Choice of chemotherapy for infection by *Staphylococcus aureus*

Problems of staphylococcal sepsis continue to threaten life and well-being and to perplex clinicians. All staphylococci are dangerous and some are more dangerous than others. Among the most fearsome are those showing multiple antibiotic resistance and resistance to mercury salts; these not only complicate therapeutic endeavour, but serve also as markers of high virulence or pathogenicity. Chemotherapy of systemic staphylococcal sepsis should proceed under consistent laboratory guidance excepting those initial emergencies where 'best guess' therapy must be invoked as a holding operation. In face of serious infection, antimicrobial agents, whether prescribed singly or in combination, must be selected according to efficacy, particularly in respect of multiply-resistant strains; bactericidal activity; potency and penetration; and toxicity. Cost becomes a secondary consideration in serious situations.

In terms of infection by *Staphylococcus aureus*, conditions which require especial consideration are bacteraemia and septicaemia, osteomyelitis, endocarditis and any infection such as brain or pulmonary abscess which may result in distortion or destruction of a vital organ. Infections which are potentially systemic or those which result in profound toxicity (including most bacteraemic states and, notably, toxic shock syndrome and toxic epidermal necrolysis) should be regarded as emergencies.

The usefulness of various single preparations and their antistaphylococcal effectiveness have been discussed elsewhere by this author (Williams, 1979a). β-Lactamase labile penicillins were discounted as antistaphylococcal agents despite their potency (and the near-perfection of benzylpenicillin as an antibiotic) because even a slight production of penicillinase can impair their efficacy, and many laboratories are unable to discern very low levels of penicillinase production. The semi-synthetic β-lactamase-resistant (isoxazolyl) penicillins were described as major agents, despite their comparatively low potency which may call for doubling or trebling of dosages in face of severe infection; incidence of staphylococcal resistance to these agents remains low. Properties of flucloxacillin, the latest commonly used agent in the series, have been described by Sutherland, Croyden & Rolinson (1970). Fusidic acid still holds its place as the major antistaphylococcal agent because of its potency, ability to penetrate tissues especially bone and meninges, and its high clinical efficacy. Most staphylococci are sensitive to this agent regardless of any other antibiotic resistances which they may display. The properties, activity and usage of fusidic acid have been reviewed by Anderson (1980).

Judgement on the ever-increasing number of cephalosporin derivatives must still be reserved at present; most modifications have impressive β-lactamase resistance (a point much emphasised by the manufacturers) but further clinical study is required before they can be regarded as first-line antistaphylococcal agents (Wise, 1978; Weinstein, 1980).

Erythromycin is a much under-used antibiotic which acts effectively and bactericidally against most staphylococci, but the incidence of staphylococcal resistance is sufficiently high for careful preliminary sensitivity testing to be essential. Clindamycin has high antistaphylococcal activity but is feared for its propensity, probably over-emphasized, to induce pseudomembranous enterocolitis (PME); this is a side-effect shared also by many other antimicrobial agents (reviewed by Williams, 1981a) and new aspects of aetiology of PME are being reported continuously. Co-trimoxazole has in my opinion no place whatever in the treatment of staphylococcal sepsis (Williams, 1979b, 1981b).

Aminoglycosides (those in common use being gentamicin, kanamycin, tobramycin, amikacin and netilmicin) have to be considered in relation to staphylococcal infection because they are widely invoked in wide-spectrum management of systemic infections of unknown causation. They are effective
against the majority of staphylococci, and impressively so in vitro, but should not be presented specifically as primary antistaphylococcal agents (Klimek & Quinthioni, 1977). Streptomycin has long been abandoned for treatment of staphylococcal infection.

Antibiotics which have been used in the past are chloramphenicol and tetracycline; these possess bacteriostatic action but are no longer considered as antistaphylococcal agents. Minocycline, a tetracycline derivative, is occasionally used to treat staphylococcal infection but usually in combination with another drug and may be utilized in localities where fusidic acid is not yet available (Yourassowsky et al., 1981).

Vancomycin is sometimes used for treatment of staphylococcal endocarditis and may be used as a drug of last resort in generalized staphylococcal sepsis; its extreme toxicity precludes routine use.

