

PIRET MITT

Healthcare-associated infections in Estonia –
epidemiology and surveillance of bloodstream
and surgical site infections



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Department of Internal Medicine, Institute of Clinical Medicine, University of Tartu, Estonia

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Supervisors: Associate Professor Matti Maimets, MD, PhD
Department of Internal Medicine, Institute of Clinical Medicine,
University of Tartu, Estonia
Senior Research Fellow Paul Naaber, MD, PhD
Department of Microbiology, Institute of Biomedicine and
Translational Medicine, University of Tartu, Estonia

Reviewers: Professor Anneli Uusküla, MD, MSc, PhD
Institute of Biomedicine and Translational Medicine,
University of Tartu, Estonia
Professor Joel Starkopf, MD, PhD
Department of Anesthesiology and Intensive Care, Institute of
Clinical Medicine, University of Tartu, Estonia

Opponent: Professor Uga Dumpis, MD, PhD
Department of Internal Medicine, Infectious Diseases, Uni-
versity of Latvia, Latvia

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LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications, which are referred to in the text by their Roman numerals:

- I Mitt P, Adamson V, Lõivukene K, Lang K, Telling K, Pärt K, Rõõm A, Naaber P, Maimets M. Epidemiology of nosocomial bloodstream infections in Estonia. *J Hosp Infect* 2009; 71: 365–70
- II Mitt P, Metsvaht T, Adamson V, Telling K, Naaber P, Lutsar I, Maimets M. Five-year prospective surveillance of nosocomial bloodstream infections in an Estonian pediatric intensive care unit. *J Hosp Infect* 2014; 86: 95–9
- III Mitt P, Lang K, Peri A, Maimets M. Surgical-site infections following cesarean section in an Estonian university hospital: postdischarge surveillance and analysis of risk factors. *Infect Control Hosp Epidemiol* 2005; 26: 449–54

Degree of the applicant's personal contribution to the preparation of the publications:

In all publications Piret Mitt participated in study design, data collection, analysis and interpretation of data from studies. She drafted all manuscripts and was responsible for the responses and updates throughout the review process.

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ABBREVIATIONS

ARPEC	Antibiotic Resistance and Prescribing in European Children
ASA	American Society of Anesthesiologists
BMI	Body Mass Index
BSI	bloodstream infection
CCI	Charlson comorbidity index
CDC	Centers for Disease Control and Prevention, USA
CLABSI	central line associated bloodstream infection
CL	central line
CLSI	Clinical and Laboratory Standards Institute, USA
CoNS	coagulase-negative staphylococci
CS	cesarean section
EARS-Net	European Antimicrobial Resistance Surveillance Network
ECDC	European Centers for Disease Control and Prevention
ELBW	extremely low birth weight
ESBL	extended spectrum beta-lactamase
HAI	healthcare-associated infection
HELICS	Hospitals in Europe Link for Infection Control through Surveillance
ICP	infection control personnel
ICU	intensive care unit
IPSE	Improving Patient Safety in Europe
IQR	interquartile range
LRTI	lower respiratory tract infection
MRSA	methicillin-resistant <i>Staphylococcus aureus</i>
NEO-KISS	German Hospital Infection Surveillance System for neonates
NICU	neonatal intensive care unit
NNIS	National Nosocomial Infections Surveillance, USA
NHSN	National Healthcare Safety Network, USA
PAP	perioperative antibiotic prophylaxis
PICU	pediatric intensive care unit
SSI	surgical site infection
UTI	urinary tract infection
VAP	ventilator-associated pneumonia
VLBW	very low birth weight

I. INTRODUCTION

Patient safety has received considerable public, professional, political, and scientific attention over the past decades (1). Healthcare-associated infections (HAIs) are infections that patients acquire while receiving treatment for medical or surgical conditions and are among the most common adverse events in healthcare contributing to increased morbidity, mortality, and healthcare costs (2, 3). The European Centers for Disease Control and Prevention (ECDC) estimated that 3.2 million patients are affected by at least one HAI episode per year in acute care hospitals in Europe (4).

HAI surveillance is the cornerstone of prevention and control since it facilitates the development of appropriate intervention measures and helps to evaluate their efficacy (5). Systems have been set up in different countries in order to describe and monitor HAIs; some of them were implemented several decades ago (6). Since 2008 ECDC has continuous surveillance system for HAIs in intensive care unit (ICU) and surgical site infections (SSIs) (7).

The most common types of HAIs are lower respiratory tract infections (LRTIs), urinary tract infections (UTIs), SSIs and bloodstream infections (BSIs) (4). Overall rates of HAI vary widely in different populations as the result of differences in distribution of the major intrinsic and extrinsic risk factors for the acquisition of HAIs, with the highest rates usually occurring in ICUs (3). The most vulnerable pediatric population are the patients in neonatal ICU (NICU) or in pediatric ICU (PICU), where BSI is the most common HAI leading to increased morbidity, mortality and long-term consequences (8).

Surveillance of HAI is also important in other wards besides ICU, but it is complicated and expensive to perform surveillance of all HAI (9). Hospital-wide surveillance of nosocomial BSI may have an advantage over other types of infection data as they represent the severe end of the spectrum of infection. Surveillance of nosocomial BSI is thought to be useful in monitoring trends of HAIs, identifying wards at risk, outbreaks and emerging multiresistant pathogens, and effects of HAI intervention programs (10). Up-to-date information on species distribution and patterns of antimicrobial resistance is also essential for drawing up guidelines of empiric antimicrobial treatment (11).

While BSIs are more likely to be associated with life-threatening illness or even death, SSI remains among the most common infections occurring in acute care hospitals (12, 13). In the point prevalence survey of HAI and antimicrobial use in European acute care hospitals, SSI were the second most common type of HAI and accounted for 19.6% of all infections (4). Since the length of post-operative hospitalization continues to decrease, the increasing number of SSI is not detected through standard surveillance method and therefore postdischarge SSI surveillance has become increasingly important in order to obtain accurate SSI rates (14). Several methods for postdischarge surveillance of SSI have been evaluated for efficiency (15). Nevertheless, there is no universally accepted strategy for monitoring these infections and postdischarge surveillance methods and practices differ considerably among countries (16).

In Estonia, before 2002 some studies investigated hospital-acquired microorganisms such as *Acinetobacter baumannii*, *Staphylococcus aureus* and *Escherichia coli* (17, 18). There was no surveillance system of HAI and no study of the epidemiology of HAIs was carried out. This research was performed to assess the epidemiological features of nosocomial BSIs and SSIs: the risk factors, species distribution, and the antimicrobial susceptibility of causative pathogens. We also evaluated a multimethod approach to postdischarge surveillance of SSI. Secondary aim of this study was to promote HAI surveillance at the hospital level.

2. REVIEW OF LITERATURE

2.1. Epidemiology of healthcare-associated infections and burden to public health

2.1.1. Definition of healthcare-associated infection

The use of standardized definitions is crucial to the reliability of HAI surveillance (3). These definitions should be precise and easily applicable that would enable different researchers to compare their results.

In 1988 the Centers for Disease Control and Prevention developed new set of definitions for surveillance of nosocomial infections. “Nosocomial” or “hospital-acquired” infection, is an infection occurring in a patient during the process of care in a hospital which was not present or incubating at the time of admission (19). In acute care setting, most nosocomial infections become evident 48 hours or more following admission (typical incubation period), which resulted in the use of the 48-hours criterion in several epidemiological surveillance systems (3). Different HAIs have been grouped into 14 major type categories according to the localization (20). The US CDC definitions are widely used around the world. Since 2008 HAI surveillance activities in Europe have been coordinated by ECDC and the network was named the Healthcare-Associated Infections surveillance Network (HAI-Net) (7). The ECDC analyzed the concordance between the US CDC and ECDC definitions of HAI and identified that case definitions do not differ significantly and do not compromise comparability of results (7).

However, in the last decade, there has been a shift in the delivery of health-care services such that increasingly complex medical and surgical services are being provided in non-acute-care settings or in the community (21). As a result, community based patients may now be admitted to hospital with infections that share many characteristics with hospital-acquired infections (22). In addition, patients move freely within elements of the health care system: between long-term care or rehabilitation facilities, to acute-care facilities, to free-standing surgical care providers, making the definition of a health care setting more problematic (21). The term “HAI” has replaced the former ones used to refer to such infections, i.e., “nosocomial” or “hospital-acquired” infection, as evidence has shown that this event can affect patients in any settings where they receive care (3). In addition to the original definition of nosocomial infection, the most widely accepted definition of HAI in literature, primarily developed for BSI, encompasses infectious diseases in patients who fulfil one or more of the following criteria (23):

1. Resident in a nursing home or a long-term care facility.
2. Intravenous therapy at home or wound care or specialized nursing care.
3. Having attended a hospital or hemodialysis clinic or received intravenous chemotherapy in the past 30 days.
4. Admission to an acute care hospital for 2 or more days in the preceding 90 days.

The proportion of patients hospitalized with HAI among those admitted from the community setting can be as high as 50% (23).

Furthermore, HAIs are not restricted only to patients; health-care workers, ancillary staff, and visitors can also be affected (3).

2.1.2. Morbidity and mortality of healthcare-associated infections

In 2011–2012 the first Europe-wide point prevalence survey of HAIs and antimicrobial use estimated that on any given day, about 80 000 patients in European hospitals have at least one HAI with a mean HAI prevalence of 6.0% (country range 2.3%–10.8%) (4). In Europe, the most frequently reported HAI types were pneumonia and other LRTIs (19.4% and 4.1% respectively), SSIs (19.6%), UTIs (19.0%), BSIs (10.6%) and gastrointestinal infections (7.6%) with *C. difficile* infections accounting for 48% of the latter or 3.6% of all HAIs (4). The HAI prevalence rate in the USA was 4.0% in acute care hospitals yielding an estimate of 648 000 inpatients with a total of approximately 721 800 such infections in 2011 (24). The most common types were pneumonia (21.8%), SSIs (21.8%), gastrointestinal infections (17.1%), UTIs (12.9%), and BSIs (9.9%) (24).

The HAI burden is much more severe in high-risk populations, such as patients admitted to ICUs, burn and transplant patients, and neonates (3). In ECDC point prevalence survey the prevalence of HAI ranged from 0.9% in psychiatry to 19.5% in ICUs (4).

Overall rates of HAI vary widely in different pediatric populations as the result of differences in distribution of the major intrinsic and extrinsic risk factors for the acquisition of HAIs. The pediatric population with the largest number of these risk factors, and thus the highest rates of HAIs, are patients in NICUs or in PICUs (25). A European study of 17 pediatric centers reported an overall HAI incidence of 2.5% (from 1% in general pediatric wards to 23.6% in PICUs) including five types of HAI: BSIs (36% of all infections), LRTIs (33%), gastrointestinal infections (14%), UTIs (11%), and SSIs (6%) (26). The US point prevalence survey of HAI in 29 NICUs and 35 PICUs revealed an overall HAI prevalence of 11.4% and 11.9%, respectively (27, 28). Pediatric patients have higher rates of BSIs (the most common HAI in all pediatric age groups) and viral gastrointestinal and respiratory infections than adult patients, whereas rates of catheter-related UTIs, ventilator-associated pneumonia (VAP), and SSI are higher in adult patients (29).

In Europe HAIs are estimated to cause 37 000 attributable deaths annually (3). Among the 1.7 million patients with HAI in the US there were approximately 99 000 deaths per year caused by or associated with the HAI, making HAIs the fifth leading cause of death in acute care hospital (2, 21).

The percentage of patients whose deaths are associated with an HAI varies by major site of infection and subpopulation. According to several studies performed in high-income countries some infections, e.g., VAP and BSI, have a

more severe impact on patient outcome than others (3). In US it was estimated that pneumonia and BSI caused 67% of all deaths (2). In the same study the highest percentage of patients with an HAI whose death was associated with the infection was among adults and children in ICUs where the percentage varied from 11% for SSIs to 25% for BSIs (2). According to the 2003–2008 International Infection Control Consortium report related to 173 ICUs in Latin America, Asia, Africa, and Europe crude excess mortality in adult patients was 18.5%, 23.6% and 29.3% for UTI, BSI and VAP, respectively (30). In pediatric setting BSI carries the highest mortality and neonates are the age-group at highest risk for poor outcome (31). Additionally and equally important, neonatal HAIs can have long-term sequelae including poor neurodevelopmental and growth outcomes (32).

Estimating the excess mortality due to HAI is challenging, especially in high-risk patients who are at greater risk of death because of severe underlying diseases (3). For example, different methods have been used to calculate the attributable mortality of VAP, yielding estimates up to 60% (33). On the basis of a recently published meta-analysis of 6284 individual patients' data from 24 trials of VAP prevention Melsen and colleagues estimated that the attributable mortality of VAP was only 13% (33). Nevertheless, patients who acquire HAI have an excess risk to death.

2.1.3. Costs of healthcare-associated infections

HAIs induce high costs which are difficult to measure with accuracy. The direct financial impact of HAIs on the healthcare budget is predominantly determined through an increased number of readmissions, length of hospitalization (e.g., about 1–4 extra days for a UTI, 7–8 days for a SSI, 7–21 days for a BSI, and 7–30 days for pneumonia), use of antimicrobials, surveillance and isolation measures, laboratory and imaging services attributable to diagnosing and managing HAIs, and costs attributable to outbreaks (34).

According to the recently published US data, annual costs for the 5 major HAIs was \$9.8 billion. On a per-case basis, central line associated bloodstream infections (CLABSIs) were found to be the most costly HAIs at \$45 814 (95% confidence interval [95% CI], \$30 919–\$65 245), followed by VAP at \$40 144 (95% CI, \$36 286–\$44 220), SSIs at \$20 785 (95% CI, \$18 902–\$22 667), *C. difficile* infection at \$11 285 (95% CI, \$9118–\$13 574), and UTI at \$896 (95% CI, \$603–\$1189) (35). For the United Kingdom the costs exceed £900 million (36). In a systematic review of the economic burden of patient safety in the acute care setting Mittmann *et al.* found that in general hospital populations the cost per case of HAI ranged from \$2132 to \$15018 (1).

However, all these estimates are related to direct healthcare-related costs. Indirect costs of HAIs such as time away from home for the person suffering from HAI, and if employed, absenteeism, sick leave, and potential loss of work and income have not been well quantified. Additionally, family members' time

lost from work in caring for his relative contributes to indirect societal costs of HAIs.(34)

2.1.4. Risk factors of healthcare-associated infections

The strongest determinants of HAI risk are the characteristics and exposures of patients that predispose them to infection and complex interactions of agent (microorganism causing infection), host (susceptible patient), and environment (e.g., hospital ICU, outpatient, hemodialysis center) (37). Risk factors for HAI can be divided into intrinsic (patient-related) and extrinsic (medical intervention or healthcare delivery related) (Table 1) (38). Among hospitalized populations admission to ICU itself is a major risk factor for development of HAI mostly due to widespread use of invasive devices in this department (39).

Table 1. Most common risk factors that predispose to HAI (40, 41).

Patient related factors	Extremes of age Nutritional status Underlying medical conditions Severity of illness Suppressed immune system
Medical intervention related factors	Invasive devices (e.g., intravascular catheters, urinary catheters, endotracheal tubes) Surgical procedures Antibiotic use Immune-suppressive medications ICU exposure Prolonged exposure to the health care system
Healthcare delivery related factors	Failure to implement basic prevention techniques (hand hygiene, aseptic technique) Environmental contamination Overcrowding, suboptimal nurse-to-patient ratios Inadequate cleaning, disinfection and sterilization of medical supplies and equipment

Pediatric and adult patients share common extrinsic risk factors (37). Additional risk factors specific to pediatric or neonatal population include gestational age, gender, birth weight, congenital abnormalities, race, nutritional status, genetically determined immune status, therapy, and vaccination (37). Newborns hospitalized in a NICU have host factors that increase their risk of acquiring HAI and developing more serious illness (42). One of the reasons for that is probably due to the differences in the function of innate and adaptive immune systems. Infants with birth weights less than 1500 g (very low birth weight –

VLBW) have rates of HAIs 3 times higher than those who weigh more than 1500 g at birth. Moreover, besides diminished immune system function the likelihood of severe illnesses needing invasive monitoring and procedures increase susceptibility to HAI of VLBW newborns.(42)

HAIs are rarely triggered by a single factor, but are mainly the result of multiple events that may lead to infection (43).

2.1.5. Sources and transmission of pathogens

Microorganisms from either endogenous or exogenous sources may cause HAI. Endogenous sources are body sites that are normally colonized by indigenous microbiota. These microbes can become invasive under certain favourable conditions and/or cause infection when they contaminate sterile sites. Exogenous sources are those external to the patient, e.g., healthcare workers, visitors, patient care equipment, medical devices, or the healthcare environment.(3)

The transmission may occur through one or more five different routes: contact (either direct or indirect), droplet, airborne, common vehicle, and vector-borne. Contact transmission is the most frequent and important mode of transmission of exogenous HAI pathogens (44). Indirect contact transmission occurs most frequently via healthcare workers' hands (45). The transmission of exogenous organisms is also called horizontal or cross-transmission.

It has been estimated that the source of pathogens causing HAI in the ICU was the patients' endogenous flora (40–60%); cross-transmission via the hands of personnel (20–40%); antibiotic driven changes in microbiota (20–25%); and other (including contamination of the environment) (20%) (46).

During outbreaks, the most frequent sources, described in a review of 1022 outbreak investigations, were patients themselves (25.7%), followed by medical equipment or devices (11.9%), the environment (11.6%), and the staff (10.9%) (47). Transmission was by contact in 45.3%, by invasive technique in 16.1%, and through the air in 15.0%. In 37% and 28.3% of the outbreaks the authors were not able to identify the sources or the mode of transmission, respectively (47).

2.1.6. Causative pathogens and antimicrobial resistance

Bacteria, fungi, and viruses have been reported as causative agents in HAIs and many infections are polymicrobial (48). In contrast to the 1970s, major shifts in the etiology of HAIs occurred in the decades between 1980 and 2000, where Gram-positive and fungal infections became more common (48). However, recent years have seen shift in the pattern of infecting organisms towards Gram-negative infections that are especially common and problematic in ICUs, where these bacteria account for about 70% of pneumonias and UTIs (49). Several Gram-negative organisms are responsible for HAIs, *Enterobacteriaceae* is the most commonly identified group overall (49).

Data from the ECDC point prevalence survey of HAI and antimicrobial use identified five most commonly reported HAI pathogens: *E. coli* (15.9% of all types of HAIs), *S. aureus* (12.3%), *Enterococcus* spp. (9.6%), *P. aeruginosa* (8.9%) and *Klebsiella* spp. (8.7%) (Table 2). The causative microorganisms varied depending on the type of HAI. The leading pathogens causing LRTI, SSI, UTI, BSI were *P. aeruginosa* (17.4% of all LRTIs), *S. aureus* (17.9% of all SSIs), *E. coli* (36.2% of all UTIs), and CoNS (18.5% of all BSIs), respectively.(4)

Table 2. Distribution of most commonly isolated microorganisms in HAIs by type of infection, ECDC point prevalence survey 2011–2012 (4).

Microorganisms	All HAIs No.	All HAIs %	LRTI %	SSI %	UTI %	BSI %
<i>E. coli</i>	1601	15.9	8.8	14.0	36.2	11.0
<i>S. aureus</i>	1243	12.3	12.6	17.9	1.8	15.9
<i>Enterococcus</i> spp.	969	9.6	2.2	14.5	12.5	8.2
<i>P. aeruginosa</i>	901	8.9	17.4	7.6	8.4	6.1
<i>Klebsiella</i> spp.	872	8.7	11.4	6.0	12.0	9.8
CoNS	752	7.5	1.7	9.6	1.4	18.5
Other	752	7.5	6.9	7.2	13.0	5.3
<i>Enterobacteriaceae</i>						
<i>Enterobacter</i> spp.	422	4.2	5.0	5.4	3.9	3.4
<i>Acinetobacter</i> spp.	366	3.6	8.7	2.9	1.5	4.1
<i>Streptococcus</i> spp.	246	2.4	2.7	3.6	0.7	2.8

In the US point prevalence survey *C. difficile* was the most commonly reported pathogen (causing 12.1% of HAIs), followed by *S. aureus* (10.7%), *K. pneumoniae* or *K. oxytoca* (9.9%), *E. coli* (9.3%) and *Enterococcus* spp. (8.7%) (24).

Among pediatric population pathogen distribution varies according to age group and setting. In contrast to adults, CoNS are the most common nosocomial pathogens among patients in NICUs and PICUs of developed countries accounting for up to half of cases, mostly because of an increase in the improved survival of infants with VLBW and the high incidence of BSI (31, 50, 51). Gram-negative organisms are major contributors to HAI in developing countries (31). Although less frequent than Gram-positive or Gram-negative microorganisms, *Candida* spp. are major pathogens among immunocompromised and critically ill children, including premature infants (31). Significant variation between centres with invasive candidiasis rates ranging from 2–20% among ELBW neonates have been described (52). In addition, children are at risk to

infections that have been prevented in older patients by vaccination or previous natural exposure (31). Namely, respiratory viruses, rotavirus, varicella zoster virus, and pertussis represent persistent challenges in children's hospitals (31).

