Treatment of opportunistic mycoses: how long is long enough?

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For most opportunistic mycoses no optimum duration of antifungal therapy has been defined. Although a long course of therapy is prudent, especially for mycelial fungal infections, excessively and unnecessarily extended courses of treatment incur a risk of toxicity and the expense of the therapeutic regimen. On the basis of existing reports on the pathogenesis and the effect of duration of therapy and other variables on outcome and response rate in fungal infections, this review proposes guidelines that may facilitate a rational approach to decision-making about the duration of antifungal therapy.

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Invasive mycoses have long been recognised as important opportunistic infections in immunocompromised hosts. Advances in mycological diagnostic techniques, an increase in the number of susceptible hosts, the use of potent immunosuppressive agents, and intensive chemotherapeutic regimens have contributed towards a substantial rise in the incidence of invasive fungal infections.[1–4] The frequency of nosocomial candidaemia has increased ten-fold during the past two decades.[5] There has been a less striking, though also substantial, increase in the incidence of invasive aspergillosis.[1,6,7] Despite an expanded armamentarium of antifungal drugs for the treatment of these infections, mortality remains unacceptably high, particularly in patients with mycelial fungal infections.

Although appropriate antifungal agents and their doses for the treatment of opportunistic mycoses have been defined, the optimum duration of therapy for most invasive fungal infections has not been established. Therapeutic trials for invasive fungal infections have proven logistically difficult and challenging because the frequency of cases is low and accrual of sufficient numbers for studies takes a long time. Not surprisingly, therefore, the appropriate duration of therapy for most opportunistic mycoses has never been investigated.

Although there is general acceptance that the duration of therapy should be individually decided, objective criteria on which such decisions can be based have not been defined. The aim of this review is to discuss the pathophysiological basis and other characteristics of fungal infections during their evolution and subsequent resolution on antifungal therapy that may facilitate decision-making about duration of therapy. The discussion focuses on three of the most commonly encountered invasive mycoses—aspergillosis, cryptococcosis, and candidaemia.

Invasive aspergillosis

The desired outcome with antifungal therapy is to obtain a complete response. Typically, complete response for invasive aspergillosis has been defined as resolution of all signs, symptoms, and radiographic abnormalities with follow-up cultures that are negative. The last of these criteria, as discussed below, may be the least reliable in guiding therapy. The pertinent issue, therefore, is how long it takes to obtain a clinical and radiographic response with therapy in invasive aspergillosis. The table summarises selected studies in which the duration of antifungal therapy for invasive aspergillosis was explicitly stated.[8–16] From these findings, I have attempted to discern the duration of therapy for survivors or responders (compared with non-responders), whether the duration of therapy influenced the response rate, whether residual disease at the end of treatment predicted failure, and variables that affect outcome and, therefore, the duration of therapy.

Duration of therapy and correlation with outcome

Careful interpretation of data on duration of therapy in the published reports shows that, although clinical response to therapy may be evident by 2–6 weeks, complete responses generally require longer courses of therapy, of 10–12 weeks. In a study that compiled published case-series of invasive aspergillosis to assess the response rate and therapeutic outcome with amphotericin B, only one of 84 patients treated for 1–13 days survived.[8] However, the response rate for patients treated for at least 14 days was 83% for recipients of heart and renal transplants, 54% for patients with leukaemia, and 33% for bone-marrow-transplant recipients.[8] A plausible explanation is that patients who received therapy for less than 14 days were more severely ill and died before they could complete 14 days of therapy. Nevertheless, this study showed that of patients who lived long enough to receive 14 days of therapy, 54% survived. A minimum of 14 days of therapy was required for a response rate of 50% in patients with aspergillus rhinosinusitis.[8] The overall response rate for invasive aspergillosis with liposomal amphotericin B in the UK compassionate-use database was 59%.[12] The mean duration of treatment was 17 days (SD 8) for the responders and 7 days (4) for those who did not respond. All six patients who

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Antifungal therapy, its duration, and outcome in selected studies of invasive aspergillosis

