Management of Pediatric Community-Acquired Pneumonia in the Era of Widespread Vaccination against Streptococcus Pneumoniae at a First-Level Hospital

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Abstract: Community-acquired pneumonia (CAP) is a common and potentially severe infection affecting children. A retrospective study was carried out at our Institution between November 2022 and January 2023. Twenty-eight patients under 14 years of age were diagnosed and treated accordingly. Median age was 35 months, half of the patients were males. The most detected pathogen was S. pneumoniae (in 36% of all patients). Other pathogens detected were RSV in 3 patients (11%), influenza B virus in two patients (7%), adenovirus in two patients (7%), and M. pneumoniae in one patient (4%). Fourteen children (50% of the total number) developed a respiratory failure that required supplemental oxygen. Among these, 8 children (57% of all children receiving oxygen supplementation) required low-flow oxygen delivery, four children (29%) required high-flow oxygen delivery, and one child (7%) required invasive ventilation. Five children (55% of children with a bacterial CAP) received intravenous antibiotics, while 44% of patients received oral antibiotics. First-line intravenous antibiotics consisted of a third-generation cephalosporin for infants and children older than 1 month, and ampicillin/sulbactam with gentamicin for newborns. Amoxy-clavulanic acid was the first-line oral antibiotic for pneumococcal CAP, while oral clarithromycin was the first line antimicrobic for CAP caused by M. pneumoniae.

Twenty-one children (75% of total patients) were fully vaccinated, three children (11%) had received two doses because of age. Regarding the 10 children with a pneumococcal CAP, seven (70%) were fully vaccinated, one had received two-doses of pneumococcal conjugate vaccine (PCV), and two were unvaccinated.

Keywords: CAP, Children, Hospitalization, Infection, North-Italy, Pneumococcal, Respiratory, Vaccine.

INTRODUCTION

Community-acquired pneumonia (CAP) is a common and potentially severe infection of the pulmonary parenchyma, acquired in the extra-hospital environment. It is a leading cause of emergency room access and hospitalization among children worldwide, including in European countries [1-3]. The incidence of CAP in North America and Europe in preschool children is approximately 36 per 1,000 child-years [4]. Streptococcus pneumoniae is the most frequent typical bacteria causing pneumonia in children, being responsible for one-third of the cases of all ages [5, 6], and it can cause serious complications requiring recourse to appropriate medical care and hospitalization [3]. Among the other pathogens, respiratory viruses are the most frequent causal agents between four months and five years of age, with respiratory syncytial virus (RSV) and rhinovirus the main viruses [7], while Mycoplasma pneumoniae is more frequently involved in children aged from 5 to 15 years [4, 8]. Moreover, up to 30% of CAP in children have a mixed etiology, both viral and bacterial, with S. pneumoniae mostly involved as a bacterial agent [9].

Since they were introduced, extensive infant vaccinations with pneumococcal and Haemophilus influenzae type b conjugate vaccines in developed countries have significantly reduced the rate of hospital admissions due to CAP in children [10-13].

In Italy, vaccination against H. influenzae type b is mandatory for all children born since 2001, while pneumococcal vaccination is strongly recommended since the 2012-2014 National Immunization Plan [14]. However Italian regions can decide autonomously about immunization programs and vaccination schedules, due to regional autonomy in the management of health services [15]. To date, Piedmont region, in the North-West of Italy, offers the 10-valent pneumococcal conjugate vaccine (PCV) administration for free of charge in the first year of life in children born as of 2012. In 2021, pediatric pneumococcal vaccination coverage in Piedmont region was 91,11%

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among children aged 24 months (birth cohort 2019), and 90,64% among children aged 36 months (birth cohort 2018) [16]. From March 1, 2023, the 10-valent PCV will be replaced by the 15-valent PCV. To date, there are no comparative studies on differences between 10-valent and 15-valent PCV in terms of incidence and severity of pediatric community-acquired pneumonia.

The aim of this study is to describe the characteristics of pediatric hospitalized CAP in a setting of a first-level hospital with a high 10-valent PCV coverage, as a preliminary data that can be useful in future to analyze epidemiological changes after shifting to an extensive 15-valent pneumococcal vaccination.

