to find 28 prior studies of middle ear fluid antibiotic concentrations in humans, but only 9 of the studies excluded specimens contaminated with blood or provided separate analysis for those specimens. (The list of references is available from the authors on request.) In those 9 studies the only drugs analyzed in patients with acute otitis media were penicillin, ampicillin, amoxicillin, oxytetracycline and cefuroxime axetil. Of those, only cefuroxime axetil is commonly used for treatment of acute otitis media, but only 4 of the subjects in that study had acute otitis media. This raises concern that some prior studies documenting good penetration of antibiotic into middle ear fluid could have used blood-contaminated specimens, resulting in falsely high estimates of drug entry.

It should be emphasized that demonstration of antibiotic entry into purulent middle ear fluid is merely correlative evidence that may be used to predict the likelihood of the effectiveness of a drug. However, we know of no evidence, either in humans or in animal models of otitis media, proving that the antibiotic must reach therapeutic concentrations in pur in order to treat otitis media. It may be that adequate amounts of antibiotic at the middle ear mucosal surface alone are sufficient to control the infection, along with host defense factors. However, it would be quite difficult to document those mucosal concentrations, and middle ear fluid values are an appropriate surrogate.

Our study does not prove that cefixime fails to enter middle ear fluid of children with acute otitis media. First of all, the number of subjects was quite small, limiting applicability to large numbers of individuals. Secondly, samples were obtained only at a single time within hours after the first dose of antibiotic. Other studies suggest that our sampling was too early and may have missed the peak serum drug values. These studies have shown that peak serum concentrations are reached approximately 4 hours after an oral dose in adult volunteers, and our samples were obtained 1 to 2 hours sooner. Furthermore serum concentrations in our patients were somewhat lower, 1.6 μg/ml than that measured in children given the same 8-mg/kg oral dose with serum concentrations averaging 3.22 to 4.72 μg/ml when measured 3.5 or 4.5 hours after the dose. This further suggests that we were not sampling at the time of peak serum concentration, and our samples certainly did not reflect steady state values, which may be more relevant to clinical outcome. Cefixime, when given intramuscularly, does penetrate into middle ear fluid in an experimental model of otitis media. From our limited study we can only conclude that it is unlikely that cefixime reaches therapeutic concentrations in middle ear fluid within 2 hours of the initial dose, even though serum concentrations have documented some drug absorption by that time.

The "gold standard" for drug approval is the randomized prospective trial which compares outcome of treatment with the newer drug to outcome of patients treated with conventional therapy. Unfortunately large numbers of subjects are necessary to assure efficacy in a disease with a high spontaneous cure rate. We agree with Silverblatt that severity of disease and economic and ethical factors be considered before embarking on massive trials of newer treatments for relatively mild infections. In 1977 the Food and Drug Administration published a set of guidelines to aid investigators in the design of studies of antibiotics. In the discussion on acute otitis media, suggestions for assuring uniformity of diagnosis, gauging outcome and assessing compliance are given. Also it was recommended that, "for a small number of patients, needle aspiration is desirable to obtain data on antibiotic concentrations in the middle ear fluid ..." We believe that demonstration of adequate amounts of antibiotic in middle ear fluid in patients with acute otitis media is important before a drug is approved for widespread use in treatment of otitis media because it can be difficult to assure clinical efficacy in limited treatment trials. Reports of drug concentrations in middle ear fluid should take care to note blood-contaminated specimens and other exclude or provide separate analysis for those subjects. In the latter group a more quantitative method for determining erythrocyte contamination could be used to assess those samples that may have had microscopic blood contamination.

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FATAL ESOPHAGEAL ASPERGILLOMA IN A LEUKEMIC ADOLESCENT

Recent trends in the infectious complications of patients undergoing therapy for leukemia indicate an increase in the frequency of fungal infections. This change has been attributed to an impaired host defense system, secondary to more intensive chemotherapy and bone marrow replacement by leukemia as well as to the prolonged administration of antibacterial coverage for empiric therapy in febrile, neutropenic patients. In leukemia patients undergoing therapy, infection with Aspergillus species is second to Candida species in frequency. Classically the pathogenesis of Aspergillus infection in the immunocompromised host is associated with local invasion of tissue with subsequent necrosis and hemorrhage. Most commonly Aspergillus infection involves the sinuomembranous tree but less frequently involves the skin, brain, gastrointestinal tract and heart.

