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Original article

Etiology and efficacy of anti-microbial treatment for community-acquired pneumonia in adults requiring hospital admission in Ukraine

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Abstract. *Background and aim:* Empiric therapy of community-acquired pneumonia (CAP) remains the standard care and guidelines are mostly based on published data from the United States or Europe. In this study, we determined the bacterial etiology of CAP and evaluated the clinical outcomes under antimicrobial treatment of CAP in Ukraine. *Methods:* A total of 98 adult subjects with CAP and PORT risk II-IV were recruited for the study. The sputum diagnostic samples were obtained from all patients for causative pathogen identification. Subjects were randomly assigned in a 1:1 ratio to receive delafloxacin 300 mg (n=51) or moxifloxacin 400 mg (n=47) with a blinding placebo. The switch to oral treatment was after a minimum of 6 IV doses according to clinical criteria. The total duration of antibacterial treatment was 5-10 days. *In vitro* susceptibility of pathogens to delafloxacin and other comparator antibiotics was determined. *Results:* The most frequently isolated pathogens in adults with CAP were *S. pneumoniae* – 19.5%, *M. pneumoniae* – 15.3%, *H. influenzae* – 13.2%, *S. aureus* – 10.5%, *K. pneumoniae* – 10.1%, and *H. parainfluenzae* – 6.4%. All isolates of *S. pneumoniae*, *S. aureus*, *M. pneumoniae* had sufficient susceptibility to appropriate antibiotics. 9.0% of *H. influenzae* strains were susceptible to azithromycin. 94.8 % of patients had a successful clinical response to delafloxacin at the end of treatment and 93.9 % – at test-of-cure. *Conclusions*: In Ukraine, the major bacterial agents that induced CAP in adults were *S. pneumoniae*, *M. pneumoniae*, *H. influenzae*, *S. aureus*, *K. pneumoniae*, *H. parainfluenzae*, *E. cloacae, L. pneumophila*. Delafloxacin is a promising effective antibiotic for monotherapy of CAP in adults and could be used in cases of antimicrobial-resistant strains. (www.actabiomedica.it)

Key words: antibiotics, community-acquired pneumonia, delafloxacin, empiric antimicrobial therapy, moxifloxacin

Community-acquired pneumonia (CAP) is one of the most common reasons for hospitalization with increased mortality (1, 2). The incidence of CAP in Europe varies by country, age, and gender. The incidence increased sharply with age and was appreciably higher in men than in women. In Europe, pneumonia costs ~ €10.1 billion annually, with € 0.5 billion for inpatient care and € 0.2 billion for medications (3). The etiology of CAP is well-known, and the most commonly identified pathogens include *Streptococcus pneumoniae, Mycoplasma pneumoniae*, and *Chlamydophila pneumoniae* (4). Most studies have been conducted in developed countries and the distribution of these pathogens varies from one country to another (5). The highest variations were observed for developing countries. For example, in Malaysia, common causative bacterial agents of CAP were *S. pneumoniae* (19.05%), *K. pneumoniae* (13.33%), *H. influenzae* (8.57%), and *P. aeruginosa* (5.71%) (6). The treatment guidelines should take into consideration the data from low- and middle-income countries because bacterial cultures are not routinely performed (7, 8).

DEFINE-CABP was a phase 3 study to assess the efficacy and safety of a novel fluoroquinolone, delafloxacin, versus moxifloxacin. The overall results of this study have been reported previously (9). The aim of this analysis was to determine the bacterial etiologies of CAP and to compare the efficacy of IV/oral delafloxacin with that of IV/oral moxifloxacin in adults with CAP in Ukraine.

Materials and Methods

Study Design and Study Sites

DEFINE-CABP [ML-3341-306 (Compare Delafloxacin to Moxifloxacin for the Treatment of Adults with Community-acquired Bacterial Pneumonia)] was a phase 3, randomized, double-blind, comparator-controlled, multicenter, global study comparing the efficacy and safety of IV/oral delafloxacin with that of IV/oral moxifloxacin in adults with CAP (10).

In Ukraine, 9 centers screened subjects. A total of 98 subjects were recruited for the study. All study sites received approvals from their independent ethics committee. The study was conducted according to the principles of the International Conference of Harmonization (ICH) E6 (R2), World Medical Association Declaration of Helsinki, Good Clinical Practice Guidelines, and Ukrainian laws and regulations, and was approved by the local Ethics Committee. All subjects provided written informed consent.

Randomization and Treatment

Subjects were randomly assigned in a 1:1 ratio to receive delafloxacin 300 mg (n=51) as a 1-hour infusion every 12 (±2) hours or moxifloxacin 400 mg (n=47) as a 1-hour infusion every 24 (±2) hours with a blinding placebo. The switch to oral treatment was after a minimum of 6 IV doses according to clinical criteria. The total duration of antibacterial treatment was 5-10 days depending on the clinical indicators.

Randomization was stratified by Pneumonia Patient Outcomes Research Team (PORT) risk class, medical history of chronic obstructive pulmonary disease (COPD) and asthma, and prior single-dose/regimen of systemic antimicrobial use. If MRSA was confirmed, subjects were switched from moxifloxacin to linezolid (600 mg IV every 12 h) in a blinded manner.

Study Population

Subjects ≥ 18 years of age with clinical and radiographic evidence consistent with CAP and PORT risk II-V comprised the trial population. Generally, enrollment included no more than 25% of subjects who were PORT Risk Class II. No more than 25% of subjects received 1 dose of a single, potentially effective, short-acting antimicrobial for treatment of CAP within 24 hours of enrollment. The complete inclusion / exclusion criteria are detailed in the publication (9).

