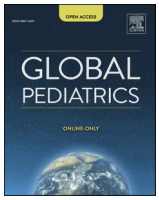
Global Pediatrics 7 (2024) 100119

Contents lists available at ScienceDirect

Global Pediatrics

journal homepage: www.elsevier.com/locate/gpeds



Complicated community-acquired pneumonia in children: How has COVID-19 impacted on?

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Introduction

Community-acquired pneumonia (CAP) is a leading cause of severe infections in children, especially among the ones below the age of five, causing on a global scale the 14 % of deaths within this age group.[1] Moreover, despite the majority of children with CAP heals, it has been estimated that complications may occurr in the 3 % of CAP. Complicated community-acquired pneumonia (CCAP) include empyema, necrotising pneumonia, and lung abscess along with systemic complications like septic shock, disseminated infection and multiorgan failure.[2] It has been proved that viral infections (influenza, respiratory syncytial virus (RSV) and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)) constitute the primary cause of CAP and an important risk factor for CCAP in children.[2,3] Through the worldwide diffusion of the 13-valent pneumococcal conjugate vaccination (PCV13) and *Haemophilus influenzae* type B conjugate vaccination, there has been a slightly increased of *Streptococcus pyogenes* and *Staphylococcus aureus* as causative pathogens of CCPA.[2,4,5]

Moreover, in the post-COVID19 pandemic era, it has been reported both an increase of out of season respiratory infections and severe/invasive infections, potentially caused by the so called "immunity debt", which is mostly consequence of the nonpharmaceutical interventions (NPI) imposed to limiting SARS-CoV-2 spread.[6,7]

Herein we describe two cases of CCAP in two previously well children, respectively due to *Staphylococcus aureus* and *Streptococcus pyogenes*.

Case presentation 1

A previously healthy and full vaccinated 12-year-old boy was referred on February 2023 to our paediatric intensive care unit (PICU) from the local Hospital due to septic shock and suspected CCPA. He had a three-day history of cough and fever, so on the fourth day of illness he was conducted to the local emergency department (ED). On the initial physical examination, he was febrile (temperature 39 °C) and his vital signs (blood pressure, pulse and respiratory rate) within the limits; chest auscultation revealed no breath sounds on the right lung. This finding was confirmed by the chest radiography (X-ray), which revealed and extensive right-sided lobe consolidation; laboratory examination showed a mild leukopenia with neutrophilia (WBC 3280 cells/mm, N 85,1 %), a C reactive protein (CRP) 4,2 mg/dl and a slightly increased creatinine (0,9 mg/dl). During the permanence in ED his condition rapidly worsened: blood pressure dropped to 80/40 mmHg, pulse and respiratory rate rose to 140 bpm and 30 breaths per minute, and oxygen saturation level was 88 % with an oxygen supply. At the same time, lactate increment to 3.8 mmol/L and a significant decrease in urine output with the increase of creatine to 1,45 mg/dl was reported. He was commenced on ceftriaxone and linezolid (a blood culture was obtained at baseline), supported with three 10 ml/kg fluid boluses and noradrenalin, and then intubated and transferred to our PICU.

Upon admission he was still febrile, and the subsequent blood tests revealed WBC reduced to 930 cells/mm, procalcitonin (PCT) markedly elevated at 286 ng/ml; an echocardiography was obtained, and it was unremarkable. On the same day, a contrast computed tomography (CT) chest scan was performed (Fig. 1) and it showed extended consolidation on the right upper and lower lobe, with several cavity with blurred edges within them, consistent with a necrotizing pneumonia. Considering the CT, antibiotic therapy was implemented with vancomycin (adjusted on renal function), suspected as possible pathogen responsible for necrotizing pneumonia in a vaccinated adolescent *Staphyloccocus aureus*. The morning after the admission in PICU, his respiratory viral panel (tested on nasal swab) turned out to be positive for influenza B, so antiviral treatment with oseltamvir was started for a five days course. Several microbiological investigations were required, and among them on culture of bronchoalveolar lavage a methicillin-resistant *S.aureus* encoding Panton-Valentine leucocidin (PVL-MRSA) growth. *Staphyloccocus aureus*

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https://doi.org/10.1016/j.gpeds.2023.100119
Received 18 December 2023; Accepted 23 December 2023
Available online 24 December 2023

was also detected through polymerase chain reaction (PCR) in blood, while all the blood cultures were negative.

On the third day of treatment, WBC levels worsened, and thrombocytopenia was reported for the first time, so linezolid was replaced by clindamycin with subsequent normalization of the blood tests. During the hospitalization the patient's conditions slowly but progressively improved, and on the 12th day it was possible to proceed with the extubation and admit him to the paediatric ward of our Hospital. Antibiotic therapy was stopped after almost 5 weeks of treatment (by intravenous and oral route), and subsequently he was discharged without any complaints. The boy was followed up by a chest X-ray examination after four months from the hospital discharge (Fig. 2), and minimal residual scarring were described. The prognosis is good and he's in good physical condition.

