Etiological agents of community-acquired pneumonia in adult patients in Turkey; a multicentric, cross-sectional study

İftihar KÖKSAL[1], Tevfik ÖZLÜ[2], Özlem BAYRAKTAR[1], Gürdal YILMAZ[1], Yılmaz BÜLBÜL[2], Funda ÖZTUNA[2], Rahmet ÇAYLAN[1], Kemalettin AYDIN[1], Nurgün SUCU[1], *TUCAP Çalışma Grubu[3]

[1] Karadeniz Teknik Üniversitesi Tıp Fakültesi, İnfeksiyon Hastalıkları ve Klinik Mikrobiyoloji Anabilim Dalı, Trabzon,

[2] Karadeniz Teknik Üniversitesi Tıp Fakültesi, Göğüs Hastalıkları Anabilim Dalı, Trabzon,

[3] Akdeniz Üniversitesi Tıp Fakültesi, Antalya/Ankara Üniversitesi Tıp Fakültesi, Ankara/Dicle Üniversitesi Tıp Fakültesi, Diyarbakır/Erciyes Üniversitesi Tıp Fakültesi, Kayseri/Fırat Üniversitesi Tıp Fakültesi, Elazığ/Pamukkale Üniversitesi Tıp Fakültesi, Denizli/Uludağ Üniversitesi Tıp Fakültesi, Bursa.

***TUCAP (Türkiye Toplum Kökenli Pnömoni Çalışma Grubu) Üyeleri**

Dilara İnan Özcan, Akdeniz Üniversitesi Tıp Fakültesi, İnfeksiyon Hastalıkları ve Klinik Mikrobiyoloji Anabilim Dalı, Antalya/Candan Öğüş, Akdeniz Üniversitesi Tıp Fakültesi, Göğüs Hastalıkları ve Tüberküloz Anabilim Dalı, Antalya/Emin Tekeli, Ankara Üniversitesi Tıp Fakültesi, İnfeksiyon Hastalıkları ve Klinik Mikrobiyoloji Anabilim Dalı, Ankara/Akın Kaya, Ankara Üniversitesi Tıp Fakültesi, Göğüs Hastalıkları ve Tüberküloz Anabilim Dalı, Ankara/Celal Ayaz, Dicle Üniversitesi Tıp Fakültesi, İnfeksiyon Hastalıkları ve Klinik Mikrobiyoloji Anabilim Dalı, Diyarbakır/Canan Eren Dağlı, Dicle Üniversitesi Tıp Fakültesi, Göğüs Hastalıkları ve Tüberküloz Anabilim Dalı, Diyarbakır/Orhan Yıldız, Erciyes Üniversitesi Tıp Fakültesi, İnfeksiyon Hastalıkları ve Klinik Mikrobiyoloji Anabilim Dalı, Kayseri/Fatma Sema Oymak, Erciyes Üniversitesi Tıp Fakültesi, Göğüs Hastalıkları ve Tüberküloz Anabilim Dalı, Kayseri/Ahmet Kalkan, Fırat Üniversitesi Tıp Fakültesi, İnfeksiyon Hastalıkları ve Klinik Mikrobiyoloji Anabilim Dalı, Elazığ/Mehmet Hamdi Muz, Fırat Üniversitesi Tıp Fakültesi, Göğüs Hastalıkları ve Tüberküloz Anabilim Dalı, Elazığ/Hüseyin Turgut, Pamukkale Üniversitesi Tıp Fakültesi, İnfeksiyon Hastalıkları ve Klinik Mikrobiyoloji Anabilim Dalı, Denizli/Fatma Fişekçi, Pamukkale Üniversitesi Tıp Fakültesi, Göğüs Hastalıkları ve Tüberküloz Anabilim Dalı, Denizli/Yasemin Heper, Uludağ Üniversitesi Tıp Fakültesi, İnfeksiyon Hastalıkları ve Klinik Mikrobiyoloji Anabilim Dalı, Bursa/Esra Uzaslan, Uludağ Üniversitesi Tıp Fakültesi, Göğüs Hastalıkları ve Tüberküloz Anabilim Dalı, Bursa.

