Treatment of Community-Acquired Pneumonia in Adults: Analysis of the National Dispensing Database

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Abstract: Crude national ambulatory antibiotic dispensing data (2007–2011) of adult patients (aged between 20 and below 65 years) with CAP were obtained and expressed as DDD per 1000 inhabitants and per day (DID). European quality indicators of antibiotic prescribing were calculated and adherence rate to the national CAP guideline was assessed. Antibiotic use for CAP in adults ranged between 0.27 and 0.30 DID in various years. The most frequently used antibacterials were levofloxacin, co-amoxiclav and clarithromycin. Antibiotic use in CAP was compliant with the European recommendations in 6.4% in 2007, which decreased to 4.9% by 2011, in contrast to the optimal compliant range of 80–100%. The consumption of fluoroquinolones mounted up to ~40% in both genders, which exceeded the recommended range (0–5%) substantially. National guideline also favoured the use of macrolides in the empiric therapy of CAP in otherwise healthy adults; hence, guideline-concordant antibiotic use ranged between 24.0–32.3%. Agents that were contra-indicated in the empiric therapy of CAP were also used in 6.5–9.0% in various years. These data reflect some worrisome figures and trends in the outpatient antibiotic treatment of adults with CAP. Clarified and updated national guidelines focusing on outpatients and incentives/regulations to increase guideline concordance are warranted.

Community-acquired pneumonia (CAP) is a major health problem worldwide and is associated with considerable morbidity, mortality and healthcare costs [1]. In 2012, lower respiratory tract infections ranked the fourth most common cause of death worldwide [2], while CAP itself is considered the most frequent cause of infection-related death both in the Europe and in the USA [3]. Also, an acute CAP episode per patient results in 25.5 days of absence from work on average [4].

Ambulatory care antibiotic treatment of CAP is basically empiric everywhere [5,6] and should be guided by professional recommendations. National guidelines for the treatment of CAP have been available for many years. Moreover, based on the consensus of several national guidelines, disease-specific prescribing quality indicators were recently defined for the most common indications of outpatient antibiotic use including pneumonia [7].

The appropriateness of antibiotic use can be assessed by adherence rate to the national guidelines and by comparison with international prescribing quality indicators. The aim of this study was to describe antibiotic treatment patterns of adult outpatients with community-acquired pneumonia (CAP) in the light of internationally developed disease-specific quality indicators and national recommendations.

Materials and Methods

The crude data on systemic ambulatory antibiotic use were purchased from the National Health Fund Administration (NHFA). According to

the age limitations of the international quality indicator and relevant section of national CAP guideline, we included all antibiotic prescriptions of adult patients (aged between 20 and below 65 years) claimed between 2007 and 2011 in the analysis.

As NHFA is the only mandatory, health insurance fund in Hungary, and antibiotics are almost exclusively reimbursed agents, this database provides nearly 100% population and drug dispensation coverage.

Antibiotic use was evaluated by the anatomical therapeutic chemical (ATC) classification and defined daily dose (DDD) measurement unit (version 2012). Population data were derived from Eurostat.

The International Classification of Diseases (ICD) codes (version 10) are displayed on Hungarian prescriptions and captured in claims data, which allow indication-specific assessment of antibiotic use.

The ESAC developed quality indicators pertained for the R-81 code of the International Classification of Primary Care, second revision (ICPC-2-R code). The conversion between the ICD-10 and the ICPC-2-R codes was performed according to the prescribing quality indicators report published on the website of the European Center for Disease Prevention and Control [8].

