

Candida Arthritis: Analysis of 112 Pediatric and Adult Cases

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Background. *Candida* arthritis is a debilitating form of deeply invasive candidiasis. However, its epidemiology, clinical manifestations, management, and outcome are not well understood.

Methods. Cases of *Candida* arthritis were reviewed from 1967 through 2014. Variables included *Candida* spp in joint and/or adjacent bone, underlying conditions, clinical manifestations, inflammatory biomarkers, diagnostic imaging, management, and outcome.

Results. Among 112 evaluable cases, 62% were males and 36% were pediatric. Median age was 40 years (range, <1–84 years). Most patients (65%) were not pharmacologically immunosuppressed. Polyarticular infection (≥ 3 joints) occurred in 31% of cases. Clinical manifestations included pain (82%), edema (71%), limited function (39%), and erythema (22%) with knees (75%) and hips (15%) most commonly infected. Median erythrocyte sedimentation rate was 62 mm/hr (10–141) and C reactive protein 26 mg/dL (0.5–95). Synovial fluid median white blood cell count was 27 500/ μ L (range, 100–220 000/ μ L) with 90% polymorphonuclear neutrophils (range, 24–98). Adjacent osteomyelitis was present in 30% of cases. *Candida albicans* constituted 63%, *Candida tropicalis* 14%, and *Candida parapsilosis* 11%. Most cases (66%) arose de novo, whereas 34% emerged during antifungal therapy. Osteolysis occurred in 42%, joint-effusion in 31%, and soft tissue extension in 21%. Amphotericin and fluconazole were the most commonly used agents. Surgical interventions included debridement in 25%, irrigation 10%, and drainage 12%. Complete or partial response was achieved in 96% and relapse in 16%.

Conclusion. *Candida* arthritis mainly emerges as a de novo infection in usually non-immunosuppressed patients with hips and knees being most commonly infected. Localizing symptoms are frequent, and the most common etiologic agents are *C albicans*, *C tropicalis*, and *C parapsilosis*. Management of *Candida* arthritis remains challenging with a clear risk of relapse, despite antifungal therapy.

Keywords. antifungal therapy; arthritis; *Candida* spp; diagnosis; invasive candidiasis.

Among the causes of septic arthritis, fungal arthritis occurs infrequently and is most commonly caused by *Candida* species [1, 2]. Early reports suggested that *Candida* arthritis most commonly develops as a complication of disseminated candidiasis [3–6]. However, little is known about the clinical settings, laboratory features, radiological characteristics, or management of this uncommon infection.

Most reports of *Candida* arthritis are limited to individual case descriptions and relatively small case series. There is no comprehensive analysis that addresses the demographic, clinical,

orthopedic, laboratory, microbiology, diagnostic imaging, and therapeutic aspects of this infection. Moreover, the possible mechanisms of infection that lead to *Candida* arthritis also are not well understood.

Therefore, we conducted a systematic review of 112 reported cases of *Candida* arthritis that fulfilled prespecified criteria. Our objective was to describe the demographics, mechanisms of infection, clinical manifestations, osteoarticular distribution, microbiology, inflammatory biomarkers, diagnostic imaging, management, and outcome of *Candida* arthritis.

PATIENTS AND METHODS

Search Strategy

We initiated our search by reviewing the English references as published in PubMed (<http://www.ncbi.nlm.nih.gov/pubmed>) using the following key words: *Candida*, candidiasis, nonprosthetic arthritis, and osteomyelitis. We then carefully included only the well described references of single case reports or

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case series. After this initial series of reports was reviewed, individual references listed in each publication were again reviewed for ascertainment of additional case reports.

Study Population

We reviewed only the well described reported cases of native nonprosthetic *Candida* arthritis as published in the English literature within the study period 1967–2014. Data regarding epidemiology, clinical and radiological features, demographic characteristics, management, and outcome of the patients were collected and presented with descriptive statistics to determine the risk factors of *Candida* arthritis.

Criteria for Inclusion of Cases of *Candida* Arthritis

Cases selected in the initial screen were then included in the final analysis if the following data were available: demographics, underlying condition, documentation of native *Candida* arthritis and anatomical location of infection, microbiology data, radiology findings, symptomatology, therapeutic intervention, and outcome.

Definitions

Direct Inoculation

Direct inoculation is defined as seeding of synovial fluid by trauma or surgical manipulation.

Hematogenous

Hematogenous is defined as seeding of synovial fluid by the bloodborne route. Patients with documented *Candida* arthritis with candidemia or disseminated candidiasis were classified as having a hematogenous mechanism of infection of the involved joint. In the absence of documented candidemia or proven disseminated candidiasis, patients who did not have a clear history of contiguous infection were classified as having hematogenous infection of the joint as the most plausible mechanism.

