ANTIBIOTICS IN ACUTE OSTEOMYELITIS IN CHILDREN

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In a previous paper (Blockey and Watson 1970) the management of acute osteomyelitis in children was discussed. In the period 1961–68, 113 patients under the age of twelve had been treated. Proof of the diagnosis was obtained either by positive blood or pus culture or by the development of specific bone changes on radiographs. Antibiotics were given on diagnosis and usually continued for twenty-one days. Operation was done only when there was definite clinical evidence of an abscess. Infecting organisms were cultured from blood or pus in seventy-nine patients (Table III): in sixty-eight (86 per cent) the organism was staphylococcus aureus. In nineteen cases the organism was sensitive to benzylpenicillin and in forty-nine it was resistant. Of the other eleven infecting bacteria, six were sensitive to benzylpenicillin and five were not. Thus in that eight-year period the organism causing the acute bone infection was resistant to benzylpenicillin in 67 per cent of cases. In the other 33 per cent, benzylpenicillin alone would have been adequate therapy. Fifty-eight of the 113 children had operations to release pus. Fifty-two of these yielded positive cultures. Successful primary treatment was defined as cure of the symptoms and signs within four weeks of the first admission to hospital, with no complications attributable to the local bone disease developing thereafter. The follow-up was one to eight years. On this definition the results showed ninety-two successes (81.4 per cent) and twenty-one failures (18.6 per cent). Of the antibiotics used benzylpenicillin and cloxacillin (fifty-five consecutive cases) gave the lowest failure rate (14.5 per cent). In all the twenty-one failures, the continuing bone infection disclosed itself within seven months of leaving hospital. We did not support early operation in this disease. We thought that antibiotics should be given early and selected on a “best guess” principle.

In this paper we trace the changes in antibiotic sensitivity of the infecting organisms and anticipate future changes. This work, with evidence from elsewhere, led us to believe that a combination of benzylpenicillin and cloxacillin is no longer the “best guess” combination. We deduce that a combination of fusidic acid and erythromycin would be superior in this disease nowadays. The results of a trial using this pair in fifty consecutive cases of acute bone or joint infection in children are reported. Among these are thirty-eight cases of proven acute osteomyelitis satisfying the same definition as used in the previous paper and treated in the same way except for the difference in antibiotics. The other twelve cases comprise six of acute pyogenic joint infections and six of “clinical” osteomyelitis, in which there were negative cultures and no specific bone changes on radiographs. A comparison is made between the results in these thirty-eight children and the 113 previously reported. The shortest follow-up of the thirty-eight children was fourteen months.

THE NEED FOR ALTERNATIVE TREATMENT

The success of benzylpenicillin and cloxacillin was related to the fact that 33 per cent of the infecting organisms were sensitive to penicillin, and the staphylococcus aureus found

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resistant to penicillin in those infections was always sensitive to cloxacillin. Published work has shown that this pattern of sensitivity is unlikely to be repeated.

Resistance to benzylpenicillin—Table I shows this increasing trend from hospital laboratories. An equally marked trend is shown by the figures for causative organisms of osteomyelitis treated in the Royal Hospital for Sick Children, Glasgow (Table II). These figures indicate that benzylpenicillin has become of less value in treating staphylococcal infections.

TABLE I
SENSITIVITY TO BENZYLPENICILLIN OF STAPHYLOCOCCUS AUREUS CULTURED IN HOSPITALS

Year	Resistant to benzylpenicillin (per cent)	Author	Hospital
1946	14.1	Barber (1947)	Hammersmith
1948	59	Barber and Whitehead (1949)	Hammersmith
1955	59	Barber and Burston (1955)	St Thomas's
1958	62	Ridley, Lynn, Barrie and Stead (1970)	St Thomas's
1969	53	Sneddon (1970)	Sheffield Royal
1970	93	McAllister (1970)	Royal Hospital for Sick Children, Glasgow

TABLE II
CHANGES IN CAUSATIVE ORGANISMS

Author and time of study	Dennison (1951) 1945-49	Blockey and Watson (1970) 1961-68	Blockey and McAllister (1972) 1969-70
Number of patients	82	113	38
Percentage of staphylococcus aureus in those with positive bacteriology	90	86	88
Percentage of staphylococcus aureus resistance to penicillin	4	72	83

Resistance of staphylococcus aureus to cloxacillin and methicillin—We have not yet cultured a staphylococcus aureus from a child with acute osteomyelitis which is resistant to these drugs, but the evidence suggests that this will occur. Jevons (1961) found 0.06 per cent of strains resistant, but Ridley, Lynn, Barrie and Stead (1970) found that this figure in the same hospital had risen to 0.89 per cent. Skirrow and Rogers (1971) found 2.7 per cent resistant strains in the Birmingham Children's Hospital. In the Royal Hospital for Sick Children, Glasgow, our figure for the year 1970 was 0.5 per cent.