PATIENTS AND METHODS

We led an active surveillance for community-acquired pneumonia requiring hospitalization among children younger than 14 years old admitted in our first level hospital of Ivrea (Piedmont), North-West of Italy, from November 1, 2022, to January 31, 2023. CAP was defined by the presence of acute infection (defined by reported fever or documented fever, and elevated serum inflammatory markers), acute respiratory illness (defined by cough, chest pain, dyspnea, tachypnea, abnormal lung examination or respiratory failure), and evidence consistent with pneumonia assessed by chest X-ray. Radiographic evidence of pneumonia was defined as the presence of consolidation (opacity with or without air bronchograms), other infiltrate (linear or patchy alveolar or interstitial densities), or pleural effusion.

Exclusion criteria were children with aspiration pneumonia, children who were already admitted to hospital for other reasons at the time of diagnosis (nosocomial pneumonia), children with pneumonia that did not require hospitalization.

Criteria for hospital admission included: patients less than 6 months of age, poor clinical conditions, moderate to severe dehydration, moderate to severe respiratory distress with the need of oxygen supplementation, difficulties in oral administration of medications, inadequate parent compliance, lack of improvement after 48 hours of treatment as outpatients.

Information on vaccination status were collected in all inpatients: pneumococcal vaccination was considered as complete in those children who received at least two doses of PCV at 2-6 months of age, followed by a booster after 11 months.

Other data collected included: clinical and epidemiological characteristics (age, sex, comorbidities, presenting signs and symptoms, physical examination findings), laboratory, microbiology and radiograph results, and short-term outcomes (length of hospital stay, need for oxygen supplementation, intensive care unit admission).

Blood cells count, C-reactive protein and serum procalcitonin were performed in all children.

For etiological diagnosis, nasopharyngeal swabs for SARS-CoV2 and influenza A and B viruses and nasal swabs for respiratory syncytial virus and adenovirus were performed in all patients. S. pneumoniae urinary antigen and M. pneumoniae serum IgM were tested in all patients. Blood cultures were performed only in septic children.

Complicated pneumonia were defined as presence of pleural effusion, empyema, respiratory failure, sepsis or intensive care admission.

Treatment during hospitalization and discharge antibiotic therapy data were recorded in all patients.

Parents or legal guardians of all patients signed informed consent for the recording of sensitive data of children, in accordance with the ASLTO4 regulation (https://www.aslto4.piemonte.it/fse.asp).

RESULTS

Overall, 117 children were admitted to our pediatric ward from November 1, 2022, to January 31, 2023. Among these, 28 patients (24% of all hospitalizations) were admitted due to community-acquired pneumonia, ranging from 9 days to 10 years of age. General characteristics of our study population are resumed in Table **1**.

The median age of our patients was 35 months (range 0 to 129 months). Four patients (14% of the total number) and eleven patients (39%) were younger than 3 months and 2 years of age, respectively. A total of 50% were boys. Five patients (18% of all children) had a history of one or more respiratory acute events (*e.g.*, bronchospasm, asthma, bronchiolitis and/or pneumonia).

All children presented with fever, while other frequent presentation symptoms included cough, anorexia, and dyspnea.

Table 1: General Characteristics of Children with CAP Requiring Hospitalization (n =28)

Age – mo.			
	Median	35	
	Range	0-129	
Gender males – no.		14	50%
Age group – no.			
	≤ 3 mo	4	14%
	4 – 36 mo	11	39%
	3 – 5 yr	7	25%
	5 – 10 yr	6	21%
Symptoms – no.			
	Fever	28	100%
	Cough	24	86%
	Anorexia	20	71%
	Dyspnea	18	64%
Comorbidities – no.			
	Bronchiolitis	4	14%
	Asthma or bronchospasm	2	7%
	Previous pneumonia	1	3%
Vaccination status – no.			
	S. pneumoniae	24	86%
	10-valent conjugate vaccine	19	68%
	13-valent conjugate vaccine	5	18%
	Haemophilus influenzae type b conjugate vaccine	24	85%

Pneumococcal vaccination status was known in all hospitalized children. Globally, 21 children (75% of total patients) were fully vaccinated, three children (11%) had received two doses of PCV before the age of 6 months but no booster as they were admitted before 1 year of age, and four children (14%) had no received any doses because they were younger than 3 months when they were hospitalized.

Radiograph findings and short-terms hospitalization outcomes are resumed in Table **2**.

The median length of stay in the hospital was 3 days (range 2 to 8 days).

