THE TREATMENT OF RESISTANT STAPHYLOCOCCAL INFECTIONS WITH OXACILLIN

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The treatment of resistant staphylococcal infections has become a serious problem in recent years. The staphylococcus appears to have replaced the streptococcus as a cause of epidemic hospital sepsis. This is no doubt due to the fact that the streptococcus has never acquired resistance to antibiotics.[1]

It is doubtful whether in fact the incidence of staphylococcal disease has increased, but since the staphylococcus has acquired resistance to antibiotics, it is now a considerably greater problem than it was during the 'golden era' just after penicillin was introduced. There appears to be no greater exposure to staphylococcal infection now than there was 10 years ago.[2]

The organism which causes lesions is probably the *Staphylococcus aureus;* it is usually coagulase positive and haemolytic. Between 50 – 80% of the population carry this organism in their anterior nares, and this applies both to hospital patients and to non-hospitalized patients. There must be some disturbance of the 'soil' before infection can occur. This means a lessened degree of resistance, and occurs under modern conditions after surgery and in the treatment of various conditions such as reticulosis which, in the past, were always rapidly fatal, and in diabetics, who are today kept alive for longer periods than previously. The organism acquired in hospital appears to be resistant to most if not all antibiotics, and is known as the 'hospital staphylococcus', but the organism found in non-hospitalized patients may still be amenable to many of the commonly available antibiotics.

The introduction of the penicillanic-acid nucleus led to the production of several new penicillin-type drugs. At least two of these have a greatly enhanced action against the resistant staphylococcus, which usually produces penicillinase which is responsible for its non-reactivity to antibiotics. The first of these substances to be introduced was methicillin and, while effective, this had to be given by injection, 4-hourly. Its use was therefore both cumbersome and expensive.

The introduction of oxacillin, which is acid resistant and can be given by mouth, has revolutionized the treatment of resistant staphylococcal infections, and it is the purpose of this paper to report on several patients with resistant staphylococcal infections treated with this drug.

Case 1 — Staphylococcal Pneumonia with Septicaemia

A 57-year-old butcher was first seen on 14 October 1961. Just before the middle of September he developed rigors which persisted for a period of about one month, on and off. These rigors occurred several times daily, and he was treated with numerous antibiotics including penicillin, streptomycin, novobiocin and tetracycline, and azo-sulphonamide — with no noticeable effect. At the beginning of October urinary examination showed 50 - 80 erythrocytes per high power field and some albumin with granular and cellular casts, but a repeat urine examination later showed no abnormality. The leucocyte count was 11,800 with 63% neutrophils, and the ESR was 39 mm. in one hour (Wintrobe). Chest X-ray on 28 September showed coarsening of the lung pattern at the right base with some increase in opacity in this area, but on 3 October the appearances were normal.

When seen on 14 October the patient complained only of morning rigors and of feeling weak and cold, but in fact he had several rigors daily. He stated that he had a slight cough which had disappeared, and complained of slight pain in both hips and some anorexia.

There was no history of a rash and he had not had any septic wounds, sore throats or upper-respiratory infections recently. He had not been out of Johannesburg for some considerable time.

On examination, apart from a temperature of 103°F., there were no abnormal findings. On admission to hospital a blood culture was taken at once and repeated the following morning; it showed a coagulase positive haemolytic *Staphylococcus aureus*. This organism was sensitive to penicillin, phenethicillin, methicillin, erythromycin and novobiocin. A leucocytosis of 24,200 per c.mm. with 80% neutrophils was present, and the ESR was 32 mm. in the first hour. No LE cells were seen, and the LE slide-flocculation test was negative. The bacterial agglutination tests were negative, as were the rickettsial, viral and complement tests. Sputum culture showed a variety of organisms and was not helpful. Examination of the urine showed a trace of sugar and albumin, but microscopically the urine was normal.

While in hospital he had 4 - 5 rigors daily for 9 days and remained very ill despite 1 G. of methicillin 4-hourly, day and night, by intramuscular injection, and various other antibiotics. On 20 October the methicillin dosage was doubled because his condition had deteriorated. A chest X-ray on 17 October showed minimal changes at the left costophrenic angle and slight haziness over the left lung field in the fourth anterior space, with a symmetrical appearance on the right. The findings suggested a bilateral peribronchial change.

