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Pneumococcal Endocarditis in Adult Patients. A Report of Five Cases and Review of the Literature

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SUMMARY

A retrospective survey of patients with pneumococcal infective endocarditis at the University Hospital, Leiden, over a 10-year period (1976–1986) yielded five cases. Applying strict case definitions, four patients had definite and one patient possible pneumococcal endocarditis. The commonest presenting signs and symptoms were malaise, fever, and congestive heart failure. Predisposing conditions were previous splenectomy in one case and a valve prosthesis in another. The aortic valve was the most common site of infection. In four of the five patients the diagnosis of endocarditis was made during life. These patients were treated appropriately, i.e. with antibiotics to which *S. pneumoniae* is sensitive. In three patients, surgical intervention was performed in the acute phase because of progressive heart failure. Paravalvular abscesses were observed at surgery in all these cases. The four patients treated in our series recovered fully; the single fatal case constituted an unrecognized case of pneumococcal endocarditis. If recognized and treated appropriately (particularly with early selective surgery) endocarditis can be cured. In a statistical analysis of 36 patients with pneumococcal endocarditis reported during the past five years, we found a significantly higher occurrence and mortality in men than in women; no other clinical features were associated with a poor outcome of illness.

INTRODUCTION

Infective endocarditis due to *Streptococcus pneumoniae* was a lethal condition before the availability of penicillin. Usually it was a complication of lobar pneumonia and its incidence among cases of lobar pneumonia ranged between 1 and 5 per cent [1–3]. The incidence of pneumococcal endocarditis among all cases of infective endocarditis varied between 12 and 25 per cent [4–6]. The incidence of pneumococcal endocarditis has declined to less than 5 per cent since penicillin became available [7–9], whereas the incidence of pneumococcal bacteraemia remained stable. Recent studies have shown that outcomes in pneumococcal

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infective endocarditis varies, with case-fatality rates ranging from 28 to as high as 60 per cent [10–12].

To determine current clinical features and outcome of patients with pneumococcal endocarditis, we made a retrospective analysis of patients with this diagnosis admitted to the University Hospital Leiden from January 1976 to January 1986.

PATIENTS AND METHODS

All records of patients older than 15 years of age, admitted to University Hospital Leiden (a 900-bed hospital with both referral and primary patient populations) from 1 January, 1976, to 1 January, 1986, with pneumococcal bacteraemia were reviewed. These included five cases in which the diagnosis of pneumococcal endocarditis was made clinically. Records of patients listed in the Department of Pathology as having infective endocarditis were also reviewed, yielding one additional case in which pneumococcal endocarditis was first discovered at autopsy. For the diagnosis of pneumococcal infective endocarditis the criteria as defined by Von Reyn *et al.* [14] were used. Only definite, probable, or possible episodes were included in this review. One case which was diagnosed and treated as pneumococcal endocarditis failed to meet these definitions and was subsequently rejected.

Statistical analysis of pooled results from four recent series [10–12], including ours, was done using the SPSS-X programme [15]. Only adult patients were considered eligible for statistical analysis. Statistical significance ($p < 0.05$) of categorical variables was calculated using the χ^2 test, and that of continuous variables using the Student *t*-test.

RESULTS

In the period studied, 147 episodes of pneumococcal bacteraemia occurred in 142 patients [13]. These included five cases of pneumococcal endocarditis meeting one of the three definitions. Four patients had definite pneumococcal endocarditis, of which three were confirmed at surgery and one at autopsy. One patient with a valve prosthesis was defined as a probable case by persistently positive blood cultures and a predisposing valvular disease. There were two male and three female patients ranging in age from 18 to 71 years. For an annual adherence population of about 180 000 adult patients (a population calculation used by the Dutch government for hospitals with a large number of referrals), the annual incidence of pneumococcal endocarditis is about 0.3 cases per 100 000 adult persons. In terms of admission rates (average 17 335 adults per year), the annual incidence of pneumococcal endocarditis is 0.03 cases per 1000 admissions. The clinical and pathological features of these patients are summarized in Table 1.

