Septic arthritis in the end-stage renal disease population

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ABSTRACT

Septic arthritis is important to consider in any patient who presents with joint pain because it is a medical emergency with an 11% fatality rate. Diagnosis and treatment may improve prognosis; however, many patients do not regain full joint function. In patients with end-stage renal disease (ESRD), immune dysfunction due to uremia and chronic vascular access leads to increased risk of infection. We examined the incidence, risk factors and sequelae of septic arthritis in a cohort of hemodialysis patients. The US Renal Data System was queried for diagnoses of septic arthritis and selected sequelae using International Statistical Classification of Diseases and Related Health Problems-9 and Current Procedural Terminology-4 codes in patients who initiated hemodialysis between 2005 and 2010. Multivariable logistic regression was used to determine potential risk factors for septic arthritis and its sequelae. 7009 cases of septic arthritis were identified, an incidence of 514.8 per 100,000 persons per year. Of these patients, 2179 were diagnosed with a documented organism within 30 days prior to or 14 days after the septic arthritis diagnosis, with methicillin-resistant *Staphylococcus aureus* infections (57.4%) being the most common. Significant risk factors for septic arthritis included history of joint disease, immune compromise (diabetes, HIV, cirrhosis), bacteremia and urinary tract infection. One of the four sequelae examined (joint replacement, amputation, osteomyelitis, *Clostridioides difficile* infection) occurred in 25% of septic arthritis cases. The high incidence of septic arthritis and the potential for serious sequelae in patients with ESRD suggest that physicians treating individuals with ESRD and joint pain/inflammation should maintain a high clinical suspicion for septic arthritis.

Significance of this study

What is already known about this subject?

- Septic arthritis carries significant morbidity and mortality.
- Septic arthritis is commonly caused by hematogenous seeding of a joint or by direct inoculation of bacteria into a joint.
- Hemodialysis patients are at increased risk of bacteremia due to the requirement for frequent intravascular access for dialysis.

What are the new findings?

- This study found that the incidence of septic arthritis in the end-stage renal disease (ESRD) population is more than 50 times that of the general population at greater than 500 per 100,000 persons.
- The most common organism associated with septic arthritis in this cohort of patients with ESRD was methicillin-resistant staphylococcus aureus.
- Septic arthritis risk was associated with vascular access via a catheter, prior joint disease, diabetes, HIV, cirrhosis and bacteremia.
- In this cohort 25% of patients with ESRD with septic arthritis later required joint replacement, amputation, osteomyelitis or had *Clostridioides difficile* infection.

How might these results change the focus of research or clinical practice?

- These findings might increase vigilance for a septic arthritis work-up for patients with catheter access, bacteremia, diabetes and HIV.
- In patients with ESRD with septic arthritis, using antibiotics appropriate to cover for methicillin-resistant staphylococcus aureus is important.

INTRODUCTION

Septic arthritis is characterized as an infection of any joint and can cause tissue damage.[1] Septic arthritis can occur via hematogenous seeding or direct inoculation of bacteria into the joint. Virtually any microbe, ranging from normal skin flora such as *Staphylococcus* species to sexually transmitted organisms such as *Neisseria gonorrhoeae*, may cause septic arthritis.[1] Due to the potential for rapid progression of the disease, septic arthritis is a crucial diagnosis that should never be missed. An 11% case fatality rate has been reported, most commonly due to dissemination of the infection, in the general population.[2 3] Swift diagnosis and treatment improve