Contiguous

Contiguous is defined as seeding of synovial fluid from an adjacent *Candida* infection.

Proven *Candida* Arthritis

Proven *Candida* arthritis is defined as a patient with evidence of a positive culture and/or histology from synovial fluid analysis.

Probable *Candida* Arthritis

Probable *Candida* arthritis is defined as a patient with evidence of a positive culture, and/or histology from other than a synovial fluid specimen, such as bone, cartilage, bone marrow, adjacent abscess, blood, central venous catheter, thrombus, tendon, disc, or operative samples, associated with compatible clinical and radiological features.

Breakthrough *Candida* Arthritis

Breakthrough *Candida* arthritis is defined as a patient receiving systemic antifungal agents before or at the onset of *Candida* arthritis.

De novo Candida Arthritis

De novo Candida arthritis is defined as a patient not receiving systemic antifungal therapy when the episode of *Candida* arthritis occurred.

Complete Response

Complete response is defined as complete resolution of clinical and radiological findings of arthritis, as assessed by 2 authors (M.N.G., M.A.B.) and, where warranted, a third author (T.J.W.).

Partial Response

Partial response is defined as partial resolution of clinical and/or radiological findings of arthritis or partial clinical improvement without availability of radiological data, as assessed by 2 authors (M.N.G., M.A.B.) and, where warranted, a third author (T.J.W.).

Data Collection and Analysis

Data regarding demographic characteristics, clinical and radiological features, inflammatory biomarkers, microbiology, management, and outcome of patients were collected and analyzed with descriptive statistics using InStat GraphPad (GraphPad Software, San Diego, CA). Continuous variables were summarized using median and range, whereas categorical variables were summarized using frequencies and percentages. Differences in proportions were analyzed by Fisher's exact test. A *P* value of $\leq .05$ was considered to be significant.

RESULTS

Literature Review

Patients included in this study consisted of 112 nonprosthetic *Candida* arthritis cases as published in the English literature within the study period from 1967 to 2014. The first case of *Candida* arthritis was reported in 1967 [71]. Since this initial report through 2014, a total of 112 published cases [7–103] of *Candida* arthritis fulfilled predefined criteria for evaluability. Thus, 112 evaluable cases were entered into the database.

Demographic Characteristics and Underlying Conditions

Amongst a total of 112 published cases of *Candida* arthritis, median age was 40 years (range, ≤ 1 month–84 years) (Table 1). Sixty-nine patients (62%) were males. Underlying conditions included surgery (35%), hematologic malignancies (16%), solid organ transplantation ([SOT] 9%), trauma (9%), intravenous drug use (9%), and solid tumors (4%). The majority of patients was not neutropenic nor was receiving corticosteroids or other pharmacological immunosuppression. Other conditions included central venous catheters, prior broad-spectrum antibiotics or antifungal agents, total parenteral nutrition, critical illness, use of illicit intravenous drugs or alcohol abuse, diabetes mellitus, hemodialysis, chronic pulmonary disease, and hypogammaglobulinemia. Ten patients (9%) had trauma or open wounds.

Candidemia and Arthritis

Before the diagnosis of *Candida* arthritis, 71 (63%) patients initially had candidemia or other form of candidiasis, including

Table 1. Demographic Characteristics and Underlying Conditions of Nonprosthetic *Candida* Arthritis (N = 112)

| Demographic Features and Underlying Conditions | N (%) |
|---|----------|
| Median age (neonates-84 years) | 40 years |
| Adults (≥19 years) | 72 (64) |
| Pediatric population | 40 (36) |
| Neonates (≤1 months) | 11 (10) |
| Infants (≤12 months) | 17 (15) |
| Toddlers/Children (1–18 years) | 10 (9) |
| Unknown age | 2 (2) |
| Gender | |
| Females | 37 (33) |
| Males | 69 (62) |
| Unknown | 6 (5) |
| Underlying conditions | |
| Solid tumors | 5 (4) |
| Hematologic malignancy | 18 (16) |
| Aplastic anemia | 1 (1) |
| Solid organ transplantation | 10 (9) |
| Bone marrow transplantation | 3 (3) |
| Surgery | 39 (35) |
| Facial/Neck | 0 (0) |
| Thoracic | 4 (4) |
| Abdominal | 20 (18) |
| Orthopedic | 15 (13) |
| Prior broad-spectrum antibiotics | 73 (65) |
| Prior antifungal agents | 35 (31) |
| Central venous catheter | 17 (15) |
| Open fracture | 0 (0) |
| Trauma/open wound | 10 (9) |
| HIV | 4 (4) |
| IVDU | 10 (9) |
| Alcohol abuse | 5 (4) |
| Hemodialysis | 6 (5) |
| Neutropenia | 10 (9) |
| Corticosteroids | 20 (18) |
| Pharmacological immunosuppression other than steroids | 19 (17) |
| Hypogammaglobulinemia | 2 (2) |
| Chronic Pulmonary Disease | 4 (4) |
| Abdominal abscess | 1 (1) |
| GI rupture | 1 (1) |
| Necrotic enterocolitis | 2 (2) |
| Congenital disorder (gastroschisis, Hirschsprung's disease) | 7 (6) |
| Total parenteral nutrition | 14 (13) |
| Diabetes mellitus | 11 (10) |
| Rheumatoid arthritis | 2 (2) |
| Intensive care unit | 6 (5) |
| None | 3 (3) |
| Preexisting invasive candidiasis | 71 (63) |
| Candidemia | 32 (29) |
| Other forms of candidiasis ^a | 39 (35) |
| Candidemia at time of diagnosis of <i>Candida</i> arthritis | 12 (11) |

