

Candida Arthritis in a Premature Infant Treated Successfully with Oral Fluconazole for Six Months

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Abstract

Introduction: *Candida arthritis in premature infants is a rare condition mainly treated with parenteral amphotericin B.* **Clinical Picture:** *Arthritis 9 weeks after birth. The infection resulted out of colonisation at birth and fungaemia at day 6 and day 13 of life.* **Treatment:** *Oral fluconazole for 6 months (5 mg/kg/day after loading with 7 mg/kg/day).* **Outcome:** *Full remission.* **Conclusions:** *Oral fluconazole is an alternative to parenteral amphotericin B in the treatment of premature infants, but proof of absorption and an extended treatment period according to prematurity might be warranted.*

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Introduction

Candida arthritis in premature infants is regarded as a rare condition. The largest published series of 8 cases from one institution was from Bombay, India.¹ The current gold standard is treatment with parenteral amphotericin B. We report a case of a premature infant colonised with *Candida albicans* at birth who developed *C. albicans* arthritis at the age of 9 weeks.

Case Report

The pregnancy of the healthy gravida two, para one mother was complicated by premature labour from 26 weeks of gestation onwards. During tocolysis, beclomethason treatment for enhanced lung maturation of the foetus was initiated. Erythromycin was given to the mother because of isolation of *Ureaplasma urealyticum* in the vagina 4 weeks before delivery. No further pathogens including *C. albicans* were isolated from the birth canal.

The child was delivered vaginally at 31 weeks of gestation, with a birth weight of 1495 g and APGAR scores of 8, 9 and 10. From day 2 of life onwards nasal continuous positive airway pressure (CPAP) respiration was installed for 13 days because of recurrent apnoeic spells. Immediately on arrival to the transitional care unit, both ears and the throat were swabbed. All specimens grew *C. albicans* with minimal inhibitory concentrations (MICs) of fluconazole of 0.5 to 1.0 µg/mL and flucytosine of 0.125 to 0.25 µg/mL,

respectively. The E-test on RPMI agar from Biotest (heipha diagnostika) was used. The performance of this test in comparison to the microdilution method according to National Committee for Clinical Laboratory Standards (NCCLS) is well documented.^{2,3} Two venous blood cultures remained without growth. The leukocyte count of 9000/µL and the differential count were unremarkable. The C-reactive protein was below 0.3 mg/dL.

On day 4 the condition of the child worsened with increasing number of apneas and symptoms suggestive of septicaemia. A further blood culture was taken and cefotaxime plus piperacillin (the local standard) were started. The blood culture grew a coagulase-negative *Staphylococcus*. As the child did not have a central line, the finding was regarded as contamination and the antibiotic regimen was not adjusted. A further blood culture on day 6 grew *C. albicans*, and another on day 13 grew *C. albicans* and coagulase-negative *Staphylococcus*. The MICs for *C. albicans* were the same as in the specimens from the initial swabs. Vancomycin was added when these results were known. No antifungal treatment was added as both isolates were regarded as contaminants by the neonatologists. Sonography of the brain was without a pathological finding. On day 19 an increased number of supraventricular extrasystols was noted, which persisted until discharge. As blood cultures on day 28, and venous and arterial this time showed no growth, the antibiotics were stopped. The child

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was transferred to the general ward and discharged on day 55 weighing 2600 g.

Five days later the child was re-admitted with a 2-day history of fever and a painful swollen right knee. The whole blood cell count revealed 16,100 leukocytes/ μ L (29% segmented neutrophils, 46% lymphocytes, 2% monocytes and 23% eosinophils) and 425,000 platelets, the ESR was 10/25 mm/h and the C-reactive protein was 1.0 mg/dL. The knee joint was punctured: 25,400 leukocytes/ μ L were counted (2% band forms, 89% segmented neutrophils and 9% lymphocytes). No bacteria or fungi were seen during microscopy, but 6 days later the culture of the joint fluid grew *C. albicans* from the enrichment broth (brain heart infusion). The MICs for fluconazole and flucytosine were 0.5 μ g/mL and 0.125 μ g/mL, respectively. As isolates from the previous hospitalisation were not available, only the MICs of the *C. albicans* isolates could be compared. They were the same within one step of dilution as pointed out.

