Cloxacillin in Treatment of Acute Osteomyelitis

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It has been said that when treating acute osteomyelitis, in this the era of antibiotic-resistant bacteria, the antibiotic given to the patient when first seen is usually chosen by "inspired" guesswork (Mercer, 1964). If an antibiotic were available to which all commonly encountered pathogens were sensitive then this guesswork would be eliminated. It would be unnecessary to change an antibiotic or give a combination of antibiotics when organism-sensitivity reports became available (Neligan and Elderkin, 1965).

Mann (1963) attributes the progression of the disease from the acute to the chronic phase in 7 out of 59 cases reviewed in 1963 to the initial use of the "wrong antibiotic" (as shown by later sensitivity reports).

It is probable that many cases of chronic osteomyelitis, often associated with the appearance of antibiotic-resistant organisms, are due to inadequate antibiotic therapy and delay in the onset of treatment.

For the treatment of acute osteomyelitis an antibiotic must have the following properties. (1) It must be effective against the organisms most often encountered. Of 709 cases of acute osteomyelitis collected from hospital records and from the literature, where organisms had been isolated, 617 (87%) were due to staphylococcal infection, 46 (6.5%) were streptococcal, and the remaining 46 (6.5%) included a wide range of organisms. (2) It is preferable to avoid multiple daily injections in children, and therefore an oral antibiotic is required. The antibiotic of choice must be readily absorbed from the gastro-intestinal tract, producing effective blood and tissue levels. (3) It should be bactericidal as well as bacteriostatic. (4) It should produce no adverse side-effects even after prolonged therapy. (5) Prolonged therapy must not lead to the formation of resistant strains.

Clinical Trial

A clinical trial of the antibiotic cloxacillin (Orbenin) was carried out in the orthopaedic wards of the Royal Liverpool Children's Hospital during the years 1964 and 1965 to find out how far this antibiotic satisfied these criteria and also to assess whether the incidence of progression of the disease to the chronic phase was reduced by its use.

Material.—In the course of the trial 62 cases of acute osteomyelitis were treated. The diagnosis was made on the following findings: (1) local signs—bone tenderness, reluctance to use the limb, and increased temperature or redness of the overlying skin; (2) raised body temperature and state of toxicity; (3) raised white blood cell count; (4) confirmation of the diagnosis was possible, in certain of the cases treated conservatively, by changes seen in the *x*-ray films taken some four weeks after the onset of symptoms—that is, localized porosis or periosteal reaction; and (5) blood culture: insufficient results were obtained in the series to establish the significance of this factor as an aid to diagnosis.

Treatment.—The decision on the method of treatment, conservative or operative, was made at the time of admission and depended on the following factors: (1) severity of the local signs, (2) degree of pyrexia and the toxic state of the patient, and (3) duration of symptoms previous to presentation at hospital. If it was believed, on clinical grounds, that pus was present then immediate bone-drilling was performed, the patient being given an intramuscular injection of cloxacillin preoperatively. All patients were given an intramuscular injection of cloxacillin on admission, irrespective of the method of treatment to follow. This antibiotic was prescribed for an arbitrary period of five weeks, the dose being based on the age of the patient rather than the weight, as follows:

Aged 1 to 3 years: 125 mg. intramuscularly stat. followed by 125 mg. by mouth six-hourly.
Aged 3 to 12 years: 250 mg. intramuscularly stat. followed by 250 mg. by mouth six-hourly
Aged 12 and over: 500 mg. intramuscularly stat. followed by 500 mg. by mouth six-hourly for seven days, and then 250 mg. by mouth six-hourly for the remaining four weeks.

Results

During February 1964 to November 1965 62 cases of acute osteomyelitis were treated—27 successfully by cloxacillin alone and 35 by bone-drilling in addition to cloxacillin therapy. The longest period of follow-up was two years, the shortest six months, with an average of 14 months.

There were no deaths. Thus absolute failure of treatment is defined as progression of the disease to the chronic phase; relative failure as recurrence of the disease, including cases requiring sequestrectomy.