Abbreviations: CNS, central nervous system; GI, gastrointestinal; HIV, human immunodeficiency virus;IVDU, intravenous drug use.

^a Central venous catheter infection, candiduria, orbital candidiasis, and otitis, cutaneous, pulmonary, or CNS infection.

central venous catheter infection, candiduria, orbital candidiasis, and central nervous system infection (Table 1). Twelve

Table 2. Classification and Apparent Mechanisms of Nonprosthetic *Candida* Arthritis

| Classification and Apparent Mechanisms | N (%) |
|--|---------|
| Classification of <i>Candida</i> arthritis | |
| Proven ^a | 99 (88) |
| Probable ^b | 13 (12) |
| Apparent mechanisms of infection | |
| Hematogenous | 91 (81) |
| Direct inoculation | 21 (19) |
| Contiguous | 0 (0) |
| Relation to antifungal therapy | |
| Breakthrough <i>Candida</i> arthritis | 38 (34) |
| De novo <i>Candida</i> arthritis | 74 (66) |

^a Proven = specimen from synovial fluid analysis that isolated *Candida*.

^b Probable = specimen that isolated *Candida* other than synovial fluid, plus (+) local symptoms/(+) radiology. This specimen is bone tissue (3), or bone and cartilage (1), bone marrow (1), adjacent abscess (1), cartilage (1), thrombus (1), tendon (1), disc (1), or operative samples (1).

patients (11%) also had candidemia at the time of diagnosis of *Candida* arthritis.

Classification of *Candida* Arthritis and Mechanisms of Articular Infection

Ninety-nine cases (88%) were proven and 13 cases (12%) were probable for *Candida* arthritis (Table 2). Apparent mechanisms of *Candida* arthritis consisted of hematogenous dissemination (81%) and direct inoculation (19%). Breakthrough *Candida* arthritis accounted for 34% versus de novo infection in 66%; these 2 groups were mutually exclusive.

Osteoarticular Distribution

Monoarticular involvement occurred in 77 cases (69%), whereas 2 or more joints were infected in 35 cases (31%). *Candida* synovial arthritis involved the knee in 84 (75%) cases, hip in 17 (15%) cases, and shoulder in 8 (7%) patients (Table 3). The most frequently infected bone sites were femur (19%), tibia (13%), and humerus (8%).

Diagnostic Procedures

The following diagnostic approaches were used for patients with *Candida* arthritis: needle aspiration in 80 (71%); open biopsy or surgery in 12 (11%); and percutaneous, closed, or guided biopsy in 4 (4%) (Table 4). *Candida* species were detected predominantly via direct culture in 98 (88%) patients and less frequently by histopathology with or without culture (Table 4). One *Candida* species was recovered in 111 patients (99%) with arthritis, whereas in 1 (1%) patient more than 1 species of *Candida* was identified.

Clinical Microbiology

Candida albicans was identified in 63% of 112 cases of arthritis (Table 4). Among non-*albicans* species, *Candida tropicalis* was recovered in 14%, *Candida parapsilosis* in 11%, *Candida krusei* in 4%, followed by *Candida glabrata* in 2%, *Candida lusitanae*

