well-appearing febrile infants currently lacks reliable evidence. This is supported by studies among well-appearing febrile children who were sent home from the PED without antibiotics and were found to have bacteremia. Most children were afebrile at the return visit to the PED, and none experienced any adverse outcomes.[46, 171] Similar results were demonstrated in studies on febrile infants. There were no deaths or severe morbidity among well-appearing febrile infants with isolated bacteremia who were discharged home without antibiotics.[44, 121, 142, 172] Furthermore, concomitant bacteremia in cases of UTI is not associated with a worse prognosis or outcome.[47, 48, 173, 174]

Moreover, Vaillancourt et al., quite surprisingly, found similar health outcomes among children aged 30 days to 5 years with bacterial meningitis who were admitted at the initial visit and those admitted at a repeat visit.[175] Similarly, McIntyre et al.

found that delayed hospital admission did not predict the combined variable of death or severe neurological sequelae in children aged 0-14 years with bacterial meningitis.[176] Other studies, also failed to find a significant association between death or neurologic abnormalities and the duration of illness before hospitalization.[177, 178]

Thus, for well-appearing febrile infants who present to the PED with only a few hours of fever, there is scarce evidence in the current literature that delayed identification of UTI, isolated bacteremia, or even meningitis necessarily equals ''harm."

Side effects of ''sepsis evaluation''

Finally, the number of febrile infant admissions and the length of stay have increased in recent decades. An increase despite the decrease in the prevalence of meningitis and advances with better and faster diagnostics tools.[179-181] Quite interestingly, DeAngelis et al., already in 1983, reported the iatrogenic complications and financial costs of hospitalizing febrile infants.[25] All studies that derived or validated management guidelines focused solely on the number of ''missed'' SBIs or IBIs. However, there is growing evidence that hospitalization is not always the ''safer'' option. A study performed in 6 academic pediatric hospitals identified 40 harmful events per 100 admitted patients.[182] Other studies have reported complications related to intravenous catheters, medication overdoses, anaphylactic reactions, and medical procedures such as LP.[26, 180, 183, 184] Another issue is the risk of hospital-acquired infections, which are reported to range from 1% in general pediatric wards to 24% in pediatric intensive care units.[185, 186] As a result, although less than 1% of hospitalized well-appearing febrile infants may have an IBI, considerably more are exposed to the risk of acquiring an infection and up to 40% to a ''harm'' from an adverse event. Furthermore, hospitalizations can be a significant economic burden for the health system and the family.[187-190] In addition to the financial burden, parents face difficulties taking caring of the rest of the family.[191, 192] Also, parents of hospitalized infants experience significant stress concerning their child's health, and hospitalization at an early age is associated with the development of the vulnerable baby syndrome.[193, 194]

Another issue that is often overlooked is the side effects of the routine administration of parenteral broad-spectrum antibiotics. There are indications that antibiotic exposure in early infancy is associated with an increased risk of chronic diseases later in life, such as inflammatory bowel disease,[195] diabetes,[196] obesity,[197] juvenile idiopathic arthritis,[198] asthma, and allergies.[199, 200] A recent systematic review described an association between antibiotic exposure and adverse long-term health outcomes in children.[201] Furthermore, antibiotic resistance is one of the greatest threats to global health, food security, and development, which also results in prolonged hospital stays, higher medical costs, and increased mortality.[202]

In addition, routine testing or overtesting has considerable disadvantages. Urine testing with bladder catheterization or suprapubic aspiration is painful, invasive, and stressful for infants and their families and is a potential cause of infection.[203-205] Newman et al. concluded that aggressive urine testing might be more harmful than helpful.[40] Lumbar puncture is painful for the infants, stressful for the parents, time- and resource-consuming for the already overwhelmed PEDs, and if traumatic or unsuccessful, increases the hospitalization rates and the length of stay.[192, 206] Blood cultures are very often contaminated, with most studies on febrile infants reporting contamination rates of approximately 80%.[44-46, 61, 207, 208] Similar high contamination rates have been reported for CSF and urine cultures, as mentioned in previous chapters. ''False-positive'' cultures can potentially lead to repeated testing, unnecessary or prolonged antibiotic courses, and increased and prolonged hospitalization.

In conclusion, the management guidelines for febrile infants with routine testing, antibiotic treatment, and hospitalization have substantial consequences that are currently overlooked. The effects and consequences of overdiagnosis, medical overuse, and medical interventions have recently begun to attract more attention in pediatrics as well. [209-211]

Management variation

The debate regarding the management guidelines is reflected in the substantial variation in the management of febrile infants. Aronson et al., in a study from 37 US hospitals, reported that the proportion of febrile infants ≤28 days who underwent the recommended investigation with urine, blood, and CSF testing was 72% (Table 7).[69] Variation was observed between the 37 hospitals, with an interquartile rate of 66.2 to 76.5 for infants ≤28 days and 38.5 to 58.8 for those 29-56 days old. Also, almost 20% of the infants aged ≤28 days were not hospitalized, and 25% were not treated with antibiotics. Other studies from the US have also reported significant variation with 62-93% rates of LP, 76-82% of antibiotic treatment, and 78-98% of hospitalization for the first month of age. The variation was even greater during the second month of life (Table 7).[157, 187, 212, 213] Similar variations have also been reported in other countries. Goldman et al. in a study on febrile infants ≤90 days in 6 Canadian PEDs, reported rates of LP 24–62%, antibiotic treatments 48–76%, and hospitalization 58–79%.[214] Gomez et al. reported that of the febrile infants ≤21 days seen in a Spanish PED during 2007-2018, 73% underwent an LP and 83% were hospitalized.[134]

An exciting finding from studies on management variation in the US is that febrile infants seen in private pediatric offices were significantly less likely to undergo laboratory tests, receive antibiotic treatment, and be hospitalized. Pantell et al., performed a study in the offices of 573 practitioners within the Pediatric Research in Office Settings (PROS) network during 1995-1998. They reported that only 46%

of the infants younger than one month underwent complete ‘‘sepsis evaluation,” were hospitalized, and treated with antibiotics.[9] Another analysis of the same cohort showed that only 68% of the infants 0–30 days old underwent urinalysis.[156] Greenhow et al., analyzed electronic records of febrile infants seen in clinician’s offices or PEDs in Northern California between 2010 and 2013. They found that infants seen in an ED were 5 times more likely to be cultured than infants seen in an office setting.[157]

Table 7. Reported variation in Management of febrile infants ≤60 days

			1st month (%)					2nd month (%)				
Author/ Pub Year	**Country**	**Study Period**	LP	BC	UC	AB	Hos	LP	BC	UC	AB	Hos
Bonilla 2019	Spain	2003-2017	62	98	88	–	–	20	98	83	–	–
Rogers 2019	USA	2008-2013	75	82	81	82	84	–	–	–	–	–
Jain 2014	USA	2010	63	75	73	–	–	26	68	65	–	–
Greenhow 2016	USA	2010-2013	75	80	81	76	78	53	80	84	51	44
Aronson 2014	USA	2011-2013	75	80	79	–	80	50	81	82		44
Aronson 2015	USA	2013	93	–	99	–	98	69	–	99	–	64

LP, lumbar puncture; BC, blood culture; UC, urine culture; AB, antibiotics; Hos, hospitalization

Outcomes

Unexpectedly, no significant association with increased morbidity or mortality was found in febrile infants who underwent fewer investigations or were sent home without antibiotic treatment. In the PROS study by Pantell et al., only 2 infants with bacterial meningitis or bacteremia were not immediately recognized at the index visit.[9] The researchers concluded that ‘‘practitioners relying on their clinical management were at least as sensitive in treating bacteremia and bacterial meningitis’’ as the current guidelines. Similarly, there were no cases of delayed recognized IBI among febrile infants discharged home in the study by Greenhow et al.[157] No cases of meningitis were identified among febrile infants ≤60 days who were sent home without an LP in a study performed in 26 pediatric hospitals in the US.[213] Similar results were reported by Jain et al. in a study of 36 pediatric hospitals in the US.[212] None of the 369 febrile neonates who were sent home were subsequently diagnosed with meningitis, and only one was diagnosed with bacteremia. The secondary analysis of the PROS cohort showed that despite no urine test was performed in one-third of the febrile infants, only 2 out of 807 (0.2%) were subsequently diagnosed with UTI without any catastrophic consequence though.[156] Furthermore, Aronson et al. reported that 3-day revisits and revisits that resulted in hospitalization did not correlate with the admission rate at the index visit. In addition, 3-day revisits were as low in hospitals without and with clinical practice guidelines.[69, 187] Finally, a Dutch study evaluated adherence to the national guidelines for managing febrile infants ≤90 days.[215] It reported that half of the

included infants did not receive the recommended investigations or treatment. Among them was only one infant with meningitis, who did receive antibiotics at presentation.

Lyons et al. studied the performance of the modified Philadelphia and Boston criteria (both included routine CSF testing) among well-appearing febrile infants 29-60 days seen in 23 PEDs in the US.[85] They reported that 23% and 32% of infants with bacterial meningitis were misclassified as low-risk, despite routine CSF testing. Aronson et al., in another study on febrile infants ≤60 days, evaluated the Philadelphia (modified as not to include CSF testing) and the Rochester (no CSF testing) criteria.[120] They reported that no infant with bacterial meningitis was misclassified as low-risk by the modified Philadelphia and 12% by the Rochester criteria. The initial ‘‘step-by-step derivation study by Mintegi et al.[27] and the validation by Gomez et al.[121] reported that 2% and 8% of infants with IBI, respectively, were misclassified as low-risk. Thus, the rates of misclassified meningitis or IBI were not lower in studies where protocols with routine sepsis evaluation’’, LP, and hospitalization were deployed than in studies where the management was less extensive and more influenced by the clinician’s judgment.

To conclude, there are several guidelines for febrile infants aged ≤60 days, and there is no consensus regarding the optimal approach. There is substantial variation in management within hospitals, between hospitals, and between hospitals and private offices. Despite this variation, no significant differences in outcomes have been reported. However, most management guidelines and studies on variation and outcomes originate in the US and Spain. At the same time, there are scarce management and variation data from other countries, and none from Sweden.

Importance of studying variation in Sweden

Sweden has no national or regionally endorsed guidelines for managing young febrile infants. Anecdotally, the usual management of febrile infants aged ≤60 days includes urine dipstick, WBC count, and CRP. Urine, blood, and CFS cultures, hospitalization, and antibiotic administration are reserved for ill-appearing infants or infants with altered test results. It has been demonstrated that PEDs without specific guidelines have lower rates of investigations with urine, blood, and CSF cultures.[190, 216] Gudjonsdottir et al. performed an epidemiological study to document the incidence of late-onset infections in infants 3-120 days old in Sweden’s second-largest city and 5 surrounding municipalities between 1997 and 2017.[217] Quite surprisingly, they identified only 102 CSF cultures during the 20-year study period. In Sweden, the consumption of broad-spectrum antibiotics and the number of hospital beds are among the lowest in OECD countries and considerably lower than in the US and Spain.[218, 219] Thus, there are indications that the management of febrile infants in Sweden is not based on the management recommended by most international guidelines. However, there are no studies describing the management

of febrile infants in Sweden, and no knowledge of the outcomes. Describing management variations and identifying differences in outcomes could provide opportunities for the improvement of current guidelines to enhance patient safety. It could also assist in the development of guidelines that are better adjusted to national, regional, or local characteristics. Furthermore, it can help optimize the utilization of resources. As pointed out by Schroeder et al., a missing component of the dialogue regarding patient safety is not only which investigations we can add or do more, but also how we can safely do less. Often the best way to prevent harm might be to avoid medical interventions.[220]

Thus, there is a need to describe the management of febrile infants in Sweden and study their outcomes. This leads to the second aim of this thesis, which is to describe the clinical management and adverse outcomes of febrile infants ≤60 days old in 4 Swedish PEDs that do not have written formalized guidelines.

Defining Fever

Almost all guidelines for febrile infants use a temperature of ≥38.0°C to define fever. Prevalence and management studies used this definition of fever as an inclusion criterion. The definition of fever dates back to 1868 when Carl Wunderlich published the results of temperature measurements of adult patients admitted to his wards.[221] He reported that axillary temperature ranged from 36.25°C to 37.5°C and the mean temperature was 37.0°C. He subsequently defined fever as a temperature ≥38.0°C. The body temperature also varies among infants. It is lowest (approximately 36.0°C) at night during sleep and highest (approximately 37.8°C) in the afternoon. Activity and feeding, especially by the bottle, can raise body temperature.[222] It is unclear whether bundling elevates body temperature, but some researchers have suggested that physicians caring for febrile neonates should inquire about bundling.[223, 224] In addition, a study demonstrated that infants aged 0–2 months might have a higher normal temperature.[225] Furthermore, the measurement site varies, with the axilla and rectum being the most common sites. Both sites are considered reliable, but the axillary temperature is shown to be 0.25–0.5°C lower than the rectal.[226] Infrared thermometers have become more affordable and commonly used in the last few years, but they have been shown to have poor accuracy in infants.[227] Consequently, this variability impedes a universal upper normal temperature definition and fever should instead be defined as body temperature elevation above the normal for the individual. However, for clinical and research purposes, a definition of fever with a temperature of ≥38.0°C has been accepted for infants without further specification for the site of measurement and the type of thermometer.

According to all guidelines, infants with recorded temperature who fulfill the definition of fever should be managed in the same way, irrespective of the height of the fever. However, recent studies have shown an association between the height of the fever and the risk of IBI in febrile infants aged ≤60 days. Pantell et al. demonstrated that well-appearing infants older than 25 days with a fever ≥38.6°C had a 3-fold higher IBI prevalence than those with a fever <38.6°C.[9] Also, Aronson et al. reported that the odds ratio for having an IBI were 2.13 and 6.57 for infants with a fever of 38.0–38.4°C and of ≥38.5°C versus infants with a temperature <38.0°C.[228] Similar association between the height of the fever and the risk of IBI has been reported in several more studies.[29, 229, 230]

As with the height of the fever, management guidelines do not differentiate whether an infant has documented fever at the PED or only fever at home reported by the parents. This is situation clinicians often encounter when parents seek medical help due to a fever measured at home and the infant is afebrile at the PED. In approximately 30% of visits, owing to fever, the infant is afebrile at the PED.[122, 231] According to all guidelines, infants afebrile at the PED should be managed as febrile. The first to investigate whether there is any difference in the risk of SBI between febrile and afebrile infants ≤28 days of age was Bonadio et al. in 1987.[232] None of the afebrile infants had an SBI versus 14.5% of the febrile infants. Despite this, the authors recommended a complete investigation for afebrile infants. Another study reported that of the afebrile infants ≤28 days, 8.3% had a UTI and none had IBI versus 14.4% UTI and 3.5% bacteremia of the febrile.[233] The authors concluded that the risk in the afebrile group was so low that an approach with fewer investigations may be appropriate. Mintegi et al. found similar rates of bacteremia in afebrile and febrile infants ≤90 days but no case of meningitis in the afebrile group. The authors concluded that the management should still be the same.[234] Ramgopal et al., in a study on infants ≤28 days and another on infants ≤60 days, observed a lower risk for the afebrile infants, but likely not low enough to alter decision making.[231, 235] Although most of the above studies did not recommend different management, several studies have reported lower rates of investigations, antibiotic treatments, and hospitalizations in afebrile infants.[212, 234] This led researchers to hypothesize that the absence of fever at the PED may influence the decision-making process and contribute to the reported variation in management

However, there were methodological differences between the studies. First, three age inclusion criteria were used. Second, Mintegi et al. and Bilavsky et al. included only infants with fever without source, while Ramgopal et al. and Bonadio et al. included febrile infants in general. Third, the baseline prevalence of bacterial infections was 3 times higher in the study by Mintegi et al. than in the 2 studies by Ramgopal et al. Thus, the current data are from a few studies with small cohorts. Therefore, they do not allow definite conclusions regarding whether afebrile infants should be managed like febrile infants.

Knowledge of accurate risk estimates is essential for the design of management guidelines. It is also important to make clinical decisions when phasing the common situation of an afebrile infant at the PED who presented due to fever measured at home. However, extrapolating prevalence data from Spain and the US to countries or settings with different characteristics could lead to over-or underestimation of disease risk.

Thus, more studies are needed to investigate the prevalence of bacterial infections among afebrile infants at the PED with reported fever at home. This leads to the third aim of this thesis, which is:1) to evaluate the risk of bacterial meningitis, bacteremia, and UTI in infants ≤60 days old with reported fever at home and 2) to investigate whether there is any difference between the infants who are afebrile when they present to the PED and infants who are still febrile.

Physicians' decision-making process when managing febrile infants

Previous chapters have described the efforts researchers have made in the last decades to develop prediction rules and guidelines for managing febrile infants. A guideline could be defined as a ''systematically developed statement to assist practitioners and patients in making decisions about appropriate health care for specific circumstances.''[236] The goal of guidelines is to enhance the quality of care, improve patient outcomes, and optimize cost-effectiveness. Guidelines are particularly useful: a) in commonly encountered diseases or symptoms, b) in conditions with significant morbidity or mortality when appropriate care can alter the outcome, c) in situations associated with high costs, and d) when significant practice variation is reported.[237] The care of febrile young infants fulfills all these prerequisites: a) fever is very common in infants, b) can be caused by life-threatening infections, such as meningitis, c) hospitalizations are costly, and 4) significant variation in management has been reported.

Few studies have investigated the effectiveness of the management guidelines for febrile infants. Byington et al. reported that implementing a guideline for the management of well-appearing febrile infants increased evidence-based care, improved patient outcomes, and reduced costs.[190] Similarly, Murray et al. demonstrated improved timelines in initiating investigations, earlier administration of antibiotics, and decreased variation of care.[238] Gomez et al. evaluated the effectiveness of the ''step by step'' approach. They reported that the implementation of the guideline increased the percentage of febrile infants aged <15 days who underwent sepsis evaluation and received antibiotics. They concluded that ''the introduction of the Step-by-Step increased the quality of care provided to young febrile infants.''[239]

Despite the potential benefits, 30 years after the publication of the first guideline for febrile infants, many PEDs and hospitals still do not have any officially endorsed clinical decision tool or management protocol. Schneider et al., in a survey among 53 pediatric emergency medicine fellowship directors in the US, found that 49% reported that there was no departmental policy regarding the evaluation of febrile infants.[240] Similarly, Burstein et al., in a survey among all 16 tertiary pediatric hospitals in Canada, reported that 8/16 PEDs and 15/16 inpatient departments did not have any officially endorsed clinical decision tool for the evaluation and management of febrile infants.[216] A study from Israel showed that 74% of the pediatric centers surveyed did not have written protocols for managing febrile infants.[241]

It has been shown that applying guidelines is difficult, takes time, and guidelines are often not applied.[242, 243] Besides the difficulties in implementation, adherence is poor and not sustainable over time.[244] Adherence to guidelines for febrile infants is poor as well. Meehan et al. conducted an online interactive case-based questionnaire with members of the Emergency Medicine section of the AAP.[245] They found low compliance with recommendations even though the participants reported following the published guidelines for febrile infants. Similar findings were reported in a survey of 164 pediatric emergency or emergency medicine directors in the US and Canada.[246] Only 11% of pediatric emergency directors and 2% of emergency medicine directors followed the guidelines in all 4 pediatric case scenarios. Several studies have investigated the barriers to following guidelines. A scoping review by Fischer et al. summarized and divided the etiologic factors into 3 main categories. First are factors related to physicians' attitudes or knowledge, such as motivation, skills, learning culture, awareness of the existence of the guideline, and familiarity with it. Second are factors related to the guideline, such as layout, accessibility, and complexity. Third are organizational constraints, such as lack of resources, time restriction, and workload.[237]

More research is needed on why and how physicians choose to follow guidelines for febrile infants. Management and variation studies have shown that febrile infants seen at private pediatric offices, well-appearing febrile infants, or infants with reported fever at home who were afebrile at the PED underwent fewer investigations and were less often hospitalized and treated with antibiotics.[9, 92, 234, 235] These findings led researchers to speculate that the clinical appearance, temperature during physical examination, possibility of adequate follow-up, and physician's experience might be among the factors influencing the decision whether to follow the guidelines.[157, 212] However, there is little insight into the decision-making process itself. Aronson et al. conducted semistructured interviews to investigate how physicians choose to perform a lumbar puncture in febrile infants 29-60 days old.[247] The factors that mainly emerged were the knowledge of the newest recommendation and the supporting evidence of the guideline. Other factors included previous experience of unfavorable outcomes, which resulted in stronger risk aversion. In

addition, the physician's clinical experience and inclination to communicate, discuss, and share the decision with parents influenced the decision to perform an LP.

Hence, despite the long-lasting efforts to develop guidelines for febrile infants, their implementation is lagging and adherence is poor. In addition, there is a paucity of knowledge regarding contributing factors. Knowing why physicians follow or do not follow management recommendations is essential to develop new guidelines, improve or adjust current guidelines, and design implementation strategies. This leads to the fourth aim of this thesis, which is: 1) to describe the decision-making process when managing febrile infants ≤60 days and 2) to describe factors that influenced this decision.

Aims

This PhD project aims to address some of the knowledge gaps in the research field of febrile infants. More specifically, it addresses the paucity of data on prevalence, management variation, and outcomes from countries other than the US and Spain. Sweden has several different population characteristics. Also, there are indications that, in Sweden, the management of febrile infants likely involves fewer investigations, hospitalizations, and antibiotic treatments than what is recommended by international guidelines. Thus, data from Sweden could provide new perspectives for the management of febrile infants. Another gap is the paucity of insight into physicians' thinking process when managing febrile infants and how they decide whether to follow or not guidelines. The specific aims of this thesis are the following:

I. To investigate age- and sex-specific prevalence of SBIs in infants ≤60 days with fever without source who presented at the Pediatric Emergency Department in four urban areas in Sweden.

II. To describe the clinical management and adverse outcomes of febrile infants ≤60 days old in 4 Swedish PEDs, which do not have written formalized guidelines.

III. To evaluate the risk of bacterial meningitis, bacteremia, and UTI in infants ≤60 days with reported fever at home and to investigate whether there is any difference between the infants who are afebrile when they present to the PED and infants who are still febrile.

IV. To describe the decision-making process when managing febrile infants ≤60 days and to describe factors that influenced this decision.

Methods

This thesis comprises two separate projects. The first is a retrospective cross-sectional study that generated papers I-III. The second is a qualitative study, with focus group discussions to better understand and explain the specific findings of the first project, which generated Paper IV.

Method used in Papers I-III

Setting

The study was performed in 4 PEDs, all parts of university pediatric hospitals. Three of these PEDs, located in Gothenburg, Lund, and Malmö, are the only PEDs in these cities. The fourth PED is part of Sachs' Children and Youth Hospital, located in the inner city of Stockholm (the capital city) and is one of Stockholm's 3 PEDs. No other public or private primary health facilities see febrile infants younger than 60 days in the catchment area of any of the study PEDs. All the sites have electronic hospital records and laboratory reporting systems.