Study Visits

Key visits included early clinical response (ECR), 96 (±24) hours after the initiation of the first dose of the study drug; end of treatment (EOT), last dose +1 calendar day; and test-of-cure (TOC), 5 to 10 days after the last dose. A follow-up (FU) visit or phone contact was conducted on day 28 (±2) days.

Efficacy Assessments and Endpoints

Efficacy was evaluated through the assessment of clinical signs and symptoms of pneumonia, pathogen

identification, and susceptibility testing of bacterial isolates.

The primary endpoint of ECR was defined as improvement (clinical success) in at least 2 of the following symptoms: chest pain, frequency or severity of cough, amount or quality of sputum, dyspnea, and without the aggravation of the other symptoms. In addition, subjects were required at ECR to show improvement and no aggravation in all vital sign assessments.

The investigators defined the clinical outcome based on the assessment of a subject's signs and symptoms of infection at EOT and TOC: success, failure, or indeterminate/missing.

Microbiological Response

Causative pathogens were identified by isolation from a baseline culture specimen (respiratory specimen and / or blood), by urinary antigen, serology, and / or quantitative polymerase chain reaction analysis. *In vitro* susceptibility of pathogens to delafloxacin and other comparator antibiotics was determined at the central microbiology laboratory according to Clinical and Laboratory Standards Institute and European Committee on Antimicrobial Susceptibility Testing guidelines for broth microdilution and disk diffusion (10, 11). The percent of susceptible isolates was determined using EUCAST 2020 breakpoints.

Multidrug resistance (MDR) was defined as resistance to 3 or more antibiotic classes (12).

Results

This study enrolled 98 adult Ukrainian subjects, hospitalized with CAP (Table 1).

Demographics were similar between the two treatment groups. Before the initiation of antimicrobial therapy, the sputum samples were obtained from all patients. One microorganism was isolated from 52% of patients, two – from 32%, three – 9%, and four – from 5 % (Fig. 1).

The most frequently isolated pathogens in adults with CAP were: *S. pneumoniae* – 19.1%, *M. pneumoniae* – 15.3%, *H. influenzae* – 13.3%, *S. aureus* – 10.5%,

Table 1. Demographics of the study population

Characteristics	Total (n=98)
Age, y	
Mean (SD)	58.19 (18.84)
Median, y	60.00
Min, max	18.86
Age category, n (%)	
<65, y	56 (57.1%)
≥65, y	25 (25.6%)
≥75, y	17(17.3%)
Sex, n (%)	
Male	68 (69%)
Female	30 (31%)
Region, n (%)	
Kyiv	19 (19.4%)
Vinnytsia	8 (8.2%)
Zhytomyr	5 (5.1%)
Dnipro	5 (5.1%)
Zaporizhzhia	39 (39.8%)
Poltava	11 (11.2%)
Kharkiv	11 (11.2%)

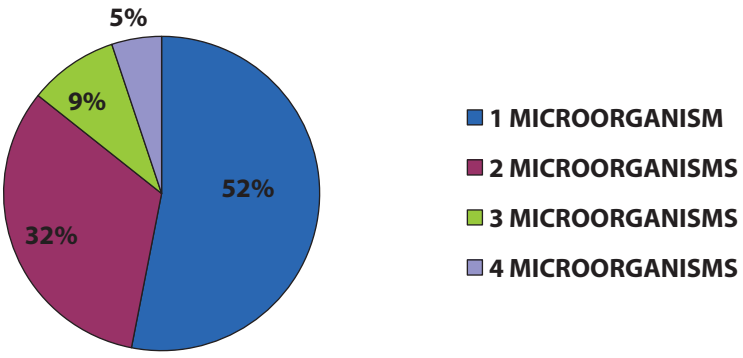

Figure 1. Mono vs polymicrobial infections in adults with community-acquired pneumonia.

K. pneumoniae – 10.1%, and *H. parainfluenzae* – 6.4% (Table 2).

At the next stage of our study, we investigated the anti-microbial susceptibilities of bacterial isolates in adults with CAP (Table 3). All isolates of *S. pneumoniae* were susceptible to levofloxacin, moxifloxacin, vancomycin, linezolid, 91.4% – to penicillin, 95.6% – to ceftriaxone, 78.3% – to clindamycin (21.7% – resistant), 70% – to azithromycin (26% – resistant).

All *S. aureus* isolates were susceptible to amoxicillin clavulanate, oxacillin, vancomycin, clindamycin, linezolid, trimethoprim/sulfamethoxazole, and 93.8% of isolates – to levofloxacin and moxifloxacin. *H. influenzae* was susceptible to amoxicillin clavulanate, ceftriaxone, meropenem, levofloxacin, moxifloxacin, clindamycin, and 9.0% – to azithromycin (82% – intermediate and 9.0% – resistant). *K. pneumoniae* had susceptibility to amikacin and meropenem 100%, 87.5% – to piperacillin/tazobactam, 81.3% – to ceftazidime, ceftriaxone, aztreonam, ciprofloxacin (18.7% – resistant), and this microorganism was resistant to moxifloxacin and levofloxacin.