Table 3. Osteoarticular Involvement of Nonprosthetic *Candida* Arthritis

| Osteoarticular Involvement | N (%) |
|---|---------|
| Number of Joints Infected | |
| 1 joint infected | 77 (69) |
| 2 joints infected | 10 (9) |
| ≥3 joints infected | 25 (22) |
| Joint Involvement | |
| Intervertebral Joint | 5 (4) |
| Synovial Joint | |
| Knee | 84 (75) |
| Hip | 17 (15) |
| Shoulder | 8 (7) |
| Ankle | 6 (5) |
| Carpal | 3 (3) |
| Elbow | 5 (4) |
| Tarsal | 2 (2) |
| Wrist | 2 (2) |
| Costochondral | 1 (1) |
| Type of Adjacent Bone Infected^a | |
| Total number of adjacent bones infected | 34 (30) |
| Femur | 21 (19) |
| Tibia | 14 (13) |
| Humerus | 9 (8) |
| Fibula | 6 (5) |
| Vertebra | 6 (5) |
| Ulna | 4 (4) |
| Ribs | 3 (3) |
| Radius | 3 (3) |
| Tarsus | 3 (3) |
| Metatarsus | 2 (2) |
| Carpus | 2 (2) |
| Other ^b | 6 (5) |

^a Some patients with polyarticular infection had more than 1 adjacent bone infected.

^b Pelvis, sternum, clavicle, patella, talus, calcaneus.

in 2%, *Candida guilliermondii* in 2%, and nonspecified *Candida* species in 4%.

Clinical Manifestations

Ninety-two (82%) of 112 patients complained of local pain and tenderness, whereas 79 (71%) had edema, and 25 (22%) patients presented with localized erythema (Table 5). Fever was present in 15 (13%) patients. Limitation of function and movement was documented in 44 (39%) patients. Sinus tracts and draining pus were observed in 6 (5%) patients.

Markers of Inflammation

The median white blood cell (WBC) counts were mildly elevated with a median of 10 750 cells/mm³ (range, 160–36 500 cells/mm³) with neutrophils consisting of a median of 45% (10%–90%). By comparison, median values of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were moderately elevated at 56 mm/hour (range, 10–118 mm/hour) and highly elevated at 28.9 mg/dL (range, 0.5–141 mg/dL), respectively, with a wide range of variation (Table 5). For the synovial fluid, there was leukocytosis with predominance of neutrophils.

Table 4. Diagnostic Procedures and Microbiology of Nonprosthetic *Candida* Arthritis

| Diagnostic Procedures and Microbiology | N (%) |
|---|----------|
| Procedures | |
| Percutaneous/Closed/Guided biopsy | 4 (4) |
| Open biopsy/surgery | 12 (11) |
| Needle aspiration | 80 (71) |
| Swab of sinus tract or wound | 1 (1) |
| Synovial fluid aspiration | 99 (88) |
| Microbiology/Histopathology^a | |
| Only direct culture | 98 (88) |
| Direct culture and histology | 13 (12) |
| Unknown | 1 (1) |
| Microbiological Identification^b | |
| Recovery of <i>Candida</i> spp | |
| 1 <i>Candida</i> spp | 111 (99) |
| >1 <i>Candida</i> spp | 1 (1) |
| Identification of <i>Candida</i> spp | |
| <i>Candida albicans</i> | 70 (63) |
| <i>Candida tropicalis</i> | 16 (14) |
| <i>Candida parapsilosis</i> | 12 (11) |
| <i>Candida krusei</i> | 4 (4) |
| <i>Candida glabrata</i> | 2 (2) |
| <i>Candida lusitanae</i> | 2 (2) |
| <i>Candida guilliermondii</i> | 2 (2) |
| <i>Candida</i> species: not specified | 5 (4) |

^a Ten patients also had positive blood cultures; 1 or more microbiological or histopathological procedures were positive for *Candida* species per patient.

^b One culture was mixed with *Sporothrix schenckii*.

Diagnostic Imaging

The most common radiological abnormalities in *Candida* arthritis were bone destruction (42%) and joint effusion (31%), followed by extension into soft tissues, decrease of articular space, osteoarthritis and periosteal reaction, and/or synovitis (Table 6). Extension into soft tissue was also observed in 21%.

Treatment and Outcome

Sixty-nine (62%) patients with *Candida* arthritis were treated with antifungal agents only, 1 (1%) underwent surgical treatment only, and 40 (36%) were treated with both antifungal therapy and surgery. The most commonly used combinations of antifungal agents were amphotericin B plus an azole or amphotericin B plus flucytosine (Table 7). There was no significant difference between patients who received surgical intervention plus medical therapy versus those who received medical therapy alone ($P = .40$). However, there were fewer deaths in those treated with antifungal therapy plus surgery (2 [4%]) versus those treated with antifungal therapy alone (12 [14%]), 3 of which were caused by disseminated candidiasis.

Median duration of therapy was 64 days (range, 14–436 days). Debridement was the most common surgical procedure (25%) followed by drainage/aspiration and irrigation/lavage.