Study Design

All infants ≤60 days of age with ''fever'' registered as the primary contact reason in the PEDs' patient electronic registration system were retrospectively identified. Only one contact reason can be chosen from the drop-down menu in the electronic registration system. For 2 PEDs (Lund and Malmö), the study period was from January 1, 2014, to December 31, 2020. In the other 2 PEDs (Gothenburg and Stockholm), the study period was from January 1, 2014, to December 31, 2017. It was not possible to collect data beyond 2017 at these 2 sites due to travel restrictions caused by the COVID-19 pandemic and changes in regulations regarding access to patient data. The electronic records of febrile infants were reviewed by 7 medical students, one resident pediatrician, and the author of this thesis, who supervised the data collection at all sites.

Study Population

Eligible for the study were infants aged ≤60 days with documented fever ≥38°C at home or the PED, without comorbidities (e.g., neuromuscular, genitourinary, gastrointestinal, cardiovascular), and who had not been hospitalized or received antibiotics in the previous 10 days. Data on demographics, clinical symptoms, physical findings, and biochemical and microbiological results were also collected. Subsequent visits to the PED within 10 days after the index visit were reviewed. The study data were collected and managed using the Research Electronic Data Capture (REDCap) tool hosted by Lund University. REDCap is a secure web-based software platform that supports data capture in research studies. Infants were excluded from the analyses if they had a clear focus of infection, such as respiratory, gastrointestinal, skin, or joint. Hence, only infants with fever without source (FWS) were included in the final analyses.

For papers I and II, infants were included if they had a fever of ≥38°C measured at home or the PED and presented between January 1, 2014, and December 31, 2017. A hospital guideline for managing febrile infants aged ≤60 days was introduced in 2 of the study's PEDs (Lund and Malmö) in 2018. Papers I and II aimed to present data from PEDs without written guidelines. Therefore, data collected from these 2 study sites after January 1, 2018, were not included.

For paper III, infants were included if they had a fever of ≥38°C measured at home. Data from 2018-2020 were also included, thus the study period was from 2014 to 2020.

Statistical analysis

Statistical analyses were performed using SPSS IBM statistics for Macintosh, versions 26.0 and 27.0. The exact binomial interval method was used to calculate the 95% confidence intervals (CIs). The x^2 test and Fisher's exact test were used for comparisons between the groups. The level of significance was set at $p \leq 0.05$. Relative risk (RR) ratios with 95% CIs were used to compare risks between the different groups.

Based on the most relevant publications, the cohort was divided into 2 age groups: ≤28 and 29–60 days. In 2021, the AAP changed the age threshold for routine investigation with LP and administration of antibiotics to 21 days. Therefore, separate analyses were performed for infants aged ≤21 and 21–28 days.

Ethics

The study was approved by the Regional Ethics committee in Lund (Dnr 2017/967)

Definitions

- Fever: temperature ≥38°C regardless of the measurement site.
- Fever without a source (FWS): fever without any apparent focus of infection, such as respiratory, gastrointestinal, skin, or joint, after medical history and physical examination.
- Urinary tract infection (UTI): urine culture with a growth of:1) any amount of a single pathogen in samples obtained by suprapubic aspiration, 2) 10,000–100,000 colony-forming units (cfu)/ml of a single pathogen and urine dipstick positive for leukocyte esterase or nitrite in samples obtained by a 'clean catch' method or catheterization, 3) >100,000 colony-forming units (cfu)/ml of a single pathogen regardless the urine dipstick result and the sampling method. ''Clean catch'' is the default urine sample collection method in all sites and urine bags are never used. The UTI definition was modified from the most used, which for 'clean catch' specimens is a growth of ≥50,000 cfu/ml,[7] because the microbiology laboratories in the study hospitals report urine culture results based on three cfu/ml intervals: <10,000, 10,000– 100,000, and >100,000 cfu/ml.
- Bacteremia: growth of a bacterial pathogen in blood culture. The growth of coagulase-negative *staphylococci*, *Propionibacterium* spp., *Bacillus cereus* spp., micrococci, alpha *hemolytic streptococci,* and diphtheroids were considered contaminants.
- Bacterial meningitis: Growth of a bacterial pathogen in cerebrospinal fluid (CSF) culture or a CSF polymerase chain reaction test positive for a bacterial pathogen.
- Serious Bacterial Infections (SBI): UTI, bacteremia, or bacterial meningitis.
- Invasive Bacterial Infection (IBI): bacteremia or bacterial meningitis.
- Ill-appearing infant: An infant was considered ill-appearing if the attending physician documented any of the following terms: ill-appearing, irritable, somnolent, lethargic, non-responsive, septic, or cyanotic.
- Initial approach: investigations and treatments performed at the PED during the first encounter or at the ward planned by the PED physician at the first encounter.
- Revisit: any return visit to the PED within 10 days from the index visit.
- Delayed-treated IBI or SBI: any case of IBI or SBI when broad-spectrum antibiotics were not administered at the initial approach.
- Adverse outcome: Death of an infant who did not receive broad-spectrum antibiotics at the initial encounter or delayed-treated IBI.

Method used in Paper IV

Setting

This study was conducted in 2 of the 4 study PEDs (Lund and Malmö). Both PEDs are part of the Skåne University Hospital in Sweden's southernmost region. A guideline for managing febrile infants ≤60 days with fever without a source (FWS), based on the ''step by step'' approach, was introduced in 2018. For ill-appearing infants and infants ≤21 days of age, it recommends LP, urine and blood cultures, parenteral antibiotics, and admission. For well-appearing infants aged 22–60 days, it recommends blood tests (ANC, procalcitonin, C-reactive protein), urine dipstick, and specific actions according to the results.

Study design

This study was based on an inductive qualitative design. A phenomenographic approach, according to Sjöström and Dahlgren,[248] was used to gain insight into the process of physicians' decision-making, including perceived barriers, facilitators, and motivators, when managing febrile infants ≤60 days. Phenomenography focuses on how a phenomenon (managing febrile infants) is perceived by physicians rather than the phenomenon itself (management of febrile infants). The aim of phenomenography is to describe the variation of physicians' perceived reasons to follow or not the guideline, and subsequently identify patterns rather than describe a singular essence.[248]

Participants

All clinically active pediatric residents and specialists at the PED were invited to enroll during staff meetings and through follow-up emails. A letter describing the study, its scope, and its aims was sent to all. Focus groups with physicians in the same role were chosen for better homogeneity and to create a better opportunity for the interviewees to interact.

Data collection

Focus group discussions were conducted by 2 researchers with experience in qualitative research, none of whom was involved in the care of infants. Before the discussions, the participating physicians filled out a questionnaire containing information regarding their demographics and professional experience. A short list of topics (Table 8) with follow-up questions was used to guide the discussion. The discussions were performed at local hospital facilities, in April and May 2022. They

were audio-recorded and transcribed verbatim using a professional transcription service. The names and roles of the participants were not mentioned in any step of the procedure. The data transcription company followed strict general data protection rules (GDPR) procedures.

Table 8. Topics and questions for focus group interviews

Topic	Example questions
Overall process of decision-making	What process of decision-making do you follow when managing fever in an infant (<21 days)?
External factors affecting decision-making	What factors affect your decisions and how? (The general condition of the infant? Input from colleagues? Wishes and needs from parents?)
Decisions on diagnostics and treatment	What factors are crucial in decisions on diagnostic procedures (such as lumbar puncture, blood, and urine culture), treatment (such as antibiotics and hospitalization), and how?

Analysis

The audio-recorded and transcribed interviews were analyzed using a stepwise phenomenographic approach. Physicians' perceptions of managing febrile infants (the phenomenon) were identified and grouped into concepts and categories. The first part of the analysis was performed using a seven-step approach, as described by Sjöström and Dahlgren.[248] The second part of the analysis comprised orienting the categories toward intrinsic and extrinsic motivators.[249] The primary analysis was conducted by two researchers. A third researcher reviewed, revised, and confirmed the results. Finally, the research group discussed the results until a joint agreement and consensus were reached. Representative quotes were used to support and exemplify these categories. The data were managed using NVivo software [QSR International Pty Ltd. (2018) NVivo (version 12]).

Results

Demographics

There were 2237 infants aged ≤60 days with FWS in the 4 study PEDs during the total study period from 2014 to 2020. The median age of the infants was 38 days, and 56% were boys. Most infants presented to the PED with a fever duration of <6 hours. One of three infants with reported fever at home was afebrile at presentation (Table 9).

Table 9. Demographics of infants aged ≤60 days with Fever Without a Source in 4 Pediatric Emergency Departments in Sweden 2014–2020

	0–28 days n= 741	**29–60 days** n= 1496	**0–60 days** n= 2237
Boys, n (%)	426 (57)	839 (56)	1265 (56)
Median Age, d (IQR)	18 (12–23)	46 (38–54)	38 (23–50)
Temp °C Home, median (IQR)	38.4 (38.1–38.8)	38.5 (38.2–38.8)	38.5 (38.1–38.8)
Temp °C PED, median (IQR)	38.2 (37.7–38.7)	38.3 (37.8–38.7)	38.2 (37.8–38.7)
Afebrile[1] at presentation, n (%)	244 (33)	463 (31)	707 (32)
Fever duration Prior PED visit, n (%)			
<6 hours	469 (63)	878 (59)	1347 (60)
6–12 hours	139 (19)	327 (22)	466 (21)
12–24 hours	84 (11)	154 (10)	238 (11)
> 24 hours	25 (3)	90 (6)	115 (5)
Unknown	24 (3)	47 (3)	71 (3)

[1]Afebrile, temperature <38°C; IQR, interquartile rate; PED, Pediatric Emergency Department

Prevalence of serious bacterial infections

Prevalence per age group

Data from all 4 study PEDs were available from 2014 to 2017. During this period, 1701 infants aged ≤60 days with FWS were included. The total prevalence of SBIs was 12.6% (95% CI, 11.0–14.3). Isolated UTIs accounted for 87% of all SBIs. The prevalence of meningitis was 0.5% (95% CI, 0.2–0.9) and of bacteremia was 1.5% (95% CI, 1.0–2.2). The prevalence of meningitis and bacteremia was 3- to 5-fold higher in infants aged ≤28 days than in those aged 29–60 days (Table 10).

Table 10. Prevalence of serious bacterial infections per age group in infants aged ≤60 days with Fever Without a Source in 4 Pediatric Emergency Departments in Sweden 2014-2017

	0-28 days n= 570 n (%; 95% CI)	**29-60 days** n= 1131 n (%; 95% CI)	**0-60 days** n= 1701 n (%; 95% CI)
UTI Isolated	72 (12.6; 10.0–15.6)	115 (10.2; 8.5–12.1)	187 (11.0; 9.5–12.6)
Meningitis Isolated	0 (0.0; 0.0–0.6)	2 (0.2; 0.0–0.6)	2 (0.1; 0.0–0.4)
Bacteremia Isolated	7 (1.2; 0.5–2.5)	4 (0.4; 0.1–0.9)	11 (0.6; 0.3–1.2)
Bacteremia + UTI	6 (1.1; 0.4–2.3)	2 (0.2; 0.0–0.6)	8 (0.5; 0.2–0.9)
Meningitis + Bacteremia	4 (0.7; 0.2–1.8)	1 (0.1; 0.0–0.5)	5 (0.3; 0.1–0.7)
Meningitis + Bacteremia + UTI	1 (0.2; 0.0–1.0)	0 (0.0; 0.0–0.3)	1 (0.1; 0.0–0.3)
Meningitis*	5 (0.9; 0.3–2.0)	3 (0.3; 0.1–0.8)	8 (0.5; 0.2–0.9)
Bacteremia*	18 (3.2; 1.9–4.9)	7 (0.6; 0.2–1.3)	25 (1.5; 1.0–2.2)
SBI Total	90 (15.8; 12.9–19.0)	124 (11.0; 9.2–12.9)	214 (12.6; 11.0–14.3)
IBI Total	18 (3.2; 1.9–4.9)	9 (0.8; 0.4–1.5)	27 (1.6; 1.0–2.3)

UTI, Urinary Tract Infection; SBI, Serious Bacterial Infection; IBI, Invasive Bacterial Infection.
*All cases (isolated or in any combination), because of the combinations, the sum of Meningitis and Bacteremia is higher than the number of IBI Total

In infants aged ≤21 days, the prevalence of meningitis was 1.3% (95% CI, 0.4–3.0) and of bacteremia 4.5% (95% CI, 2.6–7.0) (Table 11).

Table 11. Prevalence of serious bacterial infections per age group in infants aged ≤60 days with Fever Without a Source in 4 Pediatric Emergency Departments in Sweden 2014-2017

	≤21 days n= 381 n (%; 95% CI)
UTI Isolated	47 (12.3; 9.2–16.1)
Meningitis Isolated	0 (0.0; 0.0–1.0)
Bacteremia Isolated	6 (1.6; 0.6–3.4)
Bacteremia + UTI	6 (1.6; 0.6–3.4)
Meningitis + Bacteremia	4 (1.0; 0.3–2.7)
Meningitis + Bacteremia + UTI	1 (0.3; 0.0–1.5)
Meningitis*	5 (1,3; 0.4–3.0)
Bacteremia*	17 (4.5; 2.6–7.0)
SBI Total	64 (16.8; 13.2–20.9)
IBI Total	17 (4.5; 2.6–7.0)

UTI, Urinary Tract Infection; SBI, Serious Bacterial Infection; IBI, Invasive Bacterial Infection.
*All cases (isolated or in any combination), because of the combinations, the sum of Meningitis and Bacteremia is higher than the number of IBI Total

Prevalence per week of age

The prevalence of meningitis and isolated bacteremia peaked in the first week of life, declined thereafter, and remained low after the third week of life (Fig. 1)

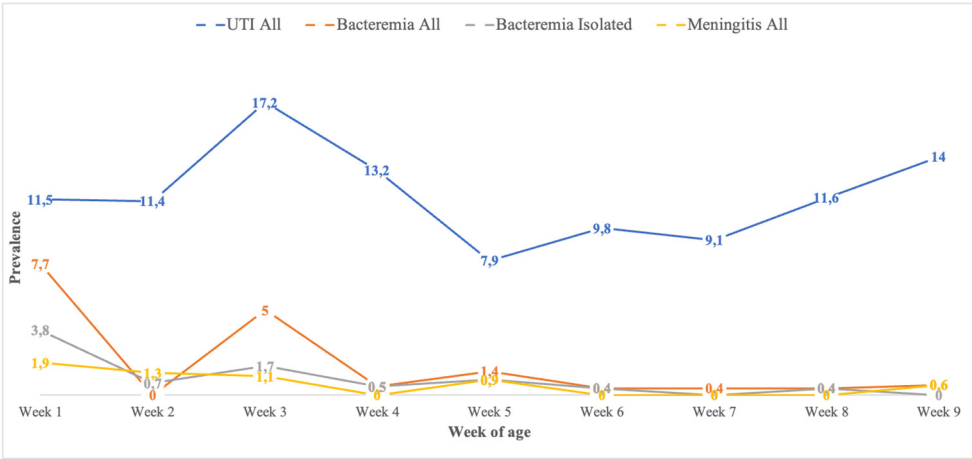

Figure 1. Prevalence of serious bacterial infections per week of age in infants aged ≤60 days with Fever Without a Source in 4 Pediatric Emergency Departments in Sweden 2014-2017

Prevalence per study site

The SBI prevalence varied from 9.4% at the site with the lowest prevalence to 16.4% at the site with the highest prevalence. This variation was primarily due to variation in the prevalence of UTIs. The prevalence of meningitis did not vary among the study sites (Table 12).

Table 12. Serious Bacterial Infection prevalence per study Pediatric Emergency Department in infants aged ≤60 days with Fever Without a Source in Sweden 2014-2017

	Lund n= 256 n (%; 95% CI)	**Malmö** n= 423 n (%; 95% CI)	**Gothenburg** n= 536 n (%; 95% CI)	**Stockholm** n= 486 n (%; 95% CI)
SBI Total	24 (9.4; 6.1–13.6)	52 (12.3; 9.3–15.8)	88 (16.4; 13.4–19.8)	50 (10.3; 7.7–13.3)
IBI Total	3 (1.2; 0.2–3.4)	3 (0.7; 0.1–2.1)	14 (2.6; 1.4–4.3)	7 (1.4; 0.6–2.9)
UTI*	22 (8.6; 5.5–12.7)	50 (11.8; 8.9–15.3)	79 (14.7; 11.8–18.0)	45 (9.3; 6.8–12.2)
Meningitis*	1 (0.4; 0.0–2.2)	0 (0; 0.0–0.9)	4 (0.7; 0.2–1.9)	3 (0.6; 0.1–1.8)
Bacteremia*	3 (1.2; 0.2–3.4)	3 (0.7; 0.1–2.1)	13 (2.4; 1.3–4.1)	6 (1.2; 0.5–2.7)

SBI, Serious Bacterial Infection; IBI, Invasive Bacterial Infection; UTI, Urinary Tract Infection
*All cases (isolated or in any combination), because of the combinations, the sum of UTI, Meningitis, and Bacteremia is higher than the number of SBI Total and IBI Total.

Sex-specific prevalence

No significant difference was observed in the prevalence of meningitis and bacteremia between boys and girls in any age group. In contrast, in the ≤28 days age group, the prevalence of UTI was almost 7-fold higher in boys than in girls (Table 13).

Table 13. Serious Bacterial Infection prevalence per sex and age group in infants aged ≤60 days with Fever Without a Source in 4 Pediatric Emergency Departments in Sweden 2014-2017

	0-28 days			29-60 days		
	Girls n= 248 n (%; 95% CI)	**Boys** n= 322 n (%; 95% CI)	**P**	**Girls** n= 486 n (%; 95% CI)	**Boys** n= 645 n (%; 95% CI)	**P**
SBI Total	13 (5.2; 2.88.8)	77 (23.9; 19.4–29.0)	<.001	46 (9.5;7.0–12.4)	78 (12.1;9.7–14.9)	.161
IBI Total	5 (2.0; 0.7–4.6)	13 (4.0; 2.2–6.8)	.171	4 (0.8; 0.2–2.1)	5 (0.8; 0.3–1.8)	1.000
UTI*	8 (3.2; 1.4–6.3)	71 (22.0;17.6–27.0)	<.001	42 (8.6;6.3–11.5)	75 (11.6;9.3–14.4)	.103
Meningitis*	2 (0.8; 0.1–2.9)	3 (0.9;0.2–2.7)	1.000	3 (0.6;0.1–1.8)	0	.079
Bacteremia*	5 (2.0; 0.7–4.6)	13 (3.7;1.9–6.4)	.228	2 (0.4;0.0–1.5)	5 (0.8;0.3–1.8)	.705

SBI, Serious Bacterial Infection; IBI, Invasive Bacterial Infection; UTI, Urinary Tract Infection
*All cases (isolated or in any combination); because of the combinations, the sum of UTI, Meningitis, and Bacteremia is higher than the number of SBI Total and IBI Total.

Epidemiology

Group B *Streptococcus* and *Escherichia coli* were isolated in 76% of the 25 bacteremia cases (Fig. 2).

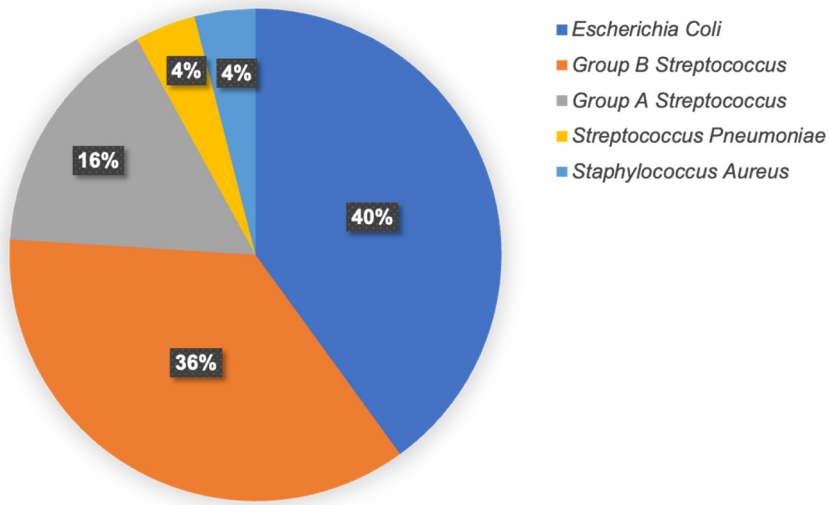

Figure 2. Bacteriology of bacteremia cases in febrile infants aged ≤60 days with Fever Without Source in 4 Pediatric Emergency Departments in Sweden 2014-2017.

Of the 11 cases of isolated bacteremia, 5 were caused by Group B *Streptococcus*, 4 by Group A *Streptococcus*, 1 by *Escherichia coli,* and 1 by *Streptococcus pneumoniae.* In total, 550 blood cultures were obtained. Bacteria grew in 102 samples, of which only 25 were considered true pathogens. Therefore, the contamination rate was 75%.

Of the 8 meningitis cases, 4 were caused by Group B *Streptococcus*, 1 by *Escherichia coli*, and 1 by *Streptococcus pneumoniae.* Two infants had pleocytosis in the CSF, but negative CSF cultures and PCR results. Because it was not possible to determine whether the lumbar puncture was performed before the administration of antibiotics, both cases were registered as bacterial meningitis. One of these 2 infants had a blood culture with growth of *Escherichia coli.* No cases of *Listeria monocytogenes* infections were identified.

Escherichia coli caused 94% of all UTI cases, while *Klebsiella spp*, *Enterococcus spp,* and Group B *Streptococcus* caused the remaining. In total, 732 urine cultures were obtained. Bacterial growth was observed in 338 of these samples, and the total number of UTIs was 196. Thus, 42% of urine cultures with bacterial growth were considered contaminants or not true pathogens.

Management and variation

Management per age group

The data from the 1701 infants aged ≤60 days with FWS seen in the 4 study PEDs during 2014 to 2017 were further analyzed to describe management. At the time of the study, most established international guidelines recommended sepsis evaluation, broad-spectrum antibiotics, and hospitalization for all infants aged ≤28 days. In infants aged ≤28 days, LP was performed in 13% (95% CI, 11–16), broad-spectrum antibiotics were administered in 30% (95% CI, 26–34), and 67% (95% CI, 63–71) were hospitalized (Table 14).

The ‘‘Step by Step’’ approach (2014) and the new AAP guidelines (2021) recommend 21 days of age as a cutoff point for sepsis evaluation, antibiotics, and hospitalization. In infants ≤21 days of age, LP was performed in 16% (95% CI, 12–20), broad-spectrum antibiotics were administered in 34% (95% CI, 29–39), and 71% (95% CI, 67–76) were hospitalized (Table 14).