Two children were transferred to a tertiary referral hospital because they required intensive care, and one of them needed invasive ventilation. Both were less than 3 months of age and had a co-infection by bacterial and viral agent. No patient died.

Table 2: Radiograph Findings and Short-terms Outcomes of Children with CAP Requiring Hospitalization (n =28)

Radiographic findings – no.			
	Consolidation	8	29%
	Alveolar or interstitial infiltrate	20	71%
	Pleural effusion or empyema	0	0%
Hospitalization			
	Length of stay - days		
	Median	3	
	Range	2-8	
	Low-flow oxygen supplementation – no.	8	29%
	High-flow oxygen supplementation – no.	4	14%
	Intensive care admission – no.	2	7%
	Mechanical ventilation – no.	1	3%
	Death in hospital – no.	0	0%

On chest radiograph, 29% of patients presented a consolidation, 71% presented an alveolar or interstitial infiltrate, while no patient presented a parapneumonic pleural effusion or empyema. Figure **1** represent a patient with a pneumococcal CAP with a consolidation in the upper right lung on chest X-ray.

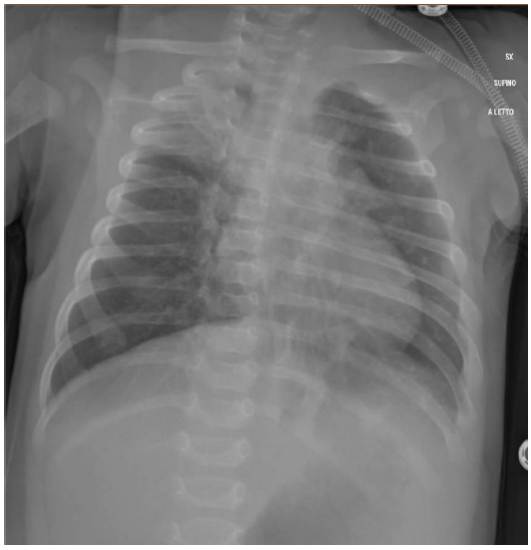
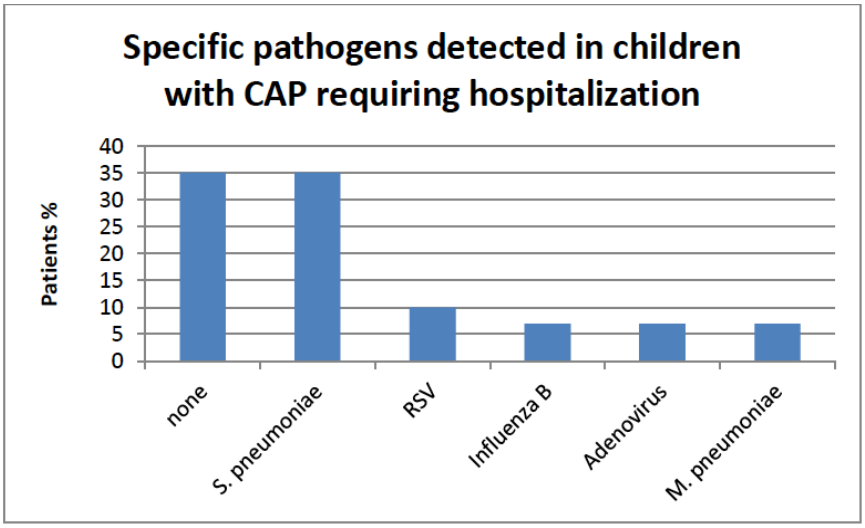


Figure 1: Consolidation in the right lung in pneumococcal pneumonia.

Fourteen children (50% of the total number) developed a respiratory failure that required supplemental oxygen. Among these, eight children (57% of all children receiving oxygen supplementation) required low-flow oxygen delivery, four children (29%) required high-flow oxygen delivery, and one child (7%) required invasive ventilation.



Graphic 1: Specific pathogens detected in children with CAP requiring hospitalization in our center.

Four children with respiratory failure (29%) had a personal history of one or more respiratory events, and they all needed high-flow oxygen supplementation.