ICD codes pertaining to pneumonia (J12, J13, J14, J15, J17, J18) were included in the analysis. The ESAC 7a indicator represents adult patients (18–65 years) with pneumonia (ICPC-2R: R81) receiving systemic antibacterial therapy (acceptable range: 90–100%). The ESAC 7b indicator shows the percentage of 7a patients receiving the recommended antibacterials (ATC: J01CA penicillins with extended spectrum and J01AA: tetracyclines; acceptable range: 80–100%) whereas 7c reflects the patients who received quinolones (ATC: J01M, acceptable range: 0–5%). Calculation of the ESAC 7a indicator was not feasible with our data set. The ESAC 7b disease-specific quality indicator was estimated by the relative use of the ESAC-recommended antibacterial agents and ESAC 7c by the relative use of quinolones. The results were compared to the pre-defined acceptable ranges.

Adherence rate to the national CAP recommendation was also assessed. The guideline – issued by the Hungarian Professional College of Infectious Diseases and Pulmonology – has been published

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each year with unchanged content since 2006, and therefore, it was valid for the whole study period [9].

The recommended empiric therapy in Group 1 patients (individuals below the age of 65 years and without comorbidities) with CAP was as follows:

1 Macrolide OR amoxicillin (min. 3 g daily) OR doxycycline without any particular order.
2 Not recommended: penamecillin, penicillin V, ampicillin, cephalexin, cefaclor, sulphamethoxazole/trimethoprim, second-generation fluoroquinolones (e.g. ciprofloxacin, ofloxacin, pefloxacin), third-generation oral cephalosporins (ceftibuten, cefixime)
3 Levofloxacin was recommended only in case of penicillin allergy or if initial empiric therapy failed. (Co-amoxiclav was not mentioned in this patient group; they were recommended only in patients with comorbidities).

As our primary data pertained to adults (aged between 20 and 65 years), we estimated guideline concordance in this patient group with the limitation that we could not exclude cases with comorbidities. However, to quantify this limitation, prevalence rate of relevant comorbidities (chronic obstructive pulmonary disease, cystic fibrosis, tuberculosis diabetes, renal failure) was retrieved from the database of the Hungarian Central Statistical Office.

For data managing, we used MS Excel and R (version 3.1.2).

Results

For adults with CAP, the recorded antibiotic use ranged between 0.27 and 0.30 DDD per 1000 inhabitants and per day (DID) in various years, which corresponded to 2.25–2.65% of total outpatient antibiotic use in Hungary. Oral antibiotics were prescribed almost exclusively (98.8% in 2007 and 99.6% in 2011). The use of the top ten agents at the two study endpoints is displayed in table 1.

Beta-lactam antibacterials headed the consumption list from 2007 to 2010, and their relative share was around 30% in each year. Combinations of penicillins with beta-lactamase inhibitors were the most prominent antibiotic subclass (representing more than 90% of the penicillin group each year). The fluoroquinolones accounted for 25.6% of antibiotic use in adults with CAP in 2007 which reached 40.4% by 2011. Levofloxacin, moxifloxacin and ciprofloxacin were among the most commonly used agents each year (table 1). In parallel, the relative use of macrolides gradually decreased from 26.3% in

2007 to 19.4% in 2011. Relative use of tetracyclines in CAP ranged from 3.9 to 4.4% without identifiable trend.

No significant gender differences in the antibiotic choice were observed.

Adherence rate to the Hungarian guideline is displayed in fig. 1, while antibiotic use according to the ESAC defined disease-specific quality indicators is summarized in table 2.

Agents recommended as first-line therapy for adults (aged 18–65 years without certain comorbidities) in the national guideline were used in 32.3% adults in 2007 and 24.3% in 2011. Agents that were discouraged to be used in the empiric therapy of CAP (e.g. sulphamethoxazole/trimethoprim and penamecillin, see complete list in the Methods section) were used in 9% in 2007, which gradually decreased to 6.5% by 2011.

The use of the internationally recommended antibacterials (quality indicator 7b) was 20 times lower than acceptable range (4.9–6.4% *versus* the optimal 80–100%) and showed a downward trend in both genders (table 2). In parallel, the gradual increase in fluoroquinolones use (quality indicator 7c) was observed in both genders, and in 2011, their use exceeded the ESAC-recommended limit more than eight times (table 2).

