Nationwide study of recurrent invasive pneumococcal infections in a population with a low prevalence of human immunodeficiency virus infection

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ABSTRACT

Recurrent invasive infections caused by Streptococcus pneumoniae are rare, and often considered to be indicative of serious underlying illness. However, the prevalence of this problem, and the relevance of specific predisposing conditions, can be hard to assess, since many of the studies are based on specific risk groups. A population-based study of recurrent invasive pneumococcal disease in Iceland during the 30-year period 1975–2004 was performed. Clinical information, including mortality and vaccine use, was analysed retrospectively. Invasive pneumococcal isolates were serotyped and susceptibility testing was performed. During this period, 36 (4.4%) of 819 patients who survived an initial infection experienced recurrence, with a median time between episodes of 9.7 months. Pneumonia with bacteraemia was the most common clinical diagnosis (48% of cases), followed by bacteraemia without a clear focus (21%) and meningitis (13%). Most (94%) of the patients had identifiable predisposing conditions, most commonly, multiple myeloma in adults, and antibody deficiencies in children. Compared with children, adults were more likely to present with pneumonia (65% vs. 18%; p 0.0001). No significant change in the 30-day mortality rate was observed during the three decades of the study. Only 26% of eligible patients received pneumococcal vaccination. Patients with recurrent invasive pneumococcal disease should be investigated thoroughly for underlying diseases. Greater use of pneumococcal vaccines should be encouraged among high-risk patients. More effective preventive and therapeutic measures are needed to improve outcomes.

Keywords Bacteraemia, invasive infections, meningitis, pneumococci, recurrent infections, Streptococcus pneumoniae

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INTRODUCTION

Infections caused by Streptococcus pneumoniae are common, and invasive infections, such as bacteraemia and meningitis, caused by this organism are associated with high rates of morbidity and mortality [1,2]. Although the incidence of pneumococcal disease is increasing in some countries [3,4], the use of a seven-valent pneumococcal conjugate vaccine in a childhood vaccination programme in the USA has reduced the rate of invasive pneumococcal disease in both children and adults [5]. Many risk-factors for pneumococcal infection have been well-established, such as antibody deficiencies [6,7], defective antibody formation [8], complement deficiencies [9], asplenia [10], age (higher likelihood with extremes of age) [3], malnutrition [11], alcoholism [12,13], tobacco use [14], infection with human immunodeficiency virus (HIV) [15–18], renal insufficiency [19] and chronic disease [20].

Recurrent invasive pneumococcal disease has been described in numerous case reports and case series [21–31]. It has been stated that recurrence is a rare event [20,26–28], with a documented risk of 2.3–5.3% [17,26–28]. Recurrence is often considered to be a strong indicator of serious underlying illness [26,28], with a mortality rate as high as 47% during the recurrent episode [26], although...
the significance of these recurrences may depend, in part, on the age of the patient. One study found that recurrent invasive pneumococcal infections in young children did not indicate the presence of an unsuspected immunodeficiency [29]. Similarly, one case series described five children with recurrent invasive pneumococcal disease, two of whom had no detectable underlying disease [30]. Thus, the prevalence of various conditions that predispose to recurrent pneumococcal infections may be highly age-dependent. However, studies of this clinical entity have been limited by small patient numbers, short follow-up periods, and a primary focus on selected patient populations such as children and individuals with HIV infection [26,28,31].

The aim of the present study was to investigate the epidemiological trends, clinical characteristics and microbiological findings among children and adults with recurrent invasive pneumococcal infections in Iceland during a 30-year period. Because the annual incidence of HIV infection in Iceland is low, it was possible to assess the contributions of other risk-factors to recurrent disease.

PATIENTS AND METHODS

Setting and patient selection

Iceland is an island in the mid-Atlantic ocean, with a population that increased from 219,033 at the end of 1975 to 293,291 by the end of 2004. The socio-economic status is high and the inhabitants have universal access to a government-based healthcare system. The country has two university or university-affiliated hospitals and 14 county hospitals, as well as numerous smaller health clinics. All hospitals and clinics were included in this study. Blood cultures were processed at two or three sites in the country, and a single reference laboratory performed serotyping on all invasive S. pneumoniae isolates. All patients, adults and children (aged ≤16 years), with pneumococci cultured from blood, cerebrospinal fluid, joint fluid or peritoneal fluid, or patients with a positive Gram-stain cerebrospinal fluid smear and a positive latex agglutination test for pneumococci, were recorded in an electronic database that was used to identify recurrences.

Definitions

Individuals at risk of recurrent invasive pneumococcal disease were those who survived for 30 days after the initial episode of infection [17]. Recurrent pneumococcal disease was defined as two or more episodes of invasive pneumococcal infection separated by >4 weeks, or episodes separated by <4 weeks but caused by different pneumococcal serotypes, during a 30-year period (1 January 1975 to 20 September 2004).

