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Clinical response to antibiotic therapy for community-acquired pneumonia

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Abstract Childhood community-acquired pneumonia is a common and potentially serious problem worldwide. Unless the patient has bacteraemia or pleural empyema, aetiological diagnostics are limited and antibiotic treatment is empirical. Published data on expected response to therapy are scarce. To determine the clinical response to antibiotic treatment in a developed country in otherwise healthy children with community-acquired pneumonia, we conducted a prospective study of 153 hospitalised children with pneumonia. The role of 17 microbes as potential causative agents was evaluated. The duration of fever (> 37.5°C) and hospitalisation were studied as objective measures of recovery. A potential aetiology was found in 83% of 153 patients: 29% of the patients had sole viral and 26% sole bacterial and 29% mixed viral-bacterial infections. The median duration of fever after the onset of antibiotic treatment (mainly penicillin G) was 14 h and the median duration of hospitalisation was 48 h. Patients with mixed viral-bacterial infection became afebrile more slowly than those with either sole viral or sole bacterial infections. *Conclusion*: The findings indicate that in a developed country, children with pneumonia make a rapid, uneventful recovery needing only a short hospital stay. Expensive and time-consuming microbiological investigations are not required once bacterial sepsis has been excluded.

Keywords Antibiotics · Pneumonia · Recovery

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Abbreviations *CAP* community-acquired pneumonia · *RSV* respiratory syncytial virus

Introduction

Childhood community-acquired pneumonia (CAP) is a common illness, annually affecting ca. 1.5 million children in the European Union (of 64 million children < 15 years of age) [3, 13, 17, 26]. Several direct and indirect aetiological studies suggest that *Streptococcus pneumoniae*, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae* and *Haemophilus influenzae* are the most common bacteria causing CAP [14, 21, 33]. Increasing lack of susceptibility of *S. pneumoniae* to penicillin and macrolides, lack of susceptibility of *M. pneumoniae* and *C. pneumoniae* to betalactams and increasing betalactamase production of *H. influenzae* suggest that one single antibiotic may not be effective in all cases of pneumonia. Furthermore, in up to 50% of CAP cases in children, there is evidence of viral infection [14, 27].

Surprisingly, few comprehensive studies of the antibiotic treatment of CAP in children have been reported from developed countries. No prospective placebo-controlled study has been reported. This explains the wide variation in the empirical treatment recommendations [3, 17, 26]. Limited study data are available on the expected response to treatment in children with CAP. We report the clinical responses and outcomes to antibiotic treatment in 153 children hospitalised for uncomplicated CAP with carefully defined possible aetiology.

Subjects and methods

Subjects

During the 3 years between January 1st 1993 and December 31st 1995, 254 patients with radiologically confirmed childhood CAP were prospectively enrolled in the study at the Department of Paediatrics, Turku University Hospital. The main causes of

hospitalisation were high fever, dyspnoea, malaise/lethargy, vomiting or poor appetite. The diagnosis was based on a simultaneous finding of infiltrates compatible with pneumonia on the chest X-ray film as well as signs and symptoms of acute infection and fever ($>37.5^{\circ}$C). The role of 17 microbes (10 viruses and 7 bacteria) was studied. The details of the methods and microbiological findings have been reported earlier [14]. In brief, antibody tests with acute and convalescent serum samples were used for bacterial diagnosis. Viral diagnosis was based on virus culture, sensitive immunoassay for the antigens of seven viruses and a polymerase-chain-reaction assay for rhinoviruses from nasopharyngeal aspirates and serological tests with acute and convalescent sera. A blood sample for blood culture was taken from 125 patients and only one patient was found positive for *S. pneumoniae*. Of the 254 patients, 61 had received antibiotic treatment before hospitalisation, 23 patients had no fever on the ward, and at the time of hospitalisation and onset of antibiotic treatment, four patients had complicated pneumonia (two patients had empyema, one patient bronchiectasis and one a cystic malformation of lung). In addition, 13 patients had severe underlying chronic conditions (six had genetic syndromes, six neurocognitive disorders and one astrocytoma). All these 101 patients were excluded from the analysis and thus 153 patients were included in the study. The antibiotic treatment was chosen by the attendant physician. The median age of the 153 patients was 2.3 years (range 0.1–16.7 years). Twenty-one (14%) patients were 0 to 11 months of age, 46 (30%) 12 to 23 months of age, 49 (32%) 2 to 4 years of age and 37 (24%) were 5 years of age or older. Of the patients, 53% were boys. Of the 153 patients, 18 had stable bronchial asthma, 5 atopy, 3 had been premature, 2 had congenital heart disease, 2 had epilepsy in addition to bronchial asthma, 1 had diabetes mellitus, 1 had recovered from acute lymphoblastic leukaemia, and 123 patients (80%) were healthy.