CASE REPORTS

Case 1

A previously healthy 39-year-old man presented with progressive congestive heart failure. Eleven days earlier, he had become ill with general malaise, myalgia, fever, nausea and vomiting. He complained of low back pain during the past month. One week after onset of symptoms, he was admitted to another hospital. Physical examination revealed normal blood pressure and a temperature of 40°C, without signs of meningeal irritation or a heart murmur. Three days later, signs of congestive heart failure developed and a new heart murmur was noted. Blood cultures yielded *S. pneumoniae* and benzylpenicillin (6 × 1.2

TABLE 1. *Clinical features of five patients with pneumococcal endocarditis*

Case no.	Sex/age (years)	Portal of entry	Underlying condition	Aortic valve destruction*	Annular abscess†	Mitral and other valves	Metastatic lesions	Category	Therapy		Outcome
									In hospital	After discharge	
1	M/39	Not known	-	+	+	Normal	-	Definite	Surgery + penicillin (6 × 2 MU)	Oral trimethoprim/sulphamethoxazole	Cure
2	F/54	Not known	Splenectomy	+	+	Normal	Metacarpophalangeal joints	Definite	Surgery + penicillin (6 × 2 MU)	Oral penicillin	Cure
3	F/71	Lung	Valve prosthesis	-	-	Normal	-	Possible	Penicillin (6 × 2 MU)	Oral penicillin	Cure
4	M/70	Skin	Bronchial carcinoma	+	-	Normal	Meningitis	Definite	None	None	Died
5	F/18	Genitourinary	Pregnancy, ruptured membranes	+	+	Normal	Embolus, femoral artery	Definite	Surgery + penicillin (6 × 2 MU)	Oral trimethoprim/sulphamethoxazole	Cure

* Shown by echocardiography in *Case 2* and *5*.

† Shown at surgery or autopsy.

million units) and kanamycin (2×500 mg) were administered intravenously for three days. Because of progressive left ventricular failure, he was transferred to our hospital. He was critically ill with blood pressure of 150/50 mmHg, pulse 110/min. A diastolic and protosystolic murmur was heard over the fourth left intercostal space. There was no evidence of peripheral emboli. Because of intractable congestive heart failure, surgery was performed five days after admission. There were large perforations at the base of the aortic valve with an abscess in the valve ring. No vegetations were present and the mitral valve was not affected. Culture of the aortic valve remained sterile, but histologic examination revealed Gram-positive cocci. After placement of a valve prosthesis, benzylpenicillin (6×2 million units daily) was continued for three months. After discharge, co-trimoxazole was given orally for six weeks, since serum levels with oral phenoxymethyl penicillin were very low. This duration of treatment was considered necessary for curing the abscess. Gallium-67 scintigraphy on the 20th day after surgery showed hot spots over the heart, as well as over the fourth thoracic vertebra, the latter possibly accounting for the back pain. He recovered fully.

Case 2

A 54-year-old woman was admitted with a one-month history of recurrent fever and chills, unresponsive to co-trimoxazole and tetracycline. Splenectomy had been performed 33 years earlier because of idiopathic thrombocytopenic purpura. No pneumococcal vaccine had been given. Blood pressure was 100/50 mmHg, pulse rate 90/min and temperature 37.4°C , rising to 40.4°C later. No heart murmur was heard. There was acute arthritis of the third and fourth metacarpophalangeal joints of the right hand, compatible with septic arthritis. No puncture was performed, but intravenous amoxicillin was started. When seven blood cultures became positive for *S. pneumoniae*, treatment was changed to benzylpenicillin (6×2 million units). Two days after admission, a diastolic heart murmur was noted, compatible with aortic regurgitation. Echocardiography revealed multiple vegetations on the aortic valve and angiography showed massive aortic regurgitation. Because left heart failure was impending, the patient was taken to surgery. Pericardial fluid (300 ml) was drained, which was proved sterile. The aortic valve showed one torn cusp, a large perforation in another, and many verrucous vegetations on the posterior cusp. A valve ring abscess was also present. A Björk-Shiley prosthesis was placed. Examination by light microscopy of the vegetations showed many Gram-positive cocci. Culture of the valve was negative. Antimicrobial treatment (benzylpenicillin 6×2 million units) was continued for six weeks after surgery. She was discharged on phenoxymethylpenicillin for another five weeks (4×3 g daily). Recovery was uneventful.

