Late onset neonatal Candida albicans osteomyelitis and arthritis: a case report and literature review

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Keywords

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Abstract

Objectives: Invasive candidiasis in neonates is an important cause of morbidity and mortality in the neonatal intensive care unit. Well known complications from invasive Candida albicans infections include kidney infections, endophthalmitis, endocarditis, meningitis and dermatitis. Candida arthritis and osteomyelitis have been reported less frequently, but have been observed months to even years after systemic antifungal therapy for candidiasis was completed.

Case report: We present a preterm neonate with a fungal proven central line associated infection, treated with antifungal therapy, who developed secondary a delayed presentation of osteomyelitis and arthritis as a complication of the Candida albicans fungemia. The infection was suspected by a positive serum beta-D-glucan (BDG) test and the diagnosis of invasive Candida infection was proven by tissue culture. Prolonged treatment during six months with oral fluconazole cured the infection in this case. A literature review revealed limited guidance on how to manage this complication in neonatal and pediatric patients. Previously described cases received amphotericin B more often than fluconazole, but both options appear to be curative. However, compared to amphotericin B, fluconazole has less adverse effects, such as nephrotoxicity, has better tissue penetration and can be administered orally.

Conclusions: Skeletal infections secondary to Candida albicans infections in the neonatal population are serious, but prolonged oral treatment is curative in most cases. It is important to raise awareness for the long lag time between initial infection and secondary complication, so these newborns receive a close follow-up. The beta-D-glucan serum antigen tests can be contributive to a timely diagnosis.

Introduction

Invasive *Candida* infections are regularly being encountered in premature infants admitted to the neonatal intensive care unit (NICU). The overall incidence is approximately 5 to 10 cases per 100.000 live births (1,2). The incidence of invasive fungal infection ranges from 2 to 4% in very low birth weight (<1500g) and from 4 to 16% in extreme low birth weight (<1000g) infants [3]. This has been attributed to many underlying factors including the improved survival of very low birth weight infants, the use of central venous catheters, prolonged administration of parenteral alimentation, the increased use of corticosteroids and broad-spectrum antibiotics, surgery and damaged or abnormal skin barrier (4-7). Disseminated disease mostly prompts simultaneous renal, cerebral, cardiac, dermatological or ophthalmic complications, whereas osteoarticular involvement is rare (6,8). Over the past few decades a small number of case reports presented delayed arthritis and osteomyelitis as a rare complication of neonatal *Candida* infection. Most cases presented after treatment completion for the initial infection (4-6,9,10). In this case report we present a premature infant with *Candida* septicemia, who developed arthritis and osteomyelitis several weeks after completion of antifungal therapy with fluconazole. We will also discuss pathogenesis, predisposing factors, diagnostic tools and treatment options based on our experience with this case and current knowledge provided by published literature. With this case report we want to summarize what is already known about this subject and propose a treatment regimen for *Candida* arthritis based on our findings.

Case report

A female infant, the first member of a dichorionic diamniotic twin with a birth weight of 840 gram (10th percentile), was born at 27 weeks of gestation to a multiparous mother by spontaneous vaginal delivery. The mother was pre-treated with one dose of penicillin for prolonged premature rupture of membranes. Only one dose of antenatal corticosteroids was administered after onset of preterm labor. The Apgar scores were 5 and 6 at 1 and 5 minutes respectively. At birth insufflation breaths and continuous positive airway pressure (CPAP) was given. There was no need to administer surfactant. An umbilical venous catheter was placed at a peripheral position to administer parenteral nutrition. The infant was empirically treated for 48 hours with penicillin and amikacin intravenously (IV) for possible early onset sepsis. Meconium culture was negative for *C. albicans,* suggesting no risk for invasive candidiasis. Fluconazole prophylaxis was therefore not started in this infant. Initial blood cultures were negative and C-reactive protein (CRP) remained low. A peripheral intravenous central catheter (PICC) was placed on the second day of life (DOL) to ensure parenteral nutrition. On DOL 9 the infant presented with progressive respiratory insufficiency requiring endotracheal intubation. A sepsis work-up was initiated and the PICC was removed. Flucloxacillin and amikacin IV were started to treat a suspected late onset sepsis. Blood tests revealed a slightly elevated white blood cell count (WBC 11,4 x10E9/L; normal 9 – 24x10E9/L) and a normal CRP level of 5,4 mg/L (normal < 20 mg/L). Cultures of blood and tip of the central catheter turned positive within 24 hours for *C. albicans.* Maternal cervical cultures turned also positive for *C. albicans.* Antibiotics were discontinued and treatment with fluconazole IV was initiated. A starting dose of 25 mg/kg was administered followed by a maintenance dose of 12 mg/kg every 72 hours. On DOL 14 treatment was changed to a dose of 12 mg/kg every 48 hours. Urine and cerebrospinal fluid cultures remained negative. Ultrasound (US) exams of