The rate of antimicrobial resistance among nosocomial pathogens is increasing for nearly all antimicrobial-pathogen combinations that have been examined, but these resistance rates differ markedly within and between countries (53). The EARS-Net collects data on resistance from invasive bacterial infections and its report shows general Europe-wide increase of antimicrobial resistance in the Gram-negative pathogens (54). Microorganisms producing extended spectrum beta-lactamase (ESBL) and carbapenemases have increased their prevalence in Europe, and in some areas are "crossing the border" from hospital settings to the community (55). Increasing percentages of carbapenem resistance in *K. pneumoniae* isolates were reported from progressively more countries in Europe between 2005 and 2010 (56). The number of countries with $\geq 1\%$ carbapenem resistance amongst invasive *K. pneumoniae* isolates increased from 2 in 2005 (Greece, 27.8%; Germany, 3.1%) to 5 in 2010 (Greece, 49.8%; Cyprus, 16.4%; Italy, 12.5%; Hungary, 5.9%; Portugal, 2.2%) (56). In 2011 15% of *P. aeruginosa* isolates were reported as resistant to at least three antimicrobial classes (57). According to the multicentre surveillance studies the proportion of imipenem resistant *A. baumannii* strains is reported to be as high as 85% in bloodstream isolates from ICU patients in Greece and 48% in clinical isolates from hospitalized patients in Spain and Turkey (58).

Resistance of Gram-negatives has also increased in Estonia, e.g., resistance of invasive *K. pneumoniae* to 3rd generation cephalosporins increased from 8.1% in 2005 to 23.3% in 2013 (54). Carbapenem resistance of *K. pneumoniae* is still relatively low (5% in 2012) in Estonia, however significant inter-hospital variation occurs (59). Since November 2014 few sporadic carbapenemase positive *Enterobacteriaceae* strains have been detected (data from synlab Eesti, personal communication) suggesting possibility of other resistance mechanisms. In the surveillance study of microbial resistance of European ICUs, 13.7% of *P. aeruginosa* strains were resistant to imipenem in Estonia (60).

Among Gram-positive microorganisms the percentage of *S. aureus* isolates reported as methicillin-resistant (MRSA) is now stabilising or decreasing in most European countries including Estonia where the rate was 3.5% in 2013. Still, the percentage of MRSA is above 25% in several countries, mainly in southern and eastern Europe.(54)

Similar to the adult setting, the emergence and dissemination of antimicrobial resistant organisms is a crucial concern in pediatric population. Data collected from 17 European hospitals in eight countries showed incidence of MRSA 18% and major resistance problems with ESBL-producing *Enterobacteriaceae* (26). According to the Antibiotic Resistance and Prescribing in European Children (ARPEC) project (focussing on blood culture isolates) MRSA accounted for 16% of all invasive *S. aureus* isolates (61). Similarly to adults the incidence was the highest in southern (24%) and the lowest in northern parts of Europe (4%) (62). Despite the rising relevance of multi drug-resistant Gram-

negative infections in adults only a few studies have evaluated this problem in pediatric population (62). ARPEC project observed that 13 % of invasive *E. coli* and 33% of *K. pneumoniae* strains were resistant to the third generation cephalosporins suggesting for ESBL production (61). In the ARPEC study carbapenem-resistance was low – <1% of *E. coli* and 7% of *K. pneumoniae* isolates were resistant to carbapenem (61).

Patients who develop infections due to antimicrobial-resistant organisms have significantly higher rates of morbidity and mortality, longer hospitalizations, and greater hospital costs (40). Because of the scarce antibiotic pipeline, the most important tools against the spread of antibiotic resistant organisms are intensified infection control, surveillance, and antimicrobial stewardship (63).

2.1.7. Prevention strategies

Every HAI has its specific prevention methods based on the risk factors. During the last decade major progress has been made in preventing specific types of HAIs (35). In a systematic review the authors estimated that as many as 65% to 70% of CLABSI and UTIs and 55% of VAPs and SSIs may be avoidable with current evidence based interventions (35, 64). Landrigan *et al.* estimated that more than 75% of identified HAIs were preventable in their retrospective medical record review study conducted at 10 hospitals (65).

HAI prevention is a very complex matter and a comprehensive approach to this includes elements, such as surveillance, benchmarking, recommendations and interventions, implementation, compliance, feedback, and education.

Surveillance is defined as “the ongoing, systematic collection, analysis, and interpretation of health data essential to the planning, implementation, and evaluation of public health practice, closely integrated with timely dissemination of these data to those who need to know” (66). At first an efficient surveillance program must be in place, by which the magnitude of the infection problem can be accurately examined in order to set (realistic) objectives and organize outcome monitoring (67).

The term benchmarking in its modern sense marks the process of making comparisons between organizations with the aim to identify and implement best practice and improve performance. Indicators that can be used in a benchmarking exercise might refer to outcomes, processes (e.g., degree of adherence to hand-hygiene procedures), or structures (e.g., existence or absence of an infection-control committee). For prevention of HAIs the outcome measures such as infection rates have been emphasized traditionally. (68)

Intervention(s) must be carefully chosen with respect of the objectives defined and the available scientific evidence and must be balanced with common sense (67). The US Institute for Healthcare Improvement recommendations for reducing HAIs include to implement “care bundles”. The definition of a bundle is “a small, straightforward set of evidence-based practices – generally three to five – that, when performed collectively and reliably, have been proven to im-

prove patient outcomes” (69). By combining the elements into a single compound process, the potential for them all to be performed is increased. Therefore, the principle of an all-or-none measure of the bundle is central to its success. Although care bundles have been criticised (especially VAP bundles), these are a popular topic and their effects have been evaluated in several studies.(70)

The main challenge is to ensure implementation of and compliance with the evidence-based recommendations in practice. For example, hand hygiene is considered the simplest and most effective measure to prevent cross-transmission of microorganisms (31). Unfortunately, healthcare workers appear to have difficulties in performing hand hygiene procedures and compliance below 50% has been repeatedly reported (31). There are many barriers that may undermine the implementation of clinical recommendations, such as lack of awareness and familiarity with guidelines, staff attitudes and lack of agreement with the guideline (71). Convincing hospital personnel to adopt recommended preventive practices is one of the most difficult tasks of an infection control program. Using information on one’s own hospital to influence personnel is one of the most effective means to address a problem and apply the recommended techniques to prevent HAIs.(66) Adequate and systematic reporting (feedback) and careful supervision of the process increases adherence rates with recommendations (67, 72). Educational support might be needed to optimise success rates of the quality improvement initiative before and during the implementation. In order to understand the rational of the intervention, proper information and instruction are necessary to achieve acceptable compliance rates.(67) Recently published systematic review concluded that audit and feedback generally leads to small but potentially important improvements in professional practice (73). The effectiveness of feedback may be increased in several ways. It is more effective when baseline performance is low, the source is a supervisor or colleague, it is provided more than once, delivered in both verbal and written formats, and it includes both explicit targets and an action plan (73). The German national nosocomial infection surveillance system has demonstrated a reduction of HAIs due to ongoing surveillance activities and appropriate feedback twice a year to the users in combination with reference data for HAI (74). All departments that achieved a reduction in infection rates were asked for possible explanations of this phenomenon. After they became aware of being in an outlier position compared to reference data, they started to reinforce existing guidelines and to implement new measures for HAI prevention (75).

In addition, sufficient staff at unit level is a prerequisite for maintaining an acceptable standard of care (76).

In conclusion, the prevention of HAIs will result in increased safety of patients and quality care (34).

2.2. Nosocomial bloodstream infections (adults, children)

The frequency of BSI, their epidemiology, and the microorganisms have changed in parallel with the development of medical care, particularly with the emergence of an increasingly ill and immunocompromised population of hospitalized patients (77).

2.2.1. Definition and classification of nosocomial bloodstream infection

The terms bacteremia/fungemia and BSI are frequently used interchangeably and generally refer to the growth of a microorganism from a blood culture obtained from a patient with clinical signs of infection and where contamination has been ruled out (78).

In the last decade, as a result of the development of ambulatory alternatives to hospitalized healthcare, a new classification of BSIs as community-acquired, healthcare-associated and nosocomial has been proposed (79). The term “nosocomial BSI” encompasses a narrower spectrum (21). It is typically defined as the demonstration of a recognized pathogen in the bloodstream of a patient who has been hospitalized for more than 48 hours. The term “laboratory-confirmed BSI” is used in case of a positive blood culture (19).

BSIs are often classified as primary (no focus) or secondary when associated with clinical or microbiological confirmation of infection at a defined body site (e.g., urinary tract, surgical site, etc.). BSIs stemming from intravascular catheters are classified as primary infections (80). If the central line (CL) is the most likely source of the BSI, the definition is CLABSI (81).

ECDC and US CDC definitions for BSI are similar and do not compromise comparability of the results (7).

2.2.1. Incidence of nosocomial bloodstream infections

Based on the population-based studies 113 000–134 000 episodes of nosocomial BSI have been estimated to occur in North-America and over 240 000 episodes in Europe per year (82).

On the basis of detailed longitudinal data from 14 hospitals in 3 continents between 1998 and 2007, Ammerlaan *et al.* demonstrated that incidence density of nosocomial BSIs increased in 12 hospitals, decreased in one hospital, and did not change significantly in another one, with the average incidence density of nosocomial BSIs per hospital ranging from 0.6 to 1.9 per 1000 patient-days (83).

Hospital-wide multicentre surveillance data on nosocomial BSI in Europe have been reported from several countries, where the mean incidence densities were 0.6 (England), 0.7 (Belgium) and 0.8 (Finland) per 1000 patient-days and incidence was 8.4 per 1000 admissions in Spain (79, 84–86).

Incidence of nosocomial BSI varies widely among different departments being the highest in ICUs. Studies conducted in medical and surgical ICUs in high-income countries typically report cumulative incidence for ICU-acquired BSI of approximately 5% (39). However, hospital-wide studies reveal that up to 51% of all nosocomial BSIs are acquired in the ICUs (85, 87, 88). In 2011 14 countries reported data from 918 hospitals and 1088 ICUs to ECDC. On average, nosocomial BSI occurred in 3.0% of patients staying more than two days in the ICU with an average incidence density of 3.5 BSI episodes per 1000 patient-days. Of those, 37% were catheter-related, 35% were secondary to another infection, and 28% were of unknown origin.(57) Although CLABSI rates obtained through surveillance programs have decreased in recent years, it is among the most common HAIs. The US National Healthcare Safety Network (NHSN) has reported the decrease of CLABSI incidence density steadily over the past 20 years from 8.1–11 per 1000 CL-days in 1990 to 1.3 per 1000 CL-days in 2010 (89, 90). The rate of CLABSI is greater in developing countries. According to the International Nosocomial Infection Control Consortium network data the overall rate of CLABSI per 1000 CL-days was 7.6 (30).

Among pediatric population nosocomial BSIs are more frequent in the very young, with one-half occurring in children <1 years of age (91). Moreover, most of these infections occur in critically ill children representing significant majority of HAIs in NICU and PICU (92, 93). In the study performed in London tertiary hospital nosocomial BSI incidence was almost 12-fold higher in the NICU compared to the pediatric wards (5.8 vs 0.5 per 100 discharges, respectively) (94). Nosocomial BSI incidence in hospitalized neonates range from 10% for all neonates to 50% in extremely preterm infants (50). Although more heterogeneous PICU population has underlying disease processes distinct from those in NICU, children are exposed to nosocomial BSI as well (25). Still, the type of PICU (e.g., surgical versus medical, referral centre or not) as well as the patients' characteristics may account for differences in nosocomial BSI incidence (95). Table 3 shows studies providing cumulative incidence of nosocomial BSI (per 100 patients) and the incidence density of nosocomial BSI (per 1000 patient-days) and CLABSI (per 1000 CL-days) in NICU and PICU.

Similarly to adults, CLABSIs are among the most common HAIs in NICU and PICU. The HAI surveillance study in the USA estimated CLABSI prevalence at 2.4% in participating NICUs (24). The CLABSI incidence density among neonatal setting varies in different countries from 2.3 in the USA to 12.5 per 1000 CL-days in Italy (96, 97). The risk of developing CLABSI in PICU is may be higher than that seen in adult ICU (96). The NHSN data revealed 1.4 and 0.9 CLABSI per 1000 CL-days in PICU and medical-surgical ICU of adults, respectively (97).

Table 3. Studies using original or modified CDC definitions and reporting both cumulative incidence of nosocomial BSI and incidence density of nosocomial BSI and CLABSI in NICU and PICU.

Country, year	Type of unit	Age-range	Percentage of neonates with very low birth weight	Cumulative incidence (per 100 patients, %)	Nosocomial BSI incidence density (per 1000 patient-days)	CLABSI incidence density (per 1000 CL days)	Ref.
Studies performed in NICU							
USA 1994–1996	NICU Level III	neonates	100%	19.1	4.8	13.7	Brodie (98)
The Netherlands 1998–2000	NICU Level III	neonates	NR	17.9 ^a	14.9 ^a	21.8	van der Zwet (99)
Germany 2003	NICU Level III	neonates	100%	12.3	3.3	14.5	Geffers (100)
Italy 2003–2006	NICU	neonates	24.9%	6.3	2.8	12.5 ^b	Orsi (101)
Saudi Arabia 2006–2007	NICU Level II/III	neonates	32.0%	12.1	6.2	9.8	Balkhy (102)
Brazil 2006–2009	NICU Level III	neonates	40.9%	14.0	14.0	17.3	Brito (103)
Greece 2009–2010	NICU	neonates	NR	4.3	3.3	6.5	Dritsakou (104)
Studies performed in PICU							
Tunisia 2004–2005	PICU Level III	0–15 years (neonates 70%)	NR	6.3	7.0	14.8	Jaballah (105)
Peru 2006–2007	PICU	0–18 years median age 19 month	NR	7.0	6.3	13.8	Becerra (106)
India 2007–2009	PICU	0–more than 6 years	10% neonates	9.6	9.1	8.3	Gupta (107)

^a includes cases with clinical sepsis (blood culture is negative); ^b calculated per 1000 umbilical-catheter days; ^c includes only primary BSI

2.2.2. Risk factors for nosocomial bloodstream infections

Identification of risk factors associated with nosocomial BSI is essential to implement intervention programs. It has been demonstrated earlier that several intrinsic factors such as older age and patients with a wide range of comorbidities like immune suppression, diabetes, congestive heart failure, chronic liver disease, peripheral vascular diseases, renal diseases, coronary heart diseases, and cancer may influence the risk for acquiring nosocomial BSI in adults (39, 108–116). Red blood cell transfusion and the use of total parenteral nutrition (particularly due to yeasts) has been associated with an increased risk for ICU-acquired BSI (117, 118). The presence of hypothermia has been demonstrated as an important risk factor for the development of ICU-acquired BSI and pneumonia (119). Although the use of invasive devices, such as CLs and arterial catheters, allows for the provision of life-saving therapies and other important medical care, these devices also introduce risks of both infectious and noninfectious complications (40). Because most device-associated BSIs have been attributed to CLs, arterial catheterization may be an under-recognized source (39, 120–122). In recent systematic review the rate seen in the systematically cultured arterial catheters (1.6 BSIs per 1000 arterial catheter days) was similar to what has been reported for BSIs associated with short-term CLs (122).

In pediatric population the birth weight and gestational age are the most important risk factors of nosocomial BSI (93). In a cohort of infants admitted to 250 NICUs in the US, there were 374 infections for every 1000 admissions for infants <750 g birth weight and only 7 infections per 1000 admissions in infants >2500 g birth weight (123). In a recent study, 36% of 9575 extremely low-gestational-age infants (22 to 28 weeks) developed nosocomial BSI (124). Furthermore, the lower the birth weight or gestational age, the more invasive technology is used (42). Perlman *et al.* analyzed a large cohort of 2935 of neonates and found that significantly more babies with nosocomial BSI weighed < 1000 g as compared with neonates who did not develop nosocomial BSI (50.7% and 8.1%, respectively) and had a CL (88.8% vs 34.8%, respectively) (125). Both adults and children with CL share common risk factors for CLABSI such as underlying disease, length of ICU stay prior to CL insertion, prolonged indwelling time of CL (from more than 6 days up to more than 15 days), number of CL lumens, exchange of CL over a guide wire, insertion site, total parenteral nutrition, receipt of blood transfusion, presence of gastrostomy tube and maintenance practices (126–132).

2.2.3. Spectrum of pathogens causing nosocomial bloodstream infections

The microbial profile of nosocomial BSI has changed considerably over the past several decades in response to changes in patient population, antibiotic use, more intensive medical care and prevention methods (80).

In the two largest hospital-wide multicentre studies of nosocomial BSI in adults and children performed between 1995–2007 in the Americas and Europe, Gram-positive bacteria caused 44%–65%, Gram-negative organisms 25%–37%, anaerobes 3% and fungi 5%–10% of the infections (83, 87). In SCOPE project CoNS and *S. aureus* were the most commonly isolated organisms both in the ICU and the non-ICU settings, followed by *Candida* spp. and *Enterococcus* spp. (87). *P. aeruginosa* and *E. coli* were the fifth most frequent isolates in ICU and non-ICU settings, respectively (87). Hospital-wide surveillance data from 14 hospitals not including possible contaminants like CoNS revealed *Enterobacteriaceae* (22.6%), *S. aureus* (11.4%) and enterococci (8.0%) as the most frequent pathogens (83). Table 4 displays the distribution of organisms from multicentre studies investigating the epidemiology of nosocomial BSIs. The most important change in the epidemiology of BSI in recent years is the emergence of highly resistant organisms, particularly with extensively resistant Gram-negative bacteria including *P. aeruginosa*, *A. baumannii*, and *Enterobacteriaceae* (39).

During the past two decades, the incidence of candidemia has been increased in North American and European studies (133–135). A shift towards more frequent isolation of non-*albicans* *Candida* species with reduced susceptibility to azole antifungal agents has been a global concern (136).

The profile of pathogens associated with CLABSI has also changed considerably during the past decade. A summary of CLABSIs reported by NHSN found that *S. aureus* CLABSI incidence density rate has fallen below those of *Candida* spp., enterococci, and Gram-negative bacteria among adults (89). These changes probably reflect the success of CLABSI prevention measures (89). Still, the most common pathogens associated with CLABSI both in children and adults are CoNS (137). On the other hand, as CoNS are abundant colonizers of the skin, they frequently contaminate blood culture samples, leading to false positive results (138). Contaminated blood cultures can have a deleterious effect on patient care; they may lead to longer hospital stays, unnecessary antibiotic therapy, needless removal of CLs, and redundant laboratory testing (138). In several studies among adults and children the contamination rate has been decreased (from 3.7%–6.7% during the preintervention period to 1.6%–2.3% during the postintervention period) by using education and protocols to standardize the process of obtaining a blood culture specimen (138–140). The use of phlebotomy teams has found to be effective practices for reducing blood culture contamination rates (141).

Table 4. Most common causative pathogens (%) of nosocomial BSI reported in hospital-wide multicentre surveillance studies.

Study	Wisplinghoff (87)	Ronveaux (84)	Lyytikäinen (85)	Valles (142)	Lenz (22)	Son (143)	Ammerlaan (83)	Marra (88)
Country	USA	Belgium	Finland	Spain	Canada ^a	Korea	Nine countries ^b	Brazil
Year	1995–2002	1992–1996	1999–2000	2003–2004	2000–2007	2006–2007	1998–2007	2007–2010
Pathogen (total, n)	20978	15410	1621	295	2350	558	36679	2447
CoNS	31.3	22.0	30.9	16.6	10.3	15.1	NR	13.8
<i>S. aureus</i>	20.2	14.1	10.5	10.5	25.8	15.2	11.4	15.4
<i>Enterococcus</i> spp.	9.4	5.2	6.2	NR	4.9	10.8	8.0	4.5
<i>E. coli</i>	5.6	13.5	11.2	20.7	14.5	14.9	NR	NR
<i>Klebsiella</i> spp.	4.8	5.4	5.1	3.1	5.7	13.3	NR	13.2
Other <i>Enterobacteriaceae</i>	5.6	15.1	3.3	NR	NR	9.7	22.6	11.2
<i>P. aeruginosa</i>	4.3	5.0	5.0	9.2	4.5	6.5	2.0	8.9
<i>A. baumannii</i>	1.3	2.7	NR ^a	NR	NR	4.8	3.3	12.5
<i>Candida</i> spp.	4.6	5.6	3.8	3.7	NR	2.3	4.9	5.6

NR, not reported; ^a only adults; ^b the Netherlands, Norway, Sweden, Germany, Switzerland, United Kingdom, Republic of Ireland, the USA, Brazil

2.2.4. Outcome of nosocomial bloodstream infections

The overall case-fatality rate of nosocomial BSIs varies in published hospital-wide surveillance reports from 12 to 32% (82). In the Eurobact cohort study that involved 1156 patients with nosocomial BSI in 165 ICUs from 24 countries, the 28-day BSI mortality was 36% (116).