Case 3

A 71-year-old woman was admitted with a one-day history of high fever, chest pain and dyspnoea. Her medical history revealed rheumatic fever in her youth resulting in mitral stenosis. Ten years earlier, a Carpentier-Edwards prosthetic valve was placed in the mitral position. She was acutely ill, and cyanotic with a temperature of 39.7°C . No murmurs were heard over the prosthetic valve. Chest radiography showed signs of congestive heart failure and a lobar pneumonia in the left upper lobe. Benzylpenicillin (6×2 million units) was started. Three blood cultures yielded *S. pneumoniae*. Despite the immediate high-dose treatment with penicillin, blood cultures taken several days after admission were still positive for the same micro-organism. Echocardiography did not reveal vegetations, although the diagnosis of possible endocarditis was made on the basis of the persistently positive blood

cultures and the presence of the prosthetic valve. Benzylpenicillin was continued for six weeks (6×2 million units); thereafter phenoxymethylpenicillin was given for another six weeks (4×2 g daily). Outcome was uneventful.

Case 4

A 70-year-old man was admitted because of fever and dyspnoea. He had had symptoms resembling influenza for several weeks. One month earlier, a right bilobectomy for squamous cell carcinoma had been performed. He was disoriented with a temperature of 38.5°C , blood pressure of 160/70 mmHg, and a pulse of 120/min. Chest radiography did not reveal an infiltrate. A blood culture grew *S. pneumoniae*. An abscess in the wound from the thoractomy occurred and was drained. No systemic treatment was started. Defervescence followed. Culture of the pus revealed a mixed isolation of *S. pneumoniae* and *Staph. epidermidis*. Fever recurred on the 14th day. Two days after, he became hypotensive and died. Five blood cultures obtained on the day before death all yielded *S. pneumoniae*. Autopsy showed endocarditis of the aortic valve, focal myocarditis, bronchopneumonia with empyema, and meningitis with encephalitis. Vegetations of the aortic valve contained Gram-positive cocci.

Case 5

An 18-year-old Turkish woman had given birth to a healthy baby two weeks before admission to our hospital. In the 35th week of pregnancy, membranes ruptured whereafter labour could only be delayed for 24 h. Two days postpartum, she developed fever. Blood cultures and cultures of the cervix yielded *S. pneumoniae*. Since spontaneous defervescence followed, treatment was withheld. She was discharged one week after delivery, to be readmitted three days later because of a white, cold left leg. Emergency embolectomy of an embolus in the left external femoral artery was performed. Because of a rapid-onset congestive heart failure with a newly developed heart murmur, she was transferred to our hospital. Echocardiography showed multiple vegetations on the aortic valve. Penicillin (6×2 million units) was started and because of progressive congestive heart failure, emergency cardiac surgery was performed. This showed a pericardial effusion (350 ml) which was drained. The aortic valve was almost completely destroyed; there were yellow verrucae on the remnants. There was an aneurysm of the sinus of Valsalva. Examination of the valvular remnants removed showed a diffuse infiltration with neutrophilic granulocytes, without micro-organisms. A Björk-Shiley prosthesis was placed. Three weeks after operation, she developed a significant left-to-right shunt. A second operation was performed and a perforation of the membranous septum with vegetations was found. Part of the mitral valve was also ruptured. After dissection of the diseased parts, which could be carried out without placement of Teflon patches, recovery was uneventful. Antibiotics were continued for six months.

DISCUSSION

Incidence. The incidence of pneumococcal infective endocarditis among all cases of infective endocarditis diagnosed at the University Hospital Leiden from 1 January, 1976 to 1 January, 1986 was 2–3 per cent (Thompson, unpublished data). This figure is similar to that from the United Kingdom during two consecutive years (1981–82) [7]. The relative incidence of

pneumococcal infective endocarditis among all cases of infective endocarditis is less than before 1940 [1-3].

The five cases of pneumococcal endocarditis reported here represent 3.4 per cent of all recorded episodes of pneumococcal bacteraemia ($n = 147$) during this 10-year period [13]. This percentage is in agreement with other recent series of pneumococcal bacteraemia [16-18], reporting endocarditis in 1, 1.7, 2.2 and 4.8 per cent respectively. It is interesting that in our series lobar pneumonia occurred in only one case. Before the 1940s, pneumococcal endocarditis was almost always associated with lobar pneumonia [3, 19, 20].