The rigors ceased on 22 October, and the blood culture was sterile, but he was obviously ill and getting worse and still ran a high continuous temperature. The urine contained more albumin, and the blood count showed a leucocytosis of 18,000 per c.mm., with 76% neutrophils. On 24 October, despite changing and adding various antibiotics, the liver was palpable 4 cm. below the costal margin and was tender, but the patient was not jaundiced. He was lethargic and drowsy. A chest X-ray showed a fairly extensive lesion involving the right upper lobe. It showed consolidation with radiating striae into the lung field. On 26 October his condition appeared to be grave, but on that day I was advised of a new penicillin derivative that was claimed to be more powerful than methicillin against resistant staphylococci. At 2 p.m. all the other antibiotics were stopped, and 250 mg. of oxacillin was given by intramuscular injection, 4-hourly, day and night, and 1 G. by mouth, 4-hourly, day and night.

In addition probenecid was given in a dose of 0·5 G. 6-hourly. By 6 p.m. there was a dramatic improvement. The temperature dropped to 97°F. and he felt well and had a normal meal. The drop in temperature at this stage is

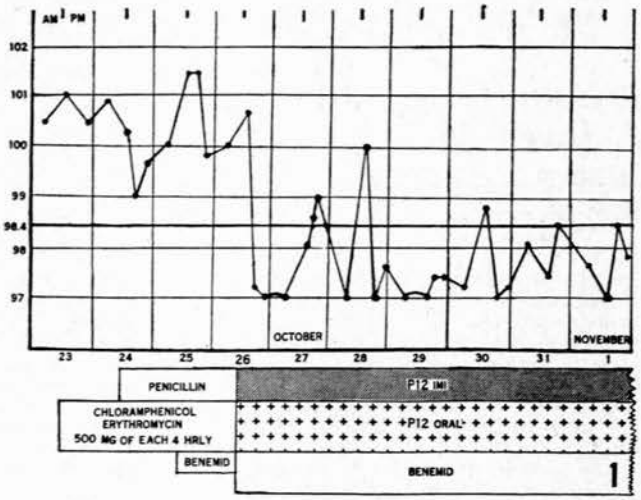

Fig. 1. Detailed section of temperature chart showing dramatic improvement on oxacillin (P 12).

illustrated in Fig. 1. Progress was then rapid and the liver soon disappeared, as did the albumin in the urine. A blood count on 3 November showed a leucocyte count of 9,400 per c.mm. with only 59% neutrophils, and the X-ray showed a homogeneous density overlying the right lateral, first anterior interspace and the second anterior rib end, but no sign of any cavitation. The lesion was smaller than on 24 October. This shadow was still present when he was discharged on 11

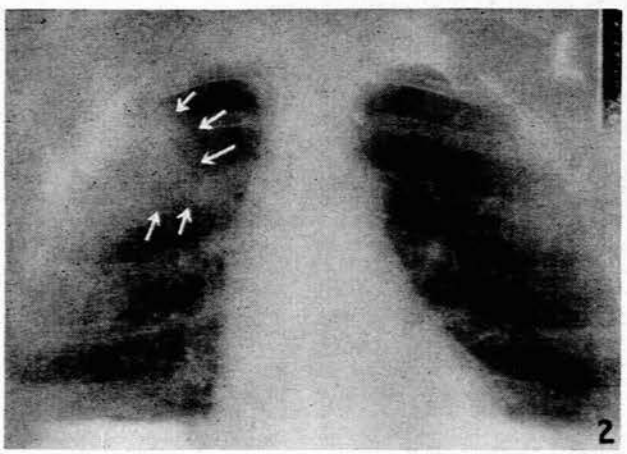

Fig 2. Apical view of consolidation or possibly a filled cavity at right apex on 11 November 1961 (case 1).

