PNEUMOCOCCEMIA IN CHILDREN – A RETROSPECTIVE STUDY BEFORE UNIVERSAL PNEUMOCOCCAL VACCINATIONS

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Avainsanat: *Streptococcus pneumoniae*, bakteremia, pneumonia

Streptococcus pneumoniae (pneumokokki) on yleisin bakteeripneumonian ja akuutin otiitin aiheuttaja lapsilla. Pneumokokki voi aiheuttaa myös vakavia invasiivisia infektioita kuten meningiittiä ja sepsistä. Eri tutkimuslähteiden mukaan 18-60 % pneumokokin aiheuttamista verenkiertoon levinneistä infektioista on kuitenkin piileviä, joilla ei ole vakavia tai tiettyyn elimeen paikannettavia oireita. Termillä pneumokokkemia tarkoitetaan juuri tällaista pneumokokin aiheuttamaa piilevää infektiota.

Tämän tutkimuksen tarkoituksena oli selvittää veriviljelypositiivisten pneumokokkemiatapausten ilmaantuvuutta ja tunnusomaisia piirteitä verrattuna veriviljelypositiivisiin radiologisesti todennettuihin pneumokokkipneumoniatapauksiin.

Tutkimusaineistona käytettiin vuosilta 2001-2010 retrospektiivisesti kerättyjä 105 lapsen potilastietoja. Laboratorion tietokannoista haettiin lapset, joiden veriviljelyssä kasvoi pneumokokki. vastasyntyneet, kirurgiset potilaat, lapset joilla oli vakava perussairaus, ja potilaat joilla todettiin invasiivinen fokus kuten meningiitti, jätettiin tutkimuksen ulkopuolelle. Kaikki tutkimuksessa mukana olleet lapset hoidettiin Tampereen yliopistollisen sairaalan lastentautien klinikassa ja asuivat sairaanhoitopiirin alueella. Pneumonia todettiin 38 potilaalla ja loppuja 67 potilasta käsiteltiin pneumokokkemiatapauksina.

Pneumokokkemian vuosittainen ilmaantuvuus oli keskimäärin 2,48 /10 000 asukasta 1-12 kuukauden, 4,96/10 000 13-24 kuukauden ja 1,86/10 000 2-4 vuoden ikäisillä lapsilla. Kaikki pneumokokkemiapotilaat olivat alle kuusivuotiaita. Pneumokokkemiatapauksissa sairaalaan tuloa edeltäneen kuumeilun ja toisaalta myös sairaalassa aloitetun suonensisäinen G-penisilliinihoidon kesto olivat lyhyempiä kuin pneumoniatapauksissa. Sairaalassa tulovaiheen veren leukosyyttiarvo oli suurempi pneumokokkemiapotilailla (keskiarvo 26,6 *vs.* 21,9 x10E9/L, p=0.012), mutta seerumin CRP-arvo oli suurempi pneumoniapotilailla (keskiarvo 160 *vs.* 37,4 mg/L, p < 0,001). Toisaalta pneumokokkemiapotilaiden CRP-arvo nousi merkittävästi ensimmäisten sairaalahoitopäivien aikana antibioottihoidosta ja kliinisestä toipumisesta huolimatta. Yleisimmät pneumokokin serotyypit olivat 6B ja 14, jotka aiheuttivat 53,2% pneumokokkemiatapauksista.

Tämän tutkimuksen perusteella pneumokokkemialle tunnusomaisia piirteitä olivat alle kuuden vuoden ikä, nopea kuumeen nousu, korkea veren valkosolumäärä ja vain hieman kohonnut seerumin CRP-arvo sairaalaan tultaessa.

Syyskuussa 2010 otettiin 10-valenttinen pneumokokkirokote (Synflorix®) kansalliseen rokotusohjelmaan. Tämä rokote olisi kattanut 82,3% tutkimuksen pneumokokkemiatapauksista.