Table 2. Prevalence of baseline pathogens isolated from adults with community-acquired pneumonia

Baseline Pathogens	Number, n	Prevalence, n/N, %
TOTAL isolates identified for any pathogen, n	189	100.0
Streptococcus pneumoniae	36	19.1
Mycoplasma pneumoniae	29	15.3
Haemophilus influenzae	25	13.2
Staphylococcus aureus	20	10.5
Klebsiella pneumoniae	19	10.1
Haemophilus parainfluenzae	12	6.4
Enterobacter cloacae complex	9	4.8
Legionella pneumophila	8	4.2
Moraxella catarrhalis	7	3.7
Chlamydia pneumoniae	7	3.7
Pseudomonas aeruginosa	6	3.2
Serratia marcescens	3	1.6
Escherichia coli	3	1.6
Bordetella avium	2	1.1
Citrobacter koseri	1	0.5
Klebsiella oxytoca	1	0.5
Proteus mirabilis	1	0.5

H. parainfluenzae was susceptible to amoxicillin clavulanate, ceftriaxone, meropenem (100%), levofloxacin 80.0% (20% – resistant), moxifloxacin 90.0% (10% – resistant), tetracycline 90%, and had intermediate susceptibility to azithromycin 100.0%. *E. cloacae* complex was susceptible to meropenem 100%, amikacin 87.5% (12.5% – intermediate), aztreonam, ceftriaxone 62.5% (37.55% – resistant), piperacillin/tazobactam 62.5% (12.5% – intermediate), ciprofloxacin 75% (25% – resistant), and was resistant to moxifloxacin and levofloxacin. *P. aeruginosae* was susceptible in 80% to piperacillin/tazobactam, ceftazidime, meropenem, ciprofloxacin, amikacin (20.0% – resistant), 40% – to aztreonam (40% – intermediate, 20.0% – resistant), and resistant to moxifloxacin and levofloxacin. *E. coli, C. koseri, P. mirabilis* and *K. oxytoca* were susceptible to piperacillin/tazobactam, ceftazidime, ceftriaxone, meropenem, aztreonam, ciprofloxacin, amikacin. *M. pneumoniae* had susceptibility to piperacillin/tazobactam, ceftazidime ceftriaxone, meropenem, aztreonam, ciprofloxacin, levofloxacin, moxifloxacin, amikacin, azithromycin, erythromycin, and tetracycline 100%. *M. catarrhalis* was susceptible to moxifloxacin, levofloxacin 83.4% (16.6% – resistant), and vancomycin, trimethoprim/sulfamethoxazole – 100%. *C. pneumoniae* had susceptibility to aztreonam – 100%. *S. marcescens* was susceptible to piperacillin/tazobactam, ceftazidime, ceftriaxone, meropenem, aztreonam, ciprofloxacin, amikacin in 100%.

Due to the limited data of EUCAST 2020, we described the susceptibility of bacterial isolates to delafloxacin as MIC and diameter of the lysis zone (Table 4).

Delafloxacin had MIC for *S. pneumoniae* 0.008143+0.003348 mg/l and 33.79+2.455 mm, *H. influenzae* – 0.0009524+0.0008009 mg/l and 40.29+4.406 mm, *S. aureus* 0.0020+0.001225 mg/l and 37.40+-1/140 mm, *K. pneumonia* 0.2650+0.5492 mg/l and 22.67+3.085 mm, *M. parainfluenzae* 0.00775+0.005148 mg/ml and 30.38+2.973 mm, *E. cloacae* 42.75 +104.5 mg/l and 21.17+7.468 mm, *M. catarrhalis* – 0.007667+0.006351 mg/l and 36.33+2.082 mm.

For evaluation of the clinical outcomes under fluoroquinolones treatment of CAP, 51 subjects were randomized to the delafloxacin group and 47 subjects were randomized to the moxifloxacin group (Table 5).

Demographics were similar between the two treatment groups as well as there were no statistically significant differences in baseline characteristics.

Table 6 shows the clinical and microbiological responses with 94.8% successful clinical response to the delafloxacin therapy at the end of treatment (EOT), and 93.8% at the test of cure (TOC). There were no differences between clinical responses for delafloxacin and moxifloxacin in hospitalized adults with community-acquired pneumonia.

Discussion

CAP is still a significant cause of morbidity and mortality. It is frequently misdiagnosed and inappropriately treated. Antimicrobial therapy should be initiated as soon as possible, particularly in those requiring hospital admissions, but typically, the physician does not know with any degree of certainty the identity of the etiologic pathogen. The international and national guidelines can provide the physician with appropriate choices of therapy (13). Empiric therapy remains the standard of care and guidelines are mostly based on published data from the United States or Europe. Blindly applying guidelines without any consideration of local etiological differences can lead to a risk of under- or overtreatment (14).

In this study, we determined the bacterial etiology of CAP and evaluated the clinical outcomes under antimicrobial treatment of CAP in Ukraine. A total of 98 adult subjects with CAP and PORT risk II-IV were recruited for the study. Before the initiation of antimicrobial therapy for all patients, the diagnostic samples were obtained for causative pathogen identification. The pathogen distribution in this trial was similar to recent reported CAP and PORT risk II – IV studies (15, 16).

It was highly important to compare our results with data obtained in the general population of the DEFINE-CABP trial (9). Thus, there was a similar profile of pathogens in adult patients with CAP in Ukraine as well as in international populations. We observed a major difference in a lower prevalence of *L. pneumophila* and *M. pneumoniae* in Ukraine.

In 2002, Woodhead M. emphasized the differences in CAP causative bacteria and resistance patterns to commonly used antibiotics between the European countries. Furthermore, the author pointed out that published data is often difficult to interpret and the impact of in vitro antibiotics resistance on the clinical outcome is still poorly understood (17). Recently, there have been a number of studies investigating the antimicrobial resistances of CAP causative bacterial species. *S. pneumoniae* isolated from adults with CAP in Mexico (18), Japan (19), Asia (20), Canada (21, 22), which had findings similar to our data. This data went in parallel with the multinational (54 countries from Africa, Asia, South America, North America and Europe) point-prevalence study that found a low global prevalence of drug-resistance *S. pneumoniae* in CAP subjects (23).