November (Fig. 2). On discharge, although the blood count was normal, an ESR (Westergren) was 82 mm. in the first hour. He continued to take 5 G. of oxacillin by mouth daily with 0·5 G. of probenecid 6-hourly for several weeks. This dosage was gradually reduced. By 23 November the right apical lesion on the X-ray was considerably improved, but the ESR (Westergren) was still 30 mm. in the first hour. The dose of oxacillin was reduced to 1·25 G. daily for 10 days and was completely stopped on 4 December when the ESR (Westergren) was 14 mm. in one hour. He has remained well since that date.

Comment. This case illustrated well the effectiveness of oxacillin in penicillin-resistant staphylococcal infections and illustrates that, although the sensitivity tests revealed *in vitro* sensitivity to numerous antibiotics, the organism was in fact resistant to all the antibiotics used apart from oxacillin. Sensitivity to oxacillin was not tested.

Case 2

A 47-year-old woman was subjected to gastrectomy for a chronic duodenal ulcer and developed a staphylococcal infection in the wound. The staphylococcus was resistant to almost every antibiotic. She continued to have a swinging temperature and pain over the liver, and on the 23rd day a laparotomy was done. This showed a normal abdomen, but the liver appeared to be enlarged. A biopsy was taken, but it only showed cholestasis with cellular infiltration. Bile withdrawn from the gall bladder at this stage showed *Staphylococcus aureus* and *Bacillus pyocyaneus* organisms. She had been treated with penicillin, streptomycin and novobiocin without response. The serum bilirubin was 11·2 mg. per 100 ml. and despite the absence of any bleeding the haemoglobin was 9 G. per 100 ml. Treatment was started with oxacillin, 250 mg. 4-hourly by intramuscular injection for 5 doses a day, with 1 G. by mouth for 5 doses a day and probenecid, 0·5 G., 6-hourly. The response was dramatic and the temperature settled within 72 hours. The jaundice disappeared. After 10 days of treatment she was discharged and allowed to take a reduced dosage at home for one week. However, 3 weeks later temperature recurred, and fluoroscopy showed an immobile diaphragm on the right with a markedly tender liver, and treatment was recommenced with 1 G. of oxacillin 4-hourly, day and night, by mouth, and probenecid 0·5 G. 6-hourly, with a very rapid response. It was intended to continue this treatment for 5 weeks at the time of writing this paper.

Comment. This case was probably one of pylephlebitis suppurativa caused by the staphylococcus, and the previously ominous outlook in this condition was overcome with the use of oxacillin. This case also illustrates the need for prolonged treatment of at least 3 - 4 weeks after any severe staphylococcal infection.

Case 3

A 30-year-old man had a gastrectomy for chronic duodenal ulceration. In the second week he developed an intestinal obstruction which had to be operated on. Following the second operation he ran a continuous temperature, which soon became intermittent in type, and he also complained of a pleuritic pain at the right base. Sputum cultures showed *Staphylococcus aureus* organisms in pure culture. Treatment with methicillin, novobiocin and penicillin was ineffective, and he was then treated with oxacillin in the same dose as the previous two patients. Within 10 days he was completely recovered, but X-ray signs still remained at the right middle zone for approximately 3 weeks. At one stage during convalescence cavitation was seen, but did not require further treatment.

Comment. This patient had a postoperative staphylococcal pneumonia, no doubt caused by a 'hospital staphylococcus', and again illustrates the effectiveness of oxacillin in resistant infections.

Case 4

This patient was a 43-year-old woman who had the fifth lumbar disc removed by an anterior approach and was left with a persistent pyrexia thereafter, although there was no evident sign of sepsis. She remained under the care of the orthopaedic surgeons and became extremely anaemic, the haemoglobin at times going down to 5 G. per 100 ml. The X-ray showed bone destruction in the fourth and fifth lumbar vertebrae, but despite the use of numerous short courses of various antibiotics her condition steadily deteriorated and she required 20 blood transfusions over a period of 19 months. The temperature fluctuated between normal and 101°F. all this time. When seen at home in the 20th month she was unable to walk. She had signs of pyramidal-tract injury and of dorsal-column loss, but there was no loss of superficial sensation, and sphincter control was normal. The haemoglobin was 8 G. per 100 ml. and a blood culture was negative. The ESR was 44 mm. in the first hour. On 5 G. of oxacillin in 5 doses per 24 hours and probenecid, 0·5 G.

