

ORIGINAL ARTICLE

ENDOCARDITIS IN GREENLAND WITH SPECIAL REFERENCE TO ENDOCARDITIS CAUSED BY *STREPTOCOCCUS PNEUMONIAE*

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ABSTRACT

Objectives. The aim of this retrospective study was to determine the incidence and outcome of infectious endocarditis in Greenland with an emphasis on pneumococcal endocarditis.

Study design. Retrospective, non-interventional study.

Methods. Review of files and medical history of all patients with infectious endocarditis from the Patient Registry in Greenland in the 11-year period 1995–2005.

Results. There were 25 cases of endocarditis, giving an incidence rate of 4.0/100,000 per year. Twenty-four percent of these cases were caused by *Streptococcus pneumoniae*, which is significantly more frequent than in studies on Caucasian populations, where pneumococcal infection was seen in 1–3% of endocarditis cases. The overall mortality rate was 12%. Pneumococcal endocarditis (PE) had the clinical characteristics of fulminant disease with frequent heart failure, complications and need for surgery. Among cases with PE, 67% needed acute valve replacement and the mortality rate was 33%.

Conclusions. The high incidence rate, clinical characteristics and grave prognosis of PE are consistent with another study of an Inuit population in Alaska.

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Keywords: Endocarditis, Streptococcus Pneumoniae, Pneumococcal infections, Inuit, Greenland

INTRODUCTION

Infectious endocarditis (IE) may be caused by a variety of microorganisms. In most series, *Staphylococcus aureus*, coagulase-negative staphylococci, *Streptococcus viridans* and enterococci are the predominant causative agents (1–4). In the pre-penicillin era, *Streptococcus pneumoniae* (*Strep. pneumoniae*) was a relatively frequent cause of endocarditis with a grave prognosis (5). In light of antibiotic therapy, the incidence rate of this infection has dramatically decreased in most populations.

Greenland is inhabited by 56,000 people. The majority (86%) are Inuit, and 12% are Caucasian, mostly Danes. One-fourth of the population live in the capital Nuuk, the remaining live in 16 small towns and a number of settlements scattered along the coastlines. Each town has its own small medical centre. All patients with severe or complicated diseases are transferred to Queen Ingrid's Hospital, where the only microbiological laboratory in Greenland is situated. Blood samples and cerebrospinal fluid (CSF) samples have to be sent by airplane from the coast medical centres to Nuuk for cultivation. The transport of these samples can take several days.

A recent study has shown a significantly elevated incidence rate of invasive pneumococcal disease among the Inuit population in Greenland (6), supporting the clinical impression that much of the observed infectious endocarditis in this population may be caused by *Strep. pneumoniae*. In this report we explore the infectious etiology of infectious endocarditis among the Inuit population of Greenland.

MATERIAL AND METHODS

The aim of this retrospective study was to investigate the incidence rate and outcome of IE in Greenland, especially regarding pneumococcal endocarditis (PE). All patients admitted to Queen Ingrid's Hospital are recorded with discharge diagnoses in a central patient registry. From this registry we identified all patients diagnosed with endocarditis over an 11-year period, from 1995–2005. Files were obtained from the archives at Queen Ingrid's Hospital in Nuuk. Requests for information were sent to the local treatment facilities for patients living outside of Nuuk. Patients eligible for thoracic surgery were sent to Rigshospitalet in Denmark, from which files describing additional medical treatment, surgery and pathology of the removed valves were obtained. One patient in a highly unstable condition was transferred to Lanspítalinn in Iceland.

Data collected from all files included race, age, gender, alcohol consumption, pre-existing heart disease, other medical conditions, antibiotic and immunosuppressant therapy at time of admission, speed of clinical progression (acute/subacute), blood cultures, echocardiographic findings, surgery, sequelae and survival. Blood cultures were performed at the local microbiology laboratory at Queen Ingrid's Hospital using standard microbiological methods. An immunochromatographic method to detect pneumococcal antigen in urine and/or cerebrospinal fluid (Binax Now) has been applied to cases with negative cultures since 2002. Analysis of valve material for pneumococcal DNA was performed by PCR technique (7).