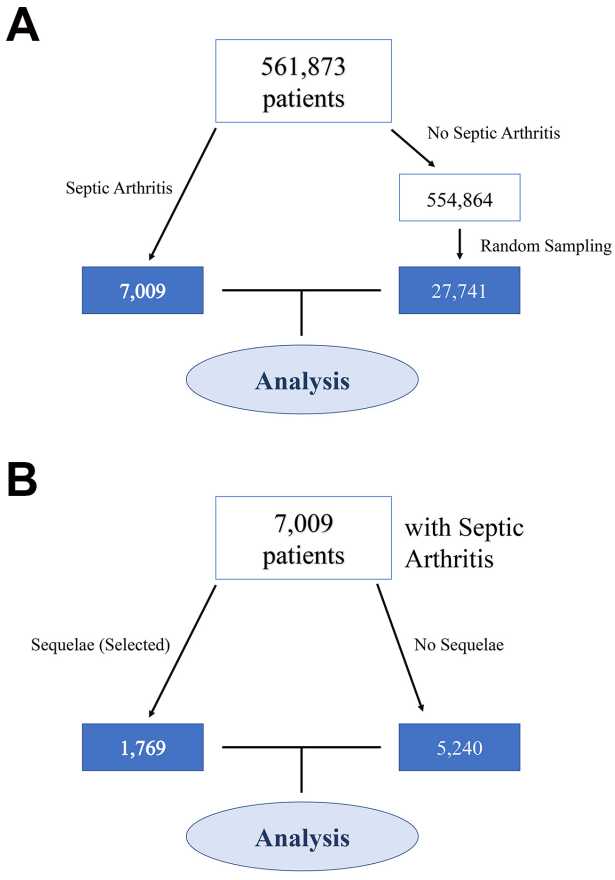

Figure 1 Derivation of sample sizes and controls for analyses of septic arthritis versus no septic arthritis (A). Derivation of sample sizes and controls for analyses of patients with septic arthritis with sequelae versus no sequelae (B).

the prognosis; however, many patients do not regain full joint function after antimicrobial therapy.[3]

Staphylococcus aureus is the most common cause of septic arthritis (37%–56% of cases).[1 2 4 5] Coagulase-negative staphylococci are isolated more frequently in joints containing foreign material.[1 4 5] In recent times, there has been an increase in methicillin-resistant *Staphylococcus aureus* (MRSA) isolated in patients with septic arthritis, with one study finding an incidence of approximately 25% of cases in an urban area.[6] Although the incidence is relatively low in the general population at <10 cases per 100,000 persons each year, the incidence of septic arthritis in hemodialysis patients increases dramatically to approximately 500 cases per 100,000 persons per year.[2 5 7]

Most patients with septic arthritis have monoarticular disease (85%–90%), with 10%–15% being polyarticular.[3 8] Septic arthritis most commonly affects the larger joints such as the knee (30.5%–48%), hip (16%–21%), ankle (6.2%–12%) and elbow (9%)[2–4 8] and presents as an erythematous, painful, restricted joint.[9] Systemic symptoms, including fever, chills and diaphoresis, may occur in a minority of patients.[1 9] However, without systemic symptoms, septic arthritis may closely resemble other arthritides and may be easily missed. A definitive diagnosis requires a joint aspiration for synovial fluid analysis and culture.[2] Blood cultures should also be obtained in order to assess for a concomitant bloodstream infection.

A history of underlying joint disease increases the risk of septic arthritis. Previous studies have shown that rheumatoid arthritis can markedly increase septic arthritis risk.[3 7 10] Other important known risk factors for septic arthritis in a population without end-stage renal disease (ESRD) include immunocompromising conditions, such as diabetes mellitus and corticosteroid therapy.[3 5 7 8 10]

ESRD and hemodialysis place patients at a great risk of infections, which can cause significant morbidity and mortality. Dysfunction of both humoral and cellular immunity is associated with uremia in chronic renal insufficiency.[11] Additionally, hemodialysis patients have increased risk of bloodstream infection due to the presence of a vascular catheter or other access creating possible entry points for pathogens.[12] According to the Centers for Disease Control and Prevention, hospitalization rates for vascular access infection in hemodialysis patients have risen 87% since 1993.[13] Furthermore, one study showed that infection accounted for 12% of all mortality in patients on hemodialysis in the USA.[14]

In hemodialysis patients with septic arthritis, systemic symptoms accompany joint pain in most cases, but may not manifest until several days after joint pain develops.[7 15] Similar to the general population, large joints (knee, hip and shoulder) comprise nearly all cases of septic arthritis in patients with ESRD.[7 15 16] A previous study systematically reviewed 16 hemodialysis patients with septic arthritis examining clinical features, risk factors and outcomes[17]; however, to our knowledge, no studies have analyzed these variables on a larger scale. Understanding the relationship between septic arthritis, risk factors and sequelae in patients with ESRD may help prioritize septic arthritis in the differential diagnosis of joint pain in this population, leading to timely intervention and improved outcomes.