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Pneumococcemia in children – a retrospective study before universal pneumococcal vaccinations

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MS Henna Karppa was primarily responsible for reviewing the hospital charts of the patients, the outcome assessment, data analysis and writing the manuscript. Prof. Matti Korppi supervised the design and execution of the study, and contributed to the development of the protocol, analytical framework for the study and writing the manuscript. Dr. Risto Vuento was responsible for blood cultures, and attended data analysis and writing. Drs. Maija Toropainen and Tarja Kaijalainen, and Lotta Siira, MSc, were responsible for serotyping of *Streptococcus pneumoniae* strains, and attended data analysis and writing.

Abstract

Aim. To evaluate the incidence and characteristics of blood culture-positive occult pneumococcemia compared with blood culture-positive pneumococcal pneumonia in children.
Methods. In years 2001-2010, 105 children with positive blood cultures for *Streptococcus pneumoniae* were identified from hospital electronic files. The patient cards were retrospectively charted for clinical and laboratory data, and 38 patients had and 67 had not penumonia.
Results. The annual incidence of pneumococcemia was, on average, 29.0/10,000 at 0-12 months, 5.3/10,000 at 13-24 months and 1.9/10,000 at 2-4 years of ages, with no increasing or decreasing trend. The incidence of bacteremic pneumococcal pneumonia increased (p=0.022) during the study period. The duration of fever before hospitalization (<24 hours 73.9% *vs.* 25.0%, p=0.022) and the duration of intravenous antibiotics, usually G-penicillin (median 72 *vs.* 96 hours, p=0.021) was shorter in pneumococcemia patients. On admission, blood leukocyte count was higher in pneumococcemia (mean 26.6 *vs.* 21.9 x10E9/L, p=0.012), but serum CRP was higher in pneumonia (median 160 *vs.* 67.4 mg/L, p<0.001). The serotypes 6B and 14 caused 53.2% of pneumococcemia cases.
Conclusion. The incidence of pneumococcemia was highest in 1-to-2-year-old children, and typical for pneumococcemia was rapid onset of fever, high blood leukocyte count and a modestly elevated CRP on admission.

Key notes. The incidence of pneumococcemia was highest in 1-2 years old children, with no increasing trend during the study period. Instead, the incidence of bacteremic pneumococcal pneumonia increased significantly. Currently available 7-valent, 10-valent and 13-valent vaccines would have covered 77.4%, 82.3% and 90.3% of pneumococcemia cases, respectively.

Keywords. Pneumococcemia, Pneumonia, *Streptococcus pneumoniae*, Children, Occult bacteremia

[Introduction]

Streptococcus pneumoniae is the most common cause of bacterial pneumonia and otitis media in children (1-2). In addition, *S. pneumoniae* is able to cause blood stream infections and invasive infections like meningitis (4-7). In children, less than 5% of pneumococcal pneumonias are bacteremic with positive blood cultures (8, 9). On the other hand, pneumonia has been present in a third of children with pneumococcal bacteremia (3, 5, 6). In different studies, 18-60% of the pneumococcal bloodstream infections in children have been occult bacteremias with no severe or localizing signs or symptoms (3, 5, 6). An alternative term to occult pneumococcal bacteremia is pneumococcemia. When blood cultures have been systemically studied in <36 months old infants with high fever, *S. pneumoniae* has grown in 1.0-2.5% before and in 0-0.5% after large-scale pneumococcal vaccinations of infants (7, 10, 11). Blood leukocytes, especially neutrophils, have usually been substantially elevated but levels of other host markers like C-reactive protein (CRP) have varied (8, 11, 12). Clinical experience strongly suggests that there are a substantial number of patients with probable pneumococcemia presenting with high fever, elevated leukocytes and increasing CRP, in whom blood cultures remain as negative.

The aim of this retrospective hospital chart review was to evaluate the occurrence and characteristics of blood culture-positive pneumococcemia compared with blood culture-positive pneumococcal pneumonia. The data were collected for 10 years before the start of universal pneumococcal vaccinations of Finnish infants.