The diagnosis of IE was based on medical history and characteristic echocardiographic findings such as vegetations or valve perfora-

tions, and supported by histological findings in the cases where valve replacement was necessary. All cases were validated and patients were excluded if their history or echocardiography did not agree with infectious endocarditis.

Acute clinical progression was defined as symptoms lasting ≤ 14 days before hospitalization. When symptoms had lasted more than 14 days, the case was defined as subacute.

Data were evaluated statistically using the chi-square test or Fisher's exact test when appropriate; $p < 0.05$ was considered significant. All incidence rates are crude rates calculated from all inhabitants in Greenland.

RESULTS

Table I gives an overview of the data collected for all cases. Twenty-five episodes of IE were recorded in 23 patients giving a crude incidence of 4.0/100,000 per year. Four cases in whom the diagnosis could not be sustained were excluded. Eighteen cases occurred in patients from the districts and 7 cases in patients from Nuuk. There was no difference in the incidence rate between Nuuk and the coast. All registered patients with IE were defined as Inuit and born in Greenland. One patient (case 10a,b,c) had a total of 3 episodes of IE. In accordance, factors related to patients individually such as predisposing conditions are described in relation to the number of different patients (23 patients), while factors related to the single episode are seen in relation to the total number of IE episodes (25 cases).

Bacterial causes could be identified in 14 (56%) of the 25 cases (Table I). In 6 cases, the endocarditis was caused by *Strep. pneumoniae* (24%). In 3 of these cases, pneumococci were

detected by blood culture. In 3 patients who had received antibiotics before blood samples were drawn for culturing, pneumococci were detected by 3 other methods: detection of pneumococcal antigen in cerebrospinal fluid from a concomitant meningitis (case 2), sputum culture from a concomitant pneumonia (case 3), and in microscopy and PCR of the removed valve (case 6) (Table I). In 11 cases (44%), no microbiological agent was detected. Seven of these patients had received antibiotics prior to blood sampling. Eleven of the 14 cases with negative blood culture came from the districts, including 2 cases with PE.

Demographic and clinical data are summarized in Table II.

Compared to other causes of IE, fewer patients with PE had pre-existing heart disease and more patients had a history of alcohol abuse. These differences were, however, not statistically significant.

Six patients had pneumonia prior to or concomitant with the endocarditis, 3 with PE and 3 with no detected microbiological agent.

One PE case presented with Austrian's syndrome, showing symptoms of pneumonia, endocarditis, meningitis and a history of alcohol abuse (case 2). One patient with culture-negative endocarditis also had septic arthritis, and 1 patient with IE caused by *Streptococcus viridans* developed osteitis of the fifth lumbar vertebra.

Sixty percent had valve replacement and 84% were discharged without disabling sequelae. Three patients died, giving an overall mortality rate of 12%. Among patients with PE, the mortality rate was 33% (Table II).

There were no statistically significant differences in clinical manifestations and outcomes between patients with PE and other causes of IE.

Table 1. Twenty-five cases with infectious endocarditis in Greenland in the period 1995–2005.

