Combined adenovirus and Mycoplasma pneumoniae infection is an independent risk factor for developing severe community-acquired pneumonia in children

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Research Article

Keywords: community-acquired pneumonia, etiology, adenovirus, Mycoplasma pneumoniae, risk factors, children

Posted Date: January 12th, 2023

DOI: https://doi.org/10.21203/rs.3.rs-2455413/v1

Abstract

Background: To investigate the pathogenic characteristics and risk factors of pediatric severe community-acquired pneumonia (CAP).

Methods: We retrospectively analyzed the clinical data of hospitalized children with severe CAP, including sex, age, results of sputum or bronchoalveolar lavage fluid (BALF) bacterial and fungal cultures, respiratory viruses, serum *Mycoplasma pneumoniae* (MP)-IgM and *Chlamydia Pneumoniae* (CP)-IgM, and BALF or blood (1-3)-β-D-glucan/galactomannan test.

Results:679 children with severe CAP were included in the analysis. The number of cases infected with MP was higher in males than in females. There were significant differences between the ≤1-year and >1-year groups, namely for bacterial, viral, MP, and CP infections. The top three bacteria cultured were *Haemophilus influenza*, *Streptococcus pneumoniae*, and *Pseudomonas aeruginosa*. The top three viruses detected were adenovirus (ADV), respiratory syncytial virus, and parainfluenza virus. The case numbers of ADV and MP infections in severe CAP were significantly higher than those of other infections, and ADV-positive infection was significantly associated with MP infection. MP infection was a risk factor for severe ADV-infected pneumonia, while sex, age, bacteria, CP, fungal, and ADV infections were risk factors for severe MP-infected pneumonia.

Conclusions: ADV-combined MP infection is an independent risk factor for the development of severe CAP in children.

Background

Community-acquired and hospital-acquired pneumonia are common in children. In particular, severe pneumonia is a serious illness with an acute onset and rapid progress that seriously threatens child health. It is the leading cause of child death if not diagnosed quickly and treated effectively.(1) Severe community-acquired pneumonia (CAP) is mostly caused by pathogenic infections with strong pathogenicity. Since children have an immature immune system and poor mucociliary clearance function to excrete pathogens, severe CAP in children is often difficult to control in clinical practice.

Severe pneumonia is caused by many pathogens, and the common ones include bacteria, viruses, atypical pathogens, and fungi. Bacterial infection plays a major role in the pathogenesis of severe CAP, whereas severe pneumonia caused by fungal infection mostly occurs in children with impaired immune function. However, in recent years, the CAP cases caused by *Mycoplasma pneumoniae* (MP) or viral infections have increased significantly, resulting in higher proportions of patients developing severe pneumonia. In general, viruses are the most common pathogens of CAP in children under five years old, accounting for approximately 50% of infant and child cases, and their incidence decreases with age.(2, 3) It is noteworthy that with the increase in resistance to macrolides, MP has become a major pathogen of pediatric CAP. MP-infected pediatric CAP has a higher incidence in the epidemic season.(4–6) However, mixed infections are commonly found in severe CAP cases in clinical practice. In addition, CAP caused by

mixed infections has more severe clinical symptoms and a significantly higher incidence of comorbidities than single pathogen-induced CAP. Therefore, rapid and accurate identification of the pathogens of severe CAP is necessary.(7, 8)

For these reasons, the ways to identify and the precise therapeutic regimens against the pathogens of severe CAP are the key to successful treatment. A variety of factors, such as age, nutritional status, comorbidities, and pathogen types affect the incidence and the progression of severe CAP. Many studies have mainly focused on the epidemiology, diagnosis, and treatment of severe CAP. However, with the increase in the proportion of severe CAP in children due to atypical pathogens and viruses, we are not fully aware of the effects of the mutual relationship between pathogens on the incidence of severe CAP. Therefore, this study retrospectively analyzed the clinical data of 679 children with severe CAP to mainly explore the pathogen–pathogen interactions of this disease.