the brain, abdomen and kidneys were normal, nor were there signs of endocarditis nor thrombi on echocardiography. Ophthalmologic examination was also normal. Clinically the patient improved with this antifungal treatment and was extubated at DOL 29. Fluconazole was given intravenously for seven consecutive days and the same dose was continued orally for 14 days after the first negative blood culture was obtained on DOL 17. Altogether the infant was treated for 21 days with fluconazole. On DOL 55 she developed a painful and swollen right knee with an impaired ability to extend the limb. Imaging studies of the affected knee (ultrasound, radiographs and magnetic resonance imaging (MRI) (Figure 1) showed signs of osteomyelitis and synovitis of the right knee and right distal femur. The patient was started empirically on IV flucloxacillin, amikacin and fluconazole for presumed septic osteoarthritis. Synovial fluid cultured stayed negative. Blood culture turned positive for a multi-sensitive *Escherichia coli*, so the antibiotic regimen was switched to amoxicillin-clavulanic acid. Because of the previously proven *C. albicans* fungemia a beta-D-glucan (BDG) blood test was requested which suggested the presence of fungi (244 pg/ml; normal <60 pg/ml). Ten days after initiation of treatment the swelling had not subsided. A second aspiration and joint lavage was performed. Cultures from this synovial fluid were positive for *C. albicans*, which was sensitive for fluconazole. A second screening for disseminated disease with cerebral MRI, echocardiography and abdominal US, was normal. New urine and cerebral fluid cultures also remained negative. Follow-up radiographs at DOL 57 showed a bilateral distal diametaphysical femur fracture and reactive periost (Figure 2). The right proximal tibia showed a fracture along with osteolysis located in the medial metaphysis. Radiographs of the wrists were taken and showed osteopenia and delayed ossification. These findings could be explained by underlying metabolic bone disease and rickets due to vitamin D deficiency (8 ng/L; normal >30 ng/L) and hyperparathyroidism (PTH 87 ng/L; normal 14 – 65 ng/L). Adequate suppletion of vitamin D, calcium and phosphorus was started. Because of the reoccurrence of the fungal infection a screening for immunodeficiency was performed; blood levels of IgG, IgA, IgM and complement C3 and C4 were all normal. Antibiotic and antifungal treatment were administered intravenously for 7 days and continued orally. Clinically and biochemically our patient improved and antibiotic treatment was discontinued after three weeks. Fluconazole (6 mg/kg once per day) was continued orally for 6 months. Radiographic follow-up after 3 months showed improved ossification and healing of the previously seen fractures (Figure 3). After discharge from the NICU laboratory monitoring showed normalization of PTH, calcium and phosphorus. Suppletion was therefore discontinued. The patient was lost to follow-up due to international relocation of the family. Therefore, no data for growth or long-term outcome were available.

Literature review

Methodology

A comprehensive literature search was undertaken using the PubMed database from their inception to December 2022. English language restriction was applied. Search terms included various combinations of the following keywords: “neonatal candidiasis”, “neonatal osteomyelitis”, “neonatal arthritis”, “neonatal candida arthritis”, “neonatal *Candida* treatment” and “neonatal Candidiasis treatment”. Furthermore, a manual review of reference lists from key articles was performed and studies who fulfilled our inclusion criteria were selected. Articles in which neonates and infants developed osteomyelitis after a *Candida* sepsis were included. Most of these articles were case reports or small case series. The most recent case report was published in 2013 (4).

Our search revealed 12 relevant articles describing a total of 87 pediatric cases of osteomyelitis due to *C. albicans* since 1976, of which 48 concerned infants admitted to the NICU.

