

RISK FACTORS FOR SEPTIC ARTHRITIS IN PATIENTS WITH JOINT DISEASE

A Prospective Study

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Objective. To quantify potential risk factors for septic arthritis, in order to identify a basis for prevention.

Methods. The occurrence of potential risk factors for septic arthritis in patients with joint diseases attending a rheumatic disease clinic was prospectively monitored at 3-month intervals over a period of 3 years. Potential risk factors investigated were type of joint disease, comorbidity, medication, joint prosthesis, infections, and invasive procedures. The frequencies of risk factors in patients with and those without septic arthritis were compared using multiple logistic regression analysis.

Results. There were 37 patients with and 4,870 without septic arthritis. Risk factors for developing septic arthritis were age ≥ 80 years (odds ratio [OR] = 3.5, 95% confidence interval [95% CI] 1.4–8.6), diabetes mellitus (OR = 3.3, 95% CI 1.1–10.1), rheumatoid arthritis (OR = 4.0, 95% CI 1.9–8.3), hip and/or knee prosthesis (OR = 15, 95% CI 4.1–54.3), joint surgery (OR = 5.1, 95% CI 2.2–11.9), and skin infection (OR = 27.2, 95% CI 7.6–97.1).

Conclusion. These findings indicate that preventive measures against septic arthritis in patients with joint diseases should mainly be directed at those with joint prostheses and/or skin infection.

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Septic arthritis is a serious medical problem. The case-fatality rate of septic arthritis is estimated to be 10–25%, and 25–50% of the surviving patients suffer a permanent loss of joint function as a result of the infection (1–3).

Risk factors for acquiring septic arthritis are patient-related or situation-related. Patient-related factors include diseases and medications that reduce immunocompetence, joint diseases, and the presence of joint prostheses (4,5). Situation-related factors are any events by which bacteria can reach a joint, e.g., joint surgery or arthrocentesis and infections or invasive procedures in other parts of the body (4,5). The reported incidence of septic arthritis varies from 2–5/100,000/year in the general population (6–8) to 28–38/100,000/year in patients with rheumatoid arthritis (RA) (7,9,10) to 40–68/100,000/year in patients with joint prostheses (11,12). Along with the aging of the population and the increasing availability of joint replacement procedures, the number of persons with prostheses is growing.

The high rates of morbidity and mortality in septic arthritis necessitate comprehensive assessment and quantification of multiple risk factors as a first step in the development of a strategy for the prevention of this condition. We have prospectively studied the incidence of septic arthritis in relation to risk factors in patients with preexisting joint diseases attending a large network of rheumatic disease clinics.

PATIENTS AND METHODS

Patient enrollment. This study was part of a prospective study on the incidence, risk factors, and outcome of septic arthritis in Amsterdam, The Netherlands, between 1990 and 1993. The Jan van Breemen Institute is a network

of outpatient rheumatology clinics serving a population of 1.1 million in the Amsterdam region. In October 1990, all patients aged 18 years and older seen in that year and diagnosed as having RA, undifferentiated oligoarthritis or polyarthritis (UA), juvenile chronic arthritis (JCA), ankylosing spondylitis (AS), psoriatic arthritis (PsA), systemic lupus erythematosus (SLE), or osteoarthritis (OA) were selected from the central diagnosis registry. A total of 7,216 patients were thus selected. In a random sample of 1% per disease category in the RA, UA, JCA, AS, and PsA groups, the information in the medical record was compared with published criteria for these diseases (13–16). There was complete concordance between the registered diagnoses and the classification according to the applied criteria. A review of the medical records of 30 of the 88 patients with SLE (34%) revealed that all fulfilled the American College of Rheumatology criteria for SLE (17) and 29 had arthritis. In 100 of the 1,365 patients with a registered diagnosis of OA of the hip or knee (7%), the radiographs were reviewed. In 96% of these, there were abnormalities of grade II or higher according to the Kellgren/Lawrence scoring system (18).