The duration of fever (>37.5°C) and the duration of hospitalisation were studied as objective measures of recovery. These data were recorded from patient charts as hours. Body temperature was measured rectally in patients <3 years of age and in the axilla in children ≥ 3 years of age. Temperature was measured in the ward every 6–8 h; when a temperature was found normal, the duration of fever was marked as 3 h of the 6–8 h period. Of the 153 patients, 120 febrile patients (78%) were treated with paracetamol or naproxen.

The follow-up examination was carried out about 3–4 weeks after discharge, when, in addition to a careful history of the time after discharge and to a clinical examination, blood samples for viral and bacterial serology and a chest radiograph were taken.

Statistical analyses

Pearson's standard chi-squared test was used to compare proportions between the groups (Fisher's exact test when the expected count was less than 5) and the Mann-Whitney test to determine the statistical differences in continuous variables. Differences in the duration of fever between the separate infection groups (Fig. 1) were analysed using the survival analysis approach with the logit model for discrete response variables. These analyses were done using the Probit Procedure of the SAS System for Windows, version 8.2 [1].

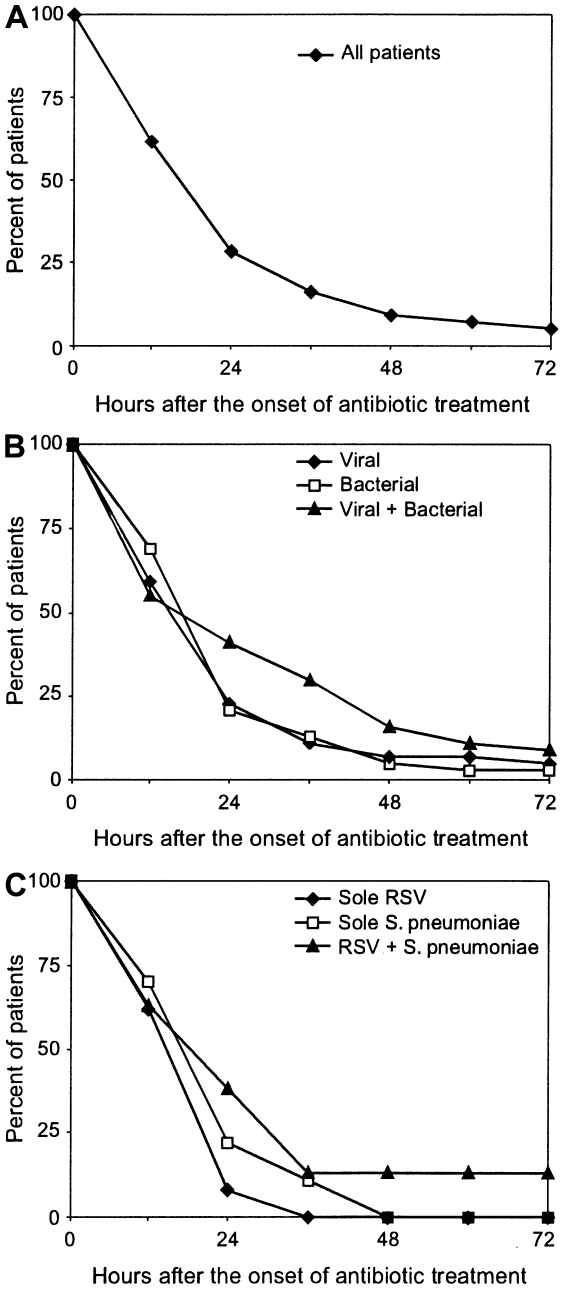

Fig. 1 Response to treatment: percentages of febrile (>37.5°C) patients after onset of antibiotics. **A** All patients. **B** Patients with either sole viral, sole bacterial, or mixed viral and bacterial infection. $P=0.89$ when comparison is made between groups of patients with sole viral and sole bacterial infection, $P=0.08$ between sole viral and mixed infection and $P=0.04$ between sole bacterial and mixed infection. **C** Patients with either sole RSV, sole pneumococcal, or mixed RSV and pneumococcal infection. $P=0.30$ when comparison is made between groups of patients with sole RSV and sole pneumococcal infection, $P=0.03$ between sole RSV and mixed infection and $P=0.04$ between sole pneumococcal and mixed infection

Results

A potential aetiology was found in 127 (83%) of 153 patients: 44 (29%) patients had evidence of sole viral and 39 (26%) of sole bacterial infection and 44 (29%) of mixed viral-bacterial infection. The probable aetiological agents were: *S. pneumoniae* in 60 (39%) patients, respiratory syncytial virus (RSV) in 35 (23%), rhinovirus in 33 (22%), parainfluenza viruses 1, 2, 3 in 20 (13%), non-typeable *H. influenzae* in 14 (9%), adenovirus in 10 (7%), *M. pneumoniae* in 9 (6%), influenza viruses A or B in 6 (4%), *M. catarrhalis* in 6 (4%), coronavirus in 4 (3%), *C. pneumoniae* in 4 (3%), human herpes virus 6 (HHV 6) in 2 (1%), *Streptococcus*