Subjects and methods

Children with positive blood cultures for *Streptococcus pneumoniae*, who were <16 years old and were treated in the Department of Pediatrics, Tampere University Hospital (Tampere, Finland) in years 2001-2010 were identified from the electronic files of the Laboratory Center of the hospital. Newborns treated in the neonatal wards, including neonatal intensive care unit, children with malignant diseases treated in the hemato-oncologic ward and children with surgical diseases treated in the ward of child surgery were not included. In all, 121 cases were found, and among them, 16 children were additionally excluded: 12 had pneumococcal meningitis, 1 had an underlying immunosuppressive illness and 3 were treated for pneumococcal sepsis in the intensive care unit. The remaining 105 patients formed the subjects of the present study.

Two blood culturing instruments were used during the study period, until 2007 BACTEC 9240 (BD Diagnostic Systems, Sparks, MD, USA) and from 2007 BacT/ALERT 3D (bioMerieux SA, Marcy L'Etoile, France).

Serotyping of the *S. pneumoniae* strains found in blood cultures was performed in the pneumococcal reference laboratory (National Public Health Institute, Oulu, Finland) by counterimmunoelectrophoresis with pneumococcal antisera (Statens Serum Institut, Copenhagen, Denmark) and for neutral serogroup 7 and serotype 14 by latex agglutination, as described previously (13). The capsular reaction test Quellung was used as a confirmation method when needed.

One of the authors (HK) reviewed retrospectively the hospital records of the patients. The collected data included patients' age, gender, underlying illness, duration of fever before admission and during the hospital stay, length of hospital stay, body temperature on admission, general condition on admission, chest radiographs, blood leukocytes and serum C-reactive protein (CRP) on admission and on day 1-2 of the hospital stay, the duration of antibiotic treatments and the names of antibiotics used.

Chest radiograph had been studied in 94 (89.5%) cases, and 38 children (36.2% of all children; 40.4% of those with chest radiographs available) with an infiltration interpreted as pneumonia by the radiologist were allocated into the group of bacteremic pneumonia. The 56 children with no pneumonia in the chest radiograph and those 12 from whom radiograph was not studied (no clinical suspicion on pneumonia), were allocated into the group on bacteremia without pneumonia. Thus there were 67 children with pneumococcal bacteremia with no pneumonia or another invasive focus, and these patients are called as pneumococcemia cases in the present study.

Statistics

The data were analyzed with PASW Statistics 18 for windows package. In the exploratory data analysis, all variables except blood leukocytes were non-normally distributed, and therefore, Mann-Whitney U test was used for these continuous variables. T-test was used for blood leukocytes. In the analyses of categorized variables, Chi-square test and Fisher`s exact test were used as appropriate. Logistic regression was used when adjustment for age was indicated. Poisson binomial regression

was used to analyze the annual trends in the occurrence of pneumococcemia and bacterial pneumococcal pneumonia.

Tampere University Hospital is the only hospital providing inpatient care for children in the area. At the end of the year 2008, the child population aged ≤15 years was 84314 meaning an average age cohort of 5270 children (The Official Statistics of Finland). The annual age-specific incidence of pneumococcemia was calculated based on these figures.

Ethics

Since only data from hospital records were applied, the study was done by the permission of the Chief Doctor of the Tampere University Hospital.

Results

As seen in Fig. 1, the annual number of pneumococcemia cases varied between 3-10, and the number of pneumonia cases varied between 1-7 with an increasing trend (p=0.022). There were 59 (56%) boys and 46 girls. As seen in Fig. 2, the pneumococcemia / pneumonia ratio decreased in relation to age (p=0.007). All pneumococcemia cases were in children <6 years of age, and 20.9% were <12 months, 62.7% <24 months and 94.0% <48 months old (Fig. 2). On average, the annual age-specific incidence of pneumococcemia was 2.9/10,000 at 0-12 months, 5.3/10,000 at 13-24 months and 1.9/10,000 at 2-4 years of age.

