The treatment of severe staphylococcal infections

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Of the many fascinating aspects of staphylococcal infection, especially notable is the variety of their clinical manifestations. Table I outlines the more serious staphylococcal infections, some rare and others still surprisingly common. The persistent problem of serious staphylococcal infection is amply documented and shows no sign of vanishing. The organism has accounted for 18 per cent of isolates from blood culture at St George's Hospital in recent years, and Humble, Eykyn & Phillips (1980)

TABLE I
Syndromes of severe staphylococcal infection

Septicaemia	Severe skin sepsis	Food poisoning
Endocarditis	Scalded skin syndrome	Enterocolitis
Pneumonia	Breast abscess	
Osteomyelitis		
Arthritis		
Meningitis		
Renal carbuncle		

record 250 patients with staphylococcal bacteraemia during the last 10 years at St Thomas' Hospital. The older forms of infection are still with us but to them have been added, more recently, an increasing number of patients with serious infection complicating cardiac, vascular and orthopaedic prostheses, while the epidemic of intravenous drug abuse has brought a spate of staphylococcal septicaemia among many other infective complications. The death rate from staphylococcal septicaemia has always been high. Overall figures are of limited value since the prognosis depends greatly on the age of the patient and the existence and nature of pre-existing

disease. Mortality rates of 50 per cent or so were recorded in series collected during the hospital staphylococcal epidemic of the 1950s and 1960s, and rates as high as this are still found in groups of patients at special risk. The overall mortality rate has now diminished but is still substantial, for example, Nolan & Beaty (1976) record a mortality of 21 per cent of 105 patients. Since a large armamentarium of powerful anti-staphylococcal drugs is available (table II), and since clinical and microbiological diagnosis of serious staphylococcal infection is rarely difficult, this suggests that other problems, additional to those of ensuring effective *in vivo* antimicrobial action, have yet to be solved.

TABLE II

Antistaphylococcal antimicrobial agents

Penicillins	Fusidic acid
Cephalosporins and cephamycins	Co-trimoxazole
Erythromycin	Rifampicin
Clindamycin	(Tetracyclines)
Gentamicin	(Chloramphenicol)
Vancomycin	

Antimicrobial Treatment

Staphylococcal infections were influenced dramatically by the introduction of penicillin, but penicillin resistance is now so widespread in hospital and community that benzyl penicillin has long been unacceptable as sole initial treatment for serious staphylococcal sepsis. If the causative strain is indeed penicillin susceptible, this agent retains pride of place, but the main emphasis must now be put on the penicillinase-resistant compounds.

The evidence that penicillinase-resistant penicillins are capable of controlling and often curing serious staphylococcal infections is ample and needs no emphasis. There is some national variation in the agent most favoured, largely for historical and commercial reasons. Since the general decline in the use of methicillin, cloxacillin and flucloxacillin have been used most generally in Britain while in the USA nafcillin and methicillin are extensively employed. Some aspects of antimicrobial treatment are,

however, controversial and it is these which I intend to discuss. They are, first, the role of combination chemotherapy and the question of penicillin-tolerant strains; second, the proper duration of treatment; and third, the value of serum bactericidal tests and tests of combined antibacterial action in controlling chemotherapy.

Combination chemotherapy

Success in the treatment of staphylococcal septicaemia can often be achieved by the use of a single agent and many alleged failures of single drug treatment can be traced to errors in the detail of antibiotic usage. The old and often neglected questions must still be asked. Was the agent appropriate? Was it given in adequate dose, at the right intervals and for long enough? Did it reach the sites of infection? Was the failure really attributable to deficiency of antibacterial chemotherapy, or to some other cause?

There is, none the less, increasing evidence from *in vitro* experiments and in animal models that combination treatment may eradicate serious staphylococcal infection more rapidly and effectively than single drug treatment, and the possible importance of these findings to disease in man needs examining. Sande & Johnson (1975) showed, in the well known experimental model of endocarditis in rabbits, that penicillin with gentamicin, which exhibited antibacterial synergy *in vitro*, also acted more rapidly than did penicillin alone in eradicating staphylococci from the cardiac vegetations. Similar findings were made with a nafcillin–gentamicin combination (Sande & Courtney, 1976). All the rabbits became afebrile within 36 h of starting therapy with nafcillin alone or in combination with gentamicin, but the number of sterile vegetations was higher and the average staphylococcal count lower, in the animals given combination chemotherapy. Gentamicin alone gave no clinical or bacteriological response. A similar trend in favour of penicillin–aminoglycoside combinations was seen in acute experiments using intraperitoneal infection in mice (Steigbigel, Greenman & Remington, 1975). Whether these findings are relevant to the treatment of staphylococcal septicaemia, especially when accompanied by endocarditis, in man is still unknown. A retrospective study of 40 patients with *S. aureus* endocarditis showed no difference in mortality, 40 per cent, between those treated with a penicillin alone and those treated with a penicillin and gentamicin (Watanakunakorn & Baird, 1977). On the other hand, control of infection has sometimes apparently been achieved in individual patients by introducing synergic combinations after a long period of ineffective treatment with persistently positive blood cultures (Murray *et al.*, 1976).

