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Chlamydia trachomatis: Diagnosis and Treatment of Urinary Tract Infections in Children

Chlamydia trachomatis – diagnostyka i leczenie zakażenia dróg moczowych u dzieci

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Abstract

Background. Urinary tract infections (UTIs) caused by *Chlamydia trachomatis* have become the subject of great interest as a result of the increasing number of UTIs observed the world over.
Objectives. Evaluating the efficacy of the treatment of children with documented UTI caused by *Chlamydia trachomatis*.
Material and Methods. Ninety-five children aged from 4 weeks to 18 years with diagnosed *Chlamydia trachomatis* were treated at the Departments of Pediatric Nephrology and of Pediatric Surgery and Urology, Sielsian Piasts University of Medicine Wrocław, in 2003–2005. The samples used in the study were urethral swabs and urine specimens taken from the patients before initiation of treatment. *Chlamydia trachomatis* antigen was determined by the direct immunoflorescence (DIF) method with the Micro Track reagent *Chlamydia trachomatis* Direct Specimen Test (Trinity Biotech plc., Ireland) and a fluorescent microscope (Olympus, Japan) at 400× and 1000× magnification. *Chlamydia trachomatis* DNA in urine specimens was detected using the PCR *Chlamydia trachomatis* Diagnostic Test (DNA-Gdańsk II s.c. Polska).
Results. The specimens from 95 children with diagnosed *Chlamydia trachomatis* were analysed by means of DIF method and specimens from 15 out of them also by PCR assay. The highest rate of positive results (52%) was shown in the group of children with vesicoureteral reflux, ureteropelvic junction obstruction, and juxtavesical ureter obstruction (7.4%). The largest group were patients with persistent symptomatic urinary tract infection (44.2%) and negative urine cultures, whereas no structural and functional disorders were observed. The children were treated according to a standard schedule, obtaining regression of clinical symptoms and changes in urine in 59% of UTI cases. In 39 children with persistent dysuria, a control urethral swab test was performed one month after the end of treatment with positive results observed in 15 children. These patients underwent re-treatment and positive urethral swabs were found in 9 of them 6 months later.
Conclusions. The antibiotic therapy in children proved to be effective, especially when it was early. The important point is that the antibiotics used in therapy did not reverse the changes caused by the inflammatory process. Due to the increasing number of infections with atypical flora and administered many complications resulting from chronic exposure to these pathogens, it seems that these etiological agents should always be taken into consideration in urinary tract infections with atypical course (**Adv Clin Exp Med 2006, 15, 4, 637–643**).

Key words: *Chlamydia trachomatis*, urinary tract infections, children.

Streszczenie

Wprowadzenie. Zakażenia układu moczowego (ZUM), wywołane przez *Chlamydia trachomatis*, stanowią obecnie przedmiot szczególnego zainteresowania. Wynika to z obserwowanego na całym świecie wzrostu liczby zachorowań.
Cel pracy. Ocena skuteczności leczenia dzieci z udokumentowanym zakażeniem układu moczowego wywołanym przez *C. trachomatis*.

Materiał i metody. W latach 2003–2005 w Klinice Nefrologii Pediatrycznej i Poradni Urologicznej Kliniki Chirurgii Dziecięcej AM we Wrocławiu leczono 95 dzieci w wieku od 4 tygodni do 18 lat, u których rozpoznano *C. trachomatis*. Przedmiotem badań były wymazy z cewki moczowej oraz mocz, pobrane przed rozpoczęciem leczenia. Antygen *C. trachomatis* oznaczano metodą immunofluorescencji bezpośredniej, z użyciem odczynnika MicroTrack *Chlamydia trachomatis* Direct Specimen Test, firmy Trinity Biotech plc., Ireland oraz mikroskopu fluorescencyjnego Olympus (Japan). Preparaty oglądano przy powiększeniu 400× i 1000×. DNA *C. trachomatis* w próbkach moczu wykrywano z zastosowaniem zestawu diagnostycznego PCR *C. trachomatis*, firmy DNA-Gdańsk II sc. Polska.