pyogenes in 1 (1%) and *Bordetella pertussis* in 1 (1%) patient. The most common viral-bacterial infections were rhinovirus + *S. pneumoniae* ($n=15$) and RSV + *S. pneumoniae* ($n=8$) infections. On admission, the median WBC was 17.5×10^9/l and the median level of serum CRP 85 mg/l. Of the patients, 72% had alveolar infiltrates on the chest X-ray film. Sole bacterial and viral pneumonias differed significantly in the number of alveolar pneumonia, median CRP and median WBC (Table 1).

Before hospitalisation, the median duration of fever in the 153 children was 2.0 days (range 0–11 days). On the ward, the median duration of fever after onset of antibiotic treatment was 14 h (range 2–127 h) (Table 1). Interestingly, the durations of fever in patients with sole bacterial and sole viral infection were similar, but patients with mixed viral and bacterial infections had longer durations of fever after onset of antibiotic treatment (Fig. 1). The same finding, statistically significant, was obtained when patients with sole (all other concomitant infections excluded) RSV, *S. pneumoniae*, and mixed RSV and *S. pneumoniae* pneumonia were compared (Fig. 1).

Of the 153 patients, 43 (28%) had fever lasting ≥24 h after onset of antibiotic treatment. Fever lasting for ≥48 h was considered treatment failure and was recorded in 13 (9%) of the 153 children (Table 1 and Fig. 1). Half of the patients (7/13) with treatment failure had evidence of mixed viral-bacterial infection, three (23%) had sole viral infection and two (15%) sole bacterial infection; in one patient no possible aetiology was found. The pathogens usually found in patients with treatment failure were RSV (46%) and *H. influenzae* (39%). Seven (5%) patients had fever lasting for ≥72 h; only one of them had sole bacterial infection (*H. influenzae*). Two patients had fever for ≥120 h; both had viral (one influenza A virus and one with RSV and coronavirus) infections. The median duration of hospital stay was 48 h (range 7–240 h).

Of the patients, 106 were treated with intravenous penicillin G, 13 with cefuroxime, and the rest 34 with other antibiotics (Table 2). The penicillin treatment group showed a trend for more treatment failures in children with either *B. pertussis*, *C. pneumoniae*, *M. catarrhalis*, or *M. pneumoniae* pneumonia (penicillin-non-susceptible bacteria) compared to children with sole *S. pneumoniae* pneumonia (2/16 versus 0/21 patients respectively; $P=0.18$). The initial antibiotic therapy was changed in six patients: three of them had sole viral, two mixed viral-bacterial infection, and in one patient the aetiology was not established. After discharge, all 153 children received oral antibiotics so that the total duration of antibiotic treatment was 7–10 days. Seven patients had fever at home immediately after discharge from the hospital; four of them had mixed viral-bacterial infection, two sole bacterial infection, and one sole viral infection.

