Leading articles

Prophylactic antibiotics for total hip arthroplasty—the significance of *Staphylococcus epidermidis*

Deep wound sepsis following total hip arthroplasty is a serious complication. Antimicrobial therapy, even in combination with surgical debridement and wound closure over an irrigation-suction system, rarely enables the patient to keep the prosthesis. In a large series of 3215 total hip arthroplasties reported recently from the Mayo Clinic, deep wound sepsis occurred in 1-3% of hips. *Staphylococcus aureus* was the commonest bacterial isolate, followed by *Staphylococcus epidermidis* (Fitzgerald et al., 1977). While some cases of deep wound sepsis are haematogenous in origin, it is probable that the majority result from the introduction of airborne bacteria at the time of surgery. Charnley & Eftekhar (1969) reduced their infection rate by operating in a specialized orthopaedic theatre with virtually sterile air. Since this is impractical in most units, an alternative approach to the reduction of sepsis rates has been the use of parenteral prophylactic antibiotics. The difficulty of establishing the efficacy of prophylactic antibiotics in an operation which has as inherently low a sepsis rate as total hip arthroplasty is well known. The results of additional follow-up of Ericson's 1973 study (Carlsson, Lidgren & Lindberg, 1977) suggest that prophylactic antibiotics can reduce the incidence of deep wound sepsis in total hip arthroplasty, but confirmation will require a controlled trial with large numbers of patients and prolonged follow-up. The best antibiotic for this purpose is not known. In many centres a single agent is used for antibiotic prophylaxis, either a β-lactamase resistant penicillin or a cephalosporin, as recommended by the Medical Letter (1977) and the Veterans Administration (Kunin, 1977).

Since no one antibiotic has been demonstrated to be superior to another as a prophylactic agent for total hip arthroplasty, the main considerations in selecting an antibiotic for this purpose are the *in vitro* sensitivities of the organisms most likely to be isolated from deep wound sepsis and the ability of the antibiotic to achieve adequate levels in bone. On account of the frequency with which *Staph. aureus* and *Staph. epidermidis* are isolated from deep wound infections following total hip arthroplasty, it is considered important to select a prophylactic agent with anti-staphylococcal activity. However, while methicillin-resistant *Staph. aureus* remains uncommon in most centres, the frequent methicillin-resistance of *Staph. epidermidis* is being increasingly recognized as cause for concern. In one series of prosthetic valve endocarditis, 70% of *Staph. epidermidis* isolates were resistant to methicillin (Johnson, 1976). Other laboratories, reporting a much lower incidence of methicillin-resistant *Staph. epidermidis*, have included in their reported isolates strains which were isolated from mixed infections and which were probably skin contaminants (Sabath et al., 1968). In part, centre to centre variation may be due to failure of conventional susceptibility testing to detect the methicillin-resistant subpopulation of cells. In *Staph. epidermidis*, as in *Staph. aureus*, the phenotypic expression of methicillin resistance is enhanced by the use of hypertonic media, low incubation temperature and prolonged incubation. Two authors have recently investigated the extent to which methicillin-resistant *Staph. epidermidis* exhibits cross-resistance to the cephalosporins. Laverdiere and his colleagues showed that, as with methicillin-resistant *Staph. aureus*, the standardized disc diffusion test may fail to detect cross-resistance to the cephalosporins in methicillin-resistant *Staph. epidermidis* (Laverdiere et al., 1978). Whereas 36 of their strains of methicillin-resistant *Staph. epidermidis* were susceptible to cephalexin by a standardized disc diffusion method, only 23 strains were susceptible by agar dilution and only 11 strains were both inhibited and killed by 6-25 mg/l. of cephalexin. Archer (1978), investigating *Staph. epidermidis* isolates from infected cerebrospinal fluid shunts and pros-
Artificial valve endocarditis, found subpopulations resistant to cephalothin in every methicillin-resistant isolate tested but their frequency was very low ($10^{-4.4}$).

