

Bloodstream infections among children with juvenile idiopathic arthritis: a prospective study from the onset of disease

P.H. Salonen¹, H. Säilä², J.H. Salonen³, M. Vuorela³, H. Kautiainen⁴, O. Lyytikäinen⁵, M.J. Kauppi³, M. Leirisalo-Repo⁶, H. Repo⁷

¹Regional Centre Oiva, Hollola, Finland and Dept. of Pediatrics, University of Helsinki, Helsinki, Finland; ²Orton Hospital, Helsinki, Finland; ³Päijät-Häme Central Hospital, Lahti, Finland; ⁴Dept. of General Practice and Primary Health Care, Institute of Clinical Medicine, University of Helsinki, Helsinki, Finland; ⁵National Institute for Health and Welfare (THL), Dept. of Infectious Disease Surveillance and Control, Helsinki, Finland; ⁶Dept. of Medicine, Helsinki University Central Hospital, and Institute of Clinical Medicine, University of Helsinki, Helsinki, Finland; ⁷Dept. of Bacteriology and Immunology, the Haartman Institute, University of Helsinki, Helsinki, Finland.

Abstract

Objective

To describe the incidence and nature of bloodstream infections (BSI) among children with juvenile idiopathic arthritis (JIA) followed-up prospectively from disease onset.

Methods

The Social Insurance Institution's (SII) national register on individuals with reimbursement for medication of chronic diseases was used to identify children with JIA from 2004 through 2011 and their medications. The National Infectious Disease Register (NIDR) collects data of all blood culture positive samples from all microbiology laboratories in Finland. We combined the NIDR and SII registers to identify JIA patients with BSI. Clinical and laboratory data of each JIA-BSI patient were collected from hospital records.

Results

There were 1604 JIA patients and 6630 person-years of follow-up. Five patients had BSI. During the first 5 years after diagnosis the cumulative emergence of BSI was 0.38% [95% confidence interval (CI) 0.16% to 0.92%]. The incidence rates were 7.5/10 000 follow-up years for JIA (95% CI 2.4–17.6) and 2.8/10 000 follow-up years for the age-matched general population (95% CI 2.7–2.9). The standardised incidence ratio was 3.0 (95% CI 1.2 to 7.2). The causative bacteria were *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Escherichia coli* and *Fusobacterium necrophorum*. Three patients were on anti-rheumatic drugs, including two on TNF inhibitors. All patients responded rapidly to antimicrobial therapy and recovered uneventfully.

Conclusion

Although BSI is rare among children with JIA, the incidence is 3-fold higher than among the general population.

Key words

juvenile idiopathic arthritis, infection, disease-modifying anti-rheumatic drugs

Päivi H. Salonen, MD
 Hanna Säilä, MD, PhD
 Juha H. Salonen, MD, PhD
 Marjo Vuorela, MD
 Hannu Kautiainen, BA,
 Outi Lyytikäinen, MD, PhD
 Markku J. Kauppi, MD, PhD
 Marjatta Leirisalo-Repo, MD, PhD
 Heikki Repo, MD, PhD

Please address correspondence
 and reprint requests to:

Dr Päivi Salonen,
 Regional Centre Oiva,
 Terveystie 4,
 15870 Hollola, Finland.

E-mail: paivi.salonen@oivappk.fi

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Introduction

Juvenile idiopathic arthritis (JIA) is the most common chronic arthritis in childhood. Although the pathogenesis is not known in detail, the different forms of JIA are considered to be of autoimmune or autoinflammatory origin (1) and evidence has accumulated that the background rate of infections is increased in children with JIA (2), perhaps due to immune dysregulation associated with JIA (3). The patient's risk to bacterial infections may be further enhanced through the use of immunosuppressive agents, like oral glucocorticosteroids (GC), disease-modifying anti-rheumatic drugs (DMARDs), *e.g.* methotrexate (MTX), and biologicals used to treat JIA (2, 4-6).

A common way to evaluate the risk of infection associated with the immunosuppressive therapy is to survey the occurrence of serious infections, *i.e.* those requiring hospitalisation or intravenous antimicrobial drugs (6). Recent studies recommend early diagnosis of JIA and early introduction of MTX (7, 8). Such therapy might render JIA patients susceptible to infections early in the course of their disease. We reasoned that the occurrence of bloodstream infections (BSI), a life-threatening form of the serious infections, might provide a useful tool to evaluate the risk of infections of JIA children undergoing aggressive antirheumatic therapy. The National Institute for Health and Welfare in Finland maintains a National Infectious Disease Register (NIDR) covering the entire country (9, 10). This provided us with an opportunity to study the incidence, etiology, duration and follow-up of BSI together with the individual risk factors predisposing Finnish children with JIA to BSI.