Ref	Number of patients	Type of study	Underlying disorders	Antifungal agent	Duration of therapy (days)	Outcome/response rate
8	1223	Review of series of four or more cases of IA	Mainly neutropenic patients and BMT recipients	Amphotericin B	1–13 ⩾14	1 of 84 survived Overall 54% survived
9	178	Compilation of data from five open-label studies	37·2% BMT, 23·6% haematological malignant disorders, 12·1% solid-organ transplants, 25·0% other	ABCD	Median 16 (range 1–409)	Overall response rate 48·8%
10	174	Randomised, double-blind trial of ABCD *vs* amphotericin B	Mainly BMT and haematological malignant disorders	ABCD Amphotericin B	Median 13 (1–35) Median 14·5 (1–87)	Complete or partial response in 18% and stable disease in 34% Complete or partial response in 22·0% and stable disease in 28·3%
11	46 (23 with IA)	Six-hospital study of ABLC use for invasive fungal infections	Mainly BMT, leukaemia, and lung-transplant patients	ABLC	Median 38·7 (6–143)	Cure in 52%, improvement in 26%
12	17	Data on liposomal amphotericin B compassionate use	Leukaemia/lymphoma	Liposomal amphotericin B	Mean 17 for responders *vs* 7 for non-responders	Overall response rate 59%
13	49	Single centre experience with liposomal amphotericin B	Mainly BMT recipients and haematological malignant disorders	Liposomal amphotericin B	Median 12 (2–96)	Complete or partial response in 62% of proven and 53% of suspected IA cases
14	20	Retrospective cohort study	BMT recipients (allogeneic)	Amphotericin B 16 patients* Liposomal amphotericin B (14 patients) Itraconazole (5 patients)	Median 8 (1–93) Median 32 (5–210) Median 38 (7–180)	Overall response rate 37%, (complete in 11% and partial 27%)
15	595	Retrospective data collection; data on duration of therapy reported in 168	Mainly BMT recipients and patients with haematological malignant disorders	Amphotericin B Itraconazole Amphotericin B (followed by itraconazole)	Median 15 (1–117) Median 90 (1–30) Median 28 of amphotericin B and 35 of itraconazole	Complete response in 25% Complete response in 90% Complete response in 39%
16	29	Proven IA cases	Haematological malignant disorders	Liposomal amphotericin B	Median 29† (8–97)	Cure in 32% and improvement in 29%

IA=invasive aspergillosis; BMT=bone-marrow transplant; ABCD=amphotericin B colloidal dispersion; ABLC=amphotericin B lipid complex. *Later changed to liposomal amphotericin B in ten. †Duration represents that for all proven mycoses in the study, including non-aspergillus fungal infections.

received therapy for 14 days or longer responded, whereas three of four treated for 5 days or less died.

Data from five studies with a total of 178 cases of invasive aspergillosis treated with amphotericin B colloidal dispersion (ABCD) gave an overall response rate of 48·8%.[9] The median duration of therapy was 16 days. An intention-to-treat analysis showed that the response rate was 2·1% in patients receiving less than 7 days of therapy, 30·0% in those treated for 7–13 days, 50·7% in those treated for 14–42 days, and 54·5% in those patients treated for longer than 42 days.[9] ABCD and amphotericin B were equally effective for the treatment of invasive aspergillosis in a randomised trial.[10] ABCD was used for a median of 13 days and amphotericin B for a median of 14·5 days.[10] Cure in 12 patients and improvement in six was documented in 23 patients with invasive aspergillosis.[11] The mean duration of therapy was 38·7 days (range 6–143).

Availability of voriconazole in an oral formulation has allowed the administration of antifungal therapy for longer periods. In a randomised trial that compared this drug with amphotericin B for the treatment of invasive aspergillosis, the response rate and survival were significantly better with voriconazole.[17] At 12 weeks, the successful outcome rate was 52·8% in the voriconazole group and 31·6% in the amphotericin B group; survival was 70·8% and 57·9%, respectively. The median duration of voriconazole treatment was 77 days (range 2–84), of which intravenous therapy accounted for a median of 10 days (range 2–78). A notable finding in that study was that the first few days of therapy were crucial in the outcome of invasive aspergillosis.[17] The survival benefit for patients receiving voriconazole was evident after only 2 weeks of therapy.