The children with pneumococcemia were significantly younger (median 18 months) than children with pneumonia (Table 1). The duration of fever before hospitalization was shorter in pneumococcemia than in pneumonia patients (<24 hours 73.9% *vs.* 25.0%; <48 hours 86.2% *vs*. 61.1%; p=0.022). Likewise, the duration of intravenous antibiotics, usually penicillin G (median (IQR) 72 (48-96) *vs.* 96 (72-120) hours, p=0.021) was shorter in pneumococcemia patients. However, there were no significant differences in the duration of fever in hospital or in the length of hospital stay (Data not shown). Two-thirds of the pneumococcemia patients became non-feverish within 12 hours in hospital, and all children recovered without any complications.

On admission, blood leukocyte count was higher in children with pneumococcemia (mean 26.6

x10E9/L) than in children with pneumonia, but serum CRP was higher in children pneumonia (median 160 mg/L) (Table 1). Serum CRP was even low (<11.4 mg/L) in 25% of pneumococcemia patients. The difference in CRP between the groups remained statistically significant in logistic regression adjusted for age (p=0.019), but the difference in blood leukocytes changed to non-significant (p=0.290). In pneumococcemia cases, serum CRP increased significantly during 1-2 days in hospital, though intravenous antibiotics were started (Table 1).

Over 70% of both pneumococcemia and pneumonia patients were treated primarily with intravenous G-penicillin, and both the start with and change to cephalosporins was rather rare (Table 2). The treatment continued with oral amoxicillin or penicillin in nearly all cases; 9.2% of pneumococcemia patients received cephalosporins, and 13.9% of pneumonia patients received cephalosporins or macrolides.

Pneumococcal serotypes 6B and 14 were the two most common being present in 53.2% of pneumococcemia cases. Other 14 identified serotypes were seen in less than 10% each. There were no significant differences in serotype distribution between pneumococcemia and pneumonia patients (Table 3). Likewise, there were no significant differences between different years or between the four age groups (Data not shown). Currently available 7-valent, 10-valent and 13-valent vaccines would have covered 77.4%, 82.3% and 90.3% of pneumococcemia cases, respectively.

Discussion

There are four main results in this retrospective, geographically representative, 10-year study on the occurrence and characteristics on blood culture-positive pneumococcemia *vs.* blood culture-positive pneumococcal pneumonia in children. First, pneumococcemia was more common than bacteremic pneumonia at <48 months of age, and all pneumococcemia cases were in children aged <6 years. Second, the duration of fever before admission was shorter in children with pneumococcemia, being less than 24 hours in over two-thirds. Third, blood leukocytes on admission were higher in children with pneumococcemia, but it is important to note that on average, blood leukocytes were high, over 20x10E9/L, in both groups. Instead, serum CRP was higher in children with bacteremic pneumonia on admission, but not anymore in hospital. Although intravenous antibiotics were introduced to all but one of pneumococcemia patients, serum CRP rose significantly during 1-2 days in hospital. And

fourth, the great majority of both pneumococcemia and pneumococcal pneumonia cases were treated with G-penicillin, and intravenous cephalosporins were used in <20% during hospitalization and oral cepahlosporins in <10% after hospitalization.

In Finland, the average annual incidence of all invasive pneumococcal infections was 2.2/ 10,000 at age <12 months, 5.2/ 10,000 at age 12-24 months and 1.3/ 10,000 at age 25-48 months in 1995-2002 (14), which fits well with our results. The present 5.3/ 10,000 incidence of pneumococcemia at 23-48 months of age was very similar to the 4.8/ 10,000 incidence in Spain (3). All these figures describe the situation before the start of universal pneumococcal vaccinations of infants and young children. The experience form other countries has shown that vaccinations are effective especially against the bacteremic forms of pneumococcal diseases, including occult pneumococcal bacteremia (10, 15, 16). In many countries, vaccinations against *Haemophilus influenzae* type b have totally eradicated invasive diseases (17), and *S. pneumoniae* has remained, regardless of the vaccination status of the area, the most frequent pathogen isolated from young children with blood stream infections (18, 19).