A follow-up examination was carried out in all 153 children 17–62 days (median 29 days) after admission to

Table 1 Characteristics of 153 children with CAP with defined aetiology treated with antibiotics in hospital

	All patients ($n=153$)	Viral infection ($n=44$)	Sole RSV infection ($n=13$)	Bacterial infection ($n=39$)	Sole pneumococcal infection ($n=27$)	Mixed viral and bacterial infection ($n=44$)	Mixed RSV and pneumococcal infection ($n=8$)
Duration of fever before hospitalisation (days)[a]	2.0 (0–11)	2.0 (0–11.0)	2.0 (0–4.0)	2.0 (0–7.0)	1.0 (0–7.0)	2.0 (0–7.0)	2.0 (0.3–5.0)
High fever ≥39°C	125 (82%)	31 (71%)	8 (62%)	33 (85%)	23 (85%)	37 (84%)	8 (100%)
WBC$\times10^9$/l[a]	17.5 (4.6–50.1)	16.3 (4.6–34.3)*	9.2 (4.6–25.5)***	19.7 (5.2–40.5)	22.51 (7.6–39.8)	14.9 (6.6–50.1)	12.5 (8–26.4)
WBC > 15×10^9/l	93 (61%)	22 (50%)	4 (31%)*	29 (74%)	20 (74%)	22 (50%)	2 (25%)
CRP (mg/l)[a]	85 (9–388)	56 (9–290)**	28 (9–147)***	123 (9–334)	120 (9–332)	81 (9–388)	48 (9–388)
CRP > 80 mg/l	80 (52%)	15 (34%)**	2 (15%)**	28 (72%)	21 (78%)	22 (50%)	2 (25%)
Alveolar infiltrates[b]	110 (72%)	27 (61%)	4 (31%)*	27 (69%)	19 (70%)	35 (80%)	4 (50%)
Lobar pneumonia	43 (28%)	7 (16%)	0	23 (59%)	18 (67%)	13 (30%)	1 (13%)
Duration of fever after onset of antibiotics (h)[a]	14 (2–127)	14 (3–127)	14 (3–35)	16 (2–86)	16 (4–45)	14 (2–100)	18 (7–100)
Treatment failure = fever lasting ≥ 48 h	13 (9%)	3 (7%)	0	2 (5%)	0	7 (16%)	2 (13%)
Duration of hospitalisation (h)[a]	48 (17–240)	57 (12–216)	72 (24–168)	48 (22–240)	48 (22–101)	48 (19–139)	51 (19–120)
Prolonged hospitalisation ≥120 h	11 (7%)	6 (14%)	3 (23%)*	1 (3%)	0	4 (9%)	1 (13%)

[a]Median (range)
[b]The rest of the patients had sole interstitial infiltrates
* $P<0.05$; ** $P<0.01$; *** $P<0.001$ in comparison between viral and bacterial infection or sole RSV and sole pneumococcal infection

Table 2 Antimicrobial therapy in 153 children with CAP

Parenteral	
Penicillin G	106
Cefuroxime	13
Penicillin G + erythromycin	6
Cefuroxime + erythromycin	2
Cefuroxime + azithromycin	2
Cefuroxime + metronidazole	1
Ceftriaxone	1
Erythromycin	1
Oral	
Erythromycin	10
Amoxycillin	4
Azithromycin	3
Penicillin V	2
Amoxycillin/clavulanate	1
Amoxycillin + erythromycin	1

the hospital. No recurrent pneumonias were recorded and 94% of the patients were reported by the parents to be free of CAP-related symptoms. However, 32 (21%) patients had received a second antibiotic treatment during the follow-up, mainly for acute otitis media.