Wyniki. Analizie poddano wyniki badań 95 dzieci, u których stwierdzono *C. trachomatis* metodą DIF, w tym u 15 również metodą PCR. Najwyższy odsetek wyników dodatnich (52%) wykazano w grupie dzieci z odpływami pęcherzowo-moczowodowymi oraz ze zwężeniem ujścia podmiedniczkowego i przypęcherzowego moczowodów (7,4%). Najliczniejszą grupę stanowiły dzieci z uporczywym objawowym zakażeniem dróg moczowych (44,2%) z ujemnymi posiewami moczu; nie stwierdzono u nich jednak zaburzeń strukturalnych ani czynnościowych. Dzieci leczono zgodnie z przyjętym schematem, uzyskując u 59% ustąpienie objawów klinicznych i zmian w moczu. U 39 dzieci z utrzymującymi się dolegliwościami dysurycznymi wykonano kontrolny wymaz z cewki moczowej, po miesiącu od zakończenia kuracji; był on dodatni u 15 dzieci. Dzieci te poddano ponownej kuracji, a 6 miesięcy później w wymazie z cewki moczowej stwierdzono ponownie dodatni wynik u 9 z nich.

Wnioski. Antybiotykoterapia zastosowana u dzieci okazała się wysoce skuteczna, szczególnie gdy wprowadzano ją odpowiednio wcześnie. Zwraca uwagę fakt, że stosowane antybiotyki nie odwracały zmian spowodowanych przez stany zapalne. Wzrastająca liczba zakażeń florą atypową oraz powikłania wynikające z przewlekłego zakażenia tymi patogenami wskazuje, że *C. trachomatis* powinna być brana pod uwagę jako czynnik etiologiczny, szczególnie przy nietypowo przebiegających zakażeniach dróg moczowych (**Adv Clin Exp Med 2006, 15, 4, 637–643**).

Słowa kluczowe: *Chlamydia trachomatis*, zakażenia dróg moczowych, dzieci.

Urinary tract infections (UTIs) caused by *Chlamydia trachomatis* have become the subject of great interest as a result of the increasing number of UTI incidences observed all over the world. According to WHO, more than 5.5 million people become infected with this pathogen every year in Western Europe [1]. The high infectivity and long period of incubation, which amounts to 21 days but may even last 5–7 weeks in some cases, are mentioned among the main causes of the infections' prevalence [2]. Untreated or poorly treated disease after different times can lead to serious consequences not only in patients, but also in their offspring. Data concerning the prevalence, course, treatment, and prognosis of disease mainly come from research in adult populations [2, 3]. Observations made in recent years indicate that the disease is also being recognized more frequently in children; however, there are only a few reports focused on this subject in the literature [4–7].

Infections in children remain problematic. The route of transmission in a child's environment has not yet been very well explored [8, 9]. While sexually transmitted infections in adults and acquired infections in children in the perinatal period via mother-fetus are well known, *Chlamydia* transmission by non-sexual routes, for example as a result of low living standards, are still not fully documented. The recognition of UTI caused by *Chlamydia trachomatis* can be difficult because of the unspecific clinical symptoms, such as abdominal pain, pruritus, burning, and dysuria, that are identical to symptoms characteristic for UTIs of different etiology. Chlamydial infection should always be suspected when sterile leukocyturia and/or erythrocyturia with atypical etiology are accompanied by vulvitis with mucopurulent secretion around the urethra, recurrent dysuric symptoms, or diurnal polyuria.

Determining the etiological agent is decisive in applying a correct and effective treatment. Moreover, *Chlamydia trachomatis* is not sensitive to antibiotics conventionally used for UTI, i.e. cephalosporins, aminoglycosides, and penicillins. They inhibit *Chlamydia* transformation to a further stage of the developmental cycle, but do not kill the pathogen and consequently lengthen the incubation period. Treatment of chlamydial infection is based on using drugs which pass through the cell membrane barrier into cells. The strongest activity of tetracyclines, macrolides, and quinolones has been indicated based on their minimal inhibitory concentration values [10, 11].