Mortality associated with nosocomial BSI is multifactorial. The final outcome is influenced by the source of infection, etiology, age, underlying disease, acute illness, and appropriateness of antimicrobial treatment. Therefore, estimates of mortality attributable to nosocomial BSI may differ largely according to the presence or absence of risk factors in distinct patient populations (144). For example, whereas nosocomial BSI has estimated attributable mortality 3% in pediatric patients, the estimate is 11% among neonates with VLBW (50). In addition to high mortality, neonatal BSI is associated with adverse neurodevelopmental outcome (145). In adult population, the attributable mortality to nosocomial BSI varies in different studies accounting for 12% in neutropenic (146), 16% in older (147), 25–35% in ICU patients (114, 148). The Charlson comorbidity index (CCI), which is based on the International Classification of Diseases (ICD)-10 codes, has been well validated for predicting mortality in patients with bacteremia (149). The CCI attributes a score varying from 0 to 6 to 17 diseases that have been shown to be associated with higher mortality (149). A total score is calculated from the sum of the weighted scores. This score is an indicator of disease burden and a strong estimator of mortality (150).

The microorganisms responsible for nosocomial BSI possess different virulence factors that may have direct impact on prognosis (151). It may be complicated to demonstrate a direct relationship between species and prognosis in ICUs independent of predisposition characteristics, inflammatory response, and organ dysfunction (39). However, in a large multicentre ICU study the adjusted OR for hospital death of ICU-acquired BSI compared to matched patients without BSI was minimal and nonsignificant for CoNS, 2 for other Gram-positive cocci, 6 for Gram-negative bacilli, and 9 for *Candida* spp. (114). Many studies have found that bacterial resistance decreased the chance of early adequate therapy contributing to the mortality increase (116, 152). In a recent review BSI caused by ESBL or carbapenem-resistant *K. pneumoniae* and delay in administration of appropriate therapy were among the most common risk factors for mortality in patients with *K. pneumoniae* BSI, while infection source control and early appropriate antimicrobial treatment were associated with increased survival (153). The abdominal and pulmonary sources of infections are usually contributing to the poorer outcome, whereas CLABSIs have better prognosis (39, 113, 114). However, important consequences of CLABSI may include extended hospital stay (median attributable length of stay from 7 to 18 days), interruption of chemotherapy or other treatment, catheter removal, intravascular thrombosis and endocarditis (154, 155). Furthermore, BSI including CLABSI is associated with increased hospital costs (155, 156).

In general, among HAIs nosocomial BSI carries the highest mortality, it is associated with increased short- and long term costs and neonates represent the age-group at highest risk for poor outcome.

2.2.5. Prevention of nosocomial bloodstream infections

The prevention of nosocomial BSI requires prevention of CLABSI and other sites of infection (pneumonia, UTI, SSI etc) as sources for secondary bacteremia (80). During the last decade much effort has been dedicated to prevent CLABSI – the most common BSI in acute care setting (157). Initial efforts focused on evidence based practices at the time of CL insertion. Subsequent studies have evaluated novel technologies to reduce CLABSI including antibiotic or antiseptic-coated catheters, needleless devices, antiseptic dressings, and chlorhexidine body wash (158, 159). Thus, prevention efforts have broadened beyond insertion practices to include evidence-based practices for appropriate maintenance of CLs (159). Policies and protocols or ‘bundles’ dictating catheter insertion and management have been demonstrated to reduce CLABSI (157, 160). The Michigan bundle (appropriate hand hygiene, use of chlorhexidine-containing products for skin preparation, use of maximal barrier precautions during CL insertion, subclavian vein placement as the preferred site, and removing unnecessary CLs) is considered minimal practice standard today (90, 157).

Unique considerations are involved in the prevention of CLABSI in pediatric patients (29). Difficult intravenous access often requires insertion of catheters in sites that have higher infection rates. Additionally, catheters need to be maintained for prolonged time because of difficult vascular access and the need to obtain blood. Maintenance practices must be altered depending on the maturity of an infant’s skin.(29) Chlorhexidine bathing has been successfully tested in PICUs and NICUs (161, 162). However, in VLBW infants, chlorhexidine may cause chemical dermatitis or burn, and chlorhexidine-impregnated biopatches may cause pressure ulcers (29, 163, 164). Antibiotic-impregnated catheters, antibiotic and antiseptic locks have been examined in pediatric oncology patients and in children on hemodialysis (96). A systematic review failed to detect a benefit of antibiotic-based lock solutions in CLABSI reduction among those patients (165). The availability of impregnated catheters for small children is limited (96).

The CLABSI prevention strategies described in adult ICUs have also been successfully tested in neonatal and pediatric ICU populations. In 2007 18 NICUs in New York State adopted common CL insertion and CL maintenance practices, followed by a 67% statewide decline in CLABSI rates (6.4 versus 2.1 per 1000 CL-days) (166). A large prospective surveillance study including nine PICUs and 1986 patients in developing countries compared CLABSI rates before and after implementation of an infection control program, which included education, evidence based practices, surveillance, and feedback of data to pa-

tient care units. Although there were significantly more CL-days in the post-implementation group, the CLABSI rate was reduced by 52% (167).

In addition, the importance of adequate staffing in ICUs and its relationship to CLABSIs has been reported (168–170). The structured training of medical trainees can lower risk for CLABSI (171).

For years, almost all CLABSI surveillance efforts and prevention studies have been limited to the ICU setting, but one-third or more of all CL-days may occur outside of the ICU (172). CLs are also used in patients who primarily receive their care as outpatients, including those requiring hemodialysis or chemotherapy, and receiving parenteral nutrition (173). Recently, the need for strategies for preventing CLABSI outside the ICU has been emphasized (131). In the Spanish non-ICU study where the intervention consisted of: 1) evidence-based bundle of practices relating to catheter insertion and maintenance; 2) a training program for healthcare workers; 3) four point-prevalence surveys to track the status of the catheters; and 4) feedback reports to the staff involved, the incidence density of CLABSI significantly decreased from 0.14 to 0.10 per 1000 patient-day (174). Infection prevention measures targeting the post-insertion time of CLs and maintenance practice are more likely to be successful in non-ICU settings (175).

2.3. Surgical site infections

2.3.1. Definition and classification of surgical site infection

The CDC term for infections associated with surgical procedures was changed from surgical wound infection to SSI in 1992 (176). SSIs are classified as being either incisional or organ/space. Incisional SSIs are further divided into those involving only skin and subcutaneous tissue (superficial incisional SSI) and those involving deeper soft tissues of the incision (deep incisional SSI). Organ/space SSIs involve any part of the anatomy (e.g., organ or space) other than incised body wall layers, that was opened or manipulated during an operation.(14) Diagnosis is based on signs and symptoms, hence SSIs cannot be reliably identified from laboratory data alone (177). Detailed criteria for these definitions have been described in Table 10.

SSI rates vary according to co-morbidities and to the contamination class and conditions of the surgical procedure. The need for adjustment has been demonstrated and most surveillance networks use the NHSN (previously National Nosocomial Infections Surveillance [NNIS]) System index for risk stratification (178). The NHSN System risk index is operation-specific and applied to prospectively collected surveillance data. The index comprises 3 dichotomous variables: American Society of Anesthesiologists (ASA) score (3, 4, or 5), wound classification (contaminated or dirty), and procedure duration in minutes (>75th percentile). Each risk factor represents 1 point; thus, the NHSN SSI risk index ranges from 0 (lowest risk) to 3 (greatest risk).(14, 20) More complex systems of risk adjustment have been recommended for some types of surgery

like CS, coronary arter bypass graft or general and vascular surgery (179–181). Development of more refined methods of case-mix adjustment of SSI is ongoing by the NHSN (20). However, any form of risk index stratification is dependent on data being available for all variables and practical problems emerge when incomplete data is captured as part of a surveillance program (182).

2.3.2. Incidence of surgical site infections following cesarean section

CS is the most common major surgical procedure performed on women. Despite the World Health Organization's estimate that CS rates should not be >15%, in the developed world, CS rates are already above 20%. The CS rate increased by 50% in the USA between 1996 and 2006, comprising 31% of births or 1.3 million procedures annually, which could reach 50% (or two million CSs each year) by 2020.(183) The proportion of CS births in England has risen substantially over the past 30 years from 9% in 1980 to 25% in 2009/10 (184). In Estonia the proportion has increased from 6.4% in 1992 to 19.7% in 2013 (185).

A number of sources exist for postoperative infectious morbidity following CS such as UTI, pneumonia, mastitis, septic pelvic thrombophlebitis, but SSI (including both incisional infection and endometritis) is the leading cause (179). Among hospitals reporting to ECDC and NHSN, the rate of SSI after CS was 2.8% to 5.5% and 1.46% to 3.82% depending on the risk index (0 to 3), respectively (186). These rates are mostly reported for women during their inpatient stay. The global trend towards reducing length of hospital stay post-surgery means that SSI will increasingly occur after hospital discharge (15). Postdischarge surveillance has been described as a possibility to assess SSI, which were missed by in-hospital surveillance systems and to obtain accurate rates of SSI. Therefore, even higher rates have been calculated in single observation studies where postdischarge survey has been used, ranging from 4.9% in Ireland to 23.5% in Brazil (Table 5) (187). However, the best way to conduct postdischarge surveillance is still a matter of dispute according to the literature.

Table 5. SSI rates following CS in studies with postdischarge surveillance and using CDC definitions (single and multicenter studies).

Country year	Number of procedures	Overall SSI rate (%)	In-hospital SSI rate (%)	Percentage of SSIs detected after initial inpatient stay (%)	Ref.
Multicenter studies					
England 2009	4107	9.8	0.5	94.8	(188)
Denmark 2007–2008	1513	7.1	3.1	56.5	(189)
Norway 2005–2007	3900	8.0	1.2	85.6	(190)
England 2003–2005	5563	8.8	1.4	84.0	(191)
Single center studies					
Ireland 2010	710	16.1	1.4	90.4	(192)
2011	824	4.9	0.8	82.5	
Brazil 2008–2009	187	23.5	1.1	95.5	(187)
Norway 2003	326	8.9	1.8	79.3	(193)
Scotland 2002–2003	715	11.2	3.1	72.5	(194)
Australia 1999	247	17.0	2.8	83.3	(195)
US 1996–1998	765	7.7	5.0	35.6	(196)

2.3.3. Risk factors for surgical site infection following cesarean section

The single most important risk factor for postpartum maternal infection is delivery by CS (197). Maternal morbidity related to infections has been shown to be 5-fold to 20-fold higher after CS compared to vaginal delivery, though this varies according to definition, classification and duration of observation (183, 198).

Various patient- and procedure-related factors affect infection rates in different settings (Table 6).

2.3.3.1. Patient-related factors

Obesity as a risk of postcesarean SSI has been known for years. Tran *et al.* identified obesity as an independent risk factor for SSI, with the odds ratio increasing 2.0 for every 5 unit increment in body mass index (BMI) (95% CI, 1.3–3.0) (199). Gong *et al.* found that obesity had an OR of 4.5 (95% CI, 1.5–12.9) (200). Possible biological explanations for this association include the relative avascularity of adipose tissue, the increase in wound area, and poor penetration of prophylactic antibiotics in adipose tissue (201). Higher BMI has also been shown to be associated with lower diet quality during pregnancy. A variety of micronutrients play critical roles in immune responses, so it is plausible that micronutrient deficiencies associated with poor diet could be associated with increased risk of endometritis in women with low socioeconomic status (202).

The increased risk of infection following a CS in hypertensive women may be explained by the chronic alteration in peripheral blood supply as a result of increased vascular resistance (203).

Younger age has been reported to be associated with an increased risk of SSI after CS in several studies. Olsen *et al.* found that younger women had significantly fewer prenatal visits than older women and therefore probably less opportunity for diagnostic testing, for example for sexually transmitted infections (202). Remote infection can increase the inoculum of microorganisms contaminating the surgical site (199).

2.3.3.2. Procedure-related factors

An obstetric-related risk factor is the length of time that the membranes are ruptured prior to CS (194). Prolonged rupture of membranes increases the likelihood of an infection ascending from vagina into uterine cavity. Chorioamnionitis is closely related to prolonged rupture of membranes and is a risk factor for SSI (199).

Excessive intraoperative blood loss is usually associated with poor control of bleeding, increased tissue damage from prolonged retraction and manipulation, and more sutures (199). Sutures may promote surgical site contamination (199). The wound closure and suturing technique is a matter of personal choice, each surgeon developing a preference for one method over another (194). Some studies, including recently published randomized controlled clinical trial, have identified a higher risk of SSI associated with closure using staples (194, 201, 204).

Absence of the antibiotic prophylaxis is the risk factor for SSI following CS (196). Perioperative antibiotic prophylaxis (PAP) for women undergoing CS has been proven to be beneficial in decreasing postcesarean infectious morbidity both in women at high-risk (in labour after membrane rupture), or low-risk (non-labouring with intact membranes) (183). A single dose perioperative of antibiotics is as effective as multiple doses, and the routine use of prophylactic

antibiotics reduces the risk of infection by more than 50% (183). This will be discussed in detail under “Prevention of SSI following CS.”

Table 6. Risk factors associated with surgical site infections following cesarean section.

Patient-related risk factors	References	Procedure-related risk factors	References
Younger age	(184, 191, 202)	Absence of antibiotic prophylaxis	(196, 200)
BMI category > 24 or obesity	(184, 191, 193, 194, 200, 201, 205, 206)	Blood loss	(191, 199)
ASA score ≥ 3	(199)	Emergency CS	(191, 195, 198, 207)
Diabetes	(207)	Wound closure with staples	(191, 194, 201, 204)
Hypertension	(187, 207)	Surgery time (longer duration of operation)	(193, 196, 200, 206)
Premature rupture of membranes	(196, 200, 207)	Development of subcutaneous hematoma after the procedure	(201)
< 7 prenatal consultations	(196)	Operation performed by the university teaching service	(201)
Preoperative remote infection	(199, 208)	Staff and Assistant Specialist grade surgeon	(184)
Chorioamnionitis	(199)	Absence of suture closure of subcutaneous tissue thickness of 2 cm	(209)
Preeclampsia	(199)	Amniotomy	(202)
Nulliparity	(199)	Manual removal of the placenta	(210)

2.3.4. Spectrum of pathogens causing surgical site infections following cesarean section

Pathogens that cause SSI may derive from the patient’s own microbial flora on the skin and in the body, or from the skin or mucous membranes of operating personnel, or from the operating room environment (including air), and less frequently from the instruments and tools used during the procedure (182). In the multicentre cohort study performed in England causative microorganisms

were recorded for 39.8% of the SSI following CS (157/394). Of these infections 24.2% were reported to be polymicrobial. The most commonly reported pathogen was *S. aureus* (40.4%) of which 17.1% were methicillin-resistant. Other pathogens included anaerobic cocci (23.2%), *Enterobacteriaceae* (13.3%) and streptococci (7.4%).(184) The most common pathogens causing obstetric/gynecologic surgery SSIs reported to the NHSN during the years 2009–2010 were *S. aureus* (19.7%), enterococci (13.6%), *E. coli* (12.9%), and CoNS (8.9%) (211). In Germany the most frequent pathogens causing SSI following CS were *S. aureus* (129 infections), enterococci (45), streptococci (42) and *E. coli* (29). In 60% of all SSIs no pathogen was reported (75). In summary, the reported causative organisms of postcesarean SSI are usually common skin or female genital tract microbiota.

2.3.5. Outcome of surgical site infections following cesarean section

Although most SSIs following CS are superficial, this represents a substantial burden to the healthcare system given the high number of women undergoing this type of surgery. Superficial SSIs are likely to result in pain and discomfort, require antimicrobial therapy and may progress to affect deeper tissues. The more severe infections involving deeper tissue or reproductive organs (e.g., endometritis) necessitate extended hospital stays or readmission to hospital.(184) The median postcesarean length of hospital stay has been 3 days in recent studies (188, 191). The crude increases in length of hospital stay (beginning with the date of CS and including length of stay during hospital readmissions that began within 30 days after CS) have been reported 2.2 days for superficial and deep SSI and 1.8 days for endometritis (212). Of the 4107 women followed up in the study in England, 0.6% (5.9% of those with SSI) were readmitted to hospital for treatment of their infection (184). In the study performed in Ireland 1.2% of 765 women with CS were readmitted due to endometritis (192).

SSI is also responsible for substantial increase in healthcare-related costs (213). In many studies attributable costs were calculated for SSI that occurred after a variety of different operations, rather than calculated for post-cesarean SSI (212). Olsen *et al.* found that the attributable costs of SSI after low transverse CS were approximately \$3500–4000 and the majority of excess costs were associated with room and board and pharmacy costs (212). In the study by Mugford *et al.* SSI added £716 and 76% of these excess costs resulted from staffing due to longer length of hospital stay in patients with infection (214).

For most pregnant women SSI is not life threatening, but on very rare occasions the development of an infection after CS can lead to devastating outcomes as documented in the 2006–2008 Confidential Enquiry into Maternal Deaths (184). A population-based case-control study performed in France revealed that the risk of postpartum maternal death was 3.6 times higher after CS than after

vaginal delivery from complications of anesthesia, puerperal infection, and venous thromboembolism (215).

Aside from short-term complications women undergoing CS, are at increased risk for a variety of long-term complications including pain, surgical adhesions (SSI may increase that risk), and infertility or subfertility. Adhesion formation contributes to the risk of complications at future deliveries such as uterine rupture, abnormal placentation and increased risk of hemorrhage leading to hysterectomy. All of these potential short and long-term maternal and fetal complications must be considered by physicians and patients when considering either elective primary or repeat CS.(216)

2.3.6. Prevention of surgical site infections following cesarean section

Approaches to the prevention and control of SSI have evolved over many years and traditionally have been classified into those interventions before surgery, during surgery and after surgery (12). General prevention methods of SSI are presented in Table 7.

Among prevention methods specific for postcesarean SSI probably the most important is administering antibiotic prophylaxis prior to incision, rather than after cord clamping (217, 218). Until recently, the practice in CS was the administration of antibiotics after cord clamping because of the concern regarding possible adverse effects on the neonate (219). Recent studies have shown a decrease in SSI following CS when antibiotics are given pre-incision. A systematic review identified that antibiotic prophylaxis administered prior to the incision decreased the overall incidence of SSI following CS. Moreover it did not increase the likelihood of neonatal infection, frequency of evaluations for neonatal sepsis, or the duration of neonatal hospitalization. The authors concluded that administration of antibiotics within 30 to 60 minutes prior to incision seems to be optimal in order to maximize tissue and blood concentrations at the surgical site. (179, 220) In hospitals in Australia and New Zealand SSI rates dropped from 10.8% in 2010 to 2.8% in 2011 with no adverse neonatal consequences, providing further evidence that antibiotic prophylaxis should be given pre-incision for CS (219). Prophylactic antibiotic regimens comparing single-dose antibiotics with extended spectrum coverage have been evaluated in randomized controlled trials that did not demonstrate improved outcomes compared with standard cephalosporin prophylaxis (218). Methods such as surgical safety checklists are a more formal way to ensure that antibiotics are administered prior to incision (221). In a Cochrane review of 5 trials (1946 women), vaginal cleansing with a povidone-iodine solution immediately before CS significantly reduced the incidence of postcesarean endometritis (7.2–3.6%; RR, 0.39; 95% CI, 0.16–0.97) (222). Doctors and midwives can also be directly responsible for other infection prevention strategies such as instructing women to not remove pubic hair before the expected date of CS and wound management education (223).

Several prevention methods are directly related to surgical technique. In recent systematic review recommendations with high levels of certainty as defined by the US Preventive Services Task Force favored cephalad-caudad blunt uterine extension, spontaneous placental removal, surgeon preference on uterine exteriorization, single-layer uterine closure when future fertility is undesired, and suture closure of the subcutaneous tissue when thickness is 2 cm or greater (218).

Although preventing all SSIs may not be feasible, guidelines of peri- and postoperative measures have been developed to minimise the risk of SSI (178). SSI surveillance is a component of these guidelines (14). Avoiding more severe infections is a priority, but monitoring superficial as well as deep infections provides a higher sensitivity with which to examine the quality of care and detect potential problems with infection prevention (184).

Table 7. Major interventions in preventing surgical site infection from UK and North American guidelines (12, 14, 225).

Preoperative phase	<ul style="list-style-type: none"> Patient showering Proper hair removal Patient and staff jewellery removal Patient and staff theatre wear Movement to and from theatre area Controlling blood glucose <i>S. aureus</i> nasal decontamination Mechanical bowel preparation (not routine) Perioperative antibiotic prophylaxis
Intraoperative phase	<ul style="list-style-type: none"> Hand hygiene Surgical attire (gowns, gloves) Antiseptic skin preparation Diathermy Patient homeostasis (oxygenation, normothermia, etc.) Operative technique Draping Wound irrigation and dressings
Postoperative phase	<ul style="list-style-type: none"> Maintaining normothermia after colorectal surgery Dressings Postoperative cleansing of surgical site Topical agents (not indicated) Antibiotic treatment and debridement for SSI Specialist wound care services

3. STUDY RATIONALE

Registration of HAI has become mandatory in EU since 2009 focussing on ICU-acquired infections and SSI. There is evidence to support the use of post-discharge SSI surveillance; however, consensus on the ideal method has yet to be met (14, 182). Some information on postdischarge methods has been collected in the ECDC surveillance of SSI since 2010, but these data have not been provided by all countries so far (16). The ECDC also requested that all member states carry out a point prevalence survey of HAIs and antimicrobial use using a standardized protocol (4). Four hospitals from Estonia (2 regionals and 2 central hospitals) participated in European point prevalence survey of HAIs and antimicrobial use in 2011. This study revealed that 5.7% of patients had at least one HAI on the day of the survey (4). Still, incidence surveys, and not only in ICU, are much better for detecting and describing related risk factors, but are more difficult to perform and more expensive (9). Hospital-wide nosocomial BSI surveillance may have some advantages compared to other HAIs (10).