Discussion

We found that the study children rapidly recovered from CAP after onset of antibiotic therapy and no one developed complications during the antibiotic treatment. Of the patients, 91% became afebrile within 48 h and the median duration of the hospital stay was 48 h. Our detailed findings are consistent with earlier studies. In developed countries, independent of aetiology and the type of antibiotics used, 70%–94% of children with uncomplicated CAP have been found to be afebrile and clinically improving within 48 h after the start of antibiotics [7, 27, 30]. The clinical responses are often reportedly good or leading to cure in 84%–98% of CAP patients, without any more detailed daily data on their recovery [2, 10, 28]. Even children with bacteraemic pneumococcal pneumonia have become afebrile within an average of 22 h after onset of antimicrobial therapy. A rapid clinical recovery has been associated with rapid normalisation of WBC and CRP [30]. This is in sharp contrast to data on pneumonia in less-developed countries, where severe pneumonia is common and 5% of the patients die in spite of parenteral antibiotic treatment and treatment failures are not rare in patients with non-severe pneumonia (18% of patients in one study still had CAP-related symptoms after 5–7 days) [4, 9].

Only 9% of the children with CAP had fever for ≥48 h after onset of antibiotic treatment. Of these patients, 75% had evidence of viral infection, usually with concomitant bacterial infection. Many findings support the view that mixed viral-bacterial infections, which may be more common than earlier recognised, may induce a more severe inflammation and clinical illness than sole bacterial or sole viral infections. Concomitant influenza virus and *Staphylococcus aureus* infection may cause severe and fatal pneumonia in children and adults [6]. In one study, children with acute otitis media showing both bacteria and virus in middle ear fluid failed to respond to therapy more often than a group with bacteria alone [5]. In a common cold study, patients having both virus and *S. pneumoniae*, *H. influenzae* or *M. catarrhalis* in the nasopharynx had more symptoms than those with virus alone [23]. Furthermore, in another study these patients with common cold seemed to benefit from antibiotic therapy [16].

A surprising finding was that children with sole viral pneumonia showed a response to antibiotic treatment similar to that of those with sole bacterial pneumonia. The same finding was obtained when only sole RSV and sole pneumococcal pneumonia were studied. It can be argued that all our patients with CAP may have had a bacterial pneumonia and the tests used to detect a bacterial infection were too insensitive. This is supported by the finding that pneumolysin PCR analysis of blood samples may detect cases overlooked by serology [18, 31]. Furthermore, serological tests do not detect all blood culture positive cases [12]. On the other hand, our patients with sole bacterial pneumonia differed significantly from those with sole viral pneumonia both in laboratory and chest radiography findings, showing that the serological tests detected a bacterial type infection [15, 32]. Another explanation could be the high spontaneous cure rate of CAP in children, as studies with acute otitis media and acute sinusitis have also shown [24, 25]. Penicillin G is still considered a drug of choice in hospitalised children with CAP in many European countries with low penicillin resistance of pneumococci [11, 19, 26]. Of our patients, 66% were treated with penicillin G and showed a rapid and uneventful recovery. Penicillin G is no longer recommended in the United States as a first-choice drug because of limited supply and the increasing resistance of pneumococci to penicillin [20], whereas in Finland, 95% of pneumococcal strains remain sensitive to penicillin [22]. Our patients received only 1–2 days of parenteral treatment, after which they were successfully switched to oral treatment. Earlier studies have shown that the majority of children with CAP can be treated as outpatients after one injection of cephalosporin [8].

The limitations of our study must be admitted. We only studied otherwise healthy children in a highly developed country. We did not include children who already had complicated pneumonia, i.e. empyema, (two children) on admission before the onset of antibiotic treatment. The relative frequency of empyema is increasing, often requiring prolonged hospitalisation [29]. Only indirect evidence of the aetiology of CAP was obtained, and causality should be considered with some caution.

Our results show that CAP in children in a developed country is not a serious illness. In clinical practice, nearly all otherwise healthy children with pneumonia become afebrile within 1–3 days and make an uneventful

recovery. Etiological investigations are not needed for the planning of therapy in these children. Only a very short parenteral treatment period is needed and the patients can then be treated with oral antibiotics as outpatients.

