

Increase in native valve endocarditis caused by coagulase negative staphylococci: an Anglo-French clinical and microbiological study

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Abstract

Native valve endocarditis caused by coagulase negative staphylococci has become more common. A study of 35 cases showed that the infections were usually acquired in the community and occurred in men (mean age 51 years). A pre-existing cardiac abnormality (mitral leaflet prolapse in a third of patients) was detected in 26 (74%). The source of the organisms in the community acquired infections was assumed to be the skin, though lesions were seldom demonstrated; most hospital acquired infections resulted from intravenous devices. Community acquired organisms were usually sensitive to penicillin, whereas those acquired in hospital were often multiresistant. Most infections were caused by *Staphylococcus epidermidis*. The frequency of acute presentation (26%) and of major neurological abnormality (23%), together with the need for valve replacement (often emergency) (51%) and the mortality (36%) suggest that coagulase negative staphylococci can be virulent aggressive pathogens, mimicking *Staphylococcus aureus*.

It has long been recognised that coagulase negative staphylococci can cause infective endocarditis on native heart valves. In series reported before valve replacement surgery became available coagulase negative staphylococcal infection was responsible for about 1% of cases.^{1,2} Some later series have reported a higher incidence,^{3,4} but these have included both native and prosthetic infections and coagulase negative staphylococci are the commonest pathogens in prosthetic valve endocarditis. We recently noticed in our two hospitals a considerable increase in infective endocarditis of native valves caused by coagulase negative staphylococci. There were no cases in St Thomas's Hospital between 1968 (when detailed records began) and 1976, but between 1977 and 1989 there were 16 cases, accounting for 10.4% of the 154 cases of infective endocarditis of native valves seen during the period. In the Hôpital Louis Pradel, Lyon, no cases were detected between 1970 (when detailed records began) and 1975, but between 1976 and 1989 there were 19 cases, accounting for 4.4% of the 430 cases of native valve endocarditis seen. We present the clinical, microbiological, and epidemiological features of the infection in these 35 patients.

Patients and methods

In both hospitals, the medical staff of the microbiology department, in close liaison with their clinical colleagues, keep detailed prospective records on every patient with infective endocarditis. These records together with hospital inpatient notes provided the data for this study.

The diagnosis of infective endocarditis was based on the isolation of the same coagulase negative staphylococcus from at least two sets of blood cultures and a compatible clinical syndrome (fever together with a new or changing cardiac murmur, embolic or cutaneous manifestations), or operative or necropsy evidence of endocarditis. In St Thomas's Hospital strains were sent to Dr R Marples of the Staphylococcus Reference Unit, Central Public Health Laboratory, Colindale, for identification and typing, though latterly they were also speciated at St Thomas's Hospital by the API STAPH (API System, Montalieu-Vercieu, France) and most recently ATB 32 STAPH (API System) systems. The French strains were identified by the same systems at the Centre National de Référence des Staphylocoques (Professor J Fleurette). Susceptibility to a range of anti-staphylococcal antibiotics was estimated by a diffusion method and results confirmed in many cases by estimation of the minimum inhibitory and bactericidal concentrations.

Results

Clinical and microbiological features and the treatment and outcome of the British and French cases seemed to be similar.

CLINICAL FEATURES

Twenty seven of the 35 patients with coagulase negative staphylococcal endocarditis on a native valve seen during the 14 year period were men (mean age 51 years (range 20-80 yr) and eight were women (mean age 52 years (range 21-76 yr)). None was a drug addict.