METHODS

Epidemiology

The study used the US Renal Data System (USRDS) database[18] to perform a retrospective analysis of septic arthritis in the ESRD population. The study population included hemodialysis patients in the USRDS who initiated dialysis, at which time they were enrolled in Medicare and the USRDS database, between the years 2005 and 2010, and were at least 18 years of age. Vascular access type for hemodialysis was limited to arteriovenous graft (AVG), arteriovenous fistula (AVF) and vascular catheter. The population constituted 561,873 patients. The USRDS was queried using International Statistical Classification of Diseases and Related Health Problems (ICD-9) codes (online supplemental table 1) to identify all patients with ESRD on hemodialysis who were diagnosed with septic arthritis during the study period, yielding 7009 patients. Specific causative organisms were defined as organisms isolated between 30 days before and 14 days after diagnosis of septic arthritis (online supplemental table 2), as determined based on ICD-9 codes, which do not provide information as to whether the microbes were cultured from blood, urine or joint aspirates. Due to the large number of individuals without a septic arthritis diagnosis (n=554,864), a 5%

random sample of those with no septic arthritis diagnosis was used for analysis (figure 1). The controls included in the analysis (n=27,741) were not different from the controls not included (n=527,123) in terms of sex, race, ethnicity, age or access type. The total sample size for the analysis was 34,750. Demographic characteristics including age, gender, race and dialysis access type were identified using the Centers for Medicare and Medicaid (CMS) Form 2728.

Risk factors for septic arthritis

Clinical conditions were identified using ICD-9 and Current Procedural Terminology codes (online supplemental table 3) in hospital claims data and CMS Form 2728. An immunocompromising condition was defined as the presence of HIV, hepatitis C virus, cirrhosis or diabetes mellitus. Rheumatoid arthritis was also analyzed as a risk factor, based on the literature. Diagnoses of systemic lupus erythematous (SLE), autoimmune hepatitis, Behcet's disease, ulcerative colitis, granulomatosis with polyangiitis and polyarteritis nodosa were included in a single category of autoimmune disease. These diseases were selected for analysis because they were likely to occur within this cohort and may come to medical attention because of joint pain; these patients also would be expected to perhaps be at increased risk of infection due to immunosuppression, without having the same risk as rheumatoid arthritis with its ability to cause destructive arthropathy. Bacteremia and urinary tract infection (UTI) were defined as risk factors for septic arthritis if diagnosed within 30 days prior to septic arthritis diagnosis. All other risk factors had to occur before the septic arthritis diagnosis.

Sequelae

Four conditions were selected as sequelae of interest: *Clostridioides difficile* infection within 3 months, osteomyelitis within 3 months, amputation within 6 months and joint prosthesis within 6 months following diagnosis of septic arthritis (figure 1). Sequelae were determined by identification of the ICD-9 codes (online supplemental table 4) in the inpatient claims data, which include all diagnosis codes and any claims that were entered during the observation period.

Statistical analysis

All statistical analyses were performed using SAS V.9.4 and statistical significance was assessed using an alpha level of 0.05. Descriptive statistics for the site of the septic arthritis infection were determined among those with septic arthritis only. Descriptive statistics (frequencies and percentages or mean and SD) were determined for each specific organism or individual risk factor for those with and without a septic arthritis diagnosis.

To examine the potential risk factors associated with septic arthritis and associated with individual sequelae of septic arthritis, a generalized linear model building strategy was used assuming an underlying Poisson distribution with log link and an offset parameter of the natural log of person years. Each risk factor, with the exception of the specific organisms, was evaluated in a simple univariable model. All variables were then entered into a full model and a backward model building strategy was used to arrive at the final model. At each step in the model building, the least significant variable was removed from the model. The final model contained all variables that were statistically significant. The crude relative risk (RR) or adjusted RR and corresponding 95% CI are presented for each risk factor in the crude, full and final models.

Table 1 Descriptive statistics of compared ESRD populations with and without septic arthritis§, ¶

