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Antibiotic treatment outcomes in community-acquired pneumonia

Aykut ÇİLLİ[1,*], Abdullah SAYINER[2], Burcu ÇELENK[1], Ayşın ŞAKAR COŞKUN[3], Oğuz KILINÇ[4], Armağan HAZAR[5], Anıl AKTAŞ SAMUR[6], Sezai TAŞBAKAN[2], Grant W. WATERER[7], Yavuz HAVLUCU[3], Öznur KILIÇ[4], Fatma TOKGÖZ[5], Uğur BİLGE[6]

[1]Department of Pulmonary Medicine, School of Medicine, Akdeniz University, Antalya, Turkey
[2]Department of Pulmonary Medicine, School of Medicine, Ege University, İzmir, Turkey
[3]Department of Pulmonary Medicine, School of Medicine, Celal Bayar University, Manisa, Turkey
[4]Department of Pulmonary Medicine, School of Medicine, Dokuz Eylül University, İzmir, Turkey
[5]Department of Chest Disease, Süreyyapaşa Chest Disease and Thoracic Surgery Training and Research Hospital, İstanbul, Turkey
[6]Department of Biostatistics and Medical Informatics, Akdeniz University, Antalya, Turkey
[7]University of Western Australia, Crawley, WA, Australia

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Background/aim: The optimal empiric antibiotic regimen for patients with community-acquired pneumonia (CAP) remains unclear. This study aimed to evaluate the clinical cure rate, mortality, and length of stay among patients hospitalized with community-acquired pneumonia in nonintensive care unit (ICU) wards and treated with a β-lactam, β-lactam and macrolide combination, or a fluoroquinolone.

Materials and methods: This prospective cohort study was performed using standardized web-based database sheets from January 2009 to September 2013 in nine tertiary care hospitals in Turkey.

Results: Six hundred and twenty-one consecutive patients were enrolled. A pathogen was identified in 78 (12.6%) patients. The most frequently isolated bacteria were *S. pneumoniae* (21.8%) and *P. aeruginosa* (19.2%). The clinical cure rate and length of stay were not different among patients treated with β-lactam, β-lactam and macrolide combination, and fluoroquinolone. Forty-seven patients (9.2%) died during the hospitalization period. There was no difference in survival among the three treatment groups.

Conclusion: In patients admitted to non-ICU hospital wards for CAP, there was no difference in clinical outcomes between β-lactam, β-lactam and macrolide combination, and fluoroquinolone regimens.

Key words: Pneumonia, beta-lactam, fluoroquinolone, macrolide

1. Introduction

Community-acquired pneumonia (CAP) is one of the most common infectious diseases worldwide. Treatment for CAP remains largely empirical since identifying the infecting pathogens is difficult. Empirical antibiotic treatment has been shown to have comparable clinical efficacy to a pathogen-directed treatment approach in the management of patients hospitalized with CAP (1).

Optimal empirical antibiotic therapy is still a debated issue. For patients hospitalized in the medical ward, most guidelines recommend the use of a combination of β-lactam with macrolide (BLM) or monotherapy with respiratory fluoroquinolone (FQ), but not β-lactam (BL) monotherapy (2–4). On the other hand, a recent randomized controlled trial (5) and a previous systematic review (6) showed that BL alone may be as effective as respiratory fluoroquinolones or combination regimens in the management of CAP, at least in patients not admitted to the intensive care unit (ICU). Several studies have shown that, in severely ill CAP patients, adding a macrolide to the antibiotic regimen is associated with better clinical outcomes (7–11), but there is less evidence on the optimal treatment of patients with CAP admitted to the ward.

A few trials have previously compared BL, BLM, and FQ regimens in patients with CAP (5,12,13). In this study, we aimed to compare the effectiveness of these most frequently used antibiotic regimens in the real-world setting. Thus, we analyzed the data collected in the TURCAP (Turkish Community-Acquired Pneumonia Network) database, including all patients admitted to the hospital with CAP and treated with one of these three regimens. Briefly, in this multicenter study we evaluated

* Correspondence: acilli@akdeniz.edu.tr

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the clinical cure rate, mortality, and length of hospital stay (LOS) among patients hospitalized in the ward with CAP and treated with BL, BLM, and respiratory FQ.