Methods

General information

We performed a retrospective analysis of general information, including sex, age, results of sputum or bronchoalveolar lavage fluid (BALF) bacterial and fungal cultures, respiratory viruses, serum *Mycoplasma pneumoniae*-specific immunoglobulin M (MP-IgM) and *Chlamydia Pneumoniae* (CP)-IgM, and BALF or blood (1–3)-β-D-glucan/galactomannan (G/GM) test, of children with severe CAP in the pediatric department of the First Affiliated Hospital of the Xiamen University (Fujian Province, China) from April 2014 to June 2019. A total of 679 severe CAP children who underwent bronchoalveolar lavage were included as research subjects in this study. All children were under 14 years of age but there were no newborns. Our study protocol was approved by the Human Research Ethics Committee of the First Affiliated Hospital of the Xiamen University. Guardians of all research subjects signed the written informed consent at the time of hospital admissions.

Diagnostic criteria for severe CAP

In this study, the diagnostic criteria for severe CAP were in accordance with the *Management Guidelines of Community-Acquired Pneumonia in children (revised in 2013)* issued by the Respiratory Subspecialty Group, Chinese Pediatric Society, Chinese Medical Association. Pediatric patients with CAP who fulfilled any of the following criteria were diagnosed as severe pneumonia:(9) poor general condition, refused eating or having signs of dehydration; impaired consciousness; significantly elevated respiratory rate (RR) (infant RR > 70 breaths/minute; older child RR > 50 breaths/minute); purpura; respiratory distress (groan; nasal flaring; and three retraction signs, i.e., intercostal retractions, substernal retractions, and suprasternal retractions), multilobar involvement or ≥ 2/3 of the lung involved; pleural effusion; ≤92% percutaneous oxygen saturation; and extra-pulmonary complications.

Collection and detection of respiratory viruses

Nasopharyngeal swabs collecting samples from nasopharynx or BALF specimens collected from bronchoscope were immediately sent for examination. In some cases, respiratory virus antigens, such as influenza viruses A and B (FLU-A and FLU-B), parainfluenza viruses 1, 2, and 3 (PIV-1, PIV-2, and PIV-3), respiratory syncytial virus (RSV), and adenovirus (ADV) were detected by direct immunofluorescence assay kits (Diagnostic Hybrids, Inc., San Diego, CA). In other cases, respiratory viruses, including type A influenza virus, H_1N_1 type A influenza virus, H_3N_2 type A influenza virus, parainfluenza virus, metapneumovirus, RSV, ADV, rhinovirus, bocavirus, type B influenza virus, and coronavirus were detected by PCR-capillary electrophoresis fragment analysis (Respiratory pathogen multiplex assay kit, Health Gene Technologies Co., Ltd., Zhejiang Province, China). All kits were used in accordance with the manufacturer's instructions.

Sputum collection

The nasopharyngeal secretion of patients who needed non-mechanical ventilation was collected from a disposable sterile suction tube. The sputum of patients who needed mechanical ventilation was collected through an endotracheal tube using negative pressure aspiration. All collected samples were placed in sterile test tubes and immediately sent for examination within 30 minutes. The pathogen test was performed immediately after confirming the specimens were qualified.

Bronchoscopy and BALF collection

All patients were fasted with no access to water six hours before the operation, and were then given 0.01 mg/kg of atropine to reduce airway secretion, an intravenous injection of 0.1 mg/kg for sedation, and 2% of lidocaine for surface anesthesia on the patient's throat skin. The bronchoscope of the Olympus BF-XP60 model or the Olympus BF-MP60 model was selected according to the age of the pediatric patients, and 3–5 ml/kg of sterile physiological saline at 37°C was then injected through the selected bronchoscope and lavage fluid was collected. Bronchoscopy was performed in accordance with the operating specifications.

Bacterial and fungal culture of sputum or BALF

The sputum and BALF specimens were prepared as suspensions, followed by the inoculation of the suspensions to the culture dishes, which were placed in an incubator containing 5–8% carbon dioxide. The cultures and the identification of the bacteria and fungi were performed according to the pathogen test procedures.