ÖZET

Türkiye'de erişkin hastalarda toplum kökenli pnömonilerde etyolojik ajanlar; çok merkezli, kesitsel çalışma

Bu kesitsel çalışma öncesinde antibiyotik tedavisi almayan erişkin hastalarda toplum kökenli pnömoniler (TKP)'in etyolojisinin araştırılması için tasarlandı. Çalışmaya alınan 218 hastanın 137 (%62.8)'sinde etyolojik ajan tespit edildi. En sık tespit edilen ajanlar Streptococcus pneumoniae (%14.7), Mycoplasma pneumoniae (%13.8) ve respiratuar sinsityal virüs (%10.1) idi. Olguların %50.9'unda tek patojen, %11.9'unda çoklu patojen belirlendi. Olguların %35.8'inde tipik patojenler,

Yazışma Adresi (Address for Correspondence):

Dr. İftihar KÖKSAL, Karadeniz Teknik Üniversitesi Tıp Fakültesi, İnfeksiyon Hastalıkları ve Klinik Mikrobiyoloji Anabilim Dalı, TRABZON - TURKEY

e-mail: iftihar@yahoo.com

%20.2'sinde atipik patojenler, %20.6'sında ise viral patojenler belirlendi. Altta yatan hastalık olarak hastaların %42.7'sinde kronik obstrüktif akciğer hastalığı vardı. S. pneumoniae TKP'li erişkin hastalarda en yaygın patojendi. Atipik patojenler 65 yaşın altında daha yaygındı. M. pneumoniae bu yaş grubunda en sık etkendi. Çalışmamız, Türkiye'de TKP'li hastalarda başlangıç antibiyotik tedavisinin, S. pneumoniae ve M. pneumoniae'yı kapsaması gerektiğini göstermektedir.

Anahtar Kelimeler: *Toplum kökenli pnömoni, risk faktörleri, pnömoni etyolojisi.*

SUMMARY

Etiological agents of community-acquired pneumonia in adult patients in Turkey; a multicentric, cross-sectional study

İftihar KÖKSAL[1], Tevfik ÖZLÜ[2], Özlem BAYRAKTAR[1], Gürdal YILMAZ[1], Yılmaz BÜLBÜL[2], Funda ÖZTUNA[2], Rahmet ÇAYLAN[1], Kemalettin AYDIN[1], Nurgün SUCU[1], *TUCAP Study Group[3]

[1] Department of Infectious Diseases and Clinical Microbiology, Faculty of Medicine, Karadeniz Technical University, Trabzon, Turkey.

[2] Department of Chest Diseases, Faculty of Medicine, Karadeniz Technical University, Trabzon, Turkey.

[3] Faculty of Medicine Akdeniz University, Antalya/Faculty of Medicine Ankara University, Ankara/ Faculty of Medicine Dicle University, Diyarbakir/Faculty of Medicine Erciyes University, Kayseri/Faculty of Medicine Firat University, Elazig/Faculty of Medicine Pamukkale University, Denizli/Faculty of Medicine Uludag University, Bursa, Turkey.

*** TUCAP (Turkish Community-Acquired Pneumonia Study Group) Members**

Dilara İnan Özcan, Department of Infectious Diseases and Clinical Microbiology, Akdeniz University Medical Faculty, Antalya/Candan Öğüş, Department of Chest Diseases and Tuberculosis, Akdeniz University Medical Faculty, Antalya/Emin Tekeli, Department of Infectious Diseases and Clinical Microbiology, Ankara University Medical Faculty, Ankara/Akın Kaya, Department of Chest Diseases and Tuberculosis, Ankara University Medical Faculty, Ankara/Celal Ayaz, Department of Infectious Diseases and Clinical Microbiology, Dicle University Medical Faculty, Diyarbakir/Canan Eren Dağlı, Department of Chest Diseases and Tuberculosis, Dicle University Medical Faculty, Diyarbakir/Orhan Yıldız, Department of Infectious Diseases and Clinical Microbiology, Erciyes University Medical Faculty, Kayseri/Fatma Sema Oymak, Department of Chest Diseases and Tuberculosis, Erciyes University Medical Faculty, Kayseri/Ahmet Kalkan, Department of Infectious Diseases and Clinical Microbiology, Firat University Medical Faculty, Elazig/Mehmet Hamdi Muz, Department of Chest Diseases and Tuberculosis, Firat University Medical Faculty, Elazig/Hüseyin Turgut, Department of Infectious Diseases and Clinical Microbiology, Pamukkale University Medical Faculty, Denizli/Fatma Fişekçi, Department of Chest Diseases and Tuberculosis, Pamukkale University Medical Faculty, Denizli/Yasemin Heper, Department of Infectious Diseases and Clinical Microbiology, Uludag University Medical Faculty, Bursa/Esra Uzaslan, Department of Chest Diseases and Tuberculosis, Uludag University Medical Faculty, Bursa, Turkey.