	Septic arthritis diagnosis	No septic arthritis diagnosis
Population size	7009	27,741
Age*	62.7±14.3	63.7±15.1
Race		
Black	2108 (30.1)	8187 (29.5)
Other	324 (4.6)	1535 (5.5)
White	4577 (65.3)	18,019 (65)
Sex		
Male	3964 (56.6)	15,630 (56.3)
Female	3045 (43.4)	12,111 (43.7)
Access type		
Catheter	5911 (84.3)	22,711 (81.9)
AVG	272 (3.9)	1084 (3.9)
AVF	826 (11.8)	3946 (14.2)
Arthropathies		
Rheumatoid arthritis	159 (2.3)	250 (0.9)
Gouty arthropathy	603 (8.6)	1411 (5.1)
Hemarthrosis	41 (0.6)	15 (0.1)
Other previous arthropathy	1062 (15.2)	1610 (5.8)
Joint prosthesis	584 (8.3)	361 (1.3)
Immunosuppressive conditions†		
HIV	79 (1.1)	194 (0.7)
Hepatitis B	75 (1.1)	138 (0.5)
Hepatitis C	33 (0.5)	70 (0.3)
Cirrhosis	257 (3.7)	523 (1.9)
History of transplanted organ	129 (1.8)	258 (0.9)
Diabetes	4403 (62.8)	11,020 (39.7)
Bacteremia	101 (1.4)	58 (0.2)
Skin infection	NR‡	NR
UTI	212 (3.0)	177 (0.6)

*Mean±SD.
†The number and percentage of patients with pancytopenia or neutropenia were not significantly different between those with and without a diagnosis of septic arthritis.
‡Not reported, based on the privacy requirements of the US Renal Data System, which requires suppression of values less than 11.
§Unless otherwise indicated, results are reported as n (%).
¶All of the indicated factors were statistically significantly different between those with and those without a diagnosis of septic arthritis.
AVF, arteriovenous fistula; AVG, arteriovenous graft; ESRD, end-stage renal disease; UTI, urinary tract infection.

RESULTS

Epidemiology

The study identified 7009 cases of septic arthritis, corresponding to an incidence of 514.8 cases per 100,000 persons per year. A summary of the demographics of the population is displayed in table 1. The average age at incident dialysis among those developing septic arthritis was

Table 2 Microbiology for diagnoses for which a specific organism was documented

Organism	Cases, n (%)
MRSA	1250 (57.4)
Staphylococcus spp†	262 (12.0)
Streptococcus spp	328 (15.1)
Gram-negative	321 (14.7)
Anaerobes	13 (0.6)
Pneumococcus	<11*
Other	<11*

*Per US Renal Data System regulations, observations of 10 or less must be suppressed.
†Methicillin-sensitive based on the ICD-9 code used.
ICD-9, International Statistical Classification of Diseases and Related Health Problems; MRSA, methicillin-resistant *Staphylococcus aureus*.

62.7 years. The average time from incident hemodialysis to diagnosis of septic arthritis was 459 days. Of the subjects, 2179 had an organism documented within 30 days before or 14 days after septic arthritis diagnosis, most commonly MRSA, which accounted for 57.4% of all cases with documented organisms. The next most common identified organisms were *Streptococcus* spp (15.1%), followed by Gram-negative organisms (14.7%) and methicillin-sensitive *Staphylococcus* spp (12.0%). The frequency of other specified organisms is displayed in table 2.

Risk factors for septic arthritis

The results of the final multivariable model of risk factors associated with septic arthritis are provided in table 3. Demographic factors associated with a decreased risk of development of septic arthritis included female gender and non-white race, including both black and other race. Initial vascular access with a vascular catheter was associated with an increased risk of septic arthritis compared with those with AVF.

History of joint disease was associated with an increased risk of septic arthritis. Joint prosthesis and hemarthrosis were associated with more than double the risk of septic arthritis. Rheumatoid arthritis, gouty arthropathy and other previous arthropathy were also associated with increased risk.

Selected immunocompromising conditions were associated with an increased risk of septic arthritis. Diabetes mellitus was associated with a doubled risk of septic arthritis (table 3). Presence of an autoimmune condition, HIV and cirrhosis were also associated with an increased risk of developing septic arthritis. Both recent bacteremia and UTI were associated with more than double the risk of septic arthritis.