Serum MP-IgM and CP-IgM detection

Venous blood samples of each patient were subject to the detection of MP-IgM and CP-IgM via the Diagnostic Kit for Measurement of Antibodies to *Mycoplasma pneumoniae* (Passive Particle Agglutination) (Fujirebio, Japan) and Anti-*Chlamydia pneumoniae* ELISA (IgM) (EUROIMMUN Medizinische Labordiagnostika AG, Germany), respectively, according to the manufacturers' instructions, with ≥ 1:160 MP-IgM dilution and ≥ 1.1 CP-IgM dilution ratios considered as positive results of MP-IgM and CP-IgM, respectively.

Fungal detection of BALF and blood samples

Fungal detection of BALF and blood samples was performed by spectrophotometry using two assays: (1–3)-β-D-glucan assay (G assay, Zhanjiang A & C Biological Ltd., Guangdong Province, China, with < 100.5 pg/ml glucan, a fungal cell wall component, considering as negative results and > 151.5 pg/ml glucan considering as positive results) and the Platelia™ Aspergillus Ag assay (GM assay, Bio-rad, with values of the *Aspergillus* galactomannan antigen in the serum and of galactomannan in the BAL considered as positive results if > 0.5 μg/L and > 1.0 μg/L, respectively). Both assays were performed strictly in accordance with the manufacturers' instructions. A positive result in either the G assay or GM assay was considered as fungal infection in the samples.

Statistical analysis

SPSS 25.0 statistical software (IBM SPSS, Chicago, IL) was used for data and statistical analysis in this study. The count data were presented as the number of case (*n*) or percentage (%). A Chi-square test was used for comparison. Risk factors were analyzed by multivariate logistic regression analysis. $P < 0.05$ was considered a statistically significant difference.

Results

First, to identify the relationship between age and sex, this study analyzed the sex and age data of 679 pediatric patients with severe CAP. The results showed that among all severe CAP cases, there were 64.80% (440/679) males and 35.20% (239/679) females. The patients with severe CAP ≤1 year old were 266, comprising 173 (65.04%) males and 93 (34.96%) females; and there were 413 patients with severe CAP >1 year old, comprising 267 (64.65%) males and 146 (35.35%) females. No significant difference in sex was found in the children with severe CAP between the two age groups ($\chi^2 = 0.011$, $P = 0.918$).

Second, to identify the relationship between the etiology and sex, this study divided all cases into positive and negative groups according to the results of pathogen detection to compare the two sexes. The results showed that the number of male cases was higher than that of female cases regardless of the presence or absence of pathogen infection. Among them, the patients with positive bacterial, viral, MP, CP, and

fungal infections accounted for 30.04%, 25.92%, 32.55%, 5.74%, and 7.95%, of the total cases, respectively. Further analysis showed that MP infection was significantly associated with the patient's sex (χ^2 = 5.939, P <0.05), whereas bacterial, viral, CP, and fungal infections had no significant association with the patient's sex (χ^2 = 0.445, 0.824, 0.009, and 0.350, respectively, all P >0.05, Table 1).

A previous study has shown that age significantly affected the incidence of severe CAP in children.(10) To investigate the relationship between age and pathogen infection in severe CAP, this study divided all cases into ≤1-year-old and >1-year-old groups, which were then compared for the presence of pathogen infection. The results showed that the bacterial, viral, MP, and CP infections were significantly associated with patient's age using 1-year-old as the age boundary (χ^2 = 8.581, 6.263, 117.403, and 5.158, respectively, P <0.05). Compared with the opposite age group, patients ≤1-year-old had a higher positive rate of CP infection, while patients >1-year-old had a higher positive rate of bacterial, viral, and MP infections. However, no significant correlation was found between the fungal infection and age (χ^2 = 0.684, P = 0.408, Table 2).