This cross-sectional study was intended to investigate the etiology of community-acquired pneumonia (CAP) in adult patients receiving no prior antibiotic therapy. Etiological agents were identified in 137 (62.8%) of 218 patients, the most frequent being Streptococcus pneumoniae (14.7%), Mycoplasma pneumoniae (13.8%) and respiratory syncytial virus (10.1%). A single pathogen was detected in 50.9% of cases and mixed pathogens in 11.9%. Typical pathogens were determined in 35.8% of cases, atypical pathogens in 20.2% and viral pathogens in 20.6%. Chronic obstructive pulmonary disease was a common (42.7%) comorbidity. S. pneumoniae was the most common pathogen in adult patients with CAP. Atypical pathogens were more common in patients < 65 years old, M. pneumoniae being the most common in this age group. Our results suggest that initial empiric antibiotic treatment in patients with CAP should cover S. pneumoniae and M. pneumoniae in Turkey.

Key Words: *Community-acquired pneumonia, risk factors, etiology of pneumonia.*

Despite recent advances in diagnosis, treatment and vaccination, community-acquired pneumonia (CAP) is still one of the most common infectious diseases worldwide. It remains a major cause of morbidity and mortality, and contributes significantly to excessive consumption of healthcare resources and related costs (1-4). In Turkey, a pneumonia rank 15th among the 20

most frequent acute and chronic diseases and is the 5th leading cause of death (5). Despite the fact that a great number of microbial agents can cause CAP, often no specific etiological diagnosis is established at the time of initial treatment, and antimicrobial therapy is usually performed using an empiric approach in such patients (2). In order to administer micro-organism-guided treatment, it is necessary to determine the causative pathogens of CAP.

The etiological agents of CAP may vary according to geographic area and patients´ underlying risk factors. Decisions on proper empiric antibiotic therapy will therefore depend on prospective epidemiological studies (3). Surveillance studies constitute an important tool for determining local and regional susceptibility patterns and guiding empiric antimicrobial therapy (6). The majority of studies that have investigated the microbial causes of CAP have been carried out with patients admitted to hospital. Only a few studies have been undertaken to determine the etiology of CAP in the ambulatory patient (7).

Only a few studies of the etiology of CAP have been performed in adult patients in an ambulatory setting in Turkey (5,8-10). In this multicentric, cross-sectional study, we determined etiological agents of CAP in ambulatory adult patients in the country.

MATERIALS and METHODS

Study Design

Eight university hospitals from different geographical regions of Turkey between November 2003 and March 2005 were included in this multicentric, cross-sectional study. In selecting centers, the following features were sought: the ability to represent different geographical areas, the ability to perform the investigative procedures in the study protocol in an optimal manner, and facility in coordination.

A Turkish Community-Acquired Pneumonia (TÜCAP) Study Group was coordinated under the Infectious Diseases and Clinical Microbiology and Chest Diseases and Tuberculosis departments of the Karadeniz Technical University Medical Faculty. TÜCAP members belong to infectious diseases and clinical microbiology departments or chest diseases and tuberculosis departments in the study centers. The study was approved by the Institutional Ethical Committee, and written informed consent was obtained from all patients or their legal representatives before enrolment.

Patients

The study population consisted of adult CAP patients > 17 years old and who attended an outpatient clinic at one of the study centers. Patients consisted of individuals living in urban as well as rural areas. All patients had clinical features and radiological findings compatible with CAP. CAP was defined as an acute illness associated with at least one of the following criteria; fever (> 38°C) or hypothermia (< 36°C), new cough with or without sputum production, pleuritic chest pain, dyspnea or altered breath sound on auscultation, plus a chest radiograph showing an opacity or new infiltrate consistent with pneumonia (11). CURB 65 score was used to determine disease severity (12). Patients with a diagnosis of immunosuppressive disorder, tuberculosis, health care associated pneumonia, aspiration pneumonia, antibiotic use in the last 48 hours, transferred from any health institution, hospitalization within the previous 2 weeks or pregnancy were excluded.

Demographic and clinical data were collected by an investigator using a standardized questionnaire. In order to establish microbial etiology, sputum, nasopharyngeal aspirate, blood and urine samples were taken from the subjects. All samples were collected before the start of antibiotic therapy. Acute serum samples were collected on admission, and convalescent serum samples 2 and 4 weeks after initial diagnosis of CAP.