References

1. Allison P (1995) In survival analysis using the SAS system: a practical guide. SAS Institute Inc., Gary, pp 212–216
2. Block S, Hedrick J, Hammerschlag MR, Cassell GH, Craft JC (1995) *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* in pediatric community-acquired pneumonia: comparative efficacy and safety of clarithromycin vs. erythromycin ethylsuccinate. Pediatr Infect Dis J 14: 471–477
3. British Thoracic Society Standards of Care Committee (2002) BTS guidelines for the management of community-acquired pneumonia in childhood. Thorax 57[Suppl 1]: i1–i24
4. CATCHUP Study Group (Co-trimoxazole Amoxcillin Trial in Children Under 5 years for Pneumonia) (2002) Clinical efficacy of co-trimoxazole versus amoxcillin twice daily for treatment of pneumonia: a randomized controlled trial in Pakistan. Arch Dis Child 86: 113–118
5. Chonmaitree T, Owen MJ, Howie VM (1990) Respiratory viruses interfere with bacteriologic response to antibiotic in children with acute otitis media. J Infect Dis 162: 546–549
6. Connor E, Powell K (1985) Fulminant pneumonia caused by concomitant infection with influenza B virus and *Staphylococcus aureus*. J Pediatr 106: 447–550
7. Dagan R (1993) Antibiotic treatment of pediatric community-acquired lower respiratory tract infections: challenges and possible solutions. Respiration 60[Suppl 1]: 38–44
8. Dagan R, Syrogiannopoulos G, Ashkenazi S, Engelhard D, Einhorn M, Gatzola-Karavelli M, Chalif I, Amir J (1994) Parenteral-oral switch in the management of paediatric pneumonia. Drugs 43[Suppl]: 43–51
9. Duke T, Poka H, Dale F, Michael A, Mgone J, Wal T (2002) Chloramphenicol versus benzylpenicillin and gentamicin for the treatment of severe pneumonia in children in Papua New Guinea: a randomized trial. Lancet 359: 474–480
10. Harris JS, Kolokathis A, Campbell M, Cassell GH, Hammerschlag MR (1998) Safety and efficacy of azithromycin in the treatment of community-acquired pneumonia in children. Pediatr Infect Dis J 17: 865–871
11. Hedlund J, Örtqvist Å (2002) Management of patients with community-acquired pneumonia treated in hospital in Sweden. Scand J Infect Dis 34: 887–892
12. Jalonen E, Paton JC, Koskela M, Kerttula Y, Leinonen M (1989) Measurement of antibody responses to pneumolysin: a promising method for the presumptive etiological diagnosis of pneumococcal pneumonia. J Infect 19: 127–134
13. Jokinen C, Heiskanen L, Juvonen H, Kallinen S, Karkola K, Korppi M, Kurki S, Ronnberg R, Seppa A, Soimakallio S, Sten M, Tanska S, Tarkiainen A, Tukiainen H, Pyorala K, Makela PH (1993) Incidence of community-acquired pneumonia in the population of four municipalities in eastern Finland. Am J Epidemiol 137: 977–988
14. Juvén T, Mertsola J, Waris M, Leinonen M, Meurman O, Roivainen M, Eskola J, Saikku P, Ruuskanen O (2000) Etiology of community-acquired pneumonia. A 3-year prospective study on 254 hospitalized children. Pediatr Infect Dis J 19: 293–298
15. Juvén T, Mertsola J, Toikka P, Virkki R, Leinonen M, Ruuskanen O (2001) Clinical profile of serologically diagnosed pneumococcal pneumonia. Pediatr Infect Dis J 20: 1030–1035
16. Kaiser L, Lew D, Hirschel B, Auckenthaler R, Morabia A, Heald A, Benedict P, Terrier F, Wunderli W, Matter L, Germann D, Voegeli J, Stalder H (1996) Effects of antibiotic treatment in the subset of common cold patients who have bacteria in nasopharyngeal secretions. Lancet 347: 1507–1510
