Today's Treatment

Use of antibiotics

Endocarditis

CELIA OAKLEY

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Infective endocarditis usually affects a heart valve but less often a septal defect, mural endocardium, or a coarctation or arteriovenous shunt. The last two are more properly referred to as endarteritis. The infection is usually bacterial but may also result from colonisation with coxiella (which causes Q fever) or chlamydia (which causes psittacosis). These organisms are cell dependent and do not grow on blood culture. Fungal infection may also occur but not as a primary event; it may follow cardiac surgery, complicate antibiotic treatment of bacterial endocarditis, or develop in patients on immunosuppressive treatment. Fungal spores almost always gain access through intravenous lines.

Diagnosis is essentially clinical, and confirmation is usually based on the circumstantial evidence, from positive blood cultures or on serological tests in the case of coxiella or chlamydia. In patients with bacterial infection who have already received some antibiotic the results of blood cultures may be persistently negative, and drug treatment has to be based on clinical judgment. A "tissue" diagnosis can be made only in cases who have emergency surgery because of valve destruction or when an infected embolus is removed from a limb artery and the infecting organism recovered from this.

Clinical diagnosis

The clinical diagnosis depends on recognising the classic triad: (a) signs of infection, (b) signs of embolism, and (c) signs of heart disorder.¹

If diagnosed early there is only unexplained fever and malaise in a patient who usually has evidence of a cardiac abnormality. Although embolism of vegetations may occur, many of the classic signs depend on local immunological reactions rather than on embolism itself.

Infective endocarditis may be divided into three clinical groups, which have relevance to the likely cause of the infection. This is important when choosing which appropriate antibiotic combination to start while awaiting the results of blood cultures.

Medical infective endocarditis—About 80% of these infections are caused by streptococci of the viridans group, 10% by enteric cocci, and 10% by other organisms. Most of these infections are "subacute", although the acuteness of the illness depends largely on the host and to a less extent on the organism. Older patients contribute an increasing proportion of the

cases, and they tend to have a lower incidence of viridans streptococci and a higher proportion of enteric organisms, including occasional Gram-negative infections.

Surgical patients—Patients who have recently undergone cardiac surgery form an important subgroup. Since these patients have nearly always received parenteral prophylactic antibiotic treatment to "cover" surgery, their infections are caused by organisms that are resistant to the common antibiotics, with a high proportion of opportunistic infections due to diphtheroids, *Staphylococcus epidermidis*, microaerophilic streptococci, and fungi. These infections are hard to prove by positive blood cultures.

Infections that appear late after surgery tend to be similar to those in the medical patients with the important exception that fungal endocarditis may pursue such an indolent course with so little constitutional reaction that presentation may be delayed a year or even two or more years after the cardiac surgery at which the fungus had gained access.

Infective endocarditis in drug addicts—The use of unsterilised syringes with water obtained from any convenient source, including the lavatory pan, may lead to multiple infection in drug addicts. The infecting inoculum is large and often infects the tricuspid valve, this being the first valve that the infected bolus reaches.

Treatment

Treatment should begin as soon as blood cultures have been taken because valve destruction is often remarkably early, occurring during the period of unchecked bacterial multiplication. Between four and six blood cultures should be taken over an hour or two. There is no virtue in spacing the blood cultures or in taking arterial or marrow cultures. Bacteraemia is constant except in patients who have already received antibiotics, and treatment should be relevant to the likely organism.

DURATION OF TREATMENT

The choice of drugs and duration of treatment depends on four considerations: (a) the infecting organism, (b) the duration of symptoms before treatment started, (c) the rapidity of the patient's clinical response, and (d) whether the patient has a prosthetic valve or other foreign material within the heart.

The absolute minimum period of treatment is three weeks. Any patient with an artificial valve should be treated for at least six weeks. The longest period of treatment is needed for fungus infections, and many of these should be treated by surgical excision because of the toxicity and relatively low efficacy of the antifungal drugs.

The antibiotic chosen should always be bactericidal towards

the isolated infecting organism as determined by in-vitro tube dilution tests to determine the minimum lethal concentration. Disc testing for bacteriostatic activity is inappropriate. The peak plasma concentration should be at least six times the in-vitro minimum lethal concentration.

ROUTE OF ADMINISTRATION

There used to be controversy about the relative merits of sustained blood levels versus high peaks and low troughs. For promptly diagnosed infections due to highly sensitive organisms this may not matter, but generally treatment should aim at achieving high peak concentrations. Parenteral treatment will probably be more effective than oral treatment once an infection has become entrenched, because the distance between the bacteria walled within an avascular fibrin platelet vegetation and the blood vessels conveying the antibiotics may be considerable. This diffusion gradient must be allowed for in planning treatment. In addition, many antibiotics react with, and are inactivated by, infusion fluids so that in planning parenteral treatment the antibiotic must not be added to the infusion bottle. Most antibiotics may be injected safely as a bolus through the side arm of an intravenous needle or subclavian venous line, thereby achieving a short-lived high peak with little loss of bacterial activity. The aminoglycosides are an exception: they should be given intramuscularly to avoid toxicity, which is related to peak concentration. Fortunately, they are low-volume injections and much less painful than penicillin by the intramuscular route.