One of the 27 conservatively treated cases had a recurrence of symptoms six months after discharge, but settled rapidly on a further course of cloxacillin, with normal *x*-ray appearances 18 months later; a relative failure rate of 3.7%. All 27 patients started treatment within 48 hours of the onset of symptoms, and in all but two cases the raised temperature began to fall within 24 hours. Two patients were initially treated conservatively; but they had "spiking" temperature charts, so on the third day of treatment the affected bone was drilled. In both cases the pus obtained was sterile.

In the operative series two patients developed sequestra within the first five weeks of treatment and three others had a recurrence of infection within six months. The remaining 30 made an uneventful recovery.

Case Reports

Cases 1 and 2.—Both patients developed sequestra in sites amenable to "excision surgery" (rib and scapular blade respectively). The sequestrum obtained in each case was sterile on culture and neither patient had any residual infection in the bone remaining.

Case 3.—This patient's lower radius was reopened at six months; the organism was still sensitive to cloxacillin. The lesion has since healed, leaving normal *x*-ray appearances.

Case 4.—This patient had a flare of infection at four months and the bone was reopened. The organism cultured was still sensitive to cloxacillin. *X*-ray examination showed cavity formation, but the patient has remained symptom-free for 12 months.

Case 5.—This boy had had five flares of infection in 10 months. His *x*-ray picture showed the typical changes associated with chronic osteomyelitis. He had been ill at home for at least four days before

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admission. When admitted he had a temperature of 102° F. (38.9° C.) and was noted to be "very toxic."

These results represent a relative failure rate of 11.4% in the operative group and an absolute failure rate of 2.8%. All but one of these patients were admitted to hospital more than 48 hours after the onset of symptoms.

Organisms were cultured from the pus obtained from 32 of the 35 patients on whom operation was performed. In all but one of these the responsible organism was *Staphylococcus aureus*. In one case a β-haemolytic streptococcus was isolated. Three cultures were sterile (two of these patients had received cloxacillin for three days before operation).

Table I shows the antibiotic sensitivity patterns of the organisms cultured from the pus obtained from these 35 patients.

TABLE I.—*Sensitivity Patterns of Organisms Obtained from 35 Patients on Whom Operation was Performed*

	No. of Cultures											
	14	5	4	2	1	1	1	1	1	1	1	3*
Penicillin	S	R	R	R	R	R	R	R	R	R	S	—
Streptomycin	S	S	S	R	R	S	R	R	R	R	S	—
Chlortetracycline	S	S	S	R	S	R	R	R	R	R	S	—
Erythromycin	S	S	S	R	S	S	S	R	R	S	S	—
Tetracycline	S	S	S	R	S	S	S	S	R	R	S	—
Sulphonamide	S	S	R	R	R	S	R	R	R	R	R	—
Chloramphenicol	S	S	S	R	R	S	S	S	S	R	S	—
Cloxacillin	S	S	S	S	S	S	S	S	S	S	S	—

* Sterile. R = Resistant. S = Sensitive.

Table II shows the incidence of antibiotic resistance of the staphylococci isolated. There is a high incidence of antibiotic-resistant organisms, yet so far as could be ascertained none of the patients had received antibiotics in the past from their general practitioner and none had previously been treated in hospital. The only antibiotic to which all the staphylococci isolated were sensitive was cloxacillin.

TABLE II.—*Incidence of Antibiotic Resistance of the Staphylococci Isolated*

Antibiotic	Total Cultures	Resistant	
		No.	%
Penicillin	31	17	55
Streptomycin	31	7	22
Chlortetracycline	31	7	22
Erythromycin	31	4	13
Tetracycline	31	4	13
Sulphonamide	31	12	39
Chloramphenicol	31	4	13
Cloxacillin	31	0	0

Of 62 patients suffering from acute osteomyelitis, 56 made an uneventful recovery. Three patients had a single flare of infection and two required sequestrectomy—a "relative failure rate" of 8%. Only one case progressed to the chronic phase—an "absolute failure rate" of 1.6%.

Discussion

Of the 62 cases of acute osteomyelitis admitted to the Royal Liverpool Children's Hospital during February 1964 to November 1965, 27 were treated with cloxacillin alone and 35 by bone-drilling in addition to cloxacillin therapy.

