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Can CAP Guideline Adherence Improve Patient Outcome in Internal Medicine Departments?

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CAP guidelines and outcome

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Abstract

We evaluated the impact of compliance with Italian Guidelines on the outcome of hospitalised community-acquired pneumonia (CAP) in Internal Medicine departments. All Fine class IV or V CAP patients were included in this multicentre, interventional, before-after study composed of three phases: 1) a retrospective phase (RP) (1443 patients); 2) Guideline implementation; 3) a prospective phase (PP) (1404 patients).

Antibiotic prescribing according to guidelines significantly increased in the PP ($p<0.01$).

The risk of failure at the end of the first line of therapy was significantly lower in the PP versus the RP ($p=0.049$; OR, 95%CI: 0.83, 0.69-1.00), particularly in Fine class V patients ($p=0.036$;OR,95%CI:0.71,0.51-0.98).

Analysis of outcome in the overall population (2847 patients) showed a statistically significant advantage for compliant vs. non-compliant therapies in terms of failure rate ($p=0.004$;OR, 95%CI:0.74,0.60-0.90) and an advantage in terms of mortality ($p=0.082$;OR,95%CI:0.77,0.58-1.04).

Antipneumococcal cephalosporin monotherapy was associated with a low success rate (68.6%) and the highest mortality (16.2%); levofloxacin alone and combination of cephalosporin and macrolide resulted in higher success rates (79.1% and 76.7%, respectively) and in a significantly lower mortality (9.1% and 5.7%, respectively).

A low compliance with guidelines in the PP(44%) was obtained, indicating the need for future more aggressive and proactive approaches

Key words: antibiotic, community-acquired pneumonia, guidelines.

In Europe, the overall incidence of community-acquired lower respiratory tract infections (LRTIs) was found to be 44 cases per 1000 population per year in a single general practice. However, the incidence was two to four times higher in people ≥ 60 years than in those < 50 (1). A study in Finland of 546 patients with community-acquired pneumonia (CAP) found that the overall incidence was 11.6 per 1000 inhabitants: 37% were < 15 years and 31% were ≥ 60 years; 42% were admitted to hospital, and the case fatality rate was 4% (2). On average, the mortality rate in patients with CAP who have been hospitalized is approximately 12% both in the United States and Europe, while in outpatients the mortality rate is lower, at around 5%. As expected, patients with more severe CAP have a higher mortality rate, of 29%. The highest death rates (40%) are found in those who are admitted to an intensive care unit (ICU).

Recent guidelines have provided a rational framework for empirical antibiotic use based on epidemiological criteria (3,4). Mortality risk may be assessed through the use of clinical prediction scores such as the Fine classification (5). It is generally recognized that patients that fall in the upper spectrum of severity (Fine classes IV and V) require hospitalization.

Although some of the guidelines are evidence based, there is limited evidence to support the recommendations regarding antimicrobial therapy, and only few studies addressed the validation of guidelines (6,7). In our study, the primary objective was to evaluate the impact of compliance to a new set of Italian guidelines on the management of patients with community-acquired pneumonia hospitalised in Internal Medicine (IM) departments.

Material and Methods

Patients characteristics

All patients with CAP classified as Fine class IV or V (excluding those in Fine V directly admitted to ICU) were included in the study (5).

CAP was defined as an acute LRTI characterized by [1] an acute pulmonary infiltrate evident on chest radiographs and compatible with pneumonia, [2] confirmatory findings on clinical examination and acquisition of the infection in the community (4). Immunocompromise was defined as primary immunodeficiency or immunodeficiency secondary to radiation treatment, use of cytotoxic drugs or steroids (daily doses of >20 mg of prednisolone or the equivalent for 12 weeks), or AIDS (8, 9). Preexisting chronic obstructive pulmonary disease was diagnosed using criteria reported elsewhere (10).

The study was approved by the local IEC/IRB and informed consent was obtained for each eligible subject prior to entry in the PP. Patients did not receive any new investigational drug or innovative diagnostic procedure, disease management being performed according to the usual clinical practice of the Centre.

Study design

This was a national, multicentre, interventional, before-after survey. The intervention was the implementation of Italian guidelines on management of CAP in IM departments.

The study was composed of three phases: 1) a retrospective phase (RP), where each centre retrospectively collected data on diagnosis and management of all patients with CAP admitted to the IM departments between January 1st and December 31st 2002 according to local guidelines/clinical practice; 2) National CAP guidelines introduction and implementation; 3) the prospective phase (PP), between June 6th 2003 and May 31st 2004, where each centre prospectively enrolled all patients hospitalized with CAP and collected clinical and disease management data. This study was performed in Italy in thirty-one centers nation-wide.

The study was designed by F. Blasi and D. Legnani, with input from an advisory board that included all authors.

Guideline implementation

During late 2001 and early 2002 a multidisciplinary group of experts prepared a new set of guidelines for the management of LRTI, including CAP, in IM setting on behalf of the Italian Federation of Internal Medicine (FADOI) (11). Guideline implementation started following its publication, between December 2002 and June 2003. The publication was distributed to all FADOI study centers, and the guidelines were presented at the Italian Internal Medicine national congress and discussed in *ad hoc* investigators groups prior to activation of the PP. Figure 1 summarizes the general management and treatment indications suggested by the FADOI treatment guidelines (11).

Data collection

Data extracted from the clinic registries and patient records were used; the total number of CAP admissions in hospital and IM department in each study period were also collected.

Patient's demographics, history, clinical status, and diagnosis were collected at baseline on a case report form (CRF). Initial empirical antibiotic therapy and outcome were recorded. Initial antibiotic, dose, frequency and duration of administrations were collected. All changes to the initial antimicrobial therapy were recorded. Antibiotic therapy assessment included: therapy outcome (success / failure); reason for failure: death / referral to ICU / intolerance / therapeutic failure/lack of efficacy. In case of failure the second antibiotic therapy cycle was also recorded.

Clinical success was defined as the resolution or improvement of the symptoms of pneumonia, at the end of the first cycle of therapy. A therapeutic failure was defined as the worsening of symptoms or fever or the need for a new course of antibiotics.

Data regarding etiology and specimen collected for pathogen isolation were also recorded. The participating sites were locally monitored by *ad hoc* trained personnel of a contract research organization (CRO - Fidea srl Milan, Italy). All CRF were centrally sent to the biostatistical department of the CRO and doubled entered into a computer database. The database was checked for consistency and data which failed were reviewed by the study sponsor (Sanofi-Aventis, Italy), with input from all authors.

