


**Systemic antibiotic prophylaxis in surgery**

In principle, three basic factors, acting singly or in combination, appear to be responsible for the development of post-operative wound infection. These are: (1) a bacterial inoculum of sufficient number and virulence; (2) a local substrate upon which the contaminating microbes can live and propagate; and (3) some impairment in host defences—local or systemic. Preventive measures, such as antibiotic skin preparation and operation within a relatively sterile environment, represent attempts to reduce the bacterial inoculum. However, once contamination has occurred, the size of the inoculum can still be diminished by careful wound toilet and application of topical antibiotics. On the other hand, creating a wound that is less hospitable to bacterial colonization and subsequent infection depends primarily upon the dedication and ability of the surgeon: his gentle handling of tissues in order to prevent clot and cellular necrosis. In this setting, the prophylactic role of a parenterally administered antibiotic is merely to increase local tissue resistance against the invading pathogens, and based on the work of Burke (1961) and later supported by other investigators (Bernard & Cole, 1964; Brøtø, 1978; Polk & Lopez-Mayor, 1969; Stone et al., 1976) it is now generally accepted that antibacterial supplementation of normal host defences must be present in the tissues before bacterial contamination, and serves no purpose if present more than 4 h after the period of bacterial contamination is ended. Accordingly, if antibiotic prophylaxis is indicated, *drug administration should be started prior to operation*.

At present, prophylactic therapy seems indicated whenever: (1) the consequences of wound infection are uniformly disastrous, even though the occurrence of this infection is uncommon; (2) the incidence of wound infection is great even though it seldom threatens life or limb; and (3) the patient has such an extreme impairment in host defence mechanisms that any infection, no matter how minor, has a propensity for becoming systemic and thereby fatal.

Usually, antibiotics are of no value in clean surgery. On the other hand, antibiotic cover may be advisable if the consequences of chance contamination may be disastrous, as in open heart surgery or the insertion of hip prosthesis. In hip replacement, however, excellent results have been obtained without using antibiotic cover. Charnley (1972)—who had performed more than 6000 operations as early as in 1970—has reported a decrease in infection rate between 1960 and 1970 from 7% to less than 1%. He feels that this reduction was due to operation in ultraclean air ('greenhouse')—a reduction to 1–5%—and measures taken to stop bacteria from penetrating the surgeons gown (aspiration suits)—a further reduction to 0.5%.

Such ultra-clean air facilities, however, are not widely available, and other methods to reduce infection include prophylactic antibiotics given systemically, applied locally to the wound or introduced into the cement. Several studies in conventional operating theatres have demonstrated that the rate of deep infections in hip replacement can be reduced to approximately 1% when systemic antibiotic prophylaxis is used. In the great majority of these studies, antibiotic cover has been used for several days up till two weeks. Recently, Pollard et al. (1979) at the Middlesex Hospital, London in a controlled prospective study of 297 patients undergoing a total of 310 hip replacements found that three doses of 1 g cephaloridine—one dose given when anaesthesia was induced and the remaining two 6 and 12 h later—were as effective as a 2-week regimen of flucloxacillin, the overall infection rate being 1–3%. So in this situation, antibiotic cover for only one day may be adequate.

It is generally accepted that antibiotic prophylaxis should be given to patients undergoing cardiac valvular replacement since the mortality from prosthetic endocarditis has been high, usually 30 to 40%. But to the best of our knowledge, no properly conducted study, i.e. double blind, randomized, prospective study has been published on this problem. It should, however, be mentioned that the incidence of mediastinal wound infections following valvular implan-
tation under antibiotic cover has been reported to be as low as 1.4% (Engelman et al., 1973). Meyerowitz et al. (1977) reported a randomized prospective study of the relative effectiveness of broadspectrum (cephalothin) versus specific antistaphylococcal (methicillin) antibiotic prophylaxis in open-heart surgery. The patients were assigned randomly to receive either 4 g/day of cephalothin or 2 g/day of methicillin (adults) beginning the night before operation and continuing for one week post-operatively. In the cephalothin group, 2 of 132 patients developed wound infection and none bacterial endocarditis compared to 1 and 11, respectively, of the 129 patients in the methicillin group. Two grams methicillin per day is a low dose for adult patients and if one can assume that this drug did not do any harm, it seems that cephalothin prophylaxis may be of value in valve replacement. However, more extensive studies of antibiotic prophylaxis in this setting are needed, particularly on the length of treatment.