Indwelling cannulae into arm or leg veins should be avoided because of the slow venous return and high risk of phlebitis with secondary invaders, which are resistant to the antibiotics given, particularly staphylococci and fungi. A central subclavian venous line is suitable. Alternatively, thin-walled needles in peripheral veins can be used, provided they are not left in longer than 48 hours. A combined fungicidal/antistaphylococcal skin cream provides further protection. Subclavian lines should be inserted under full sterile precautions. Their advantages are that flow is rapid, thrombosis is rare, and the same line can be left in for weeks. Furthermore, a subclavian cannula leaves the patient's arms unencumbered, and he can walk about reasonably freely with his drip stand. When the line is taken out the tip should be cultured to ensure that it is sterile.

CHOICE OF DRUGS

In most medical patients treatment should begin with penicillin G, 10 megaunits/24 hours, combined with an aminoglycoside such as gentamicin, 80 mg thrice daily. For most infections with *Streptococcus viridans* penicillin G alone is effective, and the aminoglycoside may be dropped once the blood culture reports are back. Some bacteriologists favour the use of high-dosage erythromycin for the final week of the antibiotic course to kill any residual forms of bacteria, which may be penicillin resistant.

The viridans groups of haemolytic streptococci comprise several different organisms (*Strep mutans*, *Strep mitis*, and *Strep sanguis*, for example). It is important, therefore, for the bacteriologist to determine the exact behaviour of the organism in relation to the continuation or not of an aminoglycoside as well as penicillin. Probenecid is no longer recommended to boost penicillin concentrations, because by blocking renal excretion of penicillin it tends to produce more sustained penicillin concentrations without raising the peak concentrations, which depend on the size of the injected bolus. Although oral amoxycillin has recently been successful in treating these infections, its use should be confined to early diagnosed cases, and it is too soon yet to comment on the relapse rate.

Streptococcus faecalis is resistant to penicillin or streptomycin alone, and synergism between these two antibiotics was first shown when the combination was found to be effective against this organism. Gentamicin is now usually preferred. The dose

of gentamicin needs to be determined according to blood concentrations to avoid eighth nerve toxicity. Peaks should not exceed 14 mg/ml nor be less than 5 mg/ml.

Staphylococcal endocarditis—*Staph albus* as well as *Staph aureus* may cause endocarditis and a coagulase-negative staphylococcus should not be dismissed as a contaminant, particularly in postoperative cardiac patients. Benzyl penicillin should always be used if the organism is sensitive to it, but most strains are now resistant because they produce penicillinase.² If so, either cloxacillin or flucloxacillin should be used in combination with fusidic acid.

Culture-negative endocarditis—The usual explanation is recent antibiotic treatment but there should be immediate suspicion of infection by coxiella or chlamydia, which are cell-dependent organisms of a size intermediate between a virus and a bacterium. Coxiella usually produces a low-grade indolent illness, often with nephritis and sometimes with hepatitis; it is not confined to country folks and is commoner than used to be realised. Chlamydia infection has been recognised more recently. It is usually transmitted by pet birds, and the budgerigar need not necessarily even have been ill. Diagnosis is by serological testing, but the organisms may be found intracellularly in the infected valve at surgery. Tetracycline is still the drug of choice because there is not yet a more effective one. It should be given by mouth in a dose of 2 g thrice daily, which should be reduced after clinical improvement has become evident down to an eventual minimal maintenance dose of 250 mg twice daily. It is probably impossible to do more than prevent multiplication of the organisms, and eradication of the infection requires surgical excision of the infected valve.

Fungal endocarditis is usually caused by candida, but aspergillus and other fungi are also seen. Endocarditis induced by candida and aspergillus may occur in patients with intravascular catheters who are receiving steroids, broad-spectrum antibiotics, or cytotoxic agents. Parenteral feeding of debilitated patients who are also receiving antibiotics carries the risk of conveying secondary infection. The course is usually subacute or positively indolent. Large friable vegetations develop and eventually give rise to large emboli. Unfortunately, blood cultures are often sterile so that confirmation of the infection is difficult until the disorder is advanced or an embolus occurs. Moreover, antifungal chemotherapy is fungistatic rather than fungicidal, and eradication is difficult. Amphotericin B and flucytosine are both toxic to the liver and kidneys, and amphotericin B is sensitive to light, has to be given intravenously, and tends to produce venous thrombosis; there is some advantage in giving them in combination, but some candida are insensitive to flucytosine.

Indications for surgery

Surgery may be needed because of acute haemodynamic catastrophes, particularly acute aortic regurgitation and, less often, acute mitral regurgitation. These can brook no delay in completing or, indeed, even starting antibiotic treatment.

Surgical excision is often the only way to eradicate fungal or coxiella infection, particularly if a prosthesis has become infected.

Another common reason for surgery is to eradicate an aortic root paravalvular abscess even when the infecting organism is sensitive to the administered antibiotics on in-vitro testing. This may be suspected because of the development of a conduction system fault or even a pericardial friction rub. The development of a ruptured sinus of Valsalva fistula is another mechanical complication needing early surgery.

References

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