In a non-comparative, open study for the treatment of invasive aspergillosis, voriconazole had been administered intravenously for a mean of 11·5 days (range 1–40) and subsequently orally for 77 days (2–219).[18] Complete and partial responses were recorded in 14% and 34% of the patients, respectively; and therapy was deemed to have failed in 31%. Patients who had a complete response were treated for a median of 133 days. By contrast, patients whose infections did not respond had received therapy for a median of 20·5 days; in 83% of the patients with failure, the duration of therapy was less than 7 days.

Salvage regimens, irrespective of the antifungal agent used, have been less effective than when the same drug was administered as primary therapy.[18] Of 116 patients with invasive aspergillosis treated with voriconazole, treatment was deemed to have failed in 39% of those who received voriconazole as salvage compared with 23% of the patients who received the drug as primary therapy (p=0·02).[18] Whether residual disease at the end of therapy affects outcome is not known, though intuitively it appears to do so. Complete or partial response was observed in 32% of the patients who received amphotericin B only compared with 54% of those who received amphotericin B followed by itraconazole.[15] The patients who received amphotericin B without sequential itraconazole however, were more severely ill, which could have contributed to the worse outcome.[19]

Evolution of imaging abnormalities in invasive aspergillosis

Computed tomography (CT) imaging of the lungs in patients with invasive aspergillosis has shown that the lesions worsen initially before improvement ensues on appropriate therapy.[19] Sequential CT scans of the chest in neutropenic patients with aspergillosis showed that the extent of the lesions as assessed by their volume increased from day 0 to days 3, 7, and 14.[16] The volume of the lesions increased three-fold between days 0 and 3 (p=0·002), four-fold between days 0 and 7 (p=0·0005), and three-fold between days 0 and 14 (p=0·009). However, from day 7 to day 14, the volume remained stable.[19]

These findings also showed that the typical thoracic CT halo sign, although short-lived (less than 5 days), was the earliest radiographic finding in patients with invasive aspergillosis. In the second week, the imaging findings were non-specific in most cases, whereas in the third week an air-crescent sign appeared and may be helpful as a delayed indicator of invasive aspergillosis. The type of antifungal agent did not influence the change in the volume of lesions. Thus, initial progression of pulmonary infiltrates on antifungal therapy may represent the normal course of events during evolution of aspergillus infection and may not imply failure of treatment.

Mycological response during therapy

A mycological response may not be a reliable criterion in guiding therapy. Cultures generally have poor sensitivity for the diagnosis of invasive mycoses, and the likelihood of a positive result can be erratic. Furthermore, follow-up cultures from deep tissue sites may not be feasible even in patients with optimum clinical response.[9] Mycological response rates are therefore judged less useful than clinical or radiographic response rates. Indeed, in up to 50% of patients in clinical studies, a mycological response was deemed unevaluable.[9] However, by 8 weeks of therapy, 79% of the cultures from body sites initially positive for aspergillus had been rendered culture negative.[20]

Histopathological and other laboratory characteristics during resolution of infection

A study in mice has provided important insights into the time line for histopathological evolution and for the decline in fungal burden during resolution of aspergillus infection.[21] That study also investigated whether the galactomannan assay can reliably monitor the course of invasive aspergillosis. In immunocompetent mice, infected intravenously with *Aspergillus fumigatus*, blood cultures were positive on day 1 in virtually all mice.[21] The rate of positive blood cultures declined steadily thereafter and aspergillus could no longer be cultured from the blood in any of the mice at day 9. On day 5, multiple granulomas had formed in the liver, kidneys, and brain. Cultures of the brain became negative in most mice by day 9. However, aspergillus was detectable in the liver and kidneys in all mice up to 18 days after infection. Complete elimination of aspergillus from these organs was documented at day 30.[21]

The galactomannan assay was positive in all mice with fungaemia.[21] The assay remained positive after the cultures from the blood became negative, but aspergillus was detectable in cultures from the brain and other parenchymal organs (eg, liver and kidneys). However, when the fungal burden declined (between days 5 and 30), the blood and brain cultures became negative and the lesions became demarcated as granulomas in the liver and kidneys, the galactomannan assay gave negative results in most animals.