Rifampicin requires special mention. The tenet that it is a drug to be kept in reserve for treatment of mycobacterial infections only (Morrison-Smith, 1975) is gradually being eroded (Lancet, 1976); its value as an antistaphylococcal agent is unquestionable (Garrod, Lambert & O'Grady, 1973) and it has high bactericidal activity even against intraleucocytic staphylococci (Mandell & Vest, 1972). Staphylococcal populations usually include a small minority of rifampicin-resistant mutants; accordingly rifampicin should always be used in combination with another agent. Various combinations have been detailed by Nessi & Fowst (1979) who review combinations of rifampicin with erythromycin, gentamicin, kanamycin, lincomycin, vancomycin, pristinamycin and fusidic acid for treatment of serious staphylococcal infection. Jensen (1975) points out the bactericidal action of rifampicin plus fusidic acid and lists combinations of rifampicin with erythromycin, lincomycin and aminoglycosides.

In terms of antibiotic resistance, current concerns lie with the phenomenon of penicillin-tolerant staphylococci (Lancet, 1980) and numerous reports testify to the increasing incidence of gentamicin-resistant strains (Lancet, 1981). Despite the problems posed by such variants, choices from among the drugs listed still provide effective treatment, though therapy must always be prompt and aimed at maximum efficacy. Actual or potential systemic staphylococcal infection can easily go beyond control and any initial concept of phased efficacy in response to severity of symptoms is unjustifiable. The most effective available bactericidal regime must be adopted from the start.

In face of life-threatening infection, it is usual to exhibit a combination of chemically unrelated antibiotics—partly to eliminate any risk of selecting mutants resistant to either one of them (though this seems to be a fairly small risk in practice) but mainly to ensure a synergistic bactericidal combination. Such an approach is mandatory in management of staphylococcal endocarditis because of the unique situation of the infected lesion and the difficulty of achieving bactericidal levels within it.

Both choice and continued use of antimicrobial agents in face of any severe staphylococcal infection should be influenced by laboratory studies. However, in-vitro determinations may not always relate to the clinical response and a flexibility of approach should be maintained.

In pragmatic terms, given that the infecting bacterium under consideration displays suitable sensitivities, a combination of flucloxacillin or fusidic acid with each other or with erythromycin or rifampicin should cover most eventualities. Where the in-vitro antibiotic responses of the staphylococcus are not yet known, a combination of fusidic acid with rifampicin is likely to be the most effective choice.

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The conference opened with a look at the great advances in the diagnosis of infectious diarrhoea; in up to 80% of cases the causative agent can now be established. But, because of the delay in obtaining laboratory results, administration of specific antibiotic therapy still tends to be a clinical decision based upon the severity and possible invasiveness of the illness. The decision to use chemotherapy in campylobacter enteritis seems to be similar to that in salmonella or shigella infections, although there is no evidence that antibiotics prolong excretion of the organism. Strains of Campylobacter spp. are resistant to cotrimoxazole, sometimes resistant to ampicillin (30-40%) but only occasionally resistant to erythromycin. Gentamicin is maintained by some to be first choice therapy for the seriously ill but erythromycin is probably a more reasonable alternative for most patients in view of its lower toxicity.

Sub-inhibitory doses of antibiotics were noted to be of clinical benefit in another symposium, where in one presentation there was no difference in the outcome of Gram-negative sepsicaemia (36% fatality), whether peak concentrations were more or less than the MIC. The effects of sub-inhibitory levels of antibiotics on bacteria were discussed and it would seem that the effects range from changes in mucosal adherence to the depression of toxin and enzyme production and changes in morphology and the ability to withstand phagocytosis, all factors which could alter pathogenicity and allow the host defences, under certain circumstances, to cope more readily with the infection. Homeopathic doses of ampicillin (10 mg/day) were thus shown to be efficacious in the treatment of urinary tract infection. Further studies on the effects of low concentration of antibiotics on bacteria and of antibiotic interactions with the immune system, both beneficial and deleterious, obviously need to be pursued. It may be that there are other factors to consider, when dosing antibiotics, than the MIC of the infecting organism and obvious toxicity problems.

At the symposium on β-lactamases their multiplicity of types was emphasized although TEM 1 is by far the most prevalent. Often they are coded for on plasmids or transposons which explains their wide distribution among species of clinical relevance. However, their mediation by plasmids ensures that their distribution is neither geographically nor clinically uniform and they are often less able to protect bacteria than would appear likely from in-vitro studies. Despite this an array of β-lactamase inhibitors is being developed including clavulanic acid, penam derivatives such as β-bromopenicillanic acid and penicillanic acid sulphone and recently a naturally occurring agent izumenolide has been discovered. Although interesting, their clinical use remains to be established and clinical trials with these substances are awaited.