Table 5. Clinical Manifestations and Inflammatory Markers of Nonprosthetic *Candida* Arthritis

| Clinical Manifestations and Inflammatory Markers | N (%) |
|--|----------------------|
| Clinical Manifestations | |
| Local symptoms | |
| Pain/Tenderness | 92 (82) |
| Edema | 79 (71) |
| Erythema | 25 (22) |
| Fever | 15 (13) |
| Limitation of function/movement | 44 (39) |
| Draining pus/sinus tract | 6 (5) |
| Inflammatory markers | |
| Serum | |
| WBC (/mm ³) | 10 750 (160–36 500) |
| PMNs (%) | 45 (10–90) |
| ESR (mm/h) | 62 (10–141) |
| CRP (mg/dL) | 26 (0.5–95) |
| Synovial Fluid | |
| Gram stain | 10 (9%) (+) |
| Culture | 100 (89%) (+) |
| Color | 10 (9%) (purulent) |
| Viscosity | 6 (5%) (low) |
| | 13 (12%) (high) |
| Clarity | 15 (13%) (cloudy) |
| | 8 (7%) (turbid) |
| Glucose (mg/dL) | 59.5 (2–119) |
| Protein (g/dL) | 5.15 (2.8–6.5) |
| WBC (/mm ³) | 27 500 (100–220 000) |
| PMNs (%) | 90 (24–98) |

Abbreviations: CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; PMNs, polymorphonuclear neutrophils; WBC, white blood cell.

Complete response of *Candida* arthritis was documented in 87 patients (78%), partial response in 21 cases (19%), relapse in 18 (16%), and failure in 4 (4%) (Table 7).

Analysis of Pediatric and Adult Patients

The majority (70%) of all pediatric patients with *Candida* arthritis were neonates and infants. There was a significant difference in the pathogenetic mechanisms of infection, because 38 (95%) of 40 pediatric patients versus 53 (74%) of 72 adult patients ($P = .005$) followed a hematogenous dissemination (Table 8). Children achieved a higher complete response rate to antifungal therapy than adults ($P = .09$). There were no other significant differences in features of *Candida* arthritis between pediatric and adult populations.

In attempting to further understand potential differences in pediatric and adult patients with *Candida* arthritis, the frequencies of underlying diseases were analyzed and found to be similar ($P = .23$). There was a total of 18 of 40 pediatric patients who had immunocompromising conditions, including neonates, hematological malignancies, and hematopoietic stem cell transplantation (HSCT) in comparison to 24 of 72 adults with hematological malignancies, HSCT, and SOT (Table 8).

Table 6. Radiological Features of Nonprosthetic *Candida* Arthritis

| Radiological Features ^a | n/N (%) |
|--|------------|
| Osteolysis/bone destruction/bone erosion | 30/72 (42) |
| Joint effusion | 22/72 (31) |
| Extension into soft tissues | 15/72 (21) |
| Increase of nuclear scan uptake (Tc ^{99m} /Ga ⁶⁷) | 14/16 (88) |
| Decreased articular space | 9/72 (13) |
| Osteoarthritis | 6/72 (8) |
| Periosteal reaction/thickened synovium/synovitis | 5/72 (7) |
| Sequestrum | 2/72 (3) |
| Increase of signal intensity-T2 (magnetic resonance imaging [MRI]) | 2/9 (22) |
| Necrotic bone | 2/72 (3) |
| Increase of contrast-enhanced T1 (MRI)/T1 weighed | 2/9 (22) |
| Fracture | 1/72 (1) |
| Osteochondrosis/chondrocalcinosis | 1/72 (1) |
| Bone abscess | 1/72 (1) |
| Muscle involvement (abscess/myositis/sinus in tissues) | 1/72 (1) |
| Radiological follow-up | |
| Improvement | 30 (27) |
| No improvement | 3 (3) |
| Not performed/reported | 79 (71) |

^a Radiological methods for which sufficiently detailed data were available included conventional radiographs (72), radionuclide scanning (16), computed tomography (5), magnetic resonance (9), and (7) patients performed ultrasound.

DISCUSSION

This study of 112 cases of nonprosthetic *Candida* arthritis demonstrated a wide range of underlying conditions and ages from neonates to >80 years old. Whereas 34% were immunocompromised, the majority of patients had no apparent underlying immune impairment. Although the majority of patients had candidemia or other causes of invasive candidiasis before or during the appearance of arthritis, 29 (26%) patients had no preexisting invasive candidiasis or concomitant candidemia at the time of diagnosis of *Candida* arthritis. Most episodes (81%) of *Candida* arthritis arose from hematogenous dissemination. *Candida albicans*, *C tropicalis*, and *C parapsilosis* were the most common causes of *Candida* arthritis. Local pain, tenderness, and edema were commonly observed; however, fever was uncommon (13%). Likewise, WBC count, ESR, and CRP were only moderately elevated in most patients. The most common radiological abnormalities in *Candida* arthritis were bone destruction and joint effusion. A complete response to medical therapy with or without surgery was achieved in 78%; however, the remainder had only partial response, failure, or relapsed, suggesting the need for better therapeutic approaches for this infection.