Organisms were isolated from 32 cases; 31 were staphylococci and one a β-haemolytic streptococcus. The hospital records of 107 previous cases of acute osteomyelitis from which organisms had been isolated were reviewed; 100 were staphylococcal infections and seven streptococcal. It is recognized that organisms other than these can be responsible for the disease, but they are rare. The essential problems today are the emergence of the antibiotic-resistant staphylococcus over the past 15 years and the necessity to give the correct antibiotic early in the course of the disease before the results of sensitivity tests become available.

In this series none of the staphylococci cultured was cloxacillin-resistant, but resistance to all other commonly used antibiotics was encountered. The organism isolated from the only case which has progressed to the chronic phase was cloxacillin-sensitive, and thus failure cannot be attributed to the initial use of the wrong antibiotic.

Table III correlates the appearance of penicillin-resistant staphylococci with the incidence of failure of treatment in this and other published series. It can be seen from Table III that there is an increasing incidence of penicillin-resistant staphylococci and that a relation exists between the failure rate and the initial use of the wrong antibiotic. In the present series the failure rate has been greatly reduced by the initial use of cloxacillin.

TABLE III.—*Penicillin Resistance of Staphylococci and Failure Rate*

Author	Period of Review	Penicillin-resistant	Relative Failure	Absolute Failure
		%	%	%
Kirker (1953)	1950	0	0	0
Dennison (1952)	1952	4	15*	0
Trueta and Morgan (1954)	1954	4	Overall 5% failure rate	
At this time resistance to other antibiotics appeared				
Harris (1960)	1951–8	41	Overall 29% failure rate	
Neligan and Elderkin (1965)	1954–7	25	5†	0
Winters and Cahen (1960)	1956–9	43	Overall 25% failure rate	
Mann (1963)	1960–1	50	Overall 22% failure rate‡	
Green	1964–5	55	8	1·6

* 4% attributed to penicillin resistance.
† 24% required a second antibiotic when sensitivity reports were available.
‡ 12% attributed to initial use of incorrect antibiotic.

None of the 27 conservatively treated patients progressed to the chronic phase and only one had a flare of infection. All received cloxacillin within 48 hours of the onset of symptoms. One patient progressed to the chronic phase, two patients had flares of infection, and two required sequestrectomy in the group of 35 patients who were treated by bone-drilling in addition to cloxacillin therapy. Only one of these patients presented for treatment earlier than 48 hours after the onset of symptoms. These findings are in agreement with those of Harris (1960), who found that the earlier the treatment the less the incidence of recurrence and progression to the chronic phase. This factor, the failure of parents to bring their child for treatment early in the course of the disease, is unfortunately the one over which the orthopaedic surgeon has no control. In spite of this, in the present series only one patient progressed to the chronic phase and three had flares of infection.

Harris stated that there was no reliable guide for the time at which antibiotic therapy could be discontinued with safety. He showed that erythrocyte sedimentation rate and white blood cell estimations were unreliable. He advocated a four-week course of the appropriate antibiotic, and on this regimen had a recurrence rate of 29%. Dennison (1952) had a 15% failure rate, and in half of his cases penicillin was given for only eight days. In the present series cloxacillin was given for five weeks, with a recurrence rate of 6% and only one absolute failure (1.6%). This length of time was chosen arbitrarily in the belief that, in the past, antibiotics had been given for too short a time to sterilize bone. There have been no untoward side-effects from the drug given for five weeks.

Summary

Sixty-two patients were treated for acute osteomyelitis during the period February 1964 to November 1965—27 with cloxacillin alone and 35 with bone-drilling in addition to cloxacillin therapy.

Organisms were isolated from 32 patients—31 of the organisms were *Staphylococcus aureus* and one was β-haemolytic streptococcus. Sensitivity tests showed that cloxacillin was the only antibiotic out of eight tested to which all were sensitive.

Complete resolution was effected in 90% of cases. There was relative failure of treatment in 8% and absolute failure in 1.6%.

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Association of Diabetes and Cataract*

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Cataract is one of the commonest causes of registration for blindness in England and Wales (Sorsby, 1966). The association of diabetes and cataract in older age groups is a subject of great controversy, but is perhaps stronger in younger persons (Chodos and Habbeger-Chodos, 1960).