The clinical significance of these methicillin and cephalothin-resistant subpopulations in *Staph. epidermidis* is unclear and it is likely that clarification will be difficult in view of the fact that there is still no agreement as to the significance of methicillin-resistant subpopulations in *Staph. aureus*. While Acar, Courvalin & Chabbert (1970) reported treatment failure when cephalosporin antibiotics were used to treat methicillin-resistant *Staph. aureus* infections, Lacey (1974) considered that there was no convincing evidence that methicillin-resistance was responsible for the treatment failure. In some institutions methicillin-resistant *Staph. epidermidis* is recognized as a significant problem. Having seen three cases of *Staph. epidermidis* prosthetic valve endocarditis in patients who had received cephalothin prophylactically, Laverdiere and his colleagues recommend that consideration be given to a combination of gentamicin and cephalothin for prophylaxis for open-heart surgery (Laverdiere et al., 1978). Since the situation in total hip arthroplasty is analogous to open-heart surgery in that the perioperative use of antibiotics is aimed at preventing infection with skin organisms introduced at the time of operation, and since the Papworth regime for prophylaxis for open-heart surgery (parenteral benzylpenicillin, cloxacillin and gentamicin) has so successfully prevented prosthetic valve endocarditis (Newsom, 1978), it seems pertinent to question the adequacy of a single antimicrobial agent for prophylaxis for total hip arthroplasty. If in addition to a β-lactamase resistant penicillin or a cephalosporin, a second prophylactic agent is to be used in total hip arthroplasty, gentamicin would seem to be a reasonable choice. Archer (1978) tested 18 antibiotics against methicillin-sensitive and methicillin-resistant *Staph. epidermidis* isolates from infected prosthetic devices and found that, with the exception of rifampicin, gentamicin had the lowest MICs and MBCs of any of the agents tested. Several areas require further study. The first is cephalothin-gentamicin interaction against *Staph. epidermidis*. While Hammond & Stiver (1978) found the combination synergistic *in vitro* against five strains of *Staph. epidermidis* from prosthetic valve endocarditis, Lowy (1977), in a mouse model of intraperitoneal infection with *Staph. epidermidis*, found decreased survival with cephalothin and gentamicin, as compared to gentamicin alone. Secondly, conflicting results have been published with regard to levels attained in normal bone after parenteral administration of gentamicin (Wiggins et al., 1978; Smilack, Flittie & Williams, 1976). This problem is not unique to gentamicin as conflicting results with regard to bone penetration have also been obtained with cephalothin and cefazolin, antibiotics currently used for prophylaxis for total hip arthroplasty. Lastly, if gentamicin is to be used for prophylaxis for total hip arthroplasty, there is the question of route of administration. An alternative to parenteral administration would be the incorporation of gentamicin into the acrylic cement, an approach which, to date, has been used mainly for revision procedures (Carlsson, Josefsson & Lindberg, 1978). None of these questions are likely to be answered in the near future. Meanwhile, in view of the disastrous consequences of deep wound infection in total hip arthroplasty, it might be prudent to select prophylactic antibiotics with a broader spectrum of coverage than that provided by a β-lactamase resistant penicillin or a cephalosporin.

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References


Erythromycin revisited

Erythromycin, isolated in 1952 from the metabolic products of Streptomyces erythreus, has withstood the test of time and, surprisingly, specific indications for its use continue to increase.

No serious toxic effects have been recorded from the administration of erythromycin base and, apart from the problem of hepatotoxicity of the estolate preparation, there is no doubt that erythromycin is one of the safest antibiotics in current use (Garrod, Lambert & O'Grady, 1973). The cholestatic jaundice, usually reversible, occasionally encountered with erythromycin estolate (Braun, 1969) remains the only serious adverse reaction, although mild gastrointestinal effects do occur.

The stearate and ethyl succinate preparations are suitable alternatives to the estolate, and, despite the lower plasma levels with these salts (Griffith & Black, 1969; Bell, 1971), therapeutic efficacy appears to be comparable. Intramuscular administration should be avoided as the injection is painful and, due to insolubility of the ethyl succinate, a volume of 10 ml is required for a 500 mg dose. The recommended intramuscular dose is 100 mg in 2 ml but the mean peak level after one hour is only 0.64 mg/l (Metzger et al., 1959) and even this may not reflect the level of active erythromycin base. The minimum inhibitory concentration (MIC) of erythromycin for Staphylococcus aureus is 0.5 mg/l illustrating the inadequacy of erythromycin administered by this route. Intravenous injection is indicated if parenteral therapy is considered necessary.

In the 1950s the value of erythromycin against Staphylococcus aureus at a time of increasing penicillin-resistance led to official warnings against unrestricted prescription. As a result, erythromycin was seldom used except when specifically indicated (Leading Article, 1956). This policy was probably unnecessary as in recent years with the increasing use of erythromycin, widespread staphylococcal resistance has not proved to be a significant problem. Resistance to erythromycin, and occasionally multiple resistance, may occur but withdrawal of the antibiotic produces a rapid fall in the number of resistant strains (Forfar, 1977; Lilly & Lowbury, 1978). Resistance is not plasmid-mediated but selective multiplication occurs during treatment. However, it appears that resistant strains are disadvantaged compared with sensitive strains which tend to reappear on withdrawal of the antibiotic.

Erythromycin has long been used as an alternative to penicillin in the treatment of streptococcal infections and for the prophylaxis of rheumatic fever in penicillin-allergic patients. In patients with heart valve lesions taking long-term oral penicillin, erythromycin has been recommended by the American Heart Association for prophylactic use during...