The research presented in current thesis started in 2002. Before that only few studies had investigated hospital-acquired microorganisms in Estonia. Karki *et al.* compared the susceptibility patterns of *S. aureus* and *E. coli* isolated from patients with hospital-acquired and outpatient infections (18). Siiri Kõljalg defended PhD thesis in 1999 and her work concentrated on nosocomial pathogen *Acinetobacter* spp. However, no study of the epidemiology of HAI had been performed and there was no surveillance system of HAI in Estonia during this time. To fill the gaps we chose to investigate SSI following SC, one of the most frequent surgical procedure worldwide (216, 224), and nosocomial BSI as the most serious and complicated HAI (66).

4. AIMS OF THE STUDY

The general aim of the present thesis was to assess the epidemiology of HAI among adult and pediatric patients in Estonia in order to promote HAI surveillance at hospital level and to create knowledge and experience base for prevention activities in the future.

The specific aims were the following:

1. To measure the incidence and outcome of nosocomial BSI in three major hospitals.
2. To analyse most frequent potential factors predisposing patients to nosocomial BSI and to find out the risk areas (wards).
3. To identify the spectrum of pathogens causing nosocomial BSI in and to study their antimicrobial resistance.
4. To identify the incidence and risk factors associated with SSIs following CS in Tartu University Hospital.
5. To evaluate a multimethod approach to postdischarge surveillance of SSIs following CS.

5. PATIENTS AND METHODS

A summary of the patients and methods included into three studies of the thesis is presented in Table 8.

Table 8. Overview of the study subjects, designs and identified healthcare-associated infections in studies I–III.

Study	Study design and location	Time period	Study subjects	Type of HAI
I	Prospective hospital-wide surveillance in the North Estonia Medical Centre, Tartu University Hospital and East-Tallinn Central Hospital	January 1, 2004 to December 31, 2005 ^a	All acute care patients (including children) meeting surveillance criteria	Laboratory-confirmed nosocomial BSIs
II	Prospective surveillance in PICU of Tartu University Hospital	January 1, 2004 to December 31, 2008	All patients aged <19 years meeting surveillance criteria	Laboratory-confirmed ICU-acquired BSIs
III	Cross-sectional survey in Women's Clinic of Tartu University Hospital	January 1 to December 31, 2002	Patients undergoing CS (elective and emergency)	Surgical site infections

^a Nineteen months in the North Estonia Medical Centre

5.1. Setting of the studies

Two referral centers (The North Estonia Medical Centre and Tartu University Hospital) providing tertiary care for the entire Estonian population and one central hospital (East-Tallinn Central Hospital) participated in the **study I** (Table 8).

East-Tallinn Central Hospital is serving approximately a population of 200 000. The hospital provides care in different clinics (Internal Medicine, Eye, Surgery, Medical Rehabilitation, Long-Term Nursing, Diagnostic and Women's Clinic). Around 25 000 patients were hospitalized annually during the study years. In 2004 there were 588 beds including 9 in the third level ICU.

The North Estonia Medical Centre is the tertiary care referral hospital that offers medical care in all specialities except ophthalmology, pediatrics and obstetrics. Each year around 40 000 patients are admitted to the hospital serving primarily North Estonia. In 2004 there were 1236 beds including 42 in the third level ICU.

Tartu University Hospital is a referral teaching hospital with approximately 43 000 admissions annually serving primarily the population in South

and North-East Estonia (about 600 000 people including 5000 births per year, 2004 data) (226). Bone marrow and organ transplantations and congenital heart disease surgeries are performed. About 16% of all patients treated at Tartu University Hospital are children. In 2004 there were 944 beds including 43 in the third level ICU.

Study II was performed at Tartu University Hospital in PICU (level III) with nine beds having annually approximately 250 admissions of which 50–60% are neonates. In this mixed PICU the patient population ranges from ELBW neonates to adolescents comprising a wide variety of conditions including congenital malformations requiring surgical repair; pediatric emergencies including multiple trauma, near-drowning or poisonings; infectious diseases and neonatal conditions. Patients are admitted from home, transferred within the hospital (including from hematology, cardiac surgery and maternity unit) or from district hospitals. In case of suspected early onset neonatal sepsis gentamicin with ampicillin in VLBW or with penicillin G in other neonates is used. In infants and children cefotaxime with gentamicin is the preferred empiric therapy for sepsis. Fluconazole prophylaxis is administered to ELBW neonates. Risk factor based intrapartum prophylaxis with penicillin G for the prevention of perinatal group B streptococcal disease is employed.

Women's Clinic of Tartu University Hospital, the setting of **study III**, had 54-beds and there were 2092 deliveries performed in this obstetric and gynecology center in 2002. The number of total CS performed in 2002 was 310. During study period hospital policy for PAP recommended intravenous administration of 1 g of cefazolin as soon as the umbilical cord was clamped for all patients undergoing non-elective CS and for patients undergoing elective CS for rupture of membranes more than 4 hours or with bacterial vaginosis diagnosed during pregnancy.

Infection control activities were started in 2001–2002 at all three hospitals.

5.2. Subjects of the studies

Data on patients included in the studies are presented in Table 8.

All acute care patients meeting definition of nosocomial BSI were included in the hospital-wide surveillance study. The patients admitted to the departments of long-term nursing, psychiatry and tuberculosis were excluded because of the low risk of HAI in these departments.

The PICU study population consisted of all children with ICU-acquired BSI.

In the surveillance study of SSI following CS the population consisted of all women who delivered by elective and emergency CS during the study period.

5.3. Definitions used in studies

Episode of BSI – isolation of bacteria/fungi from at least one blood culture set (see Table 9) (19) or repeatedly positive cultures with phenotypically similar microorganism within a 7 days period

Nosocomial BSI – bacteremia/fungemia occurring more than 48 h after admission, or resulting from earlier hospitalization within previous 30 days

ICU-acquired BSI – bacteremia/fungemia developing after 48 h of admission to ICU

Primary BSI – bacteremia/fungemia resulting from intravenous or arterial catheter infections and bacteremia/fungemia with unknown origin

CLABSI – primary BSI developing in a patient that had a CL within the 48 hours prior to the infection onset

Secondary BSI – bacteremia/fungemia secondary to infection with the same microorganism at a distant body site or with clinical suspicion without isolation of a microorganism

Polymicrobial BSI – isolation of different species from one or more blood cultures within 48 h

Probable blood culture contaminant – skin commensals (*CoNS*, *Micrococcus* sp., *Bacillus* sp., *Propionibacterium* sp., or *Corynebacterium* sp.) that do not correspond to the BSI definitions for common skin contaminants presented in Table 9

Blood culture set – culture of blood obtained from a single venipuncture and inoculated into one or multiple bottles

Appropriate antimicrobial treatment – the patient received at least one antimicrobial agent that was active against the implicated pathogen in vitro on the day of sampling

Neonate – term and preterm baby (≤ 33 gestational weeks) up to 28 and 90 days of age, respectively

SSI – infection occurring after surgery in the part of the body where the surgery took place (see Table 10) (14)

Surgical wound classification for CS (according to the modified surgical wound classification by Tran *et al.* (199)

class I (clean) – no rupture of membranes or labor

class II (clean-contaminated) – less than 2 hours of membrane rupture without labor or labor of any length with intact membranes

class III (contaminated) – rupture of membranes greater than 2 hours

class IV (dirty) – purulent amniotic fluid

Elective CS – planned procedure and performed when scheduled

Emergency CS – all cases not classified under elective CS

Table 9. The Centers for Disease Control and Prevention definition of laboratory-confirmed primary BSI used in our study (19).

Laboratory-confirmed bloodstream infection must meet at least one of the following criteria	
Criterion 1	<p>Patient has a recognized pathogen cultured from one or more blood cultures <i>and</i> organism cultured from blood is <i>not</i> related to an infection at another site.</p>
Criterion 2	<p>Patient has at least <i>one</i> of the following signs or symptoms: fever ($>38^{\circ}\text{C}$), chills, or hypotension <i>and</i> at least <i>one</i> of the following:</p> <ol style="list-style-type: none"> Common skin contaminant (e.g., diphtheroids, <i>Bacillus</i> sp., <i>Propionibacterium</i> sp., coagulase- negative staphylococci, or micrococci) is cultured from two or more blood cultures drawn on separate occasions Common skin contaminant (e.g., diphtheroids, <i>Bacillus</i> sp., <i>Propionibacterium</i> sp., coagulase-negative staphylococci, or micrococci) is cultured from at least one blood culture from a patient with an intravascular line, and the physician institutes appropriate antimicrobial therapy <i>and</i> signs and symptoms and positive laboratory results are not related to an infection at another site
Criterion 3	<p>Patient ≤ 1 year of age has at least <i>one</i> of the following signs or symptoms: fever ($>38^{\circ}\text{C}$), hypothermia ($<37^{\circ}\text{C}$), apnea, or bradycardia <i>and</i> at least <i>one</i> of the following:</p> <ol style="list-style-type: none"> Common skin contaminant (e.g., diphtheroids, <i>Bacillus</i> sp., <i>Propionibacterium</i> sp., coagulase-negative staphylococci, or micrococci) is cultured from <i>two</i> or more blood cultures drawn on separate occasions Common skin contaminant (e.g., diphtheroids, <i>Bacillus</i> sp., <i>Propionibacterium</i> sp., coagulase-negative staphylococci, or micrococci) is cultured from at least one blood culture from a patient with an intravascular line, and physician institutes appropriate antimicrobial therapy^a <i>and</i> signs and symptoms and positive laboratory results are <i>not</i> related to an infection at another site.

^a antimicrobial therapy at least 5 days or resolution of symptoms once the device was removed

Table 10. The CDC definition of SSI (14)

A superficial SSI
Infection occurs within 30 days after the operative procedure <i>and</i> involves only skin and subcutaneous tissue of the incision <i>and</i> patient has at least <i>one</i> of the following: a. Purulent drainage from the superficial incision b. Organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision c. At least one of the following signs or symptoms of infection: pain or tenderness, localized swelling, redness, or heat, <i>and</i> superficial incision is deliberately opened by surgeon, <i>unless</i> incision is culture-negative d. Diagnosis of superficial incisional SSI by the surgeon or attending physician
Deep incisional SSI
Infection occurs within 30 days after the operative procedure and the infection appears to be related to the operative procedure <i>and</i> involves deep soft tissues (e.g., fascial and muscle layers) of the incision <i>and</i> patient has at least <i>one</i> of the following: a. Purulent drainage from the deep incision but not from the organ/space component of the surgical site b. A deep incision spontaneously dehisces or is deliberately opened by a surgeon when the patient has at least one of the following signs or symptoms: fever (>38°C) or localized pain or tenderness, <i>unless</i> incision is culture-negative c. An abscess or other evidence of infection involving the deep incision is found on direct examination, during reoperation, or by histopathologic or radiologic examination d. Diagnosis of a deep incisional SSI by a surgeon or attending physician
Organ/space SSI
Infection occurs within 30 days after the operative procedure and the infection appears to be related to the operative procedure <i>and</i> infection involves any part of the body, excluding the skin incision, fascia, or muscle layers, that is opened or manipulated during the operative procedure <i>and</i> patient has at least <i>one</i> of the following: a. Purulent drainage from a drain that is placed through a stab wound into the organ/space b. Organisms isolated from an aseptically obtained culture of fluid or tissue in the organ/space c. An abscess or other evidence of infection involving the organ/space that is found on direct examination, during reoperation, or by histopathologic or radiologic examination d. Diagnosis of an organ/space SSI by a surgeon or attending physician

5.4. Data collection

5.4.1. Data collection for nosocomial bloodstream infections

Local infection control personnel (ICP) regularly received information about positive blood cultures from microbiology laboratory. Patients were followed up by trained local ICP for clinical confirmation using information from ward personnel and medical records. ICP recorded all necessary clinical and microbiological data using a specific case-report form. All completed forms were audited. Information routinely collected included age, gender, date of admission, date of the first positive blood culture, location of the patient at the onset of nosocomial BSI (ward), isolated microorganism(s) and antimicrobial susceptibility, probable source of bacteremia/fungemia and antimicrobial therapy on the day of sampling. Comorbid clinical conditions were registered for adults from their medical records using Charlson weighted index of comorbidity on the basis of the patients' International Classification of Diseases-10 coded diagnoses (150, 227). The following predisposing clinical conditions frequently described in literature (85, 87, 91) were documented: intravascular catheter, indwelling urinary catheter, presence of neutropenia (defined as an absolute neutrophil count of <500 cells/mm³, or a count of <1000 cells/mm³ with a predicted decrease to <500 cells/mm³), chemotherapy or surgery during the previous 30 days, organ transplantation, mechanical ventilation and total parenteral nutrition. Number of patient-days and number of admissions were received from hospital administrations. The use of CLs including umbilical catheters in PICU was documented daily. Survival status was recorded one week after the onset of nosocomial BSI and at hospital discharge.

5.4.2. Data collection for surgical site infections

All patient- and surgery-related data were collected prospectively by a single investigator (resident of obstetrics and gynecology). She visited patients during their hospitalization and explained the study purpose. Demographic information, potential risk factors, and surgical indications collected from the medical records were recorded into a standardized collection form. Patient-related variables included age, nationality, parity, existing comorbidities (e.g., diabetes, preeclampsia, anemia, or chorioamnionitis), bacterial vaginosis during pregnancy, a preoperative condition assessed by ASA score, number of prenatal care visits, duration of ruptured membranes, duration of labor, preoperative stay, length of hospital stay in days, use of internal fetal monitoring, and number of vaginal examinations prior to CS at the hospital. Surgery-related variables included emergency nature of the operation, indications for CS, duration of the operation, manual removal of the placenta, volume of blood loss, and antibiotic prophylaxis. The study subjects were postoperatively monitored for temperature, SSI, wound and endocervical culture, and antibiotic treatment until discharge.

The investigators identified the infections during hospital stay or readmission or by postdischarge survey using the criteria of the CDC NNIS System (Table 10). The postdischarge survey was performed according to the modified methodology developed by Stockley *et al.* (228). Briefly, the patient received a questionnaire (Paper III, Figure) to be completed by physician (i.e., gynecologist or general practitioner) if problems developed regarding the wound or if endometritis developed after discharge. All study subjects were contacted by telephone 30 to 35 days after surgery (including those patients who had been diagnosed as having SSI during hospital stay). The patients were asked about their general health and the state of their surgical wound using a standard format based on the physician's questionnaire. If a patient's complaints indicated possible infection and the questionnaire had not been received from the physician, the investigator contacted either general practitioner or gynecologist for verbal confirmation of SSI. In case the completed questionnaire arrived and the CDC criteria were met, no further contact with the physician was established. If it was not possible to contact the patient by telephone, the outpatient medical records of those patients who were known to have returned to Tartu University Women's Clinic were reviewed.

We also evaluated the time expenditure for inpatient surveillance and telephone follow-up.

5.5. Microbiological methods

Blood cultures were obtained from patients with clinical signs of infection at the discretion of attending physician (study I and II). No specific instructions for blood culture testing (e.g., indication for culture, the timing of the culture, the volume of blood drawn for culture, the number of cultures) were provided to the participating hospitals in purpose of the study.

Blood cultures were processed using BACTEC 9000 or BACTEC 9240 (Becton Dickinson, Sparks, USA) at Tartu University Hospital and East-Tallinn Central Hospital; and BacT/ALERT 3D blood culture system (bioMerieux, Marcy l'Etoile, France) in the North Estonia Medical Centre. Bacterial isolates were identified by routine methods and verified by biochemical identification system VITEK2 Compact (since 2006 at Tartu University Hospital) or API tests (bioMerieux, Marcy l'Etoile, France). Antimicrobial susceptibility was determined in each centre by disc diffusion and/or E-tests (AB Biodisk, Solna, Sweden) according to Clinical and Laboratory Standards Institute recommendation (229, 230). Information was collected from laboratories on the total number of blood culture sets processed.

5.6. Data analysis and statistics

Data were analyzed using Stata version 8.0 and version 9.0 (Stata Corp., College Station, TX, USA) in study III and I, respectively; and SPSS version 17.0 (IBM Corp., Armonk, NY, USA) in study II. To test differences between groups Fisher's exact test or chi-square was used for categorical variables as appropriate and Student's *t* test was performed for continuous variables. All comparisons were unpaired, and all tests of significance were two-tailed. Odds ratios (ORs) with 95% CI were calculated. The binomial distribution was used to calculate 95% CI. A *p* value of .05 or less was considered to indicate statistical significance. Multiple logistic regression analysis was performed to adjust for potential confounders and to identify independent risk factors. Variables with statistically significant differences in univariate analysis were added to multiple logistic regression.

SSI incidence (crude percentage of operations resulting in a SSI), BSI incidence (number of BSI episodes per 100 admissions), BSI incidence density (number of BSI episodes per 1000 patient-days), CLABSI incidence density (number of CLABSI episodes per 1000 CL days), CL utilization ratio (number of CL days per patient-days) were calculated. As blood culture with CoNS may indicate either infection or contamination, the nosocomial BSI incidence and incidence density were also reported by excluding these microorganisms in study II. Case-fatality rate was defined as proportion of patients with nosocomial BSI who died either within 7 days (7-day case fatality) or during the hospital stay (in-hospital case-fatality) after the first positive blood culture.

5.7. Ethics

Surveillance studies of nosocomial BSI were approved by the Research Ethics Committee of the University of Tartu, Estonia. Informed consent was not considered necessary because this was an observational study – the research involved no risk to the subjects and welfare of subjects was not affected.

Surveillance study of SSI following CS was conducted as part of the infection control activities at the Tartu University Hospital (*Sihtasutuse Tartu Ülikooli Kliinikum infektsioonikontrolli teenistuse põhimäärus PKL-119, 2002* [Statutes of Infection Control Department of Tartu University Hospital PKL-119, 2002]). Information sheet (can be requested from the author) was given to the patients and contained statement that the study involved research, described the purpose and methods, the role of the participant, expected duration of the subject's participation and explanation of whom to contact for answers to pertinent questions about the research. The study was also explained verbally to the patients and their verbal consent to participate was obtained. There were no interventions conducted for study purposes. The questionnaires were stored in a secure manner.

All data were analyzed anonymously.

6. RESULTS

6.1. Incidence of healthcare-associated infections

6.1.1. Incidence of hospital-wide nosocomial bloodstream infections

A total of 174 707 admissions and 971 687 patient-days occurred in three hospitals over the study period. During the study period the overall blood culture sampling rate was 17 sets per 1000 patient-days (range, 13–21). In total, 549 episodes of nosocomial BSI were recorded among 507 patients. The overall incidence of nosocomial BSI across the three hospitals was 3.1 per 1000 admissions (range, 0.7–4.3) and the incidence density was 0.6 per 1000 patient-days (range, 0.2–0.8).

Fifty-four percent of nosocomial BSI episodes were reported in ICUs, 24% in hematology units, 11% in surgical units, 7% in internal medicine units and 4% in other units. The incidence density of nosocomial BSI per 1000 patient-days was 5.9 (range, 4.4–7.4) and 0.3 (range, 0.1–0.4) in ICU and non-ICU wards respectively. Most (92%) nosocomial BSI occurred during the hospital stay in which it was acquired, 8% was related to previous hospitalisation.

Over half of episodes (321, 58%) were primary (257 CLABSI, 64 of unknown source) while 228 (42%) were secondary. Among secondary episodes the lower respiratory tract was the most common source (32% of all secondary cases). Central venous catheter and lower respiratory tract, as sources of nosocomial BSI, were significantly more frequent among BSI acquired in ICU. As compared to ICU skin and soft tissue infections and nosocomial BSI of unknown origin were significantly more frequent in non-ICU departments (Table 11).

6.1.2. Incidence of nosocomial bloodstream infections in pediatric intensive care unit

During the study period 1363 patients were admitted to PICU including 745 (55%) neonates. Through the years 2004–2006 the blood culture sampling rate was 268 sets per 1000 patient-days. In 89% of cases only one sample was taken. In total, 126 nosocomial BSI episodes were identified in 89 patients. The overall incidence of nosocomial BSI was 9.2 per 100 admissions (95% CI, 7.8–10.9) and the incidence density 12.8 per 1000 patient-days (95% CI, 10.7–15.2). Having excluded cases caused by CoNS, the respective rates were 5.1 (95% CI, 4.0–6.4) and 7.1 (95% CI, 5.5–9.0).

Multiple nosocomial BSI episodes occurred in 26 patients of which 17 patients had two, seven patients had three and two patients had four episodes.

