Successful treatment of osteomyelitis caused by *Pseudomonas aeruginosa*

J. W. HARDING, G. T. F. BRADDOCK, AND E. A. P. CROYDON

From King Edward Memorial Hospital, Ealing, and Beecham Research Laboratories

**SYNOPSIS** A case of generalized osteomyelitis due to *Ps. aeruginosa* is described. The condition had failed to respond to therapy with almost all antibiotics available but responded to long-term therapy with carbenicillin in very large doses, and it is suggested that this is now the treatment of choice for severe infections due to this organism.

The work of Batchelor, Doyle, Nayler, and Rolinson (1959) has resulted in the preparation of many semi-synthetic penicillins: of these compounds, methicillin, cloxacillin, and ampicillin are now widely used in the treatment of bacterial infections. The newest such compound, disodium a-carboxybenzyl penicillin (carbenicillin, Pyopen, B.R.L. 2064), is active against a wide range of Gram-positive and Gram-negative organisms. It is less active weight for weight than ampicillin and it cannot be given by mouth (Acred, Brown, Knudsen, Rolinson, and Sutherland, 1967). The main clinical application of this penicillin is therefore in the treatment of ampicillin-resistant, Gram-negative infections, particularly infections caused by *Pseudomonas aeruginosa*, resistant strains of proteus spp, and other resistant Gram-negative organisms (Brumfitt, Percival, and Leigh, 1967).

During clinical trials of this antibiotic, a woman suffering from multiple bone abscesses caused by *Pseudomonas aeruginosa* was admitted to hospital. Treatment in other hospitals with a variety of antibiotics had already failed, and it was decided to treat this infection with carbenicillin in a high dose for a long time.

**Clinical History**

The patient was a medical missionary, a 53-year-old nurse, who had been taking amidopyrine for headaches for about a month, when in June 1965 she was admitted to hospital in Swaziland as an abdominal emergency. Laparotomy revealed an appendix abscess and a gangrenous appendix was removed; she remained pyrexial postoperatively and she developed jaundice also. At this time she was treated with penicillin, streptomycin, and erythromycin, and she was found to have agranulocytosis, presumed to be due to amidopyrine. The total white blood count was 600 WBC/c mm, but following blood transfusion and steroid therapy the white cell count rose to 20,000 WBC/c mm. The patient remained pyrexial and by August 1965 had stomatitis, proctitis, and vaginitis. The antibiotic therapy was changed, and cephaloridine was given, together with ACTH, betamethasone, and chloroquine, although a laboratory diagnosis of malaria was never made. In mid-August she appeared better and all treatment was stopped although she still had a high temperature, and complained of pain in both hips, shoulders, elbows, and the chest. The only radiological finding at this time (September 1965) was hypostatic pneumonia, and despite courses of ampicillin and lincomycin she remained pyrexial. She had lost much weight and in view of her continuing deterioration she was flown to London for further investigation.

On admission to hospital she was anaemic (Hb 9·8 g/100 ml), the white blood count was 14,000/c mm, and the ESR was 144 mm/hr. The serum bilirubin was raised to 1·6 mg/100 ml and the plasma protein electrophoretic strip was compatible with chronic infection. The bone marrow
was normal and blood cultures were negative. Radiographs of the chest showed bilateral effusions, and bilateral fractures of the tenth ribs, possible fractures of other ribs, with appearances suggestive of secondary carcinomatous deposits or myelomatosis. A skeletal survey was negative for other deposits. Biopsy of a deposit in a rib showed only inflammatory granulomatous changes. No other investigations gave any lead to the diagnosis, but it was felt that she was suffering from either secondary carcinoma from an unknown primary growth, or multiple myelomatosis, despite the absence of Bence-Jones protein. Because at this stage of the disease chemotherapy was likely to affect only the latter, treatment with melphalan and testosterone was started in November 1965. During the whole period of these investigations the patient had remained pyrexial, and a further course of cephaloridine was given. She had repeated blood transfusions to maintain the haemoglobin level; the white blood count was raised and the ESR was repeatedly over 100 mm/hr. At this point she developed pain in the left hip with limitation of movement. Radiographs showed diminution of the joint space in the left hip, with new osteolytic lesions in the left ischium and left acetabulum. There were similar osteolytic lesions in all the ribs and the right scapula. During this period morphia was required to control bone pain.

After starting treatment for myelomatosis early in November, there was some improvement in her condition. The haemoglobin level ceased to fall but the fever persisted. A further rib biopsy, performed because the diagnosis was still in doubt, showed 'an inflammatory granulomatous process with areas of lipid granulomatosi'. No organisms or fungi were seen in the sections.

In December 1965 she developed two abscesses on the chest wall from which *Ps. aeruginosa* was isolated. Cultures for A.A.F.B. and fungi were negative. Treatment for myelomatosis was stopped, and replaced by treatment with ampicillin, colistin, and streptomycin, because the lesions were now thought to be infective. The abscesses healed rapidly, and she became apyrexial for the first time since her illness started; however, although the bone pain had become much less marked, there was now radiological evidence of increasing destruction of the left hip despite antibiotic therapy. Treatment with the above antibiotics was continued, but following deterioration of hearing, streptomycin was withdrawn after a total dose of 68 g, and steroid therapy was started in December 1965.

In February 1966 the patient developed bronchitis due to aspergillus and she was treated successfully with amphotericin B, other antibiotics being withdrawn.

