

Bloodstream Infections, Finland, 2004–2018

[Announcer] This program is presented by the Centers for Disease Control and Prevention.

[Sarah Gregory] Hello, I'm Sarah Gregory, and today I'm talking with Dr. Keiju Kontula, an infectious disease specialist at Helsinki University Hospital in Helsinki. We'll be discussing the incidence of bloodstream infections in Finland from 2004-2018.

Welcome, Dr. Kontula.

[Keiju Kontula] Thank you and thank you for having me here today.

[Sarah Gregory] Your study is about bloodstream infections. Tell us what they are.

[Keiju Kontula] So bloodstream infections (or BSIs) are severe, potentially life-threatening infections. They're defined as presence of viable bacteria or fungi in bloodstreams demonstrated by positive blood cultures. Bacteria may enter the bloodstream as a complication of an infection, such as pneumonia, or from a skin wound or via catheters, for example. And fever is a typical symptom of BSI. Other symptoms vary depending on the possible prior infection and may include cough, dysuria, or diarrhea, for example. However, the symptoms of BSIs may be vague, especially in older patients, appearing only as weak general condition, for instance. So this is a challenge in diagnosis of BSIs.

The term septicemia or "sepsis" is sometimes used in similar context as bloodstream infection. However, they're not synonyms. Sepsis is a clinical syndrome caused by a dysregulated inflammatory response to the current infection and the microbe. It's important to note that not all patients with sepsis have bacteremia, and on the other hand, not all BSI patients fulfill the sepsis criteria. And so severe sepsis can lead to organ failure and septic shock, which is associated with high mortality.

[Sarah Gregory] Okay. Going back a little bit. You said some of the things that can lead to bloodstream infections. But how do those things actually cause them? I mean, so you get pneumonia. How does that become a bloodstream infection?

[Keiju Kontula] Bloodstream infections are caused by bacteria and fungi. *Escherichia coli* and *Staphylococcus aureus* are the two most common causative pathogens of BSIs in Europe and North America. In our study, these two represented over 40% of all BSIs in Finland during 2004-2018. In general, the causative microbes of BSIs vary to some extent depending on patient's age and gender. Also, the origin of the infection, whether the infection is community-acquired or healthcare-associated, affects the range of typical causative pathogens. And also the foci or the source of the infection affects them (causative microbes). So as you asked about the pneumonia, that's typically caused by *Streptococcus pneumoniae*.

[Sarah Gregory] And why are they so serious?

[Keiju Kontula] In bloodstream infections, the causative microbe, either bacteria or fungi, invades the blood circulation and challenges the patient's immune system. Bacteria can spread through the bloodstream to other locations of the body. This is called hematogenous spread, and can result in infectious complications such as abscesses, endocarditis, osteomyelitis, and arthritis.

The elderly and immunocompromised patients, such as those with ongoing chemotherapy, are at high risk of developing severe infections and fatal outcome. On the other hand, some bacteria, such as meningococci, can cause really serious illness also in otherwise healthy patients.

[Sarah Gregory] How many people get them annually in North America and Europe?

[Keiju Kontula] Well, we don't have the exact numbers of BSI episodes, because there is only limited population-based data available from specific areas that can be utilized when assessing the burden of the disease. According to incidence rates from these older population-based studies, there is an estimate of nearly 600,000 to 700,000 episodes of BSIs in North America and 1.2 million episodes in Europe each year.

In our study, the BSI incidence rate was 309 cases per 100,000 population in Finland in 2018, which was the most previous year of the study period. By utilizing our incidence rate and general population data for USA and Canada, and Europe in 2018, we would get an estimate of up to 1.1 million BSI episodes in North America and 2.3 million episodes in Europe in 2018.

[Sarah Gregory] Do you know how many of those cases were fatal?

[Keiju Kontula] Well, it depends on the population. In our study, case fatality was 13%. But in healthcare-associated cases, case fatality is usually higher.

[Sarah Gregory] I see, okay. So you mentioned already two types of BSIs that are increasing—multidrug-resistant microbes and *E. coli* and fungi. Why did you focus on these two?

[Keiju Kontula] Yeah. So *E. coli* bacteria was the most common causative microbe in our study, accounting for nearly 30% of all BSIs. The incidence of *E. coli* BSIs was highest among the elderly, and we also noted that the overall BSI incidence in older persons increased considerably during the study period. Therefore, the increase in *E. coli* BSIs is mostly explained by the observed overall rise in BSIs among older persons.