Discussion

According to recent European antibiotic surveillance data, Hungarian ambulatory care antibiotic use ranks among the lowest consumers in the northern European countries, while the pattern of use resembles that of southern European countries [10,11]. Therefore, studies revealing the treatment pattern of certain infections are important.

Although up to 80% of the treatment of CAP is provided in the outpatient setting [12], only very few recent studies have addressed the management of outpatients [4,13–18]. Some of these studies [13,17] focused only on specific cases (i.e. patients showing up in emergency wards), and with the exception of two papers [4,18], they pertain to USA or Canada.

To overcome this scarcity, we hereby report and evaluate the patterns and trends of CAP treatment in Hungarian ambulatory care.

The quality of antibiotic use in pneumonia – by comparing with disease-specific quality indicators – has been evaluated by only one study so far [18]. The usage rate of recommended antibacterials in CAP was higher in their study (25% on aver-

Table 1.
Use of the top ten antibacterials in adults with community-acquired pneumonia.

	2007				2011			
	ATC	Active agent	DID	%	ATC	Active agent	DID	%
1	J01CR02	Co-amoxiclav	0.08	29.63	J01MA12	Levofloxacin	0.09	29.04
2	J01FA09	Clarithromycin	0.05	18.61	J01CR02	Co-amoxiclav	0.08	25.28
3	J01MA12	Levofloxacin	0.04	12.89	J01FA09	Clarithromycin	0.04	12.86
4	J01MA14	Moxifloxacin	0.02	8.67	J01MA14	Moxifloxacin	0.02	7.78
5	J01FA10	Azithromycin	0.02	6.36	J01FA10	Azithromycin	0.02	6.55
6	J01DC02	Cefuroxime	0.01	5.08	J01DC02	Cefuroxime	0.02	5.51
7	J01AA02	Doxycycline	0.01	4.28	J01AA02	Doxycycline	0.01	4.15
8	J01MA02	Ciprofloxacin	0.01	3.72	J01MA02	Ciprofloxacin	0.01	3.30
9	J01CA04	Amoxicillin	0.00	1.71	J01DD08	Cefixime	0.00	1.39
10	J01DD14	Ceftibuten	0.00	1.67	J01DD14	Ceftibuten	0.00	0.95

Table 2.

Relative use of antibacterials for the treatment of community-acquired pneumonia in adults according to disease-specific quality indicators.

	ESAC quality indicator (QI)					
	QI 7b[1] (acceptable range: 80–100%)			QI 7c[2] (acceptable range: 0–5%)		
Years	Male	Female	Both	Male	Female	Both
2007	6.0	6.9	6.4	26.5	24.8	25.6
2008	5.0	5.4	5.2	29.7	28.2	28.9
2009	5.1	5.7	5.4	31.5	30.0	30.7
2010	5.4	5.5	5.5	36.9	36.0	36.4
2011	4.6	5.1	4.9	41.1	39.7	40.4

[1]QI 7b: Percentage of adult patients with pneumonia receiving the recommended antibacterials: J01CA penicillins with extended spectrum and J01AA: tetracyclines.

[2]QI 7c: Percentage of adult patients with pneumonia receiving quinolone.

age *versus* around 5% in our study), while their proportional quinolone use was similar [18].

National guideline-concordant antibiotic use varied greatly in the literature. In a recent Spanish outpatient study, treatment of bronchitis conformed to national guideline in 17%, [19] while a previous study focusing on CAP recorded 51.1% guideline adherence [4]. Mean guideline adherence rate in a US CAP study was 53.3% [16], while in Belgium, national guideline adherence in CAP was 25% on average [18].

In Hungary, fluoroquinolone became gradually the most commonly used antibiotic class in adults with CAP with a relative share exceeding 40% in 2011. In a comparable study, similar trends have been reported in Belgium where it increased from 10% to 30% between 2003 and 2010 [18].

