Complicated Community Acquired Pneumonia in Childhood: Different Types, Clinical Course, and Outcome

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Summary. The incidence of pediatric community acquired complicated pneumonia (PCACP) is increasing. Questions addressed: Are different types of PCACP one disease? How do different treatment protocols affect the outcome? Methods: Retrospective analysis of medical records of PCACP hospitalizations in the three major hospitals in Jerusalem in the years 2001–2010 for demographics, clinical presentation, management, and outcome. Results: Of the 144 children (51% aged 1–4 years), 91% of Jewish origin; 40% had para-pneumonic effusion (PPE), 40% empyema (EMP), and 20% necrotizing pneumonia (NP). Bacterial origin was identified in 42% (empyema 79%, $P = 0.009$), most common *S. pneumoniae* (32%), *group A streptococcus* (9%). Patients with EMP, compared to PPE and NP, were less likely to receive prior antibiotic treatment (35% vs. 57% and 59%, respectively, $P = 0.04$). Mean hospitalization was longer in patients with NP followed by EMP and PPE (16.4 ± 10.6, 15.2 ± 7.9, and 12.7 ± 4.7 days, respectively), use of fibrinolysis was not associated with the outcome. All children had recovered to discharge regardless of antibiotic therapy or fibrinolysis. Answer: NP is a more severe disease with prolonged morbidity and hospitalization in spite of prior antibiotic treatment. All types had favorable outcome regardless of treatment-protocol. Complicated pneumonia has an ethnic predominance. **Pediatr Pulmonol. 2016; 9999:XX–XX**.

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INTRODUCTION

Community acquired pneumonia (CAP) is a leading cause of morbidity and mortality in children worldwide, with *Streptococcus pneumoniae* still being the most common bacterial pathogen.[1] Complications of CAP in children include para-pneumonic pleural effusion, empyema, necrotizing pneumonia, and lung abscess.[2] Pediatric para-pneumonic pleural effusion and empyema are considered different stages of the same pathophysiological process in which pleural inflammation causes fluid to accumulate in the pleural cavity. Necrotizing pneumonia results from pulmonary necrosis and tissue liquefaction. It carries poor prognosis in adults and was initially considered a rare complication in children. Recent reports have characterized the clinical presentation of this complication and have shown favorable outcomes in children.[2]

The number of children with all types of complicated CAP is increasing in the last decades. This increase in complications was reported already before the introduction of the 7-valent pneumococcal vaccine (PCV7).[3–11] Despite the rise in frequency of these complications, there is no consensus on what is the best treatment approach regarding the empirical antibiotic treatment, chest tube

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drainage, use of fibrinolysis, and need or time for surgical intervention.

The purpose of this study was to analyze the different types of pediatric community acquired complicated pneumonia (PCACP) and to compare their clinical, etiological, and epidemiological characteristics. In addition, different treatment protocols were compared for their efficacy and outcome.

METHODS

Data Source

Clinical records of pediatric patients (<18 years of age) hospitalized with PCACP over the years 2001–2010 in the three major Medical Centers in Jerusalem [Hadassah Ein Kerem (EK), Hadassah Mount Scopus (MS), Shaare Zedek (SZ)] were analyzed. The vast majority of children living in Jerusalem are treated in these hospitals. During the study period the pediatric population (<18 years) in Jerusalem increased from 238,156 in 2002 to 267,938 in 2010 (http://www.jiis.org.il/). All medical files, retrieved from the computerized database of each hospital were analyzed for demographic information, diagnostic codes, laboratory, and physiological data, treatment during hospitalization, clinical course, and discharge summary. All chest X-rays and CT scans were re-examined by an experienced pediatric radiologist (BK).

The study was approved by the Hadassah Medical Center Institutional Review Board.