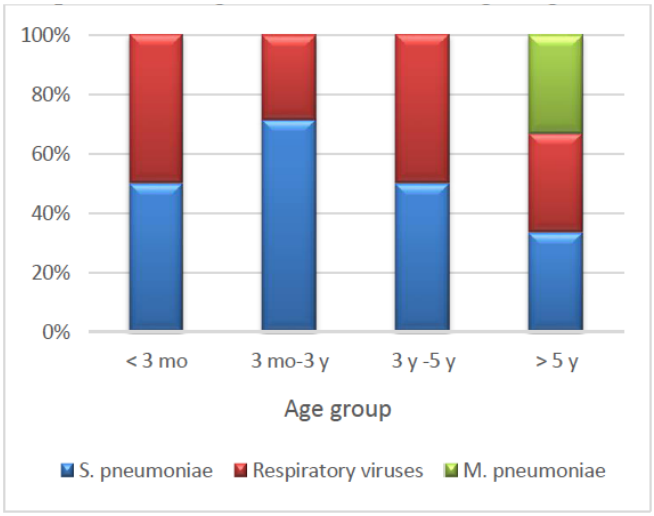
A pathogen was detected in 18 of the 28 patients (64% of all cases): a bacterial agent was found in 10 patients (36% of all children), a virus agent was detected in 6 patients (21%), and both bacterial and viral pathogens were detected in three children (11%). The most commonly detected pathogen was S. pneumoniae (in 36% of all patients). Other pathogens detected were RSV in 3 patients (11% of all children), influenza B virus in two patients (7%), adenovirus in two patients (7%), and M. pneumoniae in one patient (4%). To note that no patients had received palivizumab for the prevention of RSV infection.

Specific pathogens detected in our study population are represented in Graphic **1**.

S. pneumoniae was detected more commonly in children of 3 years of age or younger than in older children (40% vs. 17%). All the three patients infected by RSV were less than 3 months of age.

Graphic **2** represents pathogens detected according to age group in our study population.

Among inpatients with pneumococcal CAP, three (30% of patients with pneumococcal CAP) developed respiratory failure requiring oxygen delivery: one of them required low-flow oxygen supplementation, one needed high-flow nasal cannula oxygen supplementation, while the third one required invasive ventilation through endotracheal tube.



Graphic 2: Pathogens detected according to ages.

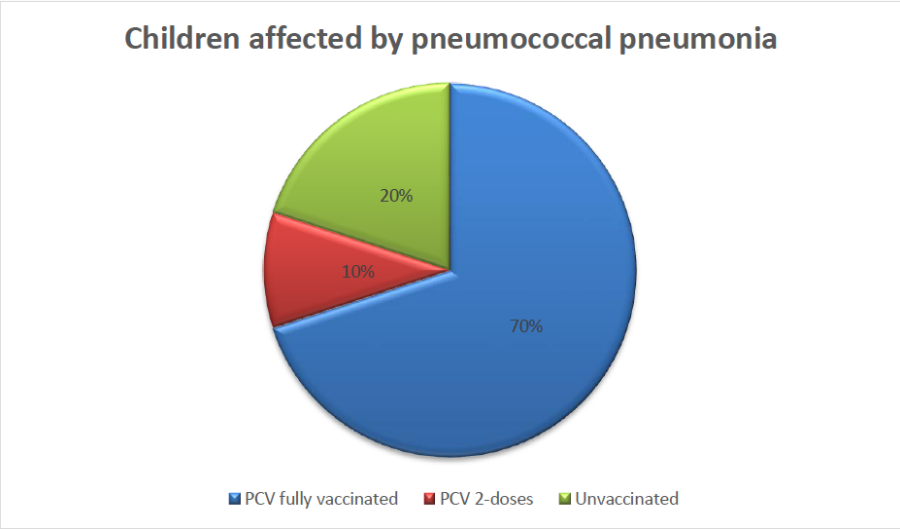
Antimicrobial agents were administered to all children diagnosed with bacterial pneumonia. Fifty percent of children with a bacterial CAP received intravenous antibiotics, while 50% of patients received oral antibiotics, with no difference in therapy effectiveness. First-line intravenous antibiotic consisted of a third-generation cephalosporin (*e.g.*, ceftriaxone or ceftazidime) for children and infants older than 1 month, and ampicillin/sulbactam with gentamicin for newborns (in the first month of life). Amoxy-clavulanic acid was the first-line oral antibiotic for pneumococcal CAP, while oral clarithromycin was the first-line antimicrobial for CAP caused by M. pneumoniae. Children with clinical, laboratory and radiograph findings suggesting a viral etiology were treated with supportive therapy, such as antipyretic, analgesic, hydration, and oxygen supplementation if needed.

