

Assessment of the impact of clinical recommendations on antibiotic use for CAP and HCAP: results from an implementation program in an Academic Hospital

G. Cattani^{1,2,3}, A. Madia², L. Arnoldo^{1,2}, L. Brunelli^{1,2}, D. Celotto², L. Grillone^{1,2}, F. Valent¹, L. Castriotta¹, F. Pea^{1,2}, M. Bassetti^{1,2}, S. Brusaferrò^{1,2}

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Abstract

Background. Local guidelines and recommendations to treat common infectious diseases are a cornerstone of most Antimicrobial Stewardship programs. The evaluation of the adherence to guidelines is an effective quality measure of the programs themselves; the proposed evaluation model aimed at examining antibiotic treatment for pneumonia.

Study design. A retrospective pre–post intervention study was conducted in a North-Eastern Italian Academic Hospital.

Methods. 231 patients with Community–Acquired Pneumonia and 95 with Healthcare-Associated Pneumonia were divided into pre- and post-intervention groups (188 and 138, respectively). A course and a pocket summary of Pneumonia Regional Recommendations were the stewardship activities adopted. The compliance degree of prescriptions with Regional Recommendations was tested for drug(s), dosage and duration of treatment in both groups for Community–Acquired and Healthcare-Associated Pneumonia and a comparison with International guidelines was performed.

Results. A significant improvement in the compliance with Regional Recommendations for the variable drug emerged for Community–Acquired (38.8% vs 52.2%), but not for Healthcare-Associated Pneumonia; no significant variation in compliance was registered for dosage and duration of treatment. The significant decrease in consumption of levofloxacin showed the positive impact of the Regional Antimicrobial Stewardship programs. A high level of adherence to International Guidelines for the variable drug for Community–Acquired Pneumonia was found in both groups (75.5% and 77.2%, respectively).

Conclusion. Our study highlighted that room for improvement in antibiotic prescription in Community–Acquired and Healthcare-Associated Pneumonia currently remains. New strategies for a better use of the adopted tools and definition of new antimicrobial stewardship initiatives are needed to improve compliance to Regional Recommendations.

Introduction

Antibiotics overuse/misuse is a Public Health threat worldwide (1). Their inappropriate use is related to increased

mortality, higher healthcare costs, increased risk of antimicrobial resistance (2). To face these challenges, the definition of guidelines and recommendations to treat common infectious diseases is a recognized

¹ Udine Healthcare and University Integrated Trust, Udine, Italy

² Department of Medicine, University of Udine, Italy

³ Present affiliation: Codroipo District, Local Health Trust no. 3, Gemona, Italy

cornerstone of most antimicrobial stewardship programs (3-6), as well as adherence to clinical guidelines is agreed as an effective quality measure (process indicator) of the programs themselves (7). Although several available experiences on the evaluation of national/international guidelines for empirical antibiotic therapy of Community-Acquired Pneumonia (CAP) and Healthcare-Associated Pneumonia (HCAP) have been performed (8-10), the compliance of physicians with guidelines adapted to local contexts still remains a challenge.

Our study assessed the impact of an Antimicrobial Stewardship (AMS) intervention aimed to implement Regional clinical Recommendations on treatment of pneumonia in a North-Eastern Italian Academic Hospital, specifically evaluating the compliance of the three main components of an antibiotic therapy: drug, dosage and duration of treatment.

Methods

A retrospective pre-post intervention study was conducted in a 1,096-bed Academic Hospital of the Region Friuli-Venezia Giulia (FVG), between October 1st, 2014 and April 30th, 2016. Patients admitted to the hospital with a diagnosis of pneumonia were recruited in two periods: pre-stewardship interventions (October 2014-March 2015) and post-stewardship interventions (December 2015-April 2016). The intervention was conducted between April 2014 and November 2015. The study was part of the surveillance program on AMS set up by the FVG Health System.

Case definition

We recruited all patients ≥ 18 years of age admitted to the hospital in the study periods, with primary or secondary diagnosis of bacterial pneumonia (ICD-9 CM codes

481-487), hospital stay ≥ 48 hours and treated with at least one antibiotic. For the purpose of the study we considered CAP and HCAP, defined according to the American Thorax Society/Infectious Diseases Society of America (ATS/IDSA) guidelines (11-12).

More in detail, when the onset of symptoms occurred outside the hospital setting or within 48 hours since hospital admission, the pneumonia was classified as CAP. Patients were designated as having HCAP if: 1) they were hospitalized for at least 48 hours within the last 30 days; or 2) they were admitted to the hospital from long-term care facilities or nursing homes; or 3) they received antibiotic therapy (intravenous or oral) for at least five days within the last 30 days; or 4) attended the hospital regularly (at least two times a week) or a hemodialysis clinic.

