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Research Article

Real-Life Management of Outpatients with Community-Acquired Pneumonia in the Gulf Region and Comparison with IDSA/ATS 2007 Practice Guidelines: A Multicentre, Prospective, Observational Study

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Abstract

Background: This multicentre, prospective, observational study aimed to describe treatment of community-acquired pneumonia (CAP) in outpatients in the Gulf region and compare treatment modalities to the 2007 IDSA/ATS guidelines.

Methods: Adult outpatients with CAP were enrolled at 41 sites in five countries. Data were collected at baseline and 7 and 30 days later. Data collected included socio-demographics, diagnostic criteria, comorbidities, antibiotic treatment and outcome.

Results: Overall, 641 patients were analysed (mean age: 41.2 years; 97.6% in PSI classes I/II). CAP diagnosis largely complied with IDSA/ATS guidelines: clinical criteria were available for 639 (99.7%) patients and pulse oximetry for 84.7%. Chest radiography was performed in 531 patients (82.8%); 457 (71.3%) had abnormal findings consistent with pneumonia. Samples were taken for microbiological analysis from 102 patients (15.9%). Pathogens not considered normal respiratory flora were isolated from 26 (25.5%). Fluoroquinolones were the most frequently prescribed antibiotics (88.2% of patients with comorbidities and 91% of those without).

Conclusions: Overall, prescriptions complied with IDSA/ATS guidelines in 78.9% with comorbidities and 3% without. After 7 days, CAP was improvead or resolved in 596 patients (93%). In conclusion, management of CAP was generally in line with IDSA/ATS guidelines. However, fluoroquinolones were overused and macrolides underused in patients without comorbidities. This may lead to rapid emergence of resistant to quinolones in common pathogen causing community-acquired pneumonia, hence we should try to use antibiotics more judiciously based on the patient's comorbidities issues and the severity of community-acquired pneumonia.

Keywords: *Community-Acquired Pneumonia; Guidelines; Gulf Countries; Management; Outpatients; Observational; Prospective Study*

Abbreviations

CAP: Community-Acquired Pneumonia; ATS: American Thoracic Society; IDSA: Infectious Disease Society of America; PSI: Pneumonia Severity Index; DRSP: Drug-Resistant *S. pneumoniae*

Background

Community-acquired pneumonia (CAP), acquired outside long-term care facilities or other healthcare services, is a serious illness which affects millions of people worldwide each year [1]. In a review of the burden of CAP in adults in North America, File and Marrie reported 4.2 million ambulatory care visits for pneumonia in 2006 and over 60 000 deaths from the disease in 2005 in the USA alone [2]. According to recent estimates, lower respiratory tract infections, including CAP, are the fourth largest cause of death worldwide [3]. The prevalence of CAP increases with age [4-7] and the clinical and economic burden of CAP is likely to increase due to the ageing population in developed countries. In the Gulf area, CAP has become a growing public health concern over the last ten years.

Many different organisations have addressed the management of adult patients with CAP with a view to standardising care and improving outcomes, and a number of guidelines for the diagnosis and management of CAP have been proposed in different countries. In 2007, a large regional/international multidisciplinary Working Group (GCC CAPWG) published guidelines on the assessment of severity and management of CAP in the Gulf region [8]. However, a recent retrospective study in Oman comparing these GCC guidelines with real-life practice in inpatients with CAP showed inadequate adherence to some elements of the guidelines [9]. In particular, the clinical coding of CAP diagnosis was poor and there was poor adherence to the assessment of CAP severity. The authors suggested that the development and implementation of a local hospital-based, integrated care pathway might result in more successful implementation of the guidelines [9]. A number of guidelines for the treatment of CAP have also been published in the USA by the American Thoracic Society (ATS) [10,11] and Infectious Diseases Society of America (IDSA) [12], culminating in the joint IDSA/ATS recommendations in 2007 [13]. These 2007 IDSA/ATS guidelines are now considered as one of the most important practice guidelines for the diagnosis and management of CAP in the Gulf region.

Several recent studies have shown that the implementation of IDSA/ATS guidelines in hospitalised adult patients with CAP on general wards is associated with improved health outcomes and diminished resource use, including a reduction of in-hospital sepsis and mortality, decreased time to achieve clinical stability, reduced length of stay and a shorter duration of parenteral therapy [14-17]. However, in a recent study comparing the management of 684 hospitalised patients with CAP in Gulf countries with IDSA/ATS guidelines, we reported that although patient management overall was in line with IDSA/ATS recommendations, the rates of pathogen characterisation by Gram's stain were low and post-discharge follow-up by chest radiography needed to be improved [18].