Table 14. Investigations, antibiotic treatment, and hospitalizations at the initial approach[1] of infants ≤60 days old with Fever Without a Source in 4 Pediatric Emergency Departments in Sweden 2014-2017

	Age ≤21 days n= 381 N (%; 95% CI)	**Age ≤28 days** n= 570 N (%; 95% CI)	**Age 29-60 days** n= 1131 N (%; 95% CI)
Lumbar Puncture	60 (16; 12–20)	76 (13; 11–16)	52 (5; 3–6)
Urine Culture	180 (47; 42–52)	264 (46; 42–50)	380 (33; 31–36)
Blood Culture	165 (43; 38–48)	226 (40; 36–40)	241 (21; 19–24)
All three[2]	37 (10; 7–13)	46 (8; 6–11)	31 (3; 2–4)
None[2]	150 (39; 34–44)	243 (43; 38–47)	685 (61; 58–63)
Urine Dipstick	314 (82; 78–86)	479 (84; 81–87)	964 (85;83–87)
C-Reactive Protein	340 (89; 86–92)	509 (90; 86–92)	1008 (89; 87–91)
White Blood Cells	229 (60; 55–65)	329 (58; 53–62)	560 (49; 47–52)
Antibiotics[3]	129 (34; 29–39)	171 (30; 26–34)	178 (16; 14–18)
Hospitalization	272 (71; 67–76)	384 (67; 63–71)	513 (45; 42–48)

[1]Initial approach, Investigations, and antibiotic treatment performed at the Pediatric Emergency Department or the ward planned by the PED physician.

[2]All three: lumbar puncture + urine culture + blood culture; None, none of these three.

[3]Antibiotics = Broad-spectrum Antibiotics, any regimen containing parenteral 3rd generation cephalosporins, aminoglycosides, or meropenem.

General appearance, presence of fever, and management

In the ≤28 days age group, LP was performed 30 times more often in febrile, ill-appearing infants and 5 times more often in febrile, well-appearing infants than in afebrile, well-appearing infants (Table 15). The rates of antibiotics and hospitalizations were also higher in ill-appearing or febrile infants than in well-appearing or afebrile infants.

Table 15. Lumbar puncture, antibiotics, and hospitalizations at the initial approach[1] of infants aged ≤60 days with Fever Without a Source in 4 Pediatric Emergency Departments in Sweden in 2014-2017 according to the general appearance and presence of fever at presentation.

	≤28 days n= 556[6]		**29-60 days** n= 1105[6]	
	Well-appearing n= 481 N (%; 95% CI)	**Ill-appearing[5]** n= 75 N (%; 95% CI)	**Well-appearing** n= 1008 N (%; 95% CI)	**Ill-appearing[5]** n= 97 N (%; 95% CI)
Febrile[2] PED[3]	303	67	685	83
Lumbar Puncture	32 (11; 7-15)	39 (58; 45-70)	22 (3; 2-5)	23 (28; 18-39)
Antibiotics[4]	99 (33; 27–38)	51 (76; 64–86)	106 (15; 13–18)	52 (63; 51–73)
Hospitalizations	237 (78; 73–83)	66 (98; 92–100)	356 (52; 48–56)	76 (92; 83–96)
Afebrile[2] PED[3]	178	8	323	14
Lumbar Puncture	3 (2; 0–5)	2 (25; 3–65)	1 (0; 0–2)	5 (36; 13–65)
Antibiotics[4]	14 (8; 4–13)	4 (50; 16–84)	11 (3; 2–6)	8 (57; 29–82)
Hospitalizations	64 (36; 29–43)	8 (100; 63–100)	59 (18; 14–23)	13 (93; 66–100)

[1]Initial approach, investigations, and antibiotic treatment performed at the PED or the ward planned by the PED physician

[2]Febrile, Temperature ≥38 °C; Afebrile, Temperature <38 °C

[3]PED, Pediatric Emergency Department

[4]Antibiotics = Broad-spectrum Antibiotics, any regimen containing parenteral 3rd generation cephalosporins, aminoglycosides, or meropenem.

[5]Ill-appearing, Documented in the medical record as any of: ill-appearing, irritable, somnolent, lethargic, non-responsive, or septic.

[6]The sum of well-appearing and ill-appearing infants is 1661, because this information was not available for 40 infants

Management per study site

Variations in management were observed among the 4 study PEDs (Table 16). In febrile infants aged ≤28 days, the rate of LP varied almost 12-fold between the sites, with the lowest (2%; 95% CI, 1–6) and highest (23%; 95% CI, 18–30) rates. Differences were observed in the rates of antibiotic administration, whereas the rates of blood tests, urinalysis, and hospitalization were similar at all 4 sites.

Table 16. Investigations, antibiotic treatment, and hospitalizations at the initial approach[1] of infants ≤60 days old with Fever Without a Source in each of the 4 Pediatric Emergency Departments in Sweden 2014-2017

	Lund n (%; 95% CI)	**Malmö** n (%; 95% CI)	**Gothenburg** n (%; 95% CI)	**Stockholm** n (%; 95% CI)
Age ≤28 days	n= 70	n= 138	n= 187	n= 175
Lumbar Puncture	11 (16; 8–26)	17 (12; 7–19)	44 (23; 18–30)	4 (2; 1–6)
Urine Culture	33 (47; 35–59)	71 (51; 43–60)	66 (35; 28–43)	94 (54; 46–61)
Blood Culture	26 (37; 26–45)	59 (43; 34–51)	83 (45; 37–52)	58 (33; 26–40)
All three[2]	10 (14; 7–25)	13 (9; 5–16)	20 (11; 7–16)	3 (2; 0–5)
None[2]	34 (49; 36–61)	57 (41; 33–50)	84 (45; 38–52)	68 (39; 32–46)
Urine Dipstick	51 (73; 61–83)	114 (83; 75–88)	169 (90; 85–94)	145 (83; 76–88)
CRP Done	58 (83; 72–91)	122 (88; 82-93)	177 (95; 90–97)	152 (87; 81–91)
WBC Done	35 (50; 38–62)	70 (51; 42–59)	147 (79; 72–84)	77 (44; 36–52)
Antibiotics[3]	22 (31; 21–44)	48 (35; 27–43)	73 (39; 32–46)	28 (16; 11–22)
Hospitalization	41 (59; 46–70)	94 (68; 60–76)	139 (74; 67–80)	110 (63; 55–70)
Age 29-60 days	n= 186	n= 285	n= 349	n= 311
Lumbar Puncture	8 (4; 2–8)	14 (5; 3–8)	28 (8; 5–11)	2 (1; 0–2)
Urine Culture	67 (36; 29–43)	103 (36; 31–42)	86 (25; 20–29)	124 (40; 34–45)
Blood Culture	56 (30; 24–37)	67 (23; 18–29)	66 (19; 15–23)	52 (17; 13–21)
All three[2]	5 (3; 1–6)	10 (3; 2–6)	14 (4; 2–7)	2 (1; 0–2)
None[2]	107 (57; 50–65)	166 (58; 52–64)	234 (67; 62–72)	178 (57; 51–63)
Urine Dipstick	151 (81; 75–86)	252 (88; 84–92)	319 (91; 88–94)	242 (78; 73–82)
CRP Done	149 (80; 74-86)	266 (95; 89–96)	317 (91; 87–94)	276 (89; 85–92)
WBC Done	93 (50; 43–57)	122 (43; 37–49)	261 (75; 70–79)	84 (27; 22–32)
Antibiotics[3]	40 (21; 16–28)	50 (17; 13–22)	54 (15; 12–20)	34 (11; 8–15)
Hospitalization	82 (44; 37–51)	130 (46; 40–52)	176 (50; 45–56)	125 (40; 35-46)

[1]Initial approach, investigations, and antibiotic treatment performed at the PED or the ward planned by the ED physician.
[2]All three, all three of lumbar puncture + urine culture + blood culture; None, none of these three.
[3]Antibiotics = Broad-spectrum Antibiotics, any regimen containing parenteral 3rd generation cephalosporins, aminoglycosides, or meropenem.

Adverse outcomes

During 2014-2017, 1701 febrile infants aged ≤60 days with FWS were seen at the 4 study PEDs. Of these, 12 (0.7%; 95% CI, 0.4–1.2) infants with an SBI did not receive antibiotics at the initial approach. Among them, 4 (0.2%; 95% CI, 0.1–0.6) had an IBI (Table 17).

In total, 1352 febrile infants aged ≤60 days did not receive antibiotics during the initial approach. Thus the percentage of the 4 delayed-treated IBIs among the infants not treated at the initial approach was 0.3% (95% CI, 0.1–0.8). All 4 infants with delayed-treated IBI were hospitalized at the index visit and received antibiotics at the latest 16 hours after their presentation to the PED. None of these infants needed intensive care. Eight infants had a delayed-treated UTI. Three of these were hospitalized at the index visit, received antibiotics at the ward, and were discharged

after 3 days (2 infants) and 6 days (1 infant). Of the 5 infants with UTIs diagnosed at a revisit, 3 were admitted and 2 were sent home with oral antibiotics. None of these infants experienced any short-term adverse outcomes.

Two infants died, one younger than 21 days due to disseminated herpes simplex infection, and one older than 28 days due to *Streptococcus pneumoniae* meningitis. Both infants appeared ill at presentation and received appropriate management.

Table 17. Characteristics, investigations, treatment, and diagnosis of Febrile Infants ≤60 days with delayed-treated Serious Bacterial Infection in 4 Pediatric Emergency Departments in Sweden 2014-2017

Age (days)	Temp (°C) Home/PED	Fever[1] (hours)	CRP/ PCT[2]	WBC/ ANC[2]	UD	UC	LP	BC	Hosp	AB	SBI
7	38.0/ –	-	0/0.18	9.8/5.2	Neg	PED	No	Ward	Yes	Ward	Bacteremia[3]
10	39.2/ 37.7	<6	21/–	–	Neg	Ward	Ward	Ward	Yes	Ward	Bacteriemic Meningitis[4]
23	39.6/38.5	<6	9/–	20/13.9	Neg	PED	Ward	PED	Yes	Ward	Bacteremia[5]
31	38.0/ 39.0	6-12	30/0.52	12.4/–	Neg	Ward	Ward	Ward	Yes	Ward	Meningitis[6]
41	39.0/ 38.3	12-24	35/–	–	No	Revisit	No	Revisit	Revisit	Revisit	UTI[4]
48	38.5/ 39.3	<6	<5/–	–	Neg	PED	Ward	No	Yes	Ward	UTI[4]
51	39.0/ 39.0	6-12	<5/–	3.7/1.9	Neg	PED	No	No	Yes	Ward	UTI[7]
54	–/ 38.4	6-12	40/–	–	No	Revisit	No	Revisit	Revisit	Revisit	UTI[4]
56	38.7/ 37.6	<6	9/–	14.4/7.2	Pos	PED	No	Ward	Yes	Ward	UTI[4]
57	39.2/ 38.9	12-24	<5/–	21/7.4	Pos	PED	No	No	No	Revisit	UTI[4]
58	38.5/ 38.0	<6	<5/–	–	Pos	PED	No	No	No	Revisit	UTI[4]
59	38.0/ 37.6	24-48	<5/–	–	Pos	Revisit	No	No	No	Revisit	UTI[4]

Abbreviations: PED, Pediatric Emergency Department; CRP, C-Reactive Protein mg/L; PCT, Procalcitonin ng/mL; WBC, White Blood Cell count 10^3/mL; ANC, Absolut Neutrophile Count 10^3/ml; UD, Urine Dipstick; UC, Urine Culture; LP, Lumbure Puncture; BC, Blood Culture; Hosp, Hospitalization; AB, Antibiotics; SBI, Serious Bacterial infection; UTI, Urinary Tract Infection;

[1]Fever, fever duration in hours; [2]Taken at presentation; [3] *Streptococcus pyogenes*; [4] *Escherichia coli*; [5] *Streptococcus agalactiae*;

[6]Patient with elevated CSF cell count, with all cultures negative. Registered as bacterial meningitis because it was not possible to specify whether the lumbar puncture was done before the administration of antibiotics; [7] *Klebsiella pneumoniae*

There were few delayed-treated IBIs and SBIs at each PED (Table18) and there were no substantial inter-site differences.

Table 18. Febrile Infants ≤60 days with delayed-treated Serious Bacterial Infection per Pediatric Emergency Department in Sweden 2014-2017

	Lund N (%; 95% CI)	**Malmö** N (%; 95% CI)	**Gothenburg** N (%; 95% CI)	**Stockholm** N (%; 95% CI)
Age ≤28 days	(n= 70)	(n= 138)	(n= 187)	(n= 175)
Delayed-treated[1] UTI[2]	0 (0; 0.0–5.1)	0 (0; 0.0–2.6)	0 (0.0; 0.0–2.0)	0 (0.0; 0.0–2.1)
Delayed-treated[1] IBI[3]	0 (0; 0.0–5.1)	0 (0; 0.0–2.6)	2 (1.1; 0.0–3.8)	1 (0.6; 0.0–3.1)
Age 29-60 days	(n= 186)	(n= 285)	(n= 349)	(n= 311)
Delayed-treated[1] UTI[2]	1 (0.5; 0.0–3.0)	2 (0.7; 0.1–2.5)	1 (0.3; 0.0–1.6)	4 (1.3; 0.4–3.3)
Delayed-treated[1] IBI[3]	0 (0; 0.0–2.0)	0 (0; 0.0–1.3)	0 (0; 0.0–1.1)	1 (0.0; 0.0–1.8)

[1]Delayed-treated, infant with an SBI/IBI not treated with broad-spectrum antibiotics at the initial presentation.
[2]UTI, Urinary Tract Infection Infection: Isolated Urinary Tract Infection.
[3]IBI, Invasive Bacterial Infection: bacterial meningitis or bacteremia

Afebrile versus febrile infants

Risk of infection in afebrile versus febrile infants

During the entire study period from 2014 to 2020, 1926 infants aged ≤60 days with FWS presented due to a reported fever of ≥38°C identified at home. Of these, 702 (36%) were afebrile and 1224 (64%) were febrile at the PED, constituting the afebrile and febrile groups, respectively. There was no difference in the risk of meningitis between febrile and afebrile infants ≤28 days, with a risk ratio (RR) of 1.05 (95% CI, 0.18–6.23). No afebrile infant 29-60 days old was diagnosed with meningitis. The risk of SBI was lower in afebrile infants than in febrile infants, with an RR of 0.43 (95% CI, 0.31–0.58), mainly due to a lower risk of UTI, with an RR of 0.43 (95% CI, 0.31–0.59) (Table 19).

Table 19. Prevalence of serious bacterial infections and risk ratio in infants ≤60 days old with Fever Without a Source in 4 Pediatric Emergency Departments in Sweden 2014-2020

	Afebrile PED n (%; 95% CI)	**Febrile PED** n (%; 95% CI)	**RR (95% CI)**
Infants 0-60 days	702	1224	
SBI	46 (6.6; 4.8-8.6)	188 (15.4; 13.4-17.5)	0.43 (0.31–0.58)
UTI all[1]	43 (6.1; 4.5-8.2)	174 (14.2; 12.3-16.3)	0.43 (0.31–0.59)
Bacteremia all[1]	5 (0.7; 0.2-1.7)	21 (1.7; 1.1-2.6)	0.41 (0.16–1.10)
Meningitis all[1]	2 (0.3; 0.0-1.0)	6 (0.5; 0.2-1.1)	0.58 (0.12–2.87)
Infants 0-28 days	243	382	
SBI	20 (8.2; 5.1-12.4)	78 (20.4; 16.5-24.8)	0.40 (0.25–0.64)
UTI all[1]	17 (7.0; 4.1-11.0)	71 (18.6; 14.8-22.9)	0.38 (0.23–0.62)
Bacteremia all[1]	3 (1.2; 0.3 – 3.6)	14 (3.7; 0.2-0.6)	0.34 (0.10–1.16)
Meningitis all[1]	2 (0.8; 0.1-2.9)	3 (0.8; 0.2-2.3)	1.05 (0.18–6.23)
Infants 29-60 days	459	842	
SBI	26 (5.7; 3.7-8.2)	110 (13.1; 10.9-15.5)	0.43 (0.29–0.65)
UTI all[1]	26 (5.7; 3.7-8.2)	103 (12.2; 10.1-14.6)	0.46 (0.31–0.70)
Bacteremia all[1]	2 (0.4; 0.1-1.6)	7 (0.8; 0.3-1.7)	0.52 (0.11–2.50)
Meningitis all[1]	0 (0.0; 0.0-0.8)	3 (0.4; 0.1-1.0)	–

Abbreviations: RR, risk ratio; PED, pediatric emergency department; SBI, serious bacterial infection; UTI, urinary tract infection

[1]All cases, isolated or in any combination, because of the combination the sum of UTI, bacteremia, and meningitis exceeds the number of SBI

Sex-specific data for afebrile versus febrile infants

The UTI prevalence in girls aged ≤60 days afebrile at the PED was 3.9% (95% CI, 2.0-6.7) versus 8.7% (95% CI, 6.1-11.9) in afebrile boys (Table 20).

Table 20. Sex-specific prevalence of serious bacterial infections in infants ≤60 days old with Fever Without a Source in 4 Pediatric Emergency Departments in Sweden 2014-2020

	Girls		Boys	
	Afebrile PED n (%; 95% CI)	**Febrile PED** n (%; 95% CI)	**Afebrile PED** n (%; 95% CI)	**Febrile PED** n (%; 95% CI)
Infants 0-60 days	309	520	393	704
SBI	12 (3.9; 2.0-6.7)	58 (11.2; 8.6-14.2)	34 (8.7; 6.1-11.9)	130 (18.5; 15.7-21.5)
UTI all[1]	11 (3.6; 1.8-6.3)	50 (9.6; 7.2-12.5)	32 (8.1; 5.6-11.3)	124 (17.6; 14.9-20.6)
Bacteremia all[1]	2 (0.6; 0.1-2.3)	5 (1.0; 0.3-2.2)	3 (0.8; 0.2-2.2)	16 (2.3; 1.3-3.7)
Meningitis all[1]	1 (0.3; 0.0-1.8)	5 (1.0; 0.3-2.2)	1 (0.3; 0.0-1.4)	1 (0.1; 0.0-0.8)
Infants 0-28 days	103	157	140	225
SBI	4 (3.9; 1.1-9.6)	14 (8.9; 5.0-14.5)	16 (11.4.2; 6.7-17.9)	64 (28.4; 22.6-34.8)
UTI all[1]	3 (2.9; 0.6-8.3)	10 (6.4; 3.1-11.4)	14 (10.0; 5.6-16.2)	61 (27.1; 21.4-33.4)
Bacteremia all[1]	1 (1.0; 0.0-5.3)	3 (1.9; 0.4-5.5)	2 (1.4; 0.2-.5.1)	11 (4.9; 2.5-8.6)
Meningitis all[1]	1 (1.0; 0.0-5.3)	2 (1.3; 0.2-4.5)	1 (0.7; 0.0-3.9)	1 (0.4.0; 0.0-2.2)
Infants 29-60 days	206	363	253	479
SBI	8 (3.9.7; 1.7-7.5)	44 (12.1; 8.9-15.9)	18 (7.1; 4.3-11.0)	66 (13.8; 10.8-17.2)
UTI all[1]	8 (3.9; 1.7-7.5)	40 (11.0; 8.0-14.7)	18 (7.1; 4.3-11.0)	63 (13.2; 10.3-16.5)
Bacteremia all[1]	1 (0.5; 0.0-2.7)	2 (0.6; 0.1-2.0)	1 (0.4; 0.0-2.2)	5 (1.0; 0.3-2.4)
Meningitis all[1]	0 (0.0; 0.0-1.8)	3 (0.8; 0.2-2.4)	0 (0.0; 0.0-1.4)	0 (0.0; 0.0-0.8)

Abbreviations: PED, pediatric emergency department; SBI, serious bacterial infection; UTI, urinary tract infection
[1]All cases, isolated or in any combination, because of the combination the sum of UTI, bacteremia, and meningitis exceeds the number of SBI

Management of afebrile versus febrile infants

More investigations were performed in febrile than in afebrile infants, with almost four times more LPs and three times more blood cultures in febrile infants (Table 21).

Table 21. Investigations performed in afebrile and febrile infants ≤60 days old with reported fever at home in 4 Pediatric Emergency Departments s in Sweden 2014-2020

	0–28 days		29–60 days		0–60 days	
	Afebrile PED 243 n (%)	**Febrile PED** 382 n (%)	**Afebrile PED** 459 n (%)	**Febrile PED** 842 n (%)	**Afebrile PED** 702 n (%)	**Febrile PED** 1224 n (%)
CRP	185 (76)	368 (96)	346 (75)	778 (92)	531 (76)	1146 (94)
WBC	92 (38)	289 (76)	158 (34)	516 (61)	250 (36)	805 (66)
Urine dipstick	177 (73)	356 (93)	365 (80)	774 (92)	542 (77)	1130 (92)
Urine culture	83 (34)	264 (69)	150 (33)	436 (52)	233 (33)	700 (57)
Blood culture	58 (24)	243 (74)	47 (11)	275 (33)	105 (15)	518 (42)
Lumbar puncture	16 (7)	123 (32)	11 (2)	70 (10)	27 (4)	203 (16)

Abbreviations: PED, pediatric emergency department; CRP, C-reactive protein; WBC, white blood cell count.

Factors that influenced physicians' decision-making process when managing febrile infants ≤60 days

A total of 19 physicians participated in the study to describe the decision-making process when managing febrile infants aged ≤60 days and to describe the factors that influenced this decision. There were 12 females and 7 males, with varying ages and clinical experience (Table 22). In total, 6 focus group discussions were conducted, which lasted between 53 and 64 minutes with 2 to 5 participants.

Table 22. Composition of the focus groups and characteristics of the participants

	On-duty Physicians	On-call Physicians
Participants	11	8
Female	7	5
Age (years)		
21–30	3	–
31–40	8	–
41–50	–	3
>50	–	3
Years of working with children		
0–3	2	–
4–5	5	–
6–9	4	–
>10	–	8
Febrile infants ≤21 days managed per month		
0	1	–
1–2	6	2
3–5	1	3
>5	3	3

The decision to perform an LP was conceived as complex and emotionally laden, and it was the component of the guideline that dominated the discussion. There were identified 3 central factors that influence the decision-making process regarding whether to perform an LP. The first was the search for a focus of infection that could explain the fever, such as signs or symptoms of upper respiratory tract infection. The second was questioning if the temperature reported by parents constituted fever, especially in cases where the infant's temperature at home was less than 38.2°C, and the infant was afebrile during the examination. The third was the infants' general condition, with physicians reasoning that LP is not motivated in cases of well-appearing infants (Fig. 3).

Fig 3. Description categories, with central categories of conception, and how they are interrelated in the decision to perform or not perform an LP and finding its justification.