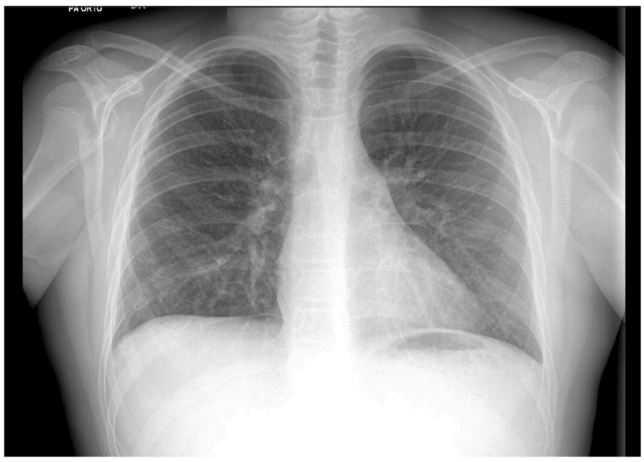

Fig. 2. Follow-up anteroposterior chest X-ray obtained 4 months after discharging. It shows subtle opacities in the right lower lobe likely representing scarring.

Case presentation 2

A previously well and fully vaccinated 6-years-old girl was referred on March 2023 to our Hospital from the local one, due to a CAP complicated by empyema.

She had a three-day history of cough and fever, so on the fourth day of illness, due to an increase work of breathing, she was conducted to the local ED. On the initial assessment she was febrile (temperature 39 °C), tachypnoeic (respiratory rate 40 breaths per minute) with low oxygen saturation level (89 %). Her respiratory examination was significant for bilateral wheezing and rhonchi and for a reduced murmur on right lower lobe. These findings were confirmed by the chest X-ray that showed a right lower lobe pneumonia. A blood culture was obtained, and laboratory test demonstrate neutrophilic leucocytosis (WBC 18.000 cells/mm N 80 %) with a considerable elevation of inflammatory indices (CRP 16 mg/dl and PCT 34 ng/ml respectively). She was provided with oxygen and nutritional support and started on intravenous ceftriaxone. After three days of hospitalization, despite the decrease of the inflammatory markers, she was still febrile with mild respiratory distress, and it wasn't possible to wean the oxygen supply. A chest CT with contrast was performed ant it highlighted an extensive right sided lower lobe consolidation associated with complex pleural effusion up to 3 cm, extended from the right costophrenic angle to the right axillary region. On the same day she was transferred to our hospital.

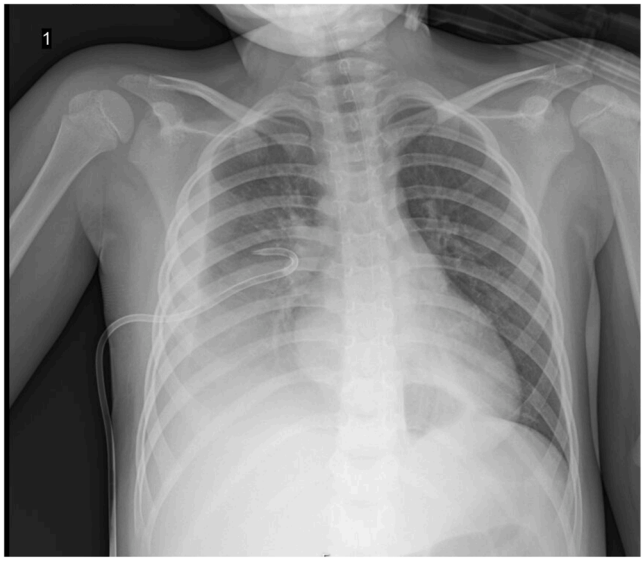

Fig. 3. Anteroposterior chest X-ray showed chest tube and extensive right-sided lower lobe consolidation associated with pleural effusion.

Considering the imaging diagnostic investigations, a right chest drainage was placed (Fig. 3) and 100 ml of turbid pleural fluid had been drained. Moreover, antibiotic therapy was implemented with clindamycin. The blood culture obtained prior the antibiotics initiations turned out to be positive for *Streptococcus pyogenes,* and it was confirmed also on pleural fluid with PCR technique.