Abrupt and complete reversal of immunosuppression may not always be feasible in patients. Nevertheless, these findings in otherwise immunocompetent mice show that resolution of infection in parenchymal sites may take up to 30 days. In the clinical setting, a gradual decline in galactomannan concentration with therapy occurs over 30–40 days. However, although a rising galactomannan concentration predicted failure of therapy, a decrease may not be apparent in successfully treated cases.[7]

Secondary prophylaxis

A history of previous invasive aspergillosis is not deemed an absolute contradiction to subsequent bone-marrow transplantation. However, a third of such patients experience a relapse and most of these die.[22] Existing evidence suggests that secondary prophylaxis can be beneficial in this setting.[22] However, the best prophylactic approach remains unclear.

Suggestions

Since there are no definitive studies or incontrovertible data for concrete recommendations on the optimum duration of therapy, this review suggests that the prudent approach is to use the most effective therapy first and to continue treatment for 10–12 weeks or for at least 4–6 weeks beyond resolution of all clinical and radiographic abnormalities, whichever is longer. Recovery from neutropenia is one of the most important determinants of outcome in patients with haematological malignant disorders and invasive aspergillosis. Extent and type of pulmonary involvement has also been related to response. Focal, peripheral disease without cavitation is predictive of a favourable response, whereas diffuse and centrally located lesions have been associated with poorer outcome.[8] After transplantation of haemopoeitic stem cells, active acute grade-2 (or higher) or extensive chronic graft-versus-host disease indicates a poorer outcome.[7] In organ-transplant recipients, dissemination beyond the lungs, requirement for dialysis, and previous cytomegalovirus

infection predicted poorer survival in patients with invasive aspergillosis.[2] In these patients at risk of poor outcome, the response to therapy may be slower and therefore, the duration of therapy may have to be longer.

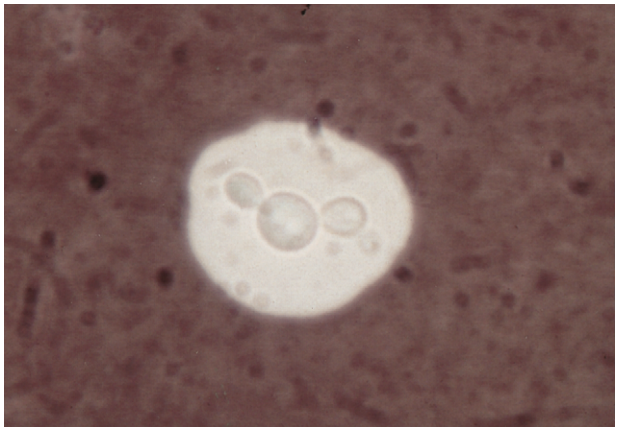
Cryptococcosis

Cryptococcus neoformans is a ubiquitous encapsulated yeast (figure) that is an important pathogen in various immunocompromised hosts. Contemporary definitive studies on the efficacy and duration of therapy for *C neoformans* have been done only in HIV-infected patients. The therapeutic recommendations for other immunosuppressed hosts have largely been extrapolated from these studies.[23] With a decline in the incidence of AIDS-associated cryptococcal infections, transplant recipients have emerged as a major group of immunosuppressed hosts at risk of cryptococcosis.[24]

C neoformans is very rare in recipients of haemopoeitic stem-cell transplants, for reasons that are not entirely clear. Thymic regeneration in such patients may render T cells more effective against cryptococci than those in recipients of solid-organ transplants.[24] *C neoformans* continues to be an important infection in patients who have undergone transplantation of solid organs. The cryptococcosis mortality rate is two to five times higher in such patients than in HIV-infected patients. Mortality rates in AIDS-associated cryptococcal meningitis have ranged from 14% to 25%. Lately, rates below 10% have been documented.[25] Nearly 55% of organ-transplant recipients with cryptococcosis have infection of the central nervous system (CNS); their mortality rate is 50%[21] and has remained unchanged over the past two decades.[26]

Most deaths in patients with AIDS-associated cryptococcosis occur during the first 2 weeks of therapy. Raised intracranial pressure is an important contributor to mortality in these patients.[25,27] The time to death differs substantially between organ-transplant recipients and HIV-infected patients with cryptococcosis. There are fewer earlier deaths in transplantation-associated cryptococcal infections: deaths occurred a median of 42 days after therapy in a review[24] and 46 days after therapy in a prospective study.[26] Since the vast majority of the organ-transplant recipients with cryptococcosis are receiving corticosteroids at the onset of the infection, and since corticosteroids lower cerebrospinal-fluid pressure in the experimental setting,[27,28] use of these drugs may account for lower earlier mortality but not the overall death rate in transplant recipients.