Around these 3 central factors evolved 6 secondary categories, which acted as barriers or motivators in following the hospital guideline for febrile infants and particularly on whether to perform an LP or not: 1) fearing the risk of failure, 2) trusting one's own judgment, 3) avoiding burdensome work, 4) taking others into account, 5) balancing guidelines and resources, and 6) seeing a need to practice and learn performing an LP (Fig. 3). These 6 secondary categories can be divided into 2 different types of motivators. The first was related to the physician, expressed as ''being driven by intrinsic motivators''. The second was more related to external factors, expressed as ''being driven by extrinsic motivators."

Discussion

Main findings

The main findings of this research project in 4 Swedish PEDs were that the prevalence of meningitis and bacteremia was low in infants with FWS aged ≤60 days. The prevalence of meningitis did not differ between boys and girls. Infants ≤28 days old with reported fever at home who were afebrile at presentation had a similar risk of meningitis as infants who were still febrile. The rates of LP, blood cultures, and broad-spectrum antibiotics were much lower than those reported internationally. Despite the fewer investigations and antibiotic treatments, there were few delayed-treated IBIs. However, 2 of the 8 infants with meningitis were not treated at presentation, indicating an opportunity for improvement with a more structured approach. The focus group discussions showed that the presence of fever and the infant's general condition influence the decision-making process on whether to follow the guideline for febrile infants, mainly whether to perform an LP. Physicians highlighted the importance of relying on their clinical judgment and making independent clinical decisions.

Prevalence of meningitis, variation in performing lumbar puncture, and implications

This thesis describes a management of infants with FWS without routine LP and contributes with knowledge that such an approach should be considered and investigated further.

Table 14 (page 50) shows that LP was performed in only 13% of infants aged ≤28 days and 16% of infants aged ≤21 days. These rates are significantly lower than all previously reported rates of 62-93% for infants aged ≤28 days (Table 7, page 32).[69, 157, 212, 213] Data for the ≤21 days age group are scarce, but Garcia et al. reported rates of 73%.[68] Thus, this research project verified the anecdotal experience and hypothesis that the management of febrile infants in Sweden does not include routine LP, contrary to international recommendations and praxis.

Eight infants were diagnosed with meningitis in the 4 study PEDs between 2014-2017. Of these, 6 were identified and treated at presentation, of which 4 were ≤21 days old and 2 were 29-60 days old. The LPs performed were 60 in infants aged ≤21 days, 76 in those aged ≤28 days, 128 in infants aged 0-60 days, and 52 in infants aged 29-60 days. Hence, the number of LPs per meningitis case was 15, 19, 21, and 26 for each age group.

Despite the low rates of LP, only 2 infants with meningitis (one 10 and one 31 days old) were not identified and treated at presentation. The ‘‘step by step’’ approach and the latest AAP guideline recommend LP for all infants ≤21 days,[27, 28] while the NICE guideline has one month of age as the cutoff point.[14] In the infants with FWS presented to the 4 Swedish PEDs, the prevalence of meningitis was 1.3% in those aged ≤21 days and 0.9% in those ≤28 days. Thus, an age threshold of 21 days would have resulted in 77 LPs for each meningitis case, instead of the 15 that were performed. Similarly, an age threshold of 28 days would have resulted in 110 LPs per meningitis case, instead of the 19 that were performed. Consequently, the ‘‘step by step’’ and the AAP guidelines would have resulted in an almost 6-fold increase in the number needed to treat (NNT).

The 31 days old infant should have undergone LP according to the Boston and Philadelphia criteria, which recommend LP for febrile infants ≤60 days.[15, 16] The prevalence of meningitis was 0.5% in infants 0-60 days old and 0.3% in those aged 29-60 days. Therefore, in infants 0-60 days old, 200 LPs should be performed for each meningitis case instead of the 21 that were performed. In infants 29-60 days, 330 LPs should be performed for each meningitis case instead of 26. Thus, the Boston and Philadelphia criteria would have resulted in a 10- to 13-fold increase in the number needed to treat (NNT).

Several studies have reported low sensitivity of routine CSF testing, mainly when performed very early in the trajectory of the illness and that 5-32% of infants with verified bacterial meningitis were not identified.[85, 141, 146] Table 9 (page 45) shows that 60% of febrile infants presented with a fever duration of less than 6 hours and almost 80% of infants with fever duration of less than 12 hours. Thus, the 2 infants with delayed-treated meningitis would not have necessarily been identified, even after a 5- to 13-fold increase in the number of LPs.

Table 17 (page 54) shows that both infants with delayed-treated meningitis had elevated CRP or PCT, which should have stratified them as high risk.[27, 91, 133, 138] Also, the ANC and PCT were not consistently measured, while they could have improved the risk stratification.[7, 27, 91, 133, 134] Furthermore, both infants had a fever of ≥39°C, which is associated with high odds of having an IBI.[228-230] Therefore, a more structured approach with defined biomarker cutoff points would likely be sufficient to identify both cases, even without routine LP at presentation. Nevertheless, LP was performed in both infants, and antibiotics were administered

in the ward soon after admission. Thus, a short observation time would have added value to any approach without a routine LP.

This research project describes, for the first time, an actual management of febrile infants aged ≤28 days without routine LP. Prediction models without routine LP have been retrospectively tested with promising results but have not been implemented in clinical practice. For well-appearing infants with a history of fever who were afebrile at the PED, Aronson et al. derived a prediction score based on age, the height of the fever, ANC, and urinalysis.[228] Also, another study by Aronson et al. tested the Philadelphia criteria without routine LP in a cohort of well-appearing febrile infants ≤60 days with IBI.[120] Similarly, Kuppermann et al. derived a prediction rule based on PCT, ANC, and urinalysis to identify low-risk febrile infants ≤60 days.[7] None of these retrospectively applied clinical scores misclassified any infant with bacterial meningitis as low risk. However, despite the high accuracy of these clinical scores, the authors recommended caution when applying them to febrile infants aged ≤28 days and suggested further validation. Tables 10-12 (pages 46-47) show that in the 4 Swedish PEDs, the IBI prevalence in infants aged ≤60 days was similar to that reported in the cohorts the above clinical scores were tested. Therefore, these clinical scores would probably also perform as well in Swedish PEDs.

This research project did not identify any statistically significant difference in the prevalence of meningitis between girls and boys. Thus, the current data from this study do not support a different meningitis risk stratification based on sex. Furthermore, Table 19 (page 56) shows that in infants aged ≤28 days, the risk of meningitis was similar between infants with reported fever at home who were afebrile at the PED and those who were still febrile. Thus, for infants aged ≤28 days, the absence of fever at the PED does not justify a different meningitis risk stratification.

This thesis shows that the management of febrile infants without routine LP in Swedish PEDs, was not associated with a high rate of unfavorable outcomes. However, 2 of the 8 cases of meningitis were not identified at presentation. These 2 infants with delayed-treated meningitis would have likely been stratified as high risk at the PED if the test results were interpreted adequately, CRP and ANC had been consistently measured, and newer biomarkers, such as PCT, were incorporated. Therefore, a more structured approach is required. In conclusion, this thesis indicates that an approach based on biomarkers and clinical parameters, as recently suggested by retrospectively derived clinical scores, would have identified the infants with bacterial meningitis. At the same time, an approach without routine LP would significantly decrease the number of LPs performed per meningitis case. Such an approach could be appropriate in settings with low meningitis prevalence and the possibility of adequate follow-up or observation.

Prevalence of bacteremia, variation in obtaining blood culture, and implications

This research project provides data that question the utility of routinely obtaining blood culture in well-appearing febrile infants aged ≤60 days.

Table 14 (page 50) shows that in the 4 Swedish PEDs, blood culture was obtained in only 27% of the infants 0-60 days old. These rates are lower than the reported blood culture rates of 70-90%.[69, 157, 212, 213] All guidelines, including the latest AAP, recommend blood culture for febrile infants aged 0-60 days to detect and eventually treat isolated bacteremia early and prevent its progression to serious infection, particularly meningitis.[14, 27, 28] According to Table 10 (page 46), the prevalence of isolated bacteremia in infants 0-60 days old was 0.6%. With this prevalence, 167 blood cultures should be obtained for every case of isolated bacteremia. This number is almost 4-fold higher than the 42 blood cultures per case of isolated bacteremia in the 4 study PEDs.

Table 17 (page 54) shows that despite the low rates of blood cultures and antibiotic treatments, only 2 infants who did not receive antibiotics at the PED were subsequently diagnosed with isolated bacteremia and none developed severe disease or experienced any adverse outcomes. Additionally, none of the 804 infants discharged home was subsequently diagnosed with bacteremia or meningitis during the following 10 days. Likewise, it has been reported that well-appearing children and infants diagnosed with isolated bacteremia after their discharge from the PED were mostly afebrile at their return visit and none suffered any unfavorable outcome.[44-46] Furthermore, the progress of isolated bacteremia to meningitis is mainly associated with *Neisseria meningitidis*, *Haemophilus influenzae*, and *Streptococcus pneumoniae*.[12, 13, 250] This study reported only one case of *Streptococcus pneumoniae,* whereas almost 90% of cases of isolated bacteremia were caused by *Escherichia coli*, Group B and Group A *Streptococcus*. Other studies reported similar epidemiology as well.[61, 71, 77] The latter 3 bacteria rarely cause sepsis in infants without comorbidities and are not associated with progression to meningitis and high case fatality rates.[43]

Table 10 (page 46) shows that the total prevalence of bacteremia was 1.5%. However, 56% of bacteremia cases were combined with meningitis or UTI. Bacteremia in combination with meningitis or UTI should not alter the choice of antibiotics or the duration of the treatment and is not associated with a worse prognosis.[47-49, 251] Thus, these positive blood cultures had no decisive management implications.

Hence, despite the low rates of blood cultures and antibiotics, no adverse outcomes were associated with untreated isolated bacteremia. Also, there is insufficient evidence in the current literature that isolated bacteremia in well-appearing infants

is associated with increased mortality or short- and long-term morbidity. Furthermore, the bacterial etiology reported in this study does not support the fear that isolated bacteremia progresses to meningitis. Additionally, positive blood cultures in cases of meningitis or UTIs should not alter the management. So, current guidelines would have resulted in a significant increase in blood cultures without any apparent benefit for febrile infants. Thus, several arguments question the utility of routine blood culture in febrile infants aged ≤60 days.

Prevalence of UTI, variation in urine testing, and implications

This research project identified that UTIs accounted for almost 90% of SBIs, which highlights the importance of urine testing for febrile infants aged ≤60 days. However, some findings of this study indicate that a more selective approach may be more appropriate than routine urinalysis at presentation for all febrile infants.

Table 16 (page 52) shows that in the study PEDs, urine testing varied from 73% to 90%. Despite this variation, the rates of delayed-treated UTIs did not differ significantly and the site with the lowest urine testing rate did not have the highest rate of delayed-treated UTIs. In 2 of the cases of delayed-treated UTIs, the urine dipstick was negative for leukocyte esterase and nitrates. This research project started almost 7 years ago, so for consistency with the current literature, the definition of UTI included urine cultures with bacterial growth of >100 000 cfu/ml irrespective of the urine dipstick result. Currently, a positive urinalysis is a prerequisite for the diagnosis of UTI. In addition, according to the latest AAP guideline, urine culture is not recommended if urinalysis is negative.[28, 53, 54] Thus, with the current definition, these 2 cases would not necessarily have been considered UTIs. Additionally, in 4 of the cases of delayed-treated UTIs, the urine dipstick test was positive for either leukocyte esterase or nitrate, but quite unexpectedly, the infants did not receive antibiotics. Hence, of the 8 cases of delayed-treated UTIs, only 2 were not tested at presentation. Nonetheless, none of the infants with delayed-treated UTI developed sepsis, needed intensive care, suffered any short-term adverse outcomes, or were hospitalized for more than 6 days. Thus, the more selective urine testing did not result in any short-term ‘‘harm’’ to any infant.

There are concerns, though, that delayed treatment increases the risk of renal scarring, which can result in renal dysfunction later in life. However, Hewitt et al. demonstrated that early treatment had no significant effect on the incidence of renal scarring.[166] Similarly, Benador et al. showed that the duration of the fever before the treatment had no significant effect on the incidence of renal scarring and that children younger than 1 year developed renal scarring less frequently than older children.[252] Additionally, Wennerstrom et al. found no association between renal

scarring and long-term renal dysfunction in adulthood.[168] Moreover, Salo et al. did not find any association between UTI during childhood and chronic kidney disease later in life in children without anatomical structural abnormalities.[42] Thus, as Newman et al. concluded almost 10 years ago, the current evidence does not support the notion that UTIs pose a significant danger that justifies such an aggressive pursuit of the diagnosis.[40]

Aggressive testing may, moreover, be harmful. Urine testing by bladder catheterization or suprapubic aspiration is painful for infants, stressful for parents, and time-consuming for PED personnel. Also, it could be a potential cause of infection.[203-205] Additionally, urinalysis has low specificity and positive predictive value, with consequently high rates of false positive results.[59, 60] Furthermore, urine cultures, even from samples collected by catheterization or suprapubic aspiration, have considerable contamination rates and asymptomatic bacteriuria is more common in infants than previously considered.[57, 58] Thus, aggressive testing can result in overdiagnosis or misdiagnosis of UTIs and lead to unnecessary hospitalizations and antibiotic treatments. Moreover, for infants with UTI diagnosis, it is often recommened follow-up with renal and bladder ultrasonography, voiding cystourethrogram, and renal cortical scintigraphy.[54] These investigations involve radiation for the infants, extra-economic constraints for the families, and additional workload and financial burden for the health system. Furthermore, long-term antibiotic prophylaxis is often initiated in infants with UTI without clear benefit.[253] Finally, after a presumed UTI diagnosis, parents are instructed to seek health care for future febrile illnesses as soon as possible, which can also result in excessive urine testing and overdiagnosis or misdiagnosis.[54] Thus, aggressive testing could have considerable side effects and even cause more harm than benefit.

Table 19 (page 56) shows that 36% of the infants with reported fever at home were afebrile at the PED. The risk of UTI was almost half in infants afebrile at the PED than in those still febrile. Additionally, the median temperature at the PED was 38.2°C and 60% of the febrile infants presented to the PED with a fever duration of less than 6 hours (Table 9, page 45). It has been shown that fever duration and height are strong predictors of UTI.[156] Moreover, Table 13 (page 48) demonstrates a lower prevalence of UTIs in girls than in boys, particularly those aged ≤28 days. Furthermore, Table 20 (page 57) shows that in girls afebrile at the PED, the prevalence of UTI was only 3.6%. Shaikh et al., in a meta-analysis, reported similar differences between boys and girls aged ≤60 days and a higher risk of UTIs in uncircumcised boys.[51] Thus, the findings of this research project indicate that for well-appearing febrile infants, it may be safe with a selective urine testing strategy based on high-risk factors such as a high fever, fever duration for more than 12-24 hours, male sex, and circumcision status.

Adverse outcomes, management variation, and implications

This thesis demonstrated that low rates and variations in testing, antibiotic treatments, and hospitalizations were not associated with differences in adverse outcomes. This finding could point to opportunities to improve the management of febrile infants and optimize the use of healthcare resources.

In the study PEDs, of the infants aged ≤28 days, only 13% underwent LP, 30% received antibiotics, and 67% were hospitalized, while blood culture was obtained in only 40%. This management contrasts with reported rates from PEDs in the US and Spain of 60-90% for LP, 75-100% for blood culture, 76-85% for antibiotics, and 80-98% for hospitalizations.[69, 77, 187, 212, 213] For the 29-60 days age group, the differences in testing, antibiotics, and hospitalizations between the study PEDs and reports from PEDs in the USA and Spain were even more remarkable. Such differences, though more minor, in the rates of investigations, treatments, and hospitalizations, were identified between private pediatricians and PEDs in the USA.[9, 157] Additionally, Table 16 (page 52) shows that the rate of LP varied almost 11-fold and of antibiotics 2.5-fold between this study's PEDs with the highest and lowest rates. Similar variations between hospitals are reported from studies in the USA and Canada.[69, 214]

However, despite the low rates of testing and antibiotics only 4 (0.2%) infants had a delayed-treated IBI. Also, the variation between the PEDs was not associated with increased rates of delayed-treated IBIs at the site with the lowest rates of investigations, antibiotics, and hospitalizations (Table 18, page 55). Similarly, variation between PEDs in the USA and Canada was not associated with differences in outcomes.[69, 157, 212-214] The PROS study showed that private pediatricians that relied on their clinical judgment without following guidelines were at least as sensitive in treating bacterial meningitis and bacteremia as the current guidelines.[9]

Thus, there are indications that management of febrile infants with fewer investigations, antibiotic treatments, and hospitalizations is not associated with increased adverse outcomes. Therefore, the current guidelines would not have necessarily resulted in significantly better patient outcomes in the study PEDs.

Possible ‘‘side effects’’ of guidelines for febrile infants

All validation studies of management guidelines for febrile infants have only reported the rate of misclassified IBIs or SBIs as a measure of efficacy. Traditionally, a delay in treating a UTI, bacteremia, or meningitis has been considered an adverse outcome. However, no accompanying evidence was provided

on whether this delay necessarily represented ‘‘harm’’ for the patient. On the other hand, the possible consequences of medical interventions when managing febrile infants have not been considered. De Angelis et al., already in 1983, warned about the possible iatrogenic complications and increased financial costs associated with the investigations and hospitalizations of febrile infants.[25]

At the time of this study, most guidelines recommended LP, parenteral antibiotics, and hospitalization for all febrile infants aged ≤28 days and blood culture for infants aged ≤60 days. In the study’s PEDs, this approach would have resulted in a 650% increase in LPs, 233% increase in antibiotics, 48% increase in hospitalizations, and a 260% increase in blood cultures. The ‘‘step by step’’ approach and the new AAP guideline recommend 21 days of age as a cutoff point for routine LP, antibiotics, and hospitalization. This approach would have resulted in a 535% increase in LPs, 195% increase in antibiotics, and 40% increase in hospitalizations. Thus, current and newer guidelines would have significantly increased investigations, antibiotic treatments, and hospitalizations, without necessarily better clinical outcomes.

Lumbar punctures, blood cultures, urine testing, antibiotics, and hospitalizations can have significant side effects, as described in the Introduction and previous chapters. Hence, increased interventions could have significant consequences and side effects on infants, their families, PED personnel, and the healthcare system. The term ‘‘medical overuse’’ describes medical care when the benefits do not outweigh the harms.[209] Unfortunately, medical overuse and its effects are not identified by the studies that recommend and initiate a medical practice. It takes subsequent studies with more robust designs, larger populations, and longer duration to identify the side effects of medical overuse.[209] Additionally, measuring the long-term effects of administering parenteral antibiotics to a 10 days old febrile infant is methodically challenging. It is difficult to establish causation with a chronic disease in adulthood, as indicated by observational studies, due to potential confounding factors and biases.[201] Even then, prescribing physicians would neither be aware nor accountable for the long-term consequences of the medical intervention they initiated. Moreover, even when measurable short-term harms occur, such as an embolism due to an intravenous catheter, a hospital-acquired infection, or an anaphylactic drug reaction, they are often attributed to suboptimal routines and practices or they are just dismissed as unavoidable side effects. It is rarely questioned whether these interventions were needed in the first place and whether there were in the patient’s interest. Thus, the harm is not associated with the guideline, which causes medical overuse. Furthermore, physicians are often unaware even of the short-term harms caused by medical overuse. Additionally, there is no accountability or legal liability for harm when the guidelines have been followed. In contrast to possible accountability and liability for any ‘‘miss’’ when guidelines have not been followed. This might explain why physicians are more risk-averse to type II errors than type I errors. In other words, they would rather investigate and treat large numbers of healthy febrile infants than miss a single case of IBI, even if their practice may cause

more harm than benefit. At the end of the shift, the physicians who obtain tests from all their patients, prescribe antibiotics to most of them, and fill up the ward are the ‘‘heroes’’ of the ED. ‘‘Heroes’’ who worked non-stop in an overcrowded ED and stayed over to facilitate and document their actions and decisions. In contrast, physicians who do ‘‘less’’ and take care of way more patients are perceived as ‘‘mavericks.” When the ‘‘mavericks’’ miss a diagnosis, it is their medical approach that failed. In contrast, when the ‘‘heroes’’ miss, it is the system, the workload, the lack of resources, or the working conditions that failed them, or it was just inevitable.

The possible harm of medical overuse is not restricted to the febrile infants involved but exceeds to the rest of the patients in an ED. When this thesis was written in the autumn of 2022, newspapers' front pages portrayed a dire picture of overcrowded EDs, overwhelmed ED personnel, and overstrained inpatient departments in Europe and the US. It is well documented that overcrowding worsens the quality of care at the ED, prolongs waiting time, and results in significant patient harm, with increased morbidity and mortality.[254, 255] A recent report form the Royal College of Emergency Medicine, estimated that 23000 excess patient deaths in 2022 in England were associated with long stays in EDs.[256] Moreover, overcrowding is also associated with significant negative effects on ED staff.[257, 258] It increases the likelihood of management errors, causes significant stress, diminishes job satisfaction, and results in staff reduction. As mentioned in the introduction, a conservative estimation is that around 200 000 febrile infants visit health facilities in the US or Europe alone. Thus, a modest reduction in LPs, blood cultures, urine testing, and hospitalizations could significantly reduce the workload, waiting times, crowding, and costs. Although it is difficult to determine whether reducing medical overuse is beneficial for the individual patient, it would likely result in significantly reduced patient harm at the population level.[210] Moreover, medical overuse causes patient harm at the population level by the lost opportunity. Healthcare resources are not infinite, and they could be diverted to medical intervention with clear patient benefits.[259]

Prevalence variation and implications

This project identified an SBI prevalence that questions whether it is optimal to extrapolate prevalence data from other countries and to adopt management guidelines based on different risk estimates.

The 12.6% prevalence of SBI (Table 10, page 46) is 30-50% lower than the prevalence of 18.2-26.2% reported by similar studies in Spain, Italy, and Israel.[8, 68, 77, 90, 260] The prevalence of bacteremia (1.5%) is also lower than the 1.7-3.3% prevalence reported in the same studies, while the prevalence of meningitis (0.5%) is similar. Recent studies from the US reported an SBI prevalence of 8.6-17.9%,

meningitis of 0.3-0.6%, and bacteremia of 1.6-3.2%.[7, 62, 69, 157] Thus, the SBI and meningitis prevalence identified by this research project are similar to those reported in the US. However, the US studies included all febrile infants, even infants with signs or symptoms of respiratory infection, in contrast to this research project, which included only infants with FWS. As mentioned in the Introduction, the prevalence of SBIs is reported to be 2- to 7-fold higher in infants with nasopharyngeal tests negative for a virus or in infants without respiratory symptoms. Moreover, no case of meningitis was identified among febrile infants with respiratory symptoms or with a positive test for influenza or RSV.[24, 34-36] Therefore, it could be safely hypothesized that in infants with FWS, the actual prevalence of SBI, particularly meningitis, is considerably higher than that reported in febrile infants in general. Thus, the prevalence of SBI in infants with FWS in Sweden appears to be lower than that in Spain and the US.