Primary BSI was diagnosed in 92 (73%) episodes, 67 of which were considered CL-associated. The median (IQR) duration of CL prior to CLABSI was 7 (5–13) days. The overall CLABSI incidence density for neonates was 19.3 per 1000 CL-days (95% CI, 14.7–24.9). Within birth weight groups there was a -fold variation in the incidence density of CLABSI with the highest rate (27.4

per 1000 CL-days, 95% CI, 19.0–39.0) among ELBW neonates. Among birth weight categories of 1001–1500, 1501–2500 and >2500 g, the respective incidence densities were 13.3 (95% CI, 5.8–26.1), 14.8 (95% CI, 7.1–27.1) and 15.1 (95% CI, 6.9–28.4) per 1000 CL-days. The CL utilization ratio was similar in different birth weight groups ranging from 0.41 to 0.57 (Paper II, Table II). A total of 34 (27%) episodes were defined as secondary, most frequently associated with lower respiratory tract (14 cases) or intra-abdominal infections (7 cases).

Table 11. Origin of 549 episodes of nosocomial BSI, stratified according to the clinical setting (ICU vs non-ICU wards) at East-Tallinn Central Hospital, the North Estonia Medical Centre and Tartu University Hospital in 2004–2005.

Origin	No. of nosocomial BSI episodes, (%)						<i>p</i> value
	Total n=549		Non-ICU n=253		ICU n=296		
Primary BSI							
Catheter-associated	257	(47)	96	(37.9)	161	(54.4)	0.0001
Unknown	64	(12)	47	(18.6)	17	(5.7)	<0.0001
Secondary BSI							
Lower respiratory tract	74	(13)	25	(9.9)	49	(16.6)	0.023
Skin/soft tissue	37	(7)	26	(10.3)	11	(3.7)	0.002
Surgical site	28	(5)	14	(5.5)	14	(4.7)	0.670
Urinary tract	27	(5)	14	(5.5)	13	(4.5)	0.538
Intraabdominal	26	(4)	9	(3.6)	17	(5.7)	0.229
Other	36	(7)	22	(8.7)	14	(4.7)	0.061

6.1.3. Incidence of surgical site infections and postdischarge surveillance following cesarean section

There were 310 cesarean sections performed among 2092 deliveries (14.8%; 95%CI, 13.3 to 16.4) during the study period. Three hundred five patients were enrolled in the study (4 patients refused to participate and one patient died during the operation due to a complication of underlying disease, rupture of an aortic aneurysm).

During the study period 19 SSIs were identified: 14 patients developed incisional (2 deep and 12 superficial) infections, 4 developed endometritis, and 1 developed intraabdominal abscess. The overall infection rate was 6.2% (95% CI, 3.8 to 9.6). Of the 19 SSIs identified, 11 (57.9%) were diagnosed before and

8 (42.1%) after discharge. Of the latter, 2 patients were readmitted to the hospital and 6 had SSIs detected by multi-method postdischarge surveillance.

During the postdischarge surveillance, 280 patients were contacted by telephone. Thirteen patients with SSIs were diagnosed in hospital (11 before discharge and 2 on readmission). Fifteen of 267 patients described a possible infection by telephone but only 6 cases were finally confirmed by the physician (4 with the questionnaire and 2 by personal contact). Information was obtained with chart review for 9 study subjects who could not be contacted by telephone and from whom a completed questionnaire was not received. None of them was diagnosed SSI (Figure). In this study, 16 of the 305 eligible patients were not available for any information during the postdischarge period. A combination of healthcare worker questionnaires, telephone calls, and chart reviews gave a postdischarge follow-up rate of 94.8%.

Inpatient surveillance (including collecting surveillance data and explaining the purpose of the study) took approximately 20 minutes per patient; for telephone follow-up an average of 3 to 5 minutes per patient was required.

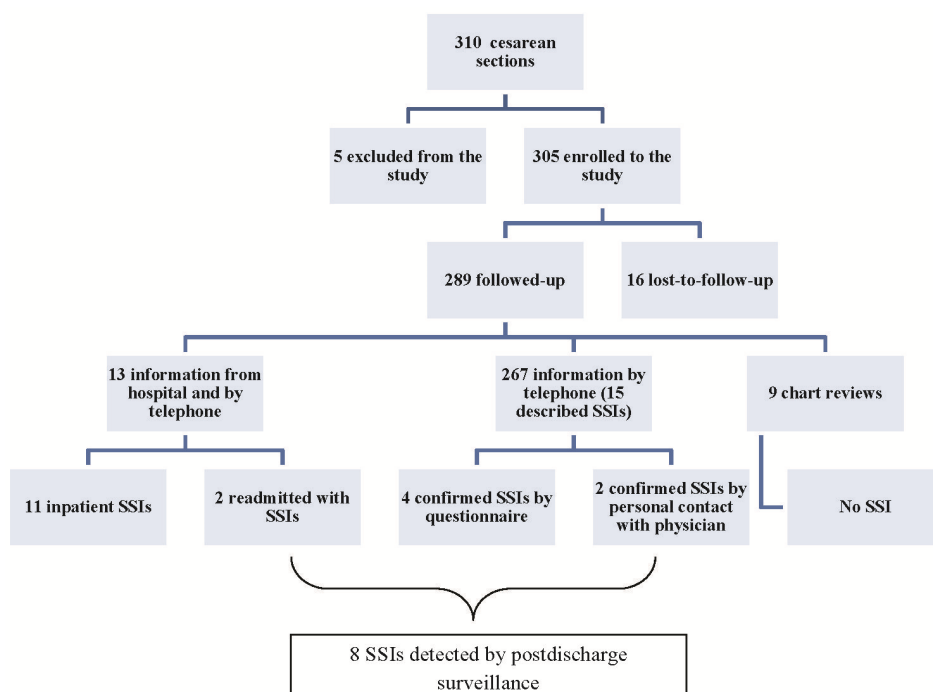


Figure. Number of patient surveyed for SSI 30 days following CS by using multi-method approach in Women’s Clinic of Tartu University Hospital in 2002.

6.2. Patient characteristics and risk factors

6.2.1. Patient characteristics and potential factors predisposing to hospital-wide nosocomial bloodstream infection

The mean (SD) age of patients with nosocomial BSI was 50 (25.5) years (range, <1–92 years). Forty-four episodes (8%) occurred in neonates (≤ 28 days of age) and 46 (10%) in pediatric patients (≤ 16 years of age). More than half (59%) of patients were male. The distribution of scores in the Charlson weighted index of comorbidity for the adult patients was 0 for 23%, 1 to 2 for 42%, 3 to 4 for 23%, and 5 or higher for 12%.

Intravascular devices were the most common potential predisposing factors: CLs were in place in 423 patients (77%) and arterial catheters in 254 (46%) patients. In total, 280 patients (51%) had two or more intravascular catheters. Other potential predisposing factors are presented in Table 12.

The median (IQR) interval between admission and nosocomial BSI was 13 days (6–22.75). The median (IQR) length of stay was 16 days (8–36) following nosocomial BSI.

6.2.2. Patient characteristics and potential factors predisposing to nosocomial bloodstream infection in pediatric intensive care unit

Nosocomial BSI episodes occurred in 74 neonates; in eight infants; and in seven patients aged 1 up to 7 years; 56% of the patients were males. The most common underlying diseases in patients with nosocomial BSI are shown in Table 13.

The majority (83%) of affected patients were neonates with 99 episodes (79% of all cases), with median (IQR) birth weight of 1000 g (740–1400) and median age at diagnosis of nosocomial BSI seven days (5.0–11.75). There were 42 (57%) neonates with ELBW. The median (IQR) age of infants was 125.5 days (110.5–163.25) at the onset of nosocomial BSI.

All patients had at least one potential predisposing factor but intravascular devices were the most frequent: 70% had CL (median duration 8 days before onset of nosocomial BSI; IQR: 5–13.25); 48% arterial catheter (7 days; 5–9.5); 57% had two or more intravascular catheters (Table 12).

The median (IQR) length of PICU stay was 9 days (5–17) before and 21 days (7–47.25) days after a nosocomial BSI episode.

Table 12. Potential factors predisposing patients to nosocomial bloodstream infection at East-Tallinn Central Hospital, the North Estonia Medical Centre and Tartu University Hospital (2004–2005) and in pediatric intensive care unit of Tartu University Hospital (2004–2008).

Potential factor	No. of nosocomial BSIs (%)			
	Three hospitals n=549		PICU n=126	
Central venous catheter	423	(77)	88	(70)
Arterial catheter	254	(46)	60	(48)
Two or more intravascular catheters	280	(51)	72	(57)
Urinary catheter	279	(51)	9	(7)
Mechanical ventilation	222	(40)	56	(44)
Surgery within the preceding 30 days	220	(40)	41	(33)
Total parenteral nutrition	132	(24)	48	(38)
Chemotherapy	126	(23)	3	(2)
Neutropenia	109	(20)	3	(2)

Table 13. Occurrence of nosocomial bloodstream infections according to underlying disease on admission to pediatric intensive care unit of Tartu University Hospital in 2004–2008.

Underlying disease	Neonates n=745	Children > 28 days n=618	Number of patients with nosocomial BSI episodes (%)	
Infection	43	100	31	(22)
Respiratory system disease	494	72	23	(4)
Cardiovascular system disease	71	79	5	(3)
Trauma and accident	0	81	2	(2)
Neurological disease	17	121	1	(1)
Other ^a	120	165	27	(9)

^a other – includes hematological diseases, developmental defects requiring surgical repair (e.g. abdominal wall anomalies)

6.2.3. Patient characteristics and risk factors for surgical site infection following cesarean section

Among the study patients, there were 192 (63%) emergency and 113 (37%) elective CS performed. Indications for CS are provided in Table 14.

Table 14. Indications for cesarean section in Women's Clinic of Tartu University Hospital in 2002.

Surgical indication	No. of patients n=305	%
Fetal distress	72	24
Breech and malpresentation	63	21
Cephalopelvic disproportion	41	13
Previous cesarean section	39	13
Preeclampsia	25	8
Dystocia	13	4
Placenta previa, increta or placental abruption	12	4
Others ^a	40	13

^a Included maternal diseases, twin pregnancy, pelvic trauma

Table 15. Analysis of risk factors for surgical site infections following cesarean section in Women's Clinic of Tartu University Hospital in 2002.

Risk factor	SSI (n=19)	No SSI (n=284)	
	Mean \pm SD	Mean \pm SD	p value
Age, years	27.7 \pm 6.5	28.5 \pm 5.9	.59
Gestational age, weeks	39.2 \pm 2.6	38.6 \pm 2.6	.38
Prenatal care visits	9.4 \pm 2.2	9.6 \pm 2.7	.75
Preoperative stay, days	1.2 \pm 1.2	1.1 \pm 1.7	.08
Vaginal examination prior to CS at hospital	2.6 \pm 1.7	1.9 \pm 1.8	.06
Duration of labor, hours	6.0 \pm 8.5	2.8 \pm 4.7	.008
Duration of ruptured membranes, hours	10.5 \pm 18.2	5.4 \pm 21.2	.31
ASA score	1.3 \pm 0.5	1.5 \pm 0.8	.18
Duration of surgery, min	40.7 \pm 6.8	40.6 \pm 15.0	.97
	n (%)	n (%)	OR (95% CI)
Chorioamnionitis	2 (11)	2 (1)	16.6 (2.8–100.3)
Internal fetal monitoring	2 (11)	3 (1)	11.0 (1.7–70.4)
Surgical wound class III and IV	12 (63)	84 (30)	4.1 (1.6–10.7)
Emergency CS	14 (74)	178 (63)	1.7 (0.6–4.6)
Nulliparity	11 (58)	133 (47)	1.6 (0.6–3.9)
Absence of antibiotic prophylaxis	7 (37)	96 (34)	1.1 (0.4–3.0)
Repeat CS	4 (21)	62 (22)	1.0 (0.3–2.9)

Two patients were excluded from the study during risk factor analysis because SSI developed more than 30 days after their CS. The characteristics of the sample are given in Table 14. Variables such as nationality, diabetes, preeclampsia, anemia, bacterial vaginosis during pregnancy, manual removal of the placenta, and volume of blood loss did not show significant differences between patients with and without SSI (data not shown). Univariate analysis identified that chorioamnionitis, duration of labor, internal fetal monitoring, and surgical wound classes III and IV were associated with SSI (Table 15). Multiple logistic regression analysis identified three variables independently associated with increased risk for developing SSI: internal fetal monitoring (OR, 16.6; 95% CI, 2.2–125.8; $p = .007$), chorioamnionitis (OR, 8.8; 95% CI, 1.1–69.6; $p = .04$), and surgical wound classes III and IV (OR, 3.8; 95% CI, 1.2–11.8; $p = .02$).

Analysis of the use of antibiotic prophylaxis revealed that 163 (85%) of the emergency CS deliveries and 37 (33%) of the elective CS deliveries received prophylaxis. In two hundred twenty-three (73%) patients the guidelines were followed according to the current hospital policy for PAP. Seventy-five (25%) patients received antibacterial treatment after the surgery without any confirmed diagnosis of infection.

The median (IQR) length of hospital stay for all patients was 5 (4.5–7) days. The median (IQR) period from surgery to detection of SSI was 5 (4–7) days.

6.3. Microbiological aspects

6.3.1. Microorganisms and their antimicrobial resistance causing hospital-wide nosocomial bloodstream infections

A total of 593 pathogenic microorganisms were isolated. Of these, 315 (53%) were Gram-positive, 232 (39%) were Gram-negative aerobes, 35 (6%) were fungi and 11 (2%) were anaerobes. Polymicrobial BSI was observed in 44 episodes (8%). CoNS, *Enterobacteriaceae* and enterococci were the most frequently isolated pathogens (Table 16). Nosocomial BSI due to *Pseudomonas* spp., CoNS and *Candida* spp. was significantly more common among ICU than non-ICU cases. Nosocomial BSIs in non-ICU patients were significantly more often caused by *S. aureus* and *E. coli* than ICU episodes. Among the 35 fungal isolates *C. albicans* was the most common (23 isolates, 66%). Among neutropenic patients the most frequent isolates were CoNS (28 of 113 isolates, 25%), *E. coli* (19 isolates, 17%) and enterococci (19 isolates, 17%).

Antimicrobial resistance data are presented in Tables 17 and 18. The methicillin-resistance among *S. aureus* isolates was 7%. One *E. coli* and three *Klebsiella* spp. produced ESBL. Of the *Pseudomonas* spp. isolates, 19%, 25%, 30% and 44% were resistant to ceftazidime, meropenem, piperacillin/tazobactam and imipenem, respectively.

Table 16. Most common causative pathogens in 549 episodes of nosocomial BSI stratified according to clinical setting (ICU vs non-ICU ward) at East-Tallinn Central Hospital, the North Estonia Medical Centre and Tartu University Hospital in 2004–2005.

Microorganism	No. of microorganisms, (%)			<i>p</i> value
	Total n=593	non-ICU n=272	ICU n=321	
CoNS	152 (26)	57 (21)	95 (30)	0.018
<i>Enterococcus</i> spp.	76 (13)	40 (15)	36 (11)	0.219
<i>Pseudomonas</i> spp.	57 (10)	12 (4)	45 (14)	0.0001
<i>Staphylococcus aureus</i>	54 (9)	35 (13)	19 (6)	0.004
<i>Klebsiella</i> spp.	52 (9)	24 (9)	28 (9)	1.0
<i>Escherichia coli</i>	49 (8)	35 (13)	14 (4)	0.0003
Other <i>Enterobacteriaceae</i>	44 (7)	18 (7)	26 (8)	0.53
<i>Candida</i> spp.	35 (6)	6 (2)	29 (9)	0.0004

Table 17. Antimicrobial resistance among Gram-positive organisms most frequently isolated from patients with nosocomial BSI at East-Tallinn Central Hospital, the North Estonia Medical Centre and Tartu University Hospital in 2004–2005.

Antibiotic	Percentage of resistant isolates (no. of resistant isolates/no. of tested)		
	Coagulase-negative staphylococci	<i>Staphylococcus aureus</i>	<i>Enterococcus</i> spp.
Oxacillin	83 (126/152)	7 (4/54)	NT
Ampicillin	NT	NT	41 (31/76)
Erythromycin	70 (95/135)	18 (9/50)	66 (33/50)
Clindamycin	55 (65/119)	12 (6/49)	NT
Ciprofloxacin	73 (88/121)	6 (3/51)	NT
Gentamicin	76 (106/140)	2 (1/51)	58 (44/76) ^a
Vancomycin	0 (0/152)	0 (0/54)	1 (1/76)

NT- not tested, ^ahigh level resistance

Table 18. Antimicrobial resistance among Gram-negative organisms most frequently isolated from patients with nosocomial BSI at East-Tallinn Central Hospital, the North Estonia Medical Centre and Tartu University Hospital in 2004–2005.

Antibiotic	Percentage of resistant isolates (no. of resistant isolates/no. of tested)			
	<i>Escherichia coli</i>	<i>Klebsiella spp.</i>	Other <i>Enterobacteriaceae</i>	<i>Pseudomonas spp.</i>
Ampicillin	45 (18/40)	93 (41/44)	82 (27/33)	NT
Ampicillin/sulbactam	26 (12/47)	37 (19/52)	62 (26/42)	NT
Piperacillin/tazobactam	2 (1/48)	15 (8/52)	7 (3/42)	30 (16/54)
Cefuroxime	3 (1/36)	31 (13/42)	58 (19/33)	NT
Cefotaxime	2 (1/44)	16 (8/49)	19 (8/42)	NT
Ceftazidime	NT	NT	NT	19 (10/52)
Cefepime	3 (1/35)	7 (3/43)	3 (1/33)	17 (6/36)
Meropenem	0 (0/45)	2 (1/52)	0 (0/40)	25 (10/40)
Imipenem	NT	NT	NT	44 (15/34)
Ciprofloxacin	4 (2/45)	8 (4/52)	2 (1/42)	22 (11/50)
Gentamicin	4 (2/46)	10 (5/52)	5 (2/41)	32 (16/50)
Amikacin	0 (0/32)	2 (1/42)	0 (0/33)	16 (8/50)

NT- not tested

6.3.2. Microorganisms and their antimicrobial resistance causing nosocomial bloodstream infections in pediatric intensive care unit

In total, 136 isolates were recovered from 126 nosocomial BSI episodes, 8% of BSI episodes were polymicrobial. Gram-positive and Gram-negative microorganisms accounted for 60% and 35%, respectively. The most common pathogens were CoNS (43%) and *Serratia marcescens* (14%) (Table 19). From July 2005 to December 2009 an outbreak occurred with 149 patients colonized and 61 infected with *S. marcescens*. (231) MRSA caused an outbreak with 17 affected patients (four BSI) in 2006–2007. There were five episodes of fungemia (two *Candida albicans*, two *Candida parapsilosis*, one *Candida glabrata*), three of them in ELBW neonates (7% of all ELBW patients).

Resistance to methicillin was detected in four out of seven of *S. aureus* isolates (all isolated during the outbreak) and in the majority (86%) of CoNS isolates. No resistance to vancomycin was detected among staphylococci and enterococci. Three of the 17 enterococci were ampicillin-resistant *Enterococcus faecium*. Among 39 *Enterobacteriaceae*, 88% were resistant to ampicillin, 65% to cefuroxime, 14% to gentamicin, 2% to ciprofloxacin and none to car-

bapenems. Three isolates of *Klebsiella pneumoniae*, three *S. marcescens* and three *Enterobacter cloacae* (23% of all *Enterobacteriaceae* isolates) produced ESBL. All *Candida* spp. except *C. glabrata* were susceptible to fluconazole and none was resistant to amphotericin B.

Table 19. Distribution of the 136 pathogens isolated in 126 episodes of nosocomial BSIs in pediatric intensive care unit of Tartu University Hospital in 2004–2008.

Microorganism	Neonates (n=109)	Children >28 days (n=27)	% of all isolates
Gram-positive organisms	68	14	60
Coagulase-negative staphylococci	53	5	43
Enterococci	9	8	13
<i>Staphylococcus aureus</i>	6	1	5
Gram-negative organisms	35	12	35
<i>Serratia marcescens</i>	13	6	14
<i>Klebsiella pneumoniae</i>	8	2	7
other Enterobacteriaceae	9	1	7
<i>Acinetobacter baumannii</i>	4	1	4
<i>Pseudomonas aeruginosa</i>	1	2	2
<i>Candida</i> spp.	4	1	4
Other	2	0	1

6.4. Outcome of patients with healthcare-associated infections

6.4.1. Outcome of patients with nosocomial bloodstream infection in hospital-wide surveillance study

Overall, 157 of the patients with nosocomial BSI died during hospitalisation, accounting for in-hospital case-fatality rate of 31% (95% CI, 27.0–35.2). Among those 60 died within one week of onset of nosocomial BSI, accounting for 7-days case-fatality rate of 12% (95% CI, 9.2–15.0). The highest in-hospital case-fatality rates occurred in those with intra-abdominal and surgical site sources (Table 20). In-hospital case-fatality ranged from 15% for *S. aureus* to 57% for enterococci (Table 20). Enterococci, *Candida* spp. and *Pseudomonas* spp. were significantly more frequently detected as pathogen of nosocomial BSI episodes among non-survivors.