Table 3 Risk factors for septic arthritis diagnosis*, †

	Septic arthritis diagnosis vs no diagnosis
Age (5-year increase)	1.04 (1.04 to 1.05)
Female sex	0.88 (0.84 to 0.93)
Black vs white race	0.90 (0.86 to 0.95)
Other vs white race	0.78 (0.69 to 0.87)
Catheter vs AVF access	1.40 (1.30 to 1.50)
AVG vs AVF access	1.09 (0.96 to 1.25)
Joint prosthesis	2.67 (2.44 to 2.92)
Hemarthrosis	2.37 (1.66 to 3.39)
Rheumatoid arthritis	1.49 (1.26 to 1.77)
Gouty arthropathy	1.22 (1.12 to 1.33)
Other previous arthropathy	1.52 (1.42 to 1.63)
Diabetes	2.13 (2.03 to 2.24)
HIV	1.77 (1.41 to 2.21)
Cirrhosis	1.74 (1.54 to 1.97)
Autoimmune conditions	1.49 (1.27 to 1.75)
Bacteremia	2.64 (2.07 to 3.35)
UTI	2.20 (1.88 to 2.58)

*Results reported as adjusted relative risk (95% CI).
†All associations found in this table are statistically significant.
AVF, arteriovenous fistula; AVG, arteriovenous graft; UTI, urinary tract infection.

Sequelae

At least one of the selected sequelae (osteomyelitis, joint replacement, amputation or *C. difficile* infection) occurred in 1769 subjects, 25.2% of the 7009 septic arthritis cases, with osteomyelitis being the most common (11.2%). Of these 1769 patients with ESRD on chronic hemodialysis with septic arthritis, the majority (84%, 1478 individuals) had only one sequela; 15.5% (274 patients) were diagnosed with two sequelae and 10% (17 individuals) were diagnosed with three. None of the patients exhibited all four sequelae within the indicated time frame. The final multivariable model of sequelae among subjects with septic arthritis is given in table 4. Factors associated with increased risk of any sequela after septic arthritis diagnosis were history of joint prosthesis and MRSA, while rheumatoid arthritis, autoimmune conditions and history of organ transplant were associated with a decreased risk of any sequela. Osteomyelitis was associated with MRSA, Gram-negative organisms, hepatitis C and diabetes mellitus. Gouty arthropathy, history of joint prosthesis, cirrhosis and autoimmune conditions were associated with a decreased risk of osteomyelitis. Joint replacement occurred after diagnosis of septic arthritis in 501 (7.1%) subjects and amputation in 474 (6.8%) subjects. *Staphylococcus* spp, MRSA and history of joint prosthesis were associated with an increased risk of joint replacement, while diabetes was associated with a decreased risk. Presence of Gram-negative organisms and diabetes mellitus were associated with an increased risk of amputation. Rheumatoid arthritis, cirrhosis and autoimmune conditions were negatively associated with amputation. *C. difficile* infection occurred in 317 (4.5%) subjects and was associated with bacteremia.

DISCUSSION

Demographics

The study identified 7009 cases of septic arthritis among the 561,873 subjects included, an incidence of 514.8 per 100,000 persons per year. This is over 50 times the reported rate of occurrence in the general population, but is similar to previous studies in dialysis patients.[6 7] The increased incidence of septic arthritis in patients with ESRD on chronic hemodialysis is likely multifactorial, with both immune dysfunction and increased exposure to possible routes of infection playing important roles. Patients with ESRD

Table 4 Risk factors for any sequelae and individual sequelae of septic arthritis among patients with septic arthritis*,†