The difference in prevalence between Sweden and US/Spain may reflect statistical variation, heterogeneity in methodology, or differences in the frequency of investigations. The rates of urine testing, blood cultures, and LPs in Swedish PEDs were much lower than those reported in Spanish and US PEDs. Therefore, this research project may have missed UTIs, bacteremias, or meningitis cases and consequently underestimated their prevalence. However, occult bacteremia and occasionally UTI can be self-limiting but not bacterial meningitis. For this research project, it was chosen a more extended 10-days follow-up, instead of the 2 or 3-days commonly used, to minimize the likelihood of missed cases, particularly meningitis.[69, 212] Thus, it is unlikely that any possible underestimation would be of significant magnitude.

The difference in the prevalence of UTIs accounted mainly for the identified difference and, to a lesser extent, for the difference in bacteremia. The percentage of febrile boys (55%) was similar between this and international studies. Additionally, the estimated prevalence of circumcision is lower in Sweden than in Spain and the US.[64] Thus, the lower UTI prevalence in Swedish PEDs cannot be attributed to factors associated with UTIs, such as male sex or circumcision status.

The higher UTI and bacteremia prevalence reported by international studies could represent misdiagnosis or overdiagnosis due to the routine testing recommended by the current guidelines. As described in previous chapters, urinalysis has low specificity and urine cultures have high contamination rates. Therefore, routine urine testing may have resulted in the misdiagnosis of UTIs. Similarly, blood cultures also have high contamination rates and true positive results do not always have clinical implications for patients. Therefore, routine blood cultures might have resulted in the misdiagnosis or overdiagnosis of bacteremia. Overdiagnosis is defined as the detection of a true abnormality that will not benefit the patient.[210]

However, the reported difference in prevalence might represent a ‘‘true difference’’ and reflect an association of social determinants of health with SBIs, as previously

suggested by Yaeger et al.[92] Sweden has one of the lowest rates of childhood poverty.[102] Additionally, as mentioned in the introduction, Sweden is among the countries with the most optimal rates of the factors associated with lower incidence of infections in infants, such as birth weight, mode of delivery, breastfeeding, maternal smoking, and maternal education. Unfortunately, because of the retrospective nature of this research project, it was not possible to collect any socioeconomic data or information on the above factors.

In conclusion, the prevalence of SBIs in infants aged ≤60 days with FWS in Sweden appears to be lower than that in the US and Spain. Consequently, the risk estimates and pre-test probabilities may differ substantially. Hence, the investigations, interpretation of test results, recommendations for administration of antibiotics, and hospitalizations, suggested by the AAP guideline and the step by step approach might not be optimal in Sweden. An ‘‘one size fits all’’ guideline may not be the best approach for countries with different characteristics and even for different settings within countries. Furthermore, a possible association between socioeconomic factors and patient characteristics highlights the need for more individualized prediction models.

Decision-making process when managing febrile infants

The qualitative study of this research project deepens the knowledge on how physicians perceive following guidelines and their decision-making processes. It described that LP was perceived as a time-consuming, emotionally laden, and often unnecessary procedure. Consequently, deciding whether to perform an LP had the most central role in the decision-making process when managing febrile infants. Physicians emphasized the significance of being able to make clinical decisions by relying on their judgment. Thus, guidelines should allow a degree of flexibility and independent thinking to enable the consideration of patients’ needs and characteristics.

The findings of the focus group discussion support previous hypotheses that the general condition of the infants and the absence of fever might influence the decision-making process regarding whether to follow guidelines. These hypotheses were based on studies that showed that well-appearing infants or infants afebrile at presentation underwent fewer investigations than infants febrile or ill-appearing.[9, 156, 231, 234] The physicians who participated in the focus group discussions described that the infant’s general condition and the presence of fever were the primary factors that influenced their management decisions. The participating physicians described that they perceived the likelihood of meningitis to be very low in afebrile infants. Therefore, they reasoned that an LP was not indicated despite the guideline’s recommendation. Additionally, physicians perceived that the management of febrile

infants based on their clinical reasoning worked well. The analysis of adverse outcomes (Table 18, page 55) showed that no infant with bacterial meningitis was ‘‘missed’’ in Malmö and Lund, where the focus group discussions were conducted. Thus, physicians’ risk estimates and decisions were not proven to be unjustified based on patient outcomes.

Physicians highlighted the importance of being able to make decisions rather than blindly following guidelines. Furthermore, they expressed concerns that guidelines may discourage independent thinking and limit physicians’ diagnostic capability. Such concerns have already been mentioned in the literature.[261] Concerns that physicians may fail to consider patients’ disease risks and needs or possible side effects of medical interventions, which can result in guidelines causing more harm than benefit for the patients.[262, 263] The potential patient harm caused by medical interventions and medical overuse and how guidelines can drive medical overuse has been extensively described in previous chapters.

In addition to patient harm, restricting the ability to make independent decisions could also harm physicians. Studies have shown that autonomy and a sense of competence are among the most important factors that increase physicians’ work satisfaction.[264] Moreover, excessive control and suboptimal challenges can result in a lack of initiative and increased stress.[265] Thus, doctors cannot thrive in their profession by blindly following guidelines. The analysis of the focus group discussions showed that participating physicians perceived the ability of clinical reasoning and decision making as important. They also expressed worries regarding possible liability and criticism if ‘‘things go wrong, ’’ and they did not follow the guidelines. The concern of being ‘‘unfairly’’ judged by colleagues, auditors, and managers based explicitly on whether they followed the guideline is reported as another downside of guidelines.[261] This might also explain why physicians are more risk-averse to type II than type I errors, as discussed in previous chapters. A medical practice, dictated mainly through guidelines and the ‘‘fear of legal liability,” might have contributed to the reported unprecedented rates of dissatisfaction and burnout among physicians.[266, 267] Physicians’ burnout and dissatisfaction lead to increased medical errors and result in patient harm.[268] Consequently, guidelines can cause patient harm in more indirect and less apparent ways than those already described in the previous chapters. Thus, guidelines should allow for more flexibility and promote medical reasoning. This would enable physicians to consider patient needs, characteristics, and individual disease risks.

Limitations of the studies and methodological considerations

This research project has several limitations. The first is the possible failure to identify all febrile infants who attended the study PEDs. Infants with fever, registered as the chief complaint in the PEDs 'electronic registration system were eligible for the study. The triage nurse can choose only one contact reason from the drop-down menu. Thus, febrile infants who attended the PEDs may have been registered with another chief complaint. However, most options, such as cough, seizures, diarrhea, and respiratory distress, would imply a focus of infection. Papers I-III focused on infants with FWS. There are only a few choices, such as fatigue, feeding refusal, or vomiting, that do not imply a source of infection. Additionally, when present, fever is often the prominent symptom that concerns parents and is first reported.

The second is the possible underestimation of the prevalence of IBIs and, consequently, the underestimation of delayed-treated IBIs rates. Table 14 (page 50) showed that CSF testing and blood cultures were not routinely performed. Thus, it is likely that cases of meningitis and bacteremia were not identified. However, bacterial meningitis is not a self-limiting condition. The follow-up period was 10 days after the infants were discharged from the PED, and it is unlikely that symptoms and signs of meningitis developed later.[175] Furthermore, no other health facilities see febrile infants younger than 60 days in the catchment areas of 3 of the 4 study PEDs. Only in the PED in Stockholm can the infants be seen at another PED. However, parents prefer to attend the PED nearest to where they live and where their children were evaluated for the first time. Thus, there is a low likelihood that the number of missed meningitis cases could alter the estimated meningitis prevalence.

The third is the possible misestimation of UTI prevalence. Urine cultures with growth of >100 000 cfu/ml^3 were considered positive, regardless of the urinalysis result. The latest AAP guideline does not recommend urine culture when there are no indications of inflammation in the urinalysis.[28] Thus, these cases might not be considered UTIs with the current definition. Furthermore, the laboratories in the study PEDs report urine culture results in 3 cfu/ml^3 intervals (i.e., <10 000, 10 000-100 000, and >100 000). Due to that, this study's UTI definition included ''clean catch'' specimens with a growth of 10 000-100 000 cfu/ml^3 instead of >50 000 cfu/ml^3.[7] Additionally, ''clean catch'' was the default urine collection method in all study PEDs instead of suprapubic aspiration or bladder catheterization. The contamination rates are reported to be higher in samples collected with ''clean catch'' than in catheterization or aspiration.[57] The above limitations might have resulted in overestimation of UTI prevalence. On the contrary, urine testing was not

routinely performed in the study PEDs. Thus, UTIs might have been missed, and their prevalence might have been underestimated

The fourth limitation is the insufficient data to interpret and explain the variation in the prevalence of SBI identified in this study. Information about socioeconomic and health factors associated with the incidence of SBIs, such as birth weight, delivery mode, breastfeeding, maternal smoking, and education, was rarely mentioned in patients' electronic files.

The fifth limitation is the size of this study, which did not allow for sound conclusions. The previously reported prevalence of meningitis in febrile infants aged ≤60 days was approximately 1%. With a level of confidence aimed at 95% and an error of precision (d) set at 25% of the expected prevalence, an appropriate sample size would be 6085 febrile infants ≤60 days.[269-271] Thus, the adequate sample size to estimate the prevalence of meningitis is almost 4-fold higher than the population size in this study. Furthermore, this study did not identify any statistically significant difference in the prevalence of meningitis between girls and boys. With an estimated meningitis prevalence for boys at around 1%, a 5% probability for type I error (alpha), a power set at 90% (beta of 10%), and knowing that in most studies, 45% of febrile infants are girls (enrollment ratio girls versus boys of 0.8), the adequate sample would be around 13000 febrile infants ≤60 days (7000 boys and 6000 girls), to detect a 50% lower meningitis prevalence. Thus, the hypothesis of sex differences cannot be disregarded because of the findings of this study, and might merit further research. Similarly, this research project did not identify any difference in the risk of meningitis between infants ≤28 days febrile and afebrile at the PED. Accepting the same parameters as for boys and girls, and that 30% of infants with reported fever at home are afebrile at the PED (enrollment ratio afebrile versus febrile of 0.4), the adequate sample size would be around 15700 infants (11200 febrile and 4500 afebrile) to detect a 50% lower meningitis prevalence.[272]

The sixth limitation is the limited temperature measurements. The retrospective nature of this study allowed only the collection of 2 temperature measurements, one reported by the parents and one registered by the triage nurse. Information on subsequent fever measurements was not reliably available. Such data could enable risk comparisons between infants who remained afebrile during their stay at the PED or inpatient ward and those who subsequently developed a fever. In addition, more measurements could have allowed the investigation of a possible association between fever height and the risk of IBIs.

The seventh limitation is the possible lack of diversity among the study sites. Although the 4 study PEDs were geographically diverse, all were part of university pediatric hospitals. The management of febrile infants may differ in PEDs in smaller towns or in medical settings without pediatric physicians. In addition, all study PEDs were in urban settings with short distances and easy patient access. The

prevalence of SBIs among febrile infants might differ in rural settings with long distances from the PED, where parents may not seek medical help within a couple of hours due to a single temperature measurement of 38.2 °C.

The eighth limitation is the definition of adverse outcomes. As in other similar studies, a delayed-treated SBI was defined as an adverse outcome. Due to the study design and duration, it was impossible to investigate whether treatment delay was associated with short- or long-term consequences for infants. Thus, it has not been established whether treatment delay necessarily represents patient harm.

Finally, there are the limitations of study IV. Few discussion groups had only 2 or 3 participants, which might have limited the expression of opinions. In addition, group discussions were conducted at 2 urban academic pediatric hospitals. Thus, physicians' perspectives might not reflect the opinions of non-pediatric physicians or physicians working in non-academic hospital settings. Furthermore, when analyzing perceptions, there is always the risk of misinterpretation and questioning ''if it is the chicken or the egg that came first''. It was concluded that the decision-making process started with 3 major categories and evolved around 6 secondary categories. However, any of the secondary factors, such as the difficulty and the time needed to perform an LP or the fear of failure, could have been the primary factor. The primary factor that influenced the decision-making process to minimize the possibility of meningitis by assuming a focus of infection, questioning the presence of fever, or relying on a good general condition.

Conclusions

This research project demonstrates:

- a management of infants aged ≤28 days with FWS without routine LP, blood culture, or broad-spectrum antibiotics.
- a management of infants aged ≤60 days with FWS with much lower rates of LP, blood cultures, and broad-spectrum antibiotics than internationally reported, but not associated with increased adverse outcomes.
- variation between the 4 study PEDs in testing, antibiotic treatments, and hospitalizations in infants aged ≤60 days with FWS not associated with differences in adverse outcomes.
- a low overall rate of delayed-treated meningitis, bacteremia, and UTIs.
- a management where 25% of meningitis cases were not treated at presentation.
- low prevalence of bacteremia and meningitis in infants aged ≤60 days with FWS.

Implications. These findings could point to opportunities to improve the management of infants aged ≤60 days with FWS and to optimize the use of healthcare resources:

- Management of infants aged ≤28 days with FWS without routine LP and antibiotics could be considered and investigated further.
- The utility of routinely obtaining blood cultures in well-appearing infants aged ≤60 days with FWS may be reconsidered.
- A more selective urine testing approach may be more appropriate than routine urinalysis for all febrile infants aged ≤60 days with FWS.
- Swedish PEDs require a more structured approach for managing febrile infants.
- A prediction rule based on clinical parameters, newer biomarkers, and observation or adequate follow-up could ensure patient safety and reduce unnecessary investigations, antibiotic treatments, and hospitalizations.

Additionally, according to this research project:

- There was no statistically significant difference in the prevalence of meningitis between boys and girls aged ≤ 60 days with FWS.
- There was no statistically significant difference in the risk of meningitis between infants aged ≤28 days with reported fever at home who were afebrile at the PED and those who were still febrile.
- Infants aged ≤28 days with reported fever at home who were afebrile at the PED underwent fewer investigations than those who were still febrile.

Implications. These findings do not justify a different risk estimation for meningitis, and consequently, a different management of:

- infants aged ≤28 days with reported fever at home who are afebrile at the PED.
- boys and girls.

Furthermore, this research project showed an SBI prevalence of 12.6% among previously healthy full-term infants aged ≤60 days with FWS, which is lower than that reported in other countries.

Implications. These findings imply the following:

- It is not optimal to extrapolate prevalence data from other countries and to adopt management guidelines based on different risk estimates.
- The difference in prevalence might reflect an association between the social determinants of health and SBIs.

Finally, this research project identified the following:

- The decision on whether to perform LP played the most central role in the decision-making process when managing febrile infants.
- General appearance, presence of fever, and possible focus of infection were the primary factors that influenced physicians to omit performing LP.
- Physicians highlighted the importance of relying on their clinical judgment and making independent decisions.

Implications. These findings indicate that guidelines may consider allowing a degree of flexibility and independent thinking to:

- consider patients' characteristics and needs.
- allow the development of physicians' medical reasoning and a sense of competence, which could increase job satisfaction.

Future perspectives

Despite immense research in the last few decades, there are many unanswered questions in the field of febrile infants.

The prevalence of meningitis, bacteremia, and UTIs in young febrile infants has been studied only in a few countries and mainly in PEDs in large urban settings. Also, the prevalence has been mostly reported in wide age intervals (weeks or months). Furthermore, no studies have thoroughly investigated the possible association of the risk of infection in young febrile infants with individual clinical parameters, such as sex, birth weight, gestational age, breastfeeding, and maternal smoking. Additionally, adverse outcomes such as bacterial meningitis are rare, thus, there is a need for large, multicenter prospective studies to study short- and long-term consequences. Such data are essential for developing stratification models to individualize the care of febrile infants. International research networks with standardized databases and data-sharing agreements can enhance knowledge accumulation.

Another aspect is the utility of biomarkers, currently used or under research, for stratifying febrile infants. Test characteristics (i.e., cutoffs, sensitivity, specificity, and positive and negative predictive values) should be studied in different settings, with likely varying disease prevalence and patient characteristics such as fever duration before presenting to the PED. Otherwise, prediction scores with test cutoffs derived from different populations could result in underestimation or overestimation of risks.

A question raised from this and previous studies is whether bacteremia should be considered an IBI alongside meningitis. There is a need to investigate whether bacteremia alters the prognosis of febrile infants with meningitis or UTI. Furthermore, there is a need to investigate whether isolated bacteremia in well-appearing febrile infants progresses to meningitis or sepsis or causes morbidity. A better understanding of whether bacteremia is associated with increased morbidity might point future research toward developing predictive rules for each infection. Given the satisfactory sensitivity and specificity of urinalysis for identifying UTI, the main focus could be a prediction tool without routine LP to rule out bacterial meningitis.

Finally, delayed treatment or missed IBIs should not be the only measured adverse outcomes of the prediction tools. Future studies should also be designed to measure

the potential harm to patients caused by medical interventions suggested by the prediction rule. The consequences of the evaluation of febrile infants and how the compulsion for diagnosis may harm patients should play a more central role when designing research projects and developing guidelines.

Ethical considerations

An ethical consideration for this research project is that informed consent to review the medical records of febrile infants was not obtained from their parents. According to the "International Ethical Guidelines for Biomedical Research Involving Human Subjects," informed consent can be waived if it is impractical to obtain it from everyone and the research project involves minimal harm to the study subjects, and the benefit of the research results outweighs the risk of invasion of personal privacy.[273] Similarly, according to the "Guidelines for the ethical evaluation of human medical research, research ethics policy and organization in Sweden, 2003", handling personal data without informed consent can be ethically justifiable in the case of research if the usefulness of the results outweighs the infringement of personal privacy (Act 2003:460 on ethical review of research involving humans).[274]

For practical reasons, it was impossible to find and reach out with information to all the parents of the 5000 febrile infants who presented to the study PEDs during 2014-2020. An essential aim of this study was to investigate the prevalence of meningitis and the frequency of adverse outcomes, such as delayed-treated meningitis, which are rare events. Failure to obtain consent from many parents and to identify any of the few meningitis cases would considerably undermine the validity of the study. The patient data were pseudonymized according to the EU regulations defined in Article 4(5) of the General Data Protection Regulation.[275] The parents of the 4 infants with delayed-treated IBIs might recognize their infants by details regarding the infants' age and the results of the investigations. However, this study does not involve any harm to the individual, and the benefits of the research results outweigh the intrusion into personal integrity.

There were also specific ethical considerations regarding the participation of the medical students who reviewed the medical records of febrile infants and collected data, which was performed as part of their master's thesis prior to graduating from medical school.

The first ethical consideration is whether the medical students should be included as co-authors in the published papers of this research project. The International Committee of Medical Journal Editors (ICMJE) recommends that authorship be based on the following 4 criteria:[276]

1. Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND

2. Drafting the work or revising it critically for important intellectual content; AND

3. Final approval of the version to be published; AND

4. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Each medical student collected approximately 5–15% of the data. All students had ideas and suggested improvements to the clinical research form during the data collection. Furthermore, they processed and ‘‘cleaned’’ parts of the database. Also, they performed various analyses of subsets of the data for their projects and discussed the interpretation of the results. Thus, all students fulfill the first criteria. Therefore, they were invited to participate as co-authors in the paper relevant to their master’s thesis.

The second ethical consideration is whether the published papers and this thesis should cite the medical students’ master’s theses. According to a court case (Administrative Court Uppsala. Decision nr 6813-13 2014-05-14), student work must be referred to. All students were informed and agreed with the plan that the data collection is part of a PhD research project aimed at publishing several papers and writing a PhD thesis. I conceived the initial research idea, designed the project plan, developed the clinical research form, and created the database. The medical students did not contribute to the initial idea or the design of the study. Thus, on an intellectual level, this PhD research project led to the students’ master’s theses and not vice versa. Furthermore, the students analyzed and presented results only for specific subsets of the database. None of their analyses or results have been used in the published papers or in this thesis. Additionally, no interpretations in the published papers or this thesis originated from the students’ master’s theses. Thus, I believe that it is ethically justified not to cite the students’ master’s theses.

However, all the students worked hard, performed well, and wrote interesting projects. Thus, despite the initial agreement, they may feel that their work should be referred to, and this feeling may not be unjustified. Would a discussion to renew the initial agreement resolve the ethical considerations? Or would it only be a ‘‘convenient way’’ for me to avoid citing their works? In such a discussion, I might be perceived as having a position of power, and the students might fear that by demanding a citation, they might not be included as co-authors. Also, I was the students’ supervisor, we collaborated well and developed a good relationship, which might prevent the students from expressing themselves freely. Additionally, I was a professional reference for a few students, which could prevent them from expressing their thoughts and feelings. Thus, I do not believe that a renewed consent would alleviate the ethical concerns regarding citing the students’ projects. Nevertheless, I believe that it is ethically justified not to cite the students’ master’s theses. I do recognize, though, this aspect could be seen and interpreted in different ways.

Populärvetenskaplig sammanfattning (Swedish summary)

Bakgrund

Vid kontakt med 1177 rekommenderas att man omedelbart ska söka vård på sjukhus när ett spädbarn som är yngre än 60 dagar får feber. Anledningen är att dessa febrila spädbarn har en relativt hög risk för urinvägsinfektioner, bakteriemi (förekomst av bakterier i blodet) och hjärnhinneinflammation (meningit), vilka är förknippade med svår sjuklighet. På grund av den eventuella farlighetsgraden, rekommenderas det i de riktlinjer för hantering av febrila spädbarn yngre än 60 dagar som används idag, att man tar urin- och blodprov. För barn som är yngre än 28 dagar rekommenderas också att man tar prov från ryggmärgsvätskan (sk lumbalpunktion) samt att barnet läggs in för observation och får antibiotika. Trots den höga risken för bakterieinfektioner har dock ca 90% av unga spädbarn med feber snälla och självbegränsande virusinfektioner och mindre än 2% har hjärnhinneinflammation eller bakteriemi.

Antalet spädbarn yngre än 60 dagar med feber som uppsöker en vårdinrättning i Europa uppskattas till cirka 200 000 per år. Alltså utsätts tusentals unga spädbarn med feber för omfattande, ofta onödiga, utredningar, sjukhusinläggningar och antibiotikabehandlingar, varje år. Dessa ingrepp kan ha skadliga effekter på barnen, deras familjer och hälsosystemet.

Sjukhusinläggning är inte alltid det "säkraste" alternativet. Det rapporteras att 1% till 24% av inlagda barn får en infektion när de är på sjukhus. En sjukhusinläggning kan dessutom utgöra en betydande ekonomisk börda för familjen och onödiga inläggningar belastar sjukvården hårt. Dessutom kan föräldrar möta svårigheter att ta hand om resten av familjen och uppleva betydande stress när det gäller deras barns hälsa.