To further analyze the etiology of children with severe CAP, this study analyzed the infectious pathogens in these patients, and specifically focused on the top three pathogenic bacteria and respiratory viruses. The results showed that the top three bacteria in the culture were *Haemophilus influenza* (n = 57 cases of infection), *Streptococcus pneumoniae* (n = 50 cases of infection), and *Pseudomonas aeruginosa* (n = 25 cases of infection). The top three viruses detected were ADV (n = 124 cases of infection), RSV (n = 24 cases of infection), and parainfluenza virus (n = 21 cases of infection). Importantly, the case numbers of ADV and MP infections were 124 (18.26%) and 221 (32.55%), respectively, which were significantly higher than other single pathogen infections (Figure 1).

The above results showed that the numbers of severe CAP cases caused by ADV or MP infection were much higher than those of the other pathogen infections. Clinically, the proportion of viral infection-induced CAP was the highest.(7, 11) Therefore, we further focused on studying the correlation between ADV infection and other pathogen infections. The results showed that ADV infection was significantly associated with MP infection (χ^2 = 44.991, P = 0.000), but not significantly associated with bacterial, CP, and fungal infection in the severe CAP (χ^2 = 0.026, 3.097, and 2.308, respectively, P >0.05, Table 3).

Lastly, to further analyze the risk factors of severe ADV-infected pneumonia, we used ADV infection as an independent variable and patient's age, sex, bacteria, MP, CP, and fungi as covariates to evaluate the effects of these factors on ADV infection. The logistic regression analysis showed that MP-positive infection was a risk factor for ADV infection (OR = 0.279, P = 0.000), while no significant correlation was found between the ADV infection and other factors, including patient's sex, age, bacteria, CP, and fungi (OR = 0.809, 1.416, 0.834, 3.070, and 0.570, respectively, P >0.05). To further verify the correlation of ADV and MP co-infection, we used MP infection as an independent variable and patient's sex, age, bacteria, fungi, CP, and ADV as covariates to identify the risk factors affecting MP infection. The results showed that the patient's sex, age, and bacterial, CP, and ADV infections were risk factors for MP infection (OR =

1.712, 10.313, 1.678, 0.332, and 0.277, respectively, P <0.05), whereas no significant correlation was found between MP infection and fungal infection (OR = 1.207, P >0.05, Tables 4 and 5).

Discussion

Based on the results of this study, the patient's age and sex and the types of pathogen were found to be factors that affected the incidence of severe CAP in children under certain circumstances. The proportions of ADV- or MP-infection-induced severe CAP were the highest. Importantly, the chance of ADV infection was significantly increased after the MP infection. Co-infection with both ADV and MP was an independent risk factor for the incidence of severe CAP in children.

This study showed no significant difference between age (using 1-year-old as the age boundary) or sex in the children with severe CAP. Comparison between pathogen infection and sex showed no significant correlation between patient's sex and most pathogen infection except for MP, suggesting that sex was not a major factor affecting the incidence of severe CAP in children with common pathogen infection. The most common pathogens in children with pneumonia are respiratory viruses, followed by bacteria, and atypical pathogens.(7, 11) However, in the extremely severe CAP cases, the rate of bacterial infection is higher than the viral infection.(12) The severity of severe pneumonia caused by respiratory viral infection in children is related to age, virus type, immune function, affected organ, and the comorbidities of the patients.(13) The incidence of MP infection increases with age.(11) To summarize our findings, except for fungal infection, severe CAP caused by bacterial, viral, MP, and CP infections were age-related. Importantly, the proportion of bacterial, viral, and MP infection in the > 1-year-old children with severe CAP was higher than in children ≤ 1-year-old, whereas the proportion of CP infection in the ≤ 1-year-old children with severe CAP was higher in the patients > 1-year-old. Children at different ages had different severe CAP-inducing pathogens, indicating that the patient's age had an important impact on severe CAP.

