

# Is routine immunological screening beneficial in children with community-acquired pneumonia?

Z. Vancikova<sup>1</sup>, A. Janda<sup>2</sup>, E. Mejstrikova<sup>2</sup>, M. Trojanek<sup>3</sup>, T. Freiberger<sup>4</sup>, L. Pelikan<sup>1</sup>, H. Zemlickova<sup>5</sup>, Z. Blechova<sup>3</sup>, V. Maresova<sup>3</sup>

<sup>1</sup> Department of Paediatrics, Motol University Hospital, Prague

<sup>2</sup> Department of Paediatric Haematology and Oncology, Motol University Hospital, Prague

<sup>3</sup> 1st Department of Infectious Diseases, Bulovka University Hospital, Prague

<sup>4</sup> Molecular Genetics Laboratory, Centre for Cardiovascular Surgery and Transplantation, Brno

<sup>5</sup> National Institute of Public Health, Prague, Czech Republic

## Introduction

Community-acquired pneumonia (CAP) affects about 155 millions of children up to 5 years worldwide. Mortality in previously well children is in developed countries very low, about 95 % of deaths in pneumonia occur in developing countries. Virulence of pathogen, early appropriate treatment and underlying conditions have impact on disease outcome. Patients at risk for CAP are predominantly those with immunodeficiency, chronic respiratory tract disease and with neurological impairment. Majority of immunodeficiencies are secondary because of various chronic illnesses or immunosuppressive treatment and are usually apparent. Primary immunodeficiencies are much less frequent but they can be more severe and for some time usually do not necessarily attract attention. Under certain circumstances, unrecognized primary immunodeficiency can be fatal (e.g. vaccination with live vaccines, transfusion of not delectocitised blood). CAP and other respiratory tract infections are the most frequent clinical presentations of primary immunodeficiency especially of humoral immunity.

## Aim of the study

The objective of this study was to assess the rate of immunopathological states (immunodeficiency, allergy) in children hospitalized for CAP.

## Materials and Methods

Prospective consecutive follow-up study included children with clinically and radiologically confirmed CAP, hospitalized since IX/2006 to X/2009 at the Department of Paediatrics of Motol University Hospital. Apart from routine laboratory examination, serum levels of IgG, IgA, IgM, IgE antibodies (Ab), complement compounds and specific post-vaccination Ab levels were determined. For further investigations the bacterial aetiology was assessed by criteria set by Don M et al. (Pediatr Int. 2009 Feb;51(1):91-6.).

## Results

Demographics	
Study period	9/2006 – 10/2009
Number of patients	254
M:F ratio	131 : 123
Age median (IQR)	4.5 (2-8)
Length of hospitalization	6 (5-8)

254 cases of CAP (131 boys, 123 girls) were involved and treated according to standard hospital protocol. The age median was 4.5 years with IQR 2-8. 22 children were younger than 1 year. The median length of hospital stay was 6 days. The percentage of bacterial aetiology (mostly *S. pneumoniae*) was 41.7 % (defined as WBC over  $15 \times 10^9/l$  and CRP over 100 mg/ml).

Outcomes and Complications	
Lethal outcome	0
Necrotizing pneumonia	9
Chest drainage	8
Mechanical ventilation	8
Thoracoscopy and decortication	4

The outcome was overall favourable with no death. The most frequent complications are listed in a table above text.

## Immunological screening results

Immunopathological findings	Diagnosed (out of 254)	
	Newly	Previously
Allergic disease	65	85
Hypogammaglobulinaemia (IgG)	33	0
Hypogammaglobulinaemia (IgA)	33	1
Specific antibody deficiency	12	0
IgA deficiency	5	1
X-linked agammaglobulinaemia	2	0

Atopy was confirmed in 121 patients (47.6 %), which exceeds the reported national prevalence 32 %. 34 children (13.4 %) presented with IgA levels under age-specific limit, 6 of them having IgA deficiency. The prevalence of IgA deficiency in our study group was approximately 1:42 (6/254), which highly exceeds reported prevalence 1:500 in general population in European countries. 33 patients (13.0 %) presented with lower IgG levels. Surprisingly X-linked agammaglobulinaemia was diagnosed in 2 boys (11M and 21M) with mutation in Bruton's tyrosine kinase. In both children CAP was their first immunodeficiency symptom. For detailed description of clinical course see paragraph 1 and 2.