2. Materials and methods

This study was performed using the TURCAP database. Briefly, this is a web-based registry for community-acquired pneumonia in which data are prospectively recorded using standard case report forms. Between January 2009 and September 2013, all consecutive patients hospitalized in non-ICU wards for CAP in nine community and university hospitals in eight different cities in Turkey were included. All adult (age > 18 years) patients with symptoms and signs of lower respiratory tract infection with a new pulmonary infiltrate on the admission chest radiograph, and whose discharge diagnosis was CAP, were included. Patients previously diagnosed with an immunocompromising condition (HIV infection), or who were on an immunosuppressive treatment (chemotherapy, high dose of immunosuppressive agents such as prednisone) were excluded. All patients were assessed upon hospital admission, followed during their hospital stay until discharge, and all relevant data were recorded. These data included patient demographics, comorbid conditions, smoking and alcohol consumption, vaccination status, antibiotic use within the preceding 3 months, physical examination findings, laboratory data, radiographic findings, arterial blood gas analysis, LOS, and clinical outcome.

For comparison of pneumonia severity within groups, the Pneumonia Severity Index (PSI) and CURB-65 scores were calculated for each patient on admission (14,15). All the data needed to calculate the PSI score were available for 583 of the 621 patients who were included in this study. Arterial blood gas analysis was not available in the remaining 38 patients, in whom oxygen saturation data (using pulse oximetry) were available. All of these patients had saturation levels equal to or higher than 94% at room air and had normal renal function; thus, no points were given for the PaO_2 level (presumed to be higher than 60 mmHg) and the pH level (presumed to be higher than 7.35).

A follow-up visit was carried out 30 days after discharge to assess the clinical outcome of the patient, including all-cause mortality at 30 days.

The choice of antibiotic treatment was left at the discretion of the attending physician. All treatment regimens were analyzed, and the patients were divided into three groups according to the most commonly used antibiotic regimen (group 1, BL; group 2, BLM; and group 3, FQ). Patients who did not receive any of these drug regimens were excluded from the study. Patients in the BL group mostly used ceftriaxone or a beta-lactam/beta-lactamase inhibitor. Clarithromycin was the only macrolide used in the BLM group, as this was the only macrolide available in parenteral form. The majority of the patients in the FQ group received moxifloxacin, while the remaining patients received levofloxacin. The initial regimen was changed only if there was failure of improvement in the clinical signs and symptoms.

Clinical cure was defined as resolution (at day 30) of clinical signs and symptoms related to infection without any need for further antibiotic therapy. Treatment failure was defined as the absence of any improvement in the clinical status of the patient and the need to switch to another antibiotic regimen > 72 h after initial treatment.

This study was approved by the ethics committee of Akdeniz University. All participants gave informed consent for these data to be used in scientific studies. All authors complied with the principles set by the Declaration of Helsinki throughout the study.

2.1. Statistical analysis

Patient characteristics were summarized using median [interquartile range (IQR)], or number (%). The numerical data were first tested for normality and then analyzed using Student's t-test and one-way ANOVA for parametric data; the Mann–Whitney U-test and Kruskal–Wallis test were used for nonparametric data for group comparisons. Categorical data were analyzed using the chi-squared test or Fisher's exact test. To evaluate the risk factors for in-hospital and 30-day mortality, multiple logistic regression analysis was performed. All analyses were done using SPSS for Windows version 18.0 (SPSS Inc., Chicago, IL, USA). A P-value of less than 0.05 was considered statistically significant.