Resistance is almost exclusively confined to staphylococcus aureus already showing resistance to benzylpenicillin, streptomycin and tetracycline, and of this selected group of bacteria 58 per cent in Newcastle were resistant in 1970 (Hale and Selkon 1970). In Denmark the comparable figures are 10 per cent in 1967 (Eriksen, Bülow, Rosendal, Faber and Jessen 1967) and 40 per cent in 1969 (Jessen, Rosendal, Bülow, Faber and Eriksen 1969). That these strains can cause severe clinical problems was shown by Martin, Sureau and Chabbert

(1965) whose cure rate in staphylococcus aureus bacteraemia was 78 per cent with cloxacillin-sensitive strains, but only 45 per cent in cloxacillin-resistant strains. Cloxacillin resistance among staphylococcus aureus is still rare, but it will grow.

These trends prompted us to test an antibiotic combination other than benzylpenicillin and cloxacillin. Table III shows the numbers of patients from whom we were able by blood or pus culture to identify the causative organism. In deciding what new combination to try we had only the information in the column headed 1961-68.

THE CHOICE OF FUSIDIC ACID AND ERYTHROMYCIN

As well as showing low toxicity, the drugs to choose should prevent the development of resistance, broaden the spectrum (for instance, to include haemophilus) and show synergy. Both the agents selected are potent antistaphylococcal drugs unaffected by staphylococcal betalactamase (Skirrow and Rogers 1971). Eight years of widespread use of fusidic acid has

TABLE III
DETAILS OF ORGANISMS CULTURED

	1961-68		1969-70	
	Number	Per cent	Number	Per cent
Positive culture from blood or pus .	79	70	26	68
Negative culture	34	30	12	32
Total patients with proven osteomyelitis	113	100	38	100
Bacteriology				
Staphylococcus aureus	68	86	23	88.4
Streptococcus pyogenes	6	7.6	1	3.9
Haemophilus influenzae	2	2.5	1	3.9
Haemophilus para influenzae	—	—	1	3.9
Proteus vulgaris	1	1.3	—	—
Salmonella panama	1	1.3	—	—
Staphylococcus albus	1	1.3	—	—

revealed no established pattern of toxicity, and erythromycin is almost completely innocuous (Garrod and O'Grady 1968). Mouton and Koelman (1966) showed synergy between these two drugs. If fusidic acid were used with benzylpenicillin for the now rare staphylococcus aureus infections sensitive to benzylpenicillin, synergy could again be expected (Barber and Waterworth 1962).

The use of erythromycin with fusidic acid could be expected to broaden the spectrum to include all strains of streptococcus pyogenes (Robertson 1965) and most strains of haemophilus influenzae (Khan, Ross and Zaremba 1967). Table III shows the theoretical value of this combination.

Although resistance to fusidic acid has been reported *in vitro* (Crosbie 1963) and in the treatment of burns (Lowbury, Cason, Jackson and Miller 1962), its combination with another antibiotic has been shown to prevent the emergence of resistant strains (Jensen and Lassen 1969).

Adequate oral doses of fusidic acid have been shown to provide bactericidal tissue concentrations. Its presence in bone, including sequestra, was shown by Hierholzer, Knothe, Rehn and Koch (1966) and in pus by both Stewart (1964) and Lauen (1969).

For these reasons, it was decided that from January 1969 all children presenting with clinical acute osteomyelitis should receive fusidic acid combined with benzylpenicillin initially and then changed to fusidic acid and erythromycin if there was evidence of an infection resistant to benzylpenicillin.

CLINICAL TRIAL

From January 1969 to May 1970 thirty-eight children with proven acute osteomyelitis were admitted and given on diagnosis benzylpenicillin (250 milligrams six-hourly) and fusidic acid (30 milligrams per kilogram body weight per day in four equal doses). If a benzylpenicillin-resistant organism was found, the drug was stopped and erythromycin stearate (30 milligrams per kilogram body weight per day in four equal doses) was substituted. In all other ways these