Patients and Definitions

Complicated pneumonia was defined as clinical pneumonia and the presence of pleural effusion, empyema (EMP) or Para-pneumonic effusion (PPE), and/or necrotizing pneumonia (NP) in imaging studies. Childhood EMP was defined as the presence of pus (purulent fluid and/or WBC count >5,000 per mm^3) or bacteria in the pleural fluid. PPE was defined by pleural fluid not fitting criteria of EMP and the diagnosis of NP was made by the presence of multiple cavity gas-filled spaces within a pulmonary consolidation on chest X-rays or liquefaction of lung tissue according to CT scans as reviewed by a pediatric radiologist.

All files of pediatric patients hospitalized in the three medical centers from January 2001 through December 2010, with an ICD nine diagnosis of NP, EMP, complicated pneumonia, pleural effusion, chest drain, lung abscess, bacterial pneumonia, viral pneumonia and pneumococcal pneumonia, were retrieved from the hospitals' records, and reviewed for the presence of complicated pneumonia.

Patient files including chronic lung or heart diseases, chronic neurological impairment, immunodeficiency, cancer, or post cancer chemotherapy were excluded from the study as were those with hospital acquired complicated pneumonia.

Outcome Measures

Primary outcome variables were total duration of fever and hospital length of stay (LOS). A secondary outcome included total duration of antibiotic therapy.

A febrile day was defined as any 24-hr period during which the patient had a recorded temperature >38.0°C.

Statistical Analysis

Demographic, clinical, and laboratory variables were summarized by standard descriptive statistics. Results were summarized as medians and interquartile range (IQR) for continuous variables, and percentages for nominal variables. Differences between groups were calculated using a linear regression model with type three analysis of fixed effects for continuous variables and a logistic regression model, with type three analysis of effects employing the Wald Chi-Square test for nominal variables, the Bonferroni correction was used for assessing paired comparisons when performing multiple comparisons, two-sided P values < 0.05 were considered to be statistically significant. For estimation of treatment effect a propensity score matching technique was employed, parameters included in the propensity score were: age, duration of fever prior to presentation, antibiotic treatment prior to admission, inflammatory indices and serum laboratory values on admission, and pleural fluid indices. Following the propensity score a linear regression mixed model, adjusted for the matching and considering the fact that the matched observations are not independent, was employed and used to calculate differences between the treatment groups. The statistical analysis was performed using SAS® 9.3 Software (Cary, NC) by a biostatistician.

RESULTS

Epidemiological and Clinical Data

During the study period 144 cases of complicated pneumonia fulfilled the inclusion criteria. Fifty-seven (40%) were EMP, 58 (40%) PPE, and 29 (20%) NP. The median age was 42 months (range 7–190 months; mean 56 months, IQR = 54.7), 65% were male. Fifty-one percent of all complicated pneumonia cases and 65% of all necrotizing pneumonia occurred at the age of 1–4 years (Fig. 1). From 2001 to 2010 an increase in rate of admissions due to complicated pneumonia was observed from 2.63 to 8.6 cases per 100,000 children, this increase was observed for all types of complicated pneumonia but was only statistically significant for NP ($r = 0.76$, $P = 0.02$) (Fig. 2). Interestingly the vast majority (91%) were of Jewish origin and 9% of Arab origin (Table 1). According to demographic data from the Israeli National