In this study, the numbers of severe CAP in children caused by ADV or MP infections were significantly high, with the proportion of either pathogen infection significantly higher than the proportion of any other single pathogen infection. Thus, we focused on analyzing the characteristics of ADV and MP infection in children with severe CAP. ADV is one of the important pathogens in infants and young children with pneumonia, especially type 7 ADV, which can cause more severe pneumonia.(14, 15) The severity of respiratory infections caused by ADV is associated with ADV typing, viral load, onset age, immune status, and comorbidities.(15–17) Compared with other respiratory pathogens, the ADV-infected children tend to have a higher and longer fever, an increased probability of developing severe pneumonia, higher probability staying in the pediatric intensive care unit, and a longer hospital stay.(18, 19) Therefore, severe ADV pneumonia is more likely to be accompanied by complications of other systems, such as toxic encephalopathy, disseminated intravascular coagulation, sepsis, and shock. The survivors still have different degrees of sequelae, and the severe cases may form non-reversible lesions, such as pulmonary fibrosis, obliterative bronchiolitis, and bronchiectasis.(18, 20, 21) A comprehensive analysis showed that the progress and prognosis of severe ADV pneumonia may be closely related to factors such as hypoxia, hypoalbuminemia, inflammatory response, and lactate dehydrogenase.(18, 22) Our results indicated that

the proportion of severe CAP cases caused by ADV infection reached up to 18.26%, which was much higher than single bacterial infection, indicating an increasing trend of severe ADV infection in children. ADV has become the main pathogen of severe CAP in Chinese children in recent years.

Epidemiological results have shown that respiratory infections in children caused by MP infection are also on the rise.(23) Although most cases of *Mycoplasma pneumoniae* pneumonia (MPP) are mild and some cases may be self-limited and reversible, with good prognosis, and low mortality,(24, 25) MP infection can also lead to sever pneumonia, and the incidence of severe MPP has increased significantly, manifesting as pulmonary consolidation involved in a large area of the lung, atelectasis, pleural effusion, and necrotizing pneumonia in severe cases,(25–27) which may eventually form obliterative bronchiolitis, pulmonary fibrosis, and other sequela.(28, 29) Our study showed that among the severe CAP cases in children, the proportion of MP infection was the highest, and the MP infection was mainly found in the children > 1-year-old, indicating that the disease distribution was age-susceptible. In addition, according to logistic regression analysis, sex, age, and co-infection of bacteria, CP, and virus were the risk factors for MP infection, suggesting that these factors may significantly increase the probability of developing MP infection into severe pneumonia.

Severe CAP often exhibits as mixed infections, and bacterial and viral co-infection is common. However, the prevalence of the co-infection of a virus and an atypical pathogen has been increasing. Among the children with ADV-positive infection, MP is the most common pathogen associated with ADV infection, with the proportion exceeding 50%.(30, 31) In addition, co-infections of MP and bacteria or other viruses are not rare. The impact of MP infection on clinical prognosis depends on the co-infected pathogens to a large extent.(32) Our study showed that after MP infection, the patients were more susceptible to be co-infected with ADV, indicating a synergistic relation between MP and ADV. Compared with the patient' age, sex, and bacterial, viral, CP, and fungal infection, the MP co-infection was an independent risk factor for the development of severe pneumonia after ADV infection. This was also a good explanation for the significant increase in the number of cases of severe pneumonia after ADV and MP co-infection.

Conclusions

In conclusion, this study revealed the pathogenic characteristics and risk factors of severe CAP in children, indicating that ADV and MP co-infection is an independent risk factor to promote the incidence of severe CAP. Therefore, it is necessary to further elucidate the synergistic pathogenicity between ADV and MP infections in the children with severe CAP to help provide a more precise treatment for severe CAP.

Abbreviations

CAP: community-acquired pneumonia; BALF: bronchoalveolar lavage fluid; MP: Mycoplasma pneumoniae; CP: Chlamydia Pneumoniae; G/GM: (1-3)-β-D-glucan/galactomannan; ADV: adenovirus; RSV: respiratory syncytial virus; MPP: Mycoplasma pneumoniae pneumonia

Declarations

Ethics approval and consent to participate

This study was approved by the Human Research Ethics Committee of the First Affiliated Hospital of the Xiamen University. Guardians of all research subjects signed the written informed consent at the time of hospital admissions. All methods were carried out in accordance with the Declaration of Helsinki and all relevant ethical guidelines and regulations.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no conflict of interest.

