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INITIAL EMPIRIC ANTIMICROBIAL TREATMENT OF *CHLAMYDIA PNEUMONIAE*: A STUDY OF 54 CASES IN THE REPUBLIC OF MACEDONIA

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A b s t r a k t: Analysis of the adequacy of the initial empiric antimicrobial treatment of patients with acute *Chlamydia pneumoniae* (CP) infection, admitted to the Infectious Diseases Clinic, Clinical Centre, Medical Faculty, Skopje, Republic of Macedonia, for community-acquired pneumonia.

Material and methods: A total number of 407 patients with community-acquired pneumonia (CAP) hospitalized at the Clinic between September 1997 and June 2002, with an average age of x=46.44 years, of whom 53.56% were male. Acute *Chlamydia pneumoniae* infection was proven serologically with MIF assay in 54 (13.27%) patients.

Results: Initial empiric treatment with antibiotics in patients with CP pneumonia was provided with antimicrobial agents with intracellular activity in 26 (48.15%) patients; with fluoroquinolones in 19 (35.19%); macrolides in 5 (9.26%) and tetracyclines in 2 (3.7%). The treatment was conducted as monotherapy in 6 patients (11.11%) and in 20 patients (37.04%) in combination with betalactams. For 28 (51.85%) patients who were treated only with betalactams, empiric treatment was re-evaluated and new therapy with fluoroquinolon was conducted in 16 (29.63%), with macrolides in 8 (14.81%) and with tetracyclines in 4 (7.41%) patients.

Conclusion: Adequate empiric treatment with antimicrobial agents with intracellular activity was performed in only 48.15% of the patients with acute CP infection.

Therefore, when designing the initial empiric treatment of patients hospitalized with pneumonia, attention should be paid to this atypical pathogen of CAP.

Key words: community acquired pneumonia, *Chlamydia pneumoniae*, atypical pneumonia, antimicrobial therapy

Background

Community acquired pneumonia (CAP) is a frequent cause of medical attention, hospital admission and antibiotic prescriptions. *Chlamydia pneumoniae* (CP) is a human pathogen, which is assumed to be responsible for 6–20% of cases of pneumonia and is among the first 4 aetiologies of CAP [1].

Chlamydia pneumoniae is an obligate intracellular parasite. Therefore, the antibiotics likely to be effective against *Chlamydia pneumoniae* are macrolides, tetracyclines and quinolones, agents able to provide intracellular antimicrobial activity [2, 3].

Macrolides show the greatest capacity for accumulation in cells, where they are contained in cytosol and lysosomes, which is in correlation with their intracellular antimicrobial activity [4, 5, 6].

Fluoroquinolones, which accumulate in cell cytoplasm, even though to a lesser extent than macrolides, show excellent antimicrobial activity [7, 8].

Doxycicline seems to be the most active of tetracyclines. The most active macrolides seem to be azythromicyne and clindamycine. Sparfloxacine and the newest derivates of the quinolones (grepafloxacin, trovafloxacin, moxifloxacin) show the best activity among fluoroquinolones. Some authors have reported high in vitro resistance on the part of *Chlamydia pneumoniae* to ciprofloxacin, with a selection of resistant mutants (on the DNA girasa and topoisomerasa IV), without cross-resistance between antimicrobial agents in the group [9, 10].

Clinical studies report that the clinical symptoms in acute *Chlamydia pneumoniae* infection may be present or recur after the usual antibiotic treatment. Therefore, 14–21 day antibiotic treatment is recommended for acute CP infection. If the symptoms persist, despite treatment with the recommended antibiotic, another treatment with a different antibiotic from the group which will be effective should be provided [11, 12].

As *Chlamydia pneumoniae* is a common cause of CAP we have analysed how adequate the initial empiric antimicrobial treatment was of patients with acute *Chlamydia pneumoniae* infection, hospitalized with community-acquired pneumonia, after their admission in hospital.

Material and methods

A total of 407 adult patients with CAP, hospitalized at the Infectious Diseases Clinic, Clinical Centre, Medical Faculty, Skopje, Republic of Macedonia, between September 1997 and June 2002, were analysed. The patients' age ranged between 18 to 75 years, with an average age of x=46.44 years. Of those, 218 (53.56%) were male and 189 (46.44%) female. Hospitalized patients with typical clinical findings such as fever, cough, sputum production, shortness of breath and crackles on auscultation were enrolled in the study. Pneumonia diagnosis was confirmed when a new pulmonary opacity was present on radiographs. At least 2 sera samples were collected from each patient; the first sample was taken on admission and the second sample was obtained 3 weeks later. Acute *Chlamydia pneumoniae* infection as a cause of CAP was proved serologically with MIF assay in 54 (13.27%) patients. The average age of the patients with acute *Chlamydia pneumoniae* infection was x = 47.67 years (σ = 18.26). Of those, 37 (68.52%) were male and 17 (31.48%) female.