Microbiological Evaluation

Sputum and nasopharyngeal aspirate samples were investigated using Gram's stain and then cultured. Only sputum samples with > 25 white blood cells and < 10 squamous cells/per low-magnification field (X10) were evaluated. Nasopharyngeal aspirate samples were also investigated for adenovirus, influenza A and B, parainfluenza viruses and respiratory syncytial virus

(RSV) antigen employing a direct immunofluorescent technique using antigen-specific monoclonal antibody kits according to the manufacturer's instructions for the detection of respiratory viruses (Argene; Biosoft, Varilhes, France). In the acute stage of illness and 2-4 weeks later, serum samples were investigated for IgM and IgG antibodies for RSV, adenovirus, influenza virus A and B, parainfluenza viruses 1, 2, 3 and 4, *Mycoplasma pneumoniae*, Coxsackie virus type 7, *Chlamydia pneumoniae*, *Legionella pneumophila* serotypes 1 and 12, *Bordetella pertussis* and *Bordetella parapertussis* using an indirect immunofluorescent technique (Argene; Biosoft, Varilhes, France). Chlamydia specific analyses were performed using a microimmunofluorescence technique (MIF) for IgG and IgM antibodies (MRL Diagnostics, IF 1200A, IF1200M, IF 1200G; California/ABD). Urine samples were assayed for *L. pneumophila* antigens by radioimmunoassay (Binax, Portland, Maine, USA).

Criteria for Etiological Diagnosis

The following criteria were used to determine etiology:

Isolation of pathogenic microorganisms (*Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis, Staphylococcus aureus* and other bacteria, including gram-negative enterobacteria and gram-positive bacteria) qualified sputum samples or nasopharyngeal aspirate samples;

Detection of adenovirus, influenza A and B and parainfluenza viruses and RSV antigens by direct immunofluorescence in nasopharyngeal aspirate;

For serological tests, a 4-fold rise in the antibody titer in paired sera, or presence of IgM antibodies;

For *C. pneumoniae*: a 4-fold rise in IgG titer or presence of IgM antibodies (≥ 1/16);

Detection of *L. pneumophila* antigens in urine. Cases that did not fulfil these diagnostic criteria were interpreted to be "No etiology determined".

Statistical Analysis

The chi-square test was used. $p < 0.05$ was regarded as statistically significant.

RESULTS

Two hundred ninety-two CAP patients were enrolled, of whom 218 were eventually analyzed. Seventy-four patients were excluded from analysis due to failure to obtain paired serum samples or to meet eligibility criteria, or else due to incomplete data. The mean age of enrolled patients was 57.5 ± 17.6. Ninety-four patients (43.1%) were older than 65. One hundred forty-seven patients were male and 71 female. All of patients had CURB-65 < 2. One hundred forty-two of the 218 patients (65.1%) had at least one comorbidity. The main demographic characteristics of the patients were summarized Table 1.

An etiological diagnosis was established in 137 out of the 218 (62.8%) patients. A total of 167 pathogens were isolated from 137 patients. A single pathogen was detected in 111 (50.9%) cases and 2 or more pathogens in 26 (11.9%) cases. No microorganism was determined in 81 (37.2%) patients. Typical pathogens were present in 35.8% of patients, atypical pathogens in 20.2% and viral pathogens in 20.6% The 3 most frequent pathogens were *S. pneumoniae* (14.7%), *M. pneumoniae* (13.8%) and RSV (10.1%) (Table 2).

Table 1. The main demographic characteristics of patients with CAP.

Characteristics	Mean ± SD, n (%)
Age (y)	57.5 ± 17.6
≥ 65 year	94 (43.1)
< 65 year	124 (56.9)
Gender	
Male	147 (67.4)
Female	71 (32.6)
Underlying diseases	
COPD	93 (42.7)
Hypertension	65 (29.8)
Congestive heart failure	21 (9.6)
Diabetes mellitus	19 (8.7)
Bronchiectasis	4 (1.8)
Chronic renal failure	3 (1.4)

CAP: Community-acquired pneumonia,
COPD: Chronic obstructive pulmonary disease.

Table 2. Distribution of etiological agents in 218 patients with CAP.

Microorganism	Number (%)	
Etiology determined	**137 (62.8)**	
Typical pathogens	**78 (35.8)**	**[46.7]***
Streptococcus pneumoniae	32 **(14.7)**	[19.2]*
Haemophilus influenzae	13 **(6.0)**	[7.8]*
Klebsiella pneumoniae	8 **(3.7)**	[4.8]*
Streptococcus spp.	5 **(2.3)**	[3]*
Moraxella catarrhalis	5 **(2.3)**	[3]*
Escherichia coli	4 **(1.8)**	[2.4]*
Pseudomonas aeruginosa	4 **(1.8)**	[2.4]*
Other gram-negative	4 **(1.8)**	[2.4]*
Other gram-positive	3 **(1.4)**	[1.8]*
Atypical pathogens	**44 (20.2)**	**[26.3]***
Mycoplasma pneumoniae	30 (13.8)	[18]*
Chlamydia pneumoniae	9 (4.1)	[5.4]*
Legionella pneumophila	5 **(2.3)**	[3]*
Viral pathogens	**45 (20.6)**	**[26.9]***
Respiratory syncytial virus	22 **(10.1)**	[13.2]*
Parainfluenzae virus	11 (5.0)	[6.6]*
Influenzae virus	10 **(4.6)**	[6]*
Coxackie virus	2 **(0.9)**	[1.2]*
No etiology determined	**81 (37.2)**	
Total	**218 (100)**	

* Percent distribution of 167 etiologic agents in 137 patients with CAP.