The universal pneumococcal vaccinations of Finnish infants with 10-valent vaccine started in September 2010. Thus, about 1400 infants aged <1 year (27% of the age cohort) were vaccinated at least once in 2010 in the study area. In addition, 2300 infants aged <18 months (22% of the age cohort) had been vaccinated in the otitis media study in 2009 and 1700 infants (16% of the age cohort) in 2010. Concerning pneumococcemia, the years 2009 and 2010 were low-incidence years, as were also the years 2003, 2006 and 2008. We consider that these variations are within the rates of spontaneous annual variations and that our results well represent the situation before universal pneumocccal vaccinations of infants.

In the present study, radiological infiltrations were seen in 36% of the patients with pneumococcal bacteremia. The pneumonia / pneumococcemia ratio sounds high, and may be due to pulmonary infiltrates caused by preceding or concomitant viral infection (8, 20). On the other hand, this may also reflect the increase of pneumococcal pneumonia, as demonstrated in the present study and in many previous studies before universal pneumococcal vaccinations (21, 22). In a Finnish, prospective, population-based study, age-, sex- and place of residence-specific incidence of serologically confirmed pneumococcal pneumonia varied between 48-188/ 10,000 in 0-4-year old children (23). Since 1-2% of pediatric pneumococcal pneumonias were blood culture-positive (23), the current incidence of bacteremic pneumococcal pneumonia, 1.6/ 10,000, is in line with

population-based incidence of overall pneumococcal pneumonia in young children.

The clinical picture of pneumococcemia is poorly characterized, as reflected by the other name of the disease, occult pneumococcal bacteremia. Clinical experience suggests that the patients are <5 years old, and present with rapid onset of high fever. The general condition is modestly but not severely decreased. Blood leukocytes and especially neutrophils are elevated, and serum CRP may be only slightly elevated, or even low (11, 12, 24) as seen in 25% of the present patients. Serum CRP reflects tissue damage and needs >8 hours to elevate in blood stream infections. In a study from Switzerland, clinical signs predictive for severe invasive pneumococcal disease in <5 years old children were tachycardia for sepsis, tachypnea for pneumonia, and meningeal signs for meningitis. Leukocyte, neutrophil and platelet counts were lower and CRP concentrations were higher on admission in children with complicated infection than in children with uncomplicated infection but, due to wide overlap, the tests were not of prognostic value (25). In two other studies, high blood leukocytes (>20.0 x10E9/L, likelihood ratio 7.1) and high blood neutrophils (>15.0 x10E9/L, likelihood ratio 10.7) were both sensitive and specific to screen pneumococcemia among young feverish children (11, 12, 24, 26). In the present study, pneumococcemia was associated with higher blood leukocytes and lower serum CRP compared to bacteremic pneumonia on admission. Though children became non-feverish rapidly and improved well after starting antibiotics, serum CRP continued to increase the next two days in hospital.

Antibiotic resistance in bacterial strains must be considered when selecting treatment for invasive or bacteremic pneumococcal infections. In Finland, <5% of *S. pneumoniae* strains are resistant to penicillin, and thus, penicillin is still the first-line drug in pneumococcal infections (27). Accordingly, the therapy was successfully started with intravenous G-penicillin in 80% and continued with oral penicillin or amoxicillin in 90% of both pneumococcemia and bacteremic pneumonia cases.

The result that serotypes 6B and 14 were the two predominating serotypes is in accordance with earlier observations from Finland. In 1985-1989, the most common serogroups / types were, in this order, 14, 6, 19, 7, 18 and 23, and formed 78% of all invasive 452 pneumococcal infections in Finnish children (28). In 1995-2002, the most common serotypes in children under 5 years were 6B, 14, 19A, 18C and 7F (14). Currently available 7-valent, 10-valent and 13-valent vaccines would have covered 77.4%, 82.3% and 90.3% of the pneumococcemia cases of the present study.

