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Chlamydia — *frequent cause of respiratory tract infections in children*

Chlamydia —
ważny czynnik przyczynowy zakażeń układu oddechowego u dzieci

The genus *Chlamydia* is a group of obligate intracellular parasites that has been known for over 50 years with a unique developmental cycle and common morphological forms [18]. *Chlamydiae* present specific tropism and cytotoxic activity towards epithelial cells of the respiratory tract, in which they multiply and destroy affected cells aiming at lysis or apoptosis [11, 47]. It has been shown that pro-inflammatory cytokines released from infected cells may induce the process of "programmed death" also of adjacent non-infected cells of the respiratory epithelium, that results in disorders in ciliostasis in *Chlamydia* infections and the development of local inflammatory process [11, 47, 51].

In children all species of the genus *Chlamydia* may cause inflammatory disorders in the respiratory tract, but infections with the ethiology of *Chlamydia trachomatis* and *Chlamydia pneumoniae* are most common. Even in cases of atypical community-acquired pneumonitis [25] no routine diagnosis for bacterial infections caused by genus *Chlamydia* is carried out, due to technical problems and high cost of investigations. But it should be stressed that the use of new sensitive diagnostic methods enabled defining the present role of *Chlamydia* as an important pathogen in the upper and lower respiratory tract infections in children due to *Chlamydia trachomatis*.

CHLAMYDIA TRACHOMATIS IN RESPIRATORY TRACT INFECTIONS

Infection of the respiratory tract due to *Chlamydia trachomatis* is found mainly in infants when they pass through the maternal birth canal infected with *Chlamydia*. Symptoms of a characteristic separate syndrome of pneumonitis due to *Chlamydia*

trachomatis in infants [1] are: good general condition, usually afebrile course, dry cough and increasing dyspnoea. Non-productive cough may subsist long after recovery and is usually accompanied by bronchial hyperreactivity and reduced spirometric parametres with symptoms of bronchial obstruction. On the physical bronchial rales and wheezing were found and the chest X-ray film revealed intraparenchymatous or patchy inflammatory infiltrates and symptoms of pulmonary distension. In 50% of children it is accompanied by conjunctivitis. It seems that up to 25% of infants under 6 months hospitalized for lower respiratory tract infections and ¾ of all infants with afebrile pneumonia are infected with *Chlamydia trachomatis* [1, 48]. Beem et al. revealed the presence of this microorganism in nasopharyngeal swab and the increased level of specific IgG and IgM [1] in 18 out of 20 (90%) examined infants with afebrile pneumonia.

Recently many authors suggest possible role of *Chlamydia trachomatis* in the respiratory tract infections even in older children [5, 52]. Carballal et al. revealed the ethiology of *Chlamydia trachomatis* in 19.2% of children with pneumonia [5]. High frequency of infection with *Chlamydia trachomatis* found by these authors among children from children's homes (35.1%) suggests airborne-droplet spread of infection. In Poland Sobiech et al. found serological evidence for infection with *Chlamydia trachomatis* in 24.8% of 1831 children aged between 2 weeks and 6 years, hospitalized for upper respiratory tract infections and pneumonia between 1993–1996 [52]. This high percentage of *Chlamydia trachomatis* in respiratory tract infections in children may be conditioned to some degree by cross reactivity of antigens of cellular wall of *Chlamydia trachomatis* and *Chlamydia pneumoniae*. It indicates the need to carry out diagnostic procedures for *Chlamydia trachomatis* infection in children with inflammation of the respiratory tract, regardless the age of patients.

CHLAMYDIA PNEUMONIAE IN THE RESPIRATORY TRACT INFECTIONS

A respiratory pathogen — *Chlamydia pneumoniae* — was first described by Graystone et al. [15] in 1986 as an important factor causing pneumonia in students of Washington College. Many further retrospective studies indicate that this strain (TWAR — Tai Wan Acyte Respiratory) might be the etiological factor of respiratory tract diseases for a long time, or — due to considerable antigen similarity with *Chlamydia psittaci* — many cases diagnosed as ornitosis were in fact caused by *Chlamydia pneumoniae* [4].

WAYS OF TRANSMISSION

Chlamydia pneumoniae is mainly a human pathogen, although infections in animals (e.g. koalas [24]) have been also reported. The way of infection is not quite clear, but the most probable is droplet infection with respiratory seretions from infected humans [12]. *Chlamydia pneumoniae* may survive in aerosol droplets 3–5 μm in diameter [56], but short survival time in the respiratory fraction of aerosol (in several min-

utes the decrease in percentage of live pathogens by 53% was observed) and on the skin of hands (10–15 min.), may indicate the importance of direct contact in the spread of infection [56]. Some cases of infecting humans during laboratory work have been reported [22], spread of infection has also been documented among family members living in the same household. Epidemics have been also reported — serological studies confirmed that the outbreak of pneumonia epidemics in Scandinavia between 1981–1982 and 1986–1987 [4, 26] was due to *Chlamydia pneumoniae*, but usually local epidemics are observed in enclosed populations such as among military recruits or residents of nursing homes [2, 10, 58].