17. McIntosh K (2002) Community-acquired pneumonia in children. N Engl J Med 346: 429–437
18. Michelow IC, Lozano J, Olsen K, Goto G, Rollins NK, Ghaffar F, Rodriguez-Cerrato V, Leinonen M, McGracken GH (2002) Diagnosis of *Streptococcus pneumoniae* lower respiratory infection in hospitalized children by culture, polymerase chain reaction, serological testing, and urinary antigen detection. Clin Infect Dis 34: e1–e11
19. Moroney JF, Fiore AE, Harrison LH, Patterson JE, Farley MM, Jorgensen JH, Phelan M, Facklam RR, Cetron MJ, Breiman R, Kolczak M, Schuchat A (2001) Clinical outcomes of bacteremic pneumococcal pneumonia in the era of antibiotic resistance. Clin Infect Dis 33: 797–805
20. Nelson JD (2000) Community-acquired pneumonia in children: guidelines for treatment. Pediatr Infect Dis J 19: 251–253
21. Principi N, Esposito S (2001) Emerging role of *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* in paediatric respiratory tract infections. Lancet Infect Dis 1: 334–344
22. Pihlajamäki M, Kotilainen P, Kaurila T, Klaukka T, Palva E, Huovinen P (2001) Macrolide-resistant *Streptococcus pneumoniae* and use of antimicrobial agents. Clin Infect Dis 33: 483–488
23. Puhakka T, Makela MJ, Malmstrom K, Uhari M, Savolainen J, Terho EO, Pulkkinen M, Ruuskanen O (1998) The common cold: effects of intranasal fluticasone propionate treatment. J Allergy Clin Immunol 101: 726–731
24. Puhakka T, Makela MJ, Alanen A, Kallio T, Korsoff L, Arstila P, Leinonen M, Pulkkinen M, Suonpaa J, Mertsola J, Ruuskanen O (1998) Sinusitis in the common cold. J Allergy Clin Immunol 102: 403–408
25. Rosenfeld RM, Vertrees JE, Carr J, Cipolle RJ, Uden DC, Giebinski GJ, Canatux DM (1994) Clinical efficacy of antimicrobial drugs for acute otitis media: meta-analysis of 5400 children from thirty-three randomized trials. J Pediatr 124: 355–367
26. Ruuskanen O, Mertsola J (1999) Childhood community-acquired pneumonia. Semin Respir Infect 14: 163–172
27. Ruuskanen O, Nohynek H, Ziegler T, Capeding R, Rikalainen H, Huovinen P, Leinonen M (1992) Pneumonia in childhood: etiology and response to antimicrobial therapy. Eur J Clin Microbiol Infect Dis 11: 217–223
28. Tan TQ, Mason EOM, Barson WJ, Wald ER, Schutze GE, Bradley JS, Arditi M, Givner LB, Yogev R, Kim KS, Kaplan SL (1998) Clinical characteristics and outcome of children with pneumonia attributable to penicillin-susceptible and penicillin-non-susceptible *Streptococcus pneumoniae*. Pediatrics 102: 1369–1375
29. Tan TQ, Mason EO, Wald ER, Barson WJ, Schutze GE, Bradley JS, Givner LB, Yogev R, Kim KS, Kaplan SL (2002) Clinical characteristics of children with complicated pneumonia caused by *Streptococcus pneumoniae*. Pediatrics 110: 1–6
30. Toikka P, Virkki R, Mertsola J, Ashorn P, Eskola J, Ruuskanen O (1999) Bacteremic pneumococcal pneumonia in children. Clin Infect Dis 29: 568–572
31. Toikka P, Nikkari S, Ruuskanen O, Leinonen M, Mertsola J (1999) Pneumolysin PCR-based diagnosis of invasive pneumococcal infection in children. J Clin Microbiol 37: 633–637
32. Virkki R, Juvén T, Rikalainen H, Svedstrom E, Mertsola J, Ruuskanen O (2002) Differentiation of bacterial and viral pneumonia in children. Thorax 57: 438–441
33. Vuori E, Peltola H, Kallio M, Leinonen M, Hedman K (1998) Etiology of pneumonia and other common childhood infections requiring hospitalization and parenteral antimicrobial therapy. Clin Infect Dis 27: 566–572