Exclusion criteria were: 1) age < 18 years, 2) admission to Day-Hospital regimen, 3) admission to Obstetrics & Gynecology ward, 4) proven or suspected pneumonia caused by virus, fungi or parasites, 5) proven or suspected HCAP including Ventilation-Acquired Pneumonia (VAP), 6) *ab-ingestis* pneumonia, 7) ongoing antibiotic treatment for infectious diseases different from pneumonia (e.g. pyelonephritis, peritonitis, etc.) or bacteremia, 8) *exitus* for infective and non-infective causes before hospital discharge.

Data collection

Data were collected from clinical records and included the following variables: gender, age, comorbidities (e.g. heart failure, arrhythmia, chronic lung disease, metastatic cancer), presence of renal failure (tested through the assessment of the glomerular filtration rate: CrCl (Creatinine Clearance) 30-50 mL/min, mild-to-moderate damage; CrCl < 30 mL/min, severely impaired), ongoing treatment (particularly with immunosuppressant) and specifically antibiotic therapy as drug(s), dosage and

treatment duration (in days); moreover, presence of specific risk factors for infection/colonization by multi-drug resistant (MDR) bacteria (Extended-Spectrum Beta-Lactamases -ESBL- *Enterobacteriaceae*, Community-Acquired Methicillin-Resistant *S. aureus* -CA-MRSA-, Methicillin-Resistant *S. aureus* -MRSA-, etc.) and *P. aeruginosa* (Chronic Obstructive Pulmonary Disease -COPD-, cystic fibrosis (13), severity of illness at hospital admission (defined through Pneumonia Severity Index for CAP: Confusion, Blood Urea Nitrogen, Respiratory Rate, Blood Pressure, Age \geq 65, CURB-65 score and sepsis severity index) and presence of allergy to Beta-Lactams, was assessed. All data were collected in a database realized through Epi-Info software ver.7.0.

Data were collected by two ad hoc trained physicians; in case of doubt, the opinion of a third physician, with expertise in infectious diseases, was requested. Data were validated by an epidemiologist. A pilot study was preliminarily conducted in order to assess the quality of the variables of interest and the feasibility of the design.

The AMS intervention

The intervention adopted was based on the introduction and promotion of the document “Regional Friuli-Venezia Giulia Recommendations for the Diagnosis and Treatment of Bacterial Pneumonia”, part of the regional Stewardship program. The document, developed by a regional multidisciplinary team of experts on antimicrobial use, was based on influential international guidelines (e.g. IDTS, ATS (11-12)) and adapted to the regional epidemiological context with the purpose of limiting the use of antimicrobials (e.g. 3rd generation cephalosporins and quinolones) known to be responsible for resistance development in most cases (14-17). In detail, the intervention consisted in two actions: 1) a four hours course targeted to all physicians

(particularly drug prescribers), illustrating the Regional Recommendations and their practical use; 2) a brief pocket summary of the available Regional Recommendations (including recommendations for bacterial pneumonia), provided by the AMS Team with the aim to guide the physician’s clinical practice at the bedside.

Compliance evaluation

Three main variables were assessed to evaluate the compliance to Regional Recommendations in CAP and HCAP: type of drug(s) prescribed (if more than one agent was administered, the compliance of each of them was assessed), dosage and overall duration of therapy. A treatment was defined fully compliant when all variables were concordant at the same time. In detail, for CAP an antimicrobial regimen based on a penicillin plus inhibitor (e.g. amoxicillin/clavulanate), possibly associated to a macrolide (clarithromycin or azithromycin), was considered the gold standard; cephalosporins and quinolones were indicated as second choice because of their massive use in recent years in FVG (2.01 DDD/1,000 inhabitant/days and 2.02 DDD/1,000 inhabitant/days for 3rd generation cephalosporins and quinolones in 2011, respectively) and their role in promoting the onset of resistance (16-18). However, since drugs belonging to several antibiotic classes other than beta-lactams and macrolides are included as first line therapy in International Guidelines (11, 19) (e.g. cephalosporins, quinolones, etc.), an evaluation of compliance with International Guidelines for the treatment of CAP was also performed, when appropriate (e.g. lack of risk factors for MDR pathogens, lack of allergy, etc.). Quinolones (ciprofloxacin or levofloxacin) were recommended in case of allergy to beta-lactams; if risk factors for CA-MRSA were present, the association between the standard therapy and an antibiotic active against this pathogen

(vancomycin or linezolid) was suggested.