There is also a possibility of haematogenic way of spreading infection with *Chlamydia pneumoniae*, that might explain a suggested role of this microorganism in the pathogenesis of arteritis and vascular and aortic atherosclerosis [30, 37]. In experimental animals following intranasal and intratracheal infection due to *Chlamydia pneumoniae* where inflammatory changes in the respiratory tract were observed, the pathogen was found (using PCR) also in the spleen, aorta and monocytes of peripheral blood [30, 38]. The fact that this pathogen may survive in monocytes and macrophages of peripheral blood, may explain the general and chronic character of infection, a resistance to antibiotic treatment and frequent reinfections [25].

EPIDEMIOLOGY

Chlamydia pneumoniae is the most common human pathogen. In epidemiologic study serological evidence for the infection with *Chlamydia pneumoniae* are found in 40–60% of total population [15, 29]. Antibodies against *Chlamydia pneumoniae* increase with age, starting from 10% in children of 5–10 years, 30–40% in adults and often over 80% in the elderly [2, 15].

The majority of researchers emphasizes low frequency of *Chlamydia pneumoniae* infections at the time of development, especially in infants and young children [6, 19, 33, 42]. It seems however, that this frequency is much higher than it was previously thought, and differences result from sensitivity and specificity of diagnostic method. Recently, Norman et al. demonstrated immunohistochemically the presence of *Chlamydia pneumoniae* in pharyngeal tonsils in all examined children aged 1 month to 5 years and 98.5% of children aged 5–15 years who underwent adenotomy [44]. The results of these studies suggest that almost all children under 15 were in contact with this pathogen or subclinical form of infection.

A possibility of asymptomatic subclinical infection or multiple reinfection may be confirmed by studies carried out in day care centres in Sweden [43]. In these studies using PCR (polymerase chain reaction). *Chlamydia pneumoniae* was found in nasopharyngeal swabs in 22.7% of healthy pre-school children and it did not differ considerably from results found in adult personnel (23.2%). Lower percentage of positive PCR (14%) was found in children < 3, but the presence of specific antibodies in this age group was revealed only in 2 children [43]. These results demonstrate that younger children probably do not produce suitable level of specific antibodies or that *Chlamy-*

dia pneumoniae is poorly immunogenic and in order to elicit humoral response a multiple subclinical infection is necessary or being a carrier for a long time [18, 25].

There are some reports of asymptomatic carrier of *Chlamydia pneumoniae* in nasopharynx in healthy children and of a dormant carrier following acute infection of respiratory tract, but the role of a carrier in the epidemiology of *Chlamydia pneumonie* infections is not known [7, 17, 22, 42].

Severe infections of the upper respiratory tract with *Chlamydia pneumoniae* occur mostly in summer [57] in 3–58% of children of all ages [16, 33, 42, 57]. Among clinical symptoms a severe persistent cough (in 50% of patients) and pertussis-like cough is most common, especially in children from 0 to 4 years [8, 42]. In the group of older children, over 4 years, the most common is pharyngitis, palatine tonsilitis, and otitis media accompanied by exudate [42, 53].

Chlamydia pneumoniae plays an important role in the pathogenesis of lower respiratory tract in children [13, 42], that is in bronchitis and pneumonia. Esposito et al. demonstrated acute infection with *Chlamydia pneumoniae* in 15.5% of children with obstructive bronchitis [11], but in other studies *Chlamydia pneumoniae* was considered an etiologic factor in bronchitis even in 75% of children aged 5–16 [42].

In epidemiological data on community-acquired pneumonia due to *Chlamydia pneumoniae* there is a considerable discrepancy between reported frequency of occurrence, from 3.4 (43%) in adults and 2.7 (31%) in children depending on the study setting, age of patients and the method used to detect the pathogen.

Prevalence in children was usually lower than in adults — this is presented in Table I. *Chlamydia pneumoniae* was most often detected in pneumonia in children over 10 years [31, 35, 36], and also using the culture method and DNA analysis by a polymerase chain reaction (PCR) in nasopharyngeal secretion. This last method (PCR) seems especially useful in the diagnosis of *Chlamydia pulmonae* infections in younger children because many of them do not demonstrate productive cough necessary to obtain sputum sample for culture [18, 19, 42], but only negative serological results due to low humoral reactiveness to *Chlamydia* surface antigen MOMP [31, 42, 43].