Pathophysiology

C. albicans remains a common cause of nosocomial bloodstream infections in children and neonates due to numerous risk factors associated with prematurity (4,7,9,11) (Table 1). Published case reports similar to our case, confirm that *C. albicans* osteomyelitis commonly runs with an indolent course, resulting in delayed diagnosis and treatment (4). The pathogenesis of *Candida* arthritis/osteomyelitis remains unclear. Harris M.C. described three cases, similar to our case, in which three infants suffered from *Candida* arthritis after a completed treatment course for systemic candidiasis (6). Preterm neonates often have a prolonged need of central lines due to the inability to feed orally. These central lines easily become colonized. *Candida* species have a special ability to adhere on endothelial and prosthetic surfaces. Formed biofilms can become the source of not only systemic spread but also end-organ complications, such as osteomyelitis (11). The indolent course of skeletal involvement may be related to a new infection or a relapse due to incomplete treatment of the initial infection. It is hypothesized that during initial *Candida* infection or mucosal reinfection, seeding of joints occur. According to Swanson et al. the infection occurs primarily in joints where the metaphysis is constraint within the joint capsule. Infection originates hematogenous and seeds either in the synovium or metaphyseal vessels, causing arthritis (9). Clinical symptoms were suppressed but the infection not eliminated due to antifungal therapy (6,11). In most cases osteomyelitis or arthritis occurred within months of initial infection. Only two articles describe a case of in immunocompetent patient who developed *Candida* arthritis one year after initial fungemia. Both patients were infants at the time of initial *Candida* infection (4,9). Swanson et al. compared DNA analysis of the initial bloodstream isolate and of the isolate from the infected joint of this patient. The strains were identical by all typing methods used in this article. Control specimens from other patients collected during the same period showed different electrophoretic karyotyping whereas both samples from this case patient were identical. This could support the theory of organ inoculation during the initial infection followed by an extended dormant period. How reinfection was triggered remains unclear (9).

Table 1: Risk factors for Candida infections in NICU patients.

Risk factors for Candida infections in NICU patients
Candida colonization (11, 15)
Indwelling catheters (4, 11, 15)
Extreme prematurity and/or very low birthweight (4, 9, 11, 15)
History of sepsis or usage of broad spectrum antibiotics (e.g. cephalosporines/carbapenem or >2 different antibiotics) (4, 11, 15).
Prolonged parenteral feeding (> 5 days) or intralipid use (>7 days) (4, 9, 11, 15)
Underlying immunodeficiency or malignancy (4, 9)
Skin immaturity or damage (9,11)
Use of antacids (15)
Use of corticosteroids (11)
Mechanical ventilation (11,15)
NEC or other gastrointestinal disease, abdominal surgery (9, 11, 15)
Male gender (11)
Thrombocytopenia (< 150x10E9/L) (11)
Cross transmission by health care professionals (11)

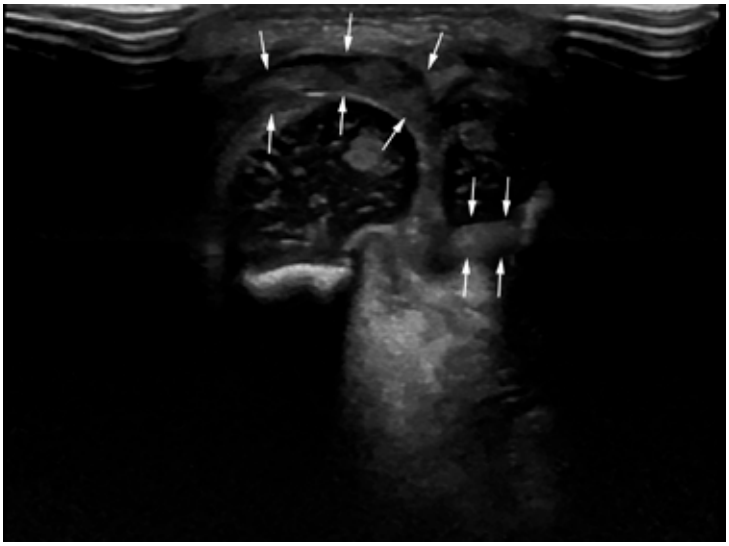
Management

Diagnostic work up

It could be suggested that removal of central lines once nosocomial infection is suspected, in combination with a thorough work-up, will facilitate early detection and therefore timely treatment of disseminated *Candida* infection (4,11). However, prompt diagnosis is chal-

Figure 1: (a) High frequency ultrasound (15MHz) of the right knee shows an irregular iso- to hypoechogenic structure between the femoral condyles and tibia (arrows), consistent with extensive synovial thickening. (b) Doppler ultrasound reveals increased vascularity of the synovium of the right knee (R) compared to the left knee (L). There is only minimal joint fluid present.