After this episode she developed a further chest wall abscess due to *Ps. aeruginosa*, and at this time she was treated with carbenicillin alone at a dose of 1 g six hourly for two weeks. This compound had just been released for clinical trial. The abscess healed well and steroid therapy was finally discontinued by April 1966. Although the condition of the patient was now much improved, she had developed a dorsal kyphosis after the collapse of a number of vertebrae due to osteoporosis following prolonged bed rest and steroid therapy. Radiographs now showed total destruction of the left hip joint, and in May 1966 a Girdlestone arthroplasty was performed. Histological examination of the femoral head showed many small abscesses. Culture of the synovial fluid and femoral head grew pure *Ps. aeruginosa*. Postoperatively she was given first polymyxin B for eight days which was stopped on account of nephrotoxicity, and then a further course of carbenicillin (1 g every hour) combined with colistin for 16 days. The patient was then mobilized and discharged from hospital to a long-stay home in August 1966.

During this illness the patient had received at various times streptomycin, erythromycin, cephaloridine, ampicillin, benzyl penicillin G, lincomycin, polymyxin B, colistin, nystatin, amphotericin B, and carbenicillin. Five of these antibiotics had been used twice and one of them on three occasions.

On 9 November 1966 the patient was admitted to King Edward Memorial Hospital complaining of pain in the right hip, shoulder joint, and lower back. She had a temperature of 99-6°F and there was a flexion deformity with limitation of movement of the right hip. On 10 November 5 ml of yellow fluid was aspirated from the hip joint: culture was sterile. On 17 November capsulectomy and synovietomy was performed on the right hip and pus was found under tension from which was cultured *Ps. aeruginosa* sensitive to streptomycin, colistin, and carbenicillin, the last at a level of 50 µg/ml. At operation the femoral head was covered with cartilage, but the superior margin of the acetabulum was diseased. On 25 November the wound started to discharge and *Ps. aeruginosa* was isolated.

On 5 December a prolonged course of carbenicillin was started. It was administered by an intracaval drip at a dose rate of 28 g daily given in 2 pints of glucose saline. This was supplemented by oral probenecid, 0.5 g eight hourly.

One week after commencing treatment the wound infection had completely resolved. The patient responded well to this therapy; she gained in weight and was able to walk daily with assistance. Treatment was discontinued on 3 March 1967, and the patient was discharged three weeks later to the long-stay home. The total treatment period was, therefore, 88 days, and, apart from two periods of 12 hours when treatment was temporarily withdrawn, the daily dose remained 28 g. Treatment was withdrawn twice when the intravenous catheter became blocked. The total quantity of antibiotic administered was therefore in excess of 2 kilograms. Since that date she has
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remained well and in October 1969 was readmitted to King Edward Memorial Hospital, Ealing. Since her discharge from hospital she had been unable to walk unassisted, on account of a completely unstable left hip due to the original infection (Fig. 1).

On 22 October she began a course of carbenicillin, given at a dose of 5 g four hourly into an intravenous drip. The following day a McKee arthroplasty of the left hip (Fig. 1) was performed, and antibiotic therapy was stopped on 30 October. Unfortunately, bone was not available for culture for any residual organisms, and the patient made an uninterrupted recovery. When she was last seen the left hip was becoming stronger and there was no sign whatever of any infective process.

Discussion

Osteomyelitis is usually caused by Staph. aureus and cases due to Gram-negative organisms are relatively uncommon; Ps. aeruginosa is a very rare cause of osteomyelitis. One case has been reported by Kaiser, Cohen, and Rankow, 1963, and another by Mattern (1965). Mattern was primarily concerned with meningitis in the same patient which was successfully treated with antibiotics, and it is not recorded whether the osteomyelitis resolved. Kaiser et al (1963), however, state that radical surgery is required in pseudomonas osteomyelitis, and that antibiotic therapy is of no value in the eradication of infection.

In this case of widespread osteomyelitis radical surgery was impossible. After the diagnosis of Ps. aeruginosa septicaemia had been made the patient received carbenicillin 4 g daily for two weeks, and following the operation on the left hip a further course of carbenicillin, 1 g eight hourly, was given for 16 days, but nevertheless there was no change in the sensitivity of the organism to carbenicillin as a result of this earlier treatment; the organism had remained sensitive to 50 μg/ml of carbenicillin. It was obvious that therapy on this scale was having no effect. Therefore it was decided as a last resort to treat the patient with massive doses of carbenicillin intravenously for a prolonged period. This was only possible on account of the negligible toxicity of carbenicillin (Knudsen, Rolinson, and Sutherland, 1967) compared with other antibiotics active against Ps. aeruginosa. The dose given was high, namely,
Carbenicillin level mcg/mL

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Table Results of repeated tests for possible toxic effects of high doses of carbenicillin

*Transfused 3 units blood

28 g daily. This corresponded to a dose of 800 mg per kg body weight at the start of treatment, but somewhat less as treatment continued and the patient's weight increased to the extent of about 10 kg. Repeated liver function tests and blood counts during treatment failed to show any evidence of toxicity (see Table), although a raised ESR was noted. During treatment blood levels of carbenicillin were estimated (Fig. 2). These levels were entirely satisfactory; the minimal inhibitory concentration of the organism was 50 μg/mL, and a permanent serum level of at least six times the MIC was maintained.

Other workers have subsequently used carbenicillin in high doses. Richardson, Spittle, James, and Robinson (1968) used 30 g daily in intravenous infusions, and Bodey, Rodriguez, and Luce (1969) and Stratford (1968) reported using the same dose daily by intermittent injections into intravenous drips thus producing even higher peak levels.

In the first week of January the patient had an unexplained fever which resolved spontaneously. Probenecid was discontinued for a week on account of epigastric discomfort which did not recur when Probenecid was continued.

In severe *P. aeruginosa* infections carbenicillin, because it can be given in massive doses without toxic effects for long periods of time, is the treatment of choice.

We are grateful to Dr R. Sutherland of Beecham Research Laboratories for checking the MIC of the organism and the serum carbenicillin levels, and to Beecham Research Laboratories for unlimited supplies of carbenicillin.

References


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