Over half of patients with CAP are treated as outpatients [19,20]. This has led to specific questions on how outpatients with CAP are currently managed in Gulf countries, their outcomes and whether their management complies with guidelines. Very few studies have evaluated outcomes in CAP patients treated as outpatients [1].

The current registry was designed to collect data on outpatients with CAP and current treatment practices in the Gulf region, comparing real-life practices with the 2007 IDSA/ATS guidelines [13]. The results of our study will help to clarify how CAP is currently managed in ambulatory patients, the outcomes of current management and compliance with treatment recommendations in Gulf countries.

The primary objectives of the study were to compare current treatment practices for outpatients with CAP in the Gulf region with the 2007 IDSA/ATS international treatment guidelines and to gain a better understanding of the short-term health outcomes of patients with CAP managed in an ambulatory setting. The secondary objectives were to assess: (i) antibiotic prescribing patterns; (ii) the duration of antibiotic treatment; (iii) antibiotic preference by physicians; (iv) any treatment changes during CAP; (v) CAP status at V2 (7 days) and V3 (30 days) (if the patient was not clinically stable at V2); (vi) outcome of CAP (see above); (vii) epidemiological data for CAP.

Materials and Methods

Study design and setting

The Gulf practices of outpatient treatment of CAP (Class I, II, III) registry (G-TinCAP II) was a regional, multicentre, non-interventional, observational, longitudinal study designed to collect data on real-life current treatment practices in outpatients diagnosed with CAP.

The physicians invited to participate in the study were selected at a country level from office- or hospital-based physicians who were routinely involved in the treatment of patients with CAP. A total 43 sites in five countries in the Gulf region participated in the study. These included four sites in Bahrain, eleven in Kuwait, five in Oman, four in Qatar and nineteen in the United Arab Emirates (UAE). The study was carried out between 26 June 2013 and 18 April 2015.

Study population

Patients were enrolled sequentially at each site if they were ≥18-years of age and had a confirmed diagnosis of CAP based on the presence of specific clinical features (notably cough, fever, sputum production, auscultatory findings, dyspnea and pleuritic chest pain), in some cases supported by imaging of the lung. All patients were classified in Class I, II or III according to the Pneumonia Severity Index (PSI) score as described by Fine., *et al.* [21] and were eligible for treatment as outpatients as they had a low risk of death.

Patients were excluded from the study if they required hospitalisation for any reason at the time of the inclusion visit, had required hospitalisation for any reason within fifteen days prior to the CAP episode, or had a diagnosis of TB, cystic fibrosis, HIV infection or current fungal or protozoal infection. In order to allow extrapolation of the results to the broadest possible population, all patients who met the study eligibility criteria were asked to participate in the registry. All patients gave their written informed consent before taking part in the study.

Data collection

Data were collected using a case report form (CRF). The following data were collected for each patient at the baseline visit (V1, enrolment): socio-demographic characteristics, medical history, comorbidities, CAP diagnosis and antimicrobial treatment (including dose, route and duration of administration). Specific information on CAP was recorded, including PSI Score and resulting risk class attribution [21], clinical symptoms and radiographic findings.

The outcome of CAP treatment (defined as either resolved, improved, resolved with sequelae, deteriorated, death, lost to follow-up or any other specified outcome) was assessed at a second visit (V2), scheduled for 7 ± 3 days after CAP diagnosis and at a third (optional) visit (V3), scheduled at 30 ± 7 days. Clinical resolution of CAP was defined as: temperature ≤ 37.8°C, heart rate ≤ 100 beats/min, respiratory rate ≤ 24 breaths/min, systolic blood pressure ≥ 90 mmHg, arterial SpO_2 ≥ 90%, ability to maintain oral intake of antibiotics (CAP symptom questionnaire at visit 2: question 10 score = 0) and normal mental status (CAP symptom questionnaire at visit 2: questions 15 and 16 score = score 0). CAP symptoms and antimicrobial treatments for CAP were also recorded at these two visits. In compliance with the regulations of each country, any adverse drug reactions (AEs) that occurred during treatment were reported to the pharmacovigilance department of Sanofi.

The data were validated for quality by checking for completeness, discrepancies and inconsistencies and any queries or requests for missing data were sent to the investigator before validation in the database.

Statistical analysis

The sample size for the study was determined *a priori* in order to estimate the key study variables with a precision (95% confidence interval) of 0.05%. To achieve the desired statistical power, 583 patients were required to be analysed. Assuming a dropout rate of 15%, a total of 670 subjects were to be enrolled into the study.