3. Results

A total of 908 patients were hospitalized in non-ICU wards with a diagnosis of CAP during the study period; 230 of these patients were excluded because of misdiagnosis (n = 6) or missing data (n = 224). Patients for whom there was no clear record of clinical outcome, no data on 30-day mortality, or the PSI and/or CURB-65 scores could not be calculated were not included in the study. The only exception was the absence of arterial blood gas levels in a minority of patients. Arterial oxygen saturation data were available in these patients, as indicated in the Methods section. Fifty-seven of the remaining 678 patients had not received any of the three selected drug regimens, were treated with a large variety of different antibiotics, could not be classified into any distinct group, and were therefore excluded from the study. The remaining 621 patients composed the study cohort (Figure).

One hundred twenty-seven patients received BL, 300 received BL + M, and 194 patients received FQ. The three treatment groups were similar with regard to demographic

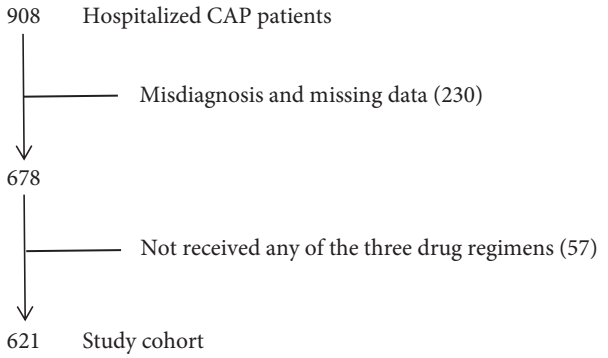

Figure. Patients flow chart.

characteristics, smoking and alcohol habits, antibiotic use within the preceding 3 months, radiographic findings, vaccination status, pneumonia severity indices, and arterial blood gas levels (Table 1). The PSI scores were similar in the BL, BLM, and FQ groups (96.2 ± 31.2, 89.9 ± 34.7, and 92.4 ± 32.5, respectively; P = 0.198). The only parameters that were associated with the choice of antibiotics were altered mental state (associated with more frequent use of BL monotherapy) and the presence of parapneumonic effusion (associated with less frequent use of FQ).

Sputum culture was collected from 265 patients and blood culture was collected from 261 patients. A causative pathogen was identified in 78 (12.6%) patients. The most frequently isolated bacteria were *S. pneumoniae* (21.8%), *P. aeruginosa* (19.2%), *H. influenzae* (12.8%), *E. coli* (9.0%), and methicillin-susceptible *S. aureus* (6.4%). Microbiologic tests for viruses and atypical bacteria were not routinely performed. There was no significant difference between groups in the distribution of these bacteria.

All patients with *P. aeruginosa* infection had risk factors for drug resistance, namely severe COPD with frequent exacerbations (n = 9) and/or a history of antibiotic use within the preceding 3 months (n = 12).

Forty-seven patients (9.2%) died within the first 30 days. The clinical cure rate, in-hospital, and 30-day mortality rates were similar in the three treatment groups (Table 2). In univariate analysis, higher PSI score, older age, presence of lung cancer, and chronic kidney disease were found to be associated with 30-day mortality (Table 3). A PSI score higher than 90 was the only independent risk factor for mortality in multivariate analysis (odds ratio [OR], 3.30) (Table 4).

4. Discussion

In this prospective, observational, multicenter study we showed that the clinical cure rate, mortality, and LOS were not different among patients who were hospitalized in the ward with CAP and initially treated with BL, BLM, or FQ. Although a pathogen was identified in a minority of the patient population, *P. aeruginosa* was the second most frequently isolated bacteria and thus needs to be taken into account in the empiric treatment of pneumonia in Turkey.

For inpatients not requiring ICU admission, empiric treatment with a respiratory FQ or BLM combination is recommended. These regimens have been studied in several studies and are generally associated with a cure rate of 90% in mild-to-moderate CAP (10). In our study BL, BLM, and FQ regimens were associated with similar cure rates (91.3–93%).