Regarding the 10 children with a pneumococcal CAP, seven (70%) were fully vaccinated, one had received two-doses of PCV, and two were unvaccinated. Among the vaccinated children with pneumococcal CAP, five patients (62%) and one patient had received three and two doses of the 10-valent PCV, respectively, while two patients (25%) had been fully vaccinated with the 13-valent PCV, as Graphic **3** and **4** show.

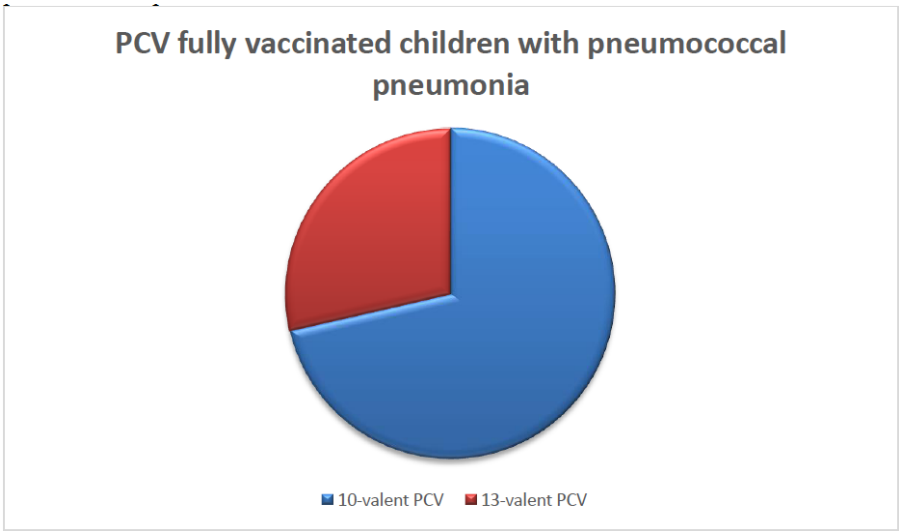
Furthermore, among the three children with pneumococcal pneumonia who developed respiratory failure, one was fully vaccinated with 10-valent PCV, while the other two were unvaccinated (Graphic **5**).

DISCUSSION

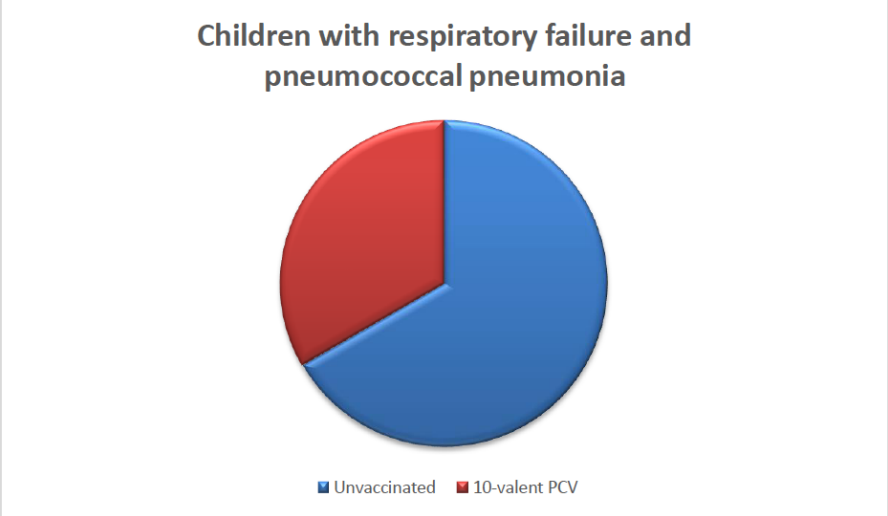
Despite the high pediatric vaccination coverage with 10-valent pneumococcal conjugate vaccines in our geographic area, pneumonia was still an important cause of hospitalization in our pediatric ward during the winter season, from November 2022 to January 2023. Overall, Streptococcus pneumoniae was the mainly involved etiological pathogen, especially in children younger than 3 years, with a frequency of CAP requiring hospitalization observed comparable to literature data [5, 6]. Fifty percent of our patients developed respiratory failure requiring supplemental oxygen with a great impact in terms of managing efforts and costs. In our study population, risk factors for worst



Graphic 3: Pneumococcal vaccination status among children with pneumococcal pneumonia.