Patients affected by HCAP should be treated with an antibiotic regimen including an agent active against MRSA (vancomycin or linezolid) and a beta-lactam with a greater coverage for Gram-negative bacteria (meropenem in patients with overt sepsis or piperacillin plus tazobactam in case of mild-moderate or no sepsis). If risk factors for *P. aeruginosa* were present (COPD, cystic fibrosis), the use of one anti-pseudomonal beta-lactam (piperacillin-tazobactam or meropenem), a cephalosporin (ceftazidime), ciprofloxacin or amikacin, was evaluated as concordant with guidelines. In patients with renal impairment, the use of a proper drug dosage in relation to the specific degree of glomerular filtration rate was assessed. A duration of therapy of five-seven days for CAP, eight-ten days for HCAP and 14 days if risk factors for *P. aeruginosa* were present, was considered the gold standard. Since the Regional Recommendations were designed for empirical treatment of bacterial pneumonia, the list of most likely involved etiological agents was included for clinicians.

Statistical analysis

The distribution of all the variables of interest was reported as mean, standard deviation, median and interquartile range for continuous variables and as frequency distribution for nominal and ordinal variables. The comparative analysis between the two groups (pre- and post-stewardship interventions) was performed using the Chi-square test for categorical variables, and the Wilcoxon Mann-Whitney test (a non-parametric test for independent samples) for continuous variables not normally distributed and ordinal variables. The assumption of normality was previously tested by the Shapiro-Wilk test. Multivariate analyses were performed through logistic regression models. The goodness of fit of the models was verified by the Hosmer-Lemeshow test.

Where appropriate, the confidence intervals were calculated at 95% and an alpha level of 0.05 was chosen as a guide for statistical significance. The software used for statistical analysis was STATA (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP).

Results

Overall 326 patients with a diagnosis of pneumonia met the inclusion criteria and were therefore included in the study: 188 (57.7%) were treated between October 1st, 2014 and March 31st, 2015 (pre-stewardship intervention) and 138 (42.3%) between December 1st, 2015 and April 30th, 2016 (post-stewardship intervention). Patients characteristics are reported in Table 1.

CAP was the most frequent type of pneumonia diagnosed by far (overall 231/326, 70.9%), followed by HCAP (95/326, 29.1%). No significant differences emerged in their distribution by sex ($p=0.452$) and by pre- and post-intervention groups ($p=0.153$). Over 92.0% (300/326) of pneumonia included in the study were treated in four hospital wards only, with no significant differences in numerical distribution and type of infection in pre- and post-intervention groups. A high level of compliance with International Guidelines of the variable drug for CAP was found in pre-intervention group (105/139, 75.5%) with a slight non-statistically significant improvement in post-intervention group: 71/92, 77.2%; ($p=0.774$). The compliance with Regional Recommendation of the variable drug was lower both for CAP and HCAP, as reported in Table 2.

A significant improvement in the compliance with Regional Recommendations emerged for CAP (pre: 54/139, 38.8% vs post: 48/92, 52.2%; $p=0.045$), but not for HCAP (pre: 3/49, 6.1% vs post: 8/46, 17.4%; $p=0.163$) (Table 2; Figure 1).

Table 1 - Clinical characteristics of patients included in the study.

Characteristics	PRE-intervention	POST-intervention	p-value
Patients n.	188	138	-
Gender			
F	92/188 (48.9%)	69/138 (50.0%)	p = 0.849
M	96/188 (51.1%)	69/138 (50.0%)	
Age (years)			
F	78.9 ± 16.7	80.1 ± 11.6	p = 0.619
M	73.6 ± 16.9	75.6 ± 11.5	p = 0.403
Type of Pneumonia			
CAP	139/188 (73.9%)	92/138 (66.7%)	p = 0.153
HCAP	49/188 (26.1%)	46/138 (33.3%)	
Comorbidities			
no	81/188 (43.1%)	30/138 (21.7%)	p = 0.000
yes	107/188 (56.9%)	108/138 (78.3%)	
Sepsis			
no	102/188 (54.3%)	57/138 (41.3%)	p = 0.020
yes	86/188 (45.7%)	81/138 (58.7%)	
Renal failure			
no	134/188 (71.3%)	80/138 (58.0%)	p = 0.012
yes	54/188 (28.7%)	58/138 (42.0%)	
MDR risk factors			
no	138/188 (73.4%)	90/138 (65.2%)	p = 0.111
yes	50/188 (26.6%)	48/138 (34.8%)	
<i>P. aeruginosa</i> risk factors			
no	156/188 (83.0%)	111/138 (80.4%)	p = 0.555
yes	32/188 (17.0%)	27/138 (19.6%)	