The occurrence of multidrug-resistant microbes (or MDR microbes) as causative pathogens of BSIs increases worldwide. We noted that the proportion of MDR BSIs of all BSIs increased from 0.4% to 2.8% during 2004-2018, with ESBL-*E. coli*, representing a majority of all MDR BSIs. ESBL means extended-spectrum beta-lactamase-producing *E. coli*. The known risk factors for developing an ESBL infection include older age, prior antimicrobial treatment, hospitalization, and travelling, for example.

In our study, the proportion of ESBL-*E. coli* BSIs of normal, susceptible *E. coli* BSIs, also increased considerably over time. And this increasing trend in ESBL-*E. coli* reflects the observed rise in all *E. coli* BSIs. In addition to ESBL-*E. coli*, our definition of MDR microbes included ESBL-*Klebsiella pneumoniae*, MRSA, VRE, and CPE. But no marked increase was noted in the occurrence of MDR pathogens other than ESBL-*E. coli*.

[Sarah Gregory] Are there others? Other BSIs?

[Keiju Kontula] Altogether, the proportion of BSIs caused by gram-negative bacteria increased during 2004-2018, whereas those caused by gram-positive bacteria decreased. In addition, we noted that polymicrobial BSIs increased slightly.

Of the most common single causative microbes, in addition to *E. coli*, the incidence of *Staphylococcus aureus*, *Klebsiella pneumoniae*, enterococci, and beta-hemolytic streptococci all increased considerably, whereas coagulase-negative staphylococci and *Streptococcus pneumoniae* remained rather stable.

[Sarah Gregory] I think you've already answered this, but is there an age group that is most affected across the board?

[Keiju Kontula] Yes, older persons are at highest risk of BSIs and of fatal outcome. We noted that the BSI incidence clearly increased with age and was highest among patients over 60 years of age, especially among patients over 80 years, but also among infants under one year.

Also some gender differences were noted in our study concerning the BSI incidence. The incidence was higher for males than for females among infants under one year and all persons over 40 years of age. So it was only among younger adults (20-29 years of age) where females had higher incidence rates than males.

[Sarah Gregory] Do you have any idea why there would be a gender difference?

[Keiju Kontula] This is a good question. It has been speculated that maybe there are some behavioral risk factors among males more than among females. That's just one thought. Or maybe differences in seeking help or treatment, just to name a few reasons. But I don't have any right answer for this.

[Sarah Gregory] Okay. You mention that the 1-month case-fatality rate decreased from 13 percent to 12.6 percent, but the 1-month all-cause mortality rate rose from 20 to 39 deaths per 100,000 people in your study. What does this mean?

[Keiju Kontula] This is a good question. First, I'll shortly define the terms. So case fatality means the proportion of patients who died from a BSI within one month of the first positive blood culture. The all-cause mortality represents deaths occurring in the population within one month. And so we did not have exact causes of death of the BSI patients, so we didn't know whether the BSI was the main cause of death or were there other contributing factors also.

As the incidence of BSIs, meaning the number of BSI episodes, increased in Finland overtime due to aging of population and rising burden of comorbidity, the number of deaths among patients with BSIs also increased as the vulnerable patients died. So this explains the noted increase in BSI mortality. The case fatality of BSIs did not increase, which might reflect improvements in treatment and diagnosis of BSIs.

[Sarah Gregory] Okay. So according to your study, there was an increase in community-acquired infections and a decrease in hospital-acquired ones. Why would this be?

[Keiju Kontula] There may be several reasons for this finding. First, the rising proportion of community-acquired BSIs over time might be a result of an increase in outpatient invasive procedures prior to the infection. In other words, possibly some procedures that were previously performed during hospitalization are now done at outpatient clinics. Our data on the origin of the infection in our study was gathered from the hospital discharge register. Some BSIs might have been classified as community-acquired instead of healthcare-associated since the register does not include all types of outpatient procedures. Instead, it contains day surgery only. For example, regular visits due to chronic hemodialysis are missing from the register.

Second, I would like to believe that maybe we have managed to prevent some hospital-acquired BSIs with effective infection control and preventive measures in healthcare facilities and possibly also with shortened hospitalization periods.

[Sarah Gregory] Why did you do this study?