## X-linked agammaglobulinaemia

### Case Report 1

A 21-month-old boy with uneventful perinatal history, good postnatal adaptation presented to emergency department of the clinic with fever, laryngeal cough, dyspnoea, malaise and diarrhoea. 3 days before admission he finished outpatient antibiotic treatment of uncomplicated CAP. The patient was not breast fed, he received full vaccination including live attenuated bacillus Calmette-Guérin vaccine and live attenuated Polio vaccine, and live attenuated measles-mumps-rubella vaccine without adverse events.

Initial investigations revealed CRP 253 mg/l, ESR 32mm/h, white blood cell count  $5.5 \times 10^9/l$  with 58% monocytes 37% lymphocytes and 1% segments and 4% bands. Residual peribronchial infiltrations were diagnosed bilaterally on chest X-ray. The diagnosis at admission was CAP, neutropenia and postantibiotic treatment diarrhoea. *Pseudomonas aeruginosa* was cultivated from stools, urine, upper respiratory tract secretion and blood. Serum levels of IgG, IgA and IgM were under detection limit. Circulating CD 19 + B cells were undetectable.

Because of severe bacterial infection and agranulocytosis, antibiotic treatment with 3rd generation cephalosporin and aminoglycoside in maximal doses was started immediately after admission. When agammaglobulinaemia was diagnosed on the second day, the boy received 10 g of intravenous immunoglobulins (0.9g/kg) and fluconazol was added to the treatment. From the second day after admission, clinical condition of the patient improved, from the 4th day he was afebrile, diarrhoea subsided. Intravenous antibiotic treatment was stopped on day 14 and on day 16, the patient was discharged with normal clinical and laboratory findings. Regular intravenous immunoglobulin substitution every 3 weeks 0.5g/kg/dose was started. After initiation of this treatment the boy is doing well and in his recent history without infectious complications.

## Case Report 2

15 months later, 11-month-old boy presented to our clinic with 3-day history of fever. Because of elevated inflammatory markers and no obvious infectious focus was admitted for further evaluation. He was born following an uneventful antenatal period in term, weight 3100g, normal postnatal adaptation. Anorectal atresia was diagnosed after birth and day after, colostomy was performed. At three months he was hospitalised and treated with intravenous antibiotics 7 days for pyelonephritis. At 6 months, plastic surgery of anus was performed and at 11 months colostomy was closed. The patient was still breast fed, he received full vaccination including live attenuated bacillus Calmette-Guérin without adverse reactions. His grandmother's brother (from the mother's kindred) died at 18 years from infection, he had history of recurrent pneumonia, encephalitis and brain abscess.



On initial investigation, chest X-ray demonstrated bilateral peribronchial infiltration and paracardial infiltration on the right side at the lower pole of hilus. CRP was 129 mg/l, ESR 36mm/h white blood cell count  $10 \times 10^9/l$ , with 55% monocytes, 43 % lymphocytes, 1% neutrophils, 1% myelocytes. The diagnosis at admission was CAP, neutropenia. Serum levels of IgG, IgM and IgA were below detection limit, IgE was 27.8IU/ml. Circulating CD 19+ B cells were undetectable. P.R28C mutation in the gene for Bruton tyrosine kinase was identified. Patient was successfully treated with intravenous crystalline penicillin 6 days. On the 2nd day of hospitalization he received 3 g (0.4 g/kg) of intravenous immunoglobulins, since then, he was afebrile and his laboratory findings normalized. After 9 days of hospitalization he was discharged. Regular intravenous immunoglobulin substitution every 3 weeks 0.5g/kg/dose was started.

In both cases pneumonia was the first serious bacterial infection which lead to hospitalization, unremarkable previous medical history, standard elevation of inflammatory markers, extreme monocytosis and neutropenia.

## Conclusion

Our experience supports at least basic immunological evaluation of previously well children hospitalized with CAP. Patients with immunodeficiencies have disease symptoms for months or years which can attract attention often only due to their higher frequency, not severity. In our study group following previously undetected immunopathologies were diagnosed: 2 cases of X-linked agammaglobulinaemia; 5 cases of IgA deficiency; 63 cases of allergic disease. Timely diagnosis of immunopathology with immediate initiation of therapy is of clear benefit to affected patients and can have significant implications including family counseling. Apart from the clear clinical benefit for the patients, socio-economical benefit can be also discussed.