Our data showed that *H. influenzae* had a high susceptibility to conventionally used antibiotics except for azithromycin. Similar data were obtained in the Czech Republic, where the susceptibility of *H. influenzae* to amoxicillin/clavulanic acid, ceftriaxone, cefuroxime, and fluoroquinolones was more than 98%. However, the susceptibility to clarithromycin was 37.1% (24). In China, for *H. influenzae* isolates, most of the antimicrobial agents exhibited good activities. However, ampicillin and trimethoprim/sulfamethoxazole showed relatively low activity with a resistance rate of 35.0% and 54.4%, respectively (25).

For *S. aureus*, high susceptibility for delafloxacin (100%) and other antibiotics was observed. Delafloxacin activity against gram-positive organisms, especially, *S. aureus* was noted in previous trials (26). In addition, delafloxacin demonstrated activity against methicillin-resistant *S. aureus* (27). The susceptibility rates of *S. aureus* isolated from patients with CAP in China to levofloxacin, moxifloxacin, trimethoprim/sulfamethoxazole, and rifampin were 83.5%, 82.8%, 89.6%, and 83.5%, respectively (28).

K. pneumoniae is a common bacterial pathogen in adult patients with CAP (29, 30). It was shown that the anti-microbial resistance of *K. pneumoniae* changed during the decade (31). According to our data, *K. pneumoniae* had a high susceptibility to levofloxacin, amikacin, meropenem, piperacillin/tazobactam, and 81.2% of strains were susceptible to ceftazidime, ceftriaxone, aztreonam, ciprofloxacin. These results showed that *K. pneumoniae* strains had different susceptibility from strains isolated from patients in Uganda (a low-income country) (32) or China (28). For example, the sensitivity pattern of *K. pneumoniae* isolated from adult CAP patients in Malaysia was as

Table 3. Susceptibility testing of bacterial isolates from adults with community-acquired pneumonia (Susceptible (S) / Susceptible, Intermediate (I) / Resistant (R)), %

Baseline Pathogens	Penicillin	Amoxicillin Clavulanate	Piperacillin/ Taz	Oxacillin	Ceftazidime	Ceftriaxone	Meropenem	Aztreonam	Ciprofloxacin	Levofloxacin
***Streptococcus pneumoniae* (n=36)**	91.4/ 8.6/0	N/A	N/A	N/A	N/A	95.6/ 4.4/0	N/A	N/A	N/A	100/0/0
***Staphylococcus aureus* (n=20)**	N/A	100/0/0	N/A	100/ 0/0	N/A	N/A	N/A	N/A	N/A	93.7/0/ 6.3
***Haemophilus influenzae* (n=25)**	N/A	100/0/0	N/A	N/A	N/A	100/0/0	100/0/0	N/A	N/A	100/0/0
***Klebsiella pneumoniae* (n=19)**	N/A	N/A	87.5/0/ 12.5	N/A	81.3/0/ 18.7	81.3/0/ 18.7	100/0/0	81.3/0/ 18.7	81.3/0/ 18.7	100/0/0
***Haemophilus parainfluenzae* (n=12)**	N/A	100/0/0	N/A	N/A	N/A	100/0/0	100/0/0	N/A	N/A	80.0/0/ 20.0
***Enterobacter cloacae complex* (n=9)**	N/A	N/A	62.5/ 12.5/ 25.0	N/A	62.5/0/ 37.5	62.5/0/ 37.5	100/0/0	62.5/0/ 37.5	75.0/0/ 25.0	0/0/100
***Pseudomonas aeruginosa* (n=6)**	N/A	N/A	80.0/0/ 20.0	N/A	80.0/0/ 20.0	N/A	80.0/0/ 20.0	40.0/ 40.0/ 20.0	80.0/0/ 20.0	0/0/100
***Escherichia coli* (n=3)**	N/A	N/A	100/0/0	N/A	100/0/0	100/0/0	100/0/0	100/0/0	100/0/0	N/A
***Bordetella avium* (n=2)**	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
***Citrobacter koseri* (n=1)**	N/A	N/A	100/0/0	N/A	100/0/0	100/0/0	100/0/0	100/0/0	100/0/0	N/A
***Klebsiella oxytoca* (n=1)**	N/A	N/A	100/0/0	N/A	100/0/0	100/0/0	100/0/0	100/0/0	100/0/0	N/A
***Proteus mirabilis* (n=1)**	N/A	N/A	100/0/0	N/A	100/0/0	100/0/0	100/0/0	100/0/0	0/0/100	N/A
***Mycoplasma pneumoniae* (n=29)**	N/A	N/A	100/0/0	N/A	100/0/0	100/0/0	100/0/0	100/0/0	100/0/0	100/0/0
***Legionella pneumophila* (n=8)**	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
***Moraxella catarrhalis* (n=7)**	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	83.4/0/ 16.6
***Chlamydia pneumoniae* (n=7)**	N/A	N/A	N/A	N/A	N/A	N/A	N/A	0/100/0	N/A	N/A
***Serratia marcescens* (n=3)**	N/A	N/A	100/0/0	N/A	100/0/0	100/0/0	100/0/0	100/0/0	100/0/0	N/A

