Predicting the Cure of Osteomyelitis Under Treatment: Concise Communication

Gordon D. Graham, Michael M. Lundy, Robert J. Frederick, David E. Berger, Arthur W. O'Brien, and Tommy J. Brown

William Beaumont Army Medical Center, El Paso, Texas

The right tibias of sixty-six rabbits were injected with a suspension of *Staphylococcus aureus* and sodium morrhuate. After four weeks, 43 rabbits developed osteomyelitis and were started on a course of antibiotics. During treatment a gallium-67 scintigram was obtained every two weeks, for up to 10 weeks. During the treatment weeks, 25 rabbits developed negative gallium-67 scintigrams and were killed. All 25 had negative bacteriologic cultures of the right tibia. At the end of 10 wk after start of treatment, the 18 rabbits with persistently positive scintigrams were killed. Eleven of these had positive bacteriologic cultures of the tibia, and seven were negative. The findings suggest that sequential gallium-67 scintigrams may be useful in predicting the cure of osteomyelitis during treatment.

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Osteomyelitis continues to present a difficult diagnostic and therapeutic problem (*1*). One of the difficulties faced by the clinician is how to determine the duration of antibiotic treatment for osteomyelitis because current assessment of disease activity is very imprecise (*2–4*). A focus of infection may persist despite complete resolution of signs and symptoms. Bony radiographic changes do not reflect accurately the progress of osteomyelitis (*2*). The bone scintigram, although useful in the diagnosis of osteomyelitis, remains positive long after resolution (*5,6*). To replace current empiric treatment, a test with high accuracy for detecting sterilization of infected bone would be very useful. Shafer et al. (*7*) mention the correlation between decreasing gallium accumulation and reduction in bacterial populations of infected rabbit tibias under treatment. Most patients with osteomyelitis have had an initial gallium-67 scintigram, and this could be followed with others on a practical basis. Kolyvas et al. (*8*) repeated gallium-67 scintigrams in ten children under treatment for osteomyelitis, and several apparently false-positive scans were found. Their study suffered from the inability to define when cure had taken place. Therefore, our project was conducted to determine the usefulness of sequential gallium-67 scintigrams to follow osteomyelitis using an animal model to obtain culture results.

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For reprints contact: Dr. GD Graham, Nuclear Medicine Svc., William Beaumont Army Medical Center, El Paso, TX 79920.

MATERIALS AND METHODS

The model of Nordin (*9*) was followed to establish osteomyelitis in adult New Zealand white rabbits. The right hindleg was shaved, cleansed with alcohol, and dried. The rabbit was then anesthetized with 0.8 cc ketamine and 0.2 cc atropine. An 18-gage bone-marrow aspiration needle was inserted into the right tibial shaft and a suspension of *Staphylococcus aureus* and 0.1 cc of sodium morrhuate (sclerosing solution) were injected. A gallium-67 scintigram and a radiograph of the right hindleg were done on each rabbit after four weeks. Osteomyelitis was considered present if the radiograph revealed periosteal elevation, the gallium-67 scintigram was positive in the right hindleg, and the rabbit was guarding that leg or had lost 1.2 kgs (approximately 10%) of initial body weight.

For control, four rabbits were separated initially and were injected with only sodium morrhuate solution. At 3 days and at 4 wk, scintigrams were obtained on each rabbit.

The *Staphlococcus aureus* strain was a clinical isolate from a patient with osteomyelitis. It was grown on

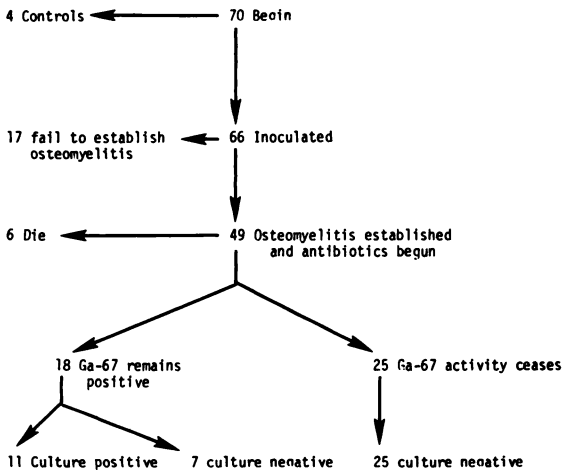

FIG. 1. Flow chart of experimental results.

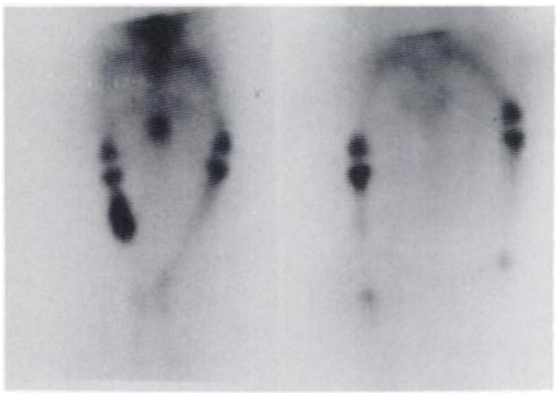

FIG. 3. Sequential gallium-67 scans beginning of treatment showing resolution of activity during antibiotic therapy. Second scan at end of treatment, 8 wk later. All such scans accompanied negative cultures.

trypticase soy agar containing 5% sheep blood and maintained by monthly transfers. Inoculation suspensions were prepared by subculturing to 5 ml of trypticase soy broth, incubating overnight at 37°C, and diluting 1:5 in a phosphate buffer, pH 7.40.