Material and methods

Study populations

This was a national register study of BSI in children with JIA. We used two national registers. First, children under 17 years of age, diagnosed with JIA during 2004-2011 were identified by scrutiny of the Finnish Social Insurance Institution's (SII) register of reimbursement of medicines. The reference population consisted of the general population of the same

age, sex and calendar year. Patients under two years of age were excluded because JIA is rare in this age group (11) and the occurrence of BSI is also significantly higher than among older children (9). The patients were followed up to the end of year 2011 or until they were 18 years old. Secondly, we used the National Infectious Disease Register (NIDR) maintained by the National Institute of Health and Welfare to collect data of all instances of positive bacterial blood cultures from all Finnish laboratories. We combined these two registers to identify JIA patients with BSI. The prescription register of SII was further used to obtain data on the use of DMARDs by the JIA patients. The coordinating ethics committee of the Helsinki and Uusimaa Hospital District approved the study protocol.

Registers

– Diagnoses and medication

In Finland, drugs are reimbursed for certain chronic diseases. Reimbursement is applied for on a form supplied by the treating physician, often a rheumatologist, that includes the patient's identity code. The date of reimbursement approval was set as the index day. SII approves reimbursement of medicines under the International Classification of Disease, 10th Revision (ICD-10) codes M08.0-M08.9. The reimbursement data and the data on purchased medicines to treat the above conditions were used to collect the medications purchased for the JIA patients.

– Bloodstream infections

All clinical microbiology laboratories in Finland are required to notify all bacterial and fungal blood-culture isolations to the NIDR. Multiple notifications of the same microbe in the one and same patient were considered as a single episode of BSI if they occurred within three months (10). The identity codes of the patients with BSI were available from 2004. With the aid of the identity number we were able to cross-link the SII and NIDR registers.

Data collection

By cross running of the SII and NIDR register data a list of individual patients

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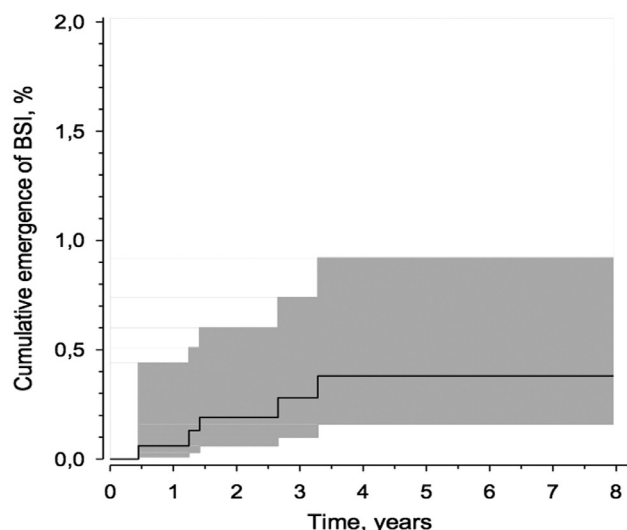


Fig. 1. Cumulative emergence of bloodstream infections (BSI) from time of diagnosis in juvenile idiopathic arthritis (JIA). Shaded area: 95% confidence interval.

with JIA and BSI was obtained. The patient records of these patients were obtained from the hospitals where the patients had been treated. The following data were collected for each individual patient: subtype and time of JIA diagnosis, history of medication, infections, comorbidities, surgical treatment, risk factors for infections (neutropenia, lymphopenia), JIA activity at the time of infection, symptoms, clinical and microbiological diagnosis of BSI, radiological findings, treatment of infection and outcome of infection.

Statistical analyses

The expected number of BSI cases was calculated by multiplying the number of person-years in each 1-year age and gender group by the corresponding av-

erage BSI incidence among all Finnish children during the same period of observation. To calculate standardised incidence ratios (SIRs), the observed numbers of cases were divided by the expected numbers of cases. Exact 95% confidence intervals were defined under the assumption that the observed numbers followed a Poisson distribution. Time-to-event analysis was based on the product limit estimate (Kaplan-Meier) of the cumulative "emergence" function. The 95% confidence bands for the Kaplan-Meier estimate of BSI were calculated using the bootstrap method.