Notes: The percent of susceptible isolates using EUCAST 2020 breakpoints; Susceptible *, EUCAST 2020
Remarks: Susceptible *, EUCAST 2020

Moxifloxacin	Delafloxacin*	Amikacin	Vancomycin	Azithromycin	Erythromycin	Clindamycin	Doxycycline	Tetracyclin	Linezolid	Trimeth/Sulfa
100/0/0	N/A	N/A	100/ 0/0	70.0/ 4.0/ 26.0	N/A	78.3/0/ 21.7	N/A	N/A	100/0/0	N/A
93.7/0/6.3	N/A	N/A	100/ 0/0	N/A	N/A	100/0/0	N/A	N/A	100/0/0	100/0/0
100/0/0	N/A	N/A	N/A	9.0/82.0/ 9.0	N/A	100/0/0	N/A	100/0/0	N/A	N/A
0/0/100	N/A	100/0/0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
90.0/0/10.0	N/A	N/A	N/A	0/100/0	N/A	N/A	N/A	80.0/0/ 20.0	N/A	N/A
0/0/100	N/A	87.5/ 12.5/0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
0/0/100	N/A	80.0/0/ 20.0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
N/A	N/A	100/0/0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
N/A	N/A	100/0/0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
N/A	N/A	100/0/0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
N/A	N/A	100/0/0	N/A	100/0/0	N/A	N/A	N/A	N/A	N/A	N/A
100/0/0	N/A	100/0/0	N/A	100/0/0	100/0/0	N/A	N/A	100/0/0	N/A	N/A
N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
83.4/0/16.6	N/A	N/A	100/0/0	N/A	N/A	N/A	N/A	N/A	N/A	100/0/0
N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
N/A	N/A	100/0/0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Table 4. Delafloxacin susceptibility testing of bacterial isolates from adults with community-acquired pneumonia

Pathogens	MIC, mg/L	D, mm
Streptococcus pneumoniae (n=14)	0.008143±0.003348 (0.0040-0.0150)	33.79±2.455 (29.00-39.00)
Haemophilus influenzae (n=21)	0.0009524±0.0008009 (0.00025-0.0040)	40.29±4.406 (34.00-51.00)
Staphylococcus aureus (n=5)	0.0020±0.001225 (0.0010-0.0040)	37.40±1.140 (36.00-39.00)
Klebsiella pneumoniae (n=12)	0.2650±0.5492 (0.0300-2.000)	22.67±3.085 (14.00-26.00)
Haemophilus parainfluenzae (n=8)	0.00775±0.005148 (0.0020-0.0150)	30.38±2.973 (24.00-34.00)
Enterobacter cloacae complex (n=6)	42.75±104.5 (0.0600-256.0)	21.17±7.468 (6.000-25.00)
Moraxella catarrhalis (n=3)	0.007667±0.006351 (0.0040-0.0150)	36.33±2.082 (34.00-38.00)
Pseudomonas aeruginosa (n=4)	4.19±7.876 (0.0080-16.00)	24.75±15.95 (6.000-45.00)
Escherichia coli (n=3)	1.363±2.283 (0.0300-4.000)	24.33±11.72 (11.00-33.00)
Bordetella avium (n=1)	0.5	20
Citrobacter koseri (n=1)	0.06	24
Klebsiella oxytoca (n=2)	3.000±1.414 (2.000-4.000)	13.00±1.414 (12.00-14.00)
Klebsiella aeruginosa (n=1)	0.12	22

follows: meropenem (100%), ceftriaxone (92.85%), clarithromycin (42.85%), amoxiclav (85.71%), ciprofloxacin (57.14%), cefixime (50%), amikacin (71.42%) and gentamycin (64.28%) (6).

Among isolates of *H. parainfluenzae* from adult CAP patients, beta-lactamase production (10.5%), co-trimoxazole (40%), and clarithromycin (40%) resistance were the prevalent threats in Italy (33). Recent data from Poland showed that 73.6% of *H. parainfluenzae* isolates were resistant to one or more antimicrobials (P=0.0010). Investigators observed sensitivity mostly to beta-lactams with or without inhibitors (ampicillin, cefuroxime, cefotaxime, amoxicillin-clavulanate, ampicillin-sulbactam), as well as macrolides (azithromycin), tetracycline, and trimethoprim-sulfamethoxazole; susceptibility increased exposure (formally intermediate) mainly to cefuroxime (62.1%), azithromycin (100%) and tetracycline (10.3%), resistance to ampicillin (36.8%), cefuroxime (37.9%), tetracycline (9.2%) and chloramphenicol (26.4%) (34).

M. pneumoniae is a major cause of CAP. The prevalence of *M. pneumoniae* as the leading causative agent of CAP depended on regions. For example, *M. pneumoniae* was isolated from CAP patients in 27.4% in Japan, 35.80% – in Italy, 14.30% – in England and Wales (2011-2012), 8.21-19% – in China, 22.7% – in Iran (35-38). In contrast, only 1.6% of patients with severe respiratory illness had positive *M. pneumoniae* cultures in South Africa (39), and 3.2% in Dutch cohorts (40). CAP with positive tests for *M. pneumoniae* increased with age (41). *M. pneumoniae* had a different susceptibility for commonly used antimicrobials and this susceptibility varied between countries. In a Chinese prospective multicenter surveillance study, macrolide resistance of *M. pneumoniae* was as high as 80% and 72% against erythromycin and azithromycin, respectively. Tetracycline, minocycline, and quinolones (moxifloxacin and fluoroquinolones) had no signs of resistance (42).