(a)



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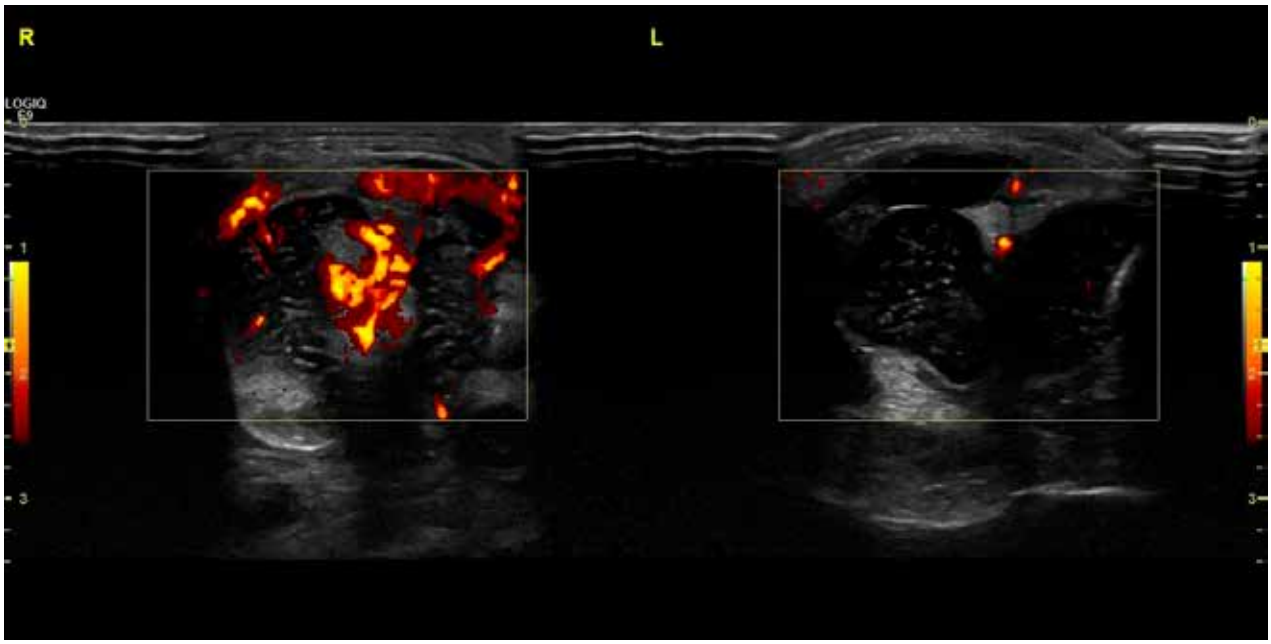


lenging due to false negative results when sampling too small volumes of blood for cultures, therefore delaying intervention and increasing risks for complications (11).

Diagnostic tools such as β-D-glucan blood test can be a used to detect invasive candidiasis. This test has a high negative predictive value, meaning it can exclude invasive candidiasis (11). A disadvantage is that the test does not differentiate between fungal species and can be false positive when other fungal and/or bacterial infections are present. False positive results have also been reported with many therapeutic interventions including antibiotics. Bassetti et al. recommend repeated measurements of BDG to increase the diagnosis accuracy. BDG concentrations decline in successfully treated patients, however usage to monitor clinical response is debated (13).

Antifungal treatments

Three published guidelines were found in our literature search. These guidelines all list recommendations for neonates with *Candida* infections. There is no specific differentiation in treatment regiments of *Candida* arthritis or osteomyelitis. Guidelines of the Infectious disease Society of America (IDSA) and Manzoni P. et al. suggest treatment with antifungals of at least 14 to 21 days for proven septicemia in neonates (Table 2).