	Septic arthritis sequelae vs no sequelae	P value
Any sequelae		
Gender (female vs male)		
Race		
Black vs white	**0.86 (0.78 to 0.94)**	**0.0019**
Other vs white	**0.8 (0.64 to 1.00)**	**0.0484**
Access type		
Catheter vs AVF	**1.31 (1.15 to 1.49)**	**<0.0001**
Graft vs AVF	0.93 (0.71 to 1.22)	0.6097
Age (5-year increase)	–	–
Streptococcus	–	–
Staphylococcus	–	–
MRSA	**1.16 (1.04 to 1.29)**	**0.0054**
Gram-negative organisms	1.17 (0.98 to 1.40)	0.0871
Gouty arthropathy	–	–
Rheumatoid arthritis	**0.63 (0.44 to 0.89)**	**0.0081**
Other arthropathy	0.90 (0.80 to 1.01)	0.0745
History of joint prosthesis	**1.56 (1.37 to 1.79)**	**<0.0001**
Hepatitis C	–	–
Cirrhosis	–	–
History of organ transplant	**0.66 (0.48 to 0.92)**	**0.0134**
Autoimmune conditions	**0.64 (0.44 to 0.93)**	**0.0178**
Diabetes	–	–
Bacteremia	–	–
Osteomyelitis		
Gender (female vs male)		–
Race		
Black vs white	**0.86 (0.74 to 1.00)**	**0.0475**
Other vs white	0.76 (0.54 to 1.06)	0.1021
Access type		
Catheter vs AVF	–	–
Graft vs AVF	–	–
Age (5-year increase)	**0.96 (0.94 to 0.98)**	**0.0008**
Streptococcus	–	–
Staphylococcus	–	–
MRSA	**1.40 (1.20 to 1.64)**	**<0.0001**
Gram-negative organisms	**1.34 (1.03 to 1.73)**	**0.0272**
Gouty arthropathy	**0.70 (0.53 to 0.93)**	**0.0145**
Rheumatoid arthritis	–	–
Other arthropathy	–	–
History of joint prosthesis	**0.59 (0.43 to 0.81)**	**0.0010**
Hepatitis C	**2.08 (1.06 to 4.06)**	**0.0329**
Cirrhosis	**0.67 (0.46 to 1.00)**	**0.0497**
History of organ transplant	–	–
Autoimmune conditions	**0.38 (0.19 to 0.76)**	**0.0065**
Diabetes	**1.4 (1.19 to 1.65)**	**<0.0001**
Bacteremia	–	–
Joint replacement		
Gender (female vs male)	–	–
Race		
Black vs white	–	–
Other vs white	–	–
Access type		
Catheter vs AVF	**1.85 (1.40 to 2.45)**	**<0.0001**
Graft vs AVF	1.07 (0.62 to 1.87)	0.7993
Age (5-year increase)	**1.13 (1.10 to 1.17)**	**<0.0001**
Streptococcus	1.25 (0.88 to 1.78)	0.2186
Staphylococcus	**1.63 (1.15 to 2.30)**	**0.0056**
MRSA	**1.31 (1.07 to 1.61)**	**0.0088**
Gram-negative organisms	–	–
Gouty arthropathy	–	–
Rheumatoid arthritis	0.66 (0.40 to 1.09)	0.1061
Other arthropathy	–	–
History of joint prosthesis	**5.16 (4.30 to 6.18)**	**<0.0001**
Hepatitis C	–	–
Cirrhosis	–	–
History of organ transplant	–	–
Autoimmune conditions	–	–
Diabetes	**0.62 (0.52 to 0.74)**	**<0.0001**
Bacteremia	–	–
Amputation		
Gender (female vs male)	**0.70 (0.58 to 0.84)**	**0.0001**
Race		
Black vs white	–	–
Other vs white	–	–
Access type		
Catheter vs AVF	–	–
Graft vs AVF	–	–
Age (5-year increase)	**0.94 (0.91 to 0.97)**	**<0.0001**
Streptococcus	–	–
Staphylococcus	–	–
MRSA	–	–
Gram-negative organisms	**1.41 (1.02 to 1.95)**	**0.0378**
Gouty arthropathy	–	–
Rheumatoid arthritis	**0.10 (0.01 to 0.74)**	**0.0238**
Other arthropathy	–	–
History of joint prosthesis	–	–
Hepatitis C	–	–
Cirrhosis	**0.55 (0.32 to 0.94)**	**0.0305**
History of organ transplant	–	–
Autoimmune conditions	**0.19 (0.05 to 0.79)**	**0.0222**
Diabetes	**2.18 (1.72 to 2.77)**	**<0.0001**
Bacteremia	–	–
Clostridioides difficile infection		
Gender (female vs male)	**1.27 (1.02 to 1.59)**	**0.0320**
Race		
Black vs white	–	–
Other vs white	–	–
Access type		
Catheter vs AVF	–	–
Graft vs AVF	–	–
Age (5-year increase)	**1.09 (1.04 to 1.13)**	**<0.0001**
Streptococcus	–	–
Staphylococcus	–	–
MRSA	–	–
Gram-negative organisms	–	–
Gouty arthropathy	–	–

Table 4 Continued

	Septic arthritis sequelae vs no sequelae	P value
Rheumatoid arthritis	–	–
Other arthropathy	–	–
History of joint prosthesis	–	–
Hepatitis C	–	–
Cirrhosis	–	–
History of organ transplant	–	–
Autoimmune conditions	–	–
Diabetes	–	–
Bacteremia	**2.66 (1.31 to 5.39)**	**0.0069**

*Results reported as adjusted relative risk (95% CI).
†Statistically significant associations are bolded.
AVF, arteriovenous fistula; MRSA, methicillin-resistant *Staphylococcus aureus*.

suffer from chronic low-grade azotemia with elevation of urea leading to chronic immunocompromise. In addition, hemodialysis patients are exposed to chronic or intermittent recurrent vascular access, providing pathogens direct access to the bloodstream. This can result in hematogenous seeding of bacteria into the joints, causing septic arthritis.