The use of this new antibiotic could reduce the treatment duration of CAP and in some cases help to avoid combined therapy (43). Delafloxacin is a newly approved antibiotic in the development of treatment for CAP (44, 45). Delafloxacin had activity against methicillin-resistant *S. aureus* and *P. aeruginosa* offering a new option for the treatment of severe community-acquired bacterial pneumonia (27). Delafloxacin retained activity against resistant phenotypes found in *S. pneumoniae* (penicillin-, macrolide- and multiple drug-resistant), Hemophilus species (βlactamase producing and macrolide-non-susceptible), and *S. aureus* (MRSA and fluoroquinolone-non-susceptible methicillin-susceptible *S. aureus* MSSA) (46). According to our research results, delafloxacin had activity against *S. pneumoniae*, *H. influenzae*, *S. aureus*, *K. pneumoniae*, *E. cloacae*, *M. catarrhalis*. This data went in parallel with

Table 5. Demographic data and baseline characteristics of the two treatment groups

Characteristic	MOXIFLOXACIN		DELAFLOXACIN		Total
	n=47	%	n=51	%	n=98
Age, y					
Mean±SD	58.66 ±17.40		58.47±20.33		58.56±18.88
Min - max	18 - 84		20 - 86		18 - 86
Age category					
<65, y	29	61.70	27	52.94 P=0.2468	56
≥65, y	18	38.30	24	47.06 P=0.5848	42
≥75, y	11	23.40	14	27.45 P=0.6128	25
Sex					
Male	33	70.21	35	68.63	68
Female	14	29.79	16	31.37	30
Comorbidities					
BMI category					
<30 kg/m^2	34	72.3	35	68.6 P=0.8669	69
≥30 kg/m^2	13	27.7	16	31.4 P=0.8341	29
Diabetes, No	7	14.9	8	15.7 P=0.9256	15
CORD/Asthma	5	10.6	7	13.7 P=0.7657	12
CrCl group					
Sever (<30 mL/min)	0	0	1	2.0 P=1.0	1
Moderate (30-<60 mL/min)	8	17.0	9	17.6 P=1.0	17
Mild (60-<90 mL/min)	16	34.0	16	31.4 P=1.0	32
Normal (≥90 mL/min)	23	49.0	26	49.0 P=1.0	48
Region					
Kyiv	7	14.89	12	23.52	19.40
Vinnytsia	5	10.63	3	5.88	8.16
Zhytomyr	2	4.25	3	5.88	5.10
Dnipro	3	6.38	2	3.92	5.10
Zaporizhzhia	17	36.17	22	43.13	39.80
Poltava	9	19.14	2	3.92	11.22
Kharkiv	4	8.51	7	13.72	11.22

P, differences between the moxifloxacin and delafloxacin groups (Fisher's exact test).

Table 6. Clinical response to delafloxacin (n=51) or moxifloxacin (n=47) treatment in adults with community-acquired pneumonia, %

CLINICAL RESPONSE	CLINICAL SUCCESS Delafloxacin / Moxifloxacin	CLINICAL FAILURE Delafloxacin / Moxifloxacin
EOT	94.1/95.7 P=0.7146	3.9/2.1 P=0.6065
TOC	92.1/95.7 P=0.4592	5.8/2.1 P=0.3480

other findings that delafloxacin showed high antimicrobial activity and had MIC 50 below 0.002 mg/ml as well as a MIC 90 of 0.003 mg/ml against penicillin non-susceptible *S. pneumoniae* isolates (47).

In our investigation, a successful clinical response to delafloxacin at the end of treatment (EOT) and at TOC was similar to results obtained for the international population (9). Delafloxacin had a similar to moxifloxacin efficacy in hospitalized adults with community-acquired pneumonia. Taken together, our results suppose that delafloxacin may be considered a treatment option as monotherapy for CAP in adults.

Conclusions

In Ukraine, the major bacterial agents that induced CAP in adults were *S. pneumoniae*, *M. pneumoniae*, *H. influenzae*, *S. aureus*, *K. pneumoniae*, *H. parainfluenzae*, *E. cloacae, L. pneumophila*.

The empiric antimicrobial therapy of CAP in adult patients should take into consideration the antimicrobial resistance of bacterial strains isolated from the Ukrainian population. The examined fluoroquinolones moxifloxacin and delafloxacin had sufficient clinical and microbiological efficacy in hospitalized adults with community-acquired pneumonia.

Delafloxacin is a promising effective antibiotic for monotherapy of CAP in adults and could be used in cases of antimicrobial-resistant strains.