Table 2: Overview of current treatment recommendations for Candida osteomyelitis in neonates

Current treatment recommendations for Candida osteomyelitis in neonates	
Manzoni P et al. (11)	Micafungin 7 – 10 mg/kg daily IV Amphotericin B IV Liposomal: 2.5 – 7 mg/kg every 24 hours Deoxycholate: 1 mg/kg every 24 hours Duration for all treatments: 12 months
Pappas G et al. (15) IDSA Guideline	Fluconazole 6 mg/kg daily IV or orally Echinocandin for 14 days IV, followed by Fluconazole 6 mg/kg daily orally Lipid formulation of Amphotericin B 3-5 mg/kg IV for 14 days followed by Fluconazole 6 mg/kg orally is a less attractive alternative Surgery is recommended in selected cases Duration for all treatment: 6 to 12 months

For osteomyelitis the IDSA recommends 6 to 12 months of continued therapy with fluconazole 6 mg/kg orally, whereas Manzoni recommends at least 12 months. The European Society of Clinical Microbiology and

Table 3: Overview of data from included articles. None of the included articles explicitly mentioned which type of amphotericin B was used. Often times details of treatment regiments were not reported on.
/= not disclosed in article, GA=gestational age, w= week, d= day, m=month, M=male, F=female, UAC = umbilical artery catheter, UVC = umbilical venous catheter

Reference	GA	Age of onset	Sex	Reported risk factors	Neonatal candidemia	C. albicans cultures	Joint involvement	Therapy	Outcome
Pan N et al. (4)	/	6 m	M	/	No	Joint fluid	Right knee	Fluconazole 12 mg/kg/d IV later switched to PO Duration: 12 months Surgical debridement	Mild leg length discrepancy
Hsieh WB et al. (5)	29 w	6 m	M	CVC, parenteral antibiotics	Yes	Joint fluid	Left knee	Fluconazole 8 mg/kg/d PO Duration: 6 weeks	Cured
Harris MC et al. (6)	28 w	98 d	M	UVC, UAC, parenteral antibiotics	Yes	Joint fluid	Right hip	Amphotericin B 1 mg/kg/d IV Duration: 3 weeks Open hip lavage	Cured
	28 w	104 d	M	Parenteral antibiotics	Yes	Joint fluid	Right hip, knee	Amphotericin B 1 mg/kg/d IV Duration: 6 weeks AND 5-fluorocytosine 15 mg/kg Duration 12 weeks	Cured
	30 w	166 d	M	CVC, UAC	Yes	Joint fluid	Right hip	Amphotericin B 1 mg/kg/d IV Duration: 6 weeks	Cured
Yousefzadeh DK et al. (8)	/	67 d	M	Parental antibiotics, hyperalimentation GI problems	No	Catheter tip, bone marrow	Humerus, elbow, both knees, right ankle	5-fluorocytosine Duration: 33 days	Cured
	/	34 d	M		Yes	Blood, catheter tip, joint fluid	All extremities and joints	5-fluorocytosine Duration: 33 days	Deformed
	34 w	4 d	M		Yes	Blood, catheter tip, joint fluid	Hip	Amphotericin B Duration: / Surgical debridement	Improved
Swanson H et al. (9)	28 w	1 yr	F	CVC, parenteral antibiotics	Yes	Joint fluid	Left knee	Fluconazole 5 mg/kg/d PO Duration: 8 days Amphotericin B 15 mg/kg Duration: 3,5 weeks	Cured
Pittard WB et al. (10)	30 w	34 d	M	UVC, UAC	/	Blood, Skin, periumbilical area, CSF, joint fluid	Knee	5-Fluorocytosine 50 mg/kg/d PO Duration: /	Deceased
	36 w	54 d	M	UVC, UAC, GI surgery	/	Skin, periumbilical area, CSF, joint fluid	Knee	Amphotericin B 1 mg/d IV Duration: / Multiple needle aspirations	Cured
	28 w	28 d	F	UVC, UAC	/	Skin, periumbilical area, joint fluid	Knee	Amphotericin B 1 mg/d IV Amphotericin B 0,1 mg/d IA Duration: /	Deceased
Brill PW et al. (10)	40 w	6w	M	UVC	No	Blood, umbilical vein catheter tip, CSF, joint fluid, stool	Both humeri, femora, tibiae, left radius and ulna	Amphotericin B AND 5-fluorocytosine Duration: /	Cured
		6 w		UVC	yes	Blood, umbilical vein catheter tip, tracheal aspirate, urine, stool	Left humerus, ulna, right radius, tibia	Amphotericin B AND 5-fluorocytosine Duration: /	improved
Adler S et al. (18)	36 w	21 d	F	UVC Parenteral antibiotics	Yes	CSF, joint fluid	Both Knees	Amphotericin B 2,4 mg/d IV Duration: 4 weeks	Cured
Bayer AS et al. (19)	/	30 d	M	UAC, corticosteroids, parenteral antibiotics GI surgery	/	Sputum, CSF, stool, gastric aspirate, umbilical catheter, joint fluid	knees	Amphotericin B 2,8 mg/d IV Duration: 10 weeks Amphotericin B 5 mg IA Duration: once Multiple needle aspirations	Cured
Pruitt AW et al (20)	/	56 d	F	Parenteral antibiotics	/	Saphenous vein, joint fluid	Knee	Amphotericin B 9,5 mg/d IV Duration: 3 weeks Amphotericin 12,5 mg – 5 mg IA Duration: twice	Cured
Merchant RH. et al. (21)	31,6 ± 1,2 w	29 d	/	Parenteral antibiotics, environmental contamination	/	Blood joint	Both knees	6 out of 8 infants received Fluconazole 7,5 mg/kg IV Fluconazole 7,5 mg/kg PO Duration 6 weeks	Cured
		19 d	/			Blood, urine, joint fluid	Both knees		Cured
		50 d	/			Blood, urine, joint fluid , CSF	Both knees		Deceased
		21 d	/			/	Both knees		Cured
		18 d	/			/	Left knee		Cured
		21 d	/			Blood, urine	Both knees		Cured
		16 d	/			Blood	Both knees		Improved
		34 d	/			Urine	Both knees		Cured
Freeman JB et al. (23)	Term	18 d	M	Hyperalimentation Parenteral antibiotics	No	Blood, urine, venous catheter, joint fluid	Right knee, elbows	5-fluorocytosine 150 mg/kg/d Duration: 4 weeks	Cured