On the 4th day after the drainage she was afebrile, and the oxygen supply was stopped. After more than two weeks of treatment,

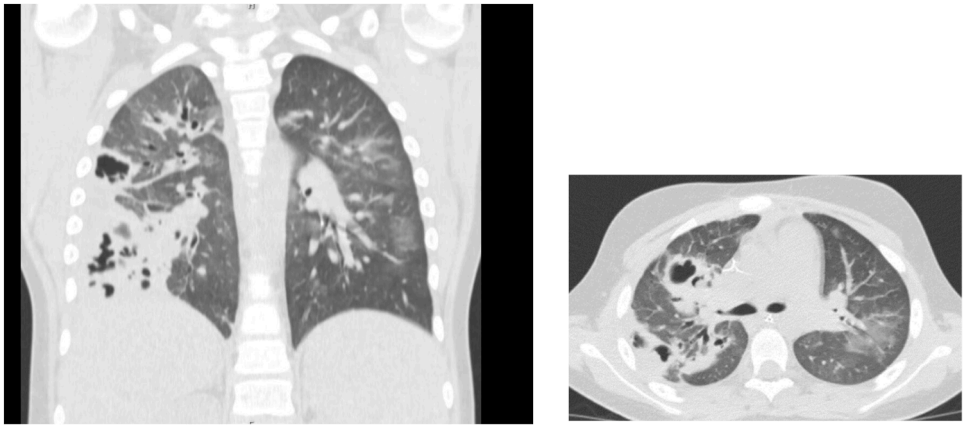

Fig. 1. Coronal and axial image of chest demonstrate the cavitary lesions.

intravenous clindamycin and ceftriaxone were discontinued and replaced with oral amoxicillin for two additional weeks to facilitate the discharge at home. The girl was followed up for a chest X-ray examination after three months from the hospital discharge and the imaging was normal. Currently she is well, she's back to her usual activities without complain any respiratory symptoms.

Discussion and conclusion

Necrotizing pneumonia and empyema are two frequent complications of CAP. Empyema is the most commonly reported, and it should be suspected in unwell children with persistent fever and respiratory symptoms, after 48–72 h since starting an appropriate antibiotic therapy.[8] The incidence of necrotizing pneumonia is lower, but it has been estimated that it can occur in a percentage between 5 and 10 % of CAP in paediatric patients.[9] The most common causative pathogen in necrotizing pneumonia seems to be *Staphyloccocus aureus*, and in particular the strains producing PVL, an exotoxin expressed by both MRSA and methicillin-susceptible S.aureus (MSSA), that cause leucocyte lyses and local tissue necrosis.[10,2] Moreover, a preceding viral illness, particularly influenza, is an important risk factor for staphylococcal diseases and in general for CCAP. On this matter, it has been described that influenza has a synergistic effect with PVL, promoting the damage on the airway epithelium.[11]

Notably, since 2022 (the first post-COVID19 pandemic year), in several European countries it has been reported an unusual increase in invasive infections, especially due to *S.pyogenes* (also called invasive Group A *Streptoccous* (iGAS) .[12] Invasive GAS may provoke different clinical pictures like pneumonia, empyema necrotizing fasciitis and streptococcal toxic shock syndrome (STSS).[12]

During the COVID-19 pandemic NPI, like social distancing, hand washing, mask, adopted to limit the diffusion of SARS-CoV2, consensually decreased the incidence of many infectious diseases in children, from the mild to the severe ones.[6] In particular, the Invasive Respiratory Infection Surveillance (IRIS), an initiative involving 26 countries, demonstrates that during the pandemic the incidence of invasive disease due to respiratory-associated bacteria like *S.pneumoniae, H.influenzae*, and *N.meningitidis* dropped.[13]

Moreover, COVID-19 pandemic had a negative impact on the vaccination coverage, with particular concern for the hexavalent, measles-mumps-rubella vaccines and DTPaP booster.[6,14]

The increased incidence of severe/invasive infections reported recently, may be related to the reduced exposure to bacterial and viral pathogens due to the NPI imposed during COVID-19. These could have negatively affected the immune system training and increased the percentage of children susceptible to infections, leading to the so called "immunity debt".[6]

A greater proportion of vulnerable children, along with an unstructured catch-up vaccination program, could enhance the risk of invasive/severe infections in the next years.

A structured surveillance network for bacterial invasive infections and the implementation of the vaccination programmes are crucial to both optimize the management of these children, and to contrast the rebound of several bacterial and viral infections.

CRediT authorship contribution statement

Lara Fusani: Conceptualization, Data curation, Writing – original draft. **Sandra Trapani:** Investigation, Resources, Writing – review & editing. **Luisa Galli:** Conceptualization, Data curation, Supervision, Validation, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

Author Contributions: Conceptualization L.G. and L.F; resources L.F, L.G and S.T; writing—original draft preparation L.F.; writing—review and editing L.G., L.F and S.T; supervision, L.G. All authors have read and agreed to the published version of the manuscript.

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