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

Irena Kondova Topuzovska¹, Dimitar Dimitriev¹, Goran Kondov², Ankica Anastasovska¹, Nikola Panovski³

¹ Infectious Diseases Clinic, Clinical Centre, Medical Faculty, Skopje, R. Macedonia
² Thoracocardiovascular Surgery Clinic, Clinical Centre, Medical Faculty, Skopje, R. Macedonia
³ Institute of Microbiology, Medical Faculty, Skopje, R. Macedonia

Abstrakt: 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].

Doxycycline seems to be the most active of tetracyclines. The most active macrolides seem to be azithromycine and clindamycine. Sparfloxacine and the newest derivates of the quinolones (grepafloxacain, trovafloxacain, moxifloxacain) show the best activity among fluoroquinolones. Some authors have reported high in vitro resistance on the part of *Chlamydia pneumoniae* to ciprofloxacain, 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 $\bar{x}=46.44$ 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 $\bar{x} = 47.67$ years ($\sigma = 18.26$). Of those, 37 (68.52%) were male and 17 (31.48%) female.

The serological study was performed by means of the microimmuno-fluorescence 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 – Таблица 1

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

<table>
<thead>
<tr>
<th>Antimicrobial treatment before hospitalisation</th>
<th>No. of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not treated</td>
<td>18 (33.33%)</td>
</tr>
<tr>
<td>Betalactams</td>
<td>25 (46.30%)</td>
</tr>
<tr>
<td>Macrolides, tetracyclines, fluoroquinolones</td>
<td>2 (3.70%)</td>
</tr>
<tr>
<td>Other antimicrobial agents</td>
<td>9 (16.67%)</td>
</tr>
</tbody>
</table>

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 – Таблица 2

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

<table>
<thead>
<tr>
<th>Initial therapy</th>
<th>No. of patients</th>
<th>Monotherapy</th>
<th>With betalactams</th>
</tr>
</thead>
<tbody>
<tr>
<td>fluoroquinolones</td>
<td>19 (35.19%)</td>
<td>4 (7.41%)</td>
<td>15 (27.78%)</td>
</tr>
<tr>
<td>macrolides</td>
<td>5 (9.26%)</td>
<td>2 (3.70%)</td>
<td>3 (5.56%)</td>
</tr>
<tr>
<td>tetracyclines</td>
<td>2 (3.7%)</td>
<td>0</td>
<td>2 (3.70%)</td>
</tr>
<tr>
<td>betalactams</td>
<td>28 (51.85%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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 fluoroquinolone 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)

Re-evaluacija na inicijalniot empiriski antimikroben tretman na hospitaliziranite pacienti so akutna Chlamydia pneumoniae dolnorespiрарно инфекција (бр. = 54)

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

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 erythromycin, conducted among children aged 3 to 12 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


**Rezime**

ИНИЦИЈАЛЕН ЕМИПИРИСКИ АНТИМИКРОБЕН ТРЕТМАН НА CHLAMYDIA PNEUMONIAE: СТУДИЈА НА 54 СЛУЧАЈИ Во РЕПУБЛИКА Македонија

Ирена Кондова Топузовска1, Димитар Димитриев1, Горан Кондов2, Анкица Анастасовска1, Никола Пановски3

1Клиника за инфекциозни болести и фебрилни синостохи, Клинички центар, Медицински факултет, Скопје, Р. Македонија
2Клиника за торакокардиоваскуларна хирургија, Клинички центар, Медицински факултет, Скопје, Р. Македонија
3Институт за микробиологија, Медицински факултет, Скопје, Р. Македонија

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

Материал и методи: Анализирано се 407 пациенти со ПДЗ госпитализирани на Клиниката помеѓу септември 1997 и јуни 2002 год., со средна возраст $x = 46.44$ год., од кои 53.56% се мажки. Акутна *Chlamydia pneumoniae* инфекција беше доказана со серолошки и миф есеj кај 54 (13,27%) пациенти.

Резултати: Иницијален емпиришки третман со антибиотици со интратекочен проодор и активност кај пациентите со СР пневмонија беше спроведен кај 26 (48,15%) пациенти; со флурококолони кај 19 (35,19%) пациенти; со флурококолони кај 5
(9,26%) и тетрациклин каж 2 (3,7%). Со монотерапија беа третирани 6 пациенти (11,11%), а 20 (37,04%) во комбинација со беталактами. Каж 28 (51,85%) пациенти кои беа третирани само со беталактами, емпиришки терапија беше реевалуира и корегирана со флуорокинолон кај 16 (29,63%), со макролид кај 8 (14,81%) и со тетрациклин кај 4 (7,41%) пациенти.

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

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

Corresponding Author:
Kondova Topuzovska Irena,
MD, Infectious Diseases Clinic,
Clinical Centre, Medical Faculty,
Vodnjanska 17, 1000 Skopje,
Republic of Macedonia,
Tel.: 00389 2 3130 081,
00389 70 365 321,
E-mail: irenakon2001@yahoo.com