Att få antibiotika i tidig spädbarnsålder är förknippat med en ökad risk för kroniska sjukdomar senare i livet, såsom inflammatorisk tarmsjukdom, diabetes, fetma, ledgångsreumatism, astma och allergier.

Rutintestning har också avsevärda nackdelar. Blodtagning, lumbalpunktion eller blåskateterisering är smärtsamma och stressande procedurer för spädbarnen och

deras familjer. De är också en möjlig orsak till infektion. Dessutom är undersökningar tid- och resurskrävande för de redan överbelastade barnakuterna, vilket resulterar i förlängda väntetider för andra patienter.

På grund av de möjligt skadliga effekterna av undersökningar, sjukhusinläggningar och antibiotika har forskare försökt utveckla nya förutsägelsemodeller som kan: a) bättre identifiera febriga spädbarn med låg risk för en allvarlig bakterieinfektion som inte har nytta av en medicinsk behandling, b) minimera komplikationerna av alltför omfattande undersökningar på spädbarnen, och c) förbättra utnyttjandet av hälsoresurser.

För att utveckla patientsäkra och effektiva modeller för hur spädbarn med feber ska hanteras, är det viktigt med korrekt och uppdaterad information kring förekomst och typ av bakteriella infektioner, sk prevalensdata. Det finns ingen sådan information som rör Sverige. Det är också avgörande att studera hur sådana riktlinjer fungerar i olika miljöer med olika populationer. Dessutom kan identifiering av handläggningsvariationer med skillnader i resultat peka på möjligheter att förbättra nuvarande riktlinjer. Det finns dock inga studier från Sverige som beskriver hanteringen av spädbarn med feber och deras utfall. Det är också viktigt att studera varför läkare följer eller inte följer rekommendationer för att utveckla nya riktlinjer, förbättra eller justera de nuvarande och utforma strategier för införande. Det finns internationellt en brist på kunskap om hur läkare bestämmer sig för att följa riktlinjerna vid hantering av spädbarn med feber.

Avsikten med denna avhandling är att undersöka förekomsten av allvarliga bakteriella infektioner hos spädbarn yngre än 60 dagar gamla med feber, att beskriva hanteringen av dessa spädbarn vid fyra svenska barnakuter, och att beskriva läkares beslutsprocess vid hantering av dem.

Metoder

Studierna I-III utfördes vid fyra barnakuter i Stockholm, Göteborg, Lund och Malmö. Alla spädbarn ≤60 dagar gamla som sökte vård på grund av feber identifierades. Studieperioden var från 1 januari 2014 till 31 december 2020. Patienterna som inkluderades i studien var tidigare friska spädbarn yngre än 60 dagar gamla med dokumenterad feber ≥38 □C i hemmet eller på barnakuten. Studien godkändes av Regionala etiska nämnden i Lund (Dnr 2017/967)

Studie IV genomfördes vid Skånes universitetssjukhus. Den baserades på fokusgruppsdiskussioner med läkare som tar hand om spädbarn med feber. Målet var att få insikt i processen för läkares beslutsfattande, inklusive barriärer, möjliggörare och motivatorer vid hantering av febrila spädbarn yngre än 60 dagar gamla.

Resultat

Det inkluderades 2237 spädbarn yngre än 60 dagar gamla med feber under den totala studieperioden från 2014 till 2020. Urinvägsinfektion var den vanligaste infektionen. Andelen barn med hjärnhinneinflammation (sk prevalens) var 0,5 % och var högst de två första levnadsveckorna. Prevalensen av bakteriella infektioner varierade från 9,4% på barnakuten i Lund med den lägsta till 16,4% på barnakuten i Göteborg med den högsta prevalensen. Det fanns ingen skillnad i risken för hjärnhinneinflammation mellan spädbarn yngre än 28 dagar gamla som fortfarande hade feber när de kom till barnakuten och de där febern hade gått ner. Ingen skillnad observerades heller i risken av hjärnhinneinflammation mellan pojkar och flickor. Förekomsten av bakteriella infektioner verkar vara lägre i Sverige än i USA och Spanien.

Lumbalpunktion utfördes hos 13% av spädbarnen ≤28 dagar, antibiotika gavs till 30% och 67% lades in på sjukhus. Klara variationer i hanteringen av dessa barn observerades mellan de fyra barnakuterna. Frekvensen av lumbalpunktion varierade nästan 12 gånger mellan barnakuterna med den lägre respektive den högre frekvensen. Vid jämförelse med barnakuter i USA eller Spanien görs färre undersökningar på de svenska barnakuterna.

Tolv (0,7%) spädbarn som hade en bakteriell infektion fick inte antibiotika vid det första undersökningstillfället. Det fanns ingen skillnad i utfall mellan de fyra barnakuterna trots skillnaderna i frekvensen av genomförda undersökningar. De spädbarn som hade en bakteriell infektion som inte behandlades direkt på barnakuten var inte fler i Sverige än i USA eller Spanien, trots det gjordes färre utredningar och antibiotikabehandlingar.

Vi identifierade tre centrala faktorer som påverkar beslutsprocessen om huruvida en lumbalpunktion ska utföras eller inte. Den första var sökandet efter ett infektionsfokus som kunde förklara febern, såsom tecken eller symtom på övre luftvägsinfektion. Den andra var att ifrågasätta om den temperatur som rapporterats av föräldrarna utgjorde feber, särskilt i de fall där spädbarns temperatur hemma var lägre än 38,2°C och spädbarnet var feberfritt vid undersökningen. Den tredje var spädbarnens allmäntillstånd, där läkare resonerade att lumbalpunktion inte är motiverat i fall av välmående spädbarn. Runt dessa tre centrala faktorer utvecklades 6 sekundära kategorier, som fungerade som barriärer eller motivatorer för att följa sjukhusets riktlinjer för spädbarn med feber och särskilt om man ska utföra en lumbalpunktion eller inte: 1) rädsla för risken att misslyckas, 2) att lita på sitt eget omdöme, 3) undvika betungande arbete, 4) ta hänsyn till föräldrarnas och sjuksköterskors önskemål, 5) balansera riktlinjer och resurser, och 6) se ett behov av att öva och lära sig att utföra lumbalpunktion.

Slutsatser

Förekomsten av allvarliga bakteriella infektioner hos spädbarn yngre än 60 dagar med feber verkar vara lägre i Sverige än i andra länder. Trots färre utredningar och antibiotikabehandlingar på de 4 svenska barnakuterna, jämfört med behandlingsriktlinjer, sågs inte ett ökat antal spädbarn där en bakteriell infektion inte behandlades direkt. Därför skulle en riktlinje baserad på klinisk information och blodprover kunna vara patientsäker och samtidigt minska onödiga, smärtsamma utredningar, antibiotikabehandlingar och sjukhusinläggningar. Riktlinjerna skulle kunna utformas så att en viss grad av flexibilitet och självständigt tänkande tillåts. Detta för att ta hänsyn till patienternas behov och tillåta utveckling av vårdpersonalens medicinska resonemang, vilken kan resultera i ökad patientsäkerhet och arbetstillfredsställelse.

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References

1. Massin MM, Montesanti J, Gérard P, Lepage P. Spectrum and frequency of illness presenting to a pediatric emergency department. *Acta Clin Belg*. 2006;61(4):161-165.
2. McCaig LF, Nawar EW. National Hospital Ambulatory Medical Care Survey: 2004 emergency department summary. *Adv Data*. 2006(372):1-29.
3. Hagedoorn NN, Borensztajn D, Nijman RG, Nieboer D, Herberg JA, Balode A, et al. Development and validation of a prediction model for invasive bacterial infections in febrile children at European Emergency Departments: MOFICHE, a prospective observational study. *Arch Dis Child*. 2021;106(7):641-647.
4. Craig JC, Williams GJ, Jones M, Codarini M, Macaskill P, Hayen A, et al. The accuracy of clinical symptoms and signs for the diagnosis of serious bacterial infection in young febrile children: prospective cohort study of 15 781 febrile illnesses. *Bmj*. 2010;340:c1594.
5. National Health Service (NHS). High temperature (fever) in children. https://www.nhs.uk/conditions/fever-in-children/. Published 2020, December
6. Vårdguide 1177. Fever in children. https://www.1177.se/en/Skane/other-languages/other-languages/symtomsjukdom---andra-sprak/feber-hos-barn--engelska/. Published 2022, March
7. Kuppermann N, Dayan PS, Levine DA, Vitale M, Tzimenatos L, Tunik MG, et al. A Clinical Prediction Rule to Identify Febrile Infants 60 Days and Younger at Low Risk for Serious Bacterial Infections. *JAMA Pediatr*. 2019;173(4):342-351.
8. Velasco R, Gomez B, Benito J, Mintegi S. Accuracy of PECARN rule for predicting serious bacterial infection in infants with fever without a source. *Arch Dis Child*. 2020.
9. Pantell RH, Newman TB, Bernzweig J, Bergman DA, Takayama JI, Segal M, et al. Management and outcomes of care of fever in early infancy. *Jama*. 2004;291(10):1203-1212.
10. de Louvois J, Halket S, Harvey D. Neonatal meningitis in England and Wales: sequelae at 5 years of age. *Eur J Pediatr*. 2005;164(12):730-734.
11. Libster R, Edwards KM, Levent F, Edwards MS, Rench MA, Castagnini LA, et al. Long-term outcomes of group B streptococcal meningitis. *Pediatrics*. 2012;130(1):e8-15.
12. Feder HM, Jr. Occult pneumococcal bacteremia and the febrile infant and young child. *Clin Pediatr (Phila)*. 1980;19(7):457-462.

13. Shapiro ED, Aaron NH, Wald ER, Chiponis D. Risk factors for development of bacterial meningitis among children with occult bacteremia. *J Pediatr*. 1986;109(1):15-19.
14. National Institute for Health and Care Excellence. Fever in under 5s: Assessment and initial management. https://www.nice.org.uk/guidance/ng143/chapter/Recommendations. Published 2019, November Updated 2021, November.
15. Baker MD, Bell LM, Avner JR. Outpatient management without antibiotics of fever in selected infants. *N Engl J Med*. 1993;329(20):1437-1441.
16. Baskin MN, O'Rourke EJ, Fleisher GR. Outpatient treatment of febrile infants 28 to 89 days of age with intramuscular administration of ceftriaxone. *J Pediatr*. 1992;120(1):22-27.
17. Centers for Disease Control and Prevention. Estimates of emergency department visits in the united states, 2016-2019. https://www.cdc.gov/nchs/dhcs/ed-visits/index.htm. Published 2022, May 18.
18. Centers for Disease Control and Prevention. National hospital ambulatory medical care survey: 2019 emergency department summary tables. https://www.cdc.gov/nchs/data/nhamcs/web_tables/2019-nhamcs-ed-web-tables-508.pdf. Published 2022, July 29.
19. Ramgopal S, Aronson PL, Marin JR. United States' Emergency Department Visits for Fever by Young Children 2007-2017. *West J Emerg Med*. 2020;21(6):146-151.
20. Ray KN, Shi Z, Ganguli I, Rao A, Orav EJ, Mehrotra A. Trends in Pediatric Primary Care Visits Among Commercially Insured US Children, 2008-2016. *JAMA Pediatr*. 2020;174(4):350-357.
21. Centers for Disease Control and Prevention. National ambulatory medical care survey: 2018 national summary tables. https://www.cdc.gov/nchs/data/ahcd/namcs_summary/2018-namcs-web-tables-508.pdf. Published 2022, August 5.
22. Eurostat. Fertility statistics,. https://ec.europa.eu/eurostat/statistics-explained/index.php?title=Fertility_statistics. Published 2022, April.
23. Centers for Disease Control and Prevention (CDC). Births: Provisional data for 2021. https://www.cdc.gov/nchs/data/vsrr/vsrr020.pdf. Published 2022, May.
24. Byington CL, Enriquez FR, Hoff C, Tuohy R, Taggart EW, Hillyard DR, et al. Serious bacterial infections in febrile infants 1 to 90 days old with and without viral infections. *Pediatrics*. 2004;113(6):1662-1666.
25. DeAngelis C, Joffe A, Wilson M, Willis E. Iatrogenic risks and financial costs of hospitalizing febrile infants. *Am J Dis Child*. 1983;137(12):1146-1149.
26. Condra CS, Parbhu B, Lorenz D, Herr SM. Charges and complications associated with the medical evaluation of febrile young infants. *Pediatr Emerg Care*. 2010;26(3):186-191.
27. Mintegi S, Bressan S, Gomez B, Da Dalt L, Blazquez D, Olaciregui I, et al. Accuracy of a sequential approach to identify young febrile infants at low risk for invasive bacterial infection. *Emerg Med J*. 2014;31(e1):e19-24.

28. Pantell RH, Roberts KB, Adams WG, Dreyer BP, Kuppermann N, O'Leary ST, et al. Evaluation and Management of Well-Appearing Febrile Infants 8 to 60 Days Old. *Pediatrics*. 2021;148(2).
29. Mahajan P, Browne LR, Levine DA, Cohen DM, Gattu R, Linakis JG, et al. Risk of Bacterial Coinfections in Febrile Infants 60 Days Old and Younger with Documented Viral Infections. *J Pediatr*. 2018;203:86-91.e82.
30. Rittichier KR, Bryan PA, Bassett KE, Taggart EW, Enriquez FR, Hillyard DR, et al. Diagnosis and outcomes of enterovirus infections in young infants. *Pediatr Infect Dis J*. 2005;24(6):546-550.
31. Messacar K, Breazeale G, Wei Q, Robinson CC, Dominguez SR. Epidemiology and clinical characteristics of infants with human parechovirus or human herpes virus-6 detected in cerebrospinal fluid tested for enterovirus or herpes simplex virus. *J Med Virol*. 2015;87(5):829-835.
32. Byington CL, Taggart EW, Carroll KC, Hillyard DR. A polymerase chain reaction-based epidemiologic investigation of the incidence of nonpolio enteroviral infections in febrile and afebrile infants 90 days and younger. *Pediatrics*. 1999;103(3):E27.
33. Dagan R, Powell KR, Hall CB, Menegus MA. Identification of infants unlikely to have serious bacterial infection although hospitalized for suspected sepsis. *J Pediatr*. 1985;107(6):855-860.
34. Levine DA, Platt SL, Dayan PS, Macias CG, Zorc JJ, Krief W, et al. Risk of serious bacterial infection in young febrile infants with respiratory syncytial virus infections. *Pediatrics*. 2004;113(6):1728-1734.
35. Mintegi S, Garcia-Garcia JJ, Benito J, Carrasco-Colom J, Gomez B, Hernández-Bou S, et al. Rapid influenza test in young febrile infants for the identification of low-risk patients. *Pediatr Infect Dis J*. 2009;28(11):1026-1028.
36. Bender JM, Ampofo K, Gesteland P, Sheng X, Korgenski K, Raines B, et al. Influenza virus infection in infants less than three months of age. *Pediatr Infect Dis J*. 2010;29(1):6-9.
37. Bender JM, Taylor CS, Cumpio J, Novak SM, She RC, Steinberg EA, et al. Infants 1-90 days old hospitalized with human rhinovirus infection. *J Clin Lab Anal*. 2014;28(5):349-352.
38. Nicholson EG, Avadhanula V, Ferlic-Stark L, Patel K, Gincoo KE, Piedra PA. The Risk of Serious Bacterial Infection in Febrile Infants 0–90 Days of Life With a Respiratory Viral Infection. *The Pediatric Infectious Disease Journal*. 2019;38(4):355-361.
39. Baraff LJ, Lee SI, Schriger DL. Outcomes of bacterial meningitis in children: a meta-analysis. *Pediatr Infect Dis J*. 1993;12(5):389-394.
40. Newman DH, Shreves AE, Runde DP. Pediatric urinary tract infection: does the evidence support aggressively pursuing the diagnosis? *Ann Emerg Med*. 2013;61(5):559-565.
41. Oh MM, Kim JW, Park MG, Kim JJ, Yoo KH, Moon du G. The impact of therapeutic delay time on acute scintigraphic lesion and ultimate scar formation in children with first febrile UTI. *Eur J Pediatr*. 2012;171(3):565-570.

42. Salo J, Ikäheimo R, Tapiainen T, Uhari M. Childhood urinary tract infections as a cause of chronic kidney disease. *Pediatrics*. 2011;128(5):840-847.
43. Watson RS, Carcillo JA, Linde-Zwirble WT, Clermont G, Lidicker J, Angus DC. The epidemiology of severe sepsis in children in the United States. *Am J Respir Crit Care Med*. 2003;167(5):695-701.
44. Levasseur KA, Stankovic C, Duffy E, Du W, Mahajan P. Prevalence of serious bacterial infections in return visits to the emergency department among infants aged 90 days or younger. *Pediatr Emerg Care*. 2014;30(10):694-698.
45. Klein-Kremer A, Goldman RD. Return visits to the emergency department among febrile children 3 to 36 months of age. *Pediatr Emerg Care*. 2011;27(12):1126-1129.
46. Alpern ER, Alessandrini EA, Bell LM, Shaw KN, McGowan KL. Occult bacteremia from a pediatric emergency department: current prevalence, time to detection, and outcome. *Pediatrics*. 2000;106(3):505-511.
47. Roman HK, Chang PW, Schroeder AR. Diagnosis and management of bacteremic urinary tract infection in infants. *Hosp Pediatr*. 2015;5(1):1-8.
48. Schroeder AR, Shen MW, Biondi EA, Bendel-Stenzel M, Chen CN, French J, et al. Bacteraemic urinary tract infection: management and outcomes in young infants. *Arch Dis Child*. 2016;101(2):125-130.
49. Goeller C, Desmarest M, Garraffo A, Bonacorsi S, Gaschignard J. Management of Febrile Urinary Tract Infection With or Without Bacteraemia in Children: A French Case-Control Retrospective Study. *Front Pediatr*. 2020;8:237.
50. Biondi EA, Lee B, Ralston SL, Winikor JM, Lynn JF, Dixon A, et al. Prevalence of Bacteremia and Bacterial Meningitis in Febrile Neonates and Infants in the Second Month of Life: A Systematic Review and Meta-analysis. *JAMA Netw Open*. 2019;2(3):e190874.
51. Shaikh N, Morone NE, Bost JE, Farrell MH. Prevalence of urinary tract infection in childhood: a meta-analysis. *Pediatr Infect Dis J*. 2008;27(4):302-308.
52. Tzimenatos L, Mahajan P, Dayan PS, Vitale M, Linakis JG, Blumberg S, et al. Accuracy of the Urinalysis for Urinary Tract Infections in Febrile Infants 60 Days and Younger. *Pediatrics*. 2018;141(2).
53. Roberts KB, Wald ER. The Diagnosis of UTI: Colony Count Criteria Revisited. *Pediatrics*. 2018;141(2).
54. Roberts KB. Urinary tract infection: clinical practice guideline for the diagnosis and management of the initial UTI in febrile infants and children 2 to 24 months. *Pediatrics*. 2011;128(3):595-610.
55. Shaikh N, Ewing AL, Bhatnagar S, Hoberman A. Risk of renal scarring in children with a first urinary tract infection: a systematic review. *Pediatrics*. 2010;126(6):1084-1091.
56. Faust WC, Diaz M, Pohl HG. Incidence of post-pyelonephritic renal scarring: a meta-analysis of the dimercapto-succinic acid literature. *J Urol*. 2009;181(1):290-297; discussion 297-298.
57. Diviney J, Jaswon MS. Urine collection methods and dipstick testing in non-toilet-trained children. *Pediatr Nephrol*. 2021;36(7):1697-1708.

58. Shaikh N, Osio VA, Wessel CB, Jeong JH. Prevalence of Asymptomatic Bacteriuria in Children: A Meta-Analysis. *J Pediatr*. 2020;217:110-117.e114.
59. Glissmeyer EW, Korgenski EK, Wilkes J, Schunk JE, Sheng X, Blaschke AJ, et al. Dipstick screening for urinary tract infection in febrile infants. *Pediatrics*. 2014;133(5):e1121-1127.
60. Bachur R, Harper MB. Reliability of the urinalysis for predicting urinary tract infections in young febrile children. *Archives of pediatrics & adolescent medicine*. 2001;155(1):60-65.
61. Greenhow TL, Hung YY, Herz AM, Losada E, Pantell RH. The changing epidemiology of serious bacterial infections in young infants. *Pediatr Infect Dis J*. 2014;33(6):595-599.
62. Mahajan P, VanBuren JM, Tzimenatos L, Cruz AT, Vitale M, Powell EC, et al. Serious Bacterial Infections in Young Febrile Infants With Positive Urinalysis Results. *Pediatrics*. 2022.
63. Morris BJ, Bailis SA, Wiswell TE. Circumcision rates in the United States: rising or falling? What effect might the new affirmative pediatric policy statement have? *Mayo Clin Proc*. 2014;89(5):677-686.
64. Morris BJ, Wamai RG, Henebeng EB, Tobian AA, Klausner JD, Banerjee J, et al. Estimation of country-specific and global prevalence of male circumcision. *Popul Health Metr*. 2016;14:4.
65. Watt K, Waddle E, Jhaveri R. Changing epidemiology of serious bacterial infections in febrile infants without localizing signs. *PLoS One*. 2010;5(8):e12448.
66. Glasgow TS, Young PC, Wallin J, Kwok C, Stoddard G, Firth S, et al. Association of intrapartum antibiotic exposure and late-onset serious bacterial infections in infants. *Pediatrics*. 2005;116(3):696-702.
67. Bizzarro MJ, Dembry LM, Baltimore RS, Gallagher PG. Changing patterns in neonatal Escherichia coli sepsis and ampicillin resistance in the era of intrapartum antibiotic prophylaxis. *Pediatrics*. 2008;121(4):689-696.
68. Garcia S, Mintegi S, Gomez B, Barron J, Pinedo M, Barcena N, et al. Is 15 days an appropriate cut-off age for considering serious bacterial infection in the management of febrile infants? *Pediatr Infect Dis J*. 2012;31(5):455-458.
69. Aronson PL, Thurm C, Alpern ER, Alessandrini EA, Williams DJ, Shah SS, et al. Variation in care of the febrile young infant <90 days in US pediatric emergency departments. *Pediatrics*. 2014;134(4):667-677.
70. Schwartz S, Raveh D, Toker O, Segal G, Godovitch N, Schlesinger Y. A week-by-week analysis of the low-risk criteria for serious bacterial infection in febrile neonates. *Arch Dis Child*. 2009;94(4):287-292.
71. Woll C, Neuman MI, Pruitt CM, Wang ME, Shapiro ED, Shah SS, et al. Epidemiology and Etiology of Invasive Bacterial Infection in Infants </=60 Days Old Treated in Emergency Departments. *J Pediatr*. 2018;200:210-217.e211.
72. Powell EC, Mahajan PV, Roosevelt G, Hoyle JD, Jr., Gattu R, Cruz AT, et al. Epidemiology of Bacteremia in Febrile Infants Aged 60 Days and Younger. *Ann Emerg Med*. 2018;71(2):211-216.