A descriptive analysis was performed for all subjects who satisfied the inclusion and exclusion criteria (eligible population) in all five countries. Quantitative variables are presented as number of data, mean ± standard deviation (SD) and 2-sided 95%CI of the mean, median and range (minimum and maximum). Qualitative variables are presented as the number of data, counts and percentages (missing data or unknown responses were not included in the percentages). All statistical tests were performed using two-tailed tests at a 5% level of significance. The statistical analysis was carried out using SSPS version 21 (IBM, Armonk, USA).

Results

Characteristics of the study population

A total of 647 patients were enrolled by the 43 centres participating in this study. Of these patients, 48 were from Bahrain, 160 from Kuwait, 75 from Oman, 59 from Qatar and 305 from the UAE. Six of these subjects were not considered eligible for the final statistical analysis as they did not satisfy the inclusion/exclusion criteria (age/date of birth not given); in consequence, the eligible population consisted of 641 patients (99%). The characteristics of these patients at inclusion are summarised in table 1.

The mean age of the study population was 41.2 ± 10.9 years and there were almost twice as many men as women (62.4% vs. 37.6%, respectively). Over half of the patients (59.3%) were Asian and 23.7% were Caucasian (data not shown). A total of 141 patients (22%) presented with comorbidities at baseline. The most common comorbidity was diabetes mellitus (14.7%) (Table 1).

	N	Total
Sex, M/F	641	400/241 (62.4%/37.6%)
Age (years)	641	
Mean ± SD		41.2 ± 10.9
[Range]		[19 - 100]
Current smoker	641	164 (25.6%)
Comorbidities	639	
Any comorbidity		141 (22%)
Diabetes mellitus		94 (14.7%)
Chronic heart disease		31 (4.8%)
Infection requiring antimicrobial use in previous 3 months		30 (4.7%)
Chronic lung disease		12 (1.9%)
Alcohol use disorder		4 (0.6%)

Table 1: *Baseline demographic characteristics and comorbidities of the study population.*

The classification of CAP risk was based on the PSI score [21], as recommended in the IDSA/ATS guidelines. All patients were classified as low risk for mortality [21] and 97.6% were in Classes I and II at baseline (Table 2). At baseline, 91.1% of patients had fever (mean temperature 38.4 ± 0.8°C), 77.1% had purulent sputum and 88.9% had a new cough. Chest examination was carried out on 99.7% of the patients, with positive auscultatory findings such as crepitation in 58.3%, and pulse oximetry was performed for 84.7% of patients (mean SpO_2: 95.6 ± 3.1%). Chest radiography was carried out on 531 patients (82.8%) and 457 (71.3% of the total population) had abnormal findings consistent with pneumonia. Forty-four patients (8%) had a normal chest X-ray and 27 had an abnormal X-ray not consistent with pneumonia. Only 4.7% of patients had received antibiotic treatment in the three months prior to the development of CAP (Table 2).

Clinical characteristics	N	Total
Clinical criteria for CAP	639	
New cough		570 (88.9%)
Increased frequency of cough		168 (26.2%)
Purulent sputum		497 (77.1%)
Auscultatory findings		374 (58.3%)
Dyspnoea		301 (47.0%)
Fever		584 (91.1%)
Leucocytosis		286 (44.6%)
Abnormal chest X ray consistent with pneumonia	531	457 (71.3%)
Vital signs		
Blood pressure (mmHg)#	625/624	127.8/81.6 [90 - 190/50 - 108]
Heart rate (bpm)	620	92.1 ± 14.0 [54 - 130]
Respiratory rate (bpm)	575	21.5 ± 4.5 [11 - 32]
Temperature (°C)	619	38.4 ± 0.8 [36 - 40.2]
SpO_2 (%)	543	95.6 ± 3.1 [80 - 100]
CAP risk classification†	634	
I		470 (73.3%)
II		156 (24.3%
III		8 (1.2%)
Microbiological evidence of pneumonia*		
Number of patients sampled		102 (15.9%)
Pathogens not considered normal respiratory flora		26 (25.5%)
Streptococcus pneumoniae		8 (30.8%)
Klebsiella spp		3 (11.5%)
Gram-positive cocci		3 (11.5%)
Haemophilus influenzae		2 (7.7%)
Citrobacter spp		2 (7.7%)

Table 2: *Baseline clinical characteristics of the study population.*

Data are presented as N (%), mean ± standard deviation (SD) and [range].