Statistical analysis

The principal measure of compliance with guideline indications was the change in antibiotic prescription behavior. The primary efficacy variables were the clinical outcome (success/failure) and mortality rate of the two survey phases at the end of the first therapy cycle. Time to clinical success within 30 days from admission was also examined.

Data were summarized using proportions if categorical and mean ± standard deviation (SD) or median with quartiles if continuous. Associations between two categorical variables were tested using the chi-square test, while associations between a categorical and a numerical variable were tested using Student's two-sample t test or the Mann-Whitney U test. Compliance with FADOI treatment recommendations was compared between study phases using both the chi-square test and a mixed-effect logistic regression model with centre as a random effect.

Analyses of clinical outcome was conducted using mixed-effect logistic regression models including study phase, Fine score in 10-point intervals (91-100 to 121-130, Fine class IV, and 131-140 to >200, Fine class V) and antibiotic treatment in the previous 2 weeks (yes/no) as fixed effects and centre as a random effect. Age, sex, origin (home vs nursing residence) and concomitant diseases were not multivariate-independent predictors as they are accounted for in the Fine score algorithm, although they could be univariately associated with outcomes. This basic model was then extended to include therapy, categorized as compliant or non-compliant to FADOI recommendations, or further divided according to main antibacterial class. In-hospital mortality was analysed as for clinical outcome, however, models comparing main antibacterial treatments were not adjusted for centre because of the small number of fatal events per treatment group. According to an intention-to-treat approach, only initial therapies irrespective of their duration were considered in all multivariate analyses. Subgroup analyses using similar models were also conducted according to Fine class. Odds ratios (ORs) with confidence intervals (CIs) and Wald-type p-values were calculated adjusting for all other factors included in the model.

Time to success, ie time to discharge, was calculated from admission to discharge after cure using the Kaplan-Meier method; This time was equivalent to the length of hospital stay in case of success within 30 days after admission, and was otherwise censored at 30 days or earlier in case of failure with the patient alive (e.g. transferred to ICU). Comparisons of time to success were carried out using Cox's proportional hazard regression models including study phase, Fine score, previous antibiotic prescription and initial therapies (compliant vs non compliant), with centre as stratification factor. Hazard ratios (HRs) with CIs and p-values were calculated, provided that the proportionality assumption (tested using time-dependent covariates) was met.

All tests were two-sided. $P< 0.05$ has been considered as statistically significant, therefore ORs have been reported with their 95%CI. For analyses of clinical outcome and mortality within subgroups, i.e. Fine class, CIs and p-values with Bonferroni correction (exact formula) for multiple comparisons have been reported.

Statistical analyses were performed using the SAS system, release 8.2.

Statistical analysis was performed by Studio Associato Airoldi, Cicogna e Ghirri (Milan, Italy), under commitment of the study sponsor. F. Blasi and D. Legnani reviewed the statistical analysis plan. I. Iori, S. Bulfoni, S. Corrao and S. Costantino played a very substantial part in the study implementation and coordination, and data collection and analysis.

Results

A total of 1443 and 1404 patients were included in the RP and the PP of the study respectively by the participating IM departments. Among the total number of pneumonia hospital admissions, 24.0% in the RP and 24.7% in the PP were admitted to IM departments; of these 60.0% in the RP and 60.9% in the PP were classified as Fine class IV-V patients. Patients' main demographic and clinical characteristics are summarized in Table 1. A significant number of elderly patients were admitted with 74.2% being aged from 65 to 90 years in the RP and 70.6% in the PP, while those aged 90 years or older were 16.0% and 19.2%, respectively. A total of 66.6% and 33.4% of patients

were of Fine class IV and V in the RP and 65.8% and 34.2% in the PP, respectively. One or more co-morbidities were present in 93.6% and 92.5% of patients in the RP and PP, respectively. Two or more chronic diseases associated with CAP were present in 69.7% of cases in RP and 67.9% in PP (Table 1).

After guideline implementation, compliant antibiotic prescribing significantly increased in the PP compared to RP from 33% to 44% ($p<0.001$). The increase in compliance was present both in Fine IV and Fine V class (Table 2). Specifically, the use of a β-lactam/ β-lactamase inhibitor combination with an advanced macrolide nearly doubled during the PP. Moreover, a shift of prescribing from β-lactams to respiratory fluoroquinolones as initial monotherapy was observed (online data). Mean daily drug dosages (± SD) for the most commonly prescribed antibiotics were the following: Ceftriaxone 1.7 g (± 0.4), Levofloxacin 0.5 g (± 0.1), Amoxicillin-clavulanate 4.4 g (± 0.9), Azithromycin 0.5 g (± 0) and Clarithromycin 1.0 g (± 0.1).

First-line antibiotic therapy was successful in 1031/1441 (71.5%) in the RP and in 1034/1400 (73.9%) patients in the PP. The OR for failure in the PP versus the RP, adjusted for risk factors and centre, was 0.83 (95% CI: 0.69-1.00; p=0.049). The benefit was particularly evident in Fine class V patients, in whom the adjusted OR was 0.71 (95%CI: 0.51-0.98; p=0.036 with Bonferroni correction). The concomitant reduction in overall mortality, from 12.4% in the RP to 11.5% in the PP, was not statistically significant, the adjusted OR being 0.81 (95%CI:0.63-1.06; p=0.12) (Table 3)

Success rates during first-line antibiotic treatment were 74.5% for compliant therapies and 70.1% for non-compliant therapies in the RP, vs. 78.2% for compliant therapies, and 70.5% for non-compliant therapies in the PP. Mortality at the end of first-line antibiotic treatment was 11.1% for compliant therapies and 13.0% for non compliant therapies in the RP, vs. 8.8% for compliant therapies and 13.7% for non-compliant therapies in the PP (online data). The interactions between compliance and study phase were not statistically significant ($p > 0.10$). The analysis of outcome and mortality at the end of initial therapy according to compliance with guidelines of the overall

population (RP and PP = 2847 patients) according to compliance with the FADOI treatment guidelines and adjusting for risk factors, study phase, and centre, showed a statistically significant advantage for compliant vs non-compliant therapies in terms of success rate with an adjusted OR for failure = 0.74 (95%CI: 0.60-0.90; p=0.004). The effect on mortality failed to achieve statistical significance although the point estimate was similar, as shown by an adjusted OR = 0.77 (95%CI: 0.58-1.04; p=0.082) (Table 4). In these models the ORs for failure and for mortality were still in favor of the PP after adjusting for compliance, although to a lesser extent than in models that do not adjust for compliance: OR in the PP vs RP after adjusting for compliance, in addition to risk factors and centre, was 0.86 for failure (95%CI: 0.71-1.03; p=0.10) and 0.84 for death (95%CI: 0.64-1.10; p=0.19), compared to 0.83 and 0.81, respectively, in models that adjust for risk factors and centre but not for compliance (online data).