A total of 258 patients (47%) were receiving appropriate antimicrobial therapy on the day of sampling. The most common pathogens causing nosocomial BSI in episodes with inappropriate therapy were CoNS and enterococci in 30% and 15% of cases, respectively.

Table 20. In-hospital case-fatality rates associated with origin of nosocomial BSI and most common causative pathogens at East-Tallinn Central Hospital, the North Estonia Medical Centre and Tartu University Hospital in 2004–2005.

Origin of nosocomial BSI	In-hospital case-fatality		Microorganism	In-hospital case-fatality	
	%	(95% CI)		%	(95% CI)
Intraabdominal	54 ^a	(33.4–73.4)	<i>Enterococcus</i> spp.	57 ^a	(44.7–67.9)
Surgical site	46 ^a	(27.5–66.1)	<i>Candida</i> spp.	51 ^a	(34.0–68.0)
Lower respiratory tract	39	(28.0–51.2)	<i>Pseudomonas</i> spp.	44 ^a	(30.7–57.6)
Catheter-associated	31	(25.2–36.8)	Other <i>Enterobacteriaceae</i>	39	(24.4–54.5)
Unknown	23	(13.8–35.7)	<i>Escherichia coli</i>	29	(16.6–43.3)
Urinary tract	19	(6.3–38.1)	CoNS	24	(17.8–32.0)
Skin/soft tissue	14	(4.5–28.8)	<i>Klebsiella</i> spp.	21	(11.1–34.7)
Other	39	(23.1–56.5)	<i>Staphylococcus aureus</i>	15	(6.6–27.1)

^a Significantly ($P < 0.05$) more frequently detected as a source or as a pathogen of nosocomial BSI episodes among non-survivors

6.4.2. Outcome of patients with nosocomial bloodstream infection in pediatric intensive care unit

Nine patients (10%), eight of them neonates, died during the hospital stay. Their nosocomial BSIs were caused by CoNS in 3 cases, *S. marcescens* in 4 cases, MRSA in one case and *E. faecalis* and *S. marcescens* in one case. The case-fatality rate within 7 days after the first positive blood culture was 1%. Nosocomial BSIs caused by *Candida* spp. were not associated with mortality in this study.

Appropriate antimicrobial therapy was started on blood culture sampling day in 47% of nosocomial BSI episodes. The most common pathogens causing nosocomial BSI in episodes with inappropriate therapy were CoNS and *Enterobacteriaceae* in 55% and 22% of cases, respectively.

6.4.3. Outcome of patients with surgical site infection following cesarean section

Patients with SSI had a longer mean (\pm SD) hospitalization time than did noninfected patients (5.8 ± 0.3 vs 7.9 ± 1.5 days; $p < .03$). Two patients out of 19 with SSI were readmitted. No hysterectomies were needed and no deaths occurred.

7. DISCUSSION

7.1. Factors influencing incidence of healthcare-associated infections

7.1.1. Incidence of nosocomial bloodstream infections

The incidence of hospital-wide nosocomial BSI recorded for the first time in Estonia was two times lower than in the SCOPE Project, one of the largest studies from the USA (3 vs 6 cases per 1000 admissions, respectively) (87). The overall hospital-wide incidence density of nosocomial BSI (0.6 per 1000 patient days) does not differ from other reported European studies where incidence densities varied from 0.6 to 0.8 per 1000 patient-days (84–86). Ammerlaan *et al.* reported the average incidence density of nosocomial BSIs from 0.6 to 1.9 per 1000 patient-days in 14 hospitals from 9 countries between 1998 and 2007 (83).

A comparison of our PICU results with other studies is challenging because most studies have described epidemiology of nosocomial BSI either in PICU or NICU, but data from mixed units are limited. In addition, systematic review of strategies for reporting of neonatal nosocomial BSI identified a wide variability in reporting of BSI indicators and risk adjustment strategies which further makes comparison more difficult (232). In our study, the overall incidence of nosocomial BSI was 9.4 per 100 admissions, which is more than twice as high as those reported from PICU surveys in UK (3.9 per 100 admissions) and other centres in Europe (4.8 per 100 admissions) (26, 95). The nosocomial BSI incidence density (12.8 per 1000 patient-days) was also higher than reported in Finland (3.2 and 2.5 in neonatology and PICU, respectively) (233). As our data represent a mixed PICU, the higher incidence of nosocomial BSI compared to non-neonatal PICU is understandable because neonates, especially ELBW infants, are at the highest risk of nosocomial BSI (51, 91). In a study of neonatal infection surveillance network in England 26% of neonatal infections (93% of which were BSIs) occurred in ELBW (51).

However, it is difficult to compare different countries as several methodological issues such as blood culture sampling rate, whether secondary BSI or whether more than one episode per patient is included, and which nosocomial BSI definition is used, may all affect the results (11, 234). Therefore comparing the facility's infection rates to its own historical rates over time seems to be more meaningful.

7.1.1.1. Blood culture sampling rate

Our hospital-wide infection rates may not be strictly comparable because the mean number of blood culture sets in Estonia, 17 per 1000 patient days, was lower than that reported from most European countries during the study period (e.g., 42–54 in Finland, 38 in UK) (85, 235). The rate of nosocomial BSI is

influenced by the physicians' threshold for ordering blood cultures; the volume of blood drawn for culture, the timing of the culture, the number of cultures taken, and the blood culture system (11). Schmitz *et al.* found considerable differences regarding preanalytic procedures of blood culture testing in four European countries (Italy, UK, France and Germany) (236). We did not produce any guideline for blood culture testing for the purpose of the study and all blood cultures were performed at the discretion of attending physician. Therefore, our results may be influenced by different blood culture practices between hospitals and our rate on nosocomial BSI can be underreported.

In our PICU the mean number of blood culture sets per 1000 patient-days was high but in most cases only one sample was taken. This is an important issue to consider when defining nosocomial BSI caused by skin commensals.

7.1.1.2. Definition of nosocomial bloodstream infection

The definition is especially important in studies reporting high rate of nosocomial BSI caused by skin commensals as in our PICU study. Usually it is recommended to include cases with at least two positive blood cultures with probable contaminants and some studies with one positive culture require at least 5 days of appropriate antimicrobial therapy (8, 51). In contrast to adults, only one blood culture is routinely drawn from premature babies because of technical difficulties and low circulating blood volumes. Modi *et al.* propose to add the requirement of ≥ 3 predefined clinical signs to have the best predictive accuracy for BSI caused by skin commensal (8). The German surveillance network for neonatal HAIs (NEO-KISS) in collaboration with clinicians has applied specified criteria for neonates to increase the acceptance of the surveillance data and its use (237). We have used previous US CDC definition of laboratory-confirmed BSI allowing us to diagnose nosocomial BSI with only one positive blood culture with CoNS (19). Sarvikivi *et al.* compared different nosocomial BSI definitions and found that due to the single blood culture policy in Finnish NICUs none of the blood cultures with skin commensals were confirmed by a second culture, and thus no cases met the revised CDC criteria for laboratory confirmed BSI (81, 234). The NEO-KISS criteria defining clinical findings in more detail diminished the number of identified cases by 15% (234). Therefore, our high rate of CoNS can be partly explained by difficulties to separate true pathogens from contaminants in this patient population. When CoNS cases were excluded from the analysis, the incidence and incidence density remained higher than in the UK network survey (5.1 versus 2.9 per 100 admissions) or in two tertiary care NICUs in London (7.1 versus 2.2 per 1000 patient-days) suggesting that factors other than the interpretation of the positive blood culture may have contributed to the high rate of nosocomial BSI (51, 238).

7.1.1.3. Outbreak situation

Surveillance in PICU which took place during the outbreaks of *S. marcescens* (231) and MRSA may have produced higher rates of nosocomial BSI caused by these organisms compared with surveillance performed when there were no outbreaks. *S. marcescens*, which has been described to cause long-lasting and difficult to control outbreaks, was the second most common pathogen of nosocomial BSI in our study in contrast to other reports (93, 239). The outbreak in our study was eventually eliminated by screening mucosal colonization, cohorting colonized and infected patients and by educating health care workers on infection control measures and hand hygiene procedures (231). Suboptimal nurse-to-patient staffing ratio (1:3, seen occasionally in our PICU and resulting in excessive workload for one nurse) may have played a role in the CLABSI rate and outbreaks (240). This ratio is a critical factor to ensure adherence to infection control measures (241). Leistner *et al.* demonstrated that high staffing levels are associated with a lower incidence of CLABSI and these results are congruent with other studies on staffing (169, 241).

7.1.2. Incidence of surgical site infections following cesarean section

The SSI incidence of 6.2% in our hospital is lower than incidence in most of the other studies that have used postdischarge surveillance, where rates have varied from 7.1% in Denmark to 23.5% in Brazil (Table 5). The comparison of our SSI rates with NNIS/NHSN System benchmarks is not meaningful because postdischarge surveillance is not required by the NNIS/NHSN System, but any comparison of SSI rates must take into account whether case-finding included the detection of SSI after discharge. Also in ECDC surveillance of SSI where the incidence was 2.9%, the intensity of postdischarge case-finding varies between European countries (16). Almost half of the SSIs (42.1%) were detected during postdischarge surveillance in our study. This finding belongs to the lower end of the range varying from 36 to 95% in reported studies using postdischarge surveillance (Table 5). It might have been caused by the fact that our median length (5 days) of hospital stay was longer compared to other studies (e.g., 3 days in England) (188, 191). In our study the median period from surgery to detection of SSI was as long as the median length of stay which enabled us to detect almost half of the cases already during the hospital stay. In case of studies with shorter length of stay it is not possible to find SSIs before discharge. The data suggest the necessity to perform postdischarge surveillance to obtain more accurate SSI rates.

Noy and Creedy recommended in their study that when the rate is being calculated, the number of responders, rather than the number of the total sample, should be used (242). As increasingly more infections emerge after discharge and in cases of a low response rate, inclusion of nonresponders may lower the infection rate and produce inaccuracies when compared with other healthcare

facilities. Thus, when these comparisons are being made, the denominator has to be taken into consideration. In our study, the response rate was high and the exclusion of nonresponders from the denominator would not have changed the results significantly (6.2% vs 6.6%).

Majority of SSIs were superficial in our study. In some surgical environments, emphasis is placed on more serious infections, like deep infections and infections in organs/body cavities, as these give rise to increased patient suffering and higher costs for the health care system (190). Still, it is important to include the superficial infections into the surveillance as well, because these involve an additional burden for patients, increased use of antibiotics, and increased costs, e.g., for doctor visits, as suggested by Eriksen *et al* (190). Monitoring superficial as well as deep infections provides higher sensitivity with which to examine the quality of care and detect potential problems with infection prevention (184).

7.2. Risk factors for healthcare-associated infections

7.2.1. Potential factors predisposing patients to nosocomial bloodstream infection

Our nosocomial BSI studies were performed in different settings – the first study involved mainly adult patients and only PICU patients, mostly neonates, were included in the second study. Therefore some risk factors differ significantly. In our study we did not have an external comparison group and thus we were unable to perform risk factor analysis. We were only able to identify potential factors commonly described in literature such as underlying diseases and use of invasive devices (85, 87, 91).

Comorbidities have an important role, because severely ill patients with multiple comorbidities are more likely to develop nosocomial infections. Charlson weighted index of comorbidity has been shown to be a useful measurement of an underlying comorbidity and a good predictor of mortality of adult patients with BSI (149, 243). In our study more than one third of the adult patients had Charlson weighted index of comorbidity score of 3 or more. It has long been known that neutropenic patients are more likely to experience nosocomial BSI (146). We investigated that 20% of the patients with nosocomial BSI had neutropenia in our hospital-wide study. In pediatric population gestational age and birth weight have a decisive role. Infants with the lowest birth weight are most at risk for nosocomial BSI due to their compromised immunological defense systems and multiple invasive procedures as reported in several studies (123–125). Also in our study the highest rate of CLABSI among ELBW infants became evident.

Consistent with other studies, intravascular devices were the most common potential predisposing factors of nosocomial BSI in both populations (85, 87, 91). It is possible that by using clinical and blood culture data we have overestimated the importance of vascular catheters because device colonisation was not

always laboratory-confirmed. However, this approach corresponds more closely to clinical circumstances and is often used to compare nosocomial BSI rates in surveillance studies (244).

According to our data most cases occurred in ICU or department of hematology and therefore efforts for prevention should be targeted at CLs in high risk specialties.

7.2.2. Risk factors for surgical site infection following cesarean section

Data on a number of risk factors for the development of SSI were collected in the course of the study. The multiple logistic regression revealed three variables such as surgical wound classes III and IV, chorioamnionitis, and internal fetal monitoring independently associated with postcesarean SSI.

We used modified wound classification where surgical wound class III was defined as rupture of membranes greater than 2 hours and class IV as purulent amniotic fluid (chorioamnionitis). Our finding is not surprising because chorioamnionitis usually results from migration of cervicovaginal flora through the cervical canal and rupture of membranes facilitates this process leading to higher risk for SSI. Several studies have reported a contaminated or dirty wound class (III and IV) as well as premature rupture of membranes and chorioamnionitis as a risk factor for SSI (190, 196, 199, 207, 245). Olsen *et al.* found that the odds of endometritis increased approximately 1.7-fold within 1 hour after rupture of membranes, but increased duration of rupture was only marginally associated with increased risk. Thus, the results were more consistent with increased risk of endometritis associated with rupture per se, regardless of the duration (202). In a Cochrane review vaginal preparation immediately before CS significantly reduced the incidence of postcesarean endometritis, especially in women with ruptured membranes (218). Given these findings, preoperative vaginal preparation with povidone-iodine scrub should be considered prior to CS (218).

Internal fetal monitoring, although this occurred in only a few cases, appeared to predispose women strongly to SSI. Starr *et al.* also found an increased risk of developing endometritis in association with use of the intrapartum internal monitors (208). The pathophysiology is theoretically an ascending polymicrobial infection of cervical and vaginal organisms into the uterus with hematogenous spread through exposed edges of incised myometrium (208). A challenge exists to decrease the frequency of internal fetal monitoring.

It is possible that well-known patient-related risk factors for SSI such as diabetes, preeclampsia or hypertension were not significant in our study due to frequent prenatal visits (mean 9.4 and 9.6 among patients with and without SSI, respectively). Killian *et al.* found that one of the significant risk factors for endometritis following CS was having fewer than seven prenatal visits and therefore less opportunity for diagnostic testing (196). Hence, increased number of

prenatal visits is important to ensure primary prevention methods to prevent many perinatal complications, including postoperative infection (196). Unfortunately, some data of the prepregnancy weight were missing and therefore we were unable to analyze obesity as an often-discussed risk factor.

There were no significant differences regarding absence of PAP between patients with or without SSI. Estimating the protective effect of prophylactic antibiotics is problematic because antibiotics were continued after CS. A Cochrane Review from 2002 recommended single dose prophylactic antibiotics to all women undergoing CS after cord clamping (197). During the study period our hospital policy recommended prophylaxis to high risk groups only but in total of 73% of the patients the prophylaxis policy was followed. Since 2010 we recommend PAP for all patients with CS within one hour prior to incision. Appropriate PAP can be one more possibility to decrease the incidence of SSIs in our hospital.

7.3. Microbiological aspects

7.3.1. Spectrum of microorganisms causing nosocomial bloodstream infections

The most frequent cause of nosocomial BSI both hospital-wide as well in PICU was CoNS. The obvious predominance of CoNS is striking, but has also been similarly described in other studies (Table 4) (26, 51, 91, 95, 246). It is possible that our finding is overestimated due to blood culture contamination. As discussed above, determining whether a positive blood culture represents a nosocomial BSI is usually not difficult with predominantly pathogenic organisms, but can be a considerable issue with common skin contaminants, such as CoNS (11). However, in preterm neonates with BSI CoNS may arise from gastrointestinal tract as have shown Soeorg *et al.* (247). They found molecular similarity between CoNS isolated from blood and gastrointestinal tract collected before BSI in more than half of the patients studied (18 out of 22) indicating that preterm neonates may harbour potentially invasive strains in gastrointestinal tract before nosocomial BSI (247). On the other hand, these bacteria are also the most important cause of real CLABSIs as they may more likely colonize the catheter during insertion and use. In our PICU study 53% of nosocomial BSI were associated with CL and 67% of these were caused by CoNS. Since 2007 we have implemented a guideline for the prevention of intravascular catheter-related infections in Tartu University Hospital and hopefully applying current evidence for CL care leads to decreased incidence of nosocomial BSI. This phenomenon has been demonstrated by several studies reporting dramatic success in reducing CLABSI (157, 160, 166). Bizzarro *et al.* observed also significant reduction of CoNS-related BSI in NICU attributable to the implementation of targeted infection prevention and elimination of blood sampling via indwelling catheters (248).

Enterococci were the second and third most common pathogens in hospital-wide and PICU study, respectively. These findings are similar to other studies in which enterococci were among most common cause of nosocomial BSI (83, 87, 249). Isolation of enterococci could indicate more serious condition of the patient and long-term treatment as they are relatively resistant to broad-spectrum antibiotics and thus can survive and overgrow after long-term treatment (250). According to the NHSN data the incidence density of CLABSI caused by *Enterococcus* spp. has remained higher than for *S. aureus* since 2004 (89). A likely explanation for this finding is that CL insertion practices may be less effective at preventing BSIs caused by enterococci than staphylococci, because this infection may arise from the gastrointestinal tract through compromised mucosal barriers (89).

The most commonly isolated Gram-negative organisms in our series (*Enterobacteriaceae* and *Pseudomonas* spp.) have also been among the leading Gram-negative pathogens in other hospital-wide surveillance studies (83–85, 87). In contrast to studies conducted in PICU or NICU where *S. marcescens* has been rare or sporadic finding, this microorganism was the second most common pathogen in our PICU because of the outbreak (93).

During recent years there has been an increase in the proportion of non-albicans *Candida* spp. (136). We found that *C. albicans* was the most frequent fungal species (66%) isolated from blood. One possible explanation to this may also be attributable to differences in the patient populations studied. Mostly non-hematological patients in ICU, probably without previous fluconazole prophylaxis dominated in our study. In contrast to studies where invasive *Candida* infections are a major cause of morbidity and mortality in preterm neonates, this pathogen was rare in our PICU study (251). This observation could in part be explained by the use of prophylactic fluconazole in high risk neonates and a conservative approach to empiric antibiotics.

7.3.2. Antimicrobial resistance of pathogens causing nosocomial bloodstream infections

During the hospital-wide study period, the rate of MRSA (7%) was higher than that identified in Nordic countries and the Netherlands but lower than rates reported from Central and Southern European countries (54). In the USA, data from hospitals participating in SCOPE showed that 41% of bloodstream *S. aureus* strains were methicillin resistant (87). Although our numbers are small in PICU study, high rate of MRSA was encountered because of the clonal spread of the outbreak strains. However, during the recent decade the percentage of invasive MRSA has been below 10% in Estonia (54). One vancomycin resistant *Enterococcus* sp. was isolated in hospital-wide BSI surveillance study. Vancomycin resistant enterococci are still rare in Estonia and only few vanB gene positive strains have been confirmed so far (data from synlab Eesti, personal communication).

Despite of the finding of only the 4 ESBL producing strains in hospital-wide BSI study, the overall ESBL percentage among *Enterobacteriaceae* was 23% in PICU. These data do not reflect the general reported epidemiology of antimicrobial resistance in Estonia (54). This is higher than the prevalence of ESBL-producing invasive strains of *K. pneumoniae* (<12%) or *E. coli* (< 5%) in Estonia during this period (54). In our PICU study ESBL was not common only in *K. pneumoniae* but also in *E. cloacae* and *S. marcescens* strains. It can be explained with the outbreak in PICU as some ESBL outbreaks have been attributed to the dissemination of plasmids carrying ESBL genes among strains of members of the family *Enterobacteriaceae* (252). One *K. pneumoniae* was reported to be resistant to meropenem in hospital-wide surveillance study. Carbapenemase production was not investigated in laboratories during the study time. However, the majority of carbapenem resistant strains isolated in Estonia have not been confirmed as carbapenemase producers in later studies (59).

The resistance percentages of different antimicrobial agents among pseudomonas strains were higher in our hospital-wide surveillance study than those reported in the USA (SCOPE) and in European studies (85, 87). When comparing *P. aeruginosa* EARS-Net data of different years high variation in resistance percentages without clear trends can be seen in Estonia (54). The reasons could be the small absolute number of invasive strains and changes in dominating clones in hospitals.

Due to the fact that our data were collected mostly from tertiary hospitals in hospital-wide surveillance study and from PICU, resistance percentages are likely to reflect the microbiological epidemiology of patients with multiple comorbidities. Isolates from ICU patients may be expected to have higher levels of resistance than isolates from non-ICU patients (61). This emphasizes the importance of local data in order to avoid antibiotic resistance with appropriate infection control measures including antibiotic policy.