[Keiju Kontula] So population-based studies, they are considered as the optimal design to define the occurrence of infections. Despite this, there has been only limited data available regarding the burden of bloodstream infections in non-selected patient populations, as most available

studies concentrate on specific causative pathogens or report results from one selected unit or one hospital. In the few recent population-based studies, an increasing trend in the incidence of BSIs over time has been demonstrated.

So our goal in the study was to get a comprehensive understanding, I would say “a big picture”, of the burden and temporal trends of bloodstream infections in Finland. And therefore, we conducted a nationwide population-based study covering all BSIs in Finland during 15 consecutive years.

[Sarah Gregory] Okay. So tell us about population-based study. How do you conduct one?

[Keiju Kontula] In our case, all clinical microbiology laboratories here in Finland, they notify all BSIs to the National Infectious Diseases Register. BSIs of both hospitalized and non-hospitalized patients are reported to this register. The notification of BSI is mandatory for the laboratories as it is regulated by law here in Finland. So we used this nationwide laboratory-based surveillance data to analyze retrospectively all BSIs in Finland during 2004–2018.

[Sarah Gregory] Okay. So maybe this is the same question, but what kind of data did you use?

[Keiju Kontula] Okay. So we gathered all BSIs in Finland during the study period from the National Infectious Diseases Register. And as said, this register contains all BSIs in our country. All residents in Finland are given a unique national identity code, and these identity codes of the BSI patients were utilized when database information was collected. To determine whether the BSI patient survived or died during one month of the positive blood culture, we retrieved the date of death from the Population Information System by linking the identity code to the database.

And similarly, we collected information on hospitalization of the patients (in other words the origin of the infection) and present and prior diagnose codes from the National Hospital Discharge Register. And with the detected ICD-10 diagnose codes we were able to calculate the Charlson comorbidity index for the particular patient.

[Sarah Gregory] Why don't you give us the main highlights of your study now?

[Keiju Kontula] Well, the highlight of our study is finding the considerable increase in the incidence and mortality of bloodstream infections here in Finland during 2004-2018. Our study provides a systematic and comprehensive analysis of the health burden caused by BSIs and may enable international comparisons regarding the occurrence and outcome of BSIs and also rates of antimicrobial resistance, for example.

[Sarah Gregory] So you think these are the most important findings? Is there one particular finding that you think is the most important?

[Keiju Kontula] So although we observed a twofold rise in the incidence and mortality of BSIs, the case fatality of BSIs remained stable. This seems to indicate positive advances in treatment of BSIs over time. In our study, the rise in the incidence of BSIs was sharpest among the elderly. And as the population in Finland (and in many other countries too) ages and the burden of underlying comorbidities grows, the proportion of those persons who are especially vulnerable to BSIs and fatal outcome constantly increases. So as a clinician, I find this important to note.

[Sarah Gregory] Were there any challenges of conducting this study?

[Keiju Kontula] Well, since the study was based on surveillance and register data and was of retrospective design, we had limited clinical information concerning the patients and the infection. We also lacked data regarding treatment of the infection, such as appropriateness of the antimicrobial therapy and possible delays in treatment which most likely have influenced the outcome.

[Sarah Gregory] Were there any surprises?

[Keiju Kontula] Well, we were surprised by the previously mentioned sharp increase in the incidence and mortality of BSIs among the elderly. Despite this increase, the case fatality did not increase as discussed earlier. This may be partly explained by the rather low overall proportion of BSIs caused by MDR pathogens in Finland. So ascending trend was noted, especially in ESBL-*E. coli*. The occurrence of infections caused by MDR microbes is higher in many other European countries and North America, for example, compared to Finland and other Scandinavian countries. So if the spread of antimicrobial resistance continues, it will complicate antimicrobial treatment in the future and may increase the risk of fatal outcome.

[Sarah Gregory] Okay. So your study looked, as you just said, at BSIs in Finland and there are some differences with other countries. But overall, do you think your findings are indicative of a global situation?

[Keiju Kontula] Yes, I do think our findings apply to those countries with ageing population and rising life expectancy. So in practice, this concerns nearly all industrialized countries and also many developing countries.

[Sarah Gregory] This is a very basic question here, but how are BSIs diagnosed?

[Keiju Kontula] Well, the diagnosis of BSIs is based on isolation of a microbe or several microbes in blood culture. So when a BSI is suspected based on patient's clinical presentation, at least two blood culture samples should be taken. Blood cultures should be obtained before initiating any antimicrobial treatment. Typically, the final results of the cultures are not ready until the second day after collecting the samples, so during that time or time period the causative microbe remains indefinite. Possibly in the future there will be rapid PCR-based tests (PCR meaning polymerase chain reaction), and these might be in general use in microbiology laboratories which will speed up the diagnosis of BSIs.

