Editorial

Antimicrobial Therapy of Streptococcal Endocarditis

Despite nearly 35 years of debate, the optimal antimicrobial therapy for streptococcal endocarditis remains controversial. Problems persist because the antibiotic regimens employed most commonly are similar, their differences subtle, and no prospective controlled trials comparing them have been performed. It is generally agreed however, that optimal therapy of infective endocarditis requires the parenteral route of administration with large doses of bactericidal antibiotics given over a prolonged period.

Although the demography of infective endocarditis has undergone remarkable changes in the antibiotic era, the most common etiologic agents of this syndrome are still the viridans streptococci (1, 2). Six species are recognized in the classification scheme of Colman and Williams (3):

- Streptococcus mitior
- Streptococcus sanguis
- Streptococcus mutans
- Streptococcus milleri
- Streptococcus salivarius
- Streptococcus pneumoniae

The first four in approximate decreasing order of frequency, are common etiologic agents in cases of endocarditis. Streptococcus bovis, a group D organism, is often grouped with these organisms since the therapeutic implications are similar. Speciation is secondary to thorough quantitative antimicrobial susceptibility testing for therapeutic decisions but it is important to recognize some clinical associations: the propensity for Streptococcus milleri to produce metastatic supplicative foci which may require drainage and/or prolonged therapy (4, 5); the association of Streptococcus bovis bacteremia with gastrointestinal tract abnormalities, including carcinoma (6, 7); and the emerging importance of vitamin B6 dependent or nutritionally variant streptococci (8) and the need for combination antibiotic therapy for endocarditis due to these strains (9). From the practical aspect of therapeutic decisions, the most essential information is the sensitivity of the organism to penicillin G. More than 90% of viridans streptococcal isolates (including Streptococcus bovis) are inhibited by 0.2 μg/ml. If the isolated pathogen is resistant to this concentration, therapy appropriate for enterococcal endocarditis should be administered (see below).

Three different antibiotic regimens have proven effective in the management of non-enterococcal endocarditis caused by organisms inhibited by ≤ 0.2 μg/ml penicillin G. The in vitro observations, activity in animal models of endocarditis, and clinical experience that led to these regimens were reviewed recently by an ad hoc subcommittee on the treatment of bacterial endocarditis of the American Heart Association. Their analysis and recommendations were published recently (10), and this report, along with the recent retrospective studies, has spurred further debate (11–13). This editorial commentary examines these issues.

Most authorities recommend combination penicillin-streptomycin therapy for streptococcal endocarditis. However, two recent reports (14, 15) of successful monotherapy, usually with penicillin alone for four weeks, have challenged this view. No relapses were observed in 66 patients surviving one month of penicillin G therapy at a dose of 10 to 20 million units intravenously daily (14) and this experience was supported by a report from Yale (15). However, morbidity was high since 25 patients developed congestive heart failure (14) which necessitated prosthetic valve replacement in 16. Of the two relapses in the Yale study, both occurred in the 13 patients with symptoms of more than three months duration (15), a subgroup of patients which may carry a graver prognosis (16). The advantage of monotherapy is the avoidance of streptomycin ototoxicity, although this is unusual (≤ 2%), vestibular, and readily reversible if the drug is given for ≤ two weeks. Nevertheless, penicillin alone for four weeks in a dosage of 10 to 20 million units daily given intravenously by continuous drip or equally divided doses every four hours is appropriate in patients of greatest risk for ototoxicity: the elderly (age > 65 years), patients...
with renal failure, blindness, or previous impairment of VIIIth nerve function. Penicillin alone should probably not be given to patients with endocarditis who received penicillin prophylaxis recently for prevention of rheumatic fever (17).

Because penicillin plus streptomycin are synergistic against viridans streptococci in vitro and in the rate of eradication of the organisms from cardiac vegetations in experimental animal models of endocarditis (18, 19), combination therapy is commonly recommended. Excellent results are obtained with the "Cornell" regimen of penicillin for four weeks (either 10 to 20 million units of penicillin G intravenously daily or 1.2 million units of procaine penicillin intramuscularly q6h) plus streptomycin, 0.5 g intramuscularly q12h, for the first two weeks (20). No relapses have been observed in over 200 patients treated in this manner. Recently, reports from the Mayo Clinic have documented only one relapse in 99 patients treated for only two weeks with procaine penicillin 1.2 million units q6h and streptomycin 0.5 g q12h, both given intramuscularly (21, 22). Similar results were obtained with short (<17 days) therapy in another report (16) but early experience with similar regimens was less satisfactory where relapse rates of 6 to 11% occurred (23). These differences between studies remain unexplained but the short course regimen has advantages of cost effectiveness and a shorter hospital stay. This regimen appears appropriate in uncomplicated cases of non-enterococcal endocarditis in young patients at low risk for streptomycin toxicity. The traditional four week penicillin—two week streptomycin regimen is preferred if any of the following are present: complicated course, shock, extra-cardiac foci of infection (especially central nervous system manifestations or documented mycotic aneurysm), duration of symptoms for three months or more, vegetation visible on echocardiogram, prosthetic valve endocarditis, or disease due to nutritionally variant streptococci.

Vancomycin, 10 mg/kg (not to exceed 500 mg) intravenously q6h, is the antibiotic of choice in the penicillin allergic patient. This agent is mandatory if the previous penicillin reaction was of the immediate-accelerated type; if only a delayed rash was present, cephalosporins may be used, albeit with a small risk of cross-allergenicity. Either cephalothin 2 g intravenously q4h or cefazolin 1.5—2 g intramuscularly or intravenously q6h for four weeks is appropriate. Although aminoglycosides are synergistic when combined with either vancomycin or the cephalosporins against these streptococci in vitro, clinical experience is scant and combination therapy is not recommended for these infections at the present time.

The above statements concern non-enterococcal endocarditis. Enterococci are in Lancefield's group D and include *Streptococcus fecalis* (var. *zymogenes* and *liquefaciens*), *Streptococcus faecium*, and *Streptococcus durans*. These organisms are still important etiologic agents of bacterial endocarditis and account for approximately 10—15% of cases (24). All enterococci are resistant to 0.2 μg/ml penicillin G and none of the antimicrobial regimens described above is appropriate for enterococcal endocarditis.

Because all β-lactams examined to date, with the possible exception of thienamycins, and vancomycin are bacteriostatic against enterococci and bactericidal synergism is obtained when these agents are combined with aminoglycosides in vitro (25) and in vivo (26) in experimental models of endocarditis, combination regimens are considered essential for cure of enterococcal endocarditis (27). After the accumulation of clinical experience, the standard regimen for enterococcal endocarditis has evolved to: penicillin G 10 to 20 million units daily for six weeks plus streptomycin 1 g q12h intramuscularly for two weeks followed by a lower dose of 0.5 g q12h for an additional four weeks. However, it now appears that four weeks of combined therapy is adequate and that streptomycin may be given in the lowered dose of 0.5 g q12h, with presumably less toxicity, for the duration of the course (28). The full six week regimen should still be administered, however, to patients with complications or with prosthetic valve endocarditis.

Another controversial area in the therapy of enterococcal endocarditis concerns streptomycin resistance, defined as MIC ≥ 2000 μg/ml. Penicillin-streptomycin combinations are not synergistic against these organisms in vitro (25) or in animals with experimental endocarditis but penicillin-gentamicin combinations are more rapidly bactericidal than either agent