The results of study by Block et al. confirm the above observations. In their study of the effectiveness of treatment of pneumonia in children aged 3–12 years carried out in various medical settings, they found a serological evidence for the acute infection due to *Chlamydia pneumoniae* in 18.5% of patients, but as many as 77% of positive results of culture did not confirm acute infection serologically [3]. Similarly, Harris et al. revealed *Chlamydia pneumoniae* using culture method in 7% of 420 examined infants and children under 16 with pneumonia, but in the majority of cases (84%) the results of serological examinations were negative [20]. In both above mentioned reports frequency of *Chlamydia pneumoniae* in pneumonia in children did not differ significantly in age groups <6 and older children [3, 20].

Therefore it is necessary to apply simultaneously several methods that are sensitive enough to detect *Chlamydia pulmonae* infections in children and to carry out routine diagnosis aimed at detecting this pathogen in respiratory infections at the time of child development, also in the youngest children [19].

Table I. Role of *Chlamydia pneumoniae* in community-aquired pneumonia in adults and children: results of selected studies

First author, yr [Ref.]	Location	Subjects n	Age yrs	Method	Prevalence of C.pneumo-niae
Kauppinen, 1995 [29]	Oulu, Finland	125	Adult	Serology (MIF): IgG, IgM, IgA	43
Kauppinen, 1996 [28]	Oulu, Finland	125	Adult	Serology (MIF): IgG, IgM, IgA	25,6
Norrby, 1997[45]	Skandinavia	383	Adult	Serology (MIF): IgG, IgM	29
File, 1997 [14]	Multicentre, USA	456	Adult	Serology (MIF): IgG, IgM	22
Lieberman, 1996 [32]	Beer-Sheva, Israel	346	Adult	Serology (MIF): IgG, IgM	17,9
Marston, 1997[34]	Ohio, USA	2776	Adult	Serology (MIF): IgG, IgM	8,9
Mundy, 1998[39]	St.Louis, USA	385	Adult	Culture PCR (nasopharyngeal swab)	7,5
Ishida ,1998[23]	Kurashiki, Japonia	339	>15	Serology (ELISA): IgG, IgM	3,4
Studies in children					
Chirgwin, 1991[7]	Brooklyn, USA	91	Adults, children	Serology(ELISA): IgG, IgM culture	18,7
Harris, 1998[20]	Multicentre, USA	420	0,5-16	Serology (MIF):IgG, IgM Culture, PCR (nasopharyngeal swab)	15
Block, 1995[3]	Multicentre, USA	260	3-12	Serology (MIF): IgG, IgM Culture, PCR (nasopharyngeal swab)	13,1
Chaudhry, 1998[6]	New Dehli, India	62	3-16	Serology (MIF): IgG, IgM	6,4
Yamada, 1995[60]	Kurume, Japan	130	0,9-12	Serology(MIF): IgG, IgM PCR (nasopharyngeal swab)	7,7
Martinez, 2000[35]	Santiago, Chile	112	0,1-14	Serology (MIF): IgG, IgM	2,7
Wubbel, 1999[59]	Dallas, USA	168	0,5-16	PCR (nasopharyngeal swab)	6
Heiskanen-Kosma, 1999[21]	Kuopio, Finland	201	5-16 5-9 >10	Serology (EIA, MIF): IgG, IgM	10 9 31
Choroszy-Król, 1998 [8]	Wrocław, Poland	78	2,5-16	DIF (pharyngeal swab)	33,3
Nitsch-Osuch,2000 [41]	Wrocław, Poland	101	0-3	DIF (pharyngeal swab)	0,03

CLINICAL COURSE

Clinical symptoms of upper respiratory infections with *Chlamydia pneumoniae* in children are usually mild and resemble a common cold: slight increase in body temperature, rhinitis or nasal congestion, pharyngitis, hoarseness and dry persistent cough that usually subside spontaneously. [18, 60]. There were reported cases of persistent cough, lateral nasal sinusitis and otitis media with excudate in the course of infection with *Chlamydia pneumoniae* in school children [16, 17, 19]. Clinical symptoms following acute infection with *Chlamydia pneumoniae* demonstrated by persistent cough and bronchial hyperactivity may last longer in the youngest children [42].

Symptomatic pneumonia due to *Chlamydia pneumoniae* is not different from other atypical pneumonia in its clinical picture, radiological changes and course of disease [18, 19]. Some features that may help in the diagnosis of Chlamydial infection are: epidemic or familial occurrence of the disease, accompanying hoarseness, pharyngitis, laryngitis, or lateral nasal sinusitis and good general condition of a child and slight aberrations on the physical and radiological examination [18, 19, 31]. More severe course of pneumonia is observed in infants, especially if accompanied by cellular and humoral deficiency [41]. In the studies by Nitsch-Osuch et al. dominant symptoms of pneumonia due to *Chlamydia pneumonia* in children aged 0–30 months with congenital heart diseases were: cough, increased body temperature, dyspnoea and rapid breathing. In these children some complications such as circulatory failure and sepsis were observed and longer hospitalization than in cases of pneumonia of other etiology was required [41].