Protocol. After approval by the medical ethics committee and attending physicians, letters of introduction were sent to the patients. Subsequently, questionnaires were mailed every 3 months to patients who had given informed consent. Four times per year the above-mentioned procedure was repeated for newly registered patients. Between October 1990 and October 1992 a maximum of 8 questionnaires per patient were sent. When a patient did not return the questionnaire twice in succession, his or her willingness to continue participating was ascertained by telephone. In the case of a negative answer or if the questionnaire was not returned a third time, the patient was not contacted again. The questionnaire concerned the preceding 3-month period and contained questions about comorbidity, joint prosthesis, joint trauma, infections, medical and dental procedures, medication, and the use of antibiotic prophylaxis at the time of procedures (Appendix 1).

Treatment with prednisone, azathioprine, methotrexate, or cyclophosphamide was recorded as immunosuppressive medication. Antibiotic prophylaxis during implantation of prosthetic joints is a standard procedure in all Amsterdam hospitals. Flucloxacillin or a cephalosporin is given intravenously one-half hour before surgery and in most hospitals again 6, 12, and 18 hours later. If a prosthetic joint is operated on, the first dose is postponed until the joint cavity is cultured.

The occurrence of septic arthritis between October 1990 and October 1993 was recorded in all patients with the above-mentioned joint diseases who attended the clinic network. Thus, case-finding was continued 1 year longer than the period in which questionnaires were mailed (October 1990 to October 1992). Septic arthritis was determined according to the modified criteria of Newman (19): a positive culture of joint aspirate, direct identification of microorganisms in synovial fluid or tissue, or a strong clinical suspicion without another explanation. Cultures with *Staphylococcus epidermidis* or *Propionibacterium acnes* were considered to be evidence of septic arthritis if there was a positive Gram stain or a second culture with the same result.

Patients with septic arthritis were identified to the

study center in several ways: 1) all participating patients were instructed to present a preprinted request to inform the study center in case of hospital admission; 2) the rheumatologists, orthopedic surgeons, internists, pediatricians, and bacteriologists in the health district of Amsterdam were informed before the start of the study and had agreed to report every patient with septic arthritis or a positive joint culture; 3) the diagnosis registries of the 12 hospitals in the district reported patients with a diagnosis of septic arthritis. In The Netherlands, all hospitals use the same system for reporting of the diagnosis at discharge (20).

All patients with septic arthritis were visited by one investigator. The same data as in the questionnaire were gathered from the history and the medical record, for the 3 months preceding the diagnosis. To check for information bias, the directly obtained history and the data in the medical records of patients with septic arthritis who participated in the questionnaire were compared with the questionnaire answers given by the patient over the same time period. The 2 sources of information were consistent with one another in all cases. Bacterial culture results were also recorded.

Data analysis. To identify risk factors for septic arthritis, data on septic arthritis patients were compared with data on patients who did not develop arthritis. All patients with septic arthritis who attended the clinic network for the above-mentioned joint diseases were identified as cases. Patients with septic arthritis who did not participate in the questionnaire study and patients who contracted septic arthritis in the year after the intake period of the questionnaire study were also included. This was done to include as many cases as possible from the relevant clinic population. All patients from the questionnaire group who did not acquire septic arthritis during the study period were identified as controls. One questionnaire per control subject was randomly selected for study; thus, information on the control patients from random 3-month periods was compared with information concerning the 3-month periods preceding the development of septic arthritis in the cases.

The following potential risk factors for septic arthritis were analyzed: age, sex, presence of malignancy, diabetes mellitus, renal disease, or liver disease, type of joint disease, use of immunosuppressive medication, presence of a hip and/or knee prosthesis, skin infection, upper or lower respiratory tract or urinary tract infection, invasive procedures at any site including dental procedures, and joint trauma. Age was dichotomized (<80 versus ≥80) to allow a straightforward interpretation. The frequencies of these factors in the 3-month periods were compared between cases and controls in univariate analyses (chi-square test for each factor). Variables were eligible for entry into a multivariate analysis if they were significantly associated with septic arthritis ($P < 0.10$). A multivariate logistic regression analysis was done with backward deletion of variables, based on the likelihood ratio test (removal P value < 0.10) in order to identify a set of statistically strong predictors for septic arthritis. Interaction between variables remaining in the model was investigated. Statistically significant ($P < 0.05$) interaction terms were included in the model in order to obtain a model that better described the data. Odds ratios (OR) and 95% confidence intervals were calculated for variables in the model. Because the OR approximates the

Table 1. Distribution of diagnoses among patients with joint diseases, and rate of response to the questionnaires