The results of the present study must be interpreted cautiously. This was a retrospective hospital chart review, though covering 10 years and a geographically defined child population. This means that in feverish children, blood bacterial cultures and chest radiographs were taken on clinical indications, and not systemically. Despite of these limits, the current study provides useful pre-vaccination data on pneumococcal bacteremia for further post-vaccination studies.

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Figure 1. Annual hospitalizations for pneumococcemia and bacteremic pneumococcal pneumonia in years 2001-2010 (p= 0.022 for the increasing trend of the incidence of bacteremic pneumococcal pneumonia)

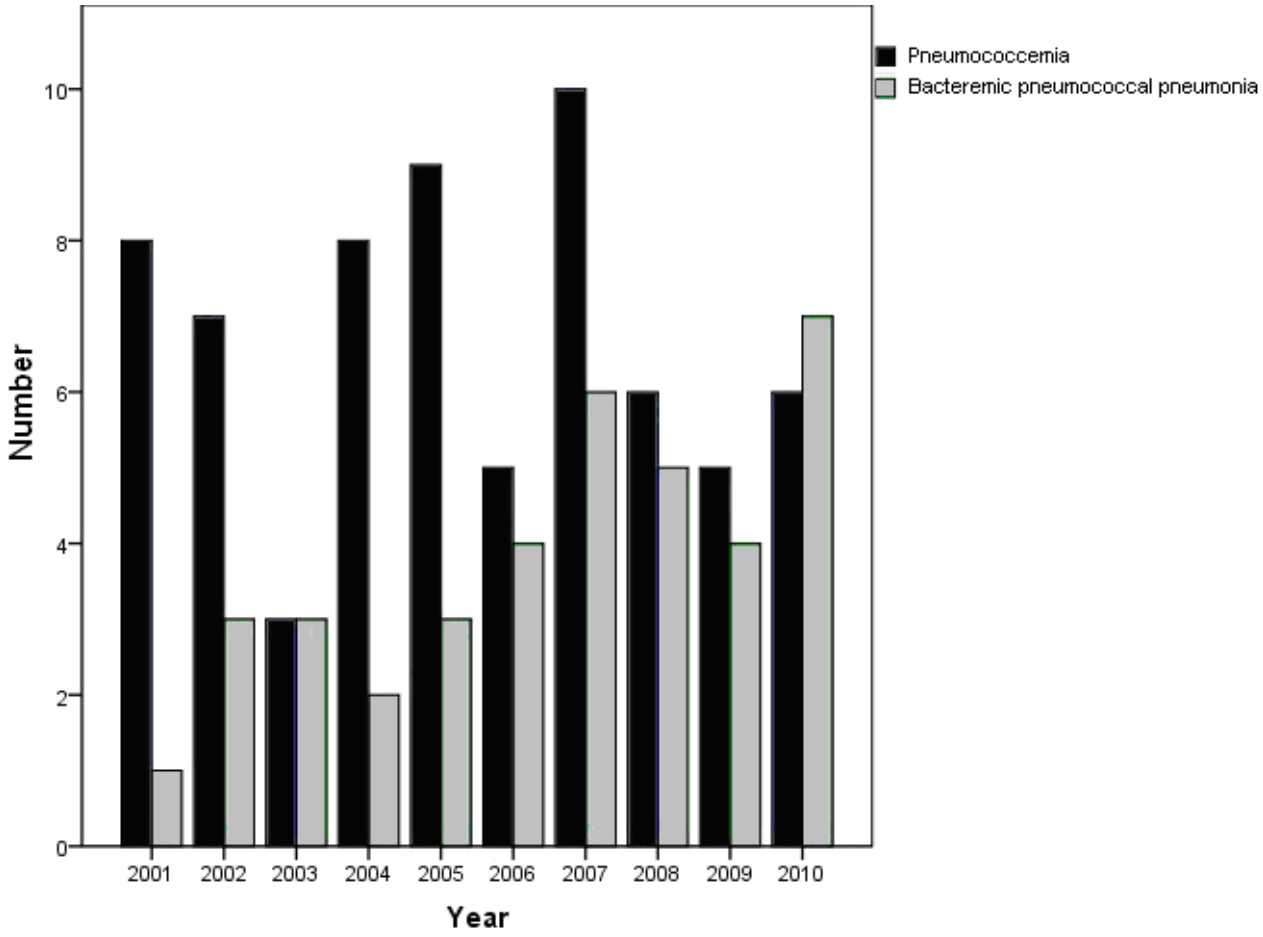

Figure 2. Pneumococcemia and bacteremic pneumococcal pneumonia in relation to age (all pneumococcemia cases were in children <6 years of age)