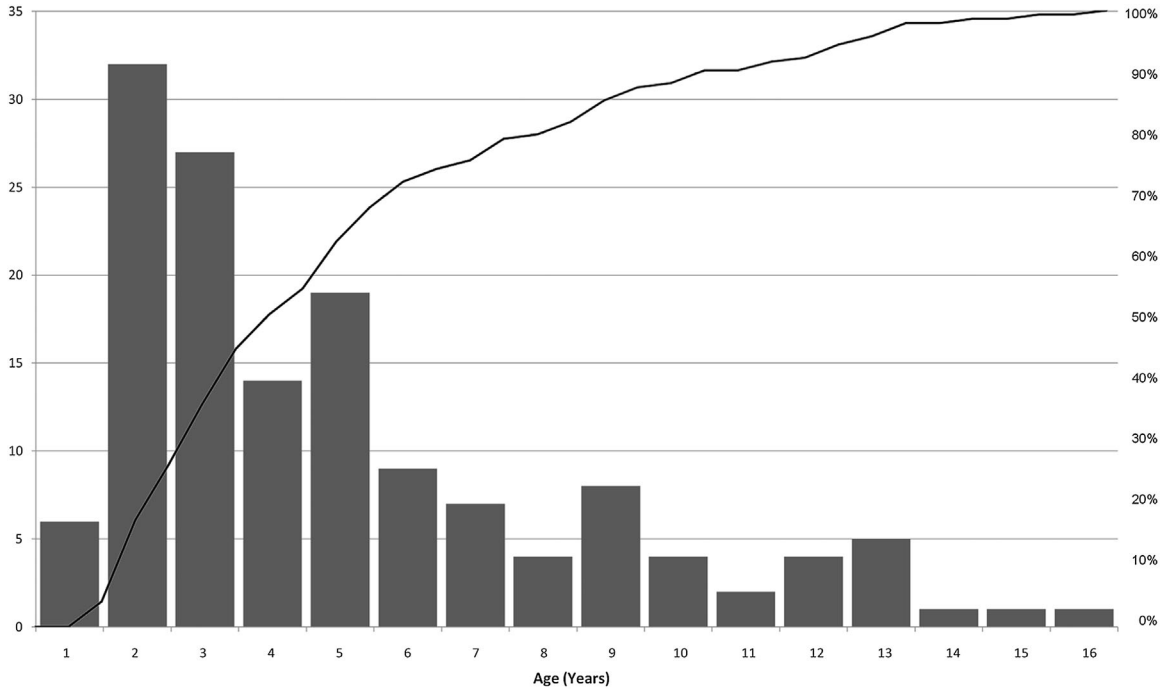

Fig. 1. Cumulative cases of patients with complicated pneumonia according to age.

Institute of Statistics, at the time of the study the ethnic population distribution of children Jerusalem was 63% Jewish and 37% Arabic (www.cbs.gov.il).

Other clinical characteristics and laboratory indices of the three types of PCACP at admission are listed in Table 1.

Microbiology

Blood cultures were available for 97% of the cases and pleural fluid cultures for 94%. Bacterial yield was significantly higher in pleural fluid cultures compared with blood cultures (34% positive vs. 21%, respectively, $P = 0.005$). Overall, a bacterial pathogen was identified in 61 patients (42%), 46 with *S. pneumoniae*, 13 *group A streptococcus*, and 3 *S. aureus* methicillin sensitive. All *S. pneumoniae* isolates were susceptible to penicillin (MIC < 0.5 mg/L). In 20 blood cultures positive for *S. pneumoniae*, a specific pneumococcal serotype was identified: serotype 1 in nine cases (45%, seven cases of EMP and two cases of PPE), serotype 5 in eight cases