The first 6 weeks of therapy are therefore crucial in transplant recipients, and the response to therapy may be protracted. The use of amphotericin B combined with flucytosine as induction therapy for 4–6 weeks is rational in these patients. This period was also the median duration of amphotericin B treatment in a study in HIV-negative patients in which 81% of those with CNS cryptococcosis were successfully treated.[29] After this stage, the patient can continue on fluconazole (400 mg four times daily) for 8–10 weeks or until clinical and radiographic findings have resolved. Serum cryptococcal antigen (detected in 86–88% of transplant recipients at the onset of infection) ultimately becomes undetectable and can be used to guide the duration of consolidation therapy. Life-long suppressive therapy is generally not necessary in transplant recipients.



*An India ink preparation showing encapsulated, budding yeast (*Cryptococcus neoformans*) in the skin lesion in a transplant recipient.*

Candidaemia

The majority of cases of candidaemia are associated with vascular-access catheters. Since candidaemia may resolve spontaneously when the catheter is removed, routine antifungal treatment was deemed unnecessary in the past. However, there are now known to be late sequelae of untreated candidaemia.[30,31] Four (15%) of 26 patients with catheter-associated candidaemia who did not receive specific antifungal therapy developed endophthalmitis, with loss of vision in three.[30] Currently, antifungal therapy therefore is recommended for all patients with candidaemia.[31,32] The appropriate duration of such therapy has never been investigated, however.

In an observational study in cancer patients, amphotericin B (0·67 mg/kg daily) and fluconazole (100 mg four times daily) were equally effective for the treatment of candidaemia. The mean duration of therapy for the surviving patients was 13 days for amphotericin B and 14 days for fluconazole.[33] In another study in which all three regimens were equivalent in efficacy, the median duration of therapy was 11 days for low-dose amphotericin B (0·5 mg/kg daily), 24 days for high-dose amphotericin B (0·7 mg/kg daily), and 13 days for fluconazole.[34] In a randomised trial on the treatment of candidaemia in non-neutropenic patients (which also showed that fluconazole and amphotericin B were equally effective), patients in the amphotericin B group had been treated for a median of 17 days (SE 1) and those in the fluconazole group for 18 days (SE 1).[35] In a recent study the median duration of therapy with caspofungin was 11 days and that for amphotericin B 10 days.[34] In 25% of the caspofungin group and 35% of the amphotericin B group treatment was switched to oral fluconazole. However, the duration of fluconazole treatment was not reported.[36] Overall, the average duration of antifungal therapy for candidaemia in these studies was 14·5 days (range 10–84).

An association between the duration of antifungal treatment and the development of delayed complications was

sought in patients with candidaemia treated over 10 years at one institution.[37] Of 81 patients who completed antifungal therapy, 20 (25%) received treatment for less than 2 weeks, 25 (31%) were treated for 2–4 weeks, and 31 (38%) for longer than 4 weeks. Delayed complications developed in only three patients; their durations of treatment were 3 weeks, 5 weeks, and 22 weeks.[37] Thus, the duration of antifungal treatment was not related to the development of late complications in patients with candidaemia, and longer courses of therapy were not especially beneficial.

Microbiological failure, variably defined as persistence of candidaemia despite antifungal therapy, has been documented in 8–12% of patients. Neutropenia, an abdominal focus of infection, and vascular-catheter retention were independent significant predictors of persistence of positive blood cultures after 72 h of antifungal therapy.[34] However, neither the type of antifungal agent nor the duration of therapy appear to influence the rate of microbiological failure.

On the basis of these data, a duration of 2 weeks of antifungal therapy after the last positive blood culture, as proposed previously,[32] is reasonable for the treatment of candidaemia. Fichtenbaum and colleagues suggested that shorter courses of therapy (5–7 days) may be appropriate in patients with transient candidaemia and in whom the vascular catheter has been removed.[38] Although there were no relapses among 29 patients thus treated,[38] the effect of short-course therapy on less frequently encountered late complications, such as endocarditis, is largely unknown.