6-hourly, her temperature settled and the pain in the back improved, and on the 7th day the haemoglobin was 10 G. per 100 ml. At this stage she was able to get out of bed and walk. She was transferred to hospital for administrative reasons and continued on this treatment for many weeks. The X-ray picture of destruction of the 4th and 5th lumbar vertebrae showed improvement, with sclerosis of large areas. However, although the haemoglobin returned to normal the mucoproteins remained at over 200 mg. per 100 ml. and the C-reactive proteins remained at 4 plus positive, while the ESR was as much as 60 mm. in one hour. After 9 weeks of treatment, despite these blood findings, the patient was completely ambulant and free of pain, and the oxacillin was discontinued. However, 4 weeks later the pain recurred, and although there were no neurological signs and no anaemia, the oxacillin was started again, this time, in combination with 'fucidin'. At present she is on this therapy and it is possible that surgical treatment for the osteitis may yet have to be considered.

Comment. This case illustrates well the fact that the soft-tissue swelling from the staphylococcal infection improved considerably on the oxacillin, and it is highly likely that if the drug had been continued the bone destruction would have completely disappeared. However, it may well be that in future she will require surgery.

Case 5

This 74-year-old woman complained of headache confined to the right side, and she had a swinging temperature for a few days until a swelling appeared over the right frontal area and temporal region. A blood culture was positive for a coagulase positive, haemolytic *Staphylococcus aureus*. It was considered that she had staphylococcal sinusitis, and an operation was performed on the right frontal sinus. Pus containing a similar type of staphylococcus was obtained. The day after the operation she developed a Jacksonian fit involving the left side of the body, and was left with slight hemiparesis of that side. She was treated first with methicillin in full dosage, but the temperature, although at a lower level, continued. On oxacillin, 0·5 G. 4-hourly, plus probenecid, she settled down completely and when last seen was very well.

Comment. This was a further case of staphylococcal infection with septicaemia which responded well to smaller doses of oxacillin. This was an infection acquired outside a hospital.

Case 6

A 19-year-old female developed an enlarged spleen and pyrexia following a diagnostic dilatation and curettage. Seven blood cultures were positive for haemolytic *Staphylococcus aureus*, coagulase positive. Oxacillin, 0·5 G. 4 times daily, partially controlled the temperature, but there was no increase in the haemoglobin, which was 10 G. per 100 ml. when she was first seen. The spleen was enlarged 3 cm. below the costal margin and was painful. X-ray of the chest showed peribronchial infiltration. An increase of the oxacillin to 1 G. orally, 4-hourly, day and night, together with 250 mg. day and night, by intramuscular injection, and the use of probenecid 6-hourly caused a complete drop in temperature and disappearance of sypmtoms. The splenic enlargement disappeared as did the anaemia. She is at present still under treatment. (I am indebted to Prof. G. A. Elliott for allowing me to see this patient.)

DISCUSSION

It is obvious that most of these patients described above would have died if they had not been treated with oxacillin ('prostaphlin'). The mortality of staphylococcal septicaemia before the introduction of the new anti-staphylococcal agents was approximately 77% in patients who acquired the infection in hospital, and 41% in patients who acquired the infection outside hospital.[3]

In one series of staphylococcal septicaemias the mortality of untreated cases was approximately 85%.[4] Penicillinase-producing staphylococci today cause more than 80% of significant staphylococcal infections and are largely responsible for the sevenfold increase in deaths from staphylococcal septicaemia reported from 1949 to 1959.[7]