CAP: Community-Acquired Pneumonia.

**: Listed according to the 2007 IDSA/ATS Consensus Guidelines on the Management of Community-Acquired Pneumonia in Adults.*

*#: Systolic/diastolic; †: Assessed and classified according to the Fine criteria [21]; *: Other pathogens including Candida spp., Enterobacter cloacae, Gram-positive bacilli, Gram-positive bacteria, H. para-influenzae, Mycoplasma, Pseudomonas and S. pneumoniae + influenzae were isolated from one case each.*

Samples for microbiological analysis were taken from 102 patients (15.9%). The majority of samples tested were sputum samples (50%), blood and sputum samples (27.5%) or blood samples only (12.7%). Pathogens not considered as normal respiratory flora were isolated from 26 of the 102 patients (25.5%). The most common pathogens isolated were *Streptococcus pneumoniae* (n = 8; 30.8%), *Klebsiella* spp (n = 3; 11.5%), Gram-positive cocci (n = 3; 11.5%), *Haemophilus influenzae* (n = 2, 7.7%) and *Citrobacter* spp (n = 2; 7.7%) (Table 2).

Empirical antimicrobial therapy

For the analysis of empirical therapy, the population was divided into two groups: patients with comorbidities and those without. The majority of patients were treated with a single antibiotic (n = 547; 85.3%), 66 patients (10.3%) were treated with a combination of two antimicrobial agents, six patients (0.9%) took three antibiotics and one patient (0.15%) was treated with four. There was no significant difference in the number of antimicrobial agents given to CAP patients with or without co-morbidities (data not shown).

Concerning the use of single antimicrobial agents, regardless of the presence or absence of comorbidity, fluoroquinolones (levofloxacin, moxifloxacin or gemifloxacin) were the most frequently prescribed antimicrobial agents (88.2% of patients with comorbidities vs. 91% of patients without comorbidities) followed by macrolides and cephalosporins (Figure 1). There were around 5% of patients in both groups (with or with comorbidities) who received antimicrobial agents via the intravenous (IV) route only. Approximately 8% of patients in the comorbidity group and 3.5% in the other group received IV antibiotics, which were later switched to oral antibiotics of the same class (Figure 1).

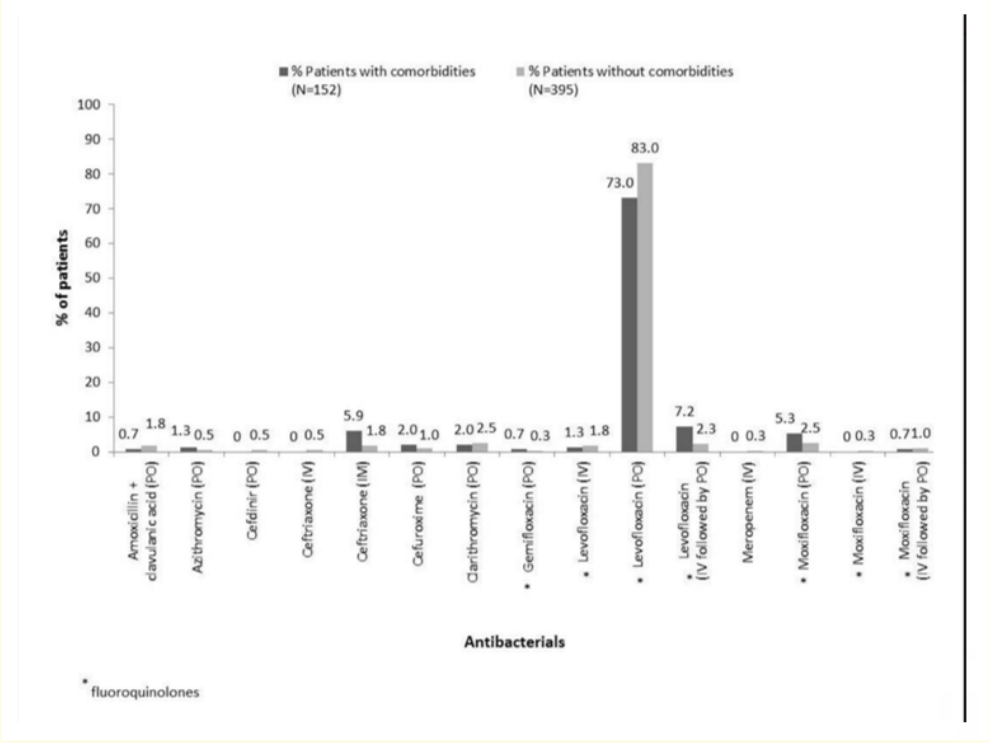

Figure 1: *Antibiotics used as single agents for the treatment of CAP (N = 547).*