An early diagnosis of *Candida* arthritis is important to prevent joint destruction, preserve function, and determine length of therapy. Understanding the host factors, clinical manifestations, inflammatory markers, diagnostic imaging, and microbiology are essential to achieving those objectives.

Table 7. Treatment and Outcome of Nonprosthetic *Candida* Arthritis

| Treatment and Outcome | N (%) |
|---|---------|
| Medical Treatment^a | |
| Only antifungal agents | 69 (62) |
| Only surgery | 1 (1) |
| Antifungal agents and surgery | 40 (36) |
| Class of Antifungal Agent(s) Used | |
| Amphotericin B | 37 (33) |
| Triazoles | 21 (19) |
| Flucytosine | 8 (7) |
| Combinations ^b | 43 (38) |
| Duration of Medical Treatment^c | |
| Median duration in days (range, 14–436) | 64 days |
| Surgical Intervention | |
| Debridement | 28 (25) |
| Drainage/aspiration | 13 (12) |
| Irrigation/lavage | 11 (10) |
| Amputation | 3 (3) |
| Bone grafting | 1 (1) |
| Insertion of metal hardware/prosthesis/arthroplasty | 1 (1) |
| Outcome | |
| Complete response | 87 (78) |
| Partial response | 21 (19) |
| Failure | 4 (4) |
| Relapse | 18 (16) |
| Overall mortality | 15 (13) |

^a Two cases received no therapy.

^b Among the 43 cases of combination antifungal therapy, the following classes were used: polyene-azole (20), polyene-flucytosine (13), polyene-azole-flucytosine (3), azole-flucytosine (1), azole-echinocandin (2), polyene-azole-echinocandin (3), and polyene-echinocandin (1).

^c Forty-six cases of unknown duration.

The age range, gender distribution, and underlying host factors of *Candida* arthritis reflect those of candidemia and deeply invasive candidiasis. *Candida* arthritis needs to be included within the differential diagnosis of osteoarticular symptoms in patients with underlying immunosuppression, including those with hematological malignancies, SOT, HSCT, and corticosteroid therapy. Likewise, surgery and trauma, particularly in patients receiving broad-spectrum antibiotics and with implanted central venous catheters, constitute other clinical settings in which *Candida* arthritis may emerge.

Candida arthritis may appear as a late manifestation of disseminated candidiasis. Kim et al [12] reported development of *Candida* arthritis 2 weeks after a chemotherapy-induced granulocytopenic period in the absence of any invasive manipulation. Joint swelling or arthralgia after recovery from neutropenia in febrile patients should raise clinical suspicion of fungal arthritis [4, 81].

The apparent pathogenesis of most cases of *Candida* arthritis is that of hematogenous dissemination to the joint. The mammalian synovium is extremely vascular and contains no limiting basement membrane, promoting easy access of blood contents to the synovial space. Therefore, hematogenous seeding of *Candida* may affect normal joints [104].

Although the exact pathogenesis of *Candida* arthritis remains to be further elucidated, the portal of entry may originate via contamination of central vascular catheters or from altered gastrointestinal microbial flora in the host with subsequent mucosal translocation and hematogenous dissemination [4, 24, 43]. Although infection of a joint is also possible via direct inoculation (surgery or intra-articular infection), hematogenous dissemination appears to be the most common mechanism of infection.

Hematogenous dissemination was significantly more common as a mechanism of *Candida* arthritis in children than in adults. This difference may be understood from the observation that all pediatric patients with *Candida* arthritis were neonates, infants, and toddlers. These populations are particularly vulnerable to the osteoarticular complications of candidemia, including *Candida* arthritis. The lack of closure of the epiphyseal plate in neonates, infants, and toddlers allows hematogenously disseminated organisms to extend into the joint space either directly through the articular cartilage or through the bony cortex of the joint capsule and then into the synovial space. Adults are more likely to have underlying surgical- and trauma-related portals of direct infection, hence accounting for these differences in pediatrics.

Because this study found that *Candida* arthritis arises in most patients with known invasive candidiasis or at the time of diagnosis of candidemia, an evaluation of musculoskeletal symptoms in overall assessment may reveal localization to 1 or more joints. However, because *Candida* arthritis also may arise de novo in more than one fourth of patients, one needs to have a high index of reaching this diagnosis in patients with the aforementioned host factors as the first manifestation of disseminated disease.