The serological study was performed by means of the microimmunofluorescence method (MIF) utilizing C. pneumoniae, C. psitaci and C. trachomatis elementary bodies (Savyon Diagnostics Ltd., Israel) as antigens to detect specific IgM, IgG and IgA antibodies. Serological evidence of acute *Chlamydia pneumoniae* infection was based on the criteria published by Greyston *et al*. which considered for MIF assay a 4-fold increase in specific IgG/IgA antibody titre in paired sera or an IgM titre of >1:20 in any serum sample as presumptive evidence of acute infection with *Chlamydia pneumoniae* [13, 14].

Other microbiological investigations such as sputum culture, blood culture, culture of throat swab, serological IF assay for other atypical and viral respiratory pathogens, had been routinely done.

The initial decision to prescribe antibiotics and their choice depended on the clinical signs, epidemiological situation, comorbidity, results of chest radiography and biochemical investigations. This decision was reconsidered after the results of serological examinations were obtained. Our choice of the initial empiric antibiotic treatment was according to the "Guidelines for management of adult community-acquired lower respiratory tract infections" published by the European Study on Community-acquired Pneumonia (ESOCAP) study group. [15]

Results

In 18 (33.33%) of the patients with acute *Chlamydia pneumoniae* infection, no treatment with antibiotics was carried out at home before hospitalization. Twenty-five patients (46.30%) were treated with betalactams at home, and just 2 patients (3.70%) were treated with an antimicrobial agent with intracellular penetration and activity (macrolide, tetracycline or fluoroquinolone) prior to hospitalization. These results are presented in Table 1.

Table 1 – Табела 1

Antimicrobial treatment of patients with acute Chlamydia pneumoniae (CP) infection before hospitalisation (n = 54)

Антимикробен третман на пациентите со акутна Chlamydia pneumoniae (CP) инфекција пред хоспитализацијата (бр. = 54)

Antimicrobial treatment before hospitalisation	No. of patients (%)
Not treated	18 (33.33%)
Betalactams	25 (46.30%)
Macrolides, tetracyclines, fluoroquinolones	2 (3.70%)
Other antimicrobial agents	9 (16.67%)

The initial choice of the antimicrobial treatment of the patients with acute *Chlamydia pneumoniae* infection upon hospitalization because of CAP is presented in Table 2. Empiric antimicrobial treatment in patients with CP acute infection was provided with fluoroquinolones, macrolides or tetracyclines in 26 patients (48.15%), in 6 (11.11%) as monotherapy and in 20 (37.04%) in combination with betalactams. 19 patients (35.19%) were treated with fluoroquinolones, 5 (9.26%) with macrolides and 2 patients (3.7%) with tetracyclines. Initial empiric therapy was started with betalactams as monotherapy in 28 (51.85%) of the patients with acute *Chlamydia pneumoniae* infection.

Table 2 – Tabela 2

Initial empiric antimicrobial treatment in the hospitalized patients with acute CP infection (n = 54)

Иницијален антимикробен третман на хоспитализираните пациенти со акутна CP инфекција (бр. = 54)

Initial therapy	No. of patients	Monotherapy	With betalactams
fluoroquinolons	19 (35,19%)	4 (7,41%)	15 (27,78%)
macrolides	5 (9,26%)	2 (3,70%)	3 (5,56%)
tetracyclines	2 (3,7%)	0	2 (3,70%)
betalactams	28 (51,85%)		

Re-evaluation of the initial empiric selection of the antimicrobial therapy because of failure of the treatment in the group of patients with acute CP infection treated with antibiotics with intracellular penetration and activity, as monotherapy or with betalactams, was necessary only in one patient when fluoroquinolon was replaced with tetracycline. In the group treated initially with only betalactams, due to failure of the initial empiric therapy after re-evaluation

of the antimicrobial therapy, correction was made by changing the antibiotic: in 16 (29.63%) patients with fluoroquinolones, in 8 (14.81%) with macrolides and in 4 (7.41%) patients with tetracyclines. These results are presented in Table 3.