Controversy still exists on the choice of antibiotic regimen for patients with moderate-to-severe CAP who are admitted to hospital. Several meta-analyses consisting mostly of observational studies revealed controversial results (6–9,16). These analyses had somewhat different aims, namely to determine the relevance of antibiotic coverage for atypical pathogens (which therefore compared the use of macrolides or fluoroquinolones versus beta-lactams); to investigate whether the use of macrolides is associated with improved outcomes due to their antiinflammatory, in addition to antibacterial effects (which compared the use of macrolides with nonmacrolide regimens); and finally to compare the effectiveness of monotherapy (mostly with beta-lactams) with combination treatments (mostly beta-lactam/macrolide).

Eliakim-Raz et al. showed no benefit of survival or clinical efficacy of atypical coverage in hospitalized patients with CAP, except for patients with *Legionella* infection, but this conclusion was mostly related to the comparison of fluoroquinolone monotherapy to beta-lactams (6). Similarly, Mills et al. showed no advantage of antibiotics active against atypical pathogens over BL antibiotics in nonsevere CAP, again with the exception of patients with *Legionella* pneumonia (16).

Regarding studies investigating whether the antiinflammatory or immunomodulatory properties of macrolides are projected to clinical outcomes, a large meta-analysis showed that macrolide-based regimens were associated with a significant 22% reduction in mortality compared to nonmacrolide regimens (7). However, this benefit was not observed in patients who received guideline-concordant antibiotics (6). In another meta-analysis that included studies in critically ill patients with CAP only, macrolide use was associated with a significant 18% relative reduction in mortality compared to nonmacrolide therapies (8).

Several observational and two recent randomized controlled studies have compared the effectiveness of beta-lactam/macrolide dual therapy with beta-lactam monotherapy. The results of these studies have recently been analyzed in a systematic review (17). Although six of the eight observational studies included in the review

Table 1. Clinical characteristics, co-morbidity, and pneumonia severity scores of the study cohort.*

	BL (n = 127)	BL + M (n = 300)	FQ (n = 194)	All (n = 621)
Age (years)	67.2 ± 15.4	63.2 ± 18.2	64.2 ± 15.5	64.3 ± 16.9
Sex				
Male	86 (67.7)	194 (64.7)	137 (70.6)	417 (67.1)
Comorbidity, n (%)	109 (85.8)	244 (81.3)	161 (83.0)	514 (82.8)
COPD	43 (33.9)	86 (28.7)	71 (36.6)	200 (32.2)
Asthma	5 (3.9)	15 (5.0)	18 (9.3)	38 (6.1)
Coronary artery disease	19 (15.0)	58 (19.3)	32(16.5)	109 (17.6)
Lung cancer	10 (7.9)	14 (4.7)	13 (6.7)	37 (6.0)
Cerebrovascular disease	11 (8.7)	18 (6.0)	8 (4.1)	37 (6.0)
Congestive heart failure	17 (13.4)	36 (12.0)	21 (10.8)	74 (11.9)
Chronic kidney disease	5 (3.9)	7 (2.3)	7 (3.6)	19 (3.1)
Chronic liver disease	-	4 (1.3)	4 (2.1)	8 (1.3)
Diabetes mellitus	32 (25.2)	58 (19.3)	35 (18.0)	125 (20.1)
Smoking history, n (%)				
Non-smoker	52 (40.9)	120 (40.0)	61 (31.4)	233 (37.7)
Ex-smoker	63 (49.6)	137 (45.7)	106 (56.2)	306 (49.3)
Current smoker	8 (6.3)	38 (12.7)	24 (12.4)	70 (11.3)
Alcohol consumption				
Regular	3 (2.4)	9 (3.0)	4 (2.1)	16 (2.6)
Social	42 (33.1)	114 (38.0)	88 (45.4)	244 (39.3)
Never	57 (44.9)	143 (47.7)	80 (41.2)	280 (45.1)
Antibiotic use within 3 months, n (%)	31 (24.4)	53 (17.7)	40 (20.6)	124 (20.0)
Influenza vaccination, n (%)	18 (14.2)	43 (14.3)	45 (23.2)	106 (17.1)
Pneumococcal vaccination, n (%) [+]	13 (10.2)	21 (7.0)	30 (15.5)	64 (10.3)
CRP	18 [7–29.5]	20 [9–52.5]	22 [11–46]	
Procalcitonin	0 [0–3]	0 [0–2]	0 [0–2.5]	
PSI-I	6 (4.7)	41 (13.7)	18 (9.3)	65 (10.5)
PSI-II	22 (17.3)	36 (12.0)	32 (16.5)	90 (14.5)
PSI-III	27 (21.3)	72 (25.0)	40 (20.6)	139 (22.4)
PSI-IV	55 (43.3)	108 (36.0)	83 (42.8)	246 (39.6)
PSI-V	12 (9.4)	28 (9.3)	17 (8.8)	57 (9.2)
CURB-65–0	-	4 (1.3)	4 (2.1)	8 (1.3)
CURB-65–1	27 (21.3)	92 (30.7)	51 (26.3)	170 (27.4)
CURB-65–2	61 (48.0)	130 (43.3)	91 (46.9)	282 (45.4)
CURB-65–3	25 (19.7)	56 (18.7)	39 (20.1)	120 (19.3)
CURB-65–4	9 (7.1)	14 (4.7)	5 (2.6)	28 (4.5)
CURB-65–5	2 (1.6)	-	1 (0.5)	3 (0.5)
Radiographic findings, n (%)				
Bilateral infiltrates	13 (10.2)	47 (15.7)	16 (8.2)	76 (12.2)
Multilobar - involvement	7(5.5)	45 (15.0)	11 (5.7)	63(10.1)
PaO_2 (mmHg)**	61.4 ± 15.1	60.8 ± 13.8	60.2 ± 13.6	60.7 ± 14.0