The mortality from bacterial endocarditis is still high and prevention is important. It has, therefore, been recommended that patients with acquired or congenital valvular heart disease and inserted valve prosthesis should receive antibiotic prophylaxis when undergoing surgery or instrumentation of the gastrointestinal or genitourinary tract, dental extraction or delivery (American Heart Association, 1972). However, these recommendations are not based on controlled trials, and clinical experience indicates that the prophylactic measures may be of questionable value. Whether ethical considerations would preclude controlled clinical trials is still a matter of debate.

Whether antibiotic cover should be given to patients undergoing coronary bypass operations is not well known. However, the incidence of mediastinal wound infection in patients undergoing myocardial revascularisation under antibiotic cover has been as low as 2.7% (Engelman et al., 1973). More recently, Sutherland et al. (1977) examined the frequency of chest wound infections in a prospectively randomized study of 904 patients. 451 received systemic antibiotics before and after operation and 453 patients received no systemic antibiotic cover. There was no significant difference in infection rate between the two groups. However, patients receiving antibiotics had a variety of infective organisms and almost all of those not receiving antibiotics had Staphylococcus aureus infections. It seems, therefore, that systemic antibiotic cover is not necessary in coronary bypass operations.

The efficacy of antibiotic cover in peripheral vascular surgery has also been debated. Controlled studies have been lacking partly because the low wound infection rate associated with this type of surgery would require a study of very large size to achieve statistically significant results. In 1978, however, Kaiser et al. (1978) reported on a randomized, prospective, double-blind study of cephazolin (1 g pre-operatively and 1 g post-operatively every 6 h for 24 h) versus placebo during 565 arterial reconstructive operations. Among the 462 patients undergoing surgery of the abdominal aorta and lower extremity arteries, there was a highly significant difference in the infection rates: 6.8% for placebo recipients versus 0.9% for cephazolin recipients. Of the 18 infections, four involved vascular grafts and all four occurred in the placebo group. No infections occurred among 103 brachiocephalic procedures. Accordingly, a brief peri-operative course of cephalothin was recommended in vascular reconstructive surgery of the abdominal aorta and lower extremity vessels.

Nowhere has the significance of antibiotic prophylaxis been more extensively debated than in patients undergoing gastrointestinal surgery, particularly elective colonic surgery. Surgeons have used non-absorbable sulphonamides, oral kanamycin, oral neomycin and a variety of other agents with enthusiastic reports of efficacy. Only during recent years, however, controlled trials have appeared. Washington et al. (1974) in a series of elective colectomies randomized patients to oral neomycin alone, neomycin and tetracycline and placebo. Whereas oral neomycin and placebo permitted infection to occur in almost 33% of patients, the combination of neomycin and tetracycline reduced the incidence of wound infection to 5%. Almost 10% of patients who received neomycin or placebo developed a faecal fistula or had wound separations. There were no faecal fistulae or wound separations in 65 patients randomized to receive the combination of neomycin and tetracycline. Using only a tetracycline (doxycycline), Hajer (1976) experienced similar results. Regimens that do not include anaerobes in their spectrum seem to be less effective in preventing wound infections after colonic surgery. On the other hand, metronidazole, which is effective only against anaerobes, seems highly satisfactory.
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(Willis et al., 1977). In our hospital, 56 patients undergoing elective surgery of the colon and rectum were assigned to a prospective, randomized, double-blind study, 25 patients receiving metronidazole 2000 mg the day before surgery and 1200 mg daily for 5 days post-operatively and 31 patients placebo (Bjerkeseth & Digranes, 1980). Wound infection and sepsis occurred in 35% of the patients in the placebo group and in only 4% of the metronidazole group. This study was performed 3 to 4 years ago. Since then metronidazole has been given in this type of surgery and the infection rate has remained at 3 to 4%. So far, the sensitivity of the anaerobes to the imidazole agent has not changed, and we feel that this is a good drug in this situation.