CAP: Community-acquired pneumonia.

Two pathogens were identified in 22 (10.1%) of the 26 patients with mixed pathogens and 3 pathogens in 4 (1.8%) patients. The most frequent combinations were a bacterial pathogen plus a viral pathogen. *S. pneumoniae* was determined in 9 patients with mixed pathogens. *H. influenzae* was the second most frequent bacteria in mixed infections, in all cases together with a viral agent.

Chronic obstructive pulmonary disease (COPD) was the most frequent comorbid factor, occurring in 42.7% of patients (93 out of 218). Other comorbidities were hypertension (29.8%), congestive heart failure (9.6%) and diabetes mellitus (8.7%). Seventy-eight pathogens were determined in 51 COPD subjects. The 4 most common pathogens were *S. pneumoniae* (27.4%), RSV (25.5%), *H. influenzae* (17.6%) and *M. pneumoniae* (17.6%).

When the distribution of the microorganisms by age was evaluated, the most frequent pathogen in patients ≥ 65 was *S. pneumoniae* (17.0%), followed by RSV (13.8%) and *M. pneumoniae* (8.5%). In patients < 65, the most frequent agent was *M. pneumoniae* (17.7%), followed by *S. pneumoniae* (12.9%), *H. influenzae* (7.3%) and RSV (7.3%). Pneumonia caused by *Streptococcus* spp. and *P. aeruginosa* was observed in individuals aged > 65, though these agents were not encountered in subjects aged < 65 (p= 0.016; p= 0.037). Pneumonia due to atypical agents was greater in subjects aged < 65 (p= 0.034) (Table 3).

DISCUSSION

In this cross-sectional study conducted in Turkey, we determined etiology in 62.8% of patients with CAP. Levels of determination of the causative micro-organisms in CAP in the literature vary from 16% to 65% (13-27). In previous small studies in Turkey, the levels of etiological agents in pneumonia have been reported as, variously, 21% and 45.5 % of patients with CAP (Table 4). Differences among these studies may be ascribed to prior antibiotic use and different methodologies and laboratory techniques (17). In particular, disparities in frequencies of viruses and atypical bacteria may be due to the use of different diagnostic laboratory techniques. For example, when only serological diagnostic methods were used, virus and atypical bacteria were diagnosed in only 16% of patients with acute bronchitis, whereas when viral and bacterial cultures of nasopharyngeal aspirates and sputum were added to the serological diagnostics these levels increased to 29-40% (16). In our study, nasopharyngeal aspirate, sputum, urine and serum samples were also investigated, etiology being determined in 62.8% of cases. This level would probably have been even higher if the molecular diagnostic method could have been used.

In our study, typical pneumonia agents were demonstrated in 35.8% of patients, atypical pneumonia agents in 20.2% and viral pneumonia agents in 20.6%. Mixed pneumonia agents were determined in 11.9% of patients. These proportions have been reported as 40%-54% for typical pathogens, 8%-63% for atypical pathogens and

Table 3. Distribution of pathogen agents by age.

Microorganism	≥ 65 years, No (%) of cases	< 65 years, No (%) of cases	p
Etiology determined	**61 (64.9)**	**76 (61.3)**	**0.586**
Typical pathogens	**38 (40.4)**	**40 (32.3)**	0.283
Streptococcus pneumoniae	16 (17.0)	16 (12.9)	0.601
Streptococcus spp.	5 (5.3)	0	**0.016**
Haemophilus influenzae	4 (4.3)	9 (7.3)	0.464
Pseudomonas aeruginosa	4 (4.3)	0	**0.037**
Moraxella catarrhalis	3 (3.2)	2 (1.6)	0.656
Klebsiella pneumoniae	3 (3.2)	5 (4.0)	1.000
Escherichia coli	0	4 (3.2)	0.130
Other gram-negative	2 (2.1)	2 (1.6)	1.000
Other gram-positive	1 (1.1)	2 (1.6)	1.000
Atypical pathogens	**13 (13.8)**	**31 (25)**	**0.034**
Mycoplasma pneumoniae	8 (8.5)	22 (17.7)	0.052
Chlamydia pneumoniae	4 (4.3)	5 (4.0)	1.000
Legionella pneumophila	1 (1.1)	4 (3.2)	0.384
Viral pathogens	**23 (24.5)**	**22 (17.7)**	**0.369**
Respiratory syncytial virus	13 (13.8)	9 (7.3)	0.205
Parainfluenzae virus	5 (5.3)	6 (4.8)	1.000
Influenzae virus	4 (4.3)	6 (4.8)	1.000
Coxacie virus	1 (1.1)	1 (0.8)	1.000
No etiology determined	33 (35.1)	48 (38.7)	0.586
Total	**94 (100)**	**124 (100)**	