The principles of treating chlamydial infections in children are the same as in adults. The major limitation concerning first- and second-generation quinolones is that they should not be used in children because of the possibility of articular cartilage destruction, and tetracyclines should not be applied before nine years of age. Erythromycin is a drug of choice in newborns and in small children, but is more often replaced by a second-generation macrolide. The aim of the study was to evaluate the efficacy of treatment in children with documented UTI caused by *Chlamydia trachomatis*.

Material and Methods

Ninety-five children aged from 4 weeks to 18 years with UTI diagnosis of chlamydial etiology were treated at the Department of Pediatric Nephrology and at the Department of Pediatric Surgery and Urology, Silesian Piasts University of Medicine in Wrocław, in 2003–2005. The samples used in the study were urethral swabs and urine taken from patients before initiation of treatment. The indications for the diagnostic tests for *Chlamydia trachomatis* are persistent or recurrent infections associated with sterile leukocyturia and the symptoms described above. The patients' histories excluded sexual abuse. The diagnosis was based on positive results of urethral swabs taken before the start of treatment and *Chlamydia trachomatis* DNA isolation from the urine of 15 patients. Selection of the method was conditioned by the possibilities of the analytic laboratory. In all children, basic examinations were performed, i.e. basic urine analysis, urine culture, and renal ultrasonography before taking the urethral swabs. Imaging tests such as polycystography, renoscintigraphy, and also, in justified cases, intravenous urography and cystoscopy, were conducted if there were indications for further diagnostic procedures of UTI. In children with suspected lower urinary tract dysfunction, uroflowmetric examination was performed. Urethral material was taken by a pediatrician from a depth of 1.5–2 cm in a way enabling abruption of the epithelial cells. Urine for bacteriological examination was taken from mid-stream according to the widely accepted rules of maintaining sterile conditions.

The material was examined after appropriate protection by a direct immunofluorescence method using the Micro Track reagent *Chlamydia trachomatis* Direct Specimen Test made by Trinity Biotech plc., Ireland, and fluorescent microscope made by Olympus Japan [12]. *Chlamydia trachomatis* DNA was discovered in urine samples by the PCR *Chlamydia trachomatis* Diagnostic Test produced by DNA-Gdańsk II s.c. Polska. The examinations were performed according to the reagents' producers' recommendations [13]. The determinations were carried out at the Department of Basic Science and the *Chlamydia* Research Unit of the Department of Microbiology.

After the diagnosis had been established, the children were treated according to widely accepted rules. One of the following macrolides was used: clarithromycine at a dose of 15 mg/kg, two doses per day, roxithromycine at a dose of 8 mg/kg, two doses per day for 14 days, or azithromycine at a dose of 10 mg/kg, one dose per day for 3 days. In case of no improvement or persistence of a positive swab in children above 12 years of age, doxycycline was used at a dose of 4 mg/kg, two doses per day, for 10–14 days, while in younger children azithromycine or the other macrolide mentioned was used once again.

The results of treatment were estimated as follows: the patient was recognized as entirely cured when there was complete regression of symptoms and there was normal urinary sediment four weeks after the end of treatment, at which time the urethral control swabs were not continued. In case of persistent clinical symptoms with accompanying leukocyturia or erythrocyturia three weeks after termination of antibiotic therapy, the control urethral swab for *Chlamydia trachomatis* was performed.

Results

The results of treatment in 95 children, 62 girls (65%) and 33 boys (35%), were analyzed. The presence of *Chlamydia trachomatis* was confirmed by the direct immunofluorescent method (DIF). The investigation of *Chlamydia trachomatis* DNA in urine samples by the polymerase chain reaction (PCR) assay was restricted to 15 children because of financial limitations. In all of these children the result obtained was positive; in one child the DIF result was negative whereas the PCR result was positive.

The control investigation was performed in 39 children with persistent clinical manifestation and leukocyturia four weeks after the end of treatment and the examination was repeated in 9 subjects six months after treatment due to recurrence of symptoms.