The clinical manifestations of *Candida* arthritis of pain, tenderness, and edema are common and should prompt an assessment for septic arthritis with *Candida* joint infection high in the differential diagnosis in the setting of a susceptible host with or without other evidence of invasive candidiasis. The knee, hip, and shoulder are the most frequently infected sites. Moderately elevated ESR and CRP further support the diagnosis in most but not all patients. The radiological features of bone destruction and joint effusion attest to the virulent nature of *Candida* arthritis but are not specific.

Because the clinical manifestations and inflammatory markers are not specific for *Candida* arthritis, arthrocentesis or arthroscopy is warranted for the definitive diagnosis. Given the paucity of fever and specific laboratory findings or radiographic features, diagnosis of fungal osteoarticular infections may be delayed in most cases [109–111]. The differential diagnosis includes bacterial septic arthritis and crystalline arthritis. Although arthrocentesis is readily performed in the knee, the procedure is more challenging in the hip and shoulder. Synovial fluid analysis in *Candida* arthritis is characterized by acute

Table 8. Effect of Age on Effect by Site of Infection, Clinical Manifestations, and Outcome in *Candida* Arthritis

| Population (N) | Mechanism (N) | Joint Sites (N) | Number of Sites Infected/Patient (N) | Clinical Manifestations (N) | Therapeutic Intervention (N) | Outcome (N) |
|-----------------------------|-------------------------|--|--|---|---|--|
| All pediatric patients (40) | Hematogenous (38)* | Knee (31) Hip (10) | 1 bone involved (20) 2 bones involved (5) ≥3 bones involved (15) | Local symptoms pain (22) Edema (31) Erythema (6) Limitation of movement (20) Fever (7) Draining pus (2) | Only AFT (28) Only Surgery (0) AFT + Surgery (11) Debridement (4) Amputation (1) Drainage (5) Lavage (4) Amphotericin (29) Azoles (9) 5-FC (14) Echinocandins (2) | CR (35) PR (5) ^a Rel (3) D (2) |
| Neonates (11) | Contiguous (0) | Ankle (5) | | | | |
| Hemato (5) | Direct inoculation (2) | Elbow (4) Shoulder (3) Others (4) Wrist (1) Carpus (1) Costochondral (1) Intervertebral (1) | | | | |
| HSCT (2) | | | | | | |
| Adults (72) | Hematogenous (53)* | Knee (53) Hip (7) | 1 bone involved (57) 2 bones involved (5) ≥3 bones involved (10) | Local symptoms pain (70) Edema (48) Erythema (19) Limitation of movement (24) Fever (8) Draining pus (4) | Only AFT (41) Only Surgery (1) AFT + Surgery (29) Debridement (24) Amputation (2) Drainage (8) Lavage (7) Amphotericin (48) Azoles (41) 5-FC (11) Echinocandins (4) | CR (52) PR (16) F (4) Rel (15) D (13) |
| Hematol (13) | Contiguous (0) | Shoulder (5) Others (11) Intervertebral (4) Carpus (2) Tarsus (2) Wrist (1) Ankle (1) Elbow (1) | | | | |
| HSCT (1) | Direct inoculation (19) | | | | | |
| SOT (10) | | | | | | |

Abbreviations: AFT, antifungal therapy; CR, complete response; Hematol, hematological malignancies; HSCT, hematopoietic stem cell transplantation; PR, partial response; Rel, relapsed; D, death; SOT, solid organ transplantation; 5-FC, 5-fluorocytosine.

^a Of the 5 patients with PR, 2 patients ultimately died.

* $P = .005$.

inflammatory response with a predominance of neutrophils; however, this is not specific. By comparison, recovery of *Candida* spp provides a definitive diagnosis. It is noteworthy that *Candida* spp are seldom laboratory contaminants from normally sterile synovial fluid.

That *C. albicans* and *C. tropicalis* constituted the 2 most common organisms causing septic arthritis is consistent with their being the most virulent causes of hematogenous disseminated candidiasis [24, 104]. The paucity of cases of *C. glabrata* arthritis, despite its constituting as much as one fourth of cases of candidemia, suggests that this organism may not have the necessary virulence factors needed to establish infection within synovial tissue. Possible virulence factors, such as adhesion molecules, cell wall hydrophobicity, as well as extracellular proteases and phospholipases differ in their properties and expression among *Candida* spp [111].