Diagnosis	Patients		Questionnaires	
	No. selected from diagnosis registry	Initial participation rate (%)	Total mailed	Response rate (%)
Rheumatoid arthritis	1,795	90	9,906	83
Undifferentiated polyarthritis	1,161	90	6,076	80
Juvenile chronic arthritis	79	92	395	80
Ankylosing spondylitis	563	92	2,905	79
Psoriatic arthritis	257	91	1,374	82
Systemic lupus erythematosus	88	92	438	80
Osteoarthritis of hip or knee	1,365	84	5,744	76
Osteoarthritis of other sites	1,908	82	7,893	69
Total	7,216	87	34,731	78

relative risk in cases of small probability, ORs in this study are interpreted as relative risks.

Data from the Amsterdam health district. Parallel to this study, the occurrence of septic arthritis in the entire Amsterdam region was recorded. Since information on the distribution of age (21) and the prevalence of RA (22) and diabetes mellitus (23) was available for the population of this region, we had the opportunity to compare the prevalence of these risk factors in the questionnaire group and in the general population. Finally, septic arthritis occurring after separate surgical procedures in joints was related to the total number of such procedures in the Amsterdam region as registered in the time period of the study (24).

RESULTS

Characteristics of the study population. The total number of patients selected from the diagnosis registry was 7,216. For 300 patients, the attending physicians objected to participation, and another 631 patients chose not to participate. Thus, the initial participation rate was 87% (Table 1). During the study period, 197 patients died (3%). Another 584 patients (8%) dropped out because of relocation or difficulties with the Dutch language. In the course of the study period, 1,675 patients (23%) objected to further participation. A total of 34,731 questionnaires was mailed to 6,285 patients, of which 27,028 (78%) were returned by 4,889 patients (78%). The response rate of patients with OA was slightly lower than that of the other patients.

For most of the potential risk factors, except for age, sex, immunosuppressive medication, and the presence of a hip and/or knee prosthesis, the prevalence was similar in the different joint disease categories. The AS group consisted predominantly of young men. Immunosuppressive medication was used frequently by patients with RA (30%) and SLE (38%) and

uncommonly in the other disease categories (2–15%). A hip or knee prosthesis was present in one-fourth of the patients with RA or OA of the hip or knee, compared with 2–9% of the other patients. The most frequent invasive procedure was a dental procedure, in 10% of the patients per 3 months. Fourteen percent of the patients with prosthetic hip and/or knee joints who underwent invasive procedures at sites other than the joints reported the use of antibiotic prophylaxis; a variety of regimens was used.

Characteristics of patients with septic arthritis. Septic arthritis was diagnosed in 37 patients attending the rheumatic disease clinics: 24 during the 2 years of questionnaire mailing and 13 in the third year of case-finding. Nineteen of the 37 patients had participated in the questionnaire. Reporting by clinicians was nearly complete; 2 patients were identified by checking the diagnosis registries. The occurrence of septic arthritis was similar between responders and nonresponders to the questionnaire (0.40% and 0.48%, respectively), as well as in patients whose physician had objected to their participation and the other patients (0.33% and 0.42%, respectively). Bacteria were cultured from joint fluid or tissue in 32 patients; in the other 5 patients, pus was present in the joint. The most frequently cultured microorganism was *Staphylococcus aureus* (in 15 patients).

There were 14 men and 23 women with septic arthritis, with a mean age of 65 years. The most common preexisting joint disease was RA, in 25 patients. The mean duration of RA in these patients was 22 years. Of the 25 patients with RA, 3 also had diabetes mellitus and 1 had a malignancy. Immunosuppressive medication was used by 12 patients (all with

RA). The dose ranges were as follows: prednisone 2.5–15 mg/day, azathioprine 50–75 mg/day, and methotrexate 10 mg/week. The 37 patients had a total of 46 infected joints; 4 patients had more than 1 infected joint. In 27 of the 37 patients, the infected joint contained foreign material (prosthesis [$n = 24$] or screws, to attain arthrodesis [$n = 2$] or for fracture stabilization [$n = 1$]). The probable cause of septic arthritis was direct inoculation of bacteria into the joint in 15 patients (10 prosthetic surgery, 2 surgery with osteosynthesis material, 2 intraarticular injection, and 1 penetrating trauma). In the remaining 22 patients with probable hematogenous septic arthritis, a source of infection was identified in 13 (59%), mainly a skin infection. A positive skin culture was recorded in 6 patients, the bacteria being the same as that cultured from the joint in all cases.