TABLE IV
RELATIONSHIP OF FAILURE TO ANTIBIOTICS USED IN 151 PROVEN CASES 1960-70

Antibiotics	Cases	Failures	
		Number	Per cent
Benzylpenicillin and tetracycline . . .	32	6	18.7
Benzylpenicillin and cloxacillin . . .	55	8	14.5
Miscellaneous drugs			
Streptomycin, lincocin, chloramphenicol, methicillin . . .	26	7	27
Benzylpenicillin and fusidic acid . . .	20	1	10.5
Fusidic acid and erythromycin . . .	18	3	
	151	25	

patients were treated exactly as those reported in the previous paper. Two of these thirty-eight children received intravenous fusidic acid. We report the results using the same criteria of successes and failure. We also report another twelve children, six with proven pyogenic arthritis and six with clinical acute osteomyelitis, but without the criteria necessary for inclusion in this study of proved osteomyelitis. We thus had an experience of fifty cases of acute bone and joint infections in children treated with fusidic acid.* The oily suspension was used, not the later-developed aqueous suspension reported equally effective by Masterton and Goldman (1970). Antibiotics were given for twenty-one days and, as before, operations were done only if there was clinical evidence of an abscess.

RESULTS

There were four failures of primary treatment in the thirty-eight proven infections and there was no failure in the other twelve children. The shortest follow-up period was fourteen months, and as in the previous report failure means that the child was not cured of the infection within four weeks of entering hospital. None developed chronic disease.

Table IV shows for comparison these thirty-eight proven cases added to the 113 previously reported.

* Supplies were made available by Leo Laboratories Ltd.

It is seen that the fusidic acid series gave slightly better results than the cloxacillin series (10.5 per cent failures as against 14.5 per cent). Closer analysis of the four failures on fusidic acid, however, revealed other factors. Each case was atypical.

Analysis of the failures—The first was a girl aged seven years with osteomyelitis of the femur. She was given benzylpenicillin and fusidic acid. On the second day her blood culture grew staphylococcus aureus resistant to benzylpenicillin. This drug was stopped and erythromycin substituted. Vomiting beginning on the second day persisted for three more days and it was necessary to stop these antibiotics and give cloxacillin. An abscess formed. Subperiosteal pus was drained and the skin closed. At four weeks she developed another abscess pointing at the site of the incision. She is thus a failure of primary treatment.

Two other children had osteomyelitis due to haemophilus. Neither showed any clinical improvement after five days of fusidic acid and erythromycin. One improved when ampicillin was given; the other developed metastatic lesions.

The fourth failure was a boy aged six who had a seven days' history of heel pain on admission. Radiographs revealed a cavity in the calcaneus. This was opened and the contents cultured staphylococcus aureus resistant to benzylpenicillin. After twenty-one days' treatment by fusidic acid and erythromycin the lesion healed, but it flared up after two months and necessitated a second operation. Osteomyelitis of the calcaneus with a central abscess on admission has always proved much less responsive than other staphylococcal bone lesions.

Thus, if we confine our attention to the main problem of staphylococcal disease of long bones there was no failure among those children who completed the course. Seven out of the eight failures in the fifty-five children in the series treated by cloxacillin had occurred in cases of staphylococcal disease of long bones.

We were unfortunate to have two haemophilus infections in these thirty-eight proven cases (Table III). We had not expected the incidence of these infections to be higher than 2.5 per cent. Nevertheless, the antibiotic combination used was selected to cope with these infections. The erythromycin used did not appear to be effective clinically.

Analysis of the successes—Among the thirty-four successes of primary treatment were four children who were critically ill on admission. Intravenous therapy was used in two of these. A twelve-year-old with acute infection of the lower femur (Fig. 1) was given diethanolamine fusidate, 580 milligrams dissolved in 50 millilitres of phosphate buffer solution and then diluted to 300 millilitres in sodium chloride. This solution was then given through an intravenous cannula over twelve hours and repeated for five days, by which time she was able to take the oral doses of fusidic acid and erythromycin. No ill effects occurred. The result was successful (Figs. 2 and 3).

A boy aged four years had been given tetracycline for pain and swelling of the thigh for the previous four days without improvement. On admission his temperature was 40 degrees Celsius, the sedimentation rate was 79 millimetres and the lower two-thirds of his thigh distended, hot and acutely tender. A radiograph (Fig. 4) showed gross soft-tissue swelling. In spite of a temptation to open the bone the boy was given fusidic acid and benzylpenicillin. His blood grew staphylococcus aureus resistant to benzylpenicillin. Erythromycin was therefore substituted; the temperature settled and the swelling localised to the lower half of his thigh. After twelve days there was a firm mass palpable in the posterior aspect of his lower femoral shaft and radiographs (Fig. 5) showed the appearance of a large subperiosteal abscess. It was again tempting to operate and drain the abscess, but it was left alone. After twenty-one days, treatment was stopped. The swelling resolved and he was allowed to get up. Figures 6 and 7 show the appearances three and twelve months later, when on both occasions he had a normal leg with full function and no limitation of movement. This is the only patient of the entire 151 patients studied in whom there was proof of absorption of an abscess.