These results are mirrored by the adjusted hazard ratios (HRs) for discharge from hospital within 30 days from admission (Figure 2). Considering the overall population (RP and PP) compliant vs non compliant therapies resulted in a HR=1.10 (95% CI 1.00-1.20; p=0.050) for an earlier discharge in patients treated according to guidelines (Figure 2 panel A). Figure 2 panel B and C shows the HRs for discharge in Fine IV and Fine V class, respectively.

Considering the efficacy of different antibiotics, table 5 shows the results in terms of success rate and adjusted ORs. Comparing the different antibiotics to antipneumococcal cephalosporin monotherapy, success rate 68.6%, levofloxacin alone resulted the most active (success rate 79.1%) with an OR=0.65 (95%CI 0.45-0.95;p=0.026), followed by the combination of levofloxacin and antipneumococcal beta-lactam (success rate 78.8%) with an OR=0.66 (95%CI 0.40-1.08; p=0.097) and by the combination of macrolide and cephalosporins (success rate 76.7%) with an OR=0.72 (95%CI 0.49-1.05; p=0.084).

Antipneumococcal cephalosporin monotherapy was associated with the highest mortality (16.2%); levofloxacin alone and the combination of cephalosporin and macrolide resulted in a significantly lower mortality (9.1% and 5.7%, respectively), whereas combination of antipneumococcal

penicillin and macrolide was not significantly different in terms of mortality when compared to cephalosporin alone (Figure 3).

At the time the study started and according to the existing guidelines, nursing home patients were included as CAP. Being a nursing home resident is acknowledged as a risk factor in the Fine scoring system by assigning 10 additional points. Therefore differences in the proportion of nursing home patients (13.5% retrospective vs 12.8% prospective, p=0.61; 11.3% compliant vs 14.3% non-compliant, p=0.023) are accounted for in the analyses of the outcomes. However, a sensitivity analysis has been performed excluding patients coming from nursing home (online data). The OR for mortality of the prospective vs retrospective phase was slightly lower, at 0.80 (95%CI: 0.59-1.09) instead of 0.81, while the OR for failure was increased from 0.83 to 0.86 (95%CI: 0.70-1.05) and the corresponding p-value increased from 0.049 to 0.14. The ORs of compliant vs non-compliant therapies were lower than in the main analysis: 0.72 (95%CI: 0.58-0.89) instead of 0.74 for failure, 0.74 (95%CI: 0.53-1.03) instead of 0.77 for mortality, the corresponding p-values being similar to the whole-sample analysis (online data).

A significant association was found between increasing Fine score and CAP mortality, with an adjusted OR of 1.43 (95% CI 1.36-1.50; $p < 0.0001$) for each 10-unit increase over the whole range of values (91 to > 200). In addition, a significant association was also identified between increasing Fine score and clinical failure, with an adjusted OR of 1.30 (95% CI 1.25-1.34; $p < 0.0001$) for each 10-unit increase between 91 and > 200 (online data).

Previous antibiotic treatment was positively associated with clinical failure, with an adjusted OR of 1.46 (95% CI 1.16-1.84; p=0.002). Conversely, previous antibiotic treatment was not significantly associated with increased mortality (OR=1.26, 95% CI 0.91-1.75; p=0.15) (online data).

Concerning the etiologic diagnostic tests performed no difference was observed between the two study phases, a possible etiologic diagnosis was obtained in less than 12% of patients in both phases, mainly from sputum specimen (data not shown).

Discussion

Notwithstanding the advances in the antimicrobial management of pneumonia, this disease is still associated with considerable morbidity and mortality, especially in elderly patients. Over the last decade, several national and international guidelines have been devised in order to improve the management of pneumonia. Guidelines deal with different aspects of pneumonia management, from site of care, to severity criteria, diagnostic tests, and empirical antibiotic therapy. So far, few studies have attempted to give an overall picture of pneumonia management in "real life" conditions, and evaluated the consequences of the disease management following guideline implementation (6,7). Following the release of the Italian guidelines for pneumonia management in 2002, thirty one IM departments from across Italy were enrolled. Centers provided retrospective data on pneumonia management in their wards for 2002, center personnel were instructed on guideline changes and modifications through ad hoc meetings and national congresses, and prospective data on pneumonia management of admitted patients were collected between 2003 and 2004. This is the first study in Italy evaluating "before and after" clinical practice changes in pneumonia following guideline implementation.

We compared antibiotic prescribing measures, outcome and habits during the RP and PP. After guideline implementation, a significant increase in the use of compliant therapies occurred, particularly combination therapy with β-lactam plus macrolide and a respiratory fluoroquinolone monotherapy as opposed to monotherapy with β-lactam was observed.

These changes were associated with a significant reduction in the OR for failure following guideline implementation, particularly in the more severe patients (Fine class V).

This clinical improvement is likely related to treatment choice as the effect is maintained after correction for confounding factors.

The analysis of the overall population (RP and PP patients) confirms that the compliance to the guidelines was associated with a significant improvement in terms of success rate and a nearly significant advantage in terms of mortality, with a faster discharge from hospital.

Levofloxacin monotherapy resulted the most active treatment in terms of success rate, followed by the combination of either levofloxacin or advanced macrolides with antipneumococcal cephalosporins. Moreover, advanced macrolides in combination with antipneumococcal cephalosporins and levofloxacin monotherapy were the best treatment approaches in terms of reduction of mortality.

These findings are consistent with retrospective data in the literature indicating that the most successful antibiotic approaches are the use of a cephalosporin plus a macrolide combination, or a fluoroquinolone alone (12-14). A more recent prospective study limited the survival benefits of combination therapy to more severely ill patients with bacteremic pneumococcal pneumonia (15). Similar conclusions were also reached in a Cochrane systematic review (16).

Interpretation of differences in the outcome of therapeutic approaches in this study, as well as in similar surveys, should be approached with caution considering that the treatment assignment was not randomized. However, in this study efforts have been made to adjust outcome analyses for known risk factors (Fine score) and for centre (a source of variation possibly related to otherwise unspecified confounders). These corrections may be expected to reduce, not eliminate, possible biases related to baseline differences between patients given different antibiotics. A further bias affecting outcome may be due to underdosing of some antibiotic classes compared to others. This does not appear to be the case in the present study as drug dosing schemes were in line with guideline indications.

The study confirms the association between Fine score and mortality but also indicates a possible role of this scoring system in predicting clinical failure. Known risk factors such as increased age, concomitant diseases and nursing home residence are included in the Fine scoring and were therefore not considered as independent predictors in our analyses.

Another interesting finding is that previous antibiotic treatment, in the two months preceding admission, is associated with clinical failure but not with mortality.

We did not report the microbiological data in detail as an etiological diagnosis was available in a very limited number of cases (< 12% of patients). This presumably justified extremely divergent data, in terms of leading pathogens, compared to recognized epidemiological data. Most available specimens were sputum samples, with very low rates of blood cultures and urinary antigen detections performed. These findings underscore the need for a better implementation of guideline recommendations regarding etiologic testing in hospitalized pneumonia cases.

In our study over 70% of cases were aged from 65 to 90 years and almost 20% of patients were aged 90 years or older. Moreover, roughly 70% of patients had two or more chronic diseases associated with CAP, and it is known that age and major co-morbidities are among the factors independently associated with mortality in very elderly patients (17, 18). A recognized major limitation of the Fine score is the impact of age on the score. Given the high number of elderly patients in our study population, this may have had a significant impact on the number of Fine class IV and V cases recorded. This may also explain the fact that a relatively high number of Fine V (>30%) patients, in both RP and PP, were treated in an IM ward and not admitted to ICU.

One of the strengths of our study is the large population of patients enrolled even though this is limited by the fact that half of these patients were retrospectively analysed. Another limit is the lack of a precise identification of changes in other factors, not directly related to antibiotic therapy, possibly linked with the better outcome in the prospective phase. These could include changes in microbiological assessment (such as urinary antigen test use), timepoint of antibiotic therapy, and drug dosage. None of these factors changed between the two phases of the study. We think that the main confounding factor during the study period could have been represented by the antimicrobial profile of resistance in pneumococci and *H. influenzae* / *M. catarrhalis*. However, on the basis of Italian data from the Protekt Study, resistance to macrolides in *S. pneumoniae* and to beta-lactams in *H. influenzae* has only slightly increased from 2000 to 2004, from 35% to 40% and from 15% to

20%, respectively. During the same time period no change in susceptibility to respiratory fluoroquinolone occurred in these respiratory pathogens. In any case this kind of changes could have impacted negatively on the outcome of monotherapies with macrolide alone, but this effect would account for less than 3% of non compliant therapies.

At the time the study started and according to the existing guidelines, nursing home patients were included as CAP. Being a nursing home resident is acknowledged as a risk factor in the Fine scoring system by assigning 10 additional points. We performed a sensitivity analysis, excluding nursing home patients, demonstrating that this did not alter the main findings of the study.

The main results of our study are the demonstration that guidelines can improve CAP management and that guideline implementation through simple educational measures such as ad hoc investigator meetings showed sufficient compliance to positively affect patient outcome. Unfortunately, this simple approach is probably insufficient as overall compliance to guidelines was still quite low during the prospective phase (44%). Nonetheless, considering that this only partial improvement in compliance was associated with clinically meaningful positive outcomes, further efforts are required to obtain greater guideline implementation.

It is worth noting that the recent studies also reported improvement in clinical outcome measures associated with CAP treatment following guideline utilization (6,7). The results of the present study underscore the need for future more "aggressive" or proactive approaches towards implementation to further improve the overall management of CAP.

Conflict of interest statement

F. Blasi reports having received consulting fees from Pfizer, Sanofi-Aventis, and Altana; lecturefees from Bayer, Sanofi-Aventis, Pfizer, Abbott, Altana, and GlaxoSmithKline; and grant support from Pfizer and Altana.

I. Iori reports having received consulting fees from Pfizer, lecture fees from GlaxoSmithKline and Sanofi-Aventis

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S. Costantino reports having no potential conflict of interest relevant to this article.

D. Legnani reports having received consulting fees from Sanofi-Aventis, Bayer; lecture fees from Bayer, Sanofi-Aventis, Pfizer, Abbott, and GlaxoSmithKline.

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Table 1. Patients demographic and baseline characteristics.

	Retrospective phase (No = 1443)	Prospective phase (No = 1404)	P †
Age (years)			0.34 ^
min - max	20.8-107.4	19.3-107.2	
median (Q_1 - Q_3)	80.5 (73.5-87.7)	81.6 (74.2-88.2)	
mean ± SD	79.3 ± 11.6	79.7 ± 12.5	
Sex, No (%)			0.023
Female	610 (42.3)	654 (46.6)	
Male	833 (57.7)	750 (53.4)	
Origin, No (%)			0.61
NR	1 (0.1)	6 (0.4)	
Home	1247 (86.4)	1219 (86.8)	
Nursing home	195 (13.5)	179 (12.7)	
Fine class, No (%)			0.69
IV	961 (66.6)	924 (65.8)	
V	482 (33.4)	480 (34.2)	
Fine score			0.92 °
min - max	91-229	91-293	
median (Q_1 - Q_3)	118 (103-138)	118 (102-140)	
mean ± SD	123.6 ± 26.0	124.2 ± 27.5	
Antibiotics over last 14 days, No (%)			0.84
NR	7 (0.5)	1 (0.1)	
No	1172 (81.2)	1140 (81.2)	
Yes	264 (18.3)	263 (18.7)	
Number of comorbid conditions, No (%)			
0	93 (6.4)	106 (7.5)	
1	344 (23.8)	344 (24.5)	
2	468 (32.4)	407 (29.0)	
> 2	538 (37.3)	547 (39.0)	

†) continuity-adjusted chi-square test (missing data excluded) unless otherwise stated.
^) Student's t test.
°) Mann-Whitney U test.

Table 2 - Initial therapy according to compliance with therapeutic FADOI Recommendations and phase of the study.

	Retrospective phase		Prospective phase		P
	No	**(%)**	**No**	**(%)**	
All patients (total)	1443	(100)	1404	(100)	
Compliant with guidelines	476	(33.0)	616	(43.9)	<0.001 †
Monotherapy	150	(10.4)	214	(15.2)	
Combination	326	(22.6)	402	(28.6)	
Non-compliant with guidelines	967	(67.0)	788	(56.1)	
Monotherapy	710	(49.2)	551	(39.2)	
Combination	257	(17.8)	237	(16.9)	
Fine class IV (total)	961	(100)	924	(100)	
Compliant with guidelines	323	(33.6)	421	(45.6)	<0.001 †
Monotherapy	101	(10.5)	142	(15.4)	
Combination	222	(23.1)	279	(30.2)	
Non-compliant with guidelines	638	(66.4)	503	(54.4)	
Monotherapy	470	(48.9)	350	(37.9)	
Combination	168	(17.5)	153	(16.6)	
Fine class V (total)	482	(100)	480	(100)	
Compliant with guidelines	153	(31.7)	195	(40.6)	<0.01 ‡
Monotherapy	49	(10.2)	72	(15.0)	
Combination	104	(21.6)	123	(25.6)	
Non-compliant with guidelines	329	(68.3)	285	(59.4)	
Monotherapy	240	(49.8)	201	(41.9)	
Combination	89	(18.5)	84	(17.5)	

†) both continuity-adjusted chi-square test and Wald chi-square test (logistic regression adjusting for Center as a random effect).
‡) continuity-adjusted chi-square test, p=0.005; Wald chi-square test, p=0.003.

Table 3 - Outcome and mortality at the end of initial therapy according to study phase.

	Retrospective phase		Prospective phase		Prospective vs Retrospective phase (adjusted analysis) *		
	No	(%)	No	(%)	OR ^	(95%CI)	P †
All patients							
Success rate**	1031 / 1441	(71.5)	1034 / 1400	(73.9)	0.83	(0.69-1.00)	0.049
Death rate	179 / 1443	(12.4)	162 / 1404	(11.5)	0.81	(0.63-1.06)	0.12
Fine class IV							
Success rate	778 / 959	(81.1)	756 / 921	(82.1)	0.94	(0.74-1.21) *(0.71-1.26)* °	0.65 *0.88* °
Death rate	52 / 961	(5.4)	51 / 924	(5.5)	1.03	(0.67-1.58) *(0.63-1.69)* °	0.89 *0.99* °
Fine class V							
Success rate	253 / 482	(52.5)	278 / 479	(58.0)	0.71	(0.53-0.94) *(0.51-0.98)* °	0.018 *0.036* °
Death rate	127 / 482	(26.3)	111 / 480	(23.1)	0.71	(0.50-0.99) *(0.48-1.05)* °	0.046 *0.090* °

*) multiple logistic regression model including study phase, Fine score (as numerical variable on a 10-unit scale), antibiotic treatment in the previous two weeks (yes/no), and Center (as a random effect).
^) odds ratios for failure or death in the prospective vs retrospective phase.
†) Wald chi-square test.
°) with Bonferroni correction for performing separate analyses in both Fine class subgroups.
**) Failures other than death in the RP: persistence of symptoms, 214; intolerance, 7; worsening leading to ICU admission, 10. Two patients with missing outcome excluded from analysis. Failures other than death in the PP: persistence of symptoms, 187; intolerance, 9; worsening leading to ICU admission, 7; not reported, 1. Four patients with missing outcome excluded from analysis

Table 4 - Outcome and mortality at the end of initial therapy according to compliance with therapeutic FADOI Recommendations and to study phase.

	Non-compliant therapy		Compliant therapy		Compliant vs Non-compliant therapy (adjusted analysis) *		
	No	(%)	No	(%)	OR ^	(95%CI)	P †
All patients							
Success rate **	1231 / 1752	(70.3)	834 / 1089	(76.6)	0.74	(0.60-0.90)	0.004
Death rate	234 / 1755	(13.3)	107 / 1092	(9.8)	0.77	(0.58-1.04)	0.082
Fine class IV							
Success rate	909 / 1139	(79.8)	625 / 741	(84.3)	0.75	(0.57-0.98) *(0.55-1.02)* °	0.036 *0.071* °
Death rate	67 / 1141	(5.9)	36 / 744	(4.8)	0.85	(0.54-1.35) *(0.50-1.45)* °	0.48 *0.73* °
Fine class V							
Success rate	322 / 613	(52.5)	209 / 348	(60.1)	0.74	(0.55-1.00) *(0.53-1.05)* °	0.053 *0.10*°
Death rate	167 / 614	(27.2)	71 / 348	(20.4)	0.76	(0.52-1.10) *(0.49-1.16)* °	0.14 *0.26* °

*) multiple logistic regression model including compliance with therapeutic recommendations, study phase, Fine score (as numerical variable on a 10-unit scale), antibiotic treatment in the previous two weeks (yes/no), and Center (as a random effect).

^) odds ratios for failure or death in compliant vs non-compliant therapy and in the prospective vs retrospective phase.

†) Wald chi-square test.

°) with Bonferroni correction for performing separate analyses in both Fine class subgroups.

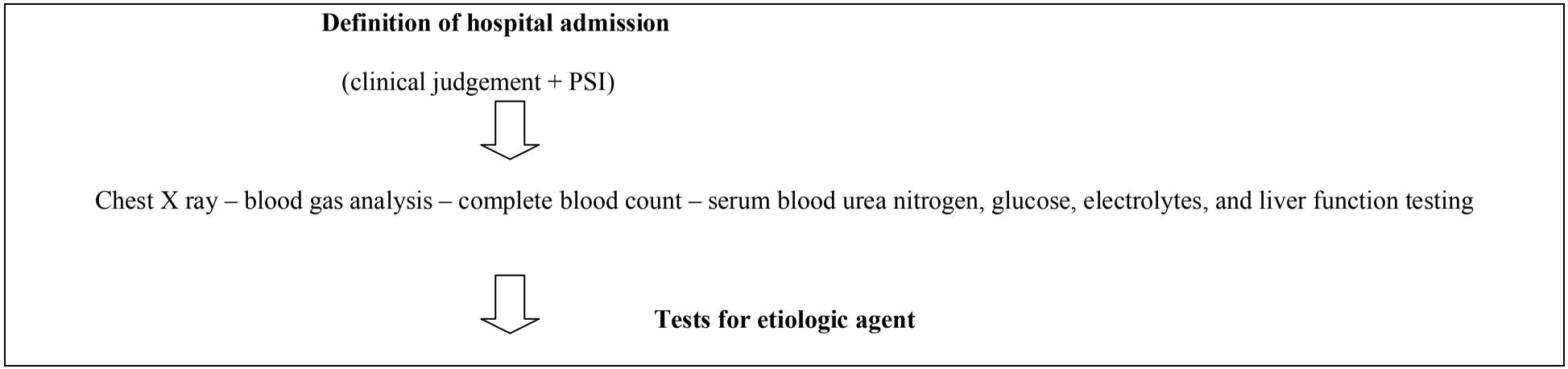
**) Failures other than death with non-compliant therapies: persistence of symptoms, 264; intolerance, 8; worsening leading to ICU admission, 14; not reported, 1. Three patients with missing outcome excluded from analysis. Failures other than death with compliant therapies: persistence of symptoms, 137; intolerance, 8; worsening leading to ICU admission, 3. Three patients with missing outcome excluded from analysis.

Table 5 - Outcome at the end of initial therapy according to type of drug.

Initial therapy	Success rates		Comparisons (adjusted analysis) *		
	No	(%)	OR ^	(95%CI)	P †
Ceftriaxone, cefotaxime or cefepime alone	310 / 452	(68.6)			
Amoxycillin/clavulanate or ampicillin/sulbactam alone	268 / 378	(70.9)	0.82	(0.58-1.16)	0.25
Levofloxacin alone	287 / 363	(79.1)	0.65	(0.45-0.95)	0.026
Other non-compliant monotherapies	309 / 428	(72.2)	0.97	(0.69-1.35)	0.85
Ceftriaxone, cefotaxime or cefepime + macrolide	253 / 330	(76.7)	0.72	(0.49-1.05)	0.084
Amoxycillin/clavulanate or ampicillin/sulbactam + macrolide	168 / 229	(73.4)	0.70	(0.46-1.07)	0.093
Levofloxacin + antipneumococcal beta-lactam §	123 / 156	(78.8)	0.66	(0.40-1.08)	0.097
Non-compliant combinations	325/463	(70.2)	0.98	(0.71-1.36)	0.90

*) multiple logistic regression model including initial therapy, study phase, Fine score (as numerical variable on a 10-unit scale), antibiotic treatment in the previous two weeks (yes/no), and Center (as a random effect).
^) odds ratios for failure with each therapy vs ceftriaxone, cefotaxime or cefepime alone.
†) Wald chi-square test.
§) ceftriaxone, cefotaxime, cefepime, amoxycillin/clavulanate or equivalent penicillin.

Figure 1. FADOI guidelines indications for initial management of hospitalised CAP



-Blood cultures (at least 2)

-Sputum Gram stain and culture

-*Legionella pneumophila* and *Streptococcus pneumoniae* urinary antigens

-Pleural fluid analysis

-Bronchoscopy (BAL and aspirate) in selected patients or in case of treatment failure

Treatment indication for hospitalised patient with CAP

MEDICAL WARD

-Preferred

- Cephalosporin i.v. (ceftriaxone, cefotaxime) + advanced macrolide* i.v.
- Levofloxacin i.v.**

-Alternative

- Amoxicillin/clavulanate i.v + advanced macrolide* i.v.

-Suspected aspiration

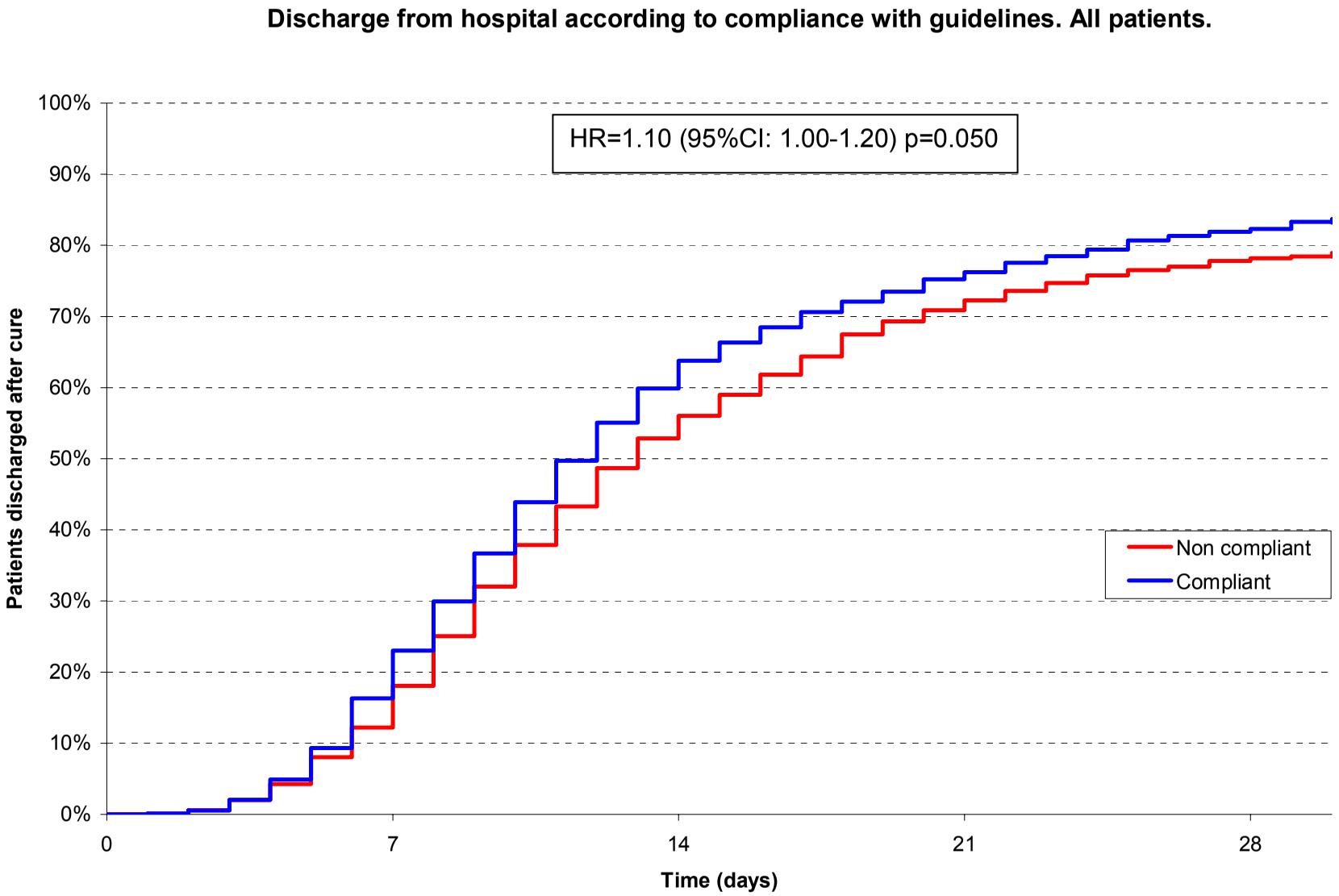
- Amoxicillin/clavulanate i.v.
- Levofloxacin i.v.** + clindamycin or metronidazole iv

*Azithromycin or clarithromycin

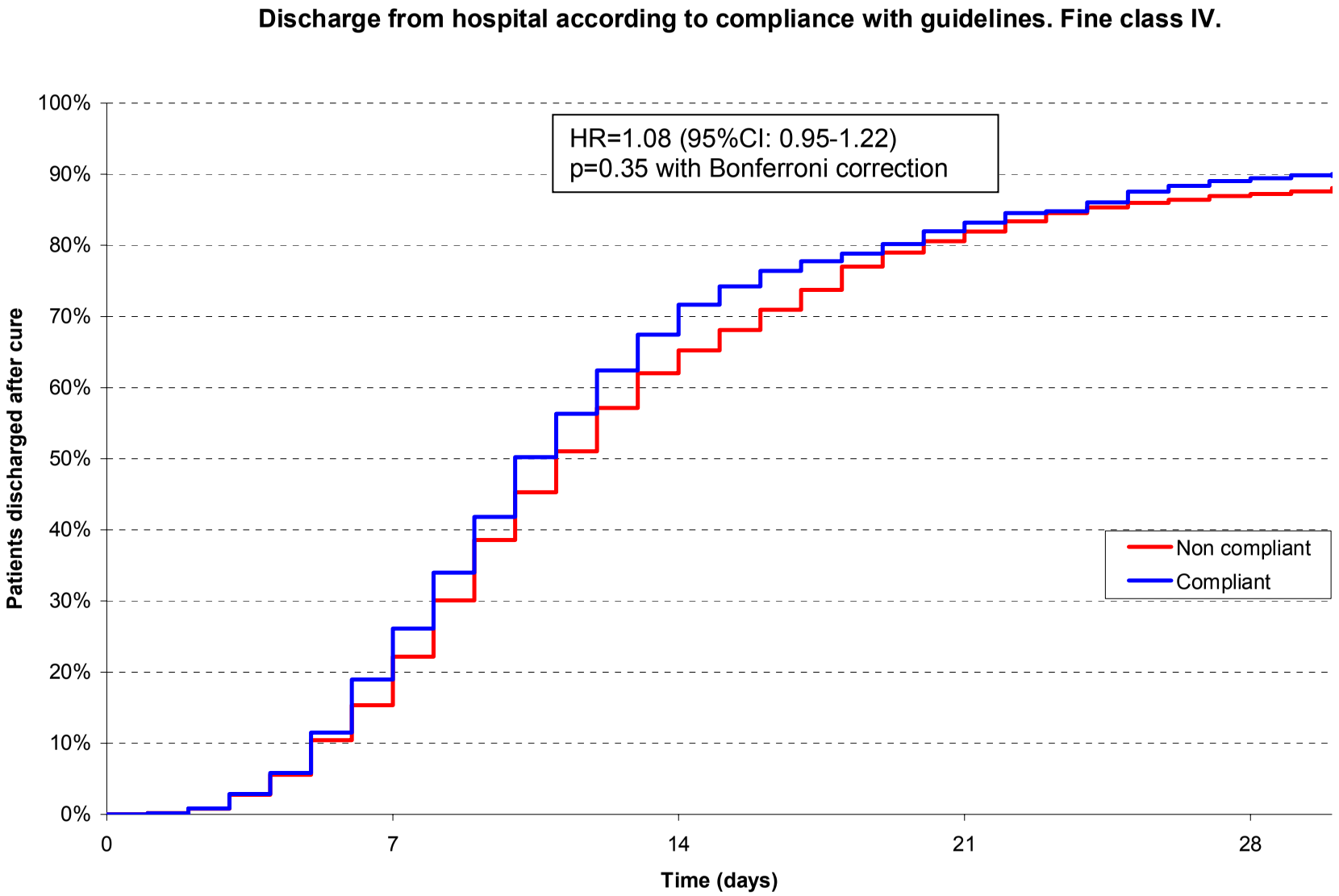
**Levofloxacin is the only fluoroquinolone with approved i.v. formulation in Italy

Figure 2. Discharge from hospital within 30 days from admission, according to compliance with therapeutic recommendations (Panel A = all patients; Panel B = Fine IV; Panel C = Fine V).
HR= ratio of the probability of being discharged for patients initially treated with compliant therapy versus non-compliant therapy, calculated using Cox's proportional-hazard regression models adjusting for study phase, Fine score, previous antibacterial treatment and centre. Results in Panels B and C are reported with Bonferroni correction for performing the same comparison in both Fine class subgroups.

Panel A


Discharge from hospital according to compliance with guidelines. All patients.
HR=1.10 (95%CI: 1.00-1.20) p=0.050
Patients discharged after cure
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
0
7
14
21
28
Time (days)
Non compliant
Compliant

Panel B


Discharge from hospital according to compliance with guidelines. Fine class IV.
HR=1.08 (95%CI: 0.95-1.22)
p=0.35 with Bonferroni correction
Patients discharged after cure
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
0
7
14
21
28
Time (days)
Non compliant
Compliant

Panel C

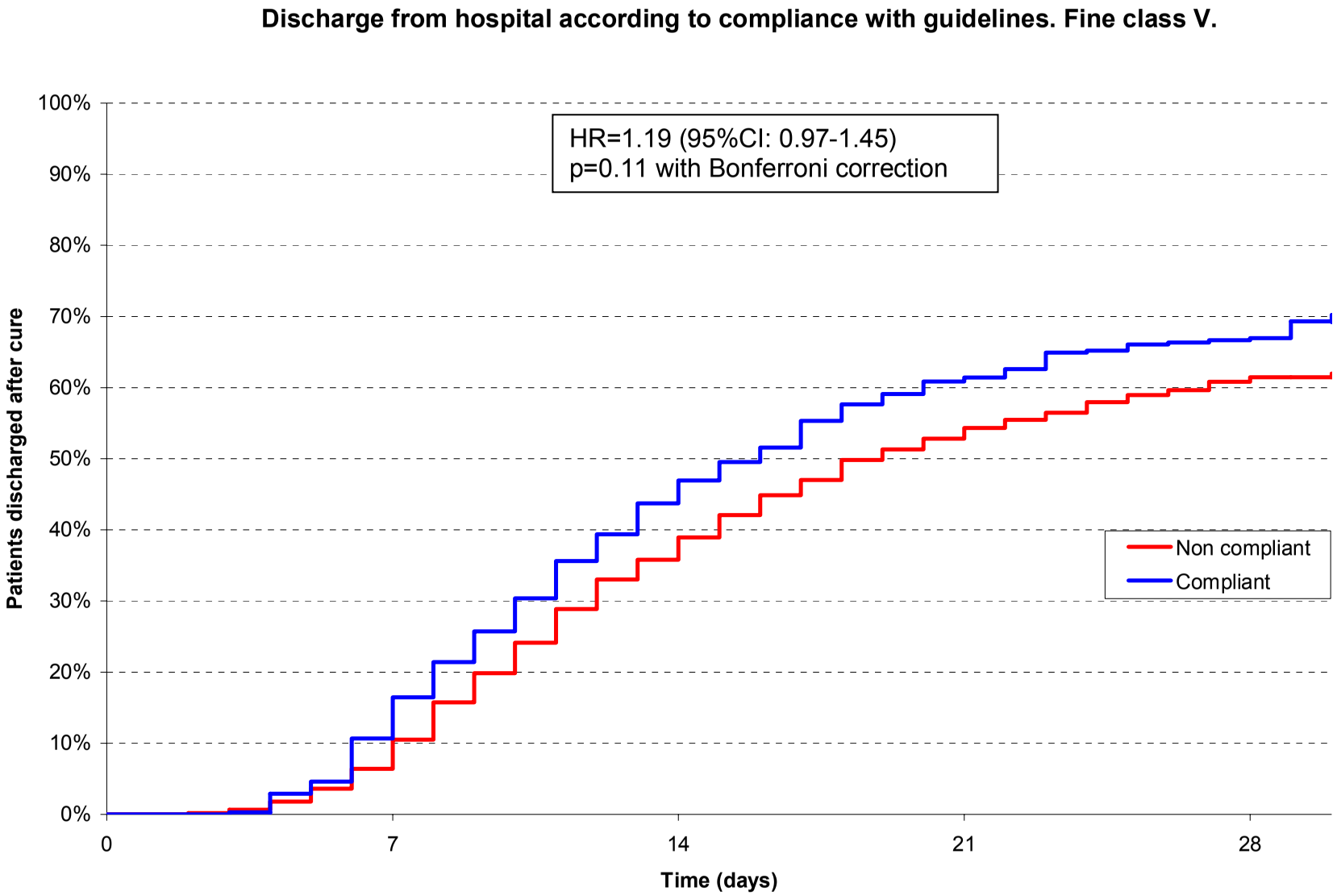
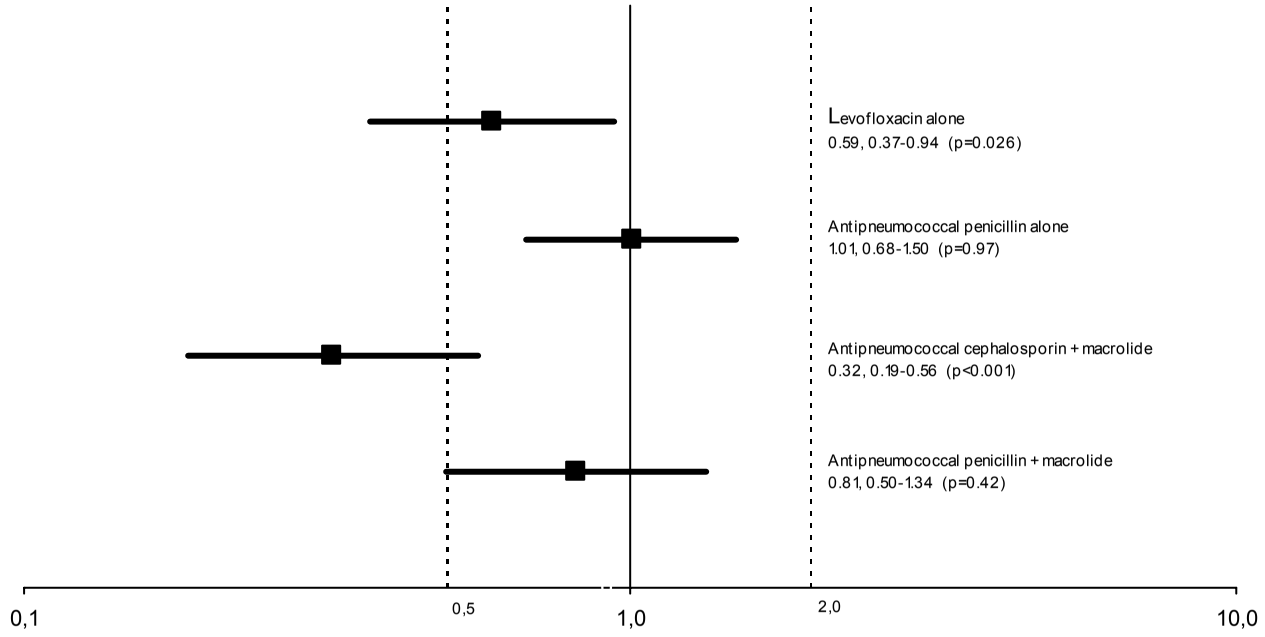

Discharge from hospital according to compliance with guidelines. Fine class V.
HR=1.19 (95%CI: 0.97-1.45)
p=0.11 with Bonferroni correction
Patients discharged after cure
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
0
7
14
21
28
Time (days)
Non compliant
Compliant

Figure 3. Mortality during first therapy cycle according to main initial therapies: adjusted ORs with 95%CIs vs antipneumococcal cephalosporin alone.



Multiple logistic regression model including initial therapy, study phase, Fine score (as numerical variable on a 10-unit scale) and previous antibacterial treatment (yes/no).
Death rates: antipneumococcal cephalosporin, 16.2%; levofloxacin, 9.1%; antipneumococcal penicillin, 15.9%; antipneumococcal cephalosporin + macrolide, 5.7%; antipneumococcal penicillin + macrolide, 12.2%.