The objectives of treatment of *Candida* arthritis are to relieve symptoms, eradicate infection, prevent joint injury, and restore function. Unfortunately, there is no evidence-based standard treatment regimen for patients with fungal osteoarticular infections of native joints due to the heterogeneous spectrum of diseases and the relatively low frequency of this disease. Current guidelines recommend initial antifungal therapy with amphotericin B or fluconazole combined with surgical debridement [105]. Ambulatory antifungal therapy may be achieved with orally administered fluconazole. Medical therapy of *Candida* arthritis in this study most commonly began with amphotericin with or without combinations, such as flucytosine or

fluconazole. Echinocandins were used as part of combination therapy in 6 patients but not used as monotherapy. However, given the activity of echinocandins on *Candida* biofilms [106–108], primary therapy with an echinocandin is a rational approach for initial medical management of *Candida* arthritis.

Surgery may also be an important adjunct to medical management of *Candida* arthritis. Treatment of *Candida* arthritis in this series was successful in the majority of patients with medical therapy alone; however, surgical intervention was considered to be warranted in 36% of patients. Because synovial fluid analysis and radiological features of *Candida* arthritis reveal this infection to be a suppurative destructive process, the surgical procedures used included irrigation, drainage, and debridement.

Although there was no significant difference in therapeutic response between those who received combined medical plus surgical therapy versus medical therapy alone, there were more deaths and disseminated candidiasis in the latter. These differences may be due to a lack of source control or more immunocompromised host. That the overall responses were similar between the 2 groups does not necessarily justify medical therapy alone for all patients. We hypothesize that there are some patients who will benefit from antifungal therapy plus adjunctive surgical intervention, whereas others may respond to medical therapy alone. The data warrant that each patient with *Candida* arthritis be assessed individually for combination medical-surgical therapy versus medical therapy alone. We suggest that a prospective study may help to further define the

factors guiding the decision for surgical intervention in *Candida* arthritis.

The rationale for medical therapy alone versus combined medical and surgical intervention in individual cases was not apparent in most reports. Although combined medical and surgical intervention is certainly considered a standard of care of septic arthritis, serious comorbidities could preclude surgery in some patients. That the overall therapeutic response was favorable in those treated with medical therapy alone, these data raise the question of whether there is a subset of patients who may be candidates for medical therapy on an individualized basis.

Lack of a favorable response to treatment with antibiotics in a possible septic arthritis, particularly in immunocompromised patients, should raise suspicion of a *Candida* osteoarticular infection. Prompt therapy in immunocompromised hosts presenting with acute arthritis should include not only antibacterial but also antifungal agents after diagnostic arthrocentesis.

An important pattern of therapeutic response was observed in those patients classified as “relapsed.” Upon discontinuation of a course of antifungal therapy, relapsed infection developed in 18 patients. However, all of such patients subsequently responded to a second course of antifungal therapy with or without further surgical intervention, suggesting that duration of therapy as well as adequate debridement and drainage are important for successful outcome. The optimal duration of antifungal therapy remains to be defined with individual considerations of immune impairments, type of joint, and adequacy of debridement. The report by Miller et al [112] also suggests that local intraoperative irrigation of an infected joint by amphotericin B may assure further local control.

Duration of therapy in this study extended a median period of 2 months. This duration is compatible with the previously reported length of therapy of approximately 3 months reported for *Candida* osteomyelitis [109]. That this duration may be decreased by aggressive joint irrigation or arthroscopic debridement is suggested by a recent study by Miller et al [112], who reported a median duration of approximately 2 months for treatment of *Candida* osteoarticular infections. Alternatively, induction therapy with an echinocandin and maintenance therapy with more potent triazoles, such as voriconazole, posaconazole, and isavuconazole, warrants further investigation for also reducing the duration of antifungal therapy.

This study design of *Candida* arthritis has several limitations. Due to the retrospective nature of the design, not all data points were uniformly obtained and documented. Although the study design is strengthened by the detail afforded in individual case reports, it also may be affected by publication bias, which may lead to the reporting of better outcomes. The lack of a denominator in the study design precludes establishing an estimate of incidence; however, this was not the objective of this study. Although the comprehensive nature of the study design from the earliest reported case to the present time increases an

understanding of the clinical manifestations, it introduces variations in advances of imaging and treatment. Although a prospective, multicenter, case-controlled observational study would address many of these concerns, such a design for *Candida* arthritis would require years of data collection. Therefore, the study design used in this review provides for a large number of protocol-selected patients analyzed through a finely detailed database to advance our understanding of this uncommon osteoarticular infection.

CONCLUSIONS

In summary, this systematic review provides a comprehensive analysis of the demographic characteristics, host factors, clinical manifestations, inflammatory biomarkers, diagnostic imaging, microbiology, and treatment of 112 cases of *Candida* arthritis. A high index of clinical and microbiological suspicion of *Candida* spp in the differential diagnosis of septic arthritis in vulnerable hosts may facilitate the timely diagnosis and rapid initiation of the appropriate therapy.

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