Risk factor analysis. The results of the univariate analysis of potential risk factors are presented in Table 2. Frequencies between cases and controls differed ($P < 0.05$) for all patient characteristics except sex, renal disease, and liver disease. Age ≥ 80 years, malignancy, diabetes mellitus, diagnosis of RA, use of immunosuppressive medication, and hip and/or knee prosthesis were significantly associated with septic arthritis. Skin infections, joint surgery, and ear/nose/throat surgery in the last 3 months were more frequent among cases. Dental treatment and joint trauma were reported more often by controls.

The variables age, malignancy, diabetes mellitus, type of joint disease, immunosuppressive medication, hip and/or knee prosthesis, skin infection, and joint surgery were eligible for inclusion in the multivariate analysis. Since RA was the only joint disease with a higher frequency among cases in the univariate analysis, diagnosis was dichotomized as RA versus all other joint disease diagnoses. Invasive procedures in the ear/nose/throat region appeared at first to be a risk factor for septic arthritis. However, in the 2 septic arthritis patients who had undergone ear/nose/throat surgery, the septic arthritis was considered to be due to a skin infection, because the same microorganism was cultured from the joint and the infected skin. Ear/nose/throat surgery was therefore not entered into the multivariate analysis. During backward deletion, malignancy and immunosuppressive medication were removed from the multivariate logistic regression model. Interaction between the remaining predictors was investigated. An interaction term between the presence of a hip and/or knee prosthesis and skin

Table 2. Results of univariate analysis of potential risk factors for septic arthritis*

Factor	Cases (n = 37)	Controls (n = 4,870)	P
Age ≥ 80 years	7 (19)	263 (5)	<0.01
Male sex	14 (38)	1,487 (31)	0.34
Malignancy	2 (5)	55 (1)	0.02
Diabetes mellitus	4 (11)	197 (4)	0.04
Renal disease	0 (0)	60 (1)	0.50
Liver disease	1 (3)	30 (1)	0.11
Joint disease			
RA	25 (68)	1,339 (27)	<0.01
UA	2 (5)	855 (18)	
AS	1 (3)	408 (8)	
JCA, SLE, or PsA	2 (5)	319 (7)	
OA hip or knee	5 (14)	842 (17)	
OA not hip or knee	2 (5)	1,107 (23)	
Immunosuppressive medication	12 (32)	648 (13)	<0.01
Hip and/or knee prosthesis	22 (59)	634 (13)	<0.01
Infection			
Skin	21 (57)	642 (13)	<0.01
Upper respiratory tract	7 (19)	1,433 (29)	0.16
Lower respiratory tract	2 (5)	309 (6)	0.82
Urinary tract	2 (5)	336 (7)	0.72
Invasive procedure			
Joint surgery	9 (24)	172 (4)	<0.01
Intraarticular injection	2 (5)	212 (4)	0.75
Skin	1 (3)	129 (3)	0.98
Ear/nose/throat	2 (5)	16 (0)	<0.01
Dental	0 (0)	503 (10)	0.04
Gastrointestinal tract	0 (0)	136 (3)	0.30
Respiratory tract	0 (0)	25 (1)	0.66
Urinary tract	1 (3)	59 (1)	0.41
Female genital tract	0 (0)	32 (1)	0.64
Joint trauma	0 (0)	518 (11)	0.04
Prosthesis without skin infection	13 (35)	555 (11)	<0.01
No prosthesis, with skin infection	12 (32)	563 (12)	
Prosthesis and skin infection	9 (24)	79 (2)	
No prosthesis, no skin infection	3 (8)	3,673 (75)	

* Values are the number (%). RA = rheumatoid arthritis; UA = undifferentiated arthritis; AS = ankylosing spondylitis; JCA = juvenile chronic arthritis; SLE = systemic lupus erythematosus; PsA = psoriatic arthritis; OA = osteoarthritis.

disease was found, and this was subsequently included in the model.