One of the major problems in managing Aspergillus into
tion in immunocompromised hosts is making the diagnosis. Early detection of _Aspergillus_ in patients at high risk is difficult. Although several assays for antigens are under active investigation, diagnosis rests on the identification of an invovled site, most commonly the lungs and paranasal sinuses. Other sites may be more clinically occult. Such extrapulmonary sites may not be detected until considerable hemorrhage and necrosis have occurred. We report an adolescent patient with a clinically undetected esophageal aspergillosis, which eroded into the descending aorta and caused a rapid, fatal exsanguination. The unique features of the case are highlighted and the diagnostic and therapeutic implications are discussed.

**Case report.** A 16 year old male with relapsed acute lymphoblastic leukemia was hospitalized because of fever and neutropenia. At the time he was undergoing reinduction therapy for a bone marrow relapse which had been diagnosed 2 months earlier. Recent therapy included t, asparaginase, cytosine arabinoside, daunorubicin, alpha interferon, prednisone, vincristine, and intravenous cytosine arabinoside, hydrocortisone, and methotrexate.

Five days before admission he was evaluated for bilateral calf pain, at which time he was afebrile and neutropenic. The main finding on examination was an erythematous macular rash on his thighs. He was discharged home with systemic analgesics. On the day of admission the patient presented with a short history of fever, 39 C, persistent calf pain and a superficial cellulitis on the thighs. After a complete physical examination revealed no other abnormalities, cultures of blood, urine and throat were sent. Empiric anti-bacterial therapy with mezlocillin, gentamicin and oxacillin was started. He did not have an intracerebral catheter. Laboratory evaluation included a hemocrit of 24%, platelet count of 29,000/mm^3^, and a white blood cell count of 66/ mm^3^ with 27% neutrophils, 57% lymphocytes, 3% monocytes and 13% lymphoblasts. Radiographic studies included a normal sphenoid venous pouch and chest roentgenogram. On the fifth day while the patient was still febrile, mezlocillin and oxacillin therapy were changed to cefazadine and vancomycin because of a presumed drug eruption over his trunk and extremities.

On the eighth day he complained of mild epigastric discomfort with occasional dysphagia. This coincided with his first day without fever. Examination of the mouth revealed no lesions or plaques. An oral antifungal agent, mstampin, was prescribed and the dysphagia subsided in several days. On the 12th day of hospitalization, fever to 39.5 C occurred and empiric anti-fungal B therapy 10.5 mg/kg/day was initiated after further blood, urine and throat cultures were obtained. Fevers persisted until the 22nd day when his neutrophil count was greater than 1000/mm^3^; antibiotics were discontinued at that time.

Coincident with the return of the peripheral white blood cell count and the resolution of the fever, he complained of worsening dysphagia. A chest radiograph revealed a possible right middle lobe lesion consistent with a local pneumonia and a small ipsilateral pleural effusion which was not sampled. Two days later a chest radiograph was repeated to determine whether the small middle lobe lesion had progressed. Although there was no change in the size of the lesion, a small right upper lobe consolidation was noted. Amphotericin B was ordered at a dose of 0.5 mg/kg/day. An upper gastrointestinal series revealed a 6- by 6-cm retrocardiac mass with an esophageal stricture. Extraluminal contrast material suggested a perforation in the posterior segment of the lower third of the esophagus. Later that same day the patient developed the sudden onset of epigastric pain, and an uncontrollable upper gastrointestinal bleed resulted in a rapidly fatal exsanguination, despite aggressive intervention.

At autopsy a 6- by 3- by 5-cm mass was detected in the distal third of the esophagus which was adherent to the posterior wall of the left atrium and extended into the atrium. The mass had eroded through the wall of the descending aorta, creating an aortic-esophageal fistula. Microscopic examination demonstrated invasion of the blood vessels with dichotomously branching septate hyphae and extensive necrosis. On microscopic examination it was determined that a dense wall of leukocytes had formed at the margin of the lesion. Adjacent to the wall was a zone of liquefactive necrosis and acute inflammation. However, the majority of observed fungal elements were in the fungal mass in the left atrial wall and in the adjacent atrial infarct. Sections of the esophageal fungal mass revealed extensive infarction of the esophageal wall with extension anteriorly through the wall of the descending thoracic aorta. _Aspergillus fumigatus_ was cultured from the esophageal mass, the left atrium and the wall of the descending aorta. A separate aspergilloma was found in the right upper lobe in the corresponding location seen on the last chest radiogram. _A. fumigatus_ was cultured from this site. _A. fumigatus_ was not cultured from any other site, including the skin and soft tissue regions where there had been an erythematous rash or cellulitis earlier in the hospitalization.