Future considerations

For several opportunistic pathogens, such as cytomegalovirus, the latest diagnostic assays based on molecular and genomic detection methods have allowed rapid and reliable detection of infection. Equally importantly, these assays have proven valuable in monitoring the therapeutic response, guiding the duration of therapy, and predicting the risk of relapse.[39,40] Assessment of the optimum length of treatment by use of these assays is a superior strategy for the management of cytomegalovirus infection than application of a defined duration of therapy for all patients.[39] Whether non-culture-based assays can be similarly effective as objective endpoints for guiding the duration of therapy for invasive mycoses remains to be resolved. Finally, combination antifungal therapy is increasingly being considered a promising therapeutic option for fungal infections. There is a precedent in antimicrobial therapy—combination therapy has greater efficacy, a lower risk of the emergence of resistance, a decreased potential for toxic effects, and offers the possibility of a shorter duration of therapy. Whether any of these goals will also be achievable with combination antifungal therapy remains to be established.

Search strategy and selection criteria

Data for this review were identified by searches of Medline with the terms "aspergillosis", "candida", and "cryptococcus", and references from relevant articles. Articles were also identified through searches of my own extensive files on these topics. Only papers relevant to the duration of antifungal therapy were considered, and only those published in English were reviewed.

Conflicts of interest

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Clinical picture

Avascular necrosis of femoral heads in a man with HIV infection

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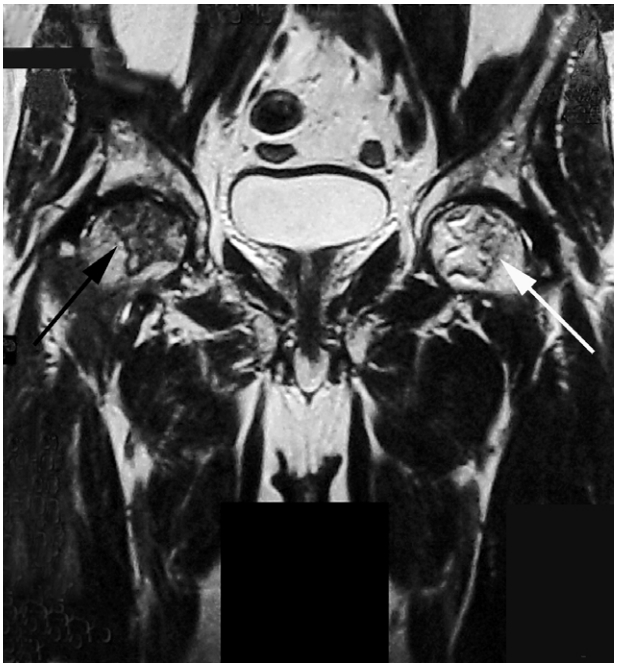
A previously well 51-year-old white man, who was diagnosed with HIV infection in March 2001 and treated with lamivudine/zidovudine and lopinavir for 22 months, was admitted to hospital in February 2003 with severe periarticular pain of both hips, which had lasted 3 months. The pain was triggered by weight bearing or moving and radiated towards the groin. Physical examination did not uncover any significant abnormalities, only slightly decreased range of motion in the affected joints. Radiography showed aseptic necrosis of both femoral heads. Because of low sensitivity of radiograph films, the diagnosis was confirmed by magnetic-resonance imaging of femoral heads (figure). An abnormal signal indicated the presence of devascularised bone tissue, severe tissue damage, and necrotic changes. These findings confirmed a previous suggestion of avascular necrosis. The patient's CD4 T cell count at the time of diagnosis was 100 cells/μL and his viral load was below 400 copies/mL. The patient lacked any typical risk factors for this complication—eg, use of systemic corticosteroids, ethanol abuse, hyperlipidaemia, rheumatoid arthritis, trauma leading to fractures and microfractures, pancreatitis, osteomyelitis. Avascular (or aseptic) necrosis of the bones has been described in the case reports of HIV-infected adults since the early 1990s. Whether this is related to HIV infection or its treatment is unknown.



T-2 weighted image. Irregular area of mixed high and low signal within the right femoral head. Increased signal area in the left femoral head.

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