The use of combination chemotherapy to achieve a full bactericidal effect has also been recommended in infection caused by penicillin-tolerant strains, and a short digression is needed to summarize the types of penicillin resistance found in staphylococci. First described and best known is that conferred by β-lactamase. The second is intrinsic resistance as exemplified by methicillin-resistant strains; the phrase 'drug-tolerant' was originally applied to this variety; now, however, a third form of resistance has been described and usage altered so that this last variety of resistance is known as penicillin tolerance. These strains, found fairly commonly in clinical infections, are penicillin-sensitive in tests of growth inhibition, i.e., show normal MIC values, but are killed only by much higher concentrations, so that the MBC/MIC ratio is high (Sabath *et al.*, 1977). The strains are apparently able to inhibit the autolytic enzyme necessary for the lethal action of penicillin. The importance of penicillin-tolerance is in dispute, especially since the striking differences between the MBC and the MIC during the first 24 h of the experiment are often no longer found on further incubation, but several authors have noted poor response to treatment in infections caused by tolerant strains, either to a penicillin or to vancomycin, and an improved response with combined therapy showing more effective bactericidal activity (Gopal, Bisno & Silverblatt, 1976; Faville *et al.*, 1978).

The discussion has mainly been concerned with penicillin-aminoglycoside combinations but another combination, penicillin-fusidic acid, has also been widely and successfully used in serious staphylococcal infections (Jensen & Lassen, 1969). Here it is feared that the powerful action and good tissue penetration of fusidic acid might be vitiated by the emergence of resistant mutants, since they occur in all staphylococcal populations and fusidic acid resistance develops after local treatment. Resistance to this antibiotic has not so far become a problem in systemic staphylococcal infection. Clinicians have also been hesitant to use fusidic acid because antagonism with penicillin can be shown *in vitro* for some strains (O'Grady & Greenwood, 1973). It is doubtful, however, if these findings are of clinical significance since a strong bactericidal effect was demonstrated for all strains with the penicillin–fusidic acid combination. Fusidic acid should not be lightly dismissed as a valuable agent in serious staphylococcal infection. It is easy to administer, can be given orally or intravenously, is not excreted by the kidney and is therefore not subject to difficulties of dosage in patients with renal failure, and is relatively non-toxic although Humble *et al.* (1980) have drawn attention to the frequency of transient jaundice after its use. By contrast, aminoglycosides are difficult to use, especially, as so often in severe septicaemia, when the

patient's renal function is poor and changing rapidly. These drugs cannot, in fact, be employed without elaborate skilled and expensive laboratory control.

The use of more than one agent is often necessary when penicillins are barred by the existence or development of serious allergic reactions. A cephalosporin is often then recommended, and these compounds have succeeded in curing many severe staphylococcal infections. There is, however, a substantial risk of cross-allergy between penicillins and cephalosporins, and a number of recorded failures with this group of compounds. Changes in treatment necessitated by antibiotic allergy or by poor bactericidal effect of initial single drug therapy often involve the use of unusual drugs or combinations, vancomycin, vancomycin and rifampicin, erythromycin and gentamicin, vancomycin and gentamicin and the choice of such combinations should be guided by preliminary tests of combined bactericidal activity.

It can be seen that drug combinations may be used for diverse reasons, in the hope of more effective control in life-threatening disease, in order to achieve full bactericidal action, especially with drug tolerant strains and when allergy to a principal drug has necessitated change of treatment, and in the hope of preventing the emergence of resistant strains.

These experimental and clinical findings do allow a tentative policy to be constructed for the antibiotic management of serious staphylococcal infections. I believe the evidence on combination chemotherapy is strong enough to recommend this as initial provisional treatment for staphylococcal endocarditis and for acutely advancing, life-threatening septicaemia even without initial evidence of endocarditis. Cloxacillin with gentamicin should be used initially in these very ill patients, with cloxacillin–fusidic acid as an acceptable alternative, initially or later in treatment, especially if aminoglycoside administration proves difficult or if evidence of the need for prolonged treatment emerges, for example, the development of osteomyelitis. Patients with known penicillin allergy should be given vancomycin, alone initially, but in combination if poor clinical response and the results of tests of combined antibacterial action indicate the need for this. These tentative policies are outlined in table III.