4%-39% for mixed pathogens in different studies (24,28-31). In a previous study from our center, on respiratory tract infections in adults, we determined viral antigens and atypical bacterial antigens in 44.4% and 23% of patients, using immunofluorescence techniques (9). Another study from Turkey reported a level of isolation of atypical agents in CAP of 43.3% (5).

Major identifiable pathogens of CAP include *S. pneumoniae*, *H. influenzae* and atypical pathogens such as *M. pneumoniae, C. pneumoniae* and *Legionella* spp. (1-3). Some studies have identified atypical microorganisms or viruses, more frequently than *S. pneumonia.* However, the distribution of etiological pathogens of CAP may vary by country and geographical conditions (4). We determined *S. pneumoniae* as the most frequent pathogen (14.7%) isolated in adult patients with CAP, confirming previous reports from other countries (17,22,25,26,31). Lim et al. reported *S. pneumoniae* as a predominant causative agent in nearly half of cases in the UK (17). Again in the UK Creer et al. identified potential pathogens in 69% of patients, and respiratory viruses were the most common cause of acute adult lower respiratory tract infections, occurring in 63% of patients, while bacteria were detected in 26% (16). The latter results differ from those of other studies. The higher proportion of viral etiology may be due the use of PCR in that study (16,22).

In the present study, *M. pneumoniae* was the most frequent atypical pathogen and the second most frequent agent in the etiology of CAP. Some other studies have also reported *M. pneumoniae* as the most frequent atypical agent (20,24,25,30,32). Cases of atypical pneumonia have increasingly been reported, particularly in studies that have applied highly sensitive diag-

Table 4. Etiological agent detection rates in CAP in Turkey and certain other countries.

Country (publication year)	Etiology known %	References
Turkey (2008)	62.8	Present study
Australia (2008)	45.6	12
Netherlands (2008)	64	13
Asian countries (2008)	44.8	14
Turkey (2007)	21-45.5	5
UK (2007)	69	15
UK (2007)	75	16
Spain (2007)	41.1	17
Spain (2006)	57	18
Japan (2005)	52.8	19
Chile (2003)	55	20
Slovenia (2003)	62.4	21
Thailand (2003)	75.5	22
UK (2001)	75	16
Switzerland (2001)	54.1	23
Taiwan (2001)	59	16
Italy (1999)	44.9	24
France (1994)	72	25
USA (1991)	40	26
Netherlands (1991)	55	26
Israel (1991)	81	26
Finland (1981)	67	26

UK: United Kingdom, USA: United States of America.

nostic methods (28). The proportion of atypical pneumonia in other studies has varied from 8% to 63% (2,24,28). Researchers have ascribed this to differences in diagnostic tests, changes in climate or the use of different diagnostic criteria (20).

We determined respiratory viral agents in 20.6% of patients. RSV has been determined as the third most frequent pathogen and the most common viral pathogen at all ages. In patients ≥ 65 it is the second most frequent agent. In recent years, RSV and other respiratory viruses have been detected more often in CAP patients due to use of new diagnostic methods. In different studies the level of respiratory virus has varied from 9% to 63% (16,19,21,24).

L. pneumophila was diagnosed in 2.3% of cases, which agrees with results obtained from previous studies (30). The incidence of *Legionella* spp. is reported to vary from 0.6% to 12.2% in sporadic CAP cases. A comprehensive study from Korea reported that *L. pneumophila* is one of the most common atypical pathogens of CAP around the world (28).

Enterobacteriaceae (*E. coli, K. pneumoniae*) spp. and *P. aeruginosa* rarely cause CAP (30). In our study these pathogens were isolated as the least common microorganisms (1.8%, each).

In our study, mixed pathogens were found in 11.9% of patients. Co-infection rates have been reported in 22.5%, 12.5%, 16%, 8.5% and 5.7% of CAP in other studies (16,22,24,24,29). Mixed bacterial-viral infections have been increasingly reported in some recent studies. The most common co-pathogens were reported to be *S. pneumoniae*, RSV, and parainfluenza virus (17,29). The detection of mixed pathogens is probably strongly dependent on the diagnostic tests employed (18).