The most frequent antibiotic combinations given to patients who received two antibiotics are presented in table 3. Quinolones with cephalosporins were the most frequently used combination followed by quinolones with macrolides. Ceftriaxone with levofloxacin (10.5% of patients with comorbidities vs. 25.5% of patients without) and clarithromycin with levofloxacin (31.6% of patients with comorbidities vs. 14.9% of patients without) were the most frequent individual combinations given to patients in both groups, followed by levofloxacin with amoxicillin-clavulanic acid (10.5% of patients with comorbidities vs. 10.6% of patient without) (Table 3).

	Patients with comorbidities (N = 19)				Patients without comorbidities* (N = 47)			
	Levofloxacin	**Azithromycin**	**Clarithromycin**	**Moxifloxacin**	**Levofloxacin**	**Azithromycin**	**Clarithromycin**	**Moxifloxacin**
Amoxicillin	0		0		4.2%		2.1%	
Amoxicillin/ clavulanic acid	10.5%	5.3%			10.6%	0		
Cefdinir	10.5%	5.3%		0	2.1%	2.1%		2.1%
Cefditoren pivoxil	10.5%		0	0	4.3%		4.3%	2.1%
Cefixime		5.3%				0		
Cefpodoxime			0	5.3%			2.1%	0
Ceftriaxone	10.5%	5.3%			25.5%	2.1%		
Cefuroxime	0		0		8.5%		2.1%	
Levofloxacin		0	31.6%			4.3%	14.9%	
Meropenem	0			0	2.1%			2.1%

Table 3: *Distribution and patterns of combination of two antimicrobial agents in CAP outpatients with or without comorbidities (N = 66).*

**One patient in this group (2.1%) received ceftriaxone + cefdinir.*

In patients with comorbidities, the mean duration of antibiotic use was 2 - 3 days (range: 1 - 5) for IV treatment, 6 days (range: 1 - 9) for IM treatment and 6 - 13 days (range: 2 - 26) for oral treatment compared to 3 - 4 days (range: 1 - 9) for IV treatment, 4 days (range: 1 - 8) for IM treatment and 5-9 days (range: 1 - 20) for oral therapy in patients without comorbidities (data not shown).

Clinical outcome

The short-term health outcomes of CAP treatment were assessed at two follow-up visits. Assessment of the outcome of CAP treatment at the first follow-up visit (7 days) was performed for 598 patients (93.3%). At this time, CAP in 222 (34.6%) patients was classified as resolved, 374 patients (58.4%) had improved and 2 (0.3%) had deteriorated. At this visit, 291 patients (45.4%) were considered to be clinically stable and 156 patients (24.3%) did not fulfil one or more criteria for clinical stability. The second follow-up visit (V3, 30 days) was performed for 108 patients (16.8%). At this visit, 38 (35.2%) patients were classed as resolved and 70 (64.8%) had improved.

Discussion

This multicentre, observational, longitudinal study aimed to compare current treatment practices for Class I, II and III CAP (according to PSI/Fine criteria) [13,21] in adult outpatients in the Gulf region with IDSA/ATS 2007 international consensus guidelines. The principal IDSA/ATS guidelines for the management of CAP in outpatients are summarised in table 4, together with the corresponding current practices identified in Gulf countries in this study.