Infectious Diseases (ESCMID) guidelines however recommend the use of echinocandins as empirical treatment, but makes no recommendation towards cases with osteomyelitis (14)]. Based on recent studies, 2016 IDSA guidelines favor treatment with fluconazole or echinocandins over liposomal amphotericin B for *Candida* osteoarthritis in neonates. When choosing echinocandins, they recommend intravenous administration for 2 weeks followed by 6 to 12 months fluconazole orally.[15] Compared to liposomal amphotericin B, fluconazole has less adverse effects, such as nephrotoxicity and has better tissue penetration. Amphotericin B deoxycholate is not as recommended to use in neonates because of a less favorable toxicity profile compared to lipid preparations (1). A meta-analysis by Chen Yu-Hung et al. assessed the efficacy and safety of echinocandins in comparison with amphotericin B in treating invasive candidiasis. They revealed no significant differences in clinical response, however the risk of discontinuing treatment due to adverse effects was significantly lower in the echinocandins group than in the amphotericin B group. No differentiation was made between liposomal and deoxycholate amphotericin B (16). Despite growing evidence of superiority of echinocandins, there is no oral formula and usage is more expensive in comparison to fluconazole (1). The IDSA guidelines therefore state that fluconazole remains an acceptable drug of choice.[15] All three guidelines underline the importance of adequate prophylaxis in very low birthweight infants (2, 3, 4).

When consulting published case reports and case series different treatment regiments are being proposed{Table 3}. Amphotericin B is the most commonly used drug to treat *Candida* osteomyelitis and arthritis in infants and children. Combination therapy of amphotericin B and fluconazole has less commonly been described (4,9,17). The use of amphotericin B for *Candida* arthritis is mostly described in older studies (6,10,18,19). Bayer et al. suggested intraarticular amphotericin B as a potential adjunctive therapeutic measure in cases without disseminated disease (19). Only two other publications to date have reported successful results using high doses of intraarticular amphotericin B (10,20). Fluconazole monotherapy has been reported to yield successful recovery in patients of multiple studies (4,5,7,21-23). Yousefzadeh et al. report treatment with 5-flucytosine for osteomyelitis in two infants for 33 days. The article did not specify whether treatment was started intravenously or orally. One was reported to make a full recovery. The other patient had a severe case of *Candida* arthritis with involvement of all long bones, follow-up visits revealed disparity of the limb lengths (7). Merchant et al. and Hsieh et al. reported successful treatment with fluconazole treatment regimens of 6 weeks. They were treated intravenously or orally with a dose of 7.5 mg/kg in three divided doses. Merchant et al. reported eight neonates with neonatal candida arthritis, treated with IV or oral fluconazole, of which six made a full recovery (5,21). Pan et al. continued treatment for 12 months whereas Weigl et al. opted to treat for 6 months. Both patients were reported to make a full recovery (4,22).