Funding

This research was funded by Natural Science Foundation of Fujian Province (No. 2020J011232) and Medical and Health Guidance Project of Xiamen (No. 3502Z20214ZD1238). The funding body provided funding for the collection of data and the software used in this research.

Authors' contributions

X.L. designed this study. X.L. and Q.C. collected, analyzed data, and drafted manuscript. Y.L. helped to collect and sort out data. N.Z., L.L. and Q.S. were responsible for the clinical work and critically reviewed the manuscript. Y.Y. critically reviewed the manuscript, and agreed the final version to be published. All authors take responsibility for the data and results.

Acknowledgements:

We thank the Computer Center of the First Affiliated Hospital of Xiamen University for its help.

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Tables

Table 1 Relationship between the etiology and sex in pediatric severe CAP

		Male *n*=440 (%)	Female *n*=239 (%)	Total	χ^2	*P*
Bacteria	Positive	136 (66.67)	68 (33.33)	204	0.445	0.505
	Negative	304 (64.00)	171 (36.00)	475		
Virus	Positive	119 (67.61)	57 (32.39)	176	0.824	0.364
	Negative	321 (63.82)	182 (36.18)	503		
MP	Positive	129 (58.37)	92 (41.63)	221	5.939	0.015*
	Negative	311 (67.90)	147 (32.10)	458		
CP	Positive	25 (64.10)	14 (35.90)	39	0.009	0.925
	Negative	415 (64.84)	225 (35.16)	640		
Fungi	Positive	33 (61.11)	21 (38.89)	54	0.350	0.554
	Negative	407 (65.12)	218 (34.88)	625		

**P* value less than 0.05 is significant

Table 2 Relationship between age and pathogen infection in pediatric severe CAP

		≤1 year *n*=266 (%)	>1 year *n*=413 (%)	χ^2	*P*
Bacteria	Positive	97 (47.55)	107 (52.45)	8.581	0.003*
	Negative	169 (35.58)	306 (64.42)		
Virus	Positive	55 (31.25)	121 (68.75)	6.263	0.012*
	Negative	211 (41.95)	292 (58.05)		
MP	Positive	22 (9.95)	199 (90.05)	117.403	0.000*
	Negative	244 (53.28)	214 (46.72)		
CP	Positive	22 (56.41)	17 (43.59)	5.158	0.023*
	Negative	244 (38.13)	396 (61.88)		
Fungi	Positive	24 (44.44)	30 (55.56)	0.684	0.408
	Negative	242 (38.72)	383 (61.28)		

**P* value less than 0.05 is significant

Table 3 Correlation between ADV infection and other pathogen infections in pediatric severe CAP

		Adenovirus Positive *n*=124 (%)	Adenovirus Negative *n*=555 (%)	χ^2	*P*
Bacteria	Positive	38 (18.63)	166 (81.37)	0.026	0.872
	Negative	86 (18.11)	389 (81.89)		
MP	Positive	72 (32.58)	149 (67.42)	44.991	0.000*
	Negative	52 (11.35)	406 (88.65)		
CP	Positive	3 (7.69)	36 (92.31)	3.097	0.078
	Negative	121 (18.91)	519 (81.09)		
Fungi	Positive	14 (25.93)	40 (74.07)	2.308	0.129
	Negative	110 (17.60)	515 (82.40)		

**P* value less than 0.05 is significant

Table 4 Multivariate logistic regression analysis of severe CAP infected with ADV

	B	Wald	Exp (B)	95% CI for Exp (B)	*P*
Sex	-0.212	0.922	0.809	0.525~1.246	0.337
Age	0.348	1.809	1.416	0.853~2.352	0.179
Bacteria	-0.181	0.608	0.834	0.529~1.316	0.435
MP	-1.277	30.188	0.279	0.177~0.440	0.000*
CP	1.122	3.231	3.070	0.904~10.431	0.072
Fungi	-0.561	2.535	0.570	0.286~1.138	0.111