73. Ladhani SN, Henderson KL, Muller-Pebody B, Ramsay ME, Riordan A. Risk of invasive bacterial infections by week of age in infants: prospective national surveillance, England, 2010-2017. *Arch Dis Child*. 2019;104(9):874-878.
74. Okike IO, Johnson AP, Henderson KL, Blackburn RM, Muller-Pebody B, Ladhani SN, et al. Incidence, etiology, and outcome of bacterial meningitis in infants aged <90 days in the United kingdom and Republic of Ireland: prospective, enhanced, national population-based surveillance. *Clin Infect Dis*. 2014;59(10):e150-157.
75. Mah V, Vanderkooi OG, Johnson DW. Epidemiology of Serious Bacterial Infections in Infants Less Than 90 Days of Age, Presenting to a Tertiary Care Emergency Department, 2010-2016. *Pediatr Infect Dis J*. 2018.
76. Luthander J, Bennet R, Giske CG, Eriksson M, Nilsson A. Trends of Pediatric Bloodstream Infections in Stockholm, Sweden: A 20-year Retrospective Study. *Pediatr Infect Dis J*. 2020;39(12):1069-1074.
77. Bonilla L, Gomez B, Pintos C, Benito J, Mintegi S. Prevalence of Bacterial Infection in Febrile Infant 61-90 Days Old Compared With Younger Infants. *Pediatr Infect Dis J*. 2019;38(12):1163-1167.
78. Song SH, Lee HJ, Song ES, Ahn JG, Park SE, Lee T, et al. Changes in Etiology of Invasive Bacterial Infections in Infants Under 3 Months of Age in Korea, 2006-2020. *Pediatr Infect Dis J*. 2022;41(12):941-946.
79. Greenhow TL, Hung YY, Herz AM. Changing epidemiology of bacteremia in infants aged 1 week to 3 months. *Pediatrics*. 2012;129(3):e590-596.
80. Verani JR, Schrag SJ. Group B streptococcal disease in infants: progress in prevention and continued challenges. *Clin Perinatol*. 2010;37(2):375-392.
81. Creti R, Imperi M, Berardi A, Lindh E, Alfarone G, Pataracchia M, et al. Invasive Group B Streptococcal Disease in Neonates and Infants, Italy, Years 2015-2019. *Microorganisms*. 2021;9(12).
82. Nanduri SA, Petit S, Smelser C, Apostol M, Alden NB, Harrison LH, et al. Epidemiology of Invasive Early-Onset and Late-Onset Group B Streptococcal Disease in the United States, 2006 to 2015: Multistate Laboratory and Population-Based Surveillance. *JAMA Pediatr*. 2019;173(3):224-233.
83. Gomez B, Mintegi S, Benito J, Egireun A, Garcia D, Astobiza E. Blood culture and bacteremia predictors in infants less than three months of age with fever without source. *Pediatr Infect Dis J*. 2010;29(1):43-47.
84. Biondi EA, Mischler M, Jerardi KE, Statile AM, French J, Evans R, et al. Blood culture time to positivity in febrile infants with bacteremia. *JAMA Pediatr*. 2014;168(9):844-849.
85. Lyons TW, Garro AC, Cruz AT, Freedman SB, Okada PJ, Mahajan P, et al. Performance of the Modified Boston and Philadelphia Criteria for Invasive Bacterial Infections. *Pediatrics*. 2020;145(4).
86. Olarte L, Ampofo K, Stockmann C, Mason EO, Daly JA, Pavia AT, et al. Invasive pneumococcal disease in infants younger than 90 days before and after introduction of PCV7. *Pediatrics*. 2013;132(1):e17-24.

87. Pilishvili T, Lexau C, Farley MM, Hadler J, Harrison LH, Bennett NM, et al. Sustained reductions in invasive pneumococcal disease in the era of conjugate vaccine. *J Infect Dis*. 2010;201(1):32-41.
88. Ralston S, Hill V, Waters A. Occult serious bacterial infection in infants younger than 60 to 90 days with bronchiolitis: a systematic review. *Archives of pediatrics & adolescent medicine*. 2011;165(10):951-956.
89. McDaniel CE, Ralston S, Lucas B, Schroeder AR. Association of Diagnostic Criteria With Urinary Tract Infection Prevalence in Bronchiolitis: A Systematic Review and Meta-analysis. *JAMA Pediatr*. 2019;173(3):269-277.
90. Carmon L, Goldbart A, Greenberg D, Ben-Shimol S. Serious Bacterial Infections in Hospitalized Febrile Infants in the First and Second Months of Life. *Pediatr Infect Dis J*. 2017;36(10):924-929.
91. Milcent K, Faesch S, Gras-Le Guen C, Dubos F, Poulalhon C, Badier I, et al. Use of Procalcitonin Assays to Predict Serious Bacterial Infection in Young Febrile Infants. *JAMA Pediatr*. 2016;170(1):62-69.
92. Yaeger JP, Moore KA, Melly SJ, Lovasi GS. Associations of Neighborhood-Level Social Determinants of Health with Bacterial Infections in Young, Febrile Infants. *J Pediatr*. 2018;203:336-344.e331.
93. Baker MG, Barnard LT, Kvalsvig A, Verrall A, Zhang J, Keall M, et al. Increasing incidence of serious infectious diseases and inequalities in New Zealand: a national epidemiological study. *Lancet*. 2012;379(9821):1112-1119.
94. Videholm S, Kostenniemi U, Lind T, Silfverdal SA. Perinatal factors and hospitalisations for severe childhood infections: a population-based cohort study in Sweden. *BMJ Open*. 2021;11(10):e054083.
95. Yusuf HR, Rochat RW, Baughman WS, Gargiullo PM, Perkins BA, Brantley MD, et al. Maternal cigarette smoking and invasive meningococcal disease: a cohort study among young children in metropolitan Atlanta, 1989-1996. *Am J Public Health*. 1999;89(5):712-717.
96. Metzger MJ, Halperin AC, Manhart LE, Hawes SE. Association of maternal smoking during pregnancy with infant hospitalization and mortality due to infectious diseases. *Pediatr Infect Dis J*. 2013;32(1):e1-7.
97. Goldacre MJ, Wotton CJ, Maisonneuve JJ. Maternal and perinatal factors associated with subsequent meningococcal, Haemophilus or enteroviral meningitis in children: database study. *Epidemiol Infect*. 2014;142(2):371-378.
98. Christensen N, Søndergaard J, Christesen HT, Fisker N, Husby S. Association Between Mode of Delivery and Risk of Infection in Early Childhood: A Cohort Study. *Pediatr Infect Dis J*. 2018;37(4):316-323.
99. Miller JE, Goldacre R, Moore HC, Zeltzer J, Knight M, Morris C, et al. Mode of birth and risk of infection-related hospitalisation in childhood: A population cohort study of 7.17 million births from 4 high-income countries. *PLoS Med*. 2020;17(11):e1003429.
100. Hviid A, Melbye M. The impact of birth weight on infectious disease hospitalization in childhood. *Am J Epidemiol*. 2007;165(7):756-761.

101. Sankar MJ, Sinha B, Chowdhury R, Bhandari N, Taneja S, Martines J, et al. Optimal breastfeeding practices and infant and child mortality: a systematic review and meta-analysis. *Acta Paediatr*. 2015;104(467):3-13.
102. The United Nations Children's Fund (UNICEF). Measuring child poverty: New league tables of child poverty in the world's rich countries. https://www.unicef-irc.org/publications/pdf/rc10_eng.pdf. Published 2012, May.
103. Organisation for Economic Co-operation and Development (OECD). Child poverty. OECD family database. http://www.oecd.org/els/family/database.htm. Published 2019, November.
104. Organisation for Economic Co-operation and Development (OECD). Maternal employment rates. OECD family database. https://www.oecd.org/els/family/LMF1_2_Maternal_Employment.pdf. Published 2020, November.
105. Lange S, Probst C, Rehm J, Popova S. National, regional, and global prevalence of smoking during pregnancy in the general population: a systematic review and meta-analysis. *Lancet Glob Health*. 2018;6(7):e769-e776.
106. Betrán AP, Ye J, Moller AB, Zhang J, Gülmezoglu AM, Torloni MR. The Increasing Trend in Caesarean Section Rates: Global, Regional and National Estimates: 1990-2014. *PLoS One*. 2016;11(2):e0148343.
107. Betran AP, Ye J, Moller AB, Souza JP, Zhang J. Trends and projections of caesarean section rates: global and regional estimates. *BMJ Glob Health*. 2021;6(6).
108. Blencowe H, Krasevec J, de Onis M, Black RE, An X, Stevens GA, et al. National, regional, and worldwide estimates of low birthweight in 2015, with trends from 2000: a systematic analysis. *Lancet Glob Health*. 2019;7(7):e849-e860.
109. Organisation for Economic Co-operation and Development (OECD). Low birth weight. OECD family database. https://www.oecd.org/els/family/CO_1_3_Low_birth_weight.pdf. Published 2020, July.
110. Organisation for Economic Co-operation and Development (OECD). Breastfeeding rates. OECD Family Database. http://www.oecd.org/els/family/database.htm. Published 2009, October 1.
111. Tan CD, El Ouasghiri S, von Both U, Carrol ED, Emonts M, van der Flier M, et al. Sex differences in febrile children with respiratory symptoms attending European emergency departments: An observational multicenter study. *PLoS One*. 2022;17(8):e0271934.
112. Muenchhoff M, Goulder PJ. Sex differences in pediatric infectious diseases. *J Infect Dis*. 2014;209 Suppl 3(Suppl 3):S120-126.
113. Vázquez-Martínez ER, García-Gómez E, Camacho-Arroyo I, González-Pedrajo B. Sexual dimorphism in bacterial infections. *Biol Sex Differ*. 2018;9(1):27.
114. Jaillon S, Berthenet K, Garlanda C. Sexual Dimorphism in Innate Immunity. *Clin Rev Allergy Immunol*. 2019;56(3):308-321.
115. Nigrovic LE, Mahajan PV, Blumberg SM, Browne LR, Linakis JG, Ruddy RM, et al. The Yale Observation Scale Score and the Risk of Serious Bacterial Infections in Febrile Infants. *Pediatrics*. 2017;140(1).

116. Caspe WB, Chamudes O, Louie B. The evaluation and treatment of the febrile infant. *Pediatr Infect Dis*. 1983;2(2):131-135.
117. Dagan R, Sofer S, Phillip M, Shachak E. Ambulatory care of febrile infants younger than 2 months of age classified as being at low risk for having serious bacterial infections. *J Pediatr*. 1988;112(3):355-360.
118. Jaskiewicz JA, McCarthy CA, Richardson AC, White KC, Fisher DJ, Dagan R, et al. Febrile infants at low risk for serious bacterial infection--an appraisal of the Rochester criteria and implications for management. Febrile Infant Collaborative Study Group. *Pediatrics*. 1994;94(3):390-396.
119. Baker MD, Bell LM, Avner JR. The efficacy of routine outpatient management without antibiotics of fever in selected infants. *Pediatrics*. 1999;103(3):627-631.
120. Aronson PL, Wang ME, Shapiro ED, Shah SS, DePorre AG, McCulloh RJ, et al. Risk Stratification of Febrile Infants </=60 Days Old Without Routine Lumbar Puncture. *Pediatrics*. 2018;142(6).
121. Gomez B, Mintegi S, Bressan S, Da Dalt L, Gervaix A, Lacroix L. Validation of the "Step-by-Step" Approach in the Management of Young Febrile Infants. *Pediatrics*. 2016;138(2).
122. Mintegi S, Gomez B, Martinez-Virumbrales L, Morientes O, Benito J. Outpatient management of selected young febrile infants without antibiotics. *Arch Dis Child*. 2017;102(3):244-249.
123. Mahajan P, Kuppermann N, Mejias A, Suarez N, Chaussabel D, Casper TC, et al. Association of RNA Biosignatures With Bacterial Infections in Febrile Infants Aged 60 Days or Younger. *JAMA*. 2016;316(8):846-857.
124. The Royal Children Hospital Melbourne A. Febrile child. Clinical practice guidelines. https://www.rch.org.au/clinicalguide/guideline_index/Febrile_child/. Published 2022, September.
125. SickKids UCH, Toronto,. Inpatient management of febrile infants (<90 days of age). Clinical Practice Guidelines. https://wapps.sickkids.ca/clinical-practice-guidelines/clinical-practice-guidelines/Export/CLINH388/Main%20Document.pdf. Published 2021 July.
126. Bleeker SE, Moll HA, Steyerberg EW, Donders AR, Derksen-Lubsen G, Grobbee DE, et al. External validation is necessary in prediction research: a clinical example. *J Clin Epidemiol*. 2003;56(9):826-832.
127. Toll DB, Janssen KJ, Vergouwe Y, Moons KG. Validation, updating and impact of clinical prediction rules: a review. *J Clin Epidemiol*. 2008;61(11):1085-1094.
128. Cruz AT, Mahajan P, Bonsu BK, Bennett JE, Levine DA, Alpern ER, et al. Accuracy of Complete Blood Cell Counts to Identify Febrile Infants 60 Days or Younger With Invasive Bacterial Infections. *JAMA Pediatr*. 2017;171(11):e172927.
129. Bonsu BK, Harper MB. Utility of the peripheral blood white blood cell count for identifying sick young infants who need lumbar puncture. *Ann Emerg Med*. 2003;41(2):206-214.
130. Clyne B, Olshaker JS. The C-reactive protein. *J Emerg Med*. 1999;17(6):1019-1025.

131. Olaciregui I, Hernández U, Muñoz JA, Emparanza JI, Landa JJ. Markers that predict serious bacterial infection in infants under 3 months of age presenting with fever of unknown origin. *Arch Dis Child*. 2009;94(7):501-505.
132. Stein M, Schachter-Davidov A, Babai I, Tasher D, Somekh E. The accuracy of C-reactive protein, procalcitonin, and s-TREM-1 in the prediction of serious bacterial infection in neonates. *Clin Pediatr (Phila)*. 2015;54(5):439-444.
133. Gomez B, Bressan S, Mintegi S, Da Dalt L, Blazquez D, Olaciregui I, et al. Diagnostic value of procalcitonin in well-appearing young febrile infants. *Pediatrics*. 2012;130(5):815-822.
134. Gomez B, Diaz H, Carro A, Benito J, Mintegi S. Performance of blood biomarkers to rule out invasive bacterial infection in febrile infants under 21 days old. *Arch Dis Child*. 2018.
135. Díaz MG, García RP, Gamero DB, González-Tomé MI, Romero PC, Ferrer MM, et al. Lack of Accuracy of Biomarkers and Physical Examination to Detect Bacterial Infection in Febrile Infants. *Pediatr Emerg Care*. 2016;32(10):664-668.
136. Aloisio E, Dolci A, Panteghini M. Procalcitonin: Between evidence and critical issues. *Clin Chim Acta*. 2019;496:7-12.
137. Maniaci V, Dauber A, Weiss S, Nylen E, Becker KL, Bachur R. Procalcitonin in young febrile infants for the detection of serious bacterial infections. *Pediatrics*. 2008;122(4):701-710.
138. Waterfield T, Maney JA, Hanna M, Fairley D, Shields MD. Point-of-care testing for procalcitonin in identifying bacterial infections in young infants: a diagnostic accuracy study. *BMC Pediatr*. 2018;18(1):387.
139. Kaforou M, Herberg JA, Wright VJ, Coin LJM, Levin M. Diagnosis of Bacterial Infection Using a 2-Transcript Host RNA Signature in Febrile Infants 60 Days or Younger. *Jama*. 2017;317(15):1577-1578.
140. Herberg JA, Kaforou M, Wright VJ, Shailes H, Eleftherohorinou H, Hoggart CJ, et al. Diagnostic Test Accuracy of a 2-Transcript Host RNA Signature for Discriminating Bacterial vs Viral Infection in Febrile Children. *Jama*. 2016;316(8):835-845.
141. Ouchenir L, Renaud C, Khan S, Bitnun A, Boisvert AA, McDonald J, et al. The Epidemiology, Management, and Outcomes of Bacterial Meningitis in Infants. *Pediatrics*. 2017;140(1).
142. Martinez E, Mintegi S, Vilar B, Martinez MJ, Lopez A, Catediano E, et al. Prevalence and predictors of bacterial meningitis in young infants with fever without a source. *Pediatr Infect Dis J*. 2015;34(5):494-498.
143. Gaschignard J, Levy C, Romain O, Cohen R, Bingen E, Aujard Y, et al. Neonatal Bacterial Meningitis: 444 Cases in 7 Years. *Pediatr Infect Dis J*. 2011;30(3):212-217.
144. Klinger G, Chin CN, Beyene J, Perlman M. Predicting the outcome of neonatal bacterial meningitis. *Pediatrics*. 2000;106(3):477-482.
145. de Jonge RC, van Furth AM, Wassenaar M, Gemke RJ, Terwee CB. Predicting sequelae and death after bacterial meningitis in childhood: a systematic review of prognostic studies. *BMC Infect Dis*. 2010;10:232.

146. Zimmermann P, Curtis N. Bacterial Meningitis in the Absence of Pleocytosis in Children: A Systematic Review. *Pediatr Infect Dis J*. 2021;40(6):582-587.
147. Scarfone R, Murray A, Gala P, Balamuth F. Lumbar Puncture for All Febrile Infants 29-56 Days Old: A Retrospective Cohort Reassessment Study. *J Pediatr*. 2017;187:200-205.e201.
148. Leazer R, Erickson N, Paulson J, Zipkin R, Stemmle M, Schroeder AR, et al. Epidemiology of Cerebrospinal Fluid Cultures and Time to Detection in Term Infants. *Pediatrics*. 2017;139(5).
149. Looker KJ, Magaret AS, May MT, Turner KME, Vickerman P, Newman LM, et al. First estimates of the global and regional incidence of neonatal herpes infection. *Lancet Glob Health*. 2017;5(3):e300-e309.
150. Melvin AJ, Mohan KM, Vora SB, Selke S, Sullivan E, Wald A. Neonatal Herpes Simplex Virus Infection: Epidemiology and Outcomes in the Modern Era. *J Pediatric Infect Dis Soc*. 2022;11(3):94-101.
151. Curfman AL, Glissmeyer EW, Ahmad FA, Korgenski EK, Blaschke AJ, Byington CL, et al. Initial Presentation of Neonatal Herpes Simplex Virus Infection. *J Pediatr*. 2016;172:121-126.e121.
152. Caviness AC, Demmler GJ, Selwyn BJ. Clinical and laboratory features of neonatal herpes simplex virus infection: a case-control study. *Pediatr Infect Dis J*. 2008;27(5):425-430.
153. Cruz AT, Nigrovic LE, Xie J, Mahajan P, Thomson JE, Okada PJ, et al. Predictors of Invasive Herpes Simplex Virus Infection in Young Infants. *Pediatrics*. 2021;148(3).
154. Melvin AJ, Mohan KM, Schiffer JT, Drolette LM, Magaret A, Corey L, et al. Plasma and cerebrospinal fluid herpes simplex virus levels at diagnosis and outcome of neonatal infection. *J Pediatr*. 2015;166(4):827-833.
155. Baker MD, Avner JR, Bell LM. Failure of infant observation scales in detecting serious illness in febrile, 4- to 8-week-old infants. *Pediatrics*. 1990;85(6):1040-1043.
156. Newman TB, Bernzweig JA, Takayama JI, Finch SA, Wasserman RC, Pantell RH. Urine testing and urinary tract infections in febrile infants seen in office settings: the Pediatric Research in Office Settings' Febrile Infant Study. *Archives of pediatrics & adolescent medicine*. 2002;156(1):44-54.
157. Greenhow TL, Hung YY, Pantell RH. Management and Outcomes of Previously Healthy, Full-Term, Febrile Infants Ages 7 to 90 Days. *Pediatrics*. 2016;138(6).
158. Sands R, Shanmugavadivel D, Stephenson T, Wood D. Medical problems presenting to paediatric emergency departments: 10 years on. *Emerg Med J*. 2012;29(5):379-382.
159. United States Census Bureau. Current population reports: Estimates and projections, 1960s. https://www.census.gov/library/publications/1960/demo/p25-1960s.html. Published 2021, October
160. Eurostat. Being young in europe today - demographic trends. https://ec.europa.eu/eurostat/statistics-explained/index.php?title=Being_young_in_Europe_today_-_demographic_trends. Published 2020, July.

161. Clericetti CM, Milani GP, Bianchetti MG, Simonetti GD, Fossali EF, Balestra AM, et al. Systematic review finds that fever phobia is a worldwide issue among caregivers and healthcare providers. *Acta Paediatr*. 2019;108(8):1393-1397.
162. Crocetti M, Moghbeli N, Serwint J. Fever phobia revisited: have parental misconceptions about fever changed in 20 years? *Pediatrics*. 2001;107(6):1241-1246.
163. Watson RS, Carcillo JA. Scope and epidemiology of pediatric sepsis. *Pediatr Crit Care Med*. 2005;6(3 Suppl):S3-5.
164. Weiss SL, Parker B, Bullock ME, Swartz S, Price C, Wainwright MS, et al. Defining pediatric sepsis by different criteria: discrepancies in populations and implications for clinical practice. *Pediatr Crit Care Med*. 2012;13(4):e219-226.
165. Karavanaki KA, Soldatou A, Koufadaki AM, Tsentidis C, Haliotis FA, Stefanidis CJ. Delayed treatment of the first febrile urinary tract infection in early childhood increased the risk of renal scarring. *Acta Paediatr*. 2017;106(1):149-154.
166. Hewitt IK, Zucchetta P, Rigon L, Maschio F, Molinari PP, Tomasi L, et al. Early treatment of acute pyelonephritis in children fails to reduce renal scarring: data from the Italian Renal Infection Study Trials. *Pediatrics*. 2008;122(3):486-490.
167. Martinell J, Lidin-Janson G, Jagenburg R, Sivertsson R, Claesson I, Jodal U. Girls prone to urinary infections followed into adulthood. Indices of renal disease. *Pediatr Nephrol*. 1996;10(2):139-142.
168. Wennerström M, Hansson S, Jodal U, Sixt R, Stokland E. Renal function 16 to 26 years after the first urinary tract infection in childhood. *Archives of pediatrics & adolescent medicine*. 2000;154(4):339-345.
169. Teele DW, Pelton SI, Grant MJ, Herskowitz J, Rosen DJ, Allen CE, et al. Bacteremia in febrile children under 2 years of age: results of cultures of blood of 600 consecutive febrile children seen in a "walk-in" clinic. *J Pediatr*. 1975;87(2):227-230.
170. McGowan JE, Jr., Bratton L, Klein JO, Finland M. Bacteremia in febrile children seen in a "walk-in" pediatric clinic. *N Engl J Med*. 1973;288(25):1309-1312.
171. Gelernter R, Lazarovitch T, Kozer E, Youngster I. Children discharged from an emergency department with bacteraemia had lower C-reactive protein and better outcomes than admissions. *Acta Paediatr*. 2021;110(5):1571-1576.
172. Pruitt CM, Neuman MI, Shah SS, Shabanova V, Woll C, Wang ME, et al. Factors Associated with Adverse Outcomes among Febrile Young Infants with Invasive Bacterial Infections. *J Pediatr*. 2019;204:177-182.e171.
173. Pitetti RD, Choi S. Utility of blood cultures in febrile children with UTI. *Am J Emerg Med*. 2002;20(4):271-274.
174. Honkinen O, Jahnukainen T, Mertsola J, Eskola J, Ruuskanen O. Bacteremic urinary tract infection in children. *Pediatr Infect Dis J*. 2000;19(7):630-634.
175. Vaillancourt S, Guttmann A, Li Q, Chan IY, Vermeulen MJ, Schull MJ. Repeated emergency department visits among children admitted with meningitis or septicemia: a population-based study. *Ann Emerg Med*. 2015;65(6):625-632.e623.