Results

During the 8-year study period, 2004–2011, JIA was diagnosed in 1604 patients (992 girls, 612 boys) aged 2–16

years. Their mean age was 8.2 years (SD 4.2 years). The patients were followed up until they were 18 years old or to the end of year 2011. There were altogether 6630 follow-up years. The mean (range) follow-up time was 4.1 (1–8) years. MTX was the most commonly used DMARD (60% of the total follow-up time), followed by hydroxychloroquine (30%) and sulfasalazine (7%).

A total of five JIA patients with BSI were identified. During the first 5 years after diagnosis the cumulative emergence of BSI was 0.38% (95% CI 0.16%–0.92%) (Fig. 1). The incidence rates of BSI were 7.5 per 10,000 person-years for JIA patients (95% CI 2.4–17.6) and 2.8 per 10 000 person-years for the general population (95% CI 2.7–2.9). JIA patients had a 3-fold risk for BSI compared with the general population [standardised incidence ratio 3.0 (95% CI 1.2–7.2)].

Two of the JIA patients with BSI had seronegative polyarthritis, two had persistent oligoarthritis and one had enthesitis related arthritis (Table I). None of the patients had neutropenia or lymphopenia before BSI.

Three patients used combination DMARD therapy (Table I). Three had MTX, one GC and two a TNF inhibitor, the first biologic drug in each. Two patients had no DMARD; one was in drug-free remission and the other had the diagnosis of JIA at the same time as the BSI. The average time between the diagnosis of JIA and the BSI was 1.4 years (0–3 years).

The causative agents of BSI were *Streptococcus pneumoniae* in two patients, *Staphylococcus aureus*, *Escherichia coli* and *Fusobacterium necrophorum* each in one patient (Table II). In practice, each patient had sepsis and a confirmed infectious focus. The patient with *E. coli* BSI had pyelonephritis and vesicoureteral reflux. She also had active JIA and a biologic agent was started after the BSI had been cured. One patient had the CATCH 22 syndrome (cardiac defects, abnormal facies, thymic hypoplasia, cleft palate, hypocalcaemia) and she also received a biologic agent. None of the five patients had had recurrent infections be-

Table I. JIA patients with bloodstream infections.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age/Sex	16/F	15/M	13/F	17/M	2/F
JIA subtype	PA, RF-	Enthesitis related arthritis	PA, RF-	OA (persistent)	OA (persistent)
JIA duration (years)	2	1	1	3	0
Active JIA	-	-	+	-	+
Comorbidity	CATCH 22	-	VUR	-	-
Biologic agents (exposure months)	ETA (1)	INF (0.5)	-	-	-
MTX	+	+	+	-	-
GC	-	-	+	-	-
Concomitant medication	HCQ	SSZ	HCQ	-	-

PA: polyarthritis; RF: rheumatoid factor; OA: oligoarthritis; CATCH 22 syndrome: cardiac defects, abnormal facies, thymic hypoplasia, cleft palate, hypocalcaemia syndrome; VUR: vesicoureteral reflux; GC: glucocorticosteroid; ETA: etanercept; INF: infliximab; MTX: methotrexate; HCQ: hydroxychloroquine; SSZ: sulfasalazine.

Table II. Bloodstream infections.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Diagnosis	Pneumonia	Osteomyelitis	Pyelonephritis	Peritonsillar abscess	Sepsis
Symptoms preceding infection	fever, flu, cough, headache	fever, buttock pain	fever, flu, sore throat, nausea, stomach ache	fever, flu, sore throat	fever, arthritis
Duration of symptoms before diagnosis (days)	4	3	6	2	1
CRP, mg/L (at time of diagnosis)	190	171	157	116	98
Etiology	<i>Str. pneumoniae</i>	<i>S. aureus</i>	<i>E. coli</i>	<i>F. necrophorum</i>	<i>Str. pneumoniae</i>

CRP: C-reactive protein; *Str. pneumoniae*: *Streptococcus pneumoniae*; *S. aureus*: *Staphylococcus aureus*; *E. coli*: *Escherichia coli*; *F. necrophorum*: *Fusobacterium necrophorum*.

fore the occurrence of BSI. All the patients required hospital treatment.