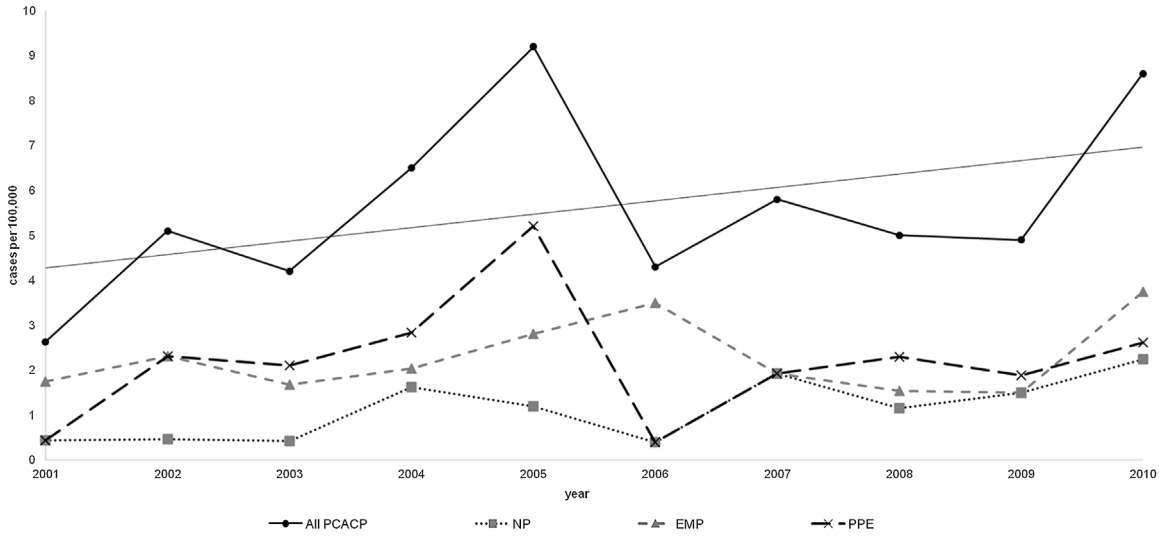

Fig. 2. Cases of pediatric complicated pneumonia per 100,000 population per year.

TABLE 1— Patient Characteristics and Therapeutic Approach According to Type of Complicated Pneumonia

	PPE (n = 58)	EMP (n = 57)	NP (n = 29)	*P*-value
Age				
Months, median [IQR]	49 [67.5]	41 [47]	37 [38.5]	$P = 0.32$
0–12 months, n (%)	3 (5)	3 (6)	0 (0)	$P = 0.45$
12–48 months, n (%)	25 (43)	27 (47)	19 (65)	$P = 0.13$
>48 months, n (%)	30 (52)	27 (47)	10 (35)	$P = 0.31$
Males, n (%)	37 (64)	39 (68)	19 (66)	$P = 0.82$
Ethnicity				
Jewish, n (%)	53 (91)	54 (95)	25 (86)	$P = 0.39$
Muslim, n (%)	5 (9)	3 (5)	4 (14)	
Days of cough before admission, median [IQR]	2 [5]	1 [4]	2 [6.5]	$P = 0.26$
Days of fever before admission, median [IQR]	4 [4]	4 [2]	5 [3]	$\mathbf{P = 0.09}$
Antibiotic treatment before admission, n (%)	33 (57)	20 (35)	17 (59)	$\mathbf{P = 0.04}$[1]
WBC count, 10^9/L, median [IQR]	14.8 [9.5]	15.8 [12.4]	14.7 [10.8]	$P = 0.32$
Initial empiric antibiotic treatment				
Penicillin, n (%)	14 (24)	14 (24)	9 (31)	$P = 0.62$
Cephalosporin, n (%)	43 (74)	42 (74)	17 (59)	$P = 0.27$
Other, n (%)	1 (2)	1 (2)	3 (10)	$P = 0.07$
Chest tube insertion, n (%)	38 (66)	50 (88)	21 (72)	$\mathbf{P = 0.01}$[1]
Use of Fibrinolysis, n (%)	10 (17)	14 (25)	6 (21)	$P = 0.63$
Urokinase, n	8	13	6	
Streptokinase, n	2	1	—	
Surgical Procedure (VATS), n (%)	4 (7)	6 (11)	1 (3)	$P = 0.48$

PPE, parapneumonic effusion; EMP, empyema; NP, necrotizing pneumonia; WBC, white blood cells; VATS, video assisted thoracoscopic surgery; IQR, interquartile range.
Bold entries signify the *P*-value adjusted after Bonferroni correction.
[1]EMP versus PPE.

(40%, five cases of EMP and three cases of NP), and one (5%) each of the serotype 4, 14, and 19A. All cases of NP in which a serotype was identified were caused by pneumococcal serotype 5.

Patients with EMP had the highest rate of identifiable bacterial pathogens (79%) compared with 41% in NP and 7% in PPE ($P = 0.009$) (Table 2). Pre-admission antibiotic therapy was associated with a significant reduction in positive cultures, from 63.5% to 22.1% ($P < 0.0001$).