7.4. Outcome of patients

7.4.1. Case-fatality rate

The in-hospital case-fatality rate observed in our hospital-wide surveillance study (31%) is consistent with previous investigations (87, 253). The BSIs secondary to abdominal and respiratory tract infections are usually associated with higher fatal outcome (39, 116). Similar finding was observed in our study as the case-fatality rate was the highest in nosocomial BSI secondary to intra-abdominal site. Case-fatality rates were highest for infections caused by enterococci (57%), *Candida* spp.(51%), and *Pseudomonas* spp. (44%). These are typical microorganisms associated with infection in severely ill patients. In-hospital mortality associated with enterococcal BSI has been estimated between 23–50% (250). In the SCOPE project the in-hospital mortality rates varied in etiology from 21% for CoNS to 39% for *P. aeruginosa* and *Candida* spp.(87)

In PICU the nosocomial BSI in-hospital case-fatality rate (10%) and the case-fatality rate within 7 days of the first positive blood culture (1%) were lower than those reported by Gray *et al.* for patients in PICU (26.5% and 10.7%, respectively) (95). In US studies of pediatric patients and VLBW neonates the BSI mortality was 14% and 18%, respectively (50, 91). The high rate of CoNS infections, which have a lower case-fatality, could help to explain the observed case-fatality in our study.

7.4.2. Length of stay and readmissions

We analysed the length of stay in our SSI study. It has been proved in several studies that one of the outcomes of SSIs is the increase in hospital stay (190, 196, 212, 228). A significantly longer hospital stay also occurred in the current study once SSI was identified. Patients with more serious SSI may need additional outpatient visits, readmission or even reoperation (190). We do not have exact data about the number of additional outpatient visits, but two patients out of 19 with SSI were readmitted in our study.

7.4.3. Appropriate antimicrobial therapy and perioperative antibiotic prophylaxis

According to our data 53% of patients with nosocomial BSI were receiving inappropriate antimicrobial treatment in both studies. Empirical treatment of patients with BSIs has become more complicated in an era of increasing antimicrobial resistance. Many studies have found that bacterial resistance decreased the chance of early adequate therapy leading to increased mortality (116). The influence of inappropriate therapy on patients' outcome falls beyond the scope of this thesis. In our studies the inappropriate therapy was given mainly for nosocomial BSI caused by low virulence Gram-positive microorganisms, like CoNS, that could also be an overestimated etiology as discussed above. Reducing the number of episodes with inadequate initial therapy would necessitate greater empiric use of glycopeptide antibiotics with the attendant risk of promoting the emergence and spread of glycopeptide resistant enterococci and other Gram-positive bacteria. Nevertheless, the surveillance programs defining the species distribution and resistance patterns of microorganisms causing nosocomial BSIs provide the basis for appropriate antimicrobial therapy and should be continued.

In SSI study 25% of the patients received antibiotics postoperatively without any confirmed diagnosis of infection and in 73% of the patients hospital antibiotic prophylaxis policy was followed. Studies have shown that single-dose antibiotic prophylaxis is as effective as multiple doses of antibiotic (220). Hence, there is no need for the so-called extended antibiotic prophylaxis. The results of this study indicate the need for intervention to improve the rational use of antibiotic prophylaxis in accordance with the guidelines.

7.5. Surveillance of healthcare-associated infections in hospital

7.5.1. Which method to use and what kind of healthcare-associated infections to study?

HAI surveillance methods can be: active vs. passive; prospective vs. retrospective; hospital-wide vs targeted; patient vs. laboratory-based, or prevalence vs. incidence survey (3, 66).

Prevalence surveys provide data at one particular pointing time, and are generally easy to conduct, relatively inexpensive and are not very time-consuming (9). Point prevalence studies have been performed at Tartu University Hospital once a year since 2003 and later in other Estonian hospitals as well (254). The ECDC requested that all member states should have carried out a point prevalence survey using a standardized protocol by June 2012. In four Estonian hospitals participating in this survey the most common HAIs were SSIs (32% of all infections), LRTIs (28%), and UTIs (13%) (4). The disadvantage of this method is that prevalence surveys are biased in favour of HAIs of longer duration compared to incidence surveys and are notably influenced by the duration of antimicrobial treatment and the propensity to discharge patients (255). Perhaps the best uses of prevalence studies are to make valuable estimates of antimicrobial usage patterns, to evaluate the adherence to proper isolation practices, and to monitor practices related to high-risk procedures, such as use of vascular catheters (66).

HAI incidence data have become the gold standard of HAI surveillance over the past 2 decades (255). Ideally, each hospital should have a continuous institution-wide prospective surveillance program assessing all HAIs for effective prevention but this requires careful consideration of the logistics of collecting the information and is often not feasible because of inadequate resources (9). Since the mid-1980s the trend has changed from continuously monitoring all patients for all HAIs in all hospital in favour of an approach that targets specific patient-care areas, patient-care processes, infection sites or infections caused by certain organisms, or (“priority-directed” surveillance) (66). Such programs are often restricted to ICU or other high-risk settings, such as oncology or neonatology. Infection preventionists must consider the advantages and disadvantages of different surveillance methods and the sensitivity of different case finding methods as they design their surveillance system (256).

By measure/criterion that reflects both the relative frequency of the HAIs and the relative degrees of morbidity as expressed by the costs of extra days and extra ancillary services necessary to treat the HAIs, BSI would constitute the most serious problem (66). Although nosocomial BSIs have been studied extensively, most of the studies and networks are focusing on ICU-acquired BSIs as we did in our PICU study. Our first study encompasses the entire hospitalized acute care population, rather than just those in ICU, in the three largest hospitals in Estonia. Besides primary BSIs we have also included all patients with

clinically significant nosocomial BSIs from any source or due to any microorganism. The surveillance of nosocomial BSI may have some advantages compared to other HAIs. First of all, it provides useful data on serious infections, causative organisms and their antibiotic resistance patterns to give feedback to different specialties (11). Hospital-wide nosocomial BSI surveillance is thought to be useful in monitoring trends including outbreaks, emerging multiresistant pathogens, and effects of intervention programs (10). Secondly, it is an easily defined condition (skin commensals excluded) and is less influenced by local laboratory testing practices and procedures. Laboratory-based surveillance methods have been used successfully to identify nosocomial BSI and methods that combine laboratory-based screening protocols with medical records review have performed well in hospital-wide surveillance models (257). In brief, the laboratory-based surveillance of nosocomial BSI provides valuable information with the smallest effort to collect hospital-wide HAI data.

7.5.2. Should we study nosocomial bloodstream infections only in intensive care unit?

Traditionally, nosocomial BSI or more specifically – CLABSI – surveillance is conducted only in ICUs because of the high use of CLs and perceived frequency of CLABSI. Weber *et al.* found that CDC-recommended ICU surveillance for CLABSI would have detected only 21% of 407 CLABSIs that occurred in the medical and surgical services of tertiary care university hospital (258). Recently, studies have revealed similar CLABSI rates in both ICU and non-ICU departments (172). Hospital-wide catheter surveillance performed in Switzerland found that although cumulative CL-days were similar, the type, dwell time, and utilization of CLs in ICU and non-ICU settings were different (175). ICU CLs have a short dwell time but are utilised more often, whereas catheters in non-ICU settings show a reverse characteristic (175). Infection prevention measures targeting the post-insertion time of CLs are more likely to be successful in non-ICU settings, probably due to the fact that unjustified catheter use is more frequent and a further reduction of catheter dwell time in the ICU is unlikely (175).

We found in our study that a quarter of nosocomial BSI cases occurred in hematology units justifying the surveillance outside ICU as well.

7.6. What is the best method for postdischarge surveillance of surgical site infections?

With the progressive reduction in the average hospital stay, an increasing percentage of some HAIs, most notably SSIs, become manifest after hospital discharge (66). The best way to conduct postdischarge surveillance is still a matter of dispute according to the literature. Different postdischarge surveillance

surgeon or patient questionnaires, electronic search of patient records, telephone interviews, or automated telephony (182, 259). From ECDC SSI surveillance data, it appeared that three methods for obtaining post-discharge information were used most frequently in European countries: hospital surveillance staff obtains information from the patient using telephone or additional questionnaires (four networks); detection of postdischarge SSI on readmission to the hospital (three networks); hospital surveillance staff obtains information from the surgeon (three networks) (16). A systematic review of the methods used to identify SSI after discharge from hospital concluded that existing studies on the subject have so far failed to identify a valid, reliable method for identifying such infections (15). The ideal methodology should have a high follow-up rate, have high sensitivity and specificity, and be cost-effective.

Several studies have used telephone interviews as a detection method for SSI (203, 260, 261). In the study performed by Taylor *et al.* the follow-up rate was 93%, and it was concluded that this method of contact is feasible and effective (261). We agree with this because we could contact 92% of the patients by telephone. Telephone questionnaire is a suitable method because approximately 65% of the population owned a mobile during the study period and most of the patients were interested in participating in the surveillance (262).

However, validity of the information obtained from patients is a matter of dispute in several research studies. Seaman and Lammers found that patients, despite using verbal or printed instructions, were unable to recognize infections (263). They reported that patients correctly identified their infections in only 11 cases, whereas medical examiners diagnosed infection in 21 wounds, and called into question the validity of data obtained using patient-returned questionnaires or telephone surveys. Whitby *et al.*, however, demonstrated that patients can accurately diagnose the absence of a wound complication, but are less accurate in diagnosing the presence of an infection (264). Patients frequently confuse serous discharge with pus and, therefore, this marker may overestimate infection rates. The results of our study also support the latter because nine of the patients self-reported the SSIs, which were not confirmed by a physician. Therefore, confidence in the results should be improved by gathering information from several sources. Stockley *et al.* found that the combination of different methods like healthcare worker's questionnaire, telephone calls and patient's questionnaire is relatively simple to use and causes minimal inconvenience to patients and healthcare workers (228). We also used a multimethod approach described by Stockley *et al.* in combination with chart review with the follow-up rate of 95%.

According to the literature the most accurate method to detect SSI is direct observation of surgical sites by trained professionals, e.g., infection control practitioners (182). However, in our study this was not feasible because we had to consider human and financial resources allotted for SSI surveillance. Nevertheless, in our survey all of the SSI diagnoses were determined by the investigator to have met the CDC criteria.

Studies have indicated that antibiotic exposure is a sensitive indicator of an infection because relatively few serious infections are managed without antibiotics. Poor specificity (too many false-positive results) has been a major problem because antibiotics are so widely used after surgery for extended prophylaxis, empiric therapy of suspected infection, and treatment of infections other than SSI (191, 265, 266). In our study 75 patients without any confirmed infection diagnosis received antimicrobial treatment after CS. Therefore, we cannot use therapy as an indicator of SSI. Inappropriate use of antimicrobial agents not only adds to the cost of medical care, but also needlessly exposes the patient to potential toxicity and risks that promote the development and spread of antimicrobial resistance in healthcare facilities (267).

Multi-method postdischarge surveillance has been described as cost-effective in several studies (203, 228, 242, 261). The method we used is not very time consuming. It is also more acceptable to patients because only those who have a problematic wound area need to go to the hospital for checkups. The data collection was simplified by the fact that most of the women returned to our clinic for postdischarge care. The same applies to the physicians; only physicians whose patients have problems should take part in the study. The current study included the costs of labor, postage, and telephone calls. Computerized systems could reduce the time and costs required to perform surveillance by automated data collection from electronic medical records of microbiology results or antibiotic dispensing and/or administrative data (268). Yokoe *et al.* screened automated ambulatory medical records, hospital and emergency department claims, and pharmacy records and found that this method allows efficient identification of postpartum infections not detected by conventional surveillance (269). Leth *et al.* validated electronic surveillance of postcesarean SSI and found that sensitivities of SSIs diagnosed in hospital and postdischarge were 77.1% and 68.9%, and the specificities 99.5% and 98.2%, respectively (189). The completeness of electronic postdischarge surveillance depends on the likelihood that patients will return to the same healthcare provider. Although surveillance using claims data can be extended over multiple care providers, discharge codes and other indirect measures are in turn more likely to suffer from misclassification (268). Thus, a computer-based surveillance system may improve identification of in-hospital and postdischarge infections cost-effectively but during the study period electronic medical records did not exist yet on a large scale in Estonia.

We believe that our surveillance method improves confidence in results and the high response rate confirms the usefulness of this kind of the approach. Telephone interview would seem to be the most effective method of patient follow-up after discharge for this group of patients, although different approaches were not formally evaluated. Our postdischarge surveillance system was most suitable in the current circumstances.

7.7. Limitations of the study

To describe epidemiology of hospital-wide nosocomial BSI in Estonia, we collected data only from selected hospitals. Thus, not all Estonian hospitals (primary and secondary care level) were included and the results may be referral biased. Nevertheless, the number of blood culture sets in these three hospitals is approximately 75% of the total amount performed during the study period in Estonia according to data collected for the European Antimicrobial Resistance Surveillance System (unpublished data). Therefore, we believe that these results provide a reliable assessment of the epidemiology of nosocomial BSI in Estonia during the study period.

Because of the limited resources we did not collect data on CL-days outside the ICU and we were unable to produce rates of CLABSI adjusted by CL use in our hospital-wide surveillance of nosocomial BSIs. Hospitals and their patient populations vary substantially, so it has become acceptable to calculate and report risk-adjusted infection rates (i.e., rates that are adjusted by important confounding factors). The rates can be adjusted by length of stay (e.g., incidence density – the number of BSI per 1000 patient days); adjusted by exposure to devices (e.g., the number of BSI per 1000 central line-days) and stratified by unit type (e.g., ICU); and adjusted by severity of illness (e.g., neonatal BSI rates stratified by the birth weight) as we did in our PICU study (270). Risk adjustment produces a more accurate estimate of risk at individual facilities (271).

We used only laboratory confirmed methods in surveillance of nosocomial BSI, but infections are missed if cultures are not sent or if microorganisms fail to grow on culture media. Surveillance definitions for primary BSI distinguish those that are microbiologically documented from those that are not. The latter is known as clinical sepsis and can be reported as primary BSI. Some surveillance systems or studies (mostly of neonates and infants) include this definition as well (99). However, detection of clinical sepsis requires prospective on-site surveillance and therefore demands more resources and the amount of work than laboratory-based method (272). In addition, the surveillance method to detect clinical sepsis will greatly impact the infection rate and make benchmarking difficult (272).

The limitation of the SSI study is that this is single hospital observation focusing on one type of surgical procedure and may not necessarily be extrapolated to other centres. The Dutch national surveillance network, PREZIES, analyzed data on 131 798 surgical procedures and the highest rate of SSI after discharge was found for appendectomy (79% of operations), followed by knee prosthesis surgery (64%), mastectomy (61%), femoropopliteal or femorotibial bypass (53%), and abdominal hysterectomy (53%) (273). With this approach it could be possible to discover the procedures for which postdischarge surveillance is most essential, which may be important for efficient allocation of resources on national or hospital level (273). However, while no universally accepted and validated method for postdischarge surveillance exists, the method used to identify postdischarge SSI on a local level is likely to be dependent on

existing resources, on the objective of surveillance, and on the nature of the data routinely available (15). Usefulness of our method for surgical procedures other than CS remains to be studied.

7.8. Future considerations

Prevention of HAIs has become a major focus of quality and patient safety programs in hospitals worldwide (3). We believe that our work has drawn attention to the problem of HAI and contributed to the development of surveillance activities on hospital level during last 10 years in Estonia. For example, besides ongoing surveillance of hospital-wide nosocomial BSI and SSI following CS we have implemented surveillance of ICU-acquired infections (VAP, catheter-associated UTI and CLABSI), *Clostridium difficile* infections, SSI following coronary artery bypass graft and multiresistant microorganisms at Tartu University Hospital. Once a year we perform hospital-wide point prevalence survey of HAI and antimicrobial use. Within 10 years (2004–2014) the overall incidence of HAI in adult ICU has decreased approximately three times at Tartu University Hospital.

Unfortunately, the effective HAI surveillance system on national level is still lacking in Estonia. For example, ideally BSI monitoring should be continuous on-going data collection and data transfer, analysis, interpretation and reporting of data (preferably in real time) (11). Population-based studies have been proposed as the best way of defining the epidemiology of BSI (78). In these designs, all cases of disease occurring among residents of a defined geographical area are ascertained allowing to calculate incidence rates across selected age groups, race and sex (78). For example, Finland is the country that monitors the epidemiology of BSI overall on a nationwide basis. All clinical microbiology laboratories in Finland notify electronically information on positive blood cultures. The unique national identity code of the patients allows linkage to data on vital status from the population registry and also makes it possible to conduct register linkage studies in which information on patient characteristics and hospital stay are obtained from other national registries.(11) Estonia needs comprehensive HAI monitoring system on national level because knowledge of the incidence of HAI is important for setting healthcare and research priorities and for evaluating the effectiveness of preventative interventions. It is also important to monitor antimicrobial resistance and to detect and characterize resistance mechanisms in real time. Unfortunately, many monitoring programs like EARS-Net rely on yearly reports that are relatively slow processes (11). We need our own system on national level to receive local data immediately. Up-to-date information on species distribution and patterns of antimicrobial resistance is essential for projecting coverage by different antibiotic regimens and are thus crucial for appropriate clinical guidelines (11).

Reliable HAI surveillance also depends on optimal and standardized sampling practice. According to EARS-Net reports during the study period less

blood cultures were taken in Estonia than for example in Nordic countries (235). Thus implementation of appropriate sampling practices will increase the quality of our diagnostics as well as makes surveillance data more comparable. Specific guideline for obtaining blood cultures has been available at Tartu University Hospital since 2006 and the blood culture sampling rate per 1000 patient-days has increased during 10 years from 21 (2004–2005) to 32 (2014). The implementation of molecular typing of pathogens in routine laboratory service will enable to detect clonal spread and thus further improve HAI surveillance quality.

Probably in the future traditional methodologies for HAI surveillance like review of medical records of all patients at risk for the specified HAI which are resource intensive and time consuming will be replaced with methods based on information technology (268). Various electronic databases exist within the healthcare setting and may be utilized to perform HAI surveillance (274). Automated systems would not be affected by cognitive biases, intentionally manipulating infection rates would be more difficult and likely transparent, and modelling strategies could be used to estimate probabilities of events (275). A further challenge for all forms of electronic surveillance is assessment of device presence, such as urinary catheters and CLs, as this determines the population at risk for device-related HAIs (268). In addition, the important challenges such as postdischarge surveillance and case-mix adjustment need to be addressed in the future (268).

Future research should focus on the effects of infection control measures, e.g., to prevent outbreaks and to decrease incidence of CLABSI in PICU. Compliance with different guidelines needs to be studied. Improving behaviour in infection prevention and control practice remains a challenge, and understanding the determinants of healthcare workers' behaviour is fundamental to develop effective and sustained behaviour change interventions (276).

As greater efforts are made to quantify and describe the characteristics of HAIs in Estonia, active surveillance, application of prevention interventions, and judicious antimicrobial use should greatly improve patient outcomes.

8. CONCLUSIONS

1. In three major hospitals the overall hospital-wide incidence density of nosocomial BSI did not differ significantly but the incidence was lower compared to other reported studies. The case-fatality rate was consistent with previous investigations. However, our rate of hospital-wide nosocomial BSI could be underreported due to low blood culture sampling rate. In our mixed PICU we observed higher incidence and incidence density of nosocomial BSI than reported previously partly because of outbreak situation and methodological issues such as case definition. Our case-fatality rates for patients in PICU were lower than those reported by other studies, which could be explained by the high rate of CoNS infections. Reporting nosocomial BSI rates with and without CoNS may provide more comparable data for benchmarking. Standardization of case definitions and methods including blood culturing could improve the quality of data, comparability of infection rates and outcomes between units and hospitals.
2. In our research intravascular devices were the most frequent potential factors predisposing patients to nosocomial BSI. Approximately half of the episodes were CLABSI. In hospital-wide nosocomial BSI study half of the cases occurred in ICUs and a quarter in hematological wards. Efforts for prevention should be primarily targeted at CL insertion and care in high risk specialties such as ICU and hematology.
3. The most commonly isolated causative organisms (CoNS followed by *Enterobacteriaceae* and enterococci) in our hospital-wide BSI surveillance study have been among the leading pathogens also in other studies. With the exception of relatively high antimicrobial resistance among *Pseudomonas* spp., the overall resistance patterns of Estonian hospital-wide nosocomial BSI pathogens were similar to those seen in Nordic countries and lower than in Central and Southern Europe. The differences in the distribution of infecting organisms in our PICU compared to previous reports, reflected the ongoing two outbreaks. High levels of antimicrobial resistance were detected in PICU, partly because of the outbreaks. This emphasises the need for local surveillance data in order to monitor trends, identify wards at risk, outbreaks and emerging resistant pathogens.
4. The incidence of SSI following CS in our hospital was lower than rates from other studies that have used postdischarge surveillance. We found three variables associated with increased risk for developing SSI: internal fetal monitoring, chorioamnionitis, and surgical wound classes III and IV. A challenge exists to decrease the frequency of internal fetal monitoring and to treat chorioamnionitis as soon as possible. One third of the patients did not receive PAP, but new guidelines are recommending single dose prophylactic antibiotics to all women undergoing CS prior to incision. Following PAP recommendations can be one more possibility to decrease the incidence of SSIs in future.