Duration of treatment. The possibility of late relapse, well recognized as a feature of the natural history of staphylococcal septicaemia, has tended to encourage prolonged treatment regimens. Since, however, long treatment courses incur increased risk of unwanted drug effects, inconvenience and cost, it is fair to ask if the indications for different durations of treatment could be better defined. Certainly in patients with endocarditis, partly by

analogy with relapse rates in other forms of endocarditis, treatment duration should not be less than four to six weeks. For the others, one useful clue lies in the presence or absence of primary foci of staphylococcal infection. Contrary to traditional textbook statements, patients with

TABLE III
Provisional treatment plan for staphylococcal infection

	Uncomplicated mild or moderate illnesses	Endocarditis and/or very ill and/or vascular prosthesis	Significant penicillin allergy
Initial	(Flu) cloxacillin	(Flu) cloxacillin + gentamicin or (Flu) cloxacillin + fusidic acid	Vancomycin or cephalosporin*
Good response	Continue 10–14 days	Continue 4–6 weeks	
Severe penicillin allergy	Change to vancomycin		
Poor† chemotherapeutic response	Change to combination therapy as indicated by bactericidal tests of patients serum and of antibiotic combinations		

* Do not use a cephalosporin if the history of penicillin allergy is one of severe reaction, e.g. anaphylaxis, angio-oedema, etc.
† Poor response is often not due to chemotherapeutic failure, e.g. untreated foci of infection, drug reactions. See text.

endocarditis rarely have an obvious primary focus of infection. By contrast, those with obvious primary foci leading to septicaemia usually do not have endocarditis and these can usually be cured by one or two weeks of antibiotic treatment, provided the focus of infection can be eliminated by drainage or removal (Nolan & Beaty, 1976; Musher & McKenzie, 1977).

Laboratory tests in the control of treatment

The essential background is good technique of culture from blood and other possible sources of infection, careful identification of isolates, and initial standard sensitivity testing. Estimation of serum concentrations is essential for aminoglycosides and certain other antimicrobials, notably vancomycin, to ensure adequate but not toxic levels. The additional tests often used in attempting to achieve optimal treatment are the serum bactericidal test, in which serial dilutions of the patient's serum are tested for their killing capacity on the isolate from his blood cultures; and tests of combined bactericidal action of different antibiotic combinations, usually done by the half chess board method.

It would be surprising if the complex relationships involving drug pharmacokinetics, and the relationship of conditions at different infection sites to the metabolic state of infecting organisms and their response to antimicrobial agents could be accurately mirrored by a simple *in vitro* test, and the value of such tests remain uncertain. Workers using experimental models of endocarditis have obtained conflicting results in attempting to correlate the results of serum bactericidal tests with success in treatment (Sande & Scheld, 1980). I believe that, in staphylococcal endocarditis and difficult staphylococcal septicaemia, serum bactericidal tests should be done at the end of a treatment period to obtain a rough serum bactericidal titre. This should ideally be 1:8 or greater. In practice, if the titre is inadequate but the patient's progress is satisfactory by every other criterion, no change of treatment need be implemented. If, however, a low titre coincides with poor drug response, changes should be made such as increased dosage or introduction of an additional agent, to increase the bactericidal action of the regimen. Combination tests can be used in a similar way. Again an *in vitro* test with each drug at a single concentration can hardly accurately reflect *in vivo* conditions, but such tests can nevertheless act as general guides to improve chemotherapy. The use of combination chemotherapy to induce full bactericidal action in drug tolerant strains has already been discussed and in several cases the change in management has been correlated with improved bactericidal capacity in the patient's serum and with clinical success. Faville *et al.* (1978) describe two patients receiving vancomycin for staphylococcal endocarditis who responded poorly. Both strains were vancomycin tolerant with an MBC/MIC ratio of at least 128. In both patients addition of rifampicin achieved immediate clinical improvement and negative blood cultures. Coinciding with this change, inhibitory titres in the patients' serum rose, from 1:16 to 1:64 in one patient and from 1:4 to

1:64 in the other; corresponding bactericidal titres rose 1:4 to 1:64 and from 1:2 to 1:8.

Non-antimicrobial aspects of treatment

Patients with serious staphylococcal infections sometimes deteriorate and die even when the diagnosis has been easily achieved and correct treatment rapidly instituted. This disappointingly common course cannot yet be explained in any precise way, although it is easy to note specific features which confer a bad prognosis. These are especially advancing age, severe immune suppression as background factors and, in the acute illness, the development of bacterial shock syndrome. Common additional problems are of water and electrolyte control and of progressive renal impairment, important both generally in management and specifically in the control of chemotherapy. Progressive anaemia, too, is common in severe septicaemia and needs correcting. In patients with endocarditis, haemodynamic function has to be frequently assessed with the aim of deferring necessary cardiac surgery, if at all possible, until infection has been at least controlled and preferably eradicated. Peripheral embolism may also complicate the clinical problems. In patients with staphylococcal infections complicating vascular prostheses, cure has occasionally been achieved with antimicrobial therapy alone. This is uncommon, however, and a planned programme combining optimal chemotherapy and further cardiac surgery must often be implemented.