The results of the multivariate analysis are presented in Table 3. Age 80 years or older and presence of diabetes mellitus increased the risk for septic arthritis by a factor of 3.5 and 3.3, respectively. If age was dichotomized at values below 80, the risk associated with a higher age was no longer statistically significant. A diagnosis of RA, compared with all other diagnoses of joint disease, implied a 4-fold increased risk for septic arthritis. Joint surgery was a somewhat stronger risk factor (OR = 5.1). The presence of a prosthesis without a skin infection increased the risk for septic arthritis 15-fold. A skin infection in patients without a prosthesis increased the risk 27-fold. After

Table 3. Results of multivariate logistic regression analysis of potential risk factors for septic arthritis

Risk factor	Odds ratio	95%
		confidence interval
Age \geq 80 years	3.5	1.4-8.6
Diabetes mellitus	3.3	1.1-10.1
Rheumatoid arthritis	4.0	1.9-8.3
Recent joint surgery	5.1	2.2-11.9
Hip or knee prosthesis without skin infection	15.0	4.1-54.3
No hip or knee prosthesis, with skin infection	27.2	7.6-97.1
Hip or knee prosthesis and skin infection	72.7	18.6-282.6

correction for interaction, the presence of both a prosthesis and a skin infection resulted in an OR of 73, compared with patients who did not have either characteristic.

Comparison with data from the Amsterdam health district. During the 3 years of case-finding, 188 episodes of septic arthritis were recorded in 186 patients in the Amsterdam health district with or without preexisting joint disease. The prevalence of risk factors in persons with and those without septic arthritis is presented in Table 4. As of January 1, 1992, 3% of the population of the Amsterdam health district was aged 80 years or older, whereas this figure was 12% (OR = 4) in the total group of patients with septic arthritis in this area. Diabetes mellitus was present in 9% of the health district population between 50 and 75 years old and in 23% of the patients with septic arthritis in the same age range (OR = 2.5). RA was found in 1% of the adult population, whereas among the group of patients with septic arthritis, 20% had RA (OR = 20). These figures are similar to the results in the questionnaire group, except for a higher risk associated with RA in the general population.

Invasive procedures in joints were classified into 3 separate categories. Category 1, Without prosthesis: Of 12,845 procedures in 3 years, 6 (0.05%) were followed by septic arthritis. Four of these were an

arthrodesis of the ankle or foot (4 of 468; 0.9%). Category 2, Implantation, reimplantation, or removal of a joint prosthesis: These procedures were performed 4,683 times, and this was followed by septic arthritis 14 times (0.3%). The procedure most frequently followed by an infection was the reimplantation of a hip prosthesis (3 of 257; 1.2%). Category 3, Procedures in which the use of foreign material was not recorded: Of 4,636 procedures, 21 (0.5%) were followed by septic arthritis. Five of these infections proved to be in prosthetic joints. In a subgroup called "other repair of joint structures" (105 procedures), 3 infected elbow prostheses were found. Therefore, the prevalence of septic arthritis after implantation of an elbow prosthesis was at least 3%.

DISCUSSION

In this large-scale prospective study of patients with joint diseases, it was found that independent risk factors for acquiring septic arthritis are age 80 years or older, diabetes mellitus, RA, a hip and/or knee prosthesis, recent joint surgery, and skin infection.

At older ages, various medical conditions that may increase the risk of joint infection occur, e.g., preexisting arthritis or joint prostheses and chronic extraarticular disease leading to immunosuppression or to hematogenous spread of infection into a joint (1). In the present analysis, the age factor is independent of the presence of RA or of a joint prosthesis; therefore, the increased risk of septic arthritis in the elderly is probably caused by the higher prevalence of chronic disease (25) and a decrease in immunocompetence in this population as compared with younger persons (26). Diabetes mellitus in itself heightens susceptibility to infections, due to the influence of hyperglycemia on polymorphonuclear cell functions. The mechanisms involved include decreased mobilization of leukocytes to the site of infection (27), a defect in chemotaxis (28), impaired intracellular glycolysis of leukocytes leading to a deficient supply of the energy needed for the uptake of microorganisms (29), and impaired intracellular killing of microorganisms (30). In addition to these factors, diabetic neuropathy can lead to septic arthritis by way of skin infection, as occurred in 1 patient in this study.