Graphic 4: Distribution of 10-valent and 13-valent PCV among children fully vaccinated affected by pneumococcal pneumonia.



Graphic 5: Pneumococcal vaccination status among children with respiratory failure and pneumococcal pneumonia.

outcomes were age less than 3 months and coinfection by viral and bacterial agents. This can be explained by the unvaccinated status of the younger infants and the naive status of their immune system that makes them more susceptible to coinfections. Moreover, history of one or more acute respiratory events made oxygen supplementation more likely. Pneumococcal etiology on its own did not correlate with the probability of developing respiratory failure: in fact, oxygen supplementation was needed more commonly in non-pneumococcal CAP than in pneumococcal CAP (67% vs 30%). On the other hand, vaccination status was an important factor in determining severity of pneumococcal pneumonia, as already described by different studies [11-13].

In Italy, vaccination against S. pneumoniae is strongly recommended since the 2012-2014 National Immunization Plan [14]. However Italian regions can decide autonomously about immunization programs and vaccination schedules, due to regional autonomy in the management of health services [15]. To date, in our geographical area, Piedmont region in the North-West of Italy, the 10-valent PCV administration is offered for free in the first year of life in children born as of 2012, with a high vaccination coverage (over 90% in the birth cohorts 2019 and 2018) [16]. From March 1, 2023, the 10-valent PCV will be replaced by the 15-valent PCV. While the impact on incidence and severity of pneumococcal CAP after replacing 7-valent PCV with 13-valent is widely proven [17-19], data about 10-valent PCV vaccination is still controversial [20, 21]. A recent multicenter study showed that extensive 10-valent PCV determined an increasing number of pneumonias caused by pneumococcal serotypes correlated to a greater severity, supporting evidence on the importance of replacing 10-valent PCV with a higher valence vaccine, such as 13-valent PCV [22]. Our population study was characterized by a high vaccination coverage with 10-valent PCV, but we didn't confirm this tendency: in fact, among 10-valent PCV-vaccinated children with pneumococcal CAP, only one (12%) developed respiratory failure, while both unvaccinated children (100%) required high-flow oxygen delivery and intensive care due to moderate to severe respiratory failure. On the other hand, no PCV13- vaccinated children developed complications. To date, there is no evidence about the impact of 15-valent PCV on incidence and severity of pediatric community-acquired pneumonia.

Despite literature data [4, 8], we observed only one case of CAP caused by Mycoplasma pneumoniae belonging to the age group more than 5 years old, and no cases in the other age groups. This data can suggest that M. pneumoniae causes most frequently pneumonia that do not require hospitalization and/or that the peak of incidence occurs in different months of the year, but further study should be performed to confirm and better understand this phenomenon.

This study has many limitations. It included only inpatients from a single institution with a small sample size. Pneumococcal serotypes were unknown, so it was impossible to state if pneumococcal CAP were caused by vaccine or non-vaccine serotypes. Worst outcomes were observed in younger children with overlapping factors for greater severity of pneumonia, such as young age, unvaccinated status, and viral and bacterial coinfection, so it was difficult to state which

factor was mostly involved. Our data should be validated in larger multicentric studies.

CONCLUSIONS

The aim of this study was to describe the characteristics of hospitalized pediatric community-acquired pneumonia in a setting of a first-level hospital with a high 10-valent PCV coverage.

The main conclusions of our study are:

1. all children with acute respiratory symptoms should be closely investigated, especially if they are less than 3 years, since pneumonia is still an important cause of hospitalization,

2. the vaccination status of all children affected by bacterial CAP should be carefully monitored as the risk of severe evolution is more marked in unvaccinated children,

3. antibiotic therapy administered enterally has been shown to be equally effective as intravenous therapy in children,

4. the availability of a high-flow respiratory support allows the management of children with respiratory failure even in peripheral centers avoiding the need of intensive care, in a large percentage of patients,

5. in case of CAP, bacterial and viral coinfections should be ruled out, especially in younger children, as they are more exposed to the risk of severe respiratory failure.

Our data should be validated in larger multicentric studies, but represents a first step that can be useful for a future comparison on effectiveness between 10-valent and 15-valent PCV in terms of impact on community-acquired pneumonia in our geographical area.

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