	IDSA/ITS recommendations	Gulf practices according to the G-Tin CAP II Registry, Wave 5
Make a correct diagnosis of CAP	Diagnosis of CAP is based on select clinical features (e.g. cough, fever, sputum production and pleuritic chest pain).	The study collected data on clinical symptoms including cough, fever, dyspnoea and production of purulent sputum.
	Consider other contributing risk factors for CAP.	Accompanying comorbidities including diabetes mellitus, chronic heart disease, chronic lung disease, malignancy, immunosuppression, use of antimicrobial agents within the previous 3 months and smoking history were included in the baseline medical history.
Confirm the diagnosis	A demonstrable infiltrate by chest radiography or other imaging technique, with or without supporting microbiological data, is required for the diagnosis of pneumonia. (*Moderate recommendation - level III evidence*).	Chest radiography was carried out for 531 (82.8%) of the eligible population at baseline. Chest infiltrates were observed in 457 patients (71.3%). Chest auscultation was carried out on 99.7% of patients to detect clinical findings such as crepitation.
	All patients should be screened by pulse oximetry.	Pulse oximetry was performed in 543 (84.7%) patients. Mean SpO_2 was 95.6 ± 3.1%.
Identify risk in patients with CAP	Severity of illness scores should be used to identify patients with CAP who may be candidates for outpatient treatment. (*Strong recommendation - level 1 evidence*). These scores should be supplemented with physician determination of subjective factors, including the ability of the patient to safely and reliably take oral medication and the availability of outpatient support resources. (*Strong recommendation - level II evidence*).	The classification of CAP risk was based on Fine criteria [21]. CAP risk was defined for 634 (98.9%) of the eligible population. All patients were classified as low risk for mortality (97.6% of patients were in classes I and II) and were suitable candidates for outpatient treatment.
Identify aetiological agent responsible for CAP	The most common aetiological agents in outpatients are *Streptococcus pneumoniae, Mycoplasma pneumoniae, Haemophilus influenza* and *Chlamydophila pneumoniae.* Patients with CAP should be investigated for specific pathogens that would significantly alter standard (empirical) management decisions, when the presence of such pathogens is suspected on the basis of clinical and epidemiological clues. (*Strong recommendation - level II evidence).* Routine diagnostic tests to identify an aetiological diagnosis are optional for outpatients with CAP. (*Moderate recommendation - level III evidence).*	Only 102 patients (15.9%) underwent pathogen isolation. The majority of samples tested (50%) were sputum samples. The most common pathogens isolated from 26/102 (25.5%) patients were *Streptococcus pneumoniae* (30.8%), *Klebsiella* (11.5%) and Gram-positive cocci (11.5%).

Recommended empirical antibiotics for outpatient treatment of CAP	The following antibiotic regimens are recommended in outpatients on the basis clinical risk: **Previously healthy and no risk factors for DRSP infection**: (i) A macrolide (azithromycin, clarithromycin, or erythromycin). (*Strong recommendation - level I evidence*). (ii) Doxycycline (*Weak recommendation - level III evidence*). **Presence of comorbidities, or use of antimicrobials within 3 months (in which case use an alternative from a different class), or other risks for DRSP infection:** (i) A respiratory fluoroquinolone (moxifloxacin, gemifloxacin or levofloxacin). (*Strong recommendation - level I evidence*). (ii) A β-lactam **plus** a macrolide (*Strong recommendation - level I evidence*). (High-dose amoxicillin [e.g., 1 g, 3 x daily] or amoxicillin-clavulanate [2 g, 2 x daily] is preferred; alternatives include ceftriaxone, cefpodoxime, and cefuroxime [500 mg, 2 x daily]; doxycycline [*level II evidence*] is an alternative to the macrolide). The use of alternative agents should be considered in regions with a high rate of macrolide-resistant *S. pneumoniae*. (*Moderate recommendation - level III evidence*).	In all participants, empirical antimicrobial therapy was initiated immediately on the day of inclusion without waiting for laboratory results. Regardless of the presence or absence of comorbidity, respiratory fluoroquinolones (moxifloxacin, gemifloxacin, or levofloxacin) were the most frequently prescribed antimicrobial agents followed by cephalosporins and macrolides. The most frequent antibiotic combinations were fluoroquinolones + cephalosporins followed by fluoroquinolones + macrolides. Ceftriaxone + levofloxacin and clarithromycin + levofloxacin were the most frequent combinations given to patients in both groups, followed by levofloxacin + amoxicillin/clavulanic acid.
Route of administration of antimicrobial therapy	Patients should be switched from IV to oral therapy when they are hemodynamically stable and improving clinically, are able to ingest medications and have a normally functioning gastrointestinal tract. (*Strong recommendation - level II evidence*).	The majority of patients received antibiotics via the oral route. Around 5% of patients in both groups received antimicrobial agents via the IV route which were later switched to oral antibiotics of the same class.
Treatment duration	Patients with CAP should be treated for a minimum of 5 days (*level I evidence*), should be afebrile for 48-72 h and should have no more than one CAP-associated sign of clinical instability before discontinuation of therapy. (*Moderate recommendation - level II evidence*). Treatment for *S. pneumoniae* should generally continue for 7-14 days or until the patient is afebrile for 72h.	Mean treatment duration was 2-3 days for IV treatment, 6 days for IM treatment and 6-13 days for oral treatment in patients with comorbidities and 3-4 days for IV treatment, 4 days for IM treatment and 5-9 days for oral therapy in patients without comorbidities.