The results of the urethral swab examinations for *Chlamydia trachomatis* in relation to patient age are showed in Table 1. The highest rate of

Table 1. The frequency of *Chlamydia trachomatis* infection in the treated children in relation to age and sex

Tabela 1. Występowanie zakażenia *Chlamydia trachomatis* u leczonych dzieci w zależności od wieku I płci

Sex (Płeć)	Age – years (Wiek – lata)				Total (Razem)
	1/12–4	4–9	9–14	14–18	
Girls (Dziewczynki)	12	17	15	8	52 (55%)
Boys (Chłopcy)	21	11	6	5	43 (45%)
Total (Razem)	33 (34.7%)	28 (29.5%)	21 (22.1%)	13 (13.7%)	

Table 2. Type of urinary tract disease in children with *Chlamydia trachomatis* infection

Tabela 2. Choroba układu moczowego u dzieci zakażonych *Chlamydia trachomatis*

Diagnosis (Rozpoznanie)	Girls (Dziewczynki)	Boys (Chłopcy)	Total (Razem)
Recurrent urinary tract infections (Nawracające zakażenia układu moczowego)	27	15	42 (44.6%)
Disunction of lower urinary tract (Zaburzenia czynnościowe dolnych dróg moczowych)	16	2	18 (19%)
Urinary tract abnormalities (Wady dróg moczowych)	15	12	27 (28.4%)
Nephrolithiasis (Kamica moczowa)	3	2	5 (5%)
Nocturnal enuresis (Mimowolne moczenie nocne)	1	2	3 (3%)

Chlamydia trachomatis infection was 35% in the investigated subjects 4 weeks to 4 years old. In the group of older children there was a predominance of girls. In more than half of the patients (53, 55.8%), pathological changes in the urinary tract were found (Table 2). The most frequently observed diagnoses were vesicoureteral reflux in 14 children (52%), and ureteropelvic junction obstruction and juxtavesical ureter obstruction in 7 children (26%). Eleven patients (20%) underwent surgical treatment because of vesicoureteral reflux in 7 cases, hydronephrosis in 3, and duplication of the kidneys and ureters in 1 case. Dysfunctions of the urinary tract were documented in 18 children (18.3%), with a predominance of girls. The disorder found most frequently was bladder instability. However, in two cases dysfunctional voiding was diagnosed. The largest group were patients with persistent symptomatic urinary tract infection (42, 44.2%) and negative urine culture, whereas no structural and functional disorders were observed.

Table 4. The results of treatment

Tabela 4. Wyniki leczenia

		Total (Razem)
Children without clinical symptoms and without urine changes (Dzieci bez objawów klinicznych i bez zmian w moczu)	56 (59%)	80 (84.2%)
Children with persistent clinical symptoms and changes in urine (Dzieci z utrzymującymi się objawami klinicznymi i zmianami w moczu)	39 (41%)	
with *C. trachomatis* negative urethral swab	24 (25.2%)	
with *C. trachomatis* positive urethral swab	15 (15.8%)	

The children were treated according to a standard schedule, obtaining regression of clinical symptoms and changes in urine in 56 (59%) of UTI

Table 3. Types of disorders in the treated children

Tabela 3. Zaburzenia u leczonych dzieci

Type of disorder (Zaburzenie)		Girls (Dziewczynki)	Boys (Chłopcy)	Total (Razem)	%
Hydronephrosis (Wodonercze)	Ureteropelvic junction (Zwężenie podmiedniczkowe)	1	5	6	26
	Juxtavesical ureter (Zwężenie ujścia pęcherzowego moczowodu)	–	1	1	
Duplication of the kidneys and ureters (Zdwojenie nerek i moczowodów)		4	–	4	15
Renal agenesis (Agenezja nerek)		–	1	1	3.5
Polycystic kidney disease (Zwyrodnienie wielotorbielowate nerek)		1	–	1	3.5
Vesicoureteral reflux (Odpływ pęcherzowo-moczowodowy)		9	5	14	52
Total (Razem)		15	12	27	100

cases (Tables 3 and 4). In these children, control urethral swabs were not taken [14]. In 39 children with persistent dysuria and/or urine changes (19 cases), the control urethral swab was performed one month after the end of treatment. It was positive in 15 children (15.8%) (Table 5). Positive results after treatment were observed mainly in girls with urinary tract dysfunction and reflux. These children were retreated. Recurrence of dysuria, leukocyturia, and positive urethral swab were observed in 9 children six months after the end of treatment. These were mainly patients with functional urinary tract disorders, and three of them without pathological changes in the urinary tract.