**P* value less than 0.05 is significant

Table 5 Multivariate logistic regression analysis of severe CAP infected with MP

	B	Wald	Exp (B)	95% CI for Exp (B)	*P*
Sex	0.538	7.497	1.712	1.165~2.516	0.006*
Age	2.333	83.192	10.313	6.246~17.027	0.000*
Bacteria	0.518	5.578	1.678	1.092~2.579	0.018*
Fungi	0.188	0.264	1.207	0.589~2.476	0.607
CP	-1.103	6.991	0.332	0.146~0.752	0.008*
Adenovirus	-1.283	29.497	0.277	0.175~0.441	0.000*

**P* value less than 0.05 is significant

Figures

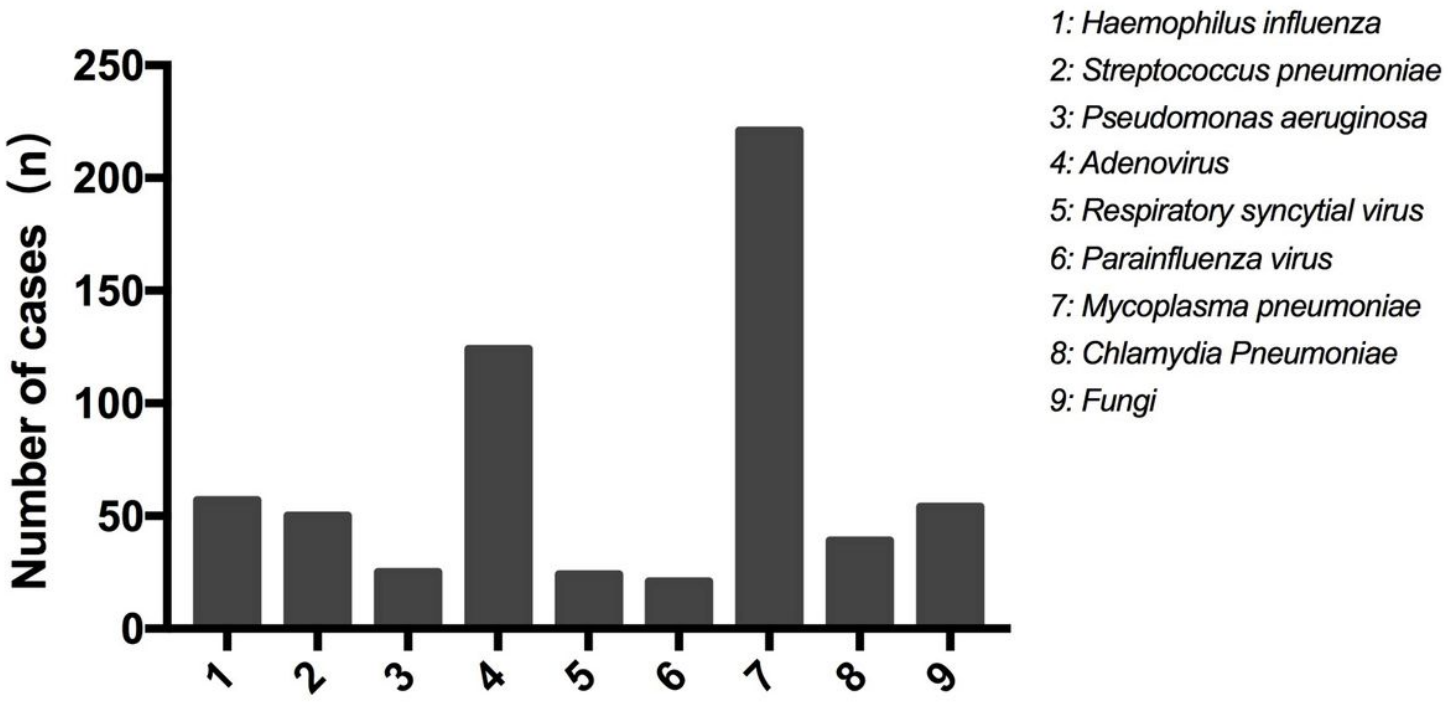

Figure 1

Analysis of the composition of pathogens in children with severe CAP. Analysis of the top three pathogens of bacteria and respiratory viruses and other pathogens infections in pediatric severe CAP.