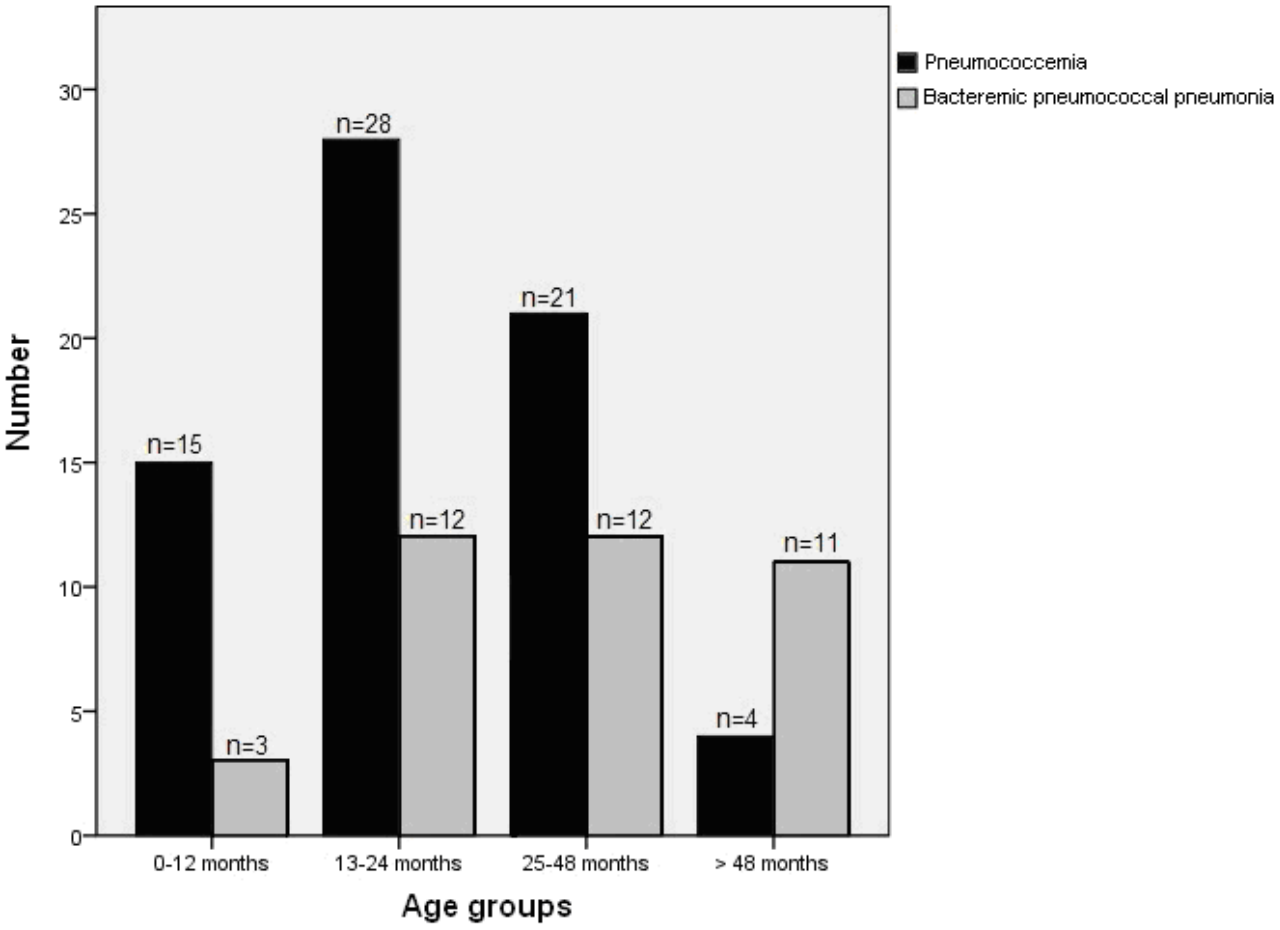

Table 1. Age, sex, fever, general condition and laboratory markers on admission and during the two first days in the hospital in the relation of pneumococcemia *vs.* bacteremic pneumococcal pneumonia

Parameter	Pneumococcemia group (N=67)	p value	Pneumonia group (N=38)
Age in months (median, range)	18 (1.2-67)	0.005	28 (4.8-192)
Males	38 (56.7%)	0.885	21 (55.3%)
Females	29 (43.3%)		17 (44.7%)
On admission			
Blood leukocytes x10E9/L (mean, SD)	26.6 (8.3)	0.012	21.9 (8.8)
Serum C-reactive protein mg/L (median, IQR)	67.4 (11.4-112.4)	<0.001	160.0 (68.5-222.2)
Body temperature °C (mean, SD)	39.7 (0.52)	0.115	39.5 (0.82)
General condition decreased	16 (23.9%)	0.158	14 (36.8%)
On day 1-2 in hospital			
Blood leukocytes x10E9/L (mean, SD)	22.5 (9.3)[1]	0.805	21.6 (13.0)[2]
Serum C-reactive protein mg/L (median, IQR)	94.6 (53.9-154.2)[3]	0.733	110.3 (69.8-165.9)[4]

SD = standard deviation; IQR = interquartile range
p_1 = 0.051 *vs*. on admission
p_2 = 0.0.114 *vs*. on admission
p_3 = <0.001 *vs*. on admission
p_4 = 0.691 *vs.* on admission