The mean duration of intravenous antibiotic treatment was 5 days (range 4–7) followed by oral antibiotics for a week. MTX and biologic DMARDs were paused during the infection. The medication was discontinued in patients no. 1 and 3 for two weeks and in patient no. 2 for 4 weeks. All patients recovered and resumed their JIA therapy.

Discussion

The results of this prospective register study show that Finnish children with JIA, who are treated according to the recommended first line treatment strategies with DMARDs (7, 8), have a 3.0-fold risk for BSI compared with the general population. The finding is in accordance with a recent study by Beukelman *et al.* (2) showing a 2.8-fold risk for severe infections in entire cohort of JIA patients, irrespective of immunosuppressive therapy. In that study the use of MTX and/or a TNF inhibitor did not, while that of GC did, increase significantly the risk for serious infections. Of the five BSI patients in the present study, one took GC, one was in drug-free remission and three were on combination therapy, which included a TNF inhibitor in two patients. Taken together, these results imply that BSI is rare in JIA children during the early phase of the disease and that BSI may not be associated with the use of immunosuppressive therapy at all.

Immunosuppressive therapy, particularly GC or TNF inhibitors, may suppress the clinical symptoms and signs of infection: fever and the acute phase responses. This may cause diagnos-

tic delay, and the patient's prognosis may deteriorate rapidly (12, 13). In the present study, each BSI patient had fever for 1–6 days prior to admission to the hospital. All had high CRP values on admission and, after sampling for blood culture, intravenous antibiotics were immediately started. Each patient recovered from the BSI rapidly and uneventfully. The BSI patients did not have a history of recurrent serious bacterial infections and they were neither neutropenic nor lymphopenic. Two patients had comorbidities, which predispose to infections: vesicourethral reflux renders the patient susceptible to pyelonephritis and the CATCH 22 syndrome with thymic hypoplasia increases the risk of infection slightly (14). Two patients had active JIA when they fell ill with BSI. The blood cultures grew *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Escherichia coli* and *Fusobacterium necrophorum* - life-threatening microbes in previously healthy subjects. We were ultimately left with the impression that the BSI infections of the five JIA patients, in terms of clinical features, were similar to those which may occur in children without JIA, as well.

The threshold for a physician to sample blood for microbial culture may be lower in the case of a child with JIA than of healthy subjects, and this might introduce bias favouring more frequent sampling in the former group of patients. Obviously increased sampling would increase the sensitivity for detecting BSI. In Finland CRP levels strongly guide sampling for blood culture. This, and the finding that all JIA patients with BSI had high CRP levels,

suggest that the 3.0-fold increase in BSI was not due to increased sampling for blood cultures in JIA patients.

The strength of this study is that comprehensive national retrospective data was used covering all BSI in JIA patients for a specified period of time (2004–2011). Although most BSI registers are maintained by single or selected hospitals, also population-based registers, like the ones used in this study, exist (15–17). Population-based registers allow the evaluation of the public health burden of BSI and to improve treatment, *e.g.* by providing information about antimicrobial resistance and by providing a basis for prevention (9, 10).

In the present study it was most reassuring to find that the bacteria causing BSI were not of strains with increased antimicrobial resistance (*e.g.* methicillin resistant *Staphylococcus aureus* or extended spectrum β -lactamase-producing bacteria). We also analysed the records of each individual patient, which made it possible to verify the diagnoses of JIA and BSI and to record the activity and medications of the JIA. The use of a prescription register based on purchased medications increases reliability of the medication data.

A limitation of the study is that we did not have the possibility to have JIA patients without BSI as controls. Still, using the general age- and gender-matched population as a control provides an adequate basis for comparison. Another limitation is that the register of reimbursement of medicine does not cover infliximab, abatacept and tocilizumab, since these pharmaceuticals are used in hospital settings. On the other hand, detailed history of

all anti-rheumatic medication was collected of each patient with BSI.

MTX was the most commonly used drug by JIA patients, which is in accordance with a previous study (8). During the study period the use of TNF inhibitors among children with JIA was low, probably since the use of TNF inhibitors was limited to patients with an insufficient response to MTX/DMARD.

In conclusion, we studied, for the first time in the literature, the incidence of BSI among children with JIA and followed them prospectively from the onset of the disease. Although low, the incidence of BSI in this population was no less than 3-fold higher than among the general population. The increased risk for BSI was not apparently associated with the use of immunosuppressive therapy, suggesting that the current guidelines for early active therapy of JIA are reasonably safe in terms of infectious adverse events.

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