Several factors have been listed as possible drivers of fluoroquinolone use such as once-daily dosing, activity against CAP pathogens, concerns about resistance to standard therapies and pharmaceutical advertising [15]. The increasing prevalence of macrolide and tetracycline resistance among *S. pneumoniae* is often cited as 'justifying reason' for prescribing fluoroquinolones [13]. This statement is slightly fallacious as tetracyclines and macrolides are primarily indicated for the treatment of atypical organisms. The fact that the Hungarian guideline emphasizes the very low resistance rate of *S. pneumonia* to fluoroquinolones [9] could also drive fluoroquinolone preference in Hungary.

It has been proven that quinolones are more prone to generate resistance compared with beta-lactams [20,21]. Increased use of fluoroquinolones for outpatient respiratory infections may lead to increased resistance rates among community-acquired Gram-negative organisms [15]. Increased fluoroquinolone resistance of *Escherichia coli* isolates in both urine and non-urine samples have been reported recently [22]. Routine prescribing of fluoroquinolones for CAP may limit the possibility of therapeutic failure due to their proven efficacy for both atypical and drug-resistant *S. pneumonia*, but may compromise the future effectiveness of this class of drugs. Therefore, empirical usage of fluoroquinolones should be limited to elderly patients and patients with comorbidities, while in otherwise healthy patients with CAP, fluoroquinolones should be used only in rare cases of true penicillin allergy or if initial treatment fails.

In Hungary, aminopenicillins – a recommended agent by the ESAC indicator and Hungarian guideline – were used infrequently, while amoxicillin combined with clavulanic acid (co-amoxiclav) was a popular agent. The high rate of co-amoxiclav use could be partly explained by the fact that – similarly to cefuroxime – national guidelines issued before 2006 recommended them as first-line agents in the empiric therapy of immunocompetent adults with CAP. Secondly,
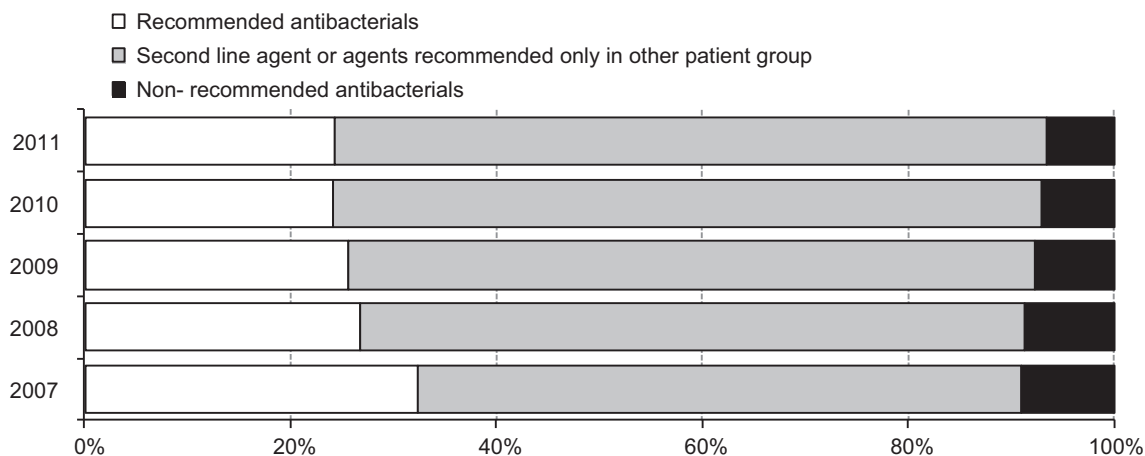