Table 4: *IDSA/ATS guidelines for outpatient treatment of CAP and corresponding current practices in the Gulf region documented by wave 5 of the G-Tin CAP II registry.*

CAP: Community-Acquired Pneumonia; DRSP: Drug-Resistant S. pneumoniae; IV: Intravenous; IM: Intramuscular.

According to the guidelines, the first step should be the correct diagnosis of CAP through a baseline clinical assessment including symptoms such as cough, fever, sputum production, pleuritic chest pain and auscultatory findings such as crackles or bronchial breath sounds. Clinical data were available for 639 (99.7%) of our patients. New cough was found in 88.9% of cases, pyrexia in 91.1%, purulent sputum in 77.1% and auscultatory findings in 58.3%.

The IDSA/ATS guidelines also suggest that the clinical diagnosis of pneumonia should be confirmed by chest radiography or another imaging technique to differentiate CAP from other common causes of cough and fever, such as acute bronchitis, and by pulse oximetry to detect hypoxemia. Despite this recommendation pulse oximetry was only performed in 543 (84.7%) patients (mean SpO_2: 95.6 ± 3.1%) and the diagnosis of CAP was only confirmed by chest X-ray in 457 (71.3%) patients at baseline. Twenty-seven (4.2%) patients had abnormal chest X-ray findings which were not compatible with pneumonia, 44 (6.9%) had a normal chest X-ray and 110 patients did not have chest imaging performed at all. Thus, 184 (28.7%) of the patients treated for CAP in this study (including three with missing data) did not have radiological confirmation of pneumonia.

According to the guidelines, the next step before initiating treatment is the classification of CAP risk based on Fine criteria. This was defined for 634 (98.9%) of our patients and all patients were classified in Fine classes I, II or III (low risk of mortality) and were therefore eligible for outpatient treatment.

Routine diagnostic tests to identify the aetiological agent responsible for CAP are optional in outpatients (Moderate recommendation - level III evidence). In this study, the number of specimens taken for microbiological examination was small (n = 102), with sputum the most common specimen tested (50% of specimens). No information about Gram staining was collected. In line with current epidemiological data for CAP, the most frequent pathogen isolated was *S. pneumoniae* (1.2% of patients overall).

According to the IDSA/ATS guidelines, the choice of initial CAP treatment will depend on the presence or absence of comorbidities. In our population, diabetes was the most common comorbidity (14%) followed by chronic heart disease (4.8%). One-quarter (25.6%) of the subjects were current smokers and 15% were former smokers. Smoking leads to immune impairment and is considered to be a risk factor for CAP as it decreases resistance to respiratory pathogens [22-24]. The enrolment of a higher proportion of males compared to females in this registry (62.4% vs. 37.6%) could be related to the harmful effects of exposure to tobacco smoke on the respiratory tract, since 85% of current or former smokers were male. A higher prevalence of CAP among men than women has been reported previously [6,7] and may be due in part to a greater lifetime exposure to cigarette smoke.

Overall, there were no major differences in prescription patterns between patients with or without comorbidities. The most frequent empiric antibiotics initiated on the day of inclusion were fluoroquinolones, which were given as monotherapy to 88.2% of patients with comorbidities and to 91% of patients without comorbidities. In patients with comorbidities this prescription is consistent with IDSA/ATS guidelines, which recommend first-line therapy with either a respiratory fluoroquinolone (moxifloxacin, gemifloxacin or levofloxacin) (Strong recommendation - level I evidence) or a β-lactam plus a macrolide (Strong recommendation - level I evidence), but in patients without comorbidities either a macrolide (Strong recommendation - level 1 evidence) or doxycycline (Weak recommendation - level II evidence) are recommended as first-line therapy. In our patients without comorbidities, macrolides were rarely prescribed and no prescription of doxycycline was recorded at all. The use of fluoroquinolones is not recommended in CAP outpatients without comorbidities and there are concerns that the widespread use of these antibiotics may lead to the development of fluoroquinolone resistance [13].

The most frequent antibiotic combinations used were fluoroquinolones with cephalosporins followed by fluoroquinolones with macrolides. Ceftriaxone with levofloxacin and clarithromycin with levofloxacin were the most frequent individual combinations given to patients in both groups. The reasons why the physicians chose to give the combination of levofloxacin with clarithromycin, which is not a recommended regime, are unknown, but this combination was given to 31.6% of patients with comorbidities and to 14.9% of those without.