Initial access via a vascular catheter was also associated with an increased rate of septic arthritis (table 3). Initiating hemodialysis via catheter may be a marker of a precipitous decline in renal function leading to dialysis, a lack of access to care during progression of chronic kidney disease or other reasons that prevent appropriate fistula placement prior to dialysis. Vascular catheters are known to be associated with higher rates of bacteremia than AVG or AVF (catheter > AVG > AVF).[19] Therefore, it is important that patients with chronic kidney disease be followed closely, with early preparation for dialysis to minimize risk of future complications.

Organisms

As in previous studies, staphylococci were the most common organisms associated with joint infection. MRSA was the most commonly documented organism. Patients with ESRD have been well documented to have higher prevalence of MRSA colonization due to increased healthcare exposure.[20] The prevalence of MRSA infection in this cohort underlines the necessity to include an agent with MRSA coverage when initiating empiric treatment for septic arthritis in patients on hemodialysis. The importance of performing an arthrocentesis in a patient with suspected septic arthritis cannot be overstated. In addition to confirming the presence of infection, analysis of the joint fluid with Gram stain and culture, preferably prior to initiation of antimicrobials to increase culture yield, may allow antibiotics to be tailored to target the implicated pathogen. Further studies with patient-level data would be necessary to confirm the prevalence of specific organisms in joint infections among patients on hemodialysis.

Factors associated with increased risk of septic arthritis in patients with ESRD

History of joint replacement was associated with the highest relative risk of joint infection. This is due to the enhanced ability of bacteria to produce biofilms on prosthetic surfaces, which are capable of resisting both the immune system and antibiotics.[21–23] History of chronic joint disease, for example, gout and rheumatoid arthritis, was associated with a mildly increased risk of septic arthritis, likely due to the predisposition of bacteria to seed damaged joint surfaces. A previous study showing that 16% of those patients with septic arthritis had pre-existing rheumatoid arthritis versus an expected frequency of 1% for rheumatoid arthritis in the general UK population suggests rheumatoid arthritis as a risk factor for septic arthritis.[3] Another study reported that rheumatoid arthritis increased the risk of septic arthritis, with an odd ratio (OR) of 4.0 (95% CI 1.9 to 8.3).[8] However, both of these studies were small, with the first analyzing 242 patients and the second 37. Also, in the first study demographic and clinical variables were not controlled for, and in the second in which these factors were controlled the small sample size likely impacted accuracy. Therefore, with the sample size of over 7000 individuals in the current study, which also controlled for a large number of demographic and clinical risk factors, the adjusted relative risk of 1.49 (95% CI 1.26 to 1.77) seems likely to be more accurate.

The increased risk of septic arthritis among patients with diabetes, cirrhosis and HIV is likely due to chronic immune compromise associated with these conditions. Diabetes mellitus is the most common cause of ESRD and was the most prevalent comorbid condition in the study population, occurring in >60% of those developing septic arthritis.[24] Immune compromise in diabetes is primarily associated with decreased function of neutrophils.[25 26] In addition, patients with diabetes often suffer from neuropathy, leading to increased incidence of skin infections, a potential source of bacteremia and subsequent septic joint infection. Cirrhosis causes immune compromise due to impaired phagocytic activity, impaired opsonic activity in serum, reduction in complement and protein C activities, and portosystemic shunting, which decreases the ability to clear gut-derived bacteria from the portal circulation.[27] HIV directly targets CD4 + T cells, leading to immune suppression if untreated, and remains associated with chronic immune dysregulation in controlled disease.

Chronic immunologic conditions, including SLE, autoimmune hepatitis, Behcet's disease, ulcerative colitis, granulomatosis with polyangiitis and polyarteritis nodosa, were collectively associated with increased risk, further indicating that dysfunction of the immune system predisposes to joint infection. In addition, several common autoimmune conditions have a component of autoimmune arthritis leading to joint damage. However, these data may be confounded by use of chronic immunosuppressive medications. History of bacteremia within the preceding 30 days likely represents the source of joint infection via hematogenous seeding. Although UTI was associated with increased risk of septic joint, patients with ESRD are often either oliguric or anuric, leading to chronic microbial colonization of their urinary tracts without symptomatic UTI.[28] Therefore, if the diagnosis of 'urinary tract infection' in patients with ESRD was made by urinalysis or urine culture, it may be suspect in the absence of additional parameters indicating infection.