Predisposing factors. Two patients in our series (*Cases 2 and 4*) had underlying conditions which adversely influenced their immune system. In particular, the splenectomy is known to predispose to infections with encapsulated bacteria [21]. *Patient 3* had a predisposing cardiac condition. None of our patients was an alcoholic, unlike 40 per cent of the patients reported in the series of Wolff [11].

Clinical features. The most consistent clinical features in our small series were unexplained fever and rapidly progressive congestive heart failure, despite appropriate antimicrobial treatment and most commonly due to severe aortic valve insufficiency. At presentation, however, a regurgitant murmur was not always heard, an observation also made by others [22-24]. One patient manifested a major vascular embolic phenomenon. No cerebral embolism occurred, unlike the series of Pruitt *et al.* where this was the most common neurological complication of bacterial endocarditis and was noted in four of the six cases with pneumococcal endocarditis [25]. Because of the acute nature of pneumococcal endocarditis, it is not entirely unexpected that none of the signs such as splenomegaly, Osler's nodes, splinter hemorrhages, Janeway lesions and Roth spots were found. Interestingly, in one patient (*Case 4*) an 'afebrile' period was seen. Meningitis also developed in this patient, an association previously reported to occur frequently [10, 24, 25]. Clinical features of an acute endocarditis such as those caused by the pneumococcus are, however, no invariably apparent. According to one series of 325 patients with pneumococcal bacteraemia, in five of the seven patients with pneumococcal endocarditis the diagnosis was made at autopsy. These patients were either alcoholics or had cirrhosis [16]. Failure to diagnose infective endocarditis also arises in the elderly, since they may show a diminished febrile response and predominance of neurological events such as confusion [26]. In the elderly and probably also in alcoholics, a paucity of signs and symptoms might be responsible for errors or a delay in diagnosis.

Therapy. The four patients in which the diagnosis was made during life were treated with high doses of benzylpenicillin parenterally, which is still the drug of choice. Valve replacement was performed in three patients, and in all three paravalvular abscesses were present. Despite meticulous inspection of all paravalvular structures, abscesses may be missed at surgery. This can result in relapse of congestive heart failure as occurred in *Patient 5*. In their pathological study of left-sided infective endocarditis, Roberts and Buchbinder found valve ring abscesses in 12 of 45 patients at necropsy [27]. Infective endocarditis in these patients who were found to have valve ring abscesses, was caused by *S. pneumoniae* in three cases. Also, this series clearly showed that the pneumococcus in particular is able to infect an anatomically normal cardiac valve. Our series confirms this observation.

Prognosis. To determine prognostic factors, we studied the issue by statistical analysis of all adult patients with pneumococcal endocarditis reported in the past five years ($n = 36$, Table

TABLE 2. Univariate analysis of clinical features in relationship to outcome of pneumococcal endocarditis, based on 36 patients from the literature

	No. of patients from indicated group with factor			<i>p</i> -Value
	All (<i>n</i> = 36)	Deaths (<i>n</i> = 17)	Survivors (<i>n</i> = 19)	
Age (years, mean \pm SD)		54 \pm 13 (30–77)	50 \pm 16 (18–77)	0.12
Sex (<i>n</i>)				
Male	27	16	11	0.03
Female	9	1	8	
Portal of entry				
Pneumonia	18	9	9	0.73
Otitis media	2	2	0	0.12
Other	4	1	3	0.34
Unknown	12	5	7	0.63
Predisposing conditions				
Splenectomy	1	0	1	0.33
Alcoholism	11	7	4	0.19
Valves(s) involved				
Aortic	22	10	12	0.08
Mitral	8	6	2	
Both	3	0	3	
Tricuspid	2	1	1	
Complications				
Meningitis	16	10	6	0.19
Congestive heart failure	21	12	9	0.18

2). The overall mortality rate was 47.2 per cent (17 of 36 patients). Interestingly, age is not a prognostic factor ($p = 0.12$), although previously considered to be so [28]. The analysis also revealed that pneumococcal endocarditis occurred significantly more often in men than women ($p = 0.01$), and mortality in men was also higher than in women ($p = 0.03$). No other variable proved to be significantly related with outcome.

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