In CAP, the pattern of causative agents depends on age (33). Fifty-seven percent of the 218 patients in our study were younger than 65. In Turkey, the 15-64 age group represents 67% of the population (Turkish Statistical Institute, General Population Census and Economic Data, 2009). While *S. pneumoniae* was determined at the same rate in both groups, atypical pathogens were found less often in the elderly compared to younger patients. In elderly patients, the most frequent pathogen was *S. pneumoniae* (17.0%), followed by RSV (13.8%) and *M. pneumoniae* (8.5%). Viral pathogens have recently been increasingly diagnosed in elderly patients. In this study, as in others, *M. pneumoniae* was the most common pathogen in younger patients (30). Lim et al. reported atypical pathogen levels of 16% in elderly patients and 27% in younger patients (17).

In this study COPD was the most important co-morbidity. COPD has also been reported as the most common co-morbidity with CAP in other studies (30).

The most important limitation in our study was the small number of CAP patients. Because university hospitals are tertiary referral centers, and because we excluded all patients who had received prior antibiotherapy, the number of CAP patients enrolled in this study was inevitably low.

In conclusion, a causative pathogen was demonstrated in 62.8% of patients with CAP. *S. pneumoniae, M. pneumoniae* and RSV were the 3 most frequent agents in adults with CAP in an ambulatory setting in this Turkish study. These results suggest that in patients with CAP in initial empiric therapy should cover *S. pneumoniae* and atypical pathogens. Our results showed that in the empirical treatment of CAP suggestions of the Turkish Thoracic Society consensus report are suitable and cover etiological agents of CAP for our country (34).

Conflicts of Interest

None of the authors had any financial or personal relationships with other individuals or organizations that might inappropriately influence their work during the submission process.

ACKNOWLEDGEMENT

1. This study was supported by grants from the Research Foundation of Republic of Turkey State Planning Organization (Project No: 2003.200.001.1).

2. This study was presented at the 17th European Congress of Clinical Microbiology and Infectious Diseases ICC, Munich, Germany, 31 March - 04 April 2007 (Abstract number: 1733_695).

We would like to thank all our assistant researchers and technical personnel for their technical assistance.

REFERENCES

1. *Mandell LA. Epidemiology and etiology of community-acquired pneumonia. Infect Dis Clin North Am 2004; 18: 761-76.*
2. *Lode HM. Managing community-acquired pneumonia: a European perspective. Respir Med 2007; 101: 1864-73.*
3. *Mandell LA, Wunderink RG, Anzueto A, et al; American Thoracic Society. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis 2007; 44(Suppl 2): S27-S72.*
4. *Lagerström F, Bader M, Foldevi M, et al. Microbiological etiology in clinically diagnosed community-acquired pneumonia in primary care in Orebro, Sweden. Clin Microbiol Infect 2003; 9: 645-52.*
5. *Ozlu T, Bulbul Y, Ozsu S. Community-acquired pneumonia based on the Turkish national data. Tuberk Toraks 2007; 55: 191-212.*
6. *Sener B, Tunçkanat F, Ulusoy S, et al. A survey of antibiotic resistance in Streptococcus pneumoniae and Haemophilus influenzae in Turkey, 2004-2005. J Antimicrob Chemother 2007; 60: 587-93.*
7. *Honeybourne D. Community-acquired pneumonia in ambulatory patients: relative importance of atypical pathogens. Int J Antimicrob Agents 2001; 18: 57-61*
8. *Ozyilmaz E, Akan OA, Gulhan M, et al. Major bacteria of community-acquired respiratory tract infections in Turkey. Jpn J Infect Dis 2005; 58: 50-2.*
9. *Kaygusuz S, Koksal I, Aydin K, Caylan R. Investigation of atypical bacteria and virus antigens in respiratory tract infections by use of an immunofluorescence method. Jpn J Infect Dis 2004; 57: 33-6.*
10. *Ozlu T, Bulbul Y, Kaygusuz S, et al. Prevalence of M. pneumoniae, C. pneumoniae and L. pneumophilia in our cases with community-acquired pneumonia. Solunum Hastalıkları 2000; 11: 135-9.*
11. *Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis 2007; (Suppl 2): 27-72.*
12. *Lim WS, van der Eerden MM, Laing R, et al. Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. Thorax 2003; 58: 377-82.*
13. *Charles PG, Whitby M, Fuller AJ, et al. Australian CAP Study Collaboration. The etiology of community-acquired pneumonia in Australia: why penicillin plus doxycycline or a macrolide is the most appropriate therapy. Clin Infect Dis 2008; 46: 1522-4.*
14. *Endeman H, Schelfhout V, Voorn GP, et al. Clinical features predicting failure of pathogen identification in patients with community acquired pneumonia. Scand J Infect Dis 2008; 8: 1-6.*
15. *Song JH, Oh WS, Kang CI, et al. Asian Network for Surveillance of Resistant Pathogens Study Group. Epidemiology and clinical outcomes of community-acquired pneumonia in adult patients in Asian countries: a prospective study by the Asian network for surveillance of resistant pathogens. Int J Antimicrob Agents 2008; 31: 107-14.*
16. *Creer DD, Dilworth JP, Gillespie SH, et al. Aetiological role of viral and bacterial infections in acute adult lower respiratory tract infection (LRTI) in primary care. Thorax 2006; 61: 75-9.*

