

Endocarditis due to nonfermentative gram-negative rods. An updated review

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This review covers endocarditis due to Pseudomonas aeruginosa, P. maltophilia (9 cases), P. cepacia (16 cases), Acinetobacter calcoaceticus (20 cases), Moraxella spp. (6 cases), and other nonfermenters. Such endocarditis cases are very rare and occur chiefly in the setting of drug addiction, on prosthetic or on previously damaged valves.

Nonfermentative gram-negative rods comprise nonfastidious species of the genera *Pseudomonas*, *Achromobacter*, *Alcaligenes*, *Bordetella*, *Agrobacterium*, *Flavobacterium*, *Acinetobacter*, *Moraxella* and several as yet unnamed taxa. This review focuses on endocarditis due to these bacteria and thus represents an update of the last review by Cohen *et al.* from 1980^[1]. Overall, these cases are quite rare and probably account for no more than 1% of all cases of endocarditis. Needless to say, correct diagnosis and susceptibility testing (including supplementation of Mueller-Hinton broth with Ca and Mg ions) are important for successful treatment. In the cases reviewed here, clinical data justified the diagnosis of endocarditis.

Pseudomonas aeruginosa

This is the most frequently isolated 'nonfermenter' in the clinical laboratory. Endocarditis is uncommon (as compared to other infections) except in drug addicts (80-90%) and following cardiac surgery or other *P. aeruginosa* infections (10-20%). In most European reports on endocarditis^[2,3] as well as in a recent American review of 104 cases^[4] *P. aeruginosa* was not reported as an agent of endocarditis.

ENDOCARDITIS IN DRUG ADDICTS^[1,5]

From 1967-76, *Pseudomonas aeruginosa* caused approximately 5% of all drug-related endocarditis cases in the United States. In that group it is the most frequent gram-negative rod (60%). In one series of nine cases from Detroit, polymicrobial endocarditis in drug addicts included *P. aeruginosa* in five^[6]. In that

city and in Chicago, *P. aeruginosa* endocarditis seems to be concentrated. In many respects, the disease resembles that of *Staphylococcus aureus* in addicts. The mean age is below 30 years, men are more frequently affected than women (6:1) and underlying valvular disease occurs in less than 20%. The course is subacute in approximately 70% of the cases, i.e. when the tricuspid valve is involved. If the left-sided valves are affected (approximately 20%), the course tends to be acute. Cutaneous signs and shock are usually absent. In right-sided disease, embolic cavitory lung lesions, in left-sided disease, congestive heart failure and systemic emboli are seen in more than 50%. Treatment for every case should be with an anti-*Pseudomonas* penicillin plus an aminoglycoside at maximal possible doses (checkerboard testing!). Refractory cases of right-sided endocarditis (approximately 60%) should be treated with valve removal, while left-sided cases should be operated on immediately. Mortality rates have decreased lately (70% for left-sided, 30% for right-sided disease); they are higher in patients over 30 years and in mixed infections.

The striking predominance of serotype 11 in Chicago^[7] in *P. aeruginosa* endocarditis (but not in other infections) should suggest a common source and/or continued transmission. In Detroit, several serotypes prevailed^[6]. In Chicago, *P. aeruginosa* endocarditis was more frequently associated with the use of pentazocine and tripeleppamine than with heroin, in striking contrast to *S. aureus* endocarditis. The source of the organism seems to be tap water or other environmental sources; the serotype involved in cases of endocarditis was found in four out of nine addict syringes^[8].

ENDOCARDITIS IN NON-ADDICTS

Recent reports of this disease are now quite rare. The last case collection from 1973^[9] lists as risk factors cardiac surgery, previously damaged valves, antibiotic treatment and *P. aeruginosa* infections elsewhere, notably in the urinary tract. The left side was more frequently affected than the right side.

Pseudomonas maltophilia

This bacterium, the most frequently isolated 'non-aeruginosa' *Pseudomonas*, is ubiquitous in the environment. The majority of clinical isolates have been recovered in mixed culture and are, even in blood cultures, aetiologically indeterminate^[10]. Bacteraemia is not an indication of endocarditis. Nine cases, eight of them reviewed previously^[11], are extant in the literature. All involved previously damaged heart valves and were associated either with intravenous drug abuse (four cases) or with open heart surgery (five cases). The latter were nosocomial and affected, like three cases in drug addicts, prosthetic valves with early or late infections and one congenital ventricular septal defect^[12]. One case showed a mixed culture with *viridans* streptococci, probably caused by blood reflux from a contaminated collection tube^[11]. The patients' mean age was 36 years (range 25–65); seven were males and two females. Three patients died; the others recovered with either medical or medical-surgical treatment (three cases each). The mitral valve was affected in six cases, the aortic in two cases, and both in one case. Other data are fragmentary. Possible sources were not traced. Treatment was tried with chloramphenicol, aminoglycosides, carbenicillin, trimethoprim-sulphamethoxazole, and polymyxin B and mixtures thereof; at present, the most promising *in vitro* combination against *P. maltophilia* seems to be trimethoprim-sulphamethoxazole plus carbenicillin, possibly supplemented with rifampin^[11].