* Frequencies (%) are shown for categorical variables; median values are given for continuous variables [IR].

** Arterial blood gases were available for 583 patients.

COPD: chronic obstructive pulmonary disease; CS: corticosteroid; PSI: pneumonia severity index; BL: β-lactam; M: macrolide; FQ: fluoroquinolone.

[+] P-value < 0.05, BL + M vs. FQ

Table 2. Clinical outcomes in groups treated with the three antibiotic regimens.*

	BL (n = 127)	BL + M (n = 300)	FQ (n = 194)	All (n = 621)	P-value
Length of hospital stay (days)	7 [5–11]	7 [5–10.6]	7 [4–10]	7 [5–10]	0.222
Clinical cure, n (%)	116 (91.3)	279 (93)	179 (92.3)	574 (92.4)	0.834
Treatment failure, n (%)	3 (2.4)	5 (1.7)	5 (2.6)	13 (2.1)	-
Mortality (in-hospital), n (%)	8 (6.3)	16 (5.4)	10 (5.2)	34 (5.5)	0.895
Mortality (30 days), n (%)	8 (8.7)	28 (11.4)	11 (6.4)	47 (9.2)	0.225

* Categorical variables are shown with frequency (%); continuous variables are shown with median [IR].
ICU: intensive care unit; BL: β-lactam; M: macrolide; FQ: fluoroquinolone.

Table 3. Univariate analysis of risk factors for 30-day mortality.

	Mortality (–) n = 574	Mortality (+) n = 47	P-value
Age (years)	63.8 ± 17.0	70.5 ± 14.2	0.009
Sex (M/F)	384/190	33/14	0.642
Comorbid diseases (n, %) COPD Lung cancer Stroke Diabetes mellitus Chronic renal failure	 189 (32.9) 30 (5.2) 32 (5.6) 115 (20.0) 22 (3.8)	 11 (23.4) 7 (14.9) 5 (10.6) 10 (21.3) 6 (12.8)	 0.179 0.007 0.159 0.838 0.005
Leucocyte/mm^3	12,270.1 ± 8505.4	12,448.4 ± 7508.0	0.889
Albumin (mg/dL)	3.5 ± 2.1	3.3 ± 0.7	0.737
CURB-65 score	2.0 ± 0.9	2.2 ± 0.9	0.053
PSI score	89.9 ± 32.5	117.5 ± 34.5	<0.001
PSI score > 90 (n, %)	266 (46.3)	37 (78.7)	<0.001
PaO_2/FiO_2	278.9 ± 66.1	291.8 ± 82.9	0.474

Table 4. Multivariate analysis of risk factors for 30-day mortality.