Case	Location	Age	Sex	Year	Microorganism	Acute/subacute	Pre-existing heart disease	Concurrent disease	Affected valve	Valve replacement	Outcome
1	Coast	70	M	1995	Strep. pneumoniae	subacute	unknown	ear infection	aortic	aortic homograft	survival
2	Coast	53	M	1998	Strep. pneumoniae	acute	none	pneumonia, meningitis	aortic/mitral	no	death
3	Nuuk	57	M	2001	Strep. pneumoniae	Subacute	rheumatic fever	pneumonia	aortic	aortic homograft	survival
4	Coast	43	M	2002	Strep. pneumoniae	acute	none	none	aortic	aortic homograft/mechanical aortic valve	survival
5	Nuuk	43	M	2004	Strep. pneumoniae	acute	none	none	aortic/mitral	no	survival
6	Coast	51	F	2005	Strep. pneumoniae	acute	none	pneumonia	aortic/mitral	biologic aortic and mitral valves	death
7	Coast	46	M	2001	Strep. Viridans	subacute	bicuspid aortic valve	none	aortic	mechanical aortic valve	survival
8	Coast	45	M	2003	Strep. Viridans	subacute	none	ostitis in 5th. Lumbal vertebra	aortic	mechanical aortic valve	survival
9	Coast	40	M	1998	Strep. Anginosus	subacute	none	none	mitral	no	survival
10a	Nuuk	46	F	1996	Staph. Aureus	acute	rheumatic fever	none	mitral	no	survival
10b	Nuuk	48	F	1998	Staph. Aureus	acute	-	none	mitral	no	survival
10c	Nuuk	50	F	2000	Staph. Aureus	acute	-	none	mitral	no	survival
11	Coast	27	M	1995	Staph. Epidermidis	acute	bicuspid aortic valve	none	aortic	pulmonal autograft (Ross)	survival
12	Coast	84	M	2000	E. Coli	subacute	none	none	aortic/mitral	no	survival
13	Coast	59	M	2000	Unknown	acute	none	apoplexia	aortic	no	survival
14	Coast	51	M	2002	Unknown	subacute	none	ear infection	aortic	mechanical aortic valve	survival
15	Coast	13	M	1995	Unknown	subacute	ventricular septal defect with aneurism	anoxic brain damage (cardiac arrest)	aortic/mitral	yes (procedure unknown)	survival
16	Coast	17	M	2001	Unknown	acute	mitral annuloplasty ring (mitral insufficiency)	none	mitral	mechanical mitral valve	survival
17	Nuuk	53	M	2000	Unknown	subacute	mitral insufficiency	none	aortic/mitral	mechanical mitral valve	survival
18	Coast	56	F	2002	Unknown	subacute	none	pneumonia	aortic/mitral	mechanical aortic valve + mitral annuloplastic	survival
19	Coast	48	M	2003	Unknown	acute	none	none	aortic	no	death
20	Coast	53	M	1997	Unknown	acute	none	None	aortic	mechanical aortic valve	survival
21	Coast	43	M	1997	Unknown	acute	aortic stenosis	apoplexia	aortic	mechanical aortic valve	survival
22	Nuuk	41	F	2000	Unknown	acute	none	pneumonia	aortic	aortic homograft	survival
23	Coast	41	M	2004	Unknown	Acute	None	pneumonia, infectious arthritis	mitral	No	Survival

M=male; F=female. Three case in the same patient (10a, 10b, 10c).

Table II. Demographic and clinical data in 6 cases of pneumococcal endocarditis compared to endocarditis from other causes.

	Pneumococcal endocarditis n=6 (24%)	Other causes of endocarditis n=19 ^a (76%)	All cases n=25 ^a
Sex M/F	5/1	14/5 ^a	19/6 ^a
Age yrs. Median (range)	52 (43-70)	45 (13-84)	51 (13-84)
Pre-existing heart disease	1 (17%)	7 (41%)	8 (35%)
Alcohol abuse	3 (50%)	3 (18%)	6 (26%)
Affected valve			
Aorta	3 (50%)	9 (47%)	12 (48%)
Mitral	0	6 ^a (32%)	6 ^a (24%)
Aorta + mitral	3 (50%)	4 (21%)	7 (28%)
Valve replacement	4 (67%)	11 (58%)	15 (60%)
Outcome			
Survival without disabling sequelae	4 (67%)	17 (89%) ^b	21 (84%) ^b
Death	2 (33%)	1 (5%)	3 (12%)

^aThree cases in the same patient.

^bOne culture negative patient had anoxic brain damage due to cardiac arrest during surgery.

DISCUSSION

The overall incidence of endocarditis in the present study of an Inuit population in Greenland was 4.0/100,000 per year. This correlates well with a recent multinational review of 3,784 patients by Moreillon et al. (8) who found an IE incidence rate of 3.6/100,000 per year. The incidence did not differ between the districts and Nuuk. Thus, there does not seem to be a recruitment bias based on geography, and the finding presumably represents the true incidence of endocarditis in Greenland.