Biliary tract surgery is often complicated by infection if the bile is infected at surgery. Factors such as presence of acute cholecystitis, common duct stones, biliary obstruction and age greater than 70 years are all indicators of infected bile, and these patients should be considered for prophylaxis. Unfortunately, studies to date in this population have been inadequate.

In gastric surgery, patients with no bacteria or low numbers (< 5 x 10⁴/ml) in gastric aspirates (i.e. patients with duodenal or gastric ulcers) have much lower incidence of wound infection than patients with large numbers of bacteria (> 5 x 10⁴/ml) i.e. cancer patients (Gatehouse et al., 1978). So in cancer patients, antibiotic prophylaxis seems indicated (Stone et al., 1976).

In most fields of gynaecologic-obstetric surgery antibiotic prophylaxis still remains an unresolved issue. The single area in gynaecology where antibiotic cover seems to be of unquestionable value is in vaginal hysterectomy in premenopausal patients (Leder, Sweet & Headington, 1973). Vaginal tubal ligation seems to be a second area in gynaecology where antibiotic cover seems to be of unquestionable value is in vaginal surgery of the colon and rectum. Surgery (1980), in press.


New cephalosporins and related compounds

Recently cephalosporins and related compounds have been developed that possess high activity against enterobacteria and at least some activity against *Pseudomonas aeruginosa*. The properties of several such compounds were reported at the 11th International Congress of Chemotherapy held in October 1979 (the proceedings being published as *Current Chemotherapy and Infectious Disease* by the American Society for Microbiology, Washington, D.C. 1980). It seems, therefore, an appropriate time to take stock of the situation.

Cefotaxime (HR 756) was developed first and can be used as a standard against which other compounds are judged. Cefotaxime has a broad spectrum of activity with, in addition to high activity against all species of enterobacteria, *Haemophilus* spp. and *Neisseria* spp., activity against *Acinetobacter* spp., most isolates of *P. aeruginosa* and some other pseudomonads, most anaerobes and most staphylococci and streptococci, but not methicillin-resistant staphylococci or *Streptococcus faecalis*. However, it is less active than cephaloridine against staphylococci and streptococci. Some doubt remains about the usefulness of its activity against the *Bacteroides fragilis* group since, although it is slightly more active than cefoxitin when a small inoculum (10^4 colony forming units or less) is tested, there is rather more inoculum effect than with cefoxitin (Wise *et al.*, 1978; King *et al.*, 1980). Very large inoculum effects on the activity of cefotaxime against enterobacteria have been observed, but the mechanism and relevance of this phenomenon are not yet known (Neu *et al.*, 1979a; King *et al.*, 1980). Cefotaxime resembles cefuroxime in stability to β-lactamases, being resistant to most but hydrolysed by the enzymes from *B. fragilis* and *Proteus vulgaris* (Fu & Neu, 1978; King *et al.*, 1980). High blood levels of cefotaxime can be achieved; reported concentrations after an intravenous dose of 2 g range from 40 to 300 mg/l with a half-life of 1 to 6 h (Lüthy *et al.*, 1979, Gialdroni Grassi *et al.*, 1980; Ho *et al.*, 1980; Wittmann & Schassan, 1980). Some of the discrepancies may be accounted for by difficulties in assaying the compound. Like cephalothin, cefotaxime is deacetylated in the body (White *et al.*, 1980; Wise *et al.*, 1980). The desacetyl metabolite is 4- to 16-fold less active than cefotaxime against some organisms (*Escherichia coli*, *Klebsiella* spp., *Proteus mirabilis*, *Staphylococcus aureus*) and virtually inactive against others (*Proteus* *morganii*, *P. aeruginosa*) (Wise *et al.*, 1980). The deacetylation also occurs in vitro in serum or urine, rapidly if haemolysis has occurred (White *et al.*, 1980). Thus misleading results may be obtained if samples are stored under unsuitable conditions before assay. Clinical experience with cefotaxime is limited, but impressions so far are favourable (Clumeeke *et al.*, 1980; McKendrick, Geddes & Wise, 1980; Newsom *et al.*, 1980).

LY127935 (6059S) is not a cephalosporin but is a 1 oxo-β-lactam compound with the 7-methoxy group characteristic of the cephalosporins. Its antibacterial activity is similar to.