Gamaletsou et al. reported on 207 pediatric (n=37) and adult (n=170) cases of *Candida* osteomyelitis, revealing a median treatment duration of 3 months. Relapse was reported in 32% of patients who eventually achieved complete response to therapy. Premature discontinuation of therapy was established to be the most common cause of these relapses regardless of which antimicrobial agent was used. However only 11 included patients were neonates (17). Previous reviews have underlined the importance of prolonged treatment to prevent relapse (4,17).

Surgical debridement

Literature review of Pan et al. revealed surgical incision and drainage in only 3 patients. The youngest patient was seven months at the time of receiving surgical intervention (24). Gamaletsou et al. reports on 201 cases of *Candida* osteomyelitis. Only 37 were pediatric patients, 10 of which received surgical intervention. Surgery was indicated in more complicated cases with persistent symptoms or clinical deterio-

Figure 2: Conventional radiographs reveal cortical buckling in both distal femurs (arrows), consistent with fractures. Lamellar periostal reaction (arrowheads) is already present. There is localized ostelysis in the proximal tibial metaphysis right (asterisk), also with associated lamellar periostal reaction (arrowheads).

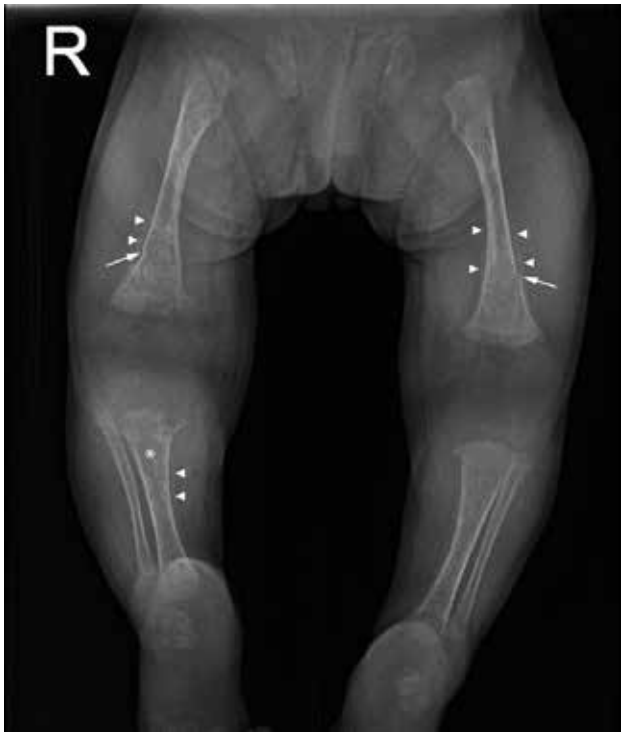
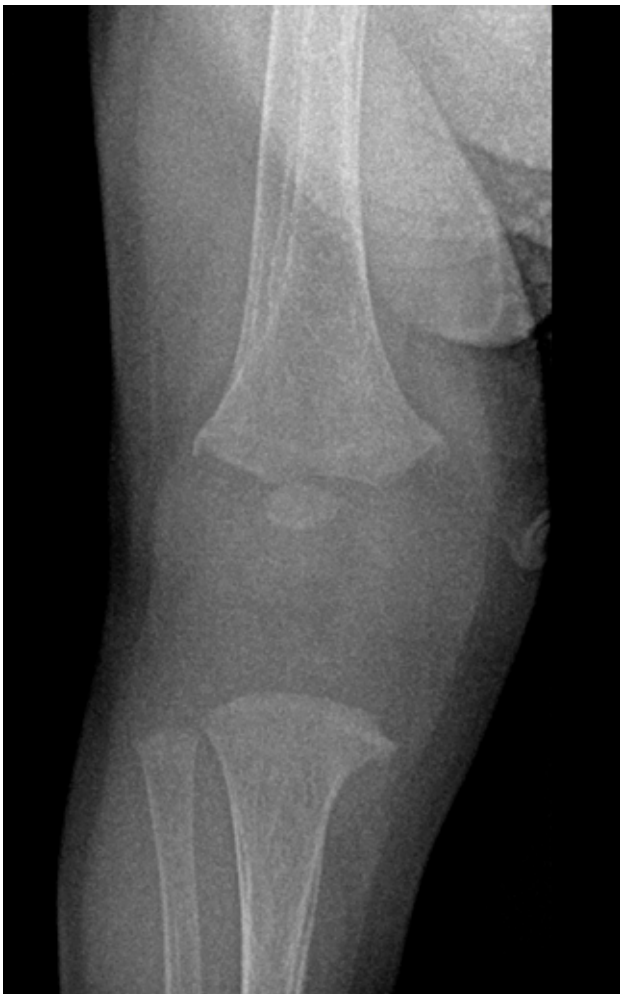