Method

A survey was undertaken in two stages:

1. The lens-opacity state of a sample of the general population was assessed on the slit-lamp microscope with full pupillary dilatation (Hollows *et al.*, 1965). As a result of this, four main groups were defined: group 1, no lens opacities; group 2, cortical opacities, subdivided into two types—(A) senile wedges and plaques, and (B) juvenile clubs; group 3, nuclear lens opacities; and group 4, aphakic (excluding traumatic aphakia) or mature lens opacity. The lenses were also graded according to nuclear colour.

2. From group 1, subjects were selected to match as nearly as possible for age and sex those in groups 2–4.

The resultant sample consisted of 374 persons of the general population of the Rhondda Fach whose age and sex distribution showed a slight excess of older age groups when compared with the Medical Research Council census figures for this area (see Table I). Of this sample 340 (91%) were examined.

TABLE I.—*Age Distribution of Population Studied*

Age	Males						Females					
	Census		Sample		Seen		Census		Sample		Seen	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
40–49	715	33·7	54	32·5	51	33·1	821	32·3	63	30·3	57	30·7
50–59	726	34·3	59	35·5	56	36·4	789	31·0	59	28·4	53	28·5
60–69	527	24·9	37	22·3	32	20·8	688	27·0	58	27·9	50	26·9
70–74	151	7·1	16	9·6	15	9·7	248	9·7	28	13·5	26	14·0
Total	2119		166		154		2546		208		186	

Patients were visited by a member of the Medical Research Council staff, and if they agreed to undergo the tests were asked to fast from 10 p.m. the night before the morning of the test. The majority of tests were carried out in the person's home or place of work. A fasting venous blood sample was taken and 50 g. of liquid glucose (Beecham Foods) given by mouth. A short questionary was asked regarding family history of diabetes and cataract and any possible relevant illness. The subject was allowed to continue normal daily routine, and two hours later a capillary blood sample and a urine sample were obtained.

Blood sugar was estimated by the method of Hoffman (1937) adapted for use on autoanalysers (S.D. of method ±1.5 mg./100 ml.). Glycosuria was assessed with Clinistix strips, any blue coloration after repeat testing being counted as positive.

Results

From Table II the mean fasting blood sugar is seen to be almost equal in all lens-opacity groups for males. For females the mean levels are seen to be equal in all groups except group 4, where the number of results available is small.

TABLE II.—*Fasting Blood Sugar in mg./100 ml.*

Age		Group 1	Group 2A	Group 2B	Group 3	Group 4
Males						
40–49	Mean	78·6 (34)	74·0 (1)	81·2 (9)	89·6 (7)	-
	S.D.	12·9		8·3	15·9	
50–59	Mean	80·8 (32)	78·3 (10)	82·6 (12)	72·0 (2)	—
	S.D.	16·6	5·3	16·4		
60–69	Mean	88·8 (9)	90·3 (16)	81·6 (5)	—	92·0 (2)
	S.D.	4·8	16·3	7·3		
70–74	Mean	88·3 (3)	86·9 (10)	93·0 (1)	—	78·0 (1)
	S.D.	21·0	10·0			
Females						
40–49	Mean	84·7 (31)	101·5 (2)	83·1 (16)	83·9 (7)	101·0 (1)
	S.D.	7·5		14·4	10·2	
50–59	Mean	92·2 (28)	101·1 (7)	85·6 (14)	122·3 (3)	104·0 (1)
	S.D.	39·6	40·1	12·0	73·3	
60–69	Mean	100·4 (21)	95·6 (17)	104·4 (10)	—	189·5 (2)
	S.D.	56·0	27·1	40·1		
70–74	Mean	97·0 (3)	100·6 (17)	68·0 (2)	90·0 (1)	128·7 (3)
	S.D.	7·6	25·7			53·3

Table III shows blood-sugar levels two hours after 50 g. of glucose challenge. The readings for males are seen to be almost equal in all groups of lens opacity types and almost equal to the fasting blood sugar levels. The readings for females are also similar to the fasting values and are not significantly different between the various groups except in group 4, where the readings are very much higher than in the other groups. The numbers in this group are too small for a test of significance. The mean blood-sugar level at two hours for all ages in group 4 combined is 173 mg./100 ml.

Frequency distribution graphs were constructed (see Chart) of the readings of group 1, representing persons without lens opacities, against the readings of groups 2–4 combined, representing persons with lens opacities. No difference can be seen between persons with and without lens opacities.

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