Combined rifampicin and chloramphenicol therapy of Enterobacter osteomyelitis

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Summary
A 2-month-old infant with Enterobacter osteomyelitis complicating total parenteral nutrition was successfully treated with rifampicin and chloramphenicol. No untoward side effects attributed to rifampicin have been noted despite prolonged administration of rifampicin.

Introduction
One of the most serious complications of total parenteral nutrition (TPN) is suppurrative phlebitis and consequent sepsicaemia. Candida spp., coagulase-positive Staphylococcus aureus and, in recent years, multiple resistant Gram-negative bacilli (especially Klebsiella and Enterobacter) have been implicated most frequently (Heird et al., 1972; Lloyd-Still, Shwachman and Filler, 1973; Maki, Goldman and Rhame, 1973). Rifampicin, rarely used in non-tuberculous infections, has proved to be useful in combination with chloramphenicol in curing an infant with resistant Enterobacter osteomyelitis complicating TPN. Because of the widespread use of intravenous alimentation in medical and surgical departments and the potential risk of complications, it was felt that the sharing with other paediatricians of this successful experience would be of value.

Case report
A 2-month-old male infant was admitted with diarrhoea from birth. He was born after normal pregnancy and delivery. Birth weight was 2900 g. The infant was fed on diluted cow’s milk.

On admission he weighed 3600 g, length 54 cm and temperature was 36.5°C. The patient looked pale, malnourished and mildly dehydrated. Diarrhoea was present and his general condition with severe diaper rash suggested that diarrhoea had been present for a long time. Physical examination revealed no other pathological findings. Hb 9.5 g/dl, white blood cell (WBC) count 5.1 x 10^9/l (band forms 16%; segmented neutrophils 24%). Urine analysis was normal and stool culture yielded growth of enteropathogenic Escherichia coli 026 B6. BUN, glucose, sodium, potassium, calcium, phosphorus, alkaline phosphatase, cholesterol and iron were normal. Bone age was normal.

Glucose oxidase test of stools was positive for glucose with oral feeding on cow’s milk and Nutramigen (Mead Johnson; Bristol Laboratories) and he was given Hyprovit (a local (Haifa, Israel) infant formula of soya protein and glucose) instead. Intestinal E. coli was eradicated with orally administered colistin and repeated stool cultures for pathogens turned negative. As diarrhoea did not subside, oral feeding was stopped and TPN was started, using a peripheral scalp vein, on the 20th hospital day (Fig. 1). TPN included soya oil emulsion, casein hydrolysate enriched by 50% glucose solution added to the infusion bottle to a final concentration of 10% glucose, electrolytes and vitamins.

After 26 days of treatment with subsequent moderate improvement of his general condition, the infant’s temperature rose to 40.5°C and he looked very ill, pale and jaundiced. Laboratory tests supported a diagnosis of severe bacterial infection complicated by toxic hepatitis and disseminated intravascular clotting. The soya oil emulsion was discontinued and penicillin G 400 000 u./kg of body weight and gentamicin 5 mg/kg of body weight daily were administered intravenously for 14 days. Unfortunately early blood cultures were sterile. Because of continued high fever, carbenicillin 400 mg/kg of body weight daily was added intravenously on the 9th day of the septic fever but without results. Meanwhile liver function tests and coagulation studies became normal.

Blood cultures taken on the 57th and 58th hospital days and pus culture taken from a purulent phlebitis of the scalp yielded growth of Enterobacter sp. resistant to tetracycline, ampicillin, kanamycin,
lincomycin, colistin, carbenicillin, cephaloridine, gentamicin and trimethoprim-sulphadiazine but sensitive to chloramphenicol and rifampicin.

On the 59th hospital day, all antibiotics were stopped and replaced by rifampicin 20 mg/kg of body weight and chloramphenicol 50 mg/kg of body weight. Clinical signs of osteomyelitis of the distal parts of the femurs, tibiae and right fibula were first seen on the 64th hospital day and were later confirmed by X-ray.

Temperature tended to be subfebrile after 7 days of combined therapy and dropped to normal after 25 days of rifampicin therapy. Chloramphenicol was administered for a total of 3 weeks and rifampicin was given for a 2-month period.

The patient improved, swelling of joints declined and ESR dropped to normal. Function of joints adjacent to the inflammatory process were restored almost entirely to normal. During rifampicin treatment, laboratory studies reflected no abnormalities of renal, hepatic or haematological function which could be attributed to rifampicin administration.