Figure 3: Follow-up radiography 10 weeks later shows complete consolidation of the fractures in the right femur and tibia.



ration, to warrant successful eradication and structural stability (17). The 2016 IDSA guidelines recommend surgical debridement in all cases of septic arthritis or in patients with persistent or worsening symptoms during therapy (15).

Outcome

Our literature search shows different treatment regiments, however clinical outcome seems to be favorable in almost all surviving patients. Yousefzadeh et al. reports 4 cases out of 13 neonates with orthopedic sequalae due to *Candida* osteomyelitis. Two of those had severe complications; one patient had femoral head dislocation three years after onset of the osteomyelitis and another patient had a severe disparity between limb lengths due to extensive and persistent arthritic involvement (7). Pan et al. also describes one case of *Candida albicans* osteomyelitis in a 13-month-old boy who developed a mid-length discrepancy (4). Other case reports reveal a full recovery six to twelve months after initial diagnosis of *Candida* osteomyelitis or arthritis. There are no long-term follow-up or growth chart data available.

Discussion

We hypothesize that our patient developed a *Candida* osteomyelitis due to hematological spreading of the yeast and eventually seeding in the joint. Since clinical symptoms were seen less than a month after completing treatment for the initial *C. albicans* infection, this supports the previously mentioned theory of inoculation followed by a dormant period (4). Since multiple cases have described dormant periods ranging from weeks to one year, close follow-up of children with a history of candidiasis is important. Awareness of a patient's history of neonatal *Candida* infection can help diagnose *Candida* arthritis faster if symptoms occur. No other case has used the BDG test as a marker for fungal infection. False positive results are definitely possible in neonates, however this test can be used if invasive candidiasis is suspected but not cultured, to make fungal etiology more or less likely. Meconium and skin cultures can be useful to determine the risk for invasive candidiasis in preterm infants. According to research provided by Mahieu L. et al. the number of sites colonized with *C. albicans* at birth contributes to invasive candidemia (25).

As shown in the literature review there is no consensus about the correct treatment regimen for neonates with *Candida* osteomyelitis/arthritis. Multiple treatment regimens have yielded various results. Our choice of treatment both for the initial candidemia as the osteomyelitis was in line with the IDSA guideline (15). However caution is warranted as the recommendations in this guideline are mostly derived from adult and pediatric studies and expert opinion. This can be explained by limited described data in current publications. Most case reports haven't included the used dosage of antimicrobial treatment neither mention exact duration. Since the condition is rare, no study has sufficient cases to draw meaningful conclusions. As to indication for surgical debridement there is very limited data. In our patient we did perform a surgical debridement which confirmed the presence of *C. albicans*, since blood cultures remained negative. The need for surgical intervention remains to be decided on a case-to-case basis. Unfortunately, similar to our case, many patients are lost to follow-up. Important findings after recovery such as growth, radiological findings and motoric development are often not included in many case reports.

Conclusion

Neonatal *Candida* osteomyelitis is a rare complication of *Candida* septicemia in neonates. Well justified use of fluconazole prophylaxis could prevent *Candida* infections in infants. Guidelines regarding optimal treatment of neonates with *Candida* osteomyelitis are limited. Prolonged and timely initiated treatment with fluconazole with oral courses of six to twelve months and surgical intervention, when indicated, can be curative. Echinocandins can be a new therapeutic option for the treatment of *Candida* osteomyelitis but are expensive and can only be given intravenously. Osteomyelitis as a complication of candidiasis is rare but early recognition and therapy may prevent residual and permanent deformity. Uniformity in reporting on similar cases is necessary to draw meaningful conclusions

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Declarations of interests

The authors report that there are no competing interests to declare.

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