Table 2. Empirically selected intravenous antibiotics before blood culture results in the pneumococcemia or bacteremic pneumococcal pneumonia groups

Intravenous antibiotics	Pneumococcemia group (N=65)	Pneumonia group (N=35)
G-penicillin primarily	52 (80.0%)	28 (80.0%)
Change to cefalosporin	8/50 (16.0%)	3/25 (12.0%)
Cefuroxime primarily	5 (7.7%)	4 (11.4%)
Total cefalosporins	14 (21.5%)	7 (20.0%)

Five patients were not included in the table: one patient in the pneumococcemia group received ceftriaxone; one in the pneumococcemia group and one in the pneumonia group did not receive intravenous antibiotics; two in the pneumonia group received antibiotics in combinations.

Table 3. Serotypes in pneumococcemia and bacteremic pneumococcal pneumonia patients

Serotype	All N=98	Pneumococcemia N=62	Bacteremic pneumonia N=36
3	3 (3.1%)	1	2
6A	2 (2.0%)	2	0
6B	23 (23.5%)	17[1]	6
7F	8 (8.2%)	3	5
9V	5 (5.1%)	3	2[2]
14	26 (26.5%)	16	10
15B	1 (1.0%)	0	1
15C	1 (1.0%)	1	0
18C	7 (7.1%)	6	1
19A	6 (6.1%)	2	4
19F	5 (5.1%)	5	0
22F	2 (2.0%)	0	2
23A	2 (2.0%)	2	0
23F	4 (4.1%)	2	2
33	1 (1.0%)	1	0
38	2 (2.0%)	1	1

1: One patient had both serotype 6B and 6A
2: One patient had both serotype 9V and 10