Table 3 – Tabela 3

Re-evaluation of the initial empiric antimicrobial treatment of hospitalized patients with acute Chlamydia pneumoniae lower respiratory infection (n = 54)

Ре-евалуација на иницијалниот емпириски антимикробен третман на хоспитализираните пациенти со акутна Chlamydia pneumoniae долнорespираторна инфекција (бр. = 54)

No of patients	Initial therapy	No of successes	No of failures	New therapy – No of patients
19 (35,19%)	fluoroquinolones	18 (33,33%)	1 (1,85%)	tetracyclines – 1 (1,85%)
5 (9,26%)	macrolides	5 (9,26%)	0	
2 (3,7%)	tetracyclines	2 (3,7%)	0	
28 (51,85%)	betalactams	0	28 (51,85%)	fluoroquinolon – 16(29,63%) macrolides – 8 (14,81%) tetracyclines – 4 (7,41%)

Discussion

Recently published guidelines for empiric antimicrobial therapy of community-acquired pneumonia (CAP) have suggested that the therapy should include antimicrobial agents effective against atypical pathogens. *Chlamydia pneumoniae* is an obligate intracellular parasite and should be treated with macrolides, fluoroquinolons or tetracyclines – antimicrobial agents with intracellular penetration and activity. The duration of the treatment is recommended to be at least 14 to 21 days [16, 17].

Reports on *in vitro* activity of antibiotics active against *Chlamydia pneumoniae* are very often discrepant. Those investigations are limited because of the difficulties of the isolation of CP and of providing the sensitivity test. The time of adding antibiotics to the culture is very important, because the minimal inhibitory concentration is eight times less if the application of the antibiotic to the culture is before the application of *Chlamydia pneumoniae* to the culture. It is emphasized that the tests in which the cells are infected with *Chlamydia pneumoniae* before the application of the antibiotic are more realistic due to similarity to the state *in vivo* [18].

Data on the effectiveness of antimicrobial treatment of *Chlamydia pneumoniae* respiratory infections in clinical studies are limited. It seems that

there is a good correlation between *in vitro* and *in vivo* results. In one randomized study of clarithromycin versus erythromicin, conducted among children aged 3 to12 years with pneumonia, it was proved that both agents showed clinical effectiveness higher than 90% in the therapy of infections caused by *Chlamydia pneumoniae*. In another randomized study on levofloxacin in the treatment of community-acquired pneumonia among adults, 98% clinical success was reported in the treatment of acute *Chlamydia pneumoniae* infections [19, 20, 21].

In the study carried out by F.Blasi (22), who analyzed the initial empiric selection of the antibiotic in adult patients hospitalized because of CAP, an antibiotic with intracellular penetration and activity was the first choice in 50% of the patients with acute CP infection. Re-evaluation and change of therapy in patients with CP infection who were initially treated with betalactams in F Blasi's study was made with macrolide in 28.57% and with quinolon in 21.43% [22].

In the study carried out by M. Kauppinen, antimicrobial therapy with antibiotics with intracellular penetration and activity was provided in 36% of the patients with acute *C. pneumoniae* infection initially as an empiric selection when they were hospitalized because of CAP [23].

In our study, patients with acute *Chlamydia pneumoniae* lower respiratory infection were treated with antibiotic with intracellular penetration and activity in only 3.7% of the cases, with betalactams in 46.30% and with various antibiotics in 33.33 % before hospitalization.

Empiric antimicrobial treatment upon hospitalization of patients with acute CP infection in our study was done with fluoroquinolones, macrolides or tetracyclines in 48.15% of them, in 11.11% as monotherapy and in 37.04% in combination with betalactams. Fluoroquinolones were used for the initial treatment of 35.19% of the patients, 9.26% were treated with macrolides and 3.7% patients with tetracyclines. Our results are in correlation with those in the clinical study by F. Blasi, who reported that empiric treatment with antimicrobial agents with intracellular penetration and activity was done in 50% of the patients with acute CP infection. Our results are also in agreement with those in the study by M. Kauppinen, who reported that adequate empiric treatment was provided in 36% of the patients with acute CP lower respiratory infection [22, 24].

In our study, of 28 patients (51.85%) who were treated only with betalactams, the empiric treatment was re-evaluated. Betalactams were replaced by fluoroquinolones in 29.63%, by macrolides in 14.81% and by tetracyclines in 7.41% patients. In the group of patients with acute CP infection treated with antibiotics with intracellular penetration and activity, as monotherapy or with betalactams, it was necessary to alter the initial therapy only in one patient, when fluoroquinolon (ciprofloxacin) was replaced by tetracycline. Some authors have reported a high *in vitro* resistance on the part of *Chlamydia pneumo-*

niae to ciprofloxacin, with a selection of resistant mutants (on the DNA girasa and topoisomerasa IV), without cross-resistance between the antimicrobial agents in the group. Thus, new derivates of the quinolones such as grepafloxacin, trovafloxacin and moxifloxacin can be used for the treatment of those patients [9, 10]. In the study by F Blasi re-evaluation and replacement with an antibiotic with intracellular penetration and activity in the patients with CP infection who were treated with betalactams was with macrolide in 28.57% and with quinolon in 21.43%, while in the patients treated initially with antibiotics with intracellular activity, correction was made in one patient because of the failure of the treatment, when macrolide was replaced with tetracycline [22].