Management

Treatment differed significantly between the three hospitals and even within each hospital there was no standard protocol that was used for the initial treatment. The most common initial empiric treatment was with cephlosporins in 102 cases (71%) [cefuroxime (90), cefazolin (4), ceftriaxone (7), and ceftazidime (1)] followed by penicillins in 39 cases (27%), and vancomycin in two cases. The use of penicillin as initial empirical antibiotic treatment increased with the patients age, from 18% in the 0–24 months age group, to 23% in 25–72 months age group, and 47% in the >72 months age group. There were significant differences in the choice of empirical antibiotic treatment between the three medical centers; in SZ 84% of patients received cefuroxime as first choice empirical antibiotic therapy and only 8.5% of patients received penicillin, whereas in EK 55% and 28.6% patients, respectively, and in MS 68% patients received penicillin, and 31% cefuroxime ($P < 0.0001$) as initial therapy.

For 63 (44%) patients, the antibiotic regimen was changed during the hospital stay. For 28 patients (44%), the treatment was adapted to the specific sensitivity of the positive cultures and for 30 (48%) the reason for change was the concern of the treating physician due to lack of clinical improvement. For 22/28 (79%), patients the antibiotic was switched to penicillin from a broad spectrum antibiotic.

The use of invasive procedures; chest tube insertion, fibrinolytic therapy, and Video Assisted Thoracoscopic Surgery (VATS), is presented in Table 1. Video Assisted Thoracoscopic Surgery (VATS) was performed in 11 (7.6%) patients. No significant differences were seen between the Medical Centers regarding the use of surgical procedures (VATS).

Outcome

All 144 patients recovered to discharge with no residual morbidity; however, four patients required mechanical ventilation and treatment in the pediatric intensive care unit due to respiratory failure.

The median overall total duration of fever was 7 days (range 1–19 days, IQR 5), and duration of hospitalization

TABLE 2— Microbiology: Isolated Microbial Agent According to Type of Complicated

	PPE (n = 58)	EMP (n = 57)	NP (n = 29)	*P*-value
Blood cultures, n	n = 56	n = 55	n = 29	
All positive cultures	4 (7)	20 (36)	3 (10)	**$P = 0.003$**[2]
Streptococcus. Pneumonia	4 (7)	17 (30)	3 (10)	
Penicillin Antibiotic susceptibility[1]	4/4	16/16	2/2	
Streptococcus Group A	0	1 (2)	0	
Staphylococcus aureus	0	2 (4)	0	
Pleural fluid cultures, n	n = 5	n = 56	n = 26	
All positive pleural cultures	0	39 (68)	9 (35)	**$P = 0.01$**[3]
Streptococcus. Pneumonia	0	24 (42)	8 (31)	
Penicillin Antibiotic susceptibility[1]	—	15/15	5/5	
Streptococcus Group A	0	12 (21)	1 (4)	
Staphylococcus aureus	0	3 (5)	0	
Total case of identifiable bacterial agent	4 (7)	45 (79)	12 (41)	**$P = 0.009$**

Data presented as n (%). PPE, parapneumonic effusion; EMP, empyema; NP, necrotizing pneumonia.
Bold entries signify the *P*-value adjusted after Bonferroni correction.
[1]Minimum inhibitory concentration (MIC) <0.5.
[2]EMP versus PPE.
[3]NP versus EMP.

was 13 days (range 3–59 days, IQR 7). As shown in Table 3, patients with NP had the longest total duration of fever, although this is largely related to fever prior to the hospitalization which was recorded according to parental report.

Treatment with fibrinolytic therapy did not affect outcome. No significant differences were observed in hospital LOS, total days of antibiotic therapy and febrile days between patients treated conservatively and those treated with a chest tube insertion with or without fibrinolysis (Table 4).

DISCUSSION

Despite, availability of treatment protocols and immunizations the incidence of complicated CAP has been increasing worldwide.[12–14] Complications of CAP remain with prolonged morbidity[15–17] and high costs.[18–20] We present clinical data from a decade of hospitalizations of pediatric community acquired complicated pneumonia in Jerusalem. The most important finding from our study is that although, complicated pneumonia is associated with prolonged and severe morbidity, irrespective of the type of complication or the treatment during the hospitalization, all children were discharged home with no reported fatality or residual morbidity.