Table 5. Children in whom eradication of *Chlamydia trachomatis* was not obtained

Tabela 5. Dzieci, u których nie uzyskano eradykacji *Chlamydia trachomatis*

Investigation (Badanie)	After one month (Po miesiącu)	After six months (Po 6 miesiącach)
Dysfunction of the lower urinary tract (Zaburzenia czynnościowe dolnych dróg moczowych)	8	6
Urinary tract abnormalities (Wady układu moczowego)	4	–
Recurrent infections (Nawracające zakażenia)	2	3
Nephrolithiasis (Kamica moczowa)	1	–
Nocturnal enuresis (Moczenie mimowolne w nocy)	–	–
Total (Razem)	15 (15.8%)	9 (9.5%)

Discussion

The treatment of *Chlamydia trachomatis* infections remains a difficult medical problem. Infections caused by this pathogen very often go unrecognized and are consequently not cured, most commonly due to the asymptomatic course of the infection. The onset of genitourinary organ infections is rarely noticeable. About 85–90% of infected adults usually present no characteristic symptoms [15]. In the rest of the patients the infection has a mild chronic course. Chemotherapeutics routinely used in these infections do not completely eradicate the pathogen.

The unique growth cycle of *Chlamydia trachomatis* is limited to only live eukaryotic cells, which leads to replication in two morphologically distinct forms, the elementary body and the reticulate body replicating only inside infected cells, which undoubtedly creates an additional difficulty in establishing the proper dose of medication and the appropriate duration of the therapy. The infectious elementary body possesses a specific cell membrane which allows it to survive for some time outside host cells, for example in submucosal tissue, without the necessity to pass immediately into the next stage of the growth cycle. This ability probably leads to latent chronic infection. Under favorable circumstances, chlamydial infection acquired in the perinatal period can already develop in the first weeks after birth. However, symptomatic infection sometimes occurs much later, even after 8 to 10 years. The exact incubation period of *Chlamydia trachomatis* is not known [12].

In presented study, the largest group involved 86% of the children, from newborns to 14 years of age. This fact may support the observations presented above. Most of them underwent mild conjunctivitis or pneumonia in the neonatal period and their mothers suffered from genital infections. After their children were diagnosed, some parents underwent examination and their cervical or urethral swabs were usually positive for *Chlamydia trachomatis*. In the group of adolescents, with a predominance of girls (72%), the infection was probably the result of "familial infection", in which a triad of clinical symptoms is characteristic: cervicitis in the mother, urethritis in the father, and conjunctivitis in the children [14]. Taking into consideration the affinity of *Chlamydia trachomatis* oculogenital serotypes to the mucous membranes of the conjunctivae and respiratory and genitourinary tracts, it can be estimated that poor sanitation and personal hygiene may lead to infection. Some authors exclude this route of transmission [3, 4].

In the therapy of chlamydial infection in children, macrolides are the drugs of choice, mainly erythromycin and its newer generations, i.e. roxithromycin, clatithromycin, and azithromycin. Only a few chlamydial serotypes that synthesize folic acid are sensitive to sulfonamides. Unfortunately, the determination of bacteria serotypes and detection of antibiotic sensitivity are examinations not commonly performed in the routine diagnostics of chlamydial infection. The recommended duration of therapy in adults with a derivative of erythromycin is 10 to 14 days, and in case of complications even 21 days [11]. Domeiko and Mardh claim that all cases of chlamydial infection in women should be considered complicated [16]. In cases of using doxycycline in therapy, the same duration of therapy is obligatory. In therapy with azithromycin, one dose

per day is sufficient in adults, while there are no data in the literature about application of this antibiotic in children with chlamydial infection. The authors did not observe any complications in the genital tract in the treated children. However, the inflammatory process in UTI was long lasting, with many recurrences, and often accompanied by defects or functional disorders, which is why the therapy was longer than recommended for uncomplicated cases.

Positive treatment results were obtained in 80 children (84.2%). The authors observed the best results in the group of children with chlamydial infection without any pathological changes in the urinary tract. In this group, 14-day therapy with one antibiotic was found to be effective in most cases. Additional treatment with a second antibiotic proved necessary only in two girls.