The length of symptoms varied: in 14 (41%) patients symptoms had been present for ≥ 2 months (maximum 7 months), in eight (24%) for 2-8 weeks, and in nine (26%) for <2 weeks (in 6 of these nine cases they had been present for less than a week). Three patients presented with an acute cerebrovascular episode, and endocarditis was diagnosed in one when she was admitted to hospital for an elective valve replacement for calcific aortic stenosis. Fever was a constant finding, with

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Accepted for publication
7 August 1990

weight loss and anorexia usual in the chronic cases. Cutaneous manifestations were detected in 11 (31%) patients (clubbing five, Osler's nodes four, splinter haemorrhages four) and splenomegaly in eight (23%). A major neurological abnormality was seen in eight (23%) patients; in seven this had precipitated referral to hospital and in the eighth hemiplegia developed after 4 days' treatment. These thromboembolic events included hemiplegia, dysphasia, and internuclear ophthalmoplegia. One patient presented with meningitis; his cerebrospinal fluid contained 1870×10^6 white blood cells per litre (95% polymorphonuclear cells) but was sterile on culture. He had a temporoparietal lesion, initially thought to be an abscess, but more probably of embolic origin. Peripheral emboli were detected in four patients.

Twenty six (74%) of the 35 patients had a pre-existing cardiac abnormality either congenital or acquired: mitral leaflet prolapse (eight) (one with Marfan's syndrome), bicuspid aortic valve (two), mitral leaflet prolapse plus bicuspid aortic valve with Marfan's syndrome (one), ventricular septal defect (one), rheumatic heart disease (two), murmurs of unknown aetiology (12). Twenty patients were known to have a predisposing cardiac abnormality, and four of them had experienced a previous episode of infective endocarditis with a different organism. In the other six patients the cardiac abnormality was detected during their admission with infective endocarditis. Infective endocarditis did not show a predilection for a particular valve. Haemodynamic failure was detected on admission in 19 (54%) patients.

Three patients complained of persistent backache; scanning and radiography showed evidence of vertebral osteomyelitis in the lumbar vertebrae in two patients and in both the lumbar and cervical vertebrae in the third. Though confirmatory biopsy specimens were not obtained, antibiotic treatment resulted in clinical and radiographic improvement.

LABORATORY INVESTIGATIONS

The mean haemoglobin at diagnosis was 113 g/l in men (range 78–155) and 104 g/l in women (range 89–132), the mean white blood cell count was 10.1×10^9 g/l (range 4.6–17.6), and the mean erythrocyte sedimentation rate for the 25 patients in whom it was measured was 63 mm/h (range 6–120). Haematuria was detected in eight (42%) of the 19 patients investigated by microscopy.

MICROBIOLOGICAL FINDINGS

In all 35 patients, at least two sets of blood cultures were positive for the same coagulase negative staphylococcus: in 25 (71%) every bottle yielded the pathogen, in seven of the other 10 patients at least 75% of bottles were positive, in two 50% were positive, and in one the coagulase negative staphylococcus was only recovered from three of 12 bottles.

In 32 (91%) patients the coagulase negative staphylococcus was *Staphylococcus epidermidis* (sensu stricto), in one patient accompanied by *S. haemolyticus* in all bottles. Organisms from the other three patients were *S. warneri*, *S. hominis* (this could have been *S. lugdunensis* because it was isolated in 1981, before *S. lugdunensis* was described²), and a strain that defied satisfactory speciation.

Antibiotic susceptibility varied: 13 (36%) strains were sensitive to all anti-staphylococcal agents tested including penicillin, and eight (22%) were resistant to four or more antibiotics, always including penicillin, methicillin, and gentamicin. All isolates were sensitive to vancomycin.

EPIDEMIOLOGY OF THE INFECTION

Infections were classified as community acquired if the patient had no relevant recent history of hospital admission or treatment or as hospital acquired. In 23 (66%) the infection was community acquired: three patients had received dental treatment within the preceding 3 months without antibiotic prophylaxis (extractions in one, and other treatment not specified in two); a man with non-insulin dependent diabetes had cut his hand a week before malaise, fever, and chest pain developed. This lesion was healed on admission. One further patient, who had had a previous splenectomy, had an infected hand wound with lymphangitis six months before the onset of symptoms of endocarditis. No other predisposing factors could be identified, though one other patient had non-insulin dependent diabetes.