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References

1. Restrepo MI, Faverio P, Anzueto A. Long-term prognosis in community-acquired pneumonia. Curr Opin Infect Dis. 2013; 26(2): 151-158.
2. Zar HJ, Madhi SA, Aston SJ, Gordon SB. Pneumonia in low and middle income countries: progress and challenges. Thorax. 2013; 68(11): 1052-1056.
3. Welte T, Torres A, Nathwani D. Clinical and economic burden of community-acquired pneumonia among adults in Europe. Thorax. 2012; 67(1): 71-9.
4. Jain S, Self WH, Wunderink RG, et al.; CDC EPIC Study Team. Community-Acquired Pneumonia Requiring Hospitalization among U.S. Adults. N Engl J Med. 2015; 373(5): 415-27.
5. Brown JS. Geography and the aetiology of community-acquired pneumonia. Respirology. 2009; 14(8): 1068-71.
6. Akter S, Shamsuzzaman SM, Jahan F. Community acquired bacterial pneumonia: aetiology, laboratory detection and antibiotic susceptibility pattern. Malays J Pathol. 2014; 36(2): 97-103.
7. Peto L, Nadjm B, Horby P, et al. The bacterial aetiology of adult community-acquired pneumonia in Asia: a systematic review. Trans R Soc Trop Med Hyg. 2014; 108(6): 326-37.
8. Lupisan S, Suzuki A, Macalalad N, et al. Etiology and epidemiology of community-acquired pneumonia in adults requiring hospital admission: A prospective study in rural Central Philippines. Int J Infect Dis. 2019; 80: 46-53.
9. Horcajada JP, Salata RA, Álvarez-Sala R, et al; DEFINE-CABP Study Group. A Phase 3 Study to Compare Delafloxacin With Moxifloxacin for the Treatment of Adults With Community-Acquired Bacterial Pneumonia (DEFINE-CABP). Open Forum Infect Dis. 2019; 7(1): ofz514.
10. Clinical and Laboratory Standards Institute (CLSI). Performance Standards for Antimicrobial Disk Susceptibility Tests. 13th ed. CLSI standard M02. (ISBN 1-56238-834-7 [Print]; ISBN 1-56238-835-5 [Electronic]). https://clsi.org/media/1925/m02ed13_sample.pdf.

11. The European Committee on Antimicrobial Susceptibility Testing. Breakpoint tables for interpretation of MICs and zone diameters. Version 9.0, 2019. http://www.eucast.org.
12. Magiorakos AP, Srinivasan A, Carey RB, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. Clin Microbiol Infect. 2012; 18(3): 268-81.
13. Mandell LA. Community-acquired pneumonia: An overview. Postgrad Med. 2015; 127(6): 607-15.
14. Waterer GW. Community-acquired Pneumonia: A Global Perspective. Semin Respir Crit Care Med. 2016; 37(6): 799-805.
15. Stets R, Popescu M, Gonong JR, et al. Omadacycline for Community-Acquired Bacterial Pneumonia. N Engl J Med. 2019; 380(6): 517-27.
16. File TM JR, Rewerska B, Vucinic-Mihailovic V, et al. SOLITAIRE-IV: A Randomized, Double-Blind, Multicenter Study Comparing the Efficacy and Safety of Intravenous-to-Oral Solithromycin to Intravenous-to-Oral Moxifloxacin for Treatment of Community-Acquired Bacterial Pneumonia. Clin Infect Dis. 2016; 63(8): 1007-16.
17. Woodhead M. Community-acquired pneumonia in Europe: causative pathogens and resistance patterns. Eur Respir J Suppl. 2002; 36: 20s-27s.
18. Echaniz-Aviles G, Garza-González E, Román-Mancha AL, et al. Clinical and microbiological characteristics of community-acquired pneumonia associated with Streptococcus pneumoniae in adult patients in Mexico. Rev Argent Microbiol. 2019; 51(3): 234-40.
19. Toda H, Tanaka Y, Satoh K, et al. Epidemiological and molecular characterization of invasive Streptococcus pneumoniae isolated following introduction of 7-valent conjugate vaccine in Kinki region, Japan, 2008-2013. J Infect Chemother. 2020; 26(5): 451-8.
20. Kim SH, Chung DR, Song JH, et al.; Asian Network for Surveillance of Resistant Pathogens (ANSORP). Changes in serotype distribution and antimicrobial resistance of Streptococcus pneumoniae isolates from adult patients in Asia: Emergence of drug-resistant non-vaccine serotypes. Vaccine. 2020; 38(38): 6065-73.
21. Zhanel GG, Adam HJ. Introduction to the SAVE study (2011-15): Streptococcus pneumoniae serotyping and antimicrobial susceptibility: Assessment for Vaccine Efficacy in Canada after the introduction of PCV-13. J Antimicrob Chemother. 2018; 73(suppl_7): vii2-vii4.
22. Karlowsky JA, Adam HJ, Golden AR, et al.; Canadian Antimicrobial Resistance Alliance (CARA). Antimicrobial susceptibility testing of invasive isolates of Streptococcus pneumoniae from Canadian patients: the SAVE study, 2011-15. J Antimicrob Chemother. 2018; 73(suppl_7): vii5-vii11.
23. Aliberti S, Cook GS, Babu BL, et al.; GLIMP investigators. International prevalence and risk factors evaluation for drug-resistant Streptococcus pneumoniae pneumonia. J Infect. 2019; 79(4): 300-11.
24. Torumkuney D, Zemlickova H, Maruscak M, Morrissey I. Results from the Survey of Antibiotic Resistance (SOAR) 2014-16 in the Czech Republic. J Antimicrob Chemother. 2018; 73(suppl_5): v22-v27.
25. Zhang Y, Zhang F, Wang H, et al. Antimicrobial susceptibility of Streptococcus pneumoniae, Haemophilus influenzae and Moraxella catarrhalis isolated from community-acquired respiratory tract infections in China: Results from the CARTIPS Antimicrobial Surveillance Program. J Glob Antimicrob Resist. 2016; 5: 36-41.
26. Shiu J, Ting G, Kiang TK. Clinical Pharmacokinetics and Pharmacodynamics of Delafloxacin. Eur J Drug Metab Pharmacokinet. 2019; 44(3): 305-17.
27. Ocheretyaner ER, Park TE. Delafloxacin: a novel fluoroquinolone with activity against methicillin-resistant Staphylococcus aureus (MRSA) and Pseudomonas aeruginosa. Expert Rev Anti Infect Ther. 2018; 16(7): 523-30.
28. Sun H, Chen L, Chen X, et al. [Antimicrobial susceptibility of community-acquired respiratory tract pathogens isolated from class B hospitals in China during 2013 and 2014]. Zhonghua Jie He He Hu Xi Za Zhi. 2016; 39(1): 30-7.
29. El-Sokkary RH, Ramadan RA, El-Shabrawy M, et al. Community acquired pneumonia among adult patients at an Egyptian university hospital: bacterial etiology, susceptibility profile and evaluation of the response to initial empiric antibiotic therapy. Infect Drug Resist. 2018; 11: 2141-50.
30. Pfaller MA, Mendes RE, Castanheira M, Flamm RK, Jones RN, Sader HS. Ceftaroline Activity Tested Against Bacterial Isolates Causing Community-acquired Respiratory Tract Infections and Skin and Skin Structure Infections in Pediatric Patients From United States Hospitals: 2012-2014. Pediatr Infect Dis J. 2017; 36(5): 486-91.
31. Hyun M, Noh CI, Ryu SY, Kim HA. Changing trends in clinical characteristics and antibiotic susceptibility of Klebsiella pneumoniae bacteremia. Korean J Intern Med. 2018; 33(3): 595-603.
32. Najjuka CF, Kateete DP, Kajumbula HM, Joloba ML, Essack SY. Antimicrobial susceptibility profiles of Escherichia coli and Klebsiella pneumoniae isolated from outpatients in urban and rural districts of Uganda. BMC Res Notes. 2016; 9: 235.
33. Marchese A, Ardito F, Fadda G, et al. The Sentinel Project: an update on the prevalence of antimicrobial resistance in community-acquired respiratory Streptococcus pneumoniae and Haemophilus spp. in Italy. Int J Antimicrob Agents. 2005; 26(1): 8-12.
34. Kosikowska U, Andrzejczuk S, Grywalska E, et al. Prevalence of susceptibility patterns of opportunistic bacteria in line with CLSI or EUCAST among Haemophilus parainfluenzae isolated from respiratory microbiota. Sci Rep. 2020; 10(1): 11512.
35. Cao B, Qu JX, Yin YD, Eldere JV. Overview of antimicrobial options for Mycoplasma pneumoniae pneumonia: focus on macrolide resistance. Clin Respir J. 2017; 11(4): 419-29.
36. Wang X, Zhang H, Zhang T, et al. Etiology of Community-Acquired Pneumonia Requiring Hospital Admission