Conclusion

The analysis of the initial empiric therapy in our study showed that adequate initial empiric treatment with antimicrobial agents with intracellular penetration and activity was provided in only 47.6% of the patients with acute *Chlamydia pneumoniae* infection among the hospitalized patients with community-acquired pneumonia when they were hospitalized. Thus, we can conclude that when designing the initial empiric treatment of patients hospitalized with pneumonia, attention should be paid to this atypical pathogen of CAP.

REFERENCES

1. Sopena N., Pedro-Botet M. L., Sabria-Leal M., Garcia-Pares D., Reynaga E., Garcia-Nunez M. (2004): Comparative study of community-acquired pneumonia caused by Streptococcus pneumoniae, Legionella pneumophila or *Chlamydia pneumoniae*, *Scand J Infect Dis;* 36: 330–334.

2. Goldstein F., Bryskier A., Appelbaum C. P., Bauernfeind A., Jacobs M., Schito C. G., Wise R. (1998): The etiology of respiratory tract infections and the antibacterial activity of fluoroquinolones and other oral antibacterial agents against respiratory pathogens, *Clin. Mic. and. Infect*; Vol. 4, Suppl., 2, 8–18, Apr.

3. Kuzman I. (2000): Lecenje atipicnih pneumonija, *Infektoloski glasnik*; 20: 4, 141–147,

4. Mayaud C. (1997): Asthma and *Chlamydia pneumoniae*. A future prospect for macrolides in general and roxithromycin in particular?; *Press med*, 26 Suppl; 2: 27–9 Mar.

5. Plouffe J., Schwartz D. B., Kolokathis A. *et al*. (2000): Clinical efficacy of intravenous followed by oral azithromycin monotherapy in hospitalized patients with community-acquired pneumonia. *Antimicrob Agents Chemother*; 44: 1796–1802.

6. Vergis E. N., Indorf A. *et al*. (2000): Azithromycin vs cefuroxime plus erythromycin for empirical treatment of community-acquired pneumonia in hospitalized patients. A prospective, randomized, multicenter trial. *Arch Int Med*; 160: 1294–1300.

7. Appelbaum P. C., Gillespie S. H., Burley C. J., Tillotson G. S. (2004): Antimicrobial selection for community-acquired lower respiratory tract infections in the 21st century: a review of gemifloxacin; *International J of Antimicrobial Agents*; 23: 533–546.

8. Burgmann H., Mayer B., Lukas A., Kumbein F., Oberbauer R. (2003): The influence of comorbidity on the effect of levofloxacin treatment success of ambulatory respiratory tract infections. *Wien Med Wochenschr*; 153(7–8): 156–62.

9. Chodosh S. (1998): Clinical efficacy and tolerability of grepafloxacin in lower respiratory tract infection, *Clin. Mic. and Infect*., Vol. 4, Suppl. 1, 25–31, Mar.

10. Dessus-Babus S., Bebear C. M., Charron A. (1998): Sequencing of gyrase and topoisomerase IV quinolone-resistence-determining regions of Chlamydia and characterisation of quinolone-resistant mutants obtained *in vitro*, *Antimicrob Agents Chemiother*; Vol. 42, No 10, 2474–2481.

11. Guthrie R. (2001): Community-acquired lower respiratory tract infections, etiology and treatment, *Chest*; Vol. 120, No 6, Dec.

12. Rubinstein E., Carbon C. (1998): Lower respiratory tract infections: etiology, current treatment and experience with fluoroquinolones; *Clin. Mic. and Infect*; Vol. 4, Suppl. 2, 42–50.

13. Paldanius M., Bloigu A., Leinonen M., Saikku P. (2003): Measurement of *Chlamydia pneumoniae*-specific immunoglobulin A(IgA) antibodies by the microimmuno-fluorescence (MIF) method: comparison of seven fluorescein-labeled anti-human IgA conjugates in an in-house MIF test using one commercial MIF and one enzyme immunoassay kit. *Clin Diagn Lab Immunol*. Jan; 10 (1): 8–12.

14. Grayston J. T., Campbell L. A., Kuo C. C., Mordhorst C. H., Saikku P., Thom D. H. (1990): A new respiratory tract pathogen: *Chlamydia pneumoniae* strain TWAR. *J Infect Dis*; 161: 618–25.