In the other 12 patients the infection was hospital acquired: in seven it resulted from an infected intravenous line, in one from the arteriovenous fistula used for haemodialysis, in one probably from a cardiac catheter two months earlier, and in one from urinary infection with the same strain after transurethral resection of prostate. In the other two patients whose infection was hospital acquired the source of the coagulase negative staphylococcus was less clear: one 21 year old woman with mitral leaflet prolapse and Marfan's syndrome became unwell within days of a forceps delivery; she had had an epidural and a single intravenous injection. The other patient became unwell after a cystoscopy and had had a peripheral cannula for intravenous access for 4 days. A constant feature of all these patients with hospital acquired infective endocarditis was previous antibiotic treatment. Whereas the coagulase negative staphylococci isolated from the community acquired infections were very sensitive to antibiotics, most strains from hospital acquired infections were multi-resistant.

PROGRESS, TREATMENT, AND OUTCOME

Full details of follow up were available for all but two of the 35 patients; one of those lost to follow up refused the proposed valve replacement operation and discharged himself

and the other had two recurrences of the infection, despite appropriate antibiotics, and returned to Iraq. Twelve (36%) of the remaining 33 patients died. Sixteen patients (46%) underwent valve(s) replacement during their admission with infective endocarditis; one required a second aortic valve replacement within 6 weeks of the first operation. Two patients required valve replacements 1 year and 3 years respectively after successful medical treatment of infective endocarditis. Six patients died after valve replacement as did six of those who did not have a valve replacement.

Both the antibiotic regimens used and the length of treatment varied. Patients nearly always received two antibiotics: usually a penicillin (occasionally a cephalosporin) plus an aminoglycoside; vancomycin, alone or in combination with various other agents was used for the multiresistant strains. The length of treatment in survivors varied from 2 weeks to 3 months. Pristinamycin, pefloxacin, and oxacillin were used in some of the French patients. No attempt was made to institute a standard regimen in either country. The choice of antibiotic was determined by the sensitivity of the organism and by the clinician in charge, advised by the microbiologist.

Discussion

This is the largest reported series of native valve endocarditis caused by coagulase negative staphylococci, an infection that has clearly become more common during the past decade. Sixty years ago, Thayer noted an incidence of "*Staphylococcus albus*" infective endocarditis of 1.96% in 306 cases observed over 40 years at Johns Hopkins Hospital,¹ but in a further 232 cases reported in the preceding 30 years he found only one other case, that reported by Lenhartz in 1901.⁶ Thayer concluded that "endocarditis due to *Staphylococcus albus* is an occasional phenomenon". Twenty years later, Cates and Christie reported a 1% incidence of "*Staphylococcus albus*" in 408 culture positive cases of infective endocarditis.² In the 1950s the advent of mitral valvotomy and later of prosthetic valve replacement saw the emergence of coagulase negative staphylococci as major pathogens in post-cardiotomy endocarditis, particularly in individuals with prosthetic valves, and their role as pathogens in endocarditis of the native valve tended to be overlooked. Recent reports, including this study, suggest that the incidence of native valve endocarditis caused by coagulase negative staphylococci has increased.^{7,8}

Coagulase negative staphylococci are normal inhabitants of the skin and mucous membranes and different species vary in their distribution throughout the body. It seems likely that coagulase negative staphylococcal endocarditis on native valves is largely an endogenous infection. There is good evidence that coagulase negative staphylococci elaborate some of the exoproteins produced by *S aureus*, some of which are recognised virulence factors.⁹ These exoproteins may have a role

in the pathogenicity of coagulase negative staphylococci. The epidemiology of coagulase negative staphylococcal endocarditis is more readily determined for infections acquired in hospital than those acquired in the community. Hospital acquired cases usually result from infection of intravascular catheters or devices. Nosocomial endocarditis is now as commonly caused by coagulase negative staphylococci as by *S aureus*.¹⁰ In common with published reports, most of our infections were community acquired, often with no discernible source. Minor abrasions may well escape detection, and, as with *S aureus* infections, one has to conclude that the organism has come from the skin but its site of entry into the blood stream remains unknown. The relevance of dental treatment is difficult to assess, though a dental source for coagulase negative staphylococcal endocarditis has been reported^{4,11} and coagulase negative staphylococci have been isolated from blood cultures taken after dental treatment.^{12,13}