In this retrospective study, we were unable to apply Duke's criteria (9) to all cases. However, all cases were secondarily validated to ensure that medical history as well as echocardiographic findings was consistent with IE.

Bacterial aetiology was only established in 14 of the 25 cases (56%). In 3 cases the microbial aetiology was found using techniques other than blood sampling. This leaves 14 cases

(56%) with culture negative IE. This is unusually high, compared to 2 recent studies with a culture-negative IE incidence rate between 13.7% (10) and 20% (11). Of these 14 cases, 7 patients had received antibiotic treatment prior to blood sampling, leaving 7 patients (28%) with true culture-negative endocarditis. Thus, antibiotic treatment prior to blood sampling can only partly explain the high incidence rate of culture-negative endocarditis. Most culture-negative cases came from the coast. This probably reflects the fact that district doctors often implement antibiotic treatments in febrile patients without taking samples of their blood for cultivation because of the longer time it takes to test results.

Furthermore, microorganisms may not survive being transported from the coast to Nuuk, which may result in false negative blood cultures. Accordingly, Meyer et al. (12) found a 3.5-fold higher incidence of invasive bacterial diseases among Nuuk patients than among

patients from the districts, based on positive cultures from normally sterile heart compartments.

Surgery was performed in 60% of all cases in our study. This is similar to other studies showing a surgery proportion of at least 45% (13,14). The 12% mortality rate in the present study is also in accordance with the in-hospital mortality rates of other studies, ranging from 11% to 26% with a median of 16% (9).

Today, PE is described as being an extremely rare disease, accounting for 1% to 3% of all cases of endocarditis (15–17). However, in the present study the relative incidence rate of PE was 6/25 cases (24%). This is significantly more frequent than the findings in a recent prospective study from Göteborg in Sweden showing a relative PE incidence rate of 3/99 patients (3%) ($p < 0.01$) (18). In our study, 43% of the microbiologically recognized episodes of endocarditis were caused by *Strep. pneumoniae*. Furthermore, it is possible that some of the culture-negative endocarditis episodes, in fact, were related to infection with *Strep. pneumoniae*, especially those with concomitant ear or lung infections. Thus, it is possible that the real PE incidences may be higher.

The comparison of the PE group with the other cases did not show any statistically significant differences, although there were trends towards a higher frequency of alcohol abuse and a lower frequency of pre-existing heart disease among the patients with PE. Alcoholism is known to be an important risk factor for the development of PE (19). The lack of statistical significance may well be a result of the small number of groups in this subgroup analysis.

The high PE incidence in the present study is in accordance with a study from Alaska among the Inuit living there, in which PE accounted for

15.8% of all cases with IE (20). Furthermore, some clinical characteristics were somewhat similar in the 2 studies regarding predisposing conditions such as alcoholism and heart disease, clinical progression, valve affection, need for medical/surgical intervention and outcome. Several studies (21–23) have shown that the incidence rate of invasive pneumococcal disease among Native American peoples (including Inuit) is significantly higher than within other populations and the prognosis tends to be adversely affected. A study in Greenland (6) showed a significantly elevated rate of invasive pneumococcal disease among the Inuit population with a yearly incidence of 54/100,000. Our study shows a yearly incidence rate of verified PE of 0.97/100,000, which means the development of PE in an estimated 1.8% of pneumococcal bacteraemia cases. In a newly published Danish study (24), PE was diagnosed in an average of 1.2% of all cases with pneumococcal bacteraemia. Given the divergence in study design, this small difference in proportion is hardly significant. Thus, it appears that PE has a higher incidence rate in Greenland because of a higher incidence rate of pneumococcal bacteraemia and not because of a particularly high cardiac susceptibility to *Strep. pneumoniae*.

Conclusions

This retrospective study showed an incidence of endocarditis of 4.0/100,000 per year. Twenty-four percent was caused by *Strep. pneumoniae*. The high incidence of pneumococcal endocarditis is related to a high incidence of invasive pneumococcal infection. Pneumococcal endocarditis had a grave prognosis with a mortality rate of 33% and with 67% needing valve replacement.

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