Two other examples are shown in which the radiographs were normal at the start, with a definite lesion at twenty-one days and complete healing at one year (Figs. 8 to 13). These

patients are typical of acute osteomyelitis treated in the way described. The absence of sequestration or periosteal new bone formation would be unusual in this disease before potent antibiotics became available. The clinical evidence seems to show that the antibiotics used are superior to those we have tried in the previous ten years.

FIG. 1

FIG. 2

FIG. 3

Figure 1—Antero-posterior radiograph of the lower femur of a girl aged 12 critically ill with acute osteomyelitis in the medial metaphysis four days after symptoms began. Figure 2—Radiograph taken after twenty-one days of antibiotics, given intravenously for the first five days. There is a cavity involving the whole medial metaphysis. Figure 3—Radiograph of the same knee one year after treatment began. There is complete resolution of the disease.

FIG. 4

FIG. 5

FIG. 6

FIG. 7

Figure 4—Lateral radiograph of the thigh of a boy aged 4 years who had been given tetracycline for the previous four days. There is a large soft-tissue swelling. He was given fusidic acid and erythromycin. Figure 5—The appearances of the same leg eleven days later. There is now a posterior abscess. Figure 6—The same leg after forty-two days. The abscess has absorbed and the subperiosteal new bone seen at ten days is absorbing. Figure 7—The appearances one year after onset. Without operation the abscess has absorbed. Function of the limb is normal.

Table III shows the identity of the causative organisms and Table V their sensitivity. Two points must again be stressed, first that the management of osteomyelitis in this way provides no bacteriological proof in about one-third of patients and, second, that the causative organisms are not changing, but their sensitivities are.

FIG. 8

FIG. 9

FIG. 10

Figure 8—Radiograph of the lower forearm of a boy aged 6 with osteomyelitis of the radius. Blood culture grew staphylococcus aureus resistant to penicillin. Figure 9—The same wrist ten days later. There is a central metaphyseal cavity. Figure 10—The same wrist one year after beginning a twenty-one day course of fusidic acid and erythromycin.

FIG. 11

FIG. 12

FIG. 13

Figure 11—Radiograph of the forearm of a 2½-year-old girl with pain and swelling for two days. The blood culture was sterile. She was given fusidic acid and benzylpenicillin on a clinical diagnosis of osteomyelitis of the lower radius. Figure 12—The same area after ten days. The clinical signs settled, but a metaphyseal cavity is seen in the lower ulna. Figure 13—The same forearm one year after starting antibiotics. The infected lesion in the lower ulna has healed.

TABLE V
INFECTING ORGANISMS AND SENSITIVITIES IN THIRTY-EIGHT CASES, TWENTY-SIX
WITH POSITIVE CULTURES

Sensitivity	Organisms			
	Staphylococcus aureus		Haemophilus	Streptococcus pyogenes
	Number	Per cent	Number	Number
	23		2	1
Benzylpenicillin	4	17	2	1
Fusidic acid	23	100	1	1
Erythromycin	23	100	2	1

TABLE VI
FUSIDIC ACID CONCENTRATION IN OSTEOMYELITIS CAUSED BY STAPHYLOCOCCUS AUREUS

	Tissue levels			Minimal inhibitory concentration in serum
	Pus	Live bone	Sequestrum	Fusidic acid
Twenty-four hours after beginning intravenous treatment for disease in lower radius in a girl aged 6	0.34 µg per millilitre	—	0.44 µg per millilitre	0.4 µg per millilitre
Level in scraping from wall of a pus-filled cavity in calcaneum in a boy aged 7	—	2.2 µg per millilitre	—	—
Ten days after beginning treatment in a girl aged 12	1.6 µg per millilitre	—	—	0.6 µg per millilitre

TABLE VII
LATE RECRDESCENCE OF INFECTION

	Other antibiotics	Fusidic acid
Total proven cases	113	38
Incomplete healing at twenty-one days	42	3
Number with recrudescence	7	0

TABLE VIII
FIFTY PATIENTS TREATED WITH FUSIDIC ACID

	Patients	Failures
Clinical osteomyelitis	6	0
Acute infection of joint (five staphylococcus aureus and one streptococcus)	6	0
Proven acute osteomyelitis (see Table III for organisms)	38	4
Totals	50	4

Tissue levels of fusidic acid—In three patients tissue levels of fusidic acid were assayed from operative specimens and compared with the minimal inhibitory concentration against the responsible staphylococcus aureus.