In the X-ray film it is sometimes possible to see peribronchial changes or irregular patchy inflammatory infiltration or intraparenchymatous condensation that usually occur unilaterally in lower portion of lungs, most often within one lobe [27]. Inflammatory infiltration in pulmonary parenchyma, affecting pleura and enlargement of perihilar lymph nodes and more severe course of disease, longer lasting clinical symptoms and radiological changes are usually true of *Chlamydia pneumoniae* infections with accompanying infection due to *Mycoplasma pneumoniae* or *Streptococcus pneumoniae* [53]. There was a case report of pneumonia and pericarditis in a child in the course of double infection due to *Chlamydia pneumoniae* and *Mycoplasma pneumoniae* [35]. Frequent co-infection of *Chlamydia pneumoniae* with other pathogens, observed in about 55% of atypical pneumonia in adults [30] and in 66% of children [35] makes the diagnosis of *Chlamydial pneumoniae* in children often difficult or even impossible to detect basing only on clinical symptoms and radiological changes [17, 18, 49]. In such cases it is advisable to extend diagnostic procedures and apply empirical therapy with well-documented effectiveness of treatment for pathogens of *Chlamydia* type.

TREATMENT

Many data indicate sensitivity of *Chlamydia* to treatment with antibiotics. The following drugs proved effective in the treatment of respiratory tract infections: macrolides, tetracyclines, beta-lactam antibiotics and fluorochinolons.

Taking into account well known limitations in administering fluorochinolons and tetracyclines, especially in small children, macrolides are considered drugs of choice in the treatment of Chlamydial community acquired pneumonia: erythromycin in pneumonia due to *Chlamydia trachomatis* in newborn and infants under 4 years of age administered for about 2 weeks. Clinical improvement is observed usually after 5–7 days of treatment accompanied by slow decline in pathogens in nasopharyngeal secretion, but cultures for *Chlamydia trachomatis* may remain positive for several weeks or even months [1, 48]. Erythromycin or new macrolides (Azithromycin, clarithromycin or roxithromycin) are considered drugs of first choice in infections of upper respiratory tract due to *Chlamydia pneumoniae* and in pneumonia with mild or moderate course [9, 40], and also in empirical therapy for community acquired pnneumonia among school children [21]. In cases of pneumonia with severe course, especially when etiological factor is not known, and the infection with atypical pathogen cannot be excluded, or when mixed etiology is suspected, it is recommended to include in the treatment one of antibiotics that is effective against atypical bacteria, e.g.: cephalosporyn of III or IV generation + macrolid [9]. In many studies on the effectiveness of the therapy for community-acquired pneumonia in children due to *Chlamydia pneumoniae*, it was impossible to prove that new macrolides are more effective than erythromycin or beta-lactam antibiotics [13, 20, 21, 32, 46, 59]. It should be stressed that higher quality of a new generation of macrolides means significantly lower frequency of adverse side effects in children [59]. The majority of authors demonstrate the necessity of extended use of antibiotics (from 14 to 21 days) in the treatment to eradicate *Chlamydia pneumoniae* from the respiratory tract, prevent recurrence of disease or prevent chronic symptoms [7, 46, 50].

Considering common occurence of infections due to bacteria of the genus *Chlamydia*, and their probable causative effect in the pathogenesis of atherosclerosis, arteritis and exacerbation of chronic diseases of the respiratory tract, it seems advisable to work on prophylaxis of infections by applying specific vaccines. Research on clinical effectiveness of intranasal and subcutaneous DNA vaccine containing a gene for hot shock protein (HSP-60) to prevent Chlamydial pneumonia seems to be very promising [55].

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STRESZCZENIE

Wszystkie gatunki rodzaju *Chlamydia* mogą wywoływać zmiany zapalne w układzie oddechowym u dzieci, przy czym najczęściej występują zakażenia o etiologii *Chlamydia trachomatis* i *Chlamydia pneumoniae*. Diagnostyka w kierunku zakażeń bakteriami z rodzaju *Chlamydia*, głównie ze względu na trudności techniczne i znaczne koszty badań, nadal nie jest rutynowo przeprowadzana nawet w przypadkach pozaszpitalnych zapaleń płuc o nietypowym przebiegu. Jednak właśnie zastosowanie nowych, czułych metod diagnostycznych pozwoliło na określenie roli *Chlamydia* jako ważnego patogenu w zakażeniach górnych i dolnych dróg oddechowych w każdej grupie wiekowej. W pracy przedstawiono dane epidemiologiczne a także omówiono postacie kliniczne, obraz radiologiczny i zasady postępowania terapeutycznego w zakażeniach układu oddechowego u dzieci o etiologii *Chlamydia trachomatis* i *Chlamydia pneumoniae*.