Similar to the observation in other countries, an increase in the incidence of complicated pneumonia in children was observed in the current study; however, the increase was significantly only for NP. In Israel the multivalent vaccine, Prevnar (Wyeth Lederle Vaccines Sa, Philadelphia, PA), was introduced on a national level only in 2008. Since, the current analysis was the period 2001–2010, vaccination was not expected to show a substantial effect on the study outcome. Furthermore, it should be noted that 90% of pneumococcal serotypes identified in the current study are not included in the 7-valent pneumococcal conjugate vaccine (serotypes 1, 5, 19A).

This study has addressed three different complications of CAP; PPE, EMP, and NP. PPE and EMP are regarded as a continuum[21] presenting different severities of the same clinical complication. In this study, only third of the patients with EMP received antibiotic treatment prior to their. This probably reflects a delay in outpatient diagnosis and it is likely that timely initiation of antibiotic therapy might prevent EMP formation, and the need for invasive interventions. Pediatric NP is a less common complication of CAP, described only lately[22] and its characteristics in the pediatric population are not as well documented. This study demonstrates that NP, compared to PPE and EMP, is a different entity, whose incidence is increasing and is characterized by a longer duration of fever before admission and subsequently a trend for a longer hospitalization, despite the timely administration of prior outpatient antibiotics. It is important to note that similar to the other complications, all our patients with NP were discharged home with no reported fatality or residual morbidity. This more severe clinical course prior to hospitalization demonstrates the exaggerated inflammatory response in NP, may suggest risk factors for the development of NP and may help early identification of this severe complication. The tissue necrosis in NP is believed to occur as a response to toxins produced by the invasive pathogen,[23] or by impaired host response, but the precise pathways explaining why some patients progress to this massive tissue damage while others do not, have not been well established.

S. pneumonia is the most frequently identified bacterial pathogen in CAP.[9,14,24,25] In contrast to most reports

TABLE 3— Outcomes According to Types of Complicated Pneumonia

	PPE (n = 58)	EMP (n = 57)	NP (n = 29)	*P*-value
Duration of fever at hospital, days	5 [4.5]	6 [6]	5.5 [5.5]	$P = 0.57$
Total duration of fever, days	6 [4]	8 [6]	9 [5]	$\mathbf{P = 0.02}$[1]
Duration of chest tube, days	5 [4]	6 [4.5]	7 [6]	$\mathbf{P = 0.04}$[1]
Total duration of antibiotic treatment, days	12 [5.2]	13 [7]	13 [9.5]	$P = 0.2$
Duration of hospitalization, days	13 [6]	14 [7]	14 [9]	$P = 0.14$
Patients with altered antibiotic treatment, n (%)	18 (31)	33 (58)	12 (41)	$\mathbf{P = 0.03}$[2]

Duration is presented as days, median [IQR- interquartile range]. NS, non significant; PPE, parapneumonic effusion; EMP, empyema; NP, necrotizing pneumonia.
Bold entries signify the *P*-value adjusted after Bonferroni correction.
[1]NP versus PPE.
[2]EMP versus PPE.

where MSSA was found to be the second most commonly identified pathogen, in our study *Group A Streptococcus* was the second most common bacterial agent (21%) and MSSA was identified in only 5% of the cultures while none were MRSA, a recent prospective etiological study described a similar finding.[26] Although, the optimal antibiotic therapy against *S. pneumoniae* is high dose penicillin, we observed significant differences between the three pediatric departments regarding the choice of empirical antibiotic treatment on presentation. In many cases treatment was not changed even after sensitivity to penicillin was determined.

The guidelines for treatment of pleural effusion and empyema in children are based on consensus and not evidence based data, and therefore inconsistency exist on how to treat affected patients. Some guidelines advocate the use of fibrinolysis in patients with empyema.[21,27,28] However, controlled studies in adults and in children did not show better outcomes compared with normal saline.[29,30] In the current study, the use of fibrinolysis did not seem to confer a significant improved outcome.