in Adults with and Without Cancers: A Single-Center Retrospective Study in China. Infect Drug Resist. 2020; 13: 1607-17.
37. Chen J, Li X, Wang W, Jia Y, Lin F, Xu J. The prevalence of respiratory pathogens in adults with community-acquired pneumonia in an outpatient cohort. Infect Drug Resist. 2019; 12: 2335-41.
38. Arfaatabar M, Aminharati F, Azimi G, et al. High frequency of Mycoplasma pneumoniae among patients with atypical pneumonia in Tehran, Iran. Germs. 2018; 8(3): 126-33.
39. Carrim M, Wolter N, Benitez AJ, et al. Epidemiology and Molecular Identification and Characterization of Mycoplasma pneumoniae, South Africa, 2012-2015. Emerg Infect Dis. 2018; 24(3): 506-13.
40. Raeven VM, Spoorenberg SM, Boersma WG, et al.; Alkmaar study group; Ovidius study group. Atypical aetiology in patients hospitalised with community-acquired pneumonia is associated with age, gender and season; a data-analysis on four Dutch cohorts. BMC Infect Dis. 2016; 16: 299.
41. Aguilera-Alonso D, López Ruiz R, Centeno Rubiano J, et al. Características clínicas y epidemiológicas de las neumonías adquiridas en la comunidad por Mycoplasma pneumoniae en una población española, 2010-2015 [Epidemiological and clinical analysis of community-acquired Mycoplasma pneumonia in children from a Spanish population, 2010-2015]. An Pediatr (Engl Ed). 2019; 91(1): 21-9.
42. Yin YD, Wang R, Zhuo C, et al. Macrolide-resistant Mycoplasma pneumoniae prevalence and clinical aspects in adult patients with community-acquired pneumonia in China: a prospective multicenter surveillance study. J Thorac Dis. 2017; 9(10): 3774-81.
43. Bondeelle L, Bergeron A, Wolff M. Place des nouveaux antibiotiques dans le traitement de la pneumonie aiguë communautaire de l'adulte [The role of new antibiotics in the treatment of acute adult community acquired pneumonia]. Rev Mal Respir. 2019; 36(1): 104-17.
44. Kollef MH, Betthauser KD. New antibiotics for community-acquired pneumonia. Curr Opin Infect Dis. 2019; 32(2): 169-75.
45. Hopkins TM, Juang P, Weaver K, Kollef MH, Betthauser KD. Outcomes of Macrolide Deescalation in Severe Community-acquired Pneumonia. Clin Ther. 2019; 41(12): 2540-8.
46. McCurdy S, Keedy K, Lawrence L, et al. Efficacy of Delafloxacin versus Moxifloxacin against Bacterial Respiratory Pathogens in Adults with Community-Acquired Bacterial Pneumonia (CABP): Microbiology Results from the Delafloxacin Phase 3 CABP Trial. Antimicrob Agents Chemother. 2020; 64(3): e01949-19.
47. Hipp M, Burckhardt I. In vitro activity of newer antimicrobials against penicillin non-susceptible strains of Streptococcus pneumoniae. Infect Drug Resist. 2019; 12: 1889-93.

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