Fig. 1. Antibiotic use in adults with community-acquired pneumonia according to the national guideline. White: Recommended antibacterials for the empiric treatment of community-acquired pneumonia of adults (<65 years) without chronic diseases: macrolides, amoxicillin (min. 3 g daily) and doxycycline. Grey: Second-line agent or agents recommended only in other patient groups (if comorbidity is present): amoxiclav, respiratory quinolones. Black: Non-recommended antibacterials (for the empiric treatment of community-acquired pneumonia in adults (<65 years) without chronic disease: penamecillin, penicillin V, ampicillin, cephalexin, cefaclor, sulphamethoxazole/trimethoprim, second-generation fluoroquinolones (e.g. ciprofloxacin, ofloxacin, pefloxacin), third-generation oral cephalosporins (ceftibuten, cefixime).

co-amoxiclav was marketed in Hungary earlier than amoxicillin alone (co-amoxiclav: 1988; amoxicillin: 1991); hence, doctors became familiar earlier with the combined agent. Thirdly, in the general introduction of the Hungarian CAP guideline, it is emphasized that *Haemophilus influenzae* and *Moraxella catarrhalis* strains produce beta-lactamase in 5–10% and 95%, respectively, and consequently therapy with instable penicillins (e.g. amoxicillin) may fail. According to data from the National Center for Epidemiology, *S. pneumoniae* strains were highly susceptible to ampicillin both in 2007 and in 2011 (88.4% and 97.6%) in outpatient samples. Moreover, *Moraxella catarrhalis* – a frequent beta-lactamase producing strain – is infrequently isolated in otherwise healthy adults with CAP [9]. Lastly, the rate of beta-lactamase producing *Haemophilus influenzae* strains might be overestimated as samples derived from both ambulatory and hospital care.

Therefore, in the light of previous and current national resistance patterns, the use of high-dose amoxicillin in the empiric treatment of healthy adults with CAP is justified, while the use of its combination with clavulanic acid is superfluous.

In Hungary, macrolide use gradually decreased and accounted for 19% of antibiotic use in 2011 in adults with CAP. Although tetracyclines have been among the recommended first-line agents in the empiric treatment of adults with CAP both in national and in European guidelines, their relative use was constantly around 4% in our study. However, some decrease in the use of macrolides and tetracyclines in Hungary is acceptable, given the fact that tetracycline or macrolide-resistant *S. pneumoniae* is more prevalent. Nevertheless their value in the treatment of atypical organism – which is a frequent aetiologic agent in the studied aged group (<65 years) – is unquestionable [23].

Our study had some limitations. The ESAC quality indicators were defined for patients who should receive the recommended antibacterial agent. Unfortunately, individual patient data were not available for us; only aggregated antibiotic consumption data linked to demography and indication. As the prescribed DDD quantity of the different antibacterials used in CAP did not differ considerably, the percentage of patients treated and the relative use of prescribed antibiotics is comparable. By the nature of the data source (aggregated data), we could not assess the rate of mono or combination therapy, could not differentiate initial and subsequent antibacterial therapies and could not take into account comorbidities or drug allergies. However, these limitations only affect results on national guideline adherence and not the international quality indicators.

Because of the inability to exclude patient with comorbidities (their general prevalence in the population was ~10%), the Hungarian CAP guideline adherence was underestimated by approximately 10% as use of more broad spectrum agents (e.g. respiratory fluoroquinolone) is justified in these patients. However, we believe this is an upper estimation of the limitation as consumption data indirectly show (by the almost exclusive use of oral antibacterials) that more severe and progressive cases (including those with comorbidities) are admitted to the hospital and not treated as outpatients. Moreover, we could calculate the additive sum of prevalence rate of these chronic conditions (diabetes, chronic lower respiratory diseases, etc.), while we did not control for disease overlap (presence of several comorbidities).

In summary, our study identified some worrisome figures and trends in the outpatient antibiotic treatment of adults with CAP: extensive co-amoxiclav and fluoroquinolone use and high rate of non-adherence to national and international recommendations. We believe it is very highly unlikely that guideline clarification and update alone will result in rational antibacterial use patterns – incentives/regulations are also warranted.

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