Data registration

The following clinical data were collected by chart review: age, gender, socio-economic status, tobacco use, alcohol consumption and vaccination status. Each episode of infection was reviewed to determine the type of infection, presenting signs, previous medication, physical examination, complete blood count and biochemical profile, treatment and diagnosis at discharge. Results of radiological, immunological and histopathological investigations, including autopsies, were documented. The numbers and types of bacterial cultures were documented. Outcome (mortality at 30 days) was calculated from hospital charts and the national population register.

Microbiology

Serotyping of available invasive isolates was performed by coagglutination with antisera from the Statens Serum Institute (Copenhagen, Denmark). The invasive isolates were screened for penicillin resistance by the oxacillin disk-diffusion test [32]. Penicillin MICs were determined for all oxacillin-resistant isolates by Etest (AB Biodisk, Solna, Sweden). Isolates with a penicillin MIC ≥0.1 mg/L were defined as penicillin nonsusceptible. Four patients had two separate infections with the same pneumococcal serotype; six of these eight isolates were available for DNA fingerprinting by pulsed-field gel electrophoresis following DNA restriction with Smal [33].

Statistical analysis

The chi-square test was used for statistical comparison of the incidence of recurrence during the two halves of the study period. Fisher’s exact test was used for comparison of types of infection among adults and children. Statistical significance was set at p < 0.05. All tests were two-tailed.

Ethical approval

The study was approved by the National Bioethics Committee of Iceland and the Data Protection Authority of Iceland.

RESULTS

Epidemiology

Invasive pneumococcal infections were diagnosed in 933 patients during the study period. Of these 933 patients, 819 survived for >30 days after the initial episode, and 36 (4.4%) of the survivors had one or more invasive pneumococcal infections subsequently (total of 77 episodes). These 36 patients included 12 children with 28 infections (primary and recurrent), and 24 adults with 49 infections. The median ages of children and adults were 2.5 years and 65.3 years, respectively. The mean time between episodes was 15.4 months, with a median of 9.7 months (range, 15 days to 7.7 years). Two patients had infections separated by <1 month, but with different pneumococcal
serotypes. Three patients had three episodes of infection, and one patient had four episodes. The overall incidence rate of invasive pneumococcal disease during the first half of the study period was 8.3 cases/100 000 inhabitants/year, which doubled to 16.7 cases/100 000 inhabitants/year during the second half. Concurrently, the incidence of recurrent disease increased from 0.37 recurrences/100 000 inhabitants/year to 0.76 recurrences/100 000 inhabitants/year (p 0.04). Thus, the recurrence rates remained unchanged (4.3% and 4.4%, respectively) during the first and second halves of the study period.

Clinical characteristics

Table 1 summarises the clinical presentations of the two age groups. Overall, bacteraemic pneumonia was the most common clinical presentation (48% of cases), followed by bacteraemia without a clear focus (20.8%) and meningitis (13%). Adults were more likely to have bacteraemic pneumonia (p 0.0001), whereas children were more likely to have bacteraemia/sepsis without a specific focus (p 0.063) and meningitis (p 0.096).

The risk-factors of the 36 patients are shown in Table 2. All but two had one or more underlying diseases. Recurrent pneumococcal infection was the presenting manifestation of the underlying disease in seven (58%) of the 12 children. The most common disease in this group was IgG subclass deficiency and/or a poor antibody response (dysglobulinaemia) to antigenic stimuli. Among the 24 adults, immunoglobulin disorders were also the most common predisposing factor, with multiple myeloma present in six, monoclonal gammopathy in two, leukaemia in three, and HIV/AIDS in two patients. One child and two adults were affected by renal disease.

Microbiology

Antibiograms were available for isolates causing 67 (86%) of the episodes. Two (3%) of these 67 isolates were multiresistant (serotypes/groups 6B and 9). All other isolates were susceptible to penicillin. Serogroups or serotypes of invasive isolates were determined for 45 (58%) of 78 infections (Table 3). The serotypes of the isolates from both the initial and recurrent episodes were known for 18 patients. Of these, four (22%) had identical serogroups and DNA fingerprints. The remaining 14 (78%) isolates belonged to different serotypes.

Outcomes

The 30-day mortality rate for adults was 25%; no children died during this period. The mortality rate for meningitis was 25%, and that for non-meningitic episodes was 11%. No difference in mortality rates was noted between the first and second halves of the study period (data not shown).

DISCUSSION

The incidence of invasive pneumococcal disease is increasing in some countries [3,4]. In Iceland, the overall incidence doubled during the 30-year period.
period of this study. Clearly, incidence rates depend heavily on a variety of factors, including the availability of diagnostic tests and their appropriate use. In addition, the sensitivity and specificity of the tests are of major importance. Other potential explanations for this increase include a greater population at risk, the introduction of more invasive/virulent pneumococcal clones into the population, a loss of herd immunity, changes in environmental factors, such as smoking and air pollution, and severe virus infections, such as influenza, that predispose to pneumococcal infections. Among these potential explanations, improved detection probably plays a large role.