Pseudomonas cepacia

This organism is not uncommonly a contaminant of the moist hospital environment (instruments, water sources, flower vases, solutions and some disinfectants, notably quaternary ammonium compounds) and is able to survive under conditions of minimal nutrition^[10]. Its pathogenic significance in blood cultures is definitely higher than that of *P. maltophilia*. Since the last review of 16 cases^[11], no new report of *P. cepacia* endocarditis has appeared. Notable features of these cases were as follows: 14 patients were

male, 12 were drug addicts, eight showed previous valve damage (four had prosthetic valves); the mean age was 37 years (range 23–66 years), two had mixed cultures and nine died. The course was acute to chronic. In five cases the tricuspid valve was affected; in the remainder, the left heart valves were affected about equally. Potential sources were not traced. Treatment was quite difficult because of the innate multiple resistance of the organism; therapy with a combination of trimethoprim-sulphamethoxazole (SXT) plus polymyxin was successful in six patients who, with the exception of one patient, eventually needed valve replacement. Notable was the emergence of SXT-resistant variants in two patients during treatment.

Acinetobacter calcoaceticus

This organism is also ubiquitous, particularly on human skin and in the upper respiratory tract^[13]. Many blood culture isolates are clinically insignificant^[13]. The previous review^[11] lists nine cases of endocarditis due to *A. calcoaceticus*. We were able to count 20, some of which were incompletely documented^[14, 22]. The ssp. (var.) *anitratus* was involved in nine cases, the ssp. *lwoffii* in 10 cases, one case was not subspecies. Conspicuous were a low mean age (26 years, range 4–60) due to five cases in children^[14, 18, 20], only one proven case each of drug addiction and mixed culture (unrelated^[11, 22]), involvement of prosthetic valves in 25% (three early, two late cases) and previous rheumatic valve damage in 33%. The aortic valve alone was affected in 38%, the mitral valve in 31% and both in 25%. There was no tricuspid involvement. Thirty percent of the patients died. Possible sources were not further identified. The course varied from acute to chronic. There was no discernible difference in these characteristics between the two subspecies. Data on treatment are fragmentary; a combination of a betalactam antibiotic and an aminoglycoside may be the best. These data differ considerably from the previous review^[11].

Moraxella spp.

The previous review^[11] lists four cases of endocarditis, two of which, however, were caused by *Kingella kingae*. We found a total of six cases^[23-26] which were quite heterogeneous and incompletely documented. Moraxellae are part of the normal flora of the upper respiratory tract. Their presence in blood cultures is, in our experience, usually of no clinical significance. Three cases were due to the species *M. nonliquefaciens*, and one each to the species *M. liquefaciens*, *M.*

* Erroneously counted as 15 cases in [1].

osloensis, and M6. The ages of the patients varied between childhood and 77 years. Two patients had mitral valve prolapse, two had prosthetic valves and one had congenital heart disease. The courses were acute to chronic. No drug addiction was involved. Treatment was with ampicillin, in some cases plus an aminoglycoside. Two patients needed prosthetic valves and two died.

Other nonfermenters

One case of endocarditis each due to *P. stutzeri*^[29], CDC group VE-1^[30], *P. alcaligenes*^[31], and two each due to *Flavobacterium meningosepticum*^[32,33] and *Bordetella bronchiseptica*^[29,34] (the latter mixed) have been reported. No general conclusion can be drawn.

Special mention must be made of endocarditis due to *Alcaligenes faecalis*. This organism could not be identified with accuracy until the 1970s; thus, these reports^[15,35-37] must remain speculative as to the true character of the organism.

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- reported the selective survival advantage of *P. aeruginosa* O11 in media containing tripeleennamine. Another:
- Wieland M, Lederman MM, Kline-King C *et al.* Left-sided endocarditis due to *Pseudomonas aeruginosa*. A report of 10 cases and review of the literature. Medicine 1986; 65: 180-9
- added 10 more cases to the literature, eight of them in addicts from Cleveland, Ohio, and reviewed the English literature. The third:
- Jimenez-Lucho VE, Saravolatz LD, Medeiros AA, Pohlod D. Failure of therapy in *Pseudomonas* endocarditis: selection of resistant mutants. J Infect Dis 1986; 154: 64-8
- reported on the failure of piperacillin-tobramycin treatment in two cases of *P. aeruginosa* endocarditis which was explained by the selection of high-level beta-lactamase producers in a large bacterial inoculum.

Note added in proof

Three papers on *P. aeruginosa* endocarditis appeared after this paper had been submitted. One: