

GP management of community-acquired pneumonia in Italy: the ISOCAP study

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ABSTRACT: *GP management of community-acquired pneumonia in Italy: the ISOCAP study. C.M. Sanguinetti, F. De Benedetto, C.F. Donner, and the ISOCAP Study Group.*

Background. Community-Acquired Pneumonia (CAP) is still a significant problem in terms of incidence, mortality rate, particularly in infants and the elderly, and socioeconomic burden. General Practitioners (GPs) are the first reference for patients with this disease, but there are few published studies regarding the outpatient treatment of CAP.

Methods. The ISOCAP study aimed to identify the type and outcome of the diagnostic-therapeutic management of CAP by GPs in Italy, within the framework of developing a closer interrelationship between GPs and pulmonary specialists. Thirty-six Pulmonary Divisions throughout Italy each contacted 5 local GPs who agreed to recruit the first 5 consecutive patients who consulted them for suspected CAP within the study's 1-year observation period.

Results. A total of 183 GPs took part in the study and enrolled, by the end of the observation period, 763 CAP patients; of these, complete data was available for 737 pa-

tients [males=373, females=364, mean age (\pm SD) 58.8 \pm 19.6 years]. 64.4% of patients had concomitant diseases, mainly systemic arterial hypertension and COPD. Diagnosis of CAP was based by GPs on physical examination only in 41.6% of cases; in the remaining chest X-ray was also performed. In only 4.6% of patients were samples sent for microbiological analysis. All patients were treated with antibiotics: 76.7% in mono-therapy, 23.3% with a combination of antibiotics. The antibiotic class most prevalently used in mono-therapy was cephalosporin, primarily ceftriaxone; the most frequently used combinations were cephalosporin+macrolide and cephalosporin+quinolone. Mono-therapy was effective in 70% of cases, the combination of two or more antibiotics in 91.2% of patients. Overall treatment efficacy was 94.7%; hospitalisation was required in 8.5% of cases.

Conclusions. Outpatient management of CAP by GPs in Italy is effective, hospitalisation being necessary only in the most severe cases due to age, co-morbidities or extent of pneumonia. This signifies a very significant savings in national health costs.

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Introduction

General practitioners (GPs) are patients' first point of reference and in the front-line concerning the management of lower respiratory tract infections (LRTIs). Among LRTIs, community-acquired pneumonia (CAP) holds a very significant position; in USA it is responsible for 4 million new cases each year [1] and constitutes the sixth most common cause of death [2]. Up to 15% of patients require hospital admission because of severity of CAP and/or presence of risk factors, with annual global costs as high as four billion dollars [3]. The mortality of hospitalised patients reaches 13.6% and increases to 36.5% in those who need management in the intensive care unit [4].

Most subjects affected with pneumonia, especially those without risk factors, are treated at home, but not many studies concerning the diagnostic and therapeutic approach to CAP in the outpatient setting have been published [5-9].

The Italian Study in Outpatients affected with Community Acquired Pneumonia (ISOCAP) was undertaken to verify and extend the little available data on GP behaviour in Italy regarding CAP, in order to enhance GPs' professional competence and to promote closer interrelationships between GPs and pulmonary specialists.

The aim of the present study was to evaluate the diagnostic workup that Italian GPs adopt in patients affected with CAP, and the efficacy and tolerability of the antibiotic therapy they prescribe in such patients.

Methods

Study design

This observational trial was carried out between 1 January 1999 and 15 May 2001. 36 Divisions of Pulmonary Disease distributed throughout Italy, following the approval of their local Ethical Committee, each selected 5 GPs who agreed in

turn to recruit 5 consecutive patients who consulted them for suspected CAP. The Pulmonary Divisions acted also as a reference for the GPs. Thus 180 GPs and some 800 CAP patients were expected to be enrolled for the study.

Upon completion of the survey, 183 GPs participated in the study, and 763 cases of CAP were collected, 737 of which were valid for analysis (92.1% of the expected) in that they fulfilled inclusion/exclusion criteria and data were complete.

Questionnaire for the GPs

GPs participating in the study had to fill in a questionnaire aimed at defining the personal characteristics of each GP. The questionnaire included the age of the GP, how long he had been practising as a physician in the national health system, the number of patients he had under his care, the site (urban or rural) of work.

The GPs were also given a form to record each patient's data concerning private and clinical data, including comorbidities diagnostic examinations, the reasons for outpatient treatment of CAP in that patient, therapeutical prescriptions, length of treatment, and outcome.

Mean age (+SD) of GPs was 47 ± 4.7 years, and they had been practising general medicine for 16 ± 6.8 years on average. The total number of patients referring to the 183 GPs was 233,316, with a mean number of 1,363 patients per GP. The mean number of patients older than 65 years was 342 (*i.e.* 24.8% of the total patient population of the study). The majority of GPs (88.4%) worked close to the hospital (within a distance of 10 km). The GP decided to treat a patient with suspected CAP at home or not on the basis of feasibility of domiciliary treatment in each case.

Definition of outcome variables

Remission ('success') was defined as the disappearance of clinical symptoms at physical examination with or without negativisation of the radiological picture.

In the case of non resolution with the initial empirical antibiotic treatment, the options were recourse to other antibiotic treatment or hospitalisation in the case of ineffective treatment or the need for further diagnostic investigation.

Inclusion/exclusion criteria

For inclusion in the study patients, of either sex, had to be 18 years or older and to present signs of CAP as defined by fever, localised rales and/or signs of consolidation at physical examination, according to international guidelines for CAP [2, 10]. Patients were excluded if they had been admitted to hospital in the two weeks preceding diagnosis of CAP, or were affected with an immunodepressive condition.

Statistical Analysis

As this was an observational trial statistical analyses were of a descriptive type: frequencies

and rates for discrete variables; mean, median, standard deviations and ranges for continuous variables.

Analysis was first performed on the sample as a whole, then separately for patients who underwent vs. did not undergo chest X-ray: this subdivision allowed us to check whether X-ray modified in some way the GPs' management of CAP.

Analyses evaluating the impact of several risk factors were also performed.

Results

Patient characteristics

The results presented here refer to all evaluable patients ($n=737$) irrespective of whether they had radiological or only clinical diagnosis of CAP. Comparison of the two subgroups of patients (with and without chest X-ray) did not evidence any difference in terms of either risk factors or diagnostic-therapeutic management.

There were 373 males and 364 females, mean (+SD) age 58.8 ± 19.6 years. Current smokers were 26.6%. 84.7% of patients did not consume alcoholic beverages, and 8.8% were exposed to an occupational risk (table 1).

The majority of patients (64.4%) reported concomitant chronic diseases, among which systemic arterial hypertension and chronic obstructive pulmonary disease (COPD) were prevalent. About half (52%) of the patients with co-morbidities presented more than one concurrent illness (table 2).

Table 1. - Characteristics of study patients ($n=737$) with CAP

	Number of patients	%
SEX		
Males	374	50.7
Females	363	49.3
AGE (years)		
Mean	58.8	
Median	62.0	
Minimum	18.0	
Maximum	104.0	
SMOKING HABIT		
Active smokers	196	26.6
Ex smokers (since at least 6 months)	111	15.1
Non smokers	410	55.7
No data available	20	2.6
ALCOHOL CONSUMPTION		
No	624	84.7
Yes	113	15.3
OCCUPATIONAL RISK		
No	672	91.2
Yes	65	8.8

Table 2. - Co-morbidities in CAP study patients (n=737)

	Number of patients	%
PRESENCE OF CO-MORBIDITIES		
Yes	475	64.5
No	262	35.5
NUMBER OF CO-MORBIDITIES PER PATIENT		
One	229	48.2
Two	144	30.3
Three	66	13.8
Four	28	6.0
Five	5	1.0
Six	3	0.6
TYPE OF CO-MORBIDITY *		
Systemic arterial hypertension	245	32.8
COPD	166	22.2
Diabetes	92	12.3
Ischemic heart disease	81	10.8
Vascular disease	61	8.1
Congestive heart failure	55	7.3
Liver complaint	22	2.9
Kidney failure	9	1.2

* Presence of more than one co-morbidity in each patient.

Table 3. - Findings at physical examination, with or without associated chest X-ray, on which the GP based diagnosis of CAP

Findings at physical examination	N° patients	%
Localised rales + chest X-ray	287	38.9
Localised rales	229	31.1
Chest X-ray	57	7.7
Localised rales + signs of consolidation in lung + chest X-ray	57	7.7
Localised rales + signs of consolidation in lung	53	7.2
Signs of consolidation in lung	18	2.4
Signs of consolidation in lung + chest X-ray	30	4.1
Not specified	6	0.8
TOTAL	737	100

Basal diagnostic procedures

The diagnosis of CAP was based by the GP only on clinical signs at the physical examination in 41.6% of cases and the prevalent finding was presence of localized rales, alone (31.1%) or associated with signs of consolidation (7.2%) (table 3). Chest x-ray was requested by GPs to confirm the clinical diagnosis of CAP in 431/737 cases (58.4%), but the diagnostic modality (chest radiography or not) does not seem to have influenced the outcome (table 4).

In only 4.6% of patients was an etiological diagnosis of CAP attempted by sending a sputum test or blood sample to a laboratory for microbiological analysis (table 5).

It is probable that the lack of availability of a reliable microbiological laboratory within close proximity often discourages the physician in this regard. In any case, international guidelines (ATS, BTS, EORTC) [10-12] do not recommend the use of microbiological examinations in outpatient management.

Total diagnostic procedures

Diagnostic procedures (blood and serological analyses and X-ray) were prescribed by GPs on average 1.65 times per patient: in particular 1.45 for blood gases analysis, 1.41 for serology and 1.75 for X-rays.

Antibiotic Therapy

All patients with CAP were treated with antibiotic therapy, 565 (76.7%) with one antimicrobial drug only, 172 (23.3%) with a combination of different antibiotics.

A) TREATMENT WITH ONE ANTIBIOTIC ONLY

The prevalent class of drugs used was cephalosporin, accounting for 42.4% of prescriptions, followed by quinolones (24.6%), macrolides (17.8%), penicillins (14.3%) and others (0.7%) (table 6). Cephalosporins, mainly ceftriaxone, prescribed in about 22% of all patients, were the preferred choice particularly for elderly patients (>65 years) and those with co-morbidities (table 7).

The preferred mode of administration for patients ≤65 years without co-morbidities was oral,

Table 4. - Outcome of CAP in relation to performance or not of chest X-ray

Chest X-ray	Whole sample		OUTCOME			
	No.	%	Success		Failure	
			No.	%	No.	%
NO	306	41.6	225	73.5	81	26.4
YES	431	58.4	328	76.1	103	23.8
TOTAL	737	100	553	75.0	184	25.0

Table 5. - Microbiological analyses requested by GPs for the etiological diagnosis of CAP

	N°	%
Patients in whom a microbiological analysis was requested	34/737	4.6
<i>Type of tests requested*</i>		
Haemoculture	1	2.4
Sputum test	18	43.9
Serology	22	53.7
TOTAL	41	100

* More than one test requested in individual patients.

Table 6. - Antibiotics prescribed in mono-therapy in 565 cases of CAP treated in the community

Antibiotic class	N° patients	%
Cephalosporin	240	42.4
Quinolone	139	24.6
Macrolide	101	17.8
Penicillin	81	14.3
Other	4	0.7
TOTAL	565	100

whereas patients >65 years and with co-morbidities were mostly treated parenterally: physicians chose the parenteral administration of the antibiotic when the severity of the pneumonia required a rapid concentration of the antibiotic at the infection's site to obtain better therapeutical results.

The median treatment duration was 10 days, decreasing to 8 days when an intravenous drug was used (table 8).

Mono-therapy showed a 70% efficacy; the rate of hospitalisation was 9.2%, rising to 14.3% in patients >65 years of age and with co-morbidities; one only death occurred in the study population during the period of observation. In 6% of cases a further drug was added, this being a quinolone, macrolide or cephalosporin. The initial antibiotic was substituted on account of ineffectiveness in 6.4% of cases.

The efficacy in the at-risk subgroup of patients (>65 years and with co-morbidities) was 65.7%, which reached 73.6% with ceftriaxone (table 9).

B) TREATMENT WITH TWO OR MORE ANTIBIOTICS

A combination of antibiotics was used from the outset in about one-fourth of patients (23.3%); in half of these this consisted of a cephalosporin plus macrolide for 10 days. The other combination largely used was that of a cephalosporin plus quinolone. Globally combination therapy achieved

Table 7. - Top 10 antibiotics most frequently utilised as mono-therapy in community-treated CAP and type of patient (n=565)

DRUG	AGE CLASS									
	TOTAL		≤ 65 yrs				> 65 yrs			
			Comorbidity		Comorbidity		Comorbidity		Comorbidity	
	N°	%	NO	YES	NO	YES	NO	YES	NO	YES
Ceftriaxone	104	21.8	24	23.0	20	19.2	7	6.7	53	50.9
Clarithromycin	89	18.6	49	55.0	21	23.5	2	2.2	17	19.1
Levofloxacin	71	14.8	23	32.3	16	22.5	4	5.6	28	39.4
Amoxi/clavul	46	9.6	19	41.3	13	28.2	–	–	14	30.4
Ciprofloxacin	37	7.7	9	24.3	11	29.7	2	5.4	15	40.5
Cefonicid	34	7.1	6	17.6	6	17.6	–	–	22	64.7
Ceftazidime	29	6.0	6	20.6	5	17.2	1	3.4	17	58.6
Moxifloxacin	27	5.6	5	18.5	13	48.1	–	–	9	33.3
Cefodizime	22	4.6	2	9.0	4	18.1	1	4.5	15	68.1
Cefotaxime	18	3.7	4	22.2	7	38.8	–	–	7	38.8

Table 8. - Length of treatment (days) of antibiotic mono-therapy for CAP in relation to the type of drug used

	TOTAL	Ceftriaxone	Clarithromycin	Levofloxacin
MEAN	9.09	8.59	10.26	9.96
MEDIAN	10.00	8.00	10.00	10.00
s.d.	3.23	3.20	3.49	3.79
MIN	1.00	1.00	3.00	1.00
MAX	25	25	21	23

Table 9. - Results of community-treatment of CAP with antibiotic mono-therapy

TOTAL		Remission		Other form of therapy		Hospitalisation		Death	
N	%	N	%	N	%	N	%	N	%
<i>Whole sample</i>									
565	100	396	70.0	116	20.5	52	9.2	1	0.1
<i>Patients >65 yrs and with co-morbidities</i>									
181	32.0	119	65.7	35	19.3	26	14.3	1	0.5

Table 10. - Efficacy of combination antibiotic therapy in outpatient management of CAP (n° cases=172)

Combination of antibiotics	Remission		Other form of therapy		Hospitalisation		TOTAL N.
	N.	%	N.	%	N.	%	
Cephalosporin + Macrolide	84	95.4	2	2.3	2	2.3	88
Cephalosporin + Quinolone	34	87.1	4	10.2	1	2.5	39
Other combinations	39	86.7	4	8.9	2	4.4	45
TOTAL	157	91.3	10	5.8	5	2.9	172