VATS was not a standard procedure in our cohort despite the fact that in the past decades it became a popular treatment for childhood empyema in many countries.[31] Controlled studies comparing the effectiveness of VATS in treatment of childhood empyema have reached discordant findings. Most prospective studies did not show any advantage for VATS over non-surgical treatments with an increase in the rate of complications and costs.[32–35] Some studies have shown a slight advantage for VATS in shortening hospital LOS but without any difference in overall treatment success or long term outcome.[36,37] Other studies reported significant complications and even death with this procedure.[38–40] Considering the favorable outcome of the patients with empyema, we believe that the role of VATS in the treatment of childhood empyema should be reconsidered.

An interesting finding in our study was the relatively low incidence of PCACP among Arab children, 9% while they consist of 37% of the pediatric population in greater Jerusalem. Furthermore, of the entire population of children that were hospitalized during the study period in the three hospitals, nearly 50% were of Arab origin. In East Jerusalem, there is a Palestinian hospital that provides treatment for only Arab children from East Jerusalem and the West bank and we could find in the hospital's records only two cases of complicated pneumonia during the study period, which were not included in the current study. Ethnic differences in rates of complicated pneumonia were found previously. A multicenter, retrospective study reported that children with complicated pneumonia were significantly more

TABLE 4— Outcomes According to Treatment Modalities

	No chest tube (n = 34)	Chest tube without Fibrinolysis (n = 80)	Chest tube with Fibrinolysis (n = 30)	*P*-value	Propensity score Adjusted *P*-value
Duration of hospitalization, days	11.5 [7.2]	14 [5.7]	11 [8.2]	$P = 0.35$	$\mathbf{P = 0.08}$
Duration of fever at hospital, days	5 [5.5]	6 [5]	5 [4.7]	$P = 0.54$	$\mathbf{P = 0.39}$
Total duration of fever, days	7 [6.2]	7 [5]	8.5 [6.2]	$P = 0.62$	$\mathbf{P = 0.003}$[1]
Total duration of antibiotic treatment, days	11 [7.2]	13 [5.7]	10.5 [6.5]	$P = 0.02$	$\mathbf{P = 0.15}$
Duration of chest tube, days	—	5 [6]	6 [4]	$P = 0.04$	$\mathbf{P = 0.2}$

Data presented as median [IQR- interquartile range]. NS, non significant.
Bold entries signify the *P*-value adjusted after propensity score.
[1]No Chest tube versus Chest tube with Fibrinolysis.

likely to be of white ethnicity[6] and another retrospective observational study reported a majority of Caucasian children in a cohort of patients with necrotizing pneumonia.[2] The marked dominance of complicated pneumonias in the Jewish population as well as among Caucasians may imply a genetic predisposition. It has been suggested that the immune host response to pneumococcus is an important factor in the predisposition to develop complications. In contrast, this may also be explained by differences in circulating community microorganisms in Jewish versus Arab neighborhoods.

There are several limitations to this study. First, the observational retrospective design may have resulted in medical registration errors. Furthermore, clinical impression and the decision regarding the choice of therapy could not be efficiently assessed. We tried to reduce this potential confounding factor by evaluating objective parameters of disease severity on presentation using by a propensity score when comparing different treatments. Second, as discussed above, in none of our patients an infection by MRSA was identified, thus our results may not be applicable in areas where CAP caused by MRSA infections are more prevalent. Third, the PCV13 vaccine, which includes all the serotypes isolated in this study, was introduced in Israel in November 2010 and thus this study may not reflect PCV13 immunized populations.

In summary, this study describes different complications of CAP. EMP might be related to a delay in administration of antibiotic treatment and thus early therapy may prevent this complication. NP is the most severe pulmonary complication, is characterized by prolonged morbidity probably not prevented by early antibiotic therapy, therefore it is important to better clarify its pathophysiological mechanisms. Importantly, despite the prolonged and severe clinical course no fatality was reported and all children were discharged home. Therefore, treatments that have weak level of evidence and may have complications, or increase the costs of the treatment should be reserved. The increased incidence among Jews compared to Arabs suggests a genetic predisposition that may elucidate the reason for the occurrence of these complications in only a small number of children with pneumonia.

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