	Beta	Odds ratio	P-value
Age	0.012	1.012	0.379
Lung cancer	0.698	2.009	0.136
Chronic kidney disease	0.229	1.275	0.770
PSI > 90	1.195	3.303	0.007

demonstrated that the combination therapy was associated with lower rates of mortality, the two randomized trials showed differing results. A multicenter Dutch study showed noninferiority of beta-lactam monotherapy with respect to 90-day mortality (5), but was criticized for several reasons (18). First, CAP was not confirmed radiographically in 25% of the study population. Second, almost 40% of the patients in the BL group ultimately received antibiotics directed against atypical organisms during the trial. Third, adherence to BLM combination therapy regimen was lower than adherence to the monotherapy regimen. In another multicenter study from

Switzerland, a significantly higher proportion of patients infected with atypical pathogens or with more severe pneumonia (PSI category IV or CURB-65 score of ≥ 2) treated with beta-lactam/macrolide combination reached clinical stability at day 7, compared to those treated with monotherapy (11). However, mortality, admission to intensive care, LOS, and recurrence of pneumonia within 90 days were not different than in patients treated with beta-lactam monotherapy. Another recent meta-analysis also concluded that, compared with BL alone, BLM decreases all-cause mortality only for severe CAP (19).

Monotherapy with fluoroquinolones has been evaluated in randomized, controlled trials, but their superiority over BL monotherapy is lacking in hospitalized patients with CAP (7,17). A recent meta-analysis consisting of 16 RCTs showed that monotherapy with respiratory FQs is as safe and efficacious as BLM combination therapy (20).

The current study aimed to contribute to the existing level of knowledge with prospectively collected real-life data from patients with CAP admitted to five tertiary care centers. Our findings thus suggest that coverage for atypical bacteria and combination treatment are not associated with better clinical outcomes in patients with CAP who are admitted to non-ICU wards.

One concern regarding the use of beta-lactam monotherapy could be the rate of penicillin resistance. This does not appear to be an important issue for respiratory infections in Turkey, as several studies have shown that, although the rate of penicillin nonsusceptibility is 25% and higher (21), high resistance is uncommon (22). Thus, beta-lactam monotherapy is a viable treatment option for respiratory infections.

A decrease in macrolide susceptibility among pneumococci in Turkey has recently been reported (23). The most recent observations show that the susceptibility rate is 61.9%, which is of major concern regarding the antibacterial effects of macrolides. The same study revealed that clarithromycin remains effective against *H. influenzae*. There is no report on the activity of macrolides against atypical bacteria.

More patients with altered mental state received beta-lactam monotherapy. One could argue that this may have been due to the limitation of care for patients with a low likelihood of recovery and may have thus altered the clinical outcomes. However, we do not think that limitation of care was an issue regarding the choice of antibiotics, as Turkish laws forbid withholding any treatment in patients at end of life. These patients mostly received beta-lactams with antianaerobic activity, as they were possibly considered to have developed aspiration pneumonia and thus did not need coverage for atypical bacteria.

The main strengths of this study are that it reflects real life from several referral centers in different regions of the country. The decisions for clinical and laboratory follow-up, the choice of antibiotic regimen, and the decisions for admission and discharge were all left at the discretion of the attending physicians. Moreover, all data were prospectively collected and registered into the database before this study was planned and performed. Even though there was no randomization, the three treatment groups were well matched with regards to age, PSI scores, individual comorbidities, clinical history, and vaccination status. Finally, pneumonia was radiographically confirmed in all cases.