Futhermore, the incidence of staphylococcal pneumonia after operation appears to be increasing in hospitals, and as a rule the staphylococcus is penicillin resistant. The mortality of staphylococcal pneumonia is still in the neighbourhood of 60 – 66% and, since in my experience this condition appears in the last year to be more common than postoperative pulmonary emboli, its importance is considerable. The introduction of newer antibiotics such as novobiocin, erythromycin, kanamycin and ristocetin have all helped to reduce the mortality to a considerable extent in all types of staphylococcal infection, but the mortality still remains extremely high and the organism has become resistant to most of these antibiotics. The introduction of methicillin ('staphcillin' and 'celbenin') has been a great advance, but is attended by the difficulty of 4-hourly intramuscular injection and the considerable expense involved. Oxacillin is said to be between 5 and 8 times more powerful than methicillin in similar concentrations and is acid-resistant, so that it can be given by mouth. This has been borne out by laboratory studies.[8] As shown by the few cases described above, the mortality from staphylococcal infection, when treated with this substance in adequate dosage, should be considerably lower than the previous mortality. This has been borne out in recent reports, in one of which 50 patients with staphylococcal infections responded very well in 40 cases and, in 10 cases, although the result was good, there was concomitant administration of other antibiotics.[5]

In a collected series of 111 patients with serious staphylococcal infection treated with oxacillin, 93 patients were cured, 16 were helped and 2 were not helped by the treatment.[6] Side-effects with oxacillin are negligible, and the only side-effects which I noted have been nausea in 2 patients. This was easily controlled by one of the phenothiazine group of drugs given by mouth. The average dose for overwhelming or severe infections should be at least 1 G. 4-hourly by mouth or intramuscular injection, and I am inclined to use 1 G. by mouth and 250 mg. by intramuscular injection 4-hourly in severe cases, as well as adding probenecid, 0·5 G. 6-hourly. However, some patients will do well on 500 mg. 4 – 6 hourly, and the dose depends entirely on the severity of the original infection and the resistance of the organism. When the dose appears to be insufficient it is always better to double it and add the probenecid to the regime. Treatment should be continued for not less than 21 days after any severe staphylococcal infection, otherwise relapse will frequently occur.

It is of interest that in addition to the above patients, I have treated one patient with recurrent boils of 12 years' duration, who was suffering from severe inanition and toxicity, with 500 mg. of oxacillin 6-hourly for 12 days, with complete disappearance of the boils on the 4th day and with no recurrence after 4 months. Five other cases of staphylococcal pneumonia following operation have been treated. These have been of lesser severity. Two have responded to the smaller dosage of oxacillin and

one responded to novobiocin, whereas the other two responded well to ampicillin ('penbritin').

It appears obvious that oxacillin is a very valuable addition to our therapeutic armamentarium, and is perhaps the greatest advance in antibiotic therapy since the discovery of penicillin itself. It is necessary, however, to add a warning that the drug should not be used for simple conditions such as boils or acne or in cases in which the organism is shown to be sensitive to some other antibiotic, since it is more than likely that some degree of resistance to oxacillin will develop in the future if its is used indiscriminately. A further point worthy of note is that although in several instances, particularly in Case 6, the *in vitro* tests did not demonstrate sensitivity to oxacillin, the result of using the drug has been dramatic. Often too, *in vitro* tests demonstrate sensitivity to some other antibiotic to which the organism does not respond clinically. This was the situation in Case 1 of this series. Thus, it is advisable to temper laboratory tests with clinical judgement, and where it appears probable that the staphylococcus is a penicillinase producer, oxacillin (prostaphlin) should be the drug of choice despite negative laboratory findings as regards sensitivity.

The recent discovery of fucidin (fusidic acid), which can also be given by mouth, makes it likely that this, in combination with oxacillin (prostaphlin), will control most staphylococcal infections, and it appears that a new era in the treatment of the staphylococcus has been opened.

SUMMARY

The use of oxacillin (prostaphlin) has been described in the treatment of severe staphylococcal infections. This drug appears to be the most convenient and certainly the most effective of all the drugs at present available against penicillin-resistant staphylococci. A warning is added against its indiscriminate use.

I wish to acknowledge the generosity of Bristol Laboratories in supplying adequate quantities of oxacillin (prostaphlin) for the above trials. I also wish to acknowledge the help of Mr. A. Shevitz of the photographic unit, Department of Medicine, University of the Witwatersrand, in the reproduction of the illustrations used for Case 1.

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