Analyzing the differences between pre- and post-stewardship interventions, in the treatment of CAP a significant increase in the use of amoxicillin/clavulanate (pre: 51/139, 36.7% vs post: 47/92, 51.1%; p=0.030) and a significant decrease in the use of levofloxacin (pre: 66/139, 47.5% vs post: 25/92, 27.2%; p=0.002) was highlighted. In the treatment of HCAP, an increase in the use of piperacillin/tazobactam (pre: 20/49, 40.8% vs post: 27/46, 58.7%; p=0.082) and a decrease in the use of levofloxacin (pre: 13/49, 26.5% vs post: 9/46, 19.6%; p=0.421), although in both cases not statistically significant, were reported. For both types of pneumonia, no significant variation in adherence to Regional Recommendations was registered for the other two considered variables (dosage and duration of treatment)

between pre- and post- intervention groups (Table 2). In detail, therapy for CAP in the pre-stewardship phase was longer than recommended in 63/139 cases (45.3%) and shorter in 31/139 cases (22.3%), while in the post-stewardship phase it was longer in 43/92 cases (46.7%) and shorter in 16/92 cases (17.4%). Conversely, therapy for HCAP in the pre-stewardship phase was longer than recommended in 10/49 cases (20.4%) and shorter in 17/49 cases (34.7%), while in the post-stewardship phase it was longer in 6/46 cases (13.0%) and shorter in 18/46 cases (39.1%). Amoxicillin-clavulanate (non-compliant dosage: pre 24/51, 47.1% vs post 26/47, 55.3%), levofloxacin (non-compliant dosage: pre 32/66, 48.5% vs post 13/25, 52.0%), and piperacillin/tazobactam (non-compliant dosage: pre

Table 2 - CAP and HCAP – Compliance of drug, dosage and duration of treatment with Regional Recommendations.

Variable	PRE-intervention	POST-intervention	p-value
CAP			
Drug			p = 0.045
compliant	54/139 (38.8%)	48/92 (52.2%)	
not compliant	85/139 (61.2%)	44/92 (47.8%)	
Dosage			p = 0.874
compliant	65/139 (46.8%)	44/92 (47.8%)	
not compliant	74/139 (53.2%)	48/92 (52.2%)	
Duration			p = 0.582
compliant	45/139 (32.4%)	33/92 (35.9%)	
not compliant	94/139 (67.6%)	59/92 (64.1%)	
Overall (Drug + Dosage + Duration)			p = 0.956
compliant therapy	20/139 (14.4%)	13/92 (14.1%)	
not compliant therapy	119/139 (85.6%)	79/92 (85.9%)	
HCAP			
Drug			p = 0.163
compliant	3/49 (6.1%)	8/46 (17.4%)	
not compliant	46/49 (93.9%)	38/46 (82.6%)	
Dosage			p = 0.110
compliant	24/49 (49.0%)	30/46 (65.2%)	
not compliant	25/49 (51.0%)	16/46 (34.8%)	
Duration			p = 0.774
compliant	22/49 (44.9%)	22/46 (47.8%)	
not compliant	27/49 (55.1%)	24/46 (52.2%)	
Overall (Drug + Dosage + Duration)			p = 0.229
compliant therapy	2/49 (4.1%)	6/46 (13.0%)	
not compliant therapy	47/49 (95.9%)	40/46 (87.0%)	

13/24, 54.2% vs post 10/19, 52.6%) were the drugs most frequently prescribed in a non-compliant dosage for CAP, with no significant differences between pre- and post-stewardship intervention. Drugs most frequently prescribed in a non-compliant dosage for HCAP were piperacillin/tazobactam (non-compliant dosage: pre 13/20, 65.0% vs post 9/27, 33.3%) and levofloxacin (non-compliant dosage: pre 6/13, 46.2% vs post 5/9, 55.6%). The decrease in non-compliance for piperacillin/tazobactam resulted statistically significant (p=0.031). Contemporary compliance of the variables drug, dosage and duration of treatment resulted low for both types

of pneumonia and the intervention did not change significantly the performance neither for CAP (pre: 20/139, 14.4% vs post: 13/92, 14.1%; p=0.956), nor for HCAP (pre: 2/49, 4.1% vs post: 6/46, 13.0%; p=0.115) (Table 2).