In children and adolescents, a routine test that confirms complete recovery after disappearing of clinical symptoms is not recommended [14]. In doubtful cases the examination should be repeated no longer than three weeks after the termination of therapy. In 15 (15.7%) of the 95 treated patients it was not possible to eradicate *Chlamydia trachomatis* despite repeated therapy; moreover, persistence of dysuric symptoms, sterile leukocyturia, and positive swab DIF were noted. These were mainly the patients with both diagnosed defects and functional disorders of the lower urinary tract. Due to recurrent clinical symptoms and leukocyturia in 24 of 39 treated children one month after the end of therapy, the control test was performed and the urethral swab was negative. Symptoms observed in this group should be associated with organic or functional disorders in the urinary tract, but not with chlamydial infection.

In the treated patients the most common defects were those with difficulty of urine flow, such as ureteropesic junction obstruction and juxtavesical ureter obstruction, vesicoureteral reflux with functional disorders of lower urinary tract, and labial adhesions in girls. Urethrostenosis with spastic external sphincter was usually accompanied by unstable detrusor and post-miction urine retention. The normal urethral flow on uroflowmetric examination after sphincter relaxation by pharmacological treatment and cured chlamydiosis confirms the functional origin of the disorders in the urinary tract. These patients, especially boys, need longer medication because of acquired urethrostenosis. Holmes says that chlamydial urethritis in men leads to this kind of complication in 2% of cases, which is connected with developing cicatrical changes as a result of chronic infection [17].

In patients with anatomic defects and functional lower urinary tract disorders, good results of treatment were obtained when antibiotic therapy was supported by treatment of coexisting disturbances by correcting the defects surgically. This was observed in two children operated for vesicoureteral reflux. However, one should strive to cure chlamydial infection before the surgical procedure because persisting infection in the perioperative period hampers the satisfactory result of the operation. The organism has great difficulties in completely eliminating bacteria that release cytokines initiating the reconstructive process; moreover, progressive fibrosis may lead to the development of cicartrix and synachiae [18]. Beatty et al. consider it very important to undertake proper therapy in the early stages of the disease because of the lower antibiotic effectiveness observed in chronic infections resulting from disturbances in antibiotic transport ability through the inflammatorily changed cell membrane into the cell [19].

Recurrence of the disease seems to be the main therapeutic problem. Natural immunity after the disease is maintained for only about half a year [18]. Moreover, an infection which apparently seems to be controlled may return after a couple of months or years. The presence of antibodies does not prevent recurrences in a child nor re-infection by other chlamydial strains. In presented study, recurrence of the disease was noted in 7% of children within 6 months. Furthermore, the results are not generally different from those obtained by other authors in adult patients [20,21]. The generally accepted principal rule assumes that treatment of *Chlamydia trachomatis* infection is aimed at eliminating the disease and preventing recurrences and further spread of the infection. The problem whether complete eradication of the pathogen living inside the host cells is possible remains a subject of discussion [18]. This problem is essential particularly because *Chlamydiae* do not attack the tissues directly, but induce an immunological response. The basic aim of this response is to control the infection by maintaining the inflammation process as long as the bacteria are present in the organism. Unfortunately, after a long time this kind of immunological response leads to host cell destruction.

Based on the obtained results of treatment, the authors found that antibiotic therapy administered to children was very effective, especially when it was used early enough. Nevertheless it should be considered that antibiotics used in therapy do not reverse the pathological changes caused by the inflammatory process, for example urethrostenosis or functional urinary tract disorders. Due to the increasing number of infections with atypical flora and the many complications resulting from chron-

ic exposure to these pathogens, it seems that these etiological agents should always be taken into consideration in urinary tract infections with atypical course, also in children. New diagnostic methods based on detecting *Chlamydia* DNA in urine allow establishing a diagnosis without the necessity of performing an invasive examination such as the urethral swab, which is mostly important in the youngest group of patients. The high costs are the principal limitation in this method. Diagnostic tests and successful antibiotic therapy are the only ways to prevent the spread of the disease until new vaccines are developed.

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