Although the clinical presentation was similar to that of infective endocarditis caused by "viridans" streptococci, certain features suggest that coagulase negative staphylococci are more aggressive pathogens: firstly, one quarter of the patients had had symptoms for <2 weeks, which is most unusual in "viridans" infection; secondly, 23% of patients had a major neurological abnormality, one with meningitis; and lastly, concomitant vertebral osteomyelitis was found in 9%. Tuazon and Miller reported two cases of osteomyelitis of the cervical spine (one with infective endocarditis, one without) among their 10 cases of serious infections with coagulase negative staphylococci,¹⁴ and Wood *et al* reported a case of lumbar vertebral osteomyelitis and native valve infective endocarditis caused by *S warneri*.¹⁵ The high mortality in our series and the need for valve replacement, in most cases during the initial period of treatment, suggest that coagulase negative staphylococci can be virulent destructive organisms resembling *S aureus* rather than "viridans" streptococci. Caputo *et al* reported a lower mortality (19%) in their 21 patients, but a similar proportion of valve replacement operations (43%).⁷ The mortality rate for "viridans" infective endocarditis on native valves was 6% in Bayliss *et al*'s study in 1981-2,³ 7% in cases seen at St Thomas's Hospital over the past 20 years, and 10% in Lyon since 1980. This compares with a mortality of 53% (26/48) in patients with *S aureus* on native valves (non-addicts) seen at St Thomas's Hospital over the same period and 39% (19/49) in Lyon.

Three quarters of our patients had a pre-existing cardiac abnormality, a similar figure to that reported by Caputo *et al* in their 21 cases of infective endocarditis caused by coagulase negative staphylococci.⁷ The commonest congenital abnormality was mitral leaflet prolapse, detected in nine (26%) of our patients; this abnormality is being increasingly recognised as a precursor of endocarditis.¹⁶ The association of coagulase negative staphylococcal endocarditis and mitral leaflet prolapse has been noted

before.^{8 17 18}

In common with other bacterial endocarditides the coagulase negative staphylococci were isolated from most blood cultures taken; and our rate of 71% of bottles resembles that reported by Caputo *et al* (67%).⁷ In contrast, Quinn and Cox found that though blood cultures were uniformly positive from their patients with post-cardiotomy coagulase negative staphylococcal endocarditis, only one of nine of those with native valve infection showed this pattern.⁴ More worrying was our patient from whom the infecting coagulase negative staphylococcus was only recovered from 3 of 12 bottles, and Quinn and Cox reported on a patient who received no antibiotic treatment for what was shown at necropsy to be infective endocarditis because the coagulase negative staphylococcus was only isolated from 2/9 blood cultures and was disregarded as a contaminant. Repeat isolation of the same coagulase negative staphylococcus from the blood, even if it is not consistent, should not lightly be dismissed as contamination.

Our series showed that *S epidermidis* (sensu stricto) was the commonest species causing infective endocarditis, but various other species can also cause the disease. Richardson *et al* found that *S epidermidis* accounted for a greater proportion of coagulase negative staphylococcal endocarditis on prosthetic valves than on native valves (85 v 56%).¹⁹ Many reports, however, refer to *S epidermidis* without giving any information on speciation, and until recently it has been usual to label any coagulase negative staphylococcus as *S epidermidis*.

Antibiotic susceptibility was variable, but a major difference emerged between those strains acquired in the community and those acquired in hospital. Two thirds of strains acquired outside hospital were sensitive to all anti-staphylococcal agents including penicillin, and most of the others were resistant only to penicillin; whereas hospital strains were always resistant to penicillin and two thirds of them were multiresistant (including methicillin). In many reported cases of coagulase negative

staphylococcal infection of a native valve the organisms were penicillin sensitive. This pattern of infection contrasts strongly with infective endocarditis caused by *S aureus* where most isolates, wherever acquired, are resistant only to penicillin.

We thank the clinicians in the Hôpital Louis Pradel and St Thomas's Hospital for permission to study their patients, and Dr Yvonne Brun and Dr Michele Bes of Lyon and Dr R Marples of Colindale for identification and typing of the strains.

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