The treatment of focal infection at sites other than the heart can also be surprisingly difficult. The possibility of undiagnosed collections of pus must always be considered, and modern imaging techniques have greatly improved the diagnosis of focal infections. The old surgical adage still applies, and foci of infection should be drained or removed as soon as possible.

DISCUSSION

It is evident that the available methods of treating staphylococcal infections are diverse and powerful, but that many problems are still unsolved. Of those relating to antimicrobials, the most immediate are to define more precisely the correct indications for, and methods of, combination chemotherapy, and the optimal ways of controlling chemotherapy by laboratory tests. It may be, too, that optimal chemotherapy for the initial stage of controlling rapidly advancing septicaemia may be different from that needed for the long term eradication of persistent staphylococcal infection. Of the general aspects, the chief risk is of death in the early days of

treatment not attributable to specifically identifiable disturbances such as bacterial shock, renal failure or heart failure. An analogy can be made with Austrian's observation that the death rate from pneumococcal bacteraemia during the first five days of hospital treatment was no different in the three eras, without specific treatment, with specific antiserum, or with penicillin (Austrian, 1963). Surely we are here witnessing, in systemic human disease, the consequences of an early decisive period of infection, so vividly demonstrated by A. A. Miles in local infections in guinea-pigs and now at last receiving its clinical application in the newer rational policies of surgical chemoprophylaxis. In these patients with rapidly lethal staphylococcal septicaemia the initial impact of their infection seems to produce rapid and sometimes irreversible forms of tissue damage, the nature of which is still quite obscure. It seems likely that these early deaths can only be reduced by more efficient prevention of staphylococcal disease and, in the future, by the development of methods of controlling and mitigating the effects of the early biochemical changes induced by severe infection.

References

AUSTRIAN, R. 1963. The current status of bacteremic pneumococcal pneumonia. Re-evaluation of an underemphasized clinical problem. *Transactions of the American College of Physicians,* **76**, 117.

FAVILLE, R. J., ZASKE, D. E., KAPLAN, E. L., CROSSLEY, K., SABATH, L. D. & QUIE, P. G. 1978. *S. aureus* endocarditis combined therapy with vancomycin and rifampicin. *J. Amer. med. Ass.* **240**, 1963.

GOPAL, V., BISNO, A. L. & SILVERBLATT, F. J. 1976. Failure of vancomycin treatment in *S. aureus* endocarditis. *J. Amer. med. Assoc.* **236**, 1604.

HUMBLE, M. W., EYKYN, S. J. & PHILLIPS, I. 1980. Staphylococcal bacteraemia, fusidic acid and jaundice. *Brit. med. J.* **280**, 1495.

JENSEN, K. & LASSEN, H. C. A. 1969. Combined treatment with antibacterial chemotherapeutic agents in staphylococcal infections. *Quart. J. Med.* **38**, 91.

MURRAY, H. W., WIGLEY, F. M., MANN, J. J. & ARTHUR, R. R. 1976. Combination antibiotic therapy in staphylococcal endocarditis. *Arch. Intern. Med.* **136**, 480.

MUSHER, D. M. & MCKENZIE, S. O. 1977. Infections due to *Staphylococcus aureus. Medicine,* **56**, 383.

NOLAN, C. M. & BEATY, H. N. 1976. *S. aureus* bacteraemia. Current clinical patterns. *Amer. J. Med.* **60**, 495.

O'GRADY, F. & GREENWOOD, D. 1973. Interactions between fusidic acid and penicillins. *J. med. Microbiol.,* **6**, 441.

SABATH, L. D., WHEELER, N., LAVERDIERE, M., BLAZEVIC, D. & WILKINSON, B. J. 1977. A new type of penicillin resistance of *S. aureus. Lancet,* **1**, 443.

SANDE, M. A. & JOHNSON, M. L. 1975. Antimicrobial therapy of experimental endocarditis caused by *S. aureus*. *J. inf. Dis.* **131,** 367.

SANDE, M. A. & COURTNEY, K. B. 1976. Nafcillin-gentamicin synergism in experimental staphylococcal endocarditis. *J. Lab. Clin. Med.* **88,** 118.

SANDE, M. A. & SCHELD, W. M., 1980. Combination antibiotic therapy of bacterial endocarditis. *Ann. Intern. Med.* **92,** 390.

STEIGBIGEL, R. T., GREENMAN, R. L. & REMINGTON, J. S. 1975. Antibiotic combinations in the treatment of experimental *S. aureus* infections. *J. inf. Dis.* **131,** 245.

WATANAKUNAKORN, C. & BAIRD, I. M. 1977. Prognostic factors in *S. aureus* endocarditis and results of therapy with a penicillin and gentamicin. *Am. J. Med. Sci.* **273,** 133.