15. European Study on Community-acquired Pneumonia (ESOCAP) study group. Guidelines for management of adult community-acquired lower respiratory tract infections; 11: 986–991; 1998.

16. Bartlett J. G., Dowell S. F., Mandell L. A. *et al*. (2000): Practice guidelines for the management of community-acquired pneumonia in adults. Infectious Diseases Society of America. *Clin Infect Dis*; 31: 347–382.

17. American Thoracic Society. Guidelines for the management of adults with community-acquired pneumonia: diagnosis, assessment of severity, antimicrobial therapy, and prevention. *Am J Respir Crit Care Med*; 163: 1730–1754, 2001.

18. Hjelm E., Hulten K., Nystrom-Rosander C. (1997): Assay of antibiotic susceptibility of *Chlamydia pneumoniae*, *Scand J Infect Dis;* Suppl. 104: 13–4.

19. Black P. N., Blasi F., Jenkins C., Allegra L. (2001): Trial of roxithromycin in subjects with asthma and serological evidence of infection with *Chlamydia pneumoniae*, Am J Respir Crit Care Med, Vol. 164, 536–541.

20. Bochud P. Y., Moser F., Erard P. (2001): Community-acquired pneumonia, a prospective outpatients study, *Medicine*; Vol. 80, No 2, March.

21. Hammerschlag M., Robin P. (2000): Microbiological efficacy of levofloxacin for treatment of CAP due to *Chlamydia pneumoniae*, *Antimicrob Agents Chemiother*; Vol. 44, No 5, 1409–1409.

22. Blasi F., Cosentini R., Legmani D., Denti F., Alegra L. (1993): Incidence of community acquired pneumonia caused by *Chlamydia pneumoniae* in Italian patients, Eur. J. Clin. Microbiol. *Infect. Dis*; Vol. 12. No 9, 696–699.

23. Kauppinen M., Saikku P., Kujala P. (1996): Clinical picture of community-acquired, *Chlamydia pneumoniae* requiring hospital treatment: comparison between chlamydial and pneumococcal pneumonia, *Thorax*; 51, 185–189.

24. Kauppinen M., Saikku P. (1995): Pneumonia due to *Chlamydia pneumoniae*: Prevalence, Clinical Features, Diagnosis, and Treatment; *Clin. Infect. Dis*; 21, Suppl. 3, 244–52.

Резиме

ИНИЦИЈАЛЕН ЕМПИРИСКИ АНТИМИКРОБЕН ТРЕТМАН НА *CHLAMYDIA PNEUMONIAE*: СТУДИЈА НА 54 СЛУЧАИ ВО РЕПУБЛИКА МАКЕДОНИЈА

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Цел: Да се анализира кај колку пациенти со акутна *Chlamydia pneumoniae* (CP) инфекција е започнато со адекватен иницијален емпириски антимикробен третман при приемот на Клиниката за инфективни болести и фебрилни состојби, поради пневмонија добиена во заедница (ПДЗ).

Материјал и методи: Анализирани се 407 пациенти со ПДЗ хоспитализирани на Клиниката помеѓу септември 1997 и јуни 2002 год., со средна возраст x = 46,44 год., од кои 53,56% се машки. Акутна *Chlamydia pneumoniae* инфекција беше докажана серолошки со MIF есеј кај 54 (13,27%) пациенти.

Резултати: Иницијален емпириски третман со антибиотици со интраклеточен продор и активност кај пациентите со CP пневмонија беше спроведен кај 26 (48,15%) пациенти; со флуорокинолони кај 19 (35,19%), макролиди кај 5

(9,26%) и тетрациклини кај 2 (3,7%). Со монотерапија беа третирани 6 пациенти (11,11%), а 20 (37,04%) во комбинација со беталацтами. Кај 28 (51,85%) пациенти кои беа третирани само со беталацтами, емпириската терапија беше реевалуирана и корегирана со флуорокинолон кај 16 (29,63%), со макролид кај 8 (14,81%) и со тетрациклин кај 4 (7,41%) пациенти.

Заклучок: Адекватна емпириска терапија со антимикробно средство со интраклеточен продор и активност беше започната само кај 48,15% од пациентите со акутна СР инфекција. Затоа, кога треба да се донесе решение за започнување со иницијален емпириски антимикробен третман кај пациентите хоспитализирани поради пневмонија, треба да се обрне внимание на можноста од овој атипичен причинител како причина за истата.

Клучни зборови: Пневмонија добиена во заедница, *Chlamydia pneumoniae,* атипична пневмонија, антимикробна терапија

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