In this study, the route of antibiotic administration was generally consistent with IDSA/ATS guidelines for outpatients. The majority of patients received oral monotherapy (81%) or IV monotherapy which was subsequently switched to oral treatment (3%). However, the duration of treatment was slightly longer than that recommended in the guidelines. The mean duration of treatment was 6 - 13 days for oral treatment in patients with comorbidities and 5 - 9 days for oral therapy in patients without comorbidities. This is compatible with the guidelines of 7 - 14 days for *S. pneumoniae* infection but longer than the recommended minimum of 5 days for infections due to other microorganisms and is possible due to the fact that the clinicians were treating blindly and did not know the infecting microorganism in the majority of the patients.

Our study has several strengths and limitations. The registry is broad and included a large number of patients (n = 641) with and without comorbidities who fulfilled the Fine criteria for outpatient treatment. One limitation of the study is that nearly one-third of the patients did not have radiographic confirmation of CAP and should perhaps not have been included in the study. However, this was an observational study and the aims were to follow patients in real-life practice. A second limitation is the fact that the registry was industry-sponsored (Sanofi) and this might have introduced some bias in the choice of empirical treatment for CAP patients. The widespread use of fluoroquinolones may also have been due to the fact that the study was performed in private clinics which are more likely to prescribe more expensive treatments. Thirdly, although data were included from five Gulf countries, the majority of the study population came from the UAE (47.1%; n = 305) or Kuwait (24.7%; n = 160), which may have introduced some bias. As explained in our previous report on the treatment of CAP in hospitalised patients in the Gulf region [18], the number of patients included in the registry reflects the population of each country, with the UAE having the highest population (8 million) in 2010. Over representation of the UAE may also have be due to the larger number of hospitals *per capita* in this country than in the other Gulf countries. Finally, it should be noted that our study did not include Saudi Arabia, which is the largest country of the Gulf region. Thus, our results cannot be generalised to the whole of the Gulf region.

The 2007 IDSA/ATS guidelines are the most widely implemented guidelines for pneumonia in the world and are one of the recommended standards of care in the Gulf region. Although regional guidelines for the treatment of CAP in the Gulf region have been published [8], a previous study in Oman showed that adherence to these guidelines was poor [9]. A previous report evaluating compliance with the IDSA/ATS guidelines in elderly patients (≥ 65-years) in Italy suggested that only 47% of patients with CAP received initial empirical antibiotics that complied with recommendations [25]. In the CAPO International Cohort Study database, which included 43 centres in 12 countries including North America, South America, Europe, Africa and Southeast Asia, only 59% of elderly patients with CAP were given antimicrobial regimens that conformed with IDSA/ATS recommendations [26].

Our study identifies the main two areas in which current practices for outpatient management of CAP in the Gulf region fall short of international guidelines, namely the lack of use of imaging techniques and pulse oximetry in all patients to confirm the diagnosis of CAP and the high level of use of fluoroquinolones as first-line therapy in patients without comorbidities.

Conclusion

This prospective observational study provides a valuable overview of current treatment practices for CAP in outpatients in the Gulf region. Our results highlight the overreliance on fluoroquinolones in this region and the limited use of macrolides. In an era of increasing antibiotic resistance, it is important to improve adherence to international guidelines in order to enhance treatment outcomes of outpatients with CAP and to limit the development of fluoroquinolone resistance hence we should try to use antibiotics more judiciously based on the patient's comorbidities issues and the severity of community-acquired pneumonia.

Declarations

Ethics Approval and Consent to Participate

This study was performed in compliance with the Guidelines for Good Epidemiology Practice and the principles laid down in the Declaration of Helsinki (1964) including all subsequent amendments, and with national laws and regulations of the countries in which the

registry was performed. The study was approved by the institutional review boards of each country according to local regulations, including patient data retention and confidentiality. Written informed consent was obtained from all eligible patients.

Consent for Publication

All authors declare and give consent for publication

Availability of Data and Material

The datasets collected and analysed during the current study are available from the corresponding author on reasonable request.

Conflicts of Interests

BM declares grant support from AstraZeneca and Novartis, has received consultancy fees from GSK, AstraZeneca, MSD and Novartis and honoraria from Sanofi for his contribution to the present study. MSN declares grant support from Merck and Bayer and has received consultancy fees from Merck, Bayer, Pfizer and Cempra. AA, MV, TQ and LD have declared no conflict of interests. REB is an employee of Sanofi.

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Author's Contributions

All authors developed the hypotheses and conceived the analysis plan. All authors contributed to the analysis and interpretation of the study results. All authors participated in the revision of the manuscript and agree to be accountable for all aspects of the work. All authors read and approved the final manuscript. The corresponding author (MV) had final responsibility for the decision to submit the manuscript for publication.

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