17. *Lim WS, Macfarlane JT, Boswell TC, et al. Study of community acquired pneumonia aetiology (SCAPA) in adults admitted to hospital: implications for management guidelines. Thorax 2001; 56: 296-301.*

18. *Almirall J, Boixeda R, Bolíbar I, et al; GEMPAC Study Group. Differences in the etiology of community-acquired pneumonia according to site of care: a population-based study. Respir Med 2007; 101: 2168-75.*

19. *Angeles Marcos M, Camps M, Pumarola T, et al. The role of viruses in the aetiology of community-acquired pneumonia in adults. Antivir Ther 2006; 11: 351-9.*

20. *Miyashita N, Fukano H, Mouri K, et al. Community-acquired pneumonia in Japan: a prospective ambulatory and hospitalized patient study. J Med Microbiol 2005; 54: 395-400.*

21. *Díaz A, Barria P, Niederman M, et al. Etiology of community-acquired pneumonia in hospitalized patients in Chile: the increasing prevalence of respiratory viruses among classic pathogens. Chest 2007; 131: 779-87.*

22. *Beovic B, Bonac B, Kese D, et al. Aetiology and clinical presentation of mild community-acquired bacterial pneumonia. Eur J Clin Microbiol Infect Dis 2003; 22: 584-91.*

23. *Wattanathum A, Chaoprasong C, Nunthapisud P, et al. Community-acquired pneumonia in southeast Asia the microbial differences between ambulatory and hospitalized patients. Chest 2003; 123: 1512-19.*

24. *Bochud PY, Moser F, Erard P, et al. Community-acquired pneumonia. A prospective outpatient study. Medicine (Baltimore). 2001; 80: 75-87.*

25. *Logroscino CD, Penza O, Locicero S, et al. Community-acquired pneumonia in adults: a multicentric observational AIPO study. Monaldi Arch Chest Dis 1999; 54: 11-7.*

26. *Moine P, Vercken JB, Chevret S, et al. Severe community-acquired pneumonia. Etiology, epidemiology, and prognosis factors. French study group for community-acquired pneumonia in the intensive care unit. Chest 1994; 105: 1487-95.*

27. *Lauderdale TL, Chang FY, Ben RJ, et al. Etiology of community acquired pneumonia among adult patients requiring hospitalization in Taiwan. Respir Med 2005; 99: 1079-86.*

28. *Sohn JW, Park SC, Choi YH, et al. Atypical pathogens as etiologic agents in hospitalized patients with community-acquired pneumonia in Korea: a prospective multicenter study. J Korean Med Sci 2006; 21: 602-7.*

29. *Gutiérrez F, Masiá M, Rodríguez JC, et al. Community-acquired pneumonia of mixed etiology: prevalence, clinical characteristics, and outcome. Eur J Clin Microbiol Infect Dis 2005; 24: 377-83.*

30. *Gutiérrez F, Masiá M, Rodríguez JC, et al. Epidemiology of community-acquired pneumonia in adult patients at the dawn of the 21st century: a prospective study on the Mediterranean coast of Spain. Clin Microbiol Infect 2005; 11: 788-800.*

31. *Howard LS, Sillis M, Pasteur MC, et al. Microbiological profile of community-acquired pneumonia in adults over the last 20 years. J Infect 2005; 50: 107-13*

32. *Arnold FW, Summersgill JT, Lajoie AS, et al. Community-acquired pneumonia organization (CAPO) investigators. A worldwide perspective of atypical pathogens in community-acquired pneumonia. Am J Respir Crit Care Med 2007; 175: 1086-93*

33. *Gutiérrez F, Masiá M, Mirete C, et al. The influence of age and gender on the population-based incidence of community-acquired pneumonia caused by different microbial pathogens. J Infect 2006; 53: 166-74.*

34. *Özlü T, Bülbül Y, Alataş F, Arseven O ve ark. Türk Toraks Derneği erişkinlerde toplumda gelişen pnömoni tanı ve tedavi uzlaşı raporu. Turkish Thoracic Journal 2009; Ek 9.*