[Sarah Gregory] Because during that one- or two-day delay, I imagine then the infection is getting worse while they're waiting on the results. Is that right?

[Keiju Kontula] So during that time when you don't have the definite name of the bacteria, you rely on your suspicion and you're not 100 percent sure about the antibiotic you have—call it the empiric initial antimicrobial treatment. So after you have gotten the final results, then you know exactly what you're treating and you know what kind of antibiotics to use.

[Sarah Gregory] When a BSI is suspected, do they give any kind of antibiotic and then switch to a specific one after the results come in? Or do they not give anything and just wait until they have the results?

[Keiju Kontula] Okay. So when you suspect a bloodstream infection, you take the blood cultures and then you typically start a broad-spectrum antibiotic to the patient and you continue with that until you get the final result from the blood cultures. And then you can go to a more specific antibiotic to narrow down to a specific antibiotic against that certain microbe.

[Sarah Gregory] I see. So what does public health need to do to stop this spread?

[Keiju Kontula] The preventive means differ depending on the origin of the infection, in other words, whether the BSI is healthcare-associated or community-acquired. For healthcare-associated infections, including bloodstream infections, there are local infection control and surveillance programs in healthcare facilities. These programs include guidelines and checklists for aseptic practices in insertion of catheters and other devices and for aseptic surgical procedures, directions for maintenance of central lines and for monitoring surgical wounds, to list a few. There are also guidelines for prophylactic antimicrobials and optimal antimicrobial use in general.

[Sarah Gregory] Is there anything people can do to protect themselves from getting a BSI?

[Keiju Kontula] Well, there are no exact guidelines for prevention of BSIs for the community and public. However, prevention of respiratory infections with influenza and pneumococcal vaccines are useful especially for older persons. Maintaining good general health by avoiding smoking is important in prevention of infections. Other general instructions for prevention of bloodstream infections include taking care of dental hygiene to prevent infections originating from teeth and drinking enough fluids to reduce the risk of urinary tract infections and keeping wounds clean, to name a few.

[Sarah Gregory] Dr. Kontula, what does your job involve and what do you like most about it?

[Keiju Kontula] So I work as an infectious diseases specialist in the Department of Infectious Diseases here in the Helsinki University Hospital. My work mostly includes consulting as a senior physician at surgical and internal medicine wards, and every now and then I also have outpatient clinic. While in my job, I enjoy the most the normal everyday patient work with challenging medical problems. I want to do my best in helping people. Every day is different from the previous one, and you constantly learn something new, so that makes my work very interesting. I am also surrounded by really wise colleagues, so it's a privilege working here.

In addition to my clinical work, I've had the opportunity to do research work at the Finnish Institute for Health and Welfare during the past years with my goal in finishing my doctoral thesis. My research work focuses on epidemiology and outcome of bloodstream infections.

[Sarah Gregory] I'm not sure what the pandemic situation is like in Finland now. Are you able to resume most of your regular activities?

[Keiju Kontula] Finland has, at least so far, survived the pandemic with quite moderate defeats when looking at the mortality rates compared to some other countries. The overall situation has been getting better here slowly, as the vaccine coverage increases. Restrictions and recommendations for the public and regions have been carefully de-escalated, and people are getting closer to their normal lives and normal activities.

I personally will enjoy resuming to normal hospital meetings and seeing friends and going out to some social events and maybe even doing some travelling again in the future. However, the strain on the healthcare system is still quite significant, so there are unfortunately still challenges with the pandemic situation in that perspective. So it remains to be seen what happens during the next weeks and months.

[Sarah Gregory] Yes. And when we think it's all better, then it gets worse again. Yes, I'm holding my breath here.

Well thank you so much for taking the time to talk with me today, Dr. Kontula.

[Keiju Kontula] Thank you, Sarah. It was my pleasure.

[Sarah Gregory] And thanks for joining me out there. You can read the October 2021 article, Population-Based Study of Bloodstream Infection Incidence and Mortality Rates, Finland, 2004–2018, online at cdc.gov/eid.

I'm Sarah Gregory for *Emerging Infectious Diseases*.

[Announcer] For the most accurate health information, visit cdc.gov or call 1-800-CDC-INFO.