Table 11. - Length of treatment (days) of CAP in relation to type of combination of antibiotics (n° patients=172)

	TOTAL	Cephalosporin+ Macrolide	Cephalosporin+ Quinolone
MEAN	10.28	10.30	10.52
MEDIAN	10.00	10.00	10.00
s.d.	3.00	2.59	2.84
MIN	3.00	6.00	6.00
MAX	20	18	20

an efficacy of 91.2%; that of cephalosporin plus macrolide had a 95.4% efficacy (table 10). The mean duration of combination therapy was 10.28 days (table 11).

Global effectiveness

The global effectiveness of the therapeutic approach, including the adding of another drug or substitution of the first one, was 94.7% with a rate of hospitalisation of 8.5%, due in most cases to a worsening of the clinical picture.

Tolerability

The drugs used in this trial did not cause any adverse drug reaction in 95.7% of patients. No serious adverse event occurred and in only 5/32 patients was there a need to substitute therapy. Pain at the Achilles tendon was reported by one patient treated with a quinolone.

Duration of disease

The mean duration of the infective episode was 15 days.

Discussion

In Italy CAP accounts for 1.35% of global death causes and over 21% of the respiratory ones, with a mortality rate of 13 per hundred thousand inhabitants, that increases to about 200 in the elderly [13]. However, few studies have dealt with the outpatient management of CAP by GPs and the most recent published European data [5] on the diagnostic-therapeutic management of CAP, including Italian data, refer to the year 1996.

A European study (ESOCAP) on GPs' behaviour regarding the decision to hospitalise patients with CAP [6] already showed that this decision was mainly based on clinical signs indicating severe CAP. Furthermore, important diversities of behaviour among the different European countries emerged. The same was eventually confirmed in the study carried out by Huchon *et al.* [5], which showed a uniform rate of recourse to complementary investigations and hospitalisation, 17% and 19% respectively, on the part of GPs in the case of suspicion of CAP, but not the same homogeneity concerning antibiotic prescription. In fact, Italian GPs almost always prescribe antibiotics (97%) but British (84%) and German (77%) GPs do so much less frequently. Even more striking was the difference found between countries concerning recourse to the intravenous mode of antibiotic administration in CAP: 71% in Italy compared to 0-17% in other European countries [5].

Similar inter-country differences emerged regarding frequency of chest X-ray, sputum tests and other diagnostic tools in the suspicion of CAP [7].

These differences may be significant because CAP accounts for a consistent proportion of health costs, especially in terms of rate of hospital referral and inappropriate antimicrobial therapy even in the presence of simple upper respiratory tract infections [14], which can only have the effect of enhancing bacterial resistance to antibiotics.

The ISOCAP trial, in terms of the number of participating GPs (n=183) distributed throughout the whole national territory and the large patient sample size (n=737), represents a significant data font. A further positive aspect of this study is its attempt to improve the collaboration between the hospital centres (pulmonary specialists) and GPs for the purposes of a shared management of CAP both in the outpatient setting and, where necessary, in hospital.

The sample studied was recruited by GPs in their daily professional practice and is thus adequately representative of the general population, not subject to the limit of a pre-selection such as when data is collected in hospital inpatients who, by virtue of being hospitalised, are not completely representative of the general population but constitute a group of subjects characterised by more severe disease.

However, even in the general population studied here we found a high incidence of chronic diseases such as COPD and systemic arterial hypertension, sometimes mutually coexisting and also combined with other medical conditions in more than one patient affected by pneumonia. Besides testifying to their wide diffusion in the context of the Italian population, these co-morbidities represent, as demonstrated in many studies [11, 12, 15-17], a high risk factor in terms of mortality, particularly if associated with old age; in this case the occurrence of pneumonia thus constitutes the pathological expression of a worse prognosis which it is often advisable to treat in hospital.