Gallium-67 scintigrams were made at 24 and 72 hr after injecting 2-3 mCi gallium-67 citrate. A small-field-of-view gamma camera with a $\frac{3}{8}''$ crystal and a parallel-hole medium-energy collimator was used. Each picture required approximately 6-10 min for acquisition of 400,000 counts. Each scintigram was interpreted independently by G.G. and M.L. If either reader interpreted a scan as positive, the scintigram was considered positive.

At the end of 4 wk, antibiotic treatment was begun on all rabbits meeting the criteria for osteomyelitis. Oxacillin (150 mg/kg-day) was administered i.m., t.i.d., and rifampin (200 mg) was suspended in cola syrup and given orally. If at the end of five weeks no improvement was noted, then gentamicin (3 mg/kg-day, i.m., t.i.d.) was added to the treatment. Scintigrams were made every other week. If a scintigram was considered negative, the rabbit was isolated for two weeks without further treatment, then killed. The right tibia was isolated, flushed with sterile phosphate buffer at pH 7.40, and cultured on trypticase soy agar. The plates were incubated for 48 hr at 37°C, and colonies counted. At the end of ten weeks, all rabbits left in the study were killed and the right tibias cultured.

FIG. 2. Radiograph of hindlegs showing periosteal elevations, an early sign of osteomyelitis.

RESULTS

Four control rabbits, injected with sodium morrhuate only, gave negative Ga-67 scintigrams. Dissection of the right tibia revealed proper location of the injection site.

During the 4-wk incubation period, ten of the 66 (15%) rabbits died of infection. Seven rabbits (11%) had negative Ga-67 scintigrams, radiographs, and bacteriological cultures of the tibia. Forty-nine rabbits (72%) met the criteria for osteomyelitis and were started on antibiotic treatment. Within 2 wk an additional six had died. Over a 10-wk period, 25 infected rabbits showed resolution of activity on Ga-67 scintigrams. These 25 rabbits had no demonstrable residual infection. The eighteen remaining rabbits had persistently positive Ga-67 scintigrams and were killed at the end of 10 wk. Eleven of these had positive tibial cultures and seven had negative cultures. The tibias of those rabbits having a positive Ga-67 scintigrams, but negative bacterial cultures, had impressive bony reactions (Fig. 4).

DISCUSSION

Induction of osteomyelitis involves the creation of a sequestrum by injecting a sclerosing agent or by direct mechanical scarification of the bone followed by inoc-

FIG. 4. Pathological specimens of involved bone that had an accumulation of gallium-67 in this area but negative culture. Note marked destruction of cortex.

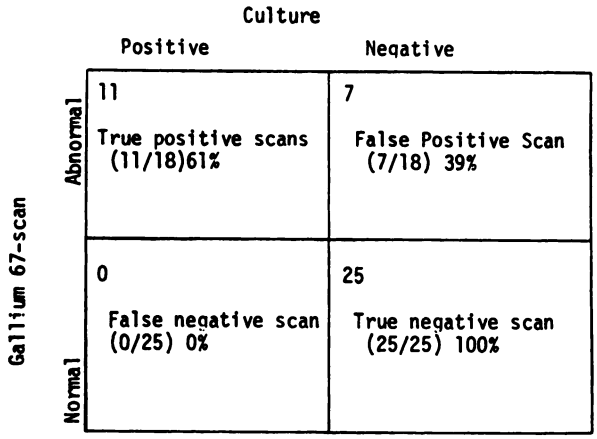

FIG. 5. Summary of results showing no false-negative scans but frequent false positives.

ulation with an infectious agent (*9,10*). The method of Nordin (*9*) was chosen because it was well described and reproducible. Our results substantiate the difficulty of establishing osteomyelitis, as evidenced by a 35% failure rate compared to the 30% and 46% failure rates seen in previous studies.

Osteomyelitis remains a difficult infection to treat, since current treatment regimens for osteomyelitis are empiric. Most series providing follow up include cases of recurrent disease (*1,3,4*). It has been suggested that the sluggish blood flow and impaired phagocytosis in bone allow establishment of a bacterial infection, and the subsequent sequestrum isolates the bacteria from drugs and host's defenses. Treatment, therefore, is prolonged and may require surgery. Clinical and radiographic signs, moreover, are unreliable in predicting cure.

Gallium-67 scintigraphy has been considered in the diagnosis of osteomyelitis, by itself (*11–12*) and in combination with Tc-99m methylene diphosphonate scintigrams (*6,7,13,14*). We extended these observations by examining the usefulness of sequential gallium-67 scintigrams to follow the progression of osteomyelitis. These initial data, as summarized in Fig. 5, suggest that a negative gallium-67 scintigram is strong evidence of sterilization of bone. The predictive value of a negative scan in our animal model was 100%. The positive scintigrams had a false-positive rate of 22% and a predictive value of 62%. The most impressive pathological feature of the tibias from the group with false-positive scintigrams was the significant bony destruction illustrated in Fig. 4. We suggest two possibilities for the false-positive scintigrams. The cortex of the bone may have been so degenerated that the culturing techniques used were not adequately sampling all intracortical areas, or the accumulation of gallium-67 may be due to abscess resolution and reparative osseous activity in the area (*15,16*). The combination of Tc-99m MDP and Ga-67 scintigrams may be helpful in this group. Further studies will be needed to assess these possibilities.

Our initial results in an animal model demonstrate that a resolution of gallium accumulation in a bone known to be associated with osteomyelitis is strong evidence for bacteriologic cure.

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