Sequelae

One of the four examined sequelae (joint replacement, amputation, osteomyelitis and *C. difficile*) occurred in 25% of patients with ESRD on chronic hemodialysis diagnosed with septic arthritis. Joint replacement after joint infection is performed due to either (1) severe joint disease-causing significant damage or (2) replacement of a prior prosthetic joint. Increased risk in patients with bacteremia may represent increased acuity and severity of infection. Amputation is a more radical surgical intervention and likely represents significant involvement of bone and soft tissues or underlying vascular disease complicating the healing process. Moreover, the association of amputation and osteomyelitis with diabetes in patients with septic arthritis may be secondary to diabetic skin ulcers. Infection from diabetic skin ulcers may progress to bone causing osteomyelitis. Joint infection may present following osteomyelitis via spread from the adjacent infected bone, often necessitating amputation for definitive source control.[29] A history of bacteremia may have contributed to the risk of *C. difficile* infection by increasing the duration or breadth of antibiotic exposure. The prevalence of these clinically significant sequelae underscores the importance of efficient diagnosis and treatment of septic arthritis. Nevertheless, the sequelae indicated cannot be definitively linked to the septic arthritis diagnosis, although in order to be considered a sequela its diagnosis code had to be entered within 3 (*C. difficile* infection and osteomyelitis) or 6 (joint replacement and amputation) months of the diagnosis of septic arthritis. Therefore, temporal association suggests a good possibility that the analyzed outcomes were related to the septic arthritis diagnosis.

Limitations

The present study used the USRDS database, an administrative claims database containing data on all patients with ESRD in the USA. While this resource allows examination of a large cross-section of the population, there are limitations in terms of specificity and completeness of hospital claims data. For instance, MRSA may have been overrepresented due to the increased risk of infection with this organism during a hospital stay, or possibly as a result of a coding artifact.[30] In addition, diagnoses were inferred from billing codes submitted to Medicare or derived from CMS Form 2728 and are not clinical data. However, the positive predictive value of discharge diagnosis codes to identify serious infections in middle-aged and older adults was previously found to be 90.2% (95% CI 87.8% to 92.2%).[31] This includes but is not limited to pneumonia, cellulitis, bacteremia/sepsis, pyelonephritis, septic arthritis/osteomyelitis and endocarditis.[31] Continuous eligibility was not assessed for Medicare Parts A and B during the observation period; however, all patients with ESRD in the USRDS are considered continuously enrolled following their initial dialysis date. To our knowledge there is no way to assess continuous eligibility in the USRDS data sets. In addition, we cannot demonstrate direct causality or account for any idiosyncrasies in coding, or inaccurate or missed codes from the data set. Moreover, the adherence of patients with ESRD to the treatment regimen cannot be accounted for, although as these patients have ESRD, it seems likely that they will be at least somewhat adherent to treatment regimens or risk rapid death. Finally, patients with ESRD may have private insurance in addition to Medicare, and any medical care received through their private insurance will not be captured in the USRDS database. These limitations are countered by the extensive volume of data contained in the USRDS, capturing billed diagnoses on all patients with ESRD in the USA and offering strong statistical power. Data presented here should be further evaluated with additional prospective and retrospective studies with patient-level data.

SUMMARY

Based on these data, septic arthritis has greater incidence in the ESRD population on chronic hemodialysis than the general population and is associated with a significant risk of morbidity. Increased vigilance on the part of healthcare professionals is necessary to prevent significant morbidity and mortality. Although patients with ESRD are predisposed to other acute arthropathies with similar clinical presentation, for example, gout,[32] septic arthritis should always be considered in the differential diagnosis. Any patient presenting with an erythematous, warm and/or swollen joint should be evaluated via joint aspiration. Given its high frequency, MRSA coverage is indicated as part of empiric coverage of septic arthritis in patients on hemodialysis, with transition to targeted antibiotics based on culture results. A timely plan for operative intervention if indicated may also improve long-term outcomes.

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