Published case reports and case series of recurrent pneumococcal infections [21–31] are limited by relatively few and/or selected patients and short follow-up periods. In the present study, an unselected population of children and adults was analysed for a 30-year period. King et al. [17] published a large population-based study of recurrent pneumococcal disease in the USA, but 44% of their 318 patients had HIV infection. Iceland has a low incidence of HIV infection (3/100 000 inhabitants/year), thereby allowing the contribution of other underlying diseases to the risk of recurrent invasive pneumococcal disease to be assessed.

Table 3. Serotypes and serogroups of invasive pneumococcal isolates from children (aged < 16 years) and adults (aged ≥ 16 years) with 77 episodes of infection

<table>
<thead>
<tr>
<th>Serogroups/types</th>
<th>Children, n (%)</th>
<th>Adults, n (%)</th>
<th>Total, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>–</td>
<td>1 (4)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>6</td>
<td>–</td>
<td>3 (12)</td>
<td>3 (7)</td>
</tr>
<tr>
<td>6A</td>
<td>–</td>
<td>1 (4)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>6B</td>
<td>2 (11)</td>
<td>1 (4)</td>
<td>3 (7)</td>
</tr>
<tr>
<td>7F</td>
<td>1 (5)</td>
<td>1 (4)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>9</td>
<td>–</td>
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<td>1 (2)</td>
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<tr>
<td>9V</td>
<td>1 (5)</td>
<td>1 (4)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>11</td>
<td>–</td>
<td>1 (4)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>14</td>
<td>4 (21)</td>
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<tr>
<td>16</td>
<td>1 (5)</td>
<td>1 (4)</td>
<td>2 (4)</td>
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<tr>
<td>17</td>
<td>–</td>
<td>1 (4)</td>
<td>1 (2)</td>
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<tr>
<td>18C</td>
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<td>1 (4)</td>
<td>2 (4)</td>
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<tr>
<td>19A</td>
<td>2 (11)</td>
<td>–</td>
<td>2 (4)</td>
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<td>–</td>
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<tr>
<td>31</td>
<td>–</td>
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<td>1 (2)</td>
</tr>
<tr>
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<td>3 (16)</td>
<td>1 (4)</td>
<td>4 (9)</td>
</tr>
<tr>
<td>38</td>
<td>0</td>
<td>2 (8)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Total</td>
<td>19 (101)</td>
<td>26 (104)</td>
<td>45 (96)</td>
</tr>
</tbody>
</table>

*Percentages do not add up to 100% because of rounding.

reported by most other studies [17,25–29,31], although a recurrence rate as low as 0.6% has also been reported [20]. Interestingly, this rate of recurrent disease in a population with few cases of HIV infection was similar to the rate of 5.3% reported by Turett et al. [27] in a population with a high prevalence of HIV infection. The recurrence rate in the present population remained stable during the 30-year study period, but the incidence of recurrent disease doubled, as did the incidence of invasive pneumococcal disease in the population as a whole.

In children, the most common risk-factor for recurrent pneumococcal disease was poor antibody formation after polysaccharide antigenic stimuli and Ig-subclass deficiencies. Patients with recurrent infections associated with defective antibody responses should be followed periodically, since this can be either a transient phenomenon related to an immature immune system, or a persistent selective impaired response [34].

The most common underlying diseases in adults were multiple myeloma and related disorders, accompanied by dysgammaglobulinaemia. Unlike the situation with children, only one adult was found to have a previously undiagnosed disease.

As reported previously [17,25], most (78%) patients were infected with different pneumococcal serotypes in the initial and recurrent episodes. Non-susceptibility to penicillin (MIC ≥ 0.1 mg/L) was found in only 3% of the isolates in the present study, a rate much lower than the rate of 12.4% found by King et al. [17] in the USA. However, the results are not entirely comparable, since penicillin resistance appeared in pneumococci in Iceland only in the late 1980s [33], and the period of the present study extended back to 1975. Nevertheless, these differences do reflect the more rapid spread of penicillin-non-susceptible pneumococci in the USA, which reached a frequency of 35.4% in 2002 [35], compared with 11% in Iceland [36]. The overall mortality rate of 17% associated with recurrent infections was similar to that of unselected patients with invasive pneumococcal disease [4], and was in good agreement with the results of Turett et al. [27].

Recommendations for vaccination with the 23-valent pneumococcal polysaccharide vaccine were introduced in Iceland in 1991, but only six (26%) of 22 patients who were infected after that date had been vaccinated. Children were more
likely than adults to receive the vaccine. Thirty-eight (84.4%) of the 45 known serogroups or serotypes detected in the present study are included in the 23-valent vaccine. Unfortunately, underuse of the 23-valent pneumococcal vaccine is still widespread [37].

Recurrent invasive pneumococcal infection in a child should prompt a thorough search for an underlying illness, but the underlying disease in adults is usually already known. Despite the availability of preventive measures, such as pneumococcal vaccination, antibiotic prophylaxis and administration of immunoglobulins, the proportion of patients with recurrent pneumococcal infections has remained stable and the mortality rate has not changed in Iceland during the past three decades. Improved compliance with vaccination guidelines should be encouraged.

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REFERENCES