A magnetic resonance tomogram of the joint and adjacent bone, sonar investigations of the heart, liver and brain and an ophthalmological examination were unremarkable. Fluconazole, 7 mg/kg/day single oral dose, was added to cefotaxime which was already started on the day of re-admission. The treatment with fluconazole 5mg/kg/day single oral dose was continued for a total of 6 months as the optimal duration of the treatment is unknown. The absorption of the drug was verified by measurement of the serum level of 9.2 μ g/mL (done at Pfizer Laboratory, Illertissen, Germany). The child was discharged after 4 weeks. Thirty-six months after ending the anti-fungal therapy the patient is doing fine without any impairment of movement of the right leg or knee joint.

Discussion

We presume that the child was contaminated with *C. albicans* during the passage through a colonised vagina during delivery despite the negative test results from the mother. Vaginal delivery is the major cause of early colonisation in the newborn.⁴ The exact route of entry of the fungi into the systemic circulation in our patient, who only had peripheral lines, monitor electrodes and a nasopharyngeal tube, is unknown. The two *C. albicans* positive blood cultures were misjudged and no consequences of treatment resulted. Not having the former blood culture and the knee joint isolates together for molecular biological comparison, as reported by Swanson et al,⁵ the author's hypothesis, however, is that the fungaemias on day 6 and/or day 13 were the cause for the joint seeding on the basis of the MICs for fluconazole and flucytosine. Later, however, unnoticed candidaemias cannot be ruled out with certainty. But the continuous improvement after the negative pair of blood cultures suggests the

previous hypothesis.

Contamination with *C. albicans* at birth was the primary disposition in this case. As reported by Swanson et al, negative cultures later in the disease course do not rule out late complications. To date, their case had the longest time interval reported between a positive blood culture and arthritis by *C. albicans* in a premature infant. It seems that *C. albicans* systemic infections can be contained to a certain extent, but not always eliminated by premature infants without antifungal treatment. But even antifungal treatment, either with amphotericin B +/- flucytosine⁵ or fluconazole cannot prevent late complications of candidaemia such as arthritis in some cases. Whether an appropriate treatment of the fungaemia in the first place would have prevented this complication in our patient remains unknown. Fungaemia, however, should be taken as a serious condition, and the necessary staging process and antifungal therapy should be initiated.

Treatment failures can have host-related reasons (immunological and pharmacokinetical) or pathogen-related reasons. For successful treatment an awareness of these variables is important.

Immunological reason for treatment failure: Premature infants may not be fully competent to eliminate the pathogen with or without antifungal therapy. Prematurity in general is a risk factor for systemic or invasive *Candida* infections (immature T-cell-mediated immunity, reduced killing). Therefore, we decided to treat over an extended period of 6 months.

Pharmacokinetical reason for treatment failure: In spite of a good absorption of fluconazole from the intestine in general, there might be failures. For this reason, we regard it as important to prove oral resorption of the drug, if it is feasible, as it is the established practice for oral treatment of bacterial arthritis and osteomyelitis in older children. O'Meeghan et al⁶ showed good penetration of the drug into the inflamed knee joint for an adult patient. This we did not investigate in our patient.

Antimycotic-resistant Candida as reason for treatment failure: *Candida* species with increased MICs are a well-known problem in today's clinical practice. Whether the current techniques to measure MICs in *Candida* spp. are valid tools is debatable. According to Rex et al,⁷ raised MICs very often do not correlate with treatment failure and vice versa. The fluconazole blood level in our case was 9 times the maximal MIC of the *C. albicans* isolates by E-test on RPMI agar.

The incidence of *Candida* arthritis in premature infants does not seem to be so rare as widely presumed. Dan⁸ reported *Candida* spp. as a cause of arthritis in premature neonates in 17% of cases. Especially in 1996 and 1997, a

variety of articles were published on the different aspects of this disease entity. In particular, case reports by Murphy et al⁹ and Swanson et al⁵ reporting 19 cases, and the series of 8 cases by Merchant et al,¹ may underline this statement. In conclusion, oral fluconazole is an alternative to parenteral amphotericin B in the treatment of premature infants,^{1,10} but proof of absorption and an extended treatment period according to prematurity might be warranted.

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