176. McIntyre PB, Macintyre CR, Gilmour R, Wang H. A population based study of the impact of corticosteroid therapy and delayed diagnosis on the outcome of childhood pneumococcal meningitis. *Arch Dis Child*. 2005;90(4):391-396.
177. Kilpi T, Anttila M, Kallio MJ, Peltola H. Length of prediagnostic history related to the course and sequelae of childhood bacterial meningitis. *Pediatr Infect Dis J*. 1993;12(3):184-188.
178. Kallio MJ, Kilpi T, Anttila M, Peltola H. The effect of a recent previous visit to a physician on outcome after childhood bacterial meningitis. *Jama*. 1994;272(10):787-791.
179. Shah SS, Volk J, Mohamad Z, Hodinka RL, Zorc JJ. Herpes simplex virus testing and hospital length of stay in neonates and young infants. *J Pediatr*. 2010;156(5):738-743.
180. Nguyen DK, Fleischman RJ, Friedlander S, Zangwill KM. Epidemiology of Admissions From the Emergency Department Among Febrile Infants Younger Than 90 Days in the United States, 2002 to 2012. *Pediatr Emerg Care*. 2020;36(8):e438-e446.
181. Stephens JR, Hall M, Cotter JM, Molloy MJ, Tchou MJ, Markham JL, et al. Trends and Variation in Length of Stay Among Hospitalized Febrile Infants </=60 Days Old. *Hosp Pediatr*. 2021;11(9):915-926.
182. Stockwell DC, Bisarya H, Classen DC, Kirkendall ES, Landrigan CP, Lemon V, et al. A trigger tool to detect harm in pediatric inpatient settings. *Pediatrics*. 2015;135(6):1036-1042.
183. Nguyen DK, Friedlander S, Fleischman RJ, Zangwill KM. Length of Stay and Complications Associated With Febrile Infants <90 Days of Age Hospitalized in the United States, 2000-2012. *Hosp Pediatr*. 2018;8(12):746-752.
184. Jumani K, Advani S, Reich NG, Gosey L, Milstone AM. Risk factors for peripherally inserted central venous catheter complications in children. *JAMA Pediatr*. 2013;167(5):429-435.
185. Yin J, Schweizer ML, Herwaldt LA, Pottinger JM, Perencevich EN. Benefits of universal gloving on hospital-acquired infections in acute care pediatric units. *Pediatrics*. 2013;131(5):e1515-1520.
186. Raymond J, Aujard Y. Nosocomial infections in pediatric patients: a European, multicenter prospective study. European Study Group. *Infect Control Hosp Epidemiol*. 2000;21(4):260-263.
187. Aronson PL, Thurm C, Williams DJ, Nigrovic LE, Alpern ER, Tieder JS, et al. Association of clinical practice guidelines with emergency department management of febrile infants ≤56 days of age. *J Hosp Med*. 2015;10(6):358-365.
188. Noorbakhsh KA, Ramgopal S, Rixe NS, Dunnick J, Smith KJ. Risk-stratification in febrile infants 29 to 60 days old: a cost-effectiveness analysis. *BMC Pediatr*. 2022;22(1):79.
189. Coyle C, Brock G, Wallihan R, Leonard JC. Cost Analysis of Emergency Department Criteria for Evaluation of Febrile Infants Ages 29 to 90 Days. *J Pediatr*. 2021;231:94-101 e102.

190. Byington CL, Reynolds CC, Korgenski K, Sheng X, Valentine KJ, Nelson RE, et al. Costs and infant outcomes after implementation of a care process model for febrile infants. *Pediatrics*. 2012;130(1):e16-24.
191. De S, Tong A, Isaacs D, Craig JC. Parental perspectives on evaluation and management of fever in young infants: an interview study. *Arch Dis Child*. 2014;99(8):717-723.
192. Paxton RD, Byington CL. An examination of the unintended consequences of the rule-out sepsis evaluation: a parental perspective. *Clin Pediatr (Phila)*. 2001;40(2):71-77.
193. Rautava P, Lehtonen L, Helenius H, Sillanpää M. Effect of newborn hospitalization on family and child behavior: a 12-year follow-up study. *Pediatrics*. 2003;111(2):277-283.
194. Chambers PL, Mahabee-Gittens EM, Leonard AC. Vulnerable child syndrome, parental perception of child vulnerability, and emergency department usage. *Pediatr Emerg Care*. 2011;27(11):1009-1013.
195. Ananthakrishnan AN, Bernstein CN, Iliopoulos D, Macpherson A, Neurath MF, Ali RAR, et al. Environmental triggers in IBD: a review of progress and evidence. *Nat Rev Gastroenterol Hepatol*. 2018;15(1):39-49.
196. Wernroth ML, Fall K, Svennblad B, Ludvigsson JF, Sjölander A, Almqvist C, et al. Early Childhood Antibiotic Treatment for Otitis Media and Other Respiratory Tract Infections Is Associated With Risk of Type 1 Diabetes: A Nationwide Register-Based Study With Sibling Analysis. *Diabetes Care*. 2020;43(5):991-999.
197. Rasmussen SH, Shrestha S, Bjerregaard LG, Ängquist LH, Baker JL, Jess T, et al. Antibiotic exposure in early life and childhood overweight and obesity: A systematic review and meta-analysis. *Diabetes Obes Metab*. 2018;20(6):1508-1514.
198. Horton DB, Scott FI, Haynes K, Putt ME, Rose CD, Lewis JD, et al. Antibiotic Exposure and Juvenile Idiopathic Arthritis: A Case-Control Study. *Pediatrics*. 2015;136(2):e333-343.
199. Ni J, Friedman H, Boyd BC, McGurn A, Babinski P, Markossian T, et al. Early antibiotic exposure and development of asthma and allergic rhinitis in childhood. *BMC Pediatr*. 2019;19(1):225.
200. Yamamoto-Hanada K, Yang L, Narita M, Saito H, Ohya Y. Influence of antibiotic use in early childhood on asthma and allergic diseases at age 5. *Ann Allergy Asthma Immunol*. 2017;119(1):54-58.
201. Duong QA, Pittet LF, Curtis N, Zimmermann P. Antibiotic exposure and adverse long-term health outcomes in children: A systematic review and meta-analysis. *J Infect*. 2022;85(3):213-300.
202. World Health Organization (WHO). Antibiotic Resistance. https://www.who.int/news-room/fact-sheets/detail/antibiotic-resistance. Published 2020.
203. Kleiber C, McCarthy AM. Parent behavior and child distress during urethral catheterization. *J Soc Pediatr Nurs*. 1999;4(3):95-104.

204. Mularoni PP, Cohen LL, DeGuzman M, Mennuti-Washburn J, Greenwald M, Simon HK. A randomized clinical trial of lidocaine gel for reducing infant distress during urethral catheterization. *Pediatr Emerg Care*. 2009;25(7):439-443.
205. Lohr JA, Downs SM, Dudley S, Donowitz LG. Hospital-acquired urinary tract infections in the pediatric patient: a prospective study. *Pediatr Infect Dis J*. 1994;13(1):8-12.
206. Pingree EW, Kimia AA, Nigrovic LE. The effect of traumatic lumbar puncture on hospitalization rate for febrile infants 28 to 60 days of age. *Acad Emerg Med*. 2015;22(2):240-243.
207. Thuler LC, Jenicek M, Turgeon JP, Rivard M, Lebel P, Lebel MH. Impact of a false positive blood culture result on the management of febrile children. *Pediatr Infect Dis J*. 1997;16(9):846-851.
208. Sard B, Bailey MC, Vinci R. An analysis of pediatric blood cultures in the postpneumococcal conjugate vaccine era in a community hospital emergency department. *Pediatr Emerg Care*. 2006;22(5):295-300.
209. Money NM, Schroeder AR, Quinonez RA, Ho T, Marin JR, Morgan DJ, et al. 2019 Update on Pediatric Medical Overuse: A Systematic Review. *JAMA Pediatr*. 2020;174(4):375-382.
210. Coon ER, Quinonez RA, Moyer VA, Schroeder AR. Overdiagnosis: how our compulsion for diagnosis may be harming children. *Pediatrics*. 2014;134(5):1013-1023.
211. Chalmers K, Gopinath V, Brownlee S, Saini V, Elshaug AG. Adverse Events and Hospital-Acquired Conditions Associated With Potential Low-Value Care in Medicare Beneficiaries. *JAMA Health Forum*. 2021;2(7):e211719.
212. Jain S, Cheng J, Alpern ER, Thurm C, Schroeder L, Black K, et al. Management of febrile neonates in US pediatric emergency departments. *Pediatrics*. 2014;133(2):187-195.
213. Rogers AJ, Kuppermann N, Anders J, Roosevelt G, Hoyle JD, Jr., Ruddy RM, et al. Practice Variation in the Evaluation and Disposition of Febrile Infants ≤60 Days of Age. *J Emerg Med*. 2019;56(6):583-591.
214. Goldman RD, Scolnik D, Chauvin-Kimoff L, Farion KJ, Ali S, Lynch T, et al. Practice variations in the treatment of febrile infants among pediatric emergency physicians. *Pediatrics*. 2009;124(2):439-445.
215. Klarenbeek NN, Keuning M, Hol J, Pajkrt D, Plötz FB. Fever Without an Apparent Source in Young Infants: A Multicenter Retrospective Evaluation of Adherence to the Dutch Guidelines. *Pediatr Infect Dis J*. 2020;39(12):1075-1080.
216. Burstein B, Gravel J, Aronson PL, Neuman MI. Emergency department and inpatient clinical decision tools for the management of febrile young infants among tertiary paediatric centres across Canada. *Paediatr Child Health*. 2019;24(3):e142-e154.
217. Gudjonsdottir MJ, Hentz E, Adlerberth I, Tessin I, Trollfors B, Elfvin A. Late-onset Neonatal Infections 1997 to 2017 Within a Cohort in Western Sweden-The Last 21 Years of a 43-Year Surveillance. *Pediatr Infect Dis J*. 2021;40(4):359-364.
218. Organisation for economic co-operation and development (oecd). Antimicrobial resistance, tackling the burden in the european union. 2019.

219. Organisation for Economic Co-operation and Development (OECD). Hospital Beds (indicator). Health at a Glance. https://data.oecd.org/healtheqt/hospital-beds.htm. Published 2021.
220. Schroeder AR, Harris SJ, Newman TB. Safely doing less: a missing component of the patient safety dialogue. *Pediatrics*. 2011;128(6):e1596-1597.
221. Wunderlich CA. *Medical thermometry, and human temperature*: William Wood & Company; 1871.
222. Anderson ES, Petersen SA, Wailoo MP. Factors influencing the body temperature of 3-4 month old infants at home during the day. *Arch Dis Child*. 1990;65(12):1308-1310.
223. Cheng TL, Partridge JC. Effect of bundling and high environmental temperature on neonatal body temperature. *Pediatrics*. 1993;92(2):238-240.
224. Grover G, Berkowitz CD, Lewis RJ, Thompson M, Berry L, Seidel J. The effects of bundling on infant temperature. *Pediatrics*. 1994;94(5):669-673.
225. Iliff A, Lee VA. Pulse rate, respiratory rate, and body temperature of children between two months and eighteen years of age. *Child Dev*. 1952;23(4):237-245.
226. Charafeddine L, Tamim H, Hassouna H, Akel R, Nabulsi M. Axillary and rectal thermometry in the newborn: do they agree? *BMC Res Notes*. 2014;7:584.
227. Tham D, Davis C, Hopper SM. Infrared thermometers and infants: The device is hot the baby maybe not. *J Paediatr Child Health*. 2022;58(4):624-629.
228. Aronson PL, Shabanova V, Shapiro ED, Wang ME, Nigrovic LE, Pruitt CM, et al. A Prediction Model to Identify Febrile Infants ≤60 Days at Low Risk of Invasive Bacterial Infection. *Pediatrics*. 2019;144(1).
229. Michelson KA, Neuman MI, Pruitt CM, Desai S, Wang ME, DePorre AG, et al. Height of fever and invasive bacterial infection. *Arch Dis Child*. 2021;106(6):594-596.
230. Bachur RG, Harper MB. Predictive model for serious bacterial infections among infants younger than 3 months of age. *Pediatrics*. 2001;108(2):311-316.
231. Ramgopal S, Walker LW, Tavarez MM, Nowalk AJ, Vitale MA. Serious Bacterial Infections in Neonates Presenting Afebrile With History of Fever. *Pediatrics*. 2019;144(2).
232. Bonadio WA. Incidence of serious infections in afebrile neonates with a history of fever. *Pediatr Infect Dis J*. 1987;6(10):911-914.
233. Yarden-Bilavsky H, Bilavsky E, Amir J, Ashkenazi S, Livni G. Serious bacterial infections in neonates with fever by history only versus documented fever. *Scand J Infect Dis*. 2010;42(11-12):812-816.
234. Mintegi S, Gomez B, Carro A, Diaz H, Benito J. Invasive bacterial infections in young afebrile infants with a history of fever. *Arch Dis Child*. 2018;103(7):665-669.
235. Ramgopal S, Janofsky S, Zuckerbraun NS, Ramilo O, Mahajan P, Kuppermann N, et al. Risk of Serious Bacterial Infection in Infants Aged </=60 Days Presenting to Emergency Departments with a History of Fever Only. *J Pediatr*. 2019;204:191-195.

236. World health organization (who). Guidelines in health care practice. https://www.euro.who.int/__data/assets/pdf_file/0011/118379/E53492.pdf. Published 1997.
237. Fischer F, Lange K, Klose K, Greiner W, Kraemer A. Barriers and Strategies in Guideline Implementation-A Scoping Review. *Healthcare (Basel)*. 2016;4(3).
238. Murray AL, Alpern E, Lavelle J, Mollen C. Clinical Pathway Effectiveness: Febrile Young Infant Clinical Pathway in a Pediatric Emergency Department. *Pediatr Emerg Care*. 2017;33(9):e33-e37.
239. Gomez B, Fernandez-Uria A, Benito J, Lejarzegi A, Mintegi S. Impact of the Step-by-Step on febrile infants. *Arch Dis Child*. 2021;106(11):1047-1049.
240. Schneider C, Blumberg S, Crain EF. A survey of the management of febrile infants in pediatric emergency departments. *Pediatr Emerg Care*. 2012;28(10):1022-1026.
241. Yarden-Bilavsky H, Ashkenazi S, Amir J, Schlesinger Y, Bilavsky E. Fever survey highlights significant variations in how infants aged ≤60 days are evaluated and underline the need for guidelines. *Acta Paediatr*. 2014;103(4):379-385.
242. Grol R. Successes and failures in the implementation of evidence-based guidelines for clinical practice. *Med Care*. 2001;39(8 Suppl 2):Ii46-54.
243. Sheldon TA, Cullum N, Dawson D, Lankshear A, Lowson K, Watt I, et al. What's the evidence that NICE guidance has been implemented? Results from a national evaluation using time series analysis, audit of patients' notes, and interviews. *Bmj*. 2004;329(7473):999.
244. Ament SM, de Groot JJ, Maessen JM, Dirksen CD, van der Weijden T, Kleijnen J. Sustainability of professionals' adherence to clinical practice guidelines in medical care: a systematic review. *BMJ Open*. 2015;5(12):e008073.
245. Meehan WP, 3rd, Fleegler E, Bachur RG. Adherence to guidelines for managing the well-appearing febrile infant: assessment using a case-based, interactive survey. *Pediatr Emerg Care*. 2010;26(12):875-880.
246. Belfer RA, Gittelman MA, Muñiz AE. Management of febrile infants and children by pediatric emergency medicine and emergency medicine: comparison with practice guidelines. *Pediatr Emerg Care*. 2001;17(2):83-87.
247. Aronson PL, Schaeffer P, Fraenkel L, Shapiro ED, Niccolai LM. Physicians' and Nurses' Perspectives on the Decision to Perform Lumbar Punctures on Febrile Infants ≤8 Weeks Old. *Hosp Pediatr*. 2019;9(6):405-414.
248. Sjöström B, Dahlgren LO. Applying phenomenography in nursing research. *J Adv Nurs*. 2002;40(3):339-345.
249. Ryan RM, Deci EL. Intrinsic and Extrinsic Motivations: Classic Definitions and New Directions. *Contemp Educ Psychol*. 2000;25(1):54-67.
250. Fleisher GR. Management of children with occult bacteremia who are treated in the emergency department. *Rev Infect Dis*. 1991;13 Suppl 2:S156-159.
251. Okike IO, Ladhani SN, Johnson AP, Henderson KL, Blackburn RM, Muller-Pebody B, et al. Clinical Characteristics and Risk Factors for Poor Outcome in Infants Less Than 90 Days of Age With Bacterial Meningitis in the United Kingdom and Ireland. *Pediatr Infect Dis J*. 2018;37(9):837-843.

252. Benador D, Neuhaus TJ, Papazyan JP, Willi UV, Engel-Bicik I, Nadal D, et al. Randomised controlled trial of three day versus 10 day intravenous antibiotics in acute pyelonephritis: effect on renal scarring. *Arch Dis Child*. 2001;84(3):241-246.
253. Dai B, Liu Y, Jia J, Mei C. Long-term antibiotics for the prevention of recurrent urinary tract infection in children: a systematic review and meta-analysis. *Arch Dis Child*. 2010;95(7):499-508.
254. Sartini M, Carbone A, Demartini A, Giribone L, Oliva M, Spagnolo AM, et al. Overcrowding in Emergency Department: Causes, Consequences, and Solutions-A Narrative Review. *Healthcare (Basel)*. 2022;10(9).
255. Jones S, Moulton C, Swift S, Molyneux P, Black S, Mason N, et al. Association between delays to patient admission from the emergency department and all-cause 30-day mortality. *Emerg Med J*. 2022;39(3):168-173.
256. Royal college of emergency medicine. RCEM explains: Long waits and excess deaths. https://rcem.ac.uk/wp-content/uploads/2023/02/RCEM_Explains_long_waits_and_excess_mortality.pdf. Published 2023. 2023.
257. Lindner G, Woitok BK. Emergency department overcrowding : Analysis and strategies to manage an international phenomenon. *Wien Klin Wochenschr*. 2021;133(5-6):229-233.
258. Crook HD, Taylor DM, Pallant JF, Cameron PA. Workplace factors leading to planned reduction of clinical work among emergency physicians. *Emerg Med Australas*. 2004;16(1):28-34.
259. Brownlee S, Chalkidou K, Doust J, Elshaug AG, Glasziou P, Heath I, et al. Evidence for overuse of medical services around the world. *Lancet*. 2017;390(10090):156-168.
260. Bressan S, Gomez B, Mintegi S, Da Dalt L, Blazquez D, Olaciregui I, et al. Diagnostic performance of the lab-score in predicting severe and invasive bacterial infections in well-appearing young febrile infants. *Pediatr Infect Dis J*. 2012;31(12):1239-1244.
261. Woolf SH, Grol R, Hutchinson A, Eccles M, Grimshaw J. Clinical guidelines: potential benefits, limitations, and harms of clinical guidelines. *Bmj*. 1999;318(7182):527-530.
262. Brichko L, Mitra B, Cameron P. When guidelines guide us to harm. *Emerg Med Australas*. 2018;30(6):740-742.
263. Guerra-Farfan E, Garcia-Sanchez Y, Jornet-Gibert M, Nuñez JH, Balaguer-Castro M, Madden K. Clinical practice guidelines: The good, the bad, and the ugly. *Injury*. 2022.
264. Babenko O. Professional Well-Being of Practicing Physicians: The Roles of Autonomy, Competence, and Relatedness. *Healthcare (Basel)*. 2018;6(1).
265. Ryan RM, Deci EL. Self-determination theory and the facilitation of intrinsic motivation, social development, and well-being. *Am Psychol*. 2000;55(1):68-78.
266. Mata DA, Ramos MA, Bansal N, Khan R, Guille C, Di Angelantonio E, et al. Prevalence of Depression and Depressive Symptoms Among Resident Physicians: A Systematic Review and Meta-analysis. *Jama*. 2015;314(22):2373-2383.

267. Kumar S. Burnout and Doctors: Prevalence, Prevention and Intervention. *Healthcare (Basel)*. 2016;4(3).
268. Bodenheimer T, Sinsky C. From triple to quadruple aim: care of the patient requires care of the provider. *Ann Fam Med*. 2014;12(6):573-576.
269. Pourhoseingholi MA, Vahedi M, Rahimzadeh M. Sample size calculation in medical studies. *Gastroenterol Hepatol Bed Bench*. 2013;6(1):14-17.
270. Charan J, Biswas T. How to calculate sample size for different study designs in medical research? *Indian J Psychol Med*. 2013;35(2):121-126.
271. Naing L, Winn T, Rusli B. Practical issues in calculating the sample size for prevalence studies. *Archives of orofacial Sciences*. 2006;1:9-14.
272. Clincalc.Com. Sample size calculator. https://clincalc.com/stats/samplesize.aspx. Updated July 24, 2019.
273. Council for international organizations of medical sciences. International ethical guidelines for health-related research involving humans. https://cioms.ch/wp-content/uploads/2017/01/WEB-CIOMS-EthicalGuidelines.pdf. Published 2016. 2023.
274. Swedish parliament. Act (2003:460) on ethical review of research involving humans. https://www.riksdagen.se/sv/dokument-lagar/dokument/svensk-forfattningssamling/lag-2003460-om-etikprovning-av-forskning-som_sfs-2003-460. Published 2003. 2023.
275. GDPR.EU. General data protection regulation (GDPR),. https://gdpr.eu/tag/gdpr/. Published 2018. 2023.
276. International committe of medical journal editors (ICMJE). Recommendations for the conduct, reporting, editing, and publication of scholarly work in medical journals. https://www.icmje.org/recommendations/. Updated May, 2022. 2023.

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