In the third example in Table VI the pus levels of fusidic acid were likely to have been effective even if given alone. In the first example the levels attained are about the same as the minimal inhibitory concentration (measured in the presence of serum) and are on the borderlines of antibacterial effect. Further *in vitro* work using a checkerboard technique (to be reported in full elsewhere) shows synergy between fusidic acid and erythromycin, particularly when the ratio of fusidic acid to erythromycin is high. This possibly explains the efficacy of the combination when the fusidic acid levels are close to the *in vitro* inhibitory levels.

Other points of comparison—Attention was drawn in a previous paper (Blockey and Watson 1970) to the management of incomplete healing after twenty-one days of antibiotics. In 113 patients forty-two had radiological evidence at the end of their course of antibiotics of metaphyseal cavities that were thought to harbour pathogens. In thirty-five children these cavities gradually became obliterated without clinical signs developing, but in seven the lesions became active, within five months in six children and at seven months in one.

In the fusidic acid series only three of the thirty-eight children had infected cavities after twenty-one days' treatment and none had further activity (Table VII).

We have used fusidic acid in fifty cases of acute bone and joint infections, all of whom have been followed up for fourteen months or longer. Vomiting occurred in six of the children which persisted for five days and made necessary a change of antibiotic. No other adverse effects occurred. The relationship of failure of primary treatment to diagnosis is shown in Table VIII.

DISCUSSION

Evidence of the effectiveness of an antibiotic in osteomyelitis can only be given after a large number are treated and followed for a time longer than that in which it is usual for a recurrence of infection to be found; all of the latter occurred within seven months of the first admission in the ten-year period under consideration. There is evidence to show the superiority of fusidic acid and erythromycin over any other combination that was used, but it must be remembered that the dosage of cloxacillin in the first fifty-five consecutive cases previously reported was one gramme per day, which gave a 14.5 per cent failure rate. A higher dose might have given better results.

Antibiotics are being developed faster than they can be tested in proper clinical trials, and although aware of the theoretical advantages of some newer drugs, we think that the place of fusidic acid and erythromycin has been established in osteomyelitis in children. Their value will be even greater if penicillin and cloxacillin resistance become commoner. It is again recommended that there is accurate recording of bacteriological data in all cases, because it is only by studying this that the trends can be seen that might require a revision of policy.

The possible increase in haemophilus infections gives rise to concern, but despite the fact that both the infections caused by these organisms were among the four failures of primary treatment in this series, the incidence was not high enough to justify a change of treatment unless there was proof of the haemophilus infection.

Treating children with acute osteomyelitis with effective antibiotics given early will thwart the infection. It either localises to a small area of the bone (Figs. 9 and 12) or produces no radiographic changes at all. If in this last group of infections the blood culture is negative (we found 54 per cent negative blood cultures in 113 cases) one has no proof of the diagnosis. Future studies of this disease may have to include cases where the diagnosis is based on clinical evidence alone.

CONCLUSIONS AND SUMMARY

1. Continued follow-up of the 113 children with acute osteomyelitis previously reported and a study of a further thirty-eight proven cases has not changed our opinion that the correct management is rest and effective antibiotics. Operation should be undertaken only if pus is detectable clinically.
2. Bacteriological evidence shows that the flora causing this disease are less sensitive to benzylpenicillin than ten years ago and that a proportion are also likely to become resistant to methicillin and cloxacillin.
3. The most effective antibiotic combination used was fusidic acid and erythromycin. This lowered the failure rate to 10.5 per cent in thirty-eight proven cases. Two of the four failures were in haemophilus infections. No staphylococcal infection of a long bone became chronic, and all lesions were healed within three months of onset.
4. The duration of treatment (twenty-one days) and the method of splintage (removable plaster slabs) remained the same as in the previous series.
5. Careful watch must be kept on the incidence of haemophilus infections. If it rises, increasing the erythromycin or adding ampicillin may be necessary.
6. Use of the newer aqueous suspension of fusidic acid may lower the incidence of troublesome vomiting (12 per cent in this series).
7. Only 7 per cent of staphylococcus aureus infections in this hospital, and 17 per cent of such infections in our thirty-eight cases were sensitive to benzylpenicillin. It is thought that this drug has outlived its usefulness in osteomyelitis.
8. It is recommended that, on diagnosis, fusidic acid aqueous suspension 5 millilitres should be given three times a day to children aged one to five, and 10 millilitres twice a day for children aged six to twelve, with erythromycin stearate 30 milligrams per kilogram of body weight each day in divided doses.

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