Two days following discontinuance of therapy, the infant seemed mildly jaundiced and his temperature rose to 38-2°C. Physical examination revealed an enlarged liver palpable 7 cm below the right costal margin and an enlarged spleen palpable 5 cm below the left costal margin. Serum bilirubin was 6.7 mg/dl of which conjugated bilirubin 3.3 mg/dl. Serum-aspartate-transaminase was 2070 i.u./l and alkaline phosphatase 707 i.u./l. Serum protein electrophoresis were: albumin 6.34 g/dl, \( \alpha \)-1-globulin 0.34 g/dl, \( \alpha \)-2-globulin 0-65 g/dl, \( \beta \)-globulin 0-57 g/dl and \( \gamma \)-globulin 2.10 g/dl. Immunoglobulins were: IgG 7.6 mg/ml, IgA 0.64 ml and IgM more than 2.5 mg/ml (normal for the patient’s age, 0.1–0.8 mg/ml). Australia antigen was positive. WBC differential count did not reveal eosinophilia. Blood and urine cultures were sterile. Chest X-ray was normal. Two days later his liver shrank to 1 cm below the right costal margin. The child developed fulminant hepatic failure and succumbed in 3 days after the onset of liver disease. Blood ammonia was 1.8 mg/dl on the day of death. Post-mortem examination revealed non-contributory finding of massive hepatic cell necrosis.

**Discussion**

A wide variety of bacteria is involved in osteomyelitis. In a series of 163 cases of osteomyelitis, *Staph. aureus* was the causative organism in 61% of the cases (Dich, Nelson and Haltalin, 1975). Therefore therapy should first be aimed against *Staph. aureus* and if blood cultures yield growth to a different species, therapy can be altered accordingly. Infants and children with impaired host defences are more likely to develop infections with Gram-negative and with opportunistic low-virulence organisms. The widespread use of parenteral alimentation in debilitated infants increases the incidence of resistant Gram-negative infections. Hence, a potent and effective antibiotic alternative to \( \beta \)-lactamins and aminoglycoside compounds is occasionally needed.

Rifampicin, an orally active bactericidal antibiotic, proved to be effective in resistant Gram-negative infections due to *Klebsiella, E. coli* and *Shigella* (Naveh and Friedman, 1973, 1974; Naveh,
Effects have not been observed in any of the patients, not even in an 8-month-old infant after prolonged administration of rifampicin for Klebsiella osteomyelitis (Naveh and Friedman, 1973). So far as the authors know, complications following rifampicin therapy have rarely, if ever, been reported in the pediatric age group. This might be owing to the limited experience with the drug in children and/or to the relatively shorter courses given to infants suffering from non-tuberculous infections. Mild hepatic injury, mostly reversible, has been reported in adults suffering from tuberculosis and getting combined therapy of rifampicin and isoniazid which also is an hepatotoxic agent (Klatskin, 1975; Mattson, 1973; Scheuer et al., 1974). It is difficult to ascribe a hepatotoxic reaction to any one anti-tuberculous agent because patients usually receive several drugs together (Scheuer et al., 1974). Rifampicin hepatitis is characterized by early onset (Graisely et al., 1971; Scheuer et al., 1974) and the earlier the onset of the hepatitis the more severe it tends to be (Scheuer et al., 1974). The jaundice appeared in the present patient 2 days after discontinuation of a 2-month course of rifampicin therapy. This late onset and the fulminant course are not characteristic of rifampicin hepatitis. In the absence of evidence of bacterial infection, increased IgM supports recent viral infection. The positivity of serum to Australia antigen makes hepatitis B virus the most probable causative organism.

Luboshitzky, Sacks and Michel (1973) found that the effect of rifampicin in combination with other antibiotics was no different from that when rifampicin was given alone. The present authors also felt that the combination of chloramphenicol and rifampicin was unnecessary and therefore chloramphenicol was discontinued after 3 weeks without any deterioration of the patient's general condition. They are convinced that similar improvement could be achieved without any combination.

In view of the paucity of papers on the use of rifampicin in non-tuberculous infections in childhood, definite conclusions relating to the efficacy of this drug should not be drawn before further experience is accumulated. The use of rifampicin in non-tuberculous infections should be restricted to those severely ill patients suffering from overwhelming Gram-negative infections resistant to other antibiotics or where a nephrotoxic agent should be discontinued or is contra-indicated.

References
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