This study also has several limitations. First, it was observational and therefore treatment assignments were not randomized. Second, microbiological data were relatively poor, in that a causative pathogen was identified in a small minority (12.6%) of patients, as observed in real life, and tests for atypical bacteria were not routinely done, limiting better interpretation of the findings. *P. aeruginosa* appeared as one of the most frequently identified bacteria. Although all patients infected with *P. aeruginosa* had risk factors for drug resistance, namely severe COPD with frequent exacerbations and/or recent use of antibiotics, a previous study from the same database (24) showed that neither the presence of comorbidities nor a history of hospitalization or antibiotic use within the preceding 3 months was associated with treatment failure. Third, although the database included the history of antibiotic use within the preceding 3 months, it did not specify which antibiotic was used. Thus, we were not able to examine whether this had any effect on the choice of antibiotic regimen. Finally, time to clinical stability was not regularly noted, preventing comparison with other studies.

The results of this multicenter study have thus shown that, for patients admitted to non-ICU wards with CAP, the clinical cure rate, mortality, and LOS are not affected by the choice of BL, BLM, or FQ antibiotic regimen. Awaiting further prospective, randomized trials with proper stratification of patients according to pneumonia severity and with stronger microbiologic data, real-life experience shows that beta-lactam monotherapy is effective in non-ICU CAP patients.