**Discussion.** _Aspergillus_ infection has been associated with many sites in the immunocompromised host, but most commonly it occurs in the sinopulmonary tract. Direct involvement of other sites has been reported in the brain, skin, gastrointestinal tract, heart, liver, spleen and kidney. In one series of Meyer et al., gastrointestinal involvement was the third most common site of infection after lung and brain. Gastrointestinal involvement has been documented in other immunosuppressed patients, renal and bone marrow transplant recipients and those infected with the human immunodeficiency virus. Although its pattern of spread is inferred to be either local extension or hematogenous spread, most series suggest that local invasion is most common. In the immunocompromised host _Aspergillus_ commonly disrupts the local vasculature by invasion of the elastic lamina, leading to edema, hemorrhage, infarction and necrosis in the vessel and in distal tissue.

This patient died from complications of direct extension of the esophageal aspergilloma into the descending aorta and heart. The size of the mass suggests that the infection was present during the period of neutropenia and it is possible that, during the return of neutrophils, the process was accelerated and accounted for the acute, massive hemorrhage. The microscopic finding of a wall of leukocytes at the margin may have produced a plane of tissue lysis which permitted the infectant to be sloughed nearly intact and lead to a rapid exsanguination. The danger of an organized _Aspergillus_ infection which erodes into a major vessel of the heart itself is similar to the report of Waish and Buckley: six patients with _Aspergillus_ pericarditis were described in whom pericardial involvement was attributed to direct extension rather than myocardial abscess or pulmonary focus. In a recent review of 500 cases of aortic-esophageal fistulas, infections etiologies accounted for less than 2% of the cases. _Aspergillus_ was not identified; tuberculosis accounted for all but one of the cases associated with infection.

The patient presented here, with esophageal complaints early in the hospitalization, initially responded to empiric therapy intended for _Candida_, the most common pathogen associated with esphagitis. However, the persistence of the complaint and its eventual progression despite intravenous amphotericin B underscores the importance of the aggres-
sive diagnostic evaluation in an immunocompromised patient. We strongly suggest that endoscopy be performed as early as possible in the case of persistent or recurrent symptomatic esophagitis in the immunocompromised host, especially during a prolonged episode of neutropenia. Furthermore several studies indicate that the success of therapy is closely associated with early diagnosis and initiation of therapy. Had endoscopy been performed early and the correct diagnosis made, the patient may have benefited from amphotericin B in a larger dosage, 1 mg/kg/day, and the addition or substitution of another antifungal agent. In addition a surgical procedure, excision of the aspergilomas, may have prevented the local extension into the aorta and left atrium with its concomitant fatal exsanguination.

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Your Diagnosis, Please

EDITED BY MOSES GROSSMAN, M.D., AND PARVIN H. AZIMI, M.D.

BACK PAIN IN AN EIGHT-YEAR-OLD

An 8-year-old Latin girl was brought to the pediatric clinic complaining of left lower back pain after being struck by a basketball. The physical examination was unremarkable and she was sent home with a prescription for Tylenol. The pain resolved in 4 days. Two weeks later the pain returned. She was evaluated by a chiropractor who reported normal spine roentgenograms. She went on separate occasions to two private physicians who reported normal blood count, chemistry panel and urinalysis. She was sent home with a prescription for a nonsteroidal antiinflammatory agent, which provided temporary relief from her symptoms. Shortly thereafter she returned to the pediatric clinic. She now localized the pain to the left iliac crest. She had no fever, no dysuria and no hematuria. Her mother said the pain was worse in the morning as the child prepared for school. The physical examination, however, revealed no abnormality, and the iliac crest pain could not be reproduced. Her provider told the mother to return with the child if the symptoms persisted or worsened.

The child returned the next day having a shaking chill and returned to the pediatric clinic. Her mother now stated that she was not eating well, had lost 5 pounds in the last week and had missed 3 days of school because of difficulty walking. Physical examination revealed a well developed child whose temperature was 38.1°C, pulse 78, blood pressure 100/68 mm Hg and respiratory rate 12. She had a 2- to 3-cm area of tenderness to palpation over the left iliac crest. There was no spinal tenderness and no soft tissue swelling. Pain could not be elicited with flexion or extension of the spine, although she appeared somewhat uncomfortable when walking. She experienced some pain when left still and on touched. Cardiopulmonary, pulmonary and neurologic examinations were normal, and there was no lymphadenopathy.

A complete blood count showed hemoglobin 11.3 g/dL, white blood cell count 7800/mm³ 17%, neutrophils, 80%,

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Key words: Aspergillus, acute lymphoblastic leukemia, esophagitis, immunocompromised host.


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