Even if from the present study it emerged that almost 60% of GPs used x-ray to confirm diagnosis in suspected pneumonia, the fact remains of the potential difficulty of access to radiology units. In fact, in more than 40% of cases GPs based the diagnosis, at least in the first instance, only on symptoms reported by the patient and on significant signs at the physical examination. An improved collaboration between GPs and hospital-based and local health services will certainly facilitate the performance of routine X-rays also in outpatients. Chest X-ray is important not only to confirm diagnosis but also to delineate the extent and morphologic features of the pneumonia; it can indicate, together with the patient's characteristics, the probability of a given etiology, and it can also enable a prognostic evaluation, since the impairment of more lobes of the same lung and/or the bilateral nature of the infection represent important factors of severity of CAP.

It appears even more difficult to probe in non-hospitalised patients the etiology of CAP through microbiological and blood examinations. In fact in this study only 4.6% of GPs requested diagnostic investigations of this type. However, aside from the difficulty in the outpatient setting of collecting and delivering to the laboratory reliable samples of bronchial or blood secretions for microbiological and blood analyses, the physician who has in front of him a patient, whether at home or in his surgery, affected by CAP must intervene rapidly with an effective antibiotic therapy and cannot wait for at least 3 days or more for the laboratory to respond to the microbiological question. This, over and above the fact that in more than half of cases no pathogen is isolated at all,

not even in the most highly specialised laboratories, signifies that therapy must of necessity be empirical. Hence it is very important to evaluate carefully the conditions of the patient and have at least a minimum knowledge of the local epidemiology and of the panorama of resistances of the various infective agents to antibiotics, as is recommended in the guidelines for pneumonia [10-12], in order to be able to prescribe a useful anti-infective treatment.

According to findings from the ISOCAP study, in three-quarters of cases the antibiotic is administered as mono-therapy and cephalosporins, especially 3rd generation, are the most commonly used. In fact GPs place wide trust in this class of drug, well known for its efficacy and tolerability, and which in many cases avoids the need for hospitalisation. In the present survey the analysis of the antibiotics most frequently used in mono-therapy for the treatment of CAP shows that ceftriaxone is the most used in outpatients affected by CAP in Italy, followed by clarithromycin, levofloxacin, amoxiclav, and other cephalosporins. More than half of the cases in which cephalosporins were used, however, were situations of greater severity, i.e. advanced age and presence of co-morbidities.

Parenteral administration of antibiotics at home has attracted much interest in the last few years, especially in anglo-saxon health systems where, in the past, such practice never existed outside of the hospital setting. This has led to the setting up of services for the administration at home or in outpatient clinics of such therapy, known as Outpatient Parenteral Antibiotic Therapy (OPAT). The costs due to hospitalisation can thus be avoided and at the same time the quality of life of the patient is improved, in particular in the case of infants or the elderly, who can remain in their own family environment and avoid the stress to which they would be inevitably subject in the case of hospitalisation [18]. Parenteral administration in the outpatient setting has been usual practice for many years in our country and is satisfactorily carried out by GPs and by the patients themselves, who often expressly request such a mode of treatment to enhance rapidly the good outcome of the disease. We can only speculate whether the Italian practice of treating CAP outpatients with parenteral administration of cephalosporins or protected penicillins could somehow have addressed the favourable outcome of many infections, including pneumonia, and possibly contributed to the low incidence of high-level resistance of *S.pneumoniae* to penicillin, that are features characterising our country in comparison to others [19].

In conclusion, from an overall look at the ISOCAP data it may be affirmed that Italian GPs are correctly managing CAP: the effectiveness of their therapeutic approach in the overwhelming majority of patients (94.7% global efficacy) and the diagnostic-therapeutic workup adopted (which represent a translation of international guideline recommendations into the local context) are reflected without doubt in savings in health and social services costs, especially in relation to the low percentage of patients who need to be admitted to hospital, which is the most heavy burden from all points of view.

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