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References

1. Van der Eerden MM, Vlaspolder F, de Graaff CS, Groot T, Bronsveld W, Jansen HM, Boersma WG. Comparison between pathogen directed antibiotic treatment and empirical broad spectrum antibiotic treatment in patients with community acquired pneumonia: a prospective randomised study. Thorax 2005; 60: 672-678.
2. Lim WS, Baudouin SV, George RC, Hill AT, Jamieson C, Le Jeune I, Macfarlane JT, Read RC, Roberts HJ, Levy ML et al. BTS guidelines for the management of community acquired pneumonia in adults: update 2009. Thorax 2009; 64: 1-55.
3. Mandell LA, Wunderink RG, Anzueto A, Bartlett JG, Campbell GD, Dean NC, Dowell SF, File TM Jr, Musher DM, Niederman MS 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; 44: 27-72.
4. Woodhead M, Blasi F, Ewig S, Garau J, Huchon G, Ieven M, Ortqvist A, Schaberg T, Torres A, van der Heijden G et al. Guidelines for the management of adult lower respiratory tract infections – full version. Clin Microbiol Infec 2011; 17: 1-59.
5. Postma DF, van Werkhoven CH, van Elden LJ, Thijsen SF, Hoepelman AI, Kluytmans JA, Boersma WG, Compaijen CJ, van der Wall E, Prins JM et al. CAP-START Study Group. Antibiotic treatment strategies for community-acquired pneumonia in adults. New Engl J Med 2015; 372: 1312-1323.
6. Eliakim-Raz N, Robenshtok E, Shefet D, Gafter-Gvili A, Vidal L, Paul M, Leibovici L. Empiric antibiotic coverage of atypical pathogens for community-acquired pneumonia in hospitalized adults. Cochrane Db Syst Rev 2012; 9: CD004418.
7. Asadi L, Sligl WI, Eurich DT, Colmers IN, Tjosvold L, Marrie TJ, Majumdar SR. Macrolide-based regimens and mortality in hospitalized patients with community-acquired pneumonia: a systematic review and meta-analysis. Clin Infect Dis 2012; 55: 371-380.
8. Sligl WI, Asadi L, Eurich DT, Tjosvold L, Marrie TJ, Majumdar SR. Macrolides and mortality in critically ill patients with community-acquired pneumonia: a systematic review and meta-analysis. Crit Care Med 2014; 42: 420-432.
9. Nie W, Li B, Xiu Q. β-Lactam/macrolide dual therapy versus β-lactam monotherapy for the treatment of community-acquired pneumonia in adults: a systematic review and meta-analysis. J Antimicrob Chemoth 2014; 69: 1441-1446.
10. Rodrigo C, McKeever TM, Woodhead M, Lim WS. Single versus combination antibiotic therapy in adults hospitalised with community acquired pneumonia. Thorax 2013; 68: 493-495.
11. Garin N, Genné D, Carballo S, Chuard C, Eich G, Hugli O, Lamy O, Nendaz M, Petignat PA, Perneger T et al. β-Lactam monotherapy vs β-lactam-macrolide combination treatment in moderately severe community-acquired pneumonia: A randomized noninferiority trial. JAMA Intern Med 2014; 174: 1894-1901.
12. Blasi F, Iori I, Bulfoni A, Corrao S, Costantino S, Legnanie D. Can CAP guideline adherence improve patient outcome in internal medicine departments? Eur Respir J 2008; 32: 902-910.
13. Reyes Calzada S, Martínez Tomas R, Cremades Romero MJ, Martínez Moragón E, Soler Cataluña JJ, Menéndez Villanueva R. Empiric treatment in hospitalized community-acquired pneumonia. Impact on mortality, length of stay and re-admission. Respir Med 2007; 101: 1909-1915.
14. Fine MJ, Auble TE, Yealy DM, Hanusa BH, Weissfeld LA, Singer DE, Coley CM, Marrie TJ, Kapoor WN. A prediction rule to identify low-risk patients with community-acquired pneumonia. New Engl J Med 1997; 336: 243-250.
15. Lim WS, van der Eerden MM, Laing R, Boersma WG, Karalus N, Town GI, Lewis SA, Macfarlane JT. Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. Thorax 2003; 58: 377-382.
16. Mills GD, Oehley MR, Arrol B. Effectiveness of beta lactam antibiotics compared with antibiotics active against atypical pathogens in non-severe community acquired pneumonia: meta-analysis. BMJ Brit Med J 2005; 330: 456.
17. Lee JS, Giesler DL, Gellad WF, Fine MJ. Antibiotic therapy for adults hospitalized with community-acquired pneumonia. A systematic review. JAMA-J Am Med Assoc 2016; 315: 593-602.
18. Bender MT, Niederman MS. Lessons learned from 2 decades of CAP therapy data: ways to improve patient management. J Thorac Dis 2016; 8: 6.
19. Horita N, Otsuka T, Haranaga S, Namkoong H, Miki M, Miyashita N, Higa F, Takahashi H, Yoshida M, Kohno S et. al. Beta-lactam plus macrolides or beta-lactam alone for community-acquired pneumonia: a systematic review and meta-analysis. Respirology 2016; doi: 10.1111/resp.12835.
20. Raz-Pasteur A, Shasha D, Paul M. Fluoroquinolones or macrolides alone versus combined with β-lactams for adults with community-acquired pneumonia: Systematic review and meta-analysis. Int J Antimicrob Ag 2015; 46: 242-248.
21. Borg MA, Tiemersma E, Scicluna E, van de Sande-Bruinsma N, de Kraker M, Grundmann H. Prevalence of penicillin and erythromycin resistance among invasive *Streptococcus pneumoniae* isolates reported by laboratories in the southern and eastern Mediterranean region. European Society of Clinical Microbiology and Infectious Diseases 2009; 15: 232-237.
22. Zarakolu P, Soyletir G, Gur D, Unal S. Antimicrobial resistance patterns of respiratory pathogens: a local report from Turkey. Clin Microbiol Infect 2003; 9: 1257-1258.
23. Torumkuney D, Gur D, Soyletir G, Gurler N, Aktas Z, Sener B, Tunger A, Bayramoglu G, Koksal I, Yalcin AN et al. Results from the survey of antibiotic resistance (SOAR) 2002–2009 in Turkey. J Antimicrob Chemoth 2016; 71: 85-91.
24. Gündüz C, Taşbakan MS, Sayıner A, Çilli A, Kılınç O, Şakar Coşkun A. Factors affecting treatment success in community-acquired pneumonia. Turk J Med Sci 2016; 46: 1469-1474.