5. Almost half of SSIs were detected during postdischarge surveillance highlighting the importance of this approach to obtain accurate rate of SSI. The multi-method approach using a combination of telephone calls, healthcare worker questionnaire, and outpatient medical records review resulted in high SSI follow-up rate and was not particularly time consuming. We can recommend this method for surveillance of SSIs following CS.

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10. SUMMARY IN ESTONIAN

Haiglatekkeseid infektsioonid Eestis – vereringe- ja operatsioonipiirkonna infektsioonide epidemioloogia ja järelevalve

Viimastel aastakümnetel on haiglates üha rohkem tähelepanu pööratud ravi ohutusele, kuna see on oluline ravikvaliteedi problem (1). Haiglatekkene infektsioon (HI) on seotud arstiabi osutamisega ning ning see avaldub patsiendil kas tervishoiuasutuses viibides või pärast sealt lahkumist. HI kaasneb suurem haigestumus, suremus ja tervishoiukulutuste kasv (2, 3). Euroopas diagnoositakse vähemalt üks HI igal aastal 3,2 miljonil patsiendil (4).

HI vältimises on oluline järelevalve, kuna see võimaldab leida parimaid meetodeid HI ennetamiseks (5). Paljudes maades on loodud riiklikud HI järelevalvesüsteemid, kuid alates 2008. aastast on Haiguste Ennetamise ja Tõrje Euroopa Keskus käivitanud üleeuroopalise intensiivravitekkete infektsioonide ja operatsioonipiirkonna infektsioonide (OPI) järelevalvesüsteemi (6).

Kõige sagedasemad HI liigid on alumiste hingamisteede infektsioonid, OPI, kuseteede infektsioonid ja vereringeinfektsioonid (VRI) (4). HI haigestumus varieerub erinevate patsiendigruppide lõikes sõltuvalt riskifaktoritest nagu näiteks patsiendi enda tervislikust seisundist (vanus, kaasuvad haigused jm) kui ka invasiivsete vahendite kasutamisest. Kõige rohkem on ohustatud intensiivravi osakonna patsiendid. Lastel on HI suurim risk vastsündinute- ja lasteintensiivravi osakonnas. Nendes osakondades on kõige sagedasem infektsioon VRI, mis põhjustab lisaks suuremale haigestumusele ning suremusele ka kaugtägajärgi nagu arenguhäireid ja kasvupeetust (8).

Samas on HI järelevalve oluline ka väljaspool intensiivravi osakonda, kuid kõikide HI järelevalvet on keeruline ja kulukas teostada (9). Eelistatud võiks olla ülehaiglaline VRI järelevalve, kuna need esindavad infektsioonide spektri kõige tõsisemat osa (10). Ülehaiglaline VRI järelevalve võimaldab jälgida haigestumuse trende, välja selgitada riskiosakondi, avastada puhanguid ja resistentsid mikroorganisme ning hinnata HI vältimismeetodite rakendamise mõju (10). Haigustekitajate spektri ja ravimresistentsuse järelevalve on abiks ka antimikroobse ravi juhendite koostamisel (11).

Kui VRI on üheks kõige raskema kuluga infektsiooniks, siis OPI on üheks sagedasemaks (12, 13). Euroopa antibiootikumide kasutamise ja HI hetkelevimusuuringu oli OPI sageduselt teine infektsioon (19,6% kõikidest HI) (4). Kuna operatsioonijärgne haiglasviibimise aeg jätkuvalt lüheneb, on haiglajärgne järelevalve muutunud üha olulisemaks, et saada täpsemaid tulemusi OPI haigestumuse kohta (14). Hinnatud on mitmete haiglajärgsete OPI järelevalvemeetodite efektiivsust, kuid sellest hoolimata ei ole leitud ühtegi universaalselt aktsepteeritavat strateegiat nimetatud infektsioonide jälgimiseks (15). Haiglajärgsed järelevalvemeetodid ja -tegevused erinevad riikide lõikes (4).

Enne 2002. aastat oli Eestis uuritud vaid HI mikroorganisme nagu *Acinetobacter baumannii*, *Staphylococcus aureus* ja *Escherichia coli* (17, 18). Eestis ei

olnud ühtset HI järelevalvesüsteemi ja puudus ülevaade HI epidemioloogiast. Selle lünga täitmiseks alustasime keisrilõikejärgse OPI uurimisega, kuna keisrilõige on üks kõige sagedasematest operatsioonidest maailmas (216, 224). Teiseks valisime VRI, mis on kõige raskem ja komplitseeritum HI (66).

Uurimistöö eesmärgid

Uurimistöö peamiseks eesmärgiks oli välja selgitada HI epidemioloogia Eestis täiskasvanutel ja lastel ning aidata kaasa järelevalvesüsteemide loomisele haiglates ning luua uusi teadmisi ja oskusi HI ennetamiseks tulevikus.

Konkreetsed eesmärgid:

1. Selgitada välja VRI haigestumus ja surmavusmäär kolmes suuremas haiglas
2. Selgitada välja VRI teket soodustavad faktorid ning riskipiirkonnad (osakonnad)
3. Selgitada välja VRI etioloogia ja mikroorganismide antibiootikumresistentsus
4. Selgitada välja keisrilõikejärgse OPI haigestumus ja riskifaktorid Tartu Ülikooli Kliinikumi naistekliinikus
5. Hinnata haiglajärgse OPI kombineeritud järelevalvemeetodi sobivust

Patsiendid ja meetodid

Ülehaiglalise VRI uuringu (**1. uuringu**) viisime läbi kolme Eesti haigla (Ida-Tallinna Keskhaigla, Põhja-Eesti Regionaalhaigla, Tartu Ülikooli Kliinikum) aktiivraviosakondades aastatel 2004–2005. VRI **2. uuringu** viisime läbi TÜK lasteintensiivravi osakonnas (LIRO) aastatel 2004–2008. Mõlemasse uuringusse kaasasime kõik patsiendid, kelle laboratoorselt kinnitatud VRI vastas USA Haiguste Ennetamise ja Tõrje Keskuse definitsioonile. LIRO uuritavateks olid patsiendid, kel oli diagnoositud intensiivravi osakonna tekkene VRI. Andmeid kogusid nende haiglate infektsioonikontrolliarstid ja -õed prospektiivselt vastavalt standardiseeritud uuringuprotokollile. LIRO kogusime ka igapäevaselt tsentraalveenikateetri kasutamise andmeid. Verekülvid võeti raviarsti korraldusel vastavalt kliinilisele näidustusele. Verekülvidest isoleeritud patogeene identifitseeriti ja antibiootikumtundlikkus (disk- ja gradientdifusioonimeetodil) määrati iga haigla laboris. Uuritud verekülvide arvu saime laboritest.

Keisrilõikejärgse OPI uuringu (**3. uuringu**) viisime läbi TÜK naistekliinikus kõikidel nii erakorralise kui plaanilise keisrilõikega sünnitanud patsientidel aastal 2002. Kogusime andmeid võimalike riskifaktorite kohta. Kõigile patsientidele andsime enne haiglast väljakirjutamist küsimustiku ja palusime selle anda arstile täitmiseks juhul, kui tekib OPI. 30–35 päeva pärast operatsiooni helistasime patsientidele. Kui jäi kahtlus OPI-le ning arst ei olnud tagastanud küsimustikku, võtsime ühendust raviarstiga kinnitamaks OPI olemasolu või saime

kinnituse ambulatoorsest kaardist. OPI diagnoosisime 30 päeva jooksul pärast keisrilõiget vastavalt USA Haiguste Ennetamise ja Tõrje Keskuse definitsoonile kas haiglas pärast operatsiooni, rehospitalseerimisel või haiglajärgse järelevalve meetodi abil.

Statistiliseks analüüsiks kasutasime tarkvara STATA versioon 8.0 ja 9.0 ning SPSS versioon 17.0. Arvutasime OPI esmashaigestumuse, VRI esmashaigestumuse ja haigestumuskordaja (LIRO vastavad näitajad ka koagulaasnegatiivseid stafülokokke kaasates ja välja arvates), TVK seotud VRI haigestumuskordaja, tsentraalveenikateetri kasutusmäära, VRI surmavusmäära. OPI riskifaktorite välja selgitamisel kasutasime mitmest logistilist regressioonianalüüsi.

Peamised tulemused

Ülehaiglaline VRI uuring (1. uuring)

Uuringuperioodil võeti 13–21 verekülvi 1000 voodipäeva kohta kolmes Eesti haiglas. Diagnoosisime kokku 549 VRI episoodi 507 patsiendil. VRI esmashaigestumus 100 hospitaliseerimise kohta oli 3,1 (haare, 0,7–4,3) ja haigestumuskordaja 1000 voodipäeva kohta oli 0,6 (haare, 0,2–0,8). Patsientide keskmine vanus oli 49 a. (haare, <1–92 a.) ning 59% olid mehed. Patsientidest 44 (8%) olid vastsündinud ja 46 (10%) lapsed vanuses ≤16 a. Kõikidest VRI episoodidest 54% tekkis intensiivravi ja 24% hematoloogia osakondades. Kõige sagedasemaks VRI lähtekohaks (47%) oli tsentraalveenikateeter ja alumised hingamisteed (13%). Kõige sagedasemaks potentsiaalseks VRI riskifaktoriks olid veresoonesisesed vahendid: tsentraalveenikateetreid kasutati 77% ja arterikanüüle 46% patsientidest.

Kolme haigla VRI haigustekitajatest (593 tüve) moodustasid Gram-positiivsed aeroobid 53%, Gram-negatiivsed aeroobid 39%, seened 6% ning anaeroobid 2%. Kõige sagedasemad mikroobid olid koagulaasnegatiivsed stafülokokid (26%), *Enterobacteriaceae* (24%), enterokokid (13%) and *Pseudomonas spp.* (10%). VRI episoodidest 8% olid polümikroobsed. *Staphylococcus aureus* tüvedest 7% olid metitsilliin-resistentsed. Üks *Escherichia coli* ja 3 *Klebsiella pneumoniae* tüve produtseerisid laia toimespektriga beeta-laktamaasi. *Pseudomonas spp.* tüvedest 19%, 25%, 30% ja 44% olid vastavalt resistentsed tseftasidiimile, meropenemile, piperatsilliin/tasobaktaamile ning imipenemile.

Üldine surmavusmäär haiglas oli 31% varieerudes 15% *S. aureus* poolt põhjustatud VRI korral kuni 57% enterokokkide puhul. Intraabdomiaalse ja operatsioonipiirkonnast lähtunud VRI korral oli surmavusmäär kõige suurem võrreldes teiste lähtekohtadega. Seitsme päeva surmavusmäär oli 12%.

Lasteintensiivravi osakonna VRI uuring (2. uuring)

Aastatel 2004–2006 võeti LIRO-s 268 verekülvi 1000 voodipäeva kohta, 89% juhtudest võeti ainult üks verekülvi. Uuringuperioodil diagnoosisime 126 VRI episoodi 89 patsiendil. VRI esmashaigestumus 100 hospitaliseerimise kohta oli

9,2 (95% usaldusvahemik 7,8–10,9) ja haigestumuskordaja 1000 voodipäeva kohta 12,8 (95% usaldusvahemik 10,7–15,2). Kui me arvasime tulemustest välja koagulaasnegatiivsete stafülokokkide kui võimalike verekülvi kontaminantide poolt põhjustatud VRI, siis olid vastavad tulemused 5,1 (95% usaldusvahemik 4,0–6,4) ja 7,1 (95% usaldusvahemik 5,5–9,0). Patsientide hulgas oli 74 vastsündinut, 8 imikut ja 7 last vanuses 1–7 aastat. Vastsündinute seas oli < 1000 g sünnikaaluga patsiente 57%.

Kõige rohkem esines primaarset VRI (92 episoodi), nendest 67 olid tsentraalveenikateetriga seotud infektsioonid. Vastsündinute tsentraalveenikateetriga seotud VRI haigestumuskordaja oli 19,3 1000 tsentraalveenikateetripäeva kohta (95% usaldusvahemik 14,7–24,9) ning kõige kõrgem vastav näitaja (27,4) esines < 1000 g sünnikaaluga vastsündinutel. Kõige sagedasemaks potentsiaalseks VRI riskifaktoriks olid veresoonesisesed vahendid: tsentraalveenikateetreid kasutati 70% ja arterikanüüle 48% VRI juhtude korral.

VRI haigustekitajatest (136) moodustasid Gram-positiivsed ja Gram-negatiivsed mikroorganismid vastavalt 60 ja 35%. Kõige sagedasemad olid koagulaasnegatiivsed stafülokokid (43%) ja *Serratia marcescens* (14%). Viimase tekitaja suur sagedus oli tingitud puhangust uuringuperioodil. Neli *S. aureus* tüve seitsmest olid metitsilliin-resistentsed, mis kõik kuulusid metitsilliin-resistentse *S. aureus* puhangu tüvede hulka aastatel 2006–2007. Kolm *Klebsiella pneumoniae*, 3 *S. marcescens* ja 3 *Enterobacter cloacae* tüve (23% kõikidest *Enterobacteriaceae* tüvedest) produtseerisid laia toimespektriga beeta-laktamaasi.

Üheksa patsienti (10%), nendest 8 vastsündinut, suri haiglasviibimise jooksul. Seitsme-päeva surmavusmäär oli 1%.

Keisrilõikejärgse OPI uuring (3. uuring)

Uuringuperioodil sünnitas 2092 naist, nendest keisrilõike teel 310 (14,8%; 95% usaldusvahemik, 13,3–16,4). Uuringus oli nõus osalema 305 patsienti. Peamine põhjus keisrilõikega sünnitamiseks oli loote distress (24%).

OPI tekkis 19 patsiendil (6,2 %; 95% usaldusvahemik, 3,8–9,6): 4 endometriiti, 1 intraabdominaalne abstsess, 14 haavainfektsiooni. OPI diagnoosisime 11 patsiendil haiglas ja 8 patsiendil haiglajärgselt, kellest 2 rehospitalseeriti.

Pärast haiglast lahkumist helistasime 267 patsiendile, kellel OPI ei olnud diagnoositud haiglas. Nendest 15 kirjeldas võimalikku infektsiooni, kuid raviarsti kinnitas seda kuuel juhul. Üheksa patsiendi kohta, kellele ei õnnestunud helistada ega kelle puhul ka raviarst ei tagastanud küsimustikku, saime informatsiooni ambulatoorsest kaardist. Pärast haiglast lahkumist saime telefoniküsitluse, küsimustiku ja ambulatoorsete kaartide abil informatsiooni 95% patsientide kohta. Haiglajärgselt diagnoosisime 42% OPI juhtudest.

Leidsime kolm statistiliselt olulist riskifaktorit: invasiivne loote monitooring (šansside suhe 16,6; 95% usaldusvahemik 2,2–125,8), koorioamnioniit (šansside suhe 8,8; 95% usaldusvahemik 1,1–69,6) ja kirurgiline haavaklass III ja IV (šansside suhe 3,8; 95% usaldusvahemik 1,2–11,8). Perioperatiivset

antibiootikumprofülaktikat ei tehtud 103 patsiendile. Uuringuperioodil kehtinud perioperatiivse antibiootikumprofülakika juhendi järgitavus oli 73%.

Järeldused

1. Võrreldes mujal läbiviidud uuringute tulemustega ei erinenud kolme haigla VRI haigestumuskordaja ja surmavusmäär märkmisväärselt, kuid esmashaigestumus oli madalam. Samas võeti uuringuperioodil vähe verekülve, mis võis mõjutada tulemust. Lasteintensiivravi osakonna VRI haigestumus oli kõrgem kui eelnevalt avaldatud uuringutes. Seda võisid mõjutada nii kaks bakteriaalset puhangut uuringuperioodil kui ka VRI definitsiooniga seotud metodoloogilised probleemid. Surmavusmäär võrreldes teiste lasteintensiivravi osakonnas tehtud uurimistöödega oli madal, kuid seda võis mõjutada suur koagulaasnegatiivsete stafülokokkide poolt põhjustatud VRI osakaal. Nii koagulaasnegatiivseid stafülokokke kaasavad kui välistavad VRI tulemused võiksid parandada andmete võrreldavust. Definitsioonide ja meetodite, sealhulgas verekülvi võtmise praktika, standardiseerimine parandab andmete kvaliteeti ning tulemuste osakondade- ning haiglatevahelist võrreldavust.
2. Mõlemas VRI uuringus esines potentsiaalsetest VRI riskifaktoritest kõige rohkem veresoonesiseseid kateetreid ja kanüüle. Peaaegu pooled episoodid olid tsentraalveenikateetriga seotud vereringeinfektsioonid. Ülehaiglasises VRI uuringus diagnoosisime pooled juhud intensiivravi ja neljandik juhtudest hematoloogia osakondades. Sellest lähtuvalt tuleks riskiosakondades nagu intensiivravi ja hematoloogia pöörata erilist tähelepanu veresoonesiseste vahendite sisestamisele ja hooldusele.
3. Ülehaiglasise VRI uuringu haigustekitajate spekter sarnanes teiste uuringute tulemustega. Üldine antibiootikumresistentsus (v.a. kõrge *Pseudomonas* spp. antibiootikumresistentsus) oli sarnane Põhjamaadele ja madalam kui Kesk- ja Lõuna-Euroopas. Lasteintensiivravi osakonna VRI haigustekitajate spektrit ja antibiootikumresistentsust mõjutasid kaks bakteriaalset puhangut. See rõhutab kohaliku järelevalve olulisust, sest see võimaldab jälgida haigestumuse trende, välja selgitada riskiosakondi, avastada puhanguid ja resistentseid mikroorganisme.
4. Keisrilõikejärgse OPI esmashaigestumus oli madalam võrreldes teiste haiglajärgset järelevalvet kasutanud uuringute tulemustega. Riskiteguriteks osutusid korioamnioniit, invasiivne loote jälgimine ja kirurgiline haavaklass III ja IV. OPI edaspidiseks vähendamiseks tuleks piirata invasiivset loote jälgimist ja ravida korioamnioniiti võimalikult varakult. Kolmandikule patsientidest ei tehtud perioperatiivset antibiootikumprofülaktikat, kuid praegu kehtivad PAP juhendid soovitavad seda kõikidele keisrilõikega sünnitajatele. PAP juhendite järgimine oleks edaspidi üheks võimaluseks, et veelgi vähendada operatsioonipiirkonna infektsioone.

5. Peaaegu pooled OPI juhud diagnoosime pärast haiglas viibimist, mis rõhutab haiglajärgse järelevalve olulisust. Meie valitud meetod osutus sobivaks keisrilõikejärgse OPI haiglaväliseks järelevalveks ning oli suhteliselt lihtsalt teostatav. See meetod sobib ka edaspidiseks kasutamiseks.

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CURRICULUM VITAE

Name: Piret Mitt
Date of birth: 7.06.1974
Citizenship: Estonian
Address: Tartu University Hospital, Department of Infection Control, L. Puusepa 8, Tartu 51014
Phone: +372 731 8113
E-mail: Piret.Mitt@kliinikum.ee

Education

1980–1992 Tartu Secondary School No. 1
1992–1998 University of Tartu, Faculty of Medicine
1998–1999 University of Tartu, internship
1999–2003 University of Tartu, residency in infectious diseases
2003–2009 University of Tartu, Faculty of Medicine, Phd studies

Professional employment

2003–... Tartu University Hospital, Department of Infection Control,
infectious disease physician

Main research fields and publications

Epidemiology and surveillance of healthcare-associated infections. Surveillance of antimicrobial use and antimicrobial resistance. 8 articles in the international peer reviewed medical journals, 4 articles in *Eesti Arst*

List of positions in professional organizations or societies

Estonian Society of Infectious Diseases – member of the board
European Society of Clinical Microbiology and Infectious Diseases – member
Estonian Medical Association – member

ELULOOKIRJELDUS

Nimi: Piret Mitt
Sünniaeg: 07.06.1974
Kodakondsus: eesti
Aadress: SA Tartu Ülikooli Kliinikum, infektsioonikontrolli teenistus;
L. Puusepa 8, Tartu 51014
Telefon: +372 7 318 113
E-post: Piret.Mitt@kliinikum.ee

Haridus

1980–1992 Tapa 1. Keskkool
1992–1998 Tartu Ülikool, arstiteaduskond
1998–1999 Tartu Ülikool, üldarstlik internatuur
1999–2003 Tartu Ülikool, infektsioonhaiguste eriala residentuur
2003–2009 Tartu Ülikool, doktoriõpe

Teenistuskäik

2003–... SA Tartu Ülikooli Kliinikum, infektsioonikontrolli teenistus,
infektsionist

Peamised uurimisvaldkonnad ja publikatsioonid

Haiglatekkestes infektsioonide epidemioloogia ja järelevalve. Antimikroobsete ravimite kasutuse ja antibiootikumresistentsuse järelevalve. 8 artiklit rahvusvahelistes eelretsenseeritavates ajakirjades, 4 artiklit ajakirjas „Eesti Arst“

Osalemine erialastes seltsides

Eesti Infektsioonhaiguste Selts – juhatuse liige
Euroopa Kliinilise Mikrobioloogia ja Infektsioonhaiguste Selts – liige
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