RA was by far the most common joint disease among patients with septic arthritis. The chronic synovitis and the abnormal joint structure that are characteristic of RA provide good conditions for bacterial survival and growth (5). Regular intraarticular injec-

Table 4. Prevalence of risk factors for septic arthritis among persons in the Amsterdam health district with septic arthritis (cases) and those without septic arthritis (controls)*

	Cases (n = 188)	Controls (n = 10 ⁶)
Age \geq 80 years	12	3
Diabetes mellitus [†]	23	9
Rheumatoid arthritis	20	1

* Values are percentages.

[†] In the age group 50-75 years old.

tions also increase the risk of infection in patients with RA (31), although our data confirm that the absolute risk is low. In the present analysis, immunosuppressive medication had no independent association with the occurrence of septic arthritis.

Septic arthritis occurred infrequently in patients with joint diseases other than RA. Of 12 such patients, 9 had an infected prosthesis or infected osteosynthetic material, and 2 developed septic arthritis after direct inoculation of bacteria into the joint. It appears that these factors are more important than the type of joint disease per se. The difference in susceptibility to septic arthritis in patients with RA as compared with other joint diseases may be related to a greater area with involvement of synovitis and a higher degree of joint destruction in RA: most of these patients had longstanding and destructive disease, as has been noted before in series of RA patients with septic arthritis (32).

Prosthesis infections can originate during implantation of the prosthesis or by hematogenous spread from a distant source. The pathogenesis of these infections is related to preferential colonization of foreign material (33). In this analysis, cases and controls were compared over 3-month periods. Since the interval between surgery and the diagnosis of septic arthritis was longer than 3 months in 4 of the 12 patients whose joints were presumably infected during surgery, the risk of joint surgery is underestimated. Data on septic arthritis in relation to the frequency of separate surgical procedures revealed that implantations of elbow prostheses and revisions of hip prostheses are associated with the highest rate of subsequent septic arthritis. The standard use of antibiotic prophylaxis with implantation of prostheses is apparently not entirely effective in preventing septic arthritis.

Skin infection is an important risk factor for septic arthritis. This association was confirmed by the congruent culture results at both sites, in cases in which culture results were available. All septic arthritis patients with skin infection had a clinically obvious infection at the site of the involved skin. Since the skin infection item in the questionnaire also included eczema, the OR as calculated for skin infection probably underestimates the effect of skin infections. All patients with a skin infection as the cause of septic arthritis had RA; in half of these patients, the infection was located on the foot. The integrity of the skin of RA patients is threatened by deformations, nodules, and atrophy due to medication (34).

The typical patient at risk for development of

septic arthritis in this study was an RA patient with 1 or more joint prostheses and skin infection. Since the first 2 risk factors cannot be influenced, a reduction of the risk for septic arthritis in this patient population can be achieved only by intensive treatment and prophylaxis of skin infections.

In conclusion, the prevention of septic arthritis in patients with joint diseases should focus on patients who are age 80 years or older and have diabetes mellitus, RA, joint prostheses, joint surgery, and/or skin infections. To investigate the balance between the cost and the effect of preventive measures, information is needed on all aspects of the outcome of septic arthritis. Such an analysis is currently under way in this group of patients.

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APPENDIX 1: QUESTIONNAIRE ON POTENTIAL RISK FACTORS FOR SEPTIC ARTHRITIS

1. Do you have any disease, other than your joint disorder, at this moment?
2. Do you have one or more joint prostheses?
3. Did you visit a doctor or dentist because of inflammation or an infection in the past 3 months?
4. Have you undergone a medical procedure in the past 3 months, for example, joint surgery?
5. Did you receive antibiotics (e.g., penicillin) in relation to the procedure(s) mentioned in question 4?
6. Did an inflammation occur after the procedure(s) mentioned in question 4, for example, wound infection?
7. Did you have any complaints about your health, other than your joint disease, in the past 3 months?
8. Did you injure a joint severely in the past 3 months, for example, by falling?
9. Did you use any medication during the past 3 months?
A positive answer is followed by a list of possibilities from which the patient is asked to mark what fits his or her situation.
In question 7 the following items could be marked:
Fever
Cough, cold, angina, sinusitis, otitis
Pneumonia, bronchitis
Pain on urinating, cystitis, kidney stone, nephritis
Venereal disease
Diarrhea
Eczema, infected wound, burn, boil, abscess, decubitus ulcer, wound after injury, ingrown nail