Analyzing some specific risk factors in the studied population (Table 3), no improvement in the compliance of drug(s)' dosage between pre- and post-intervention emerged in patients with renal failure. In the totality of cases of non-compliance (over 50% both pre- and post-intervention), dosages were higher than recommended. A slight but not significant improvement in the drug choice between pre- and post-

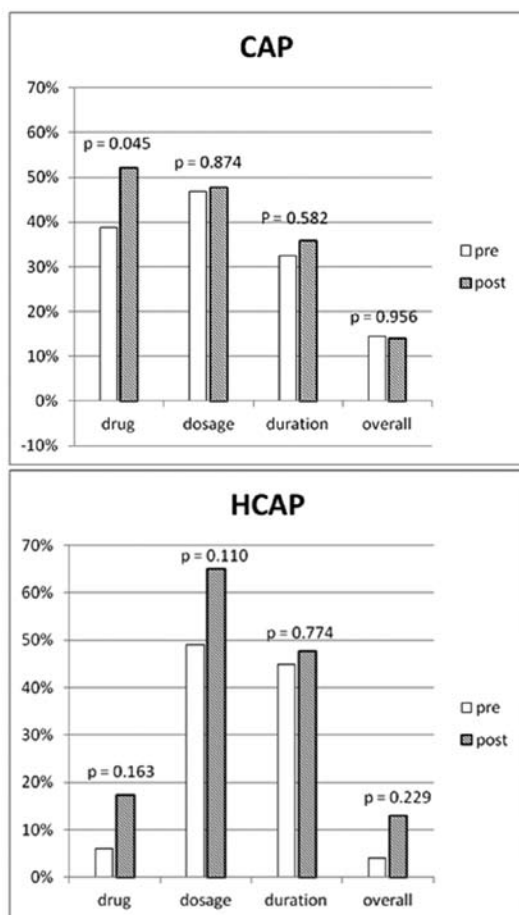


Figure 1 - Comparison of compliance with Regional Recommendations between pre- and post-intervention groups for drug, dosage and duration of treatment in CAP and HCAP.

intervention emerged in patients with risk factors for *P.aeruginosa*. Finally, the (re-) evaluation of empiric therapy after 72 hours from its start, showed no significant differences between the two phases (pre: 68/188, 36.2% vs post 52/138, 37.7%) (Table 3).

Results from multivariate regression models suggested that the intervention was significantly associated (OR 2.1, 95% CI 1.2-3.6) with a higher likelihood of being treated with one or more drugs in agreement with Regional Recommendations, as was

“having a CAP instead of a HCAP” (OR 6.8, 95%CI 3.4-13.9) (Table 4).

In older people, the possibility of receiving a treatment adherent to Regional Recommendations is lower than in younger ones (OR 0.98, 95%CI 0.96-1.00). Patients with no risk factors for *Pseudomonas* spp. are more likely to receive the correct drug (OR 3.8, 95%CI 1.7-8.1), the correct dosage (OR 2.2, 95%CI 1.2-4.0) and the correct duration of therapy (OR 4.2, 95%CI 2.0-9.0).

Discussion

This study stresses the need to assess the impact of programs aimed at increasing the appropriate use of antibiotics at local level in addition to the adoption of bundle, procedures and best practices aiming at reducing the preventable proportion pneumonia (20). Our results can be useful to most hospitals since our study population is largely comparable to similar studies (19, 21-22), confirming a higher prevalence of CAP (70.9%) over HCAP. Conversely, the 70% adherence to International Guidelines for CAP (type of drug) differs significantly from available international data (21, 23-25) suggesting on one side a good widespread knowledge of the basic therapeutic management of pneumonia among professionals, on the other the need to focus on the interaction between internationally accepted recommendations and those proposed at a local level according to local epidemiology.

In our study, while drug compliance to International Recommendations did not change in pre- and post- intervention (it was not the target of our intervention), we achieved a statistically significant increase for drug compliance in CAP. The adherence to Regional Recommendations for the variable drug increased also in HCAP but the limited number of cases made it difficult to achieve statistical significance.

Table 3 - Compliance with Regional Recommendations in patients with renal failure and risk factors for *P. aeruginosa*; (re-)evaluation of empiric therapy after 72 h from its start.

Variable	PRE-intervention	POST-intervention	p-value
Dosage in patients with renal failure			p = 0.876
compliant	25/54 (46.3%)	26/58 (44.8%)	
not compliant	29/54 (53.7%)	32/58 (55.2%)	
Drug for <i>P. aeruginosa</i> in patients with risk factors			p = 0.115
yes	6/32 (18.8%)	10/27 (37.0%)	
no	26/32 (81.2%)	17/27 (63.0%)	
Therapy (re-)evaluation after 72 hours			p = 0.882
yes	68/188 (36.2%)	52/138 (37.7%)	
no	117/188 (62.2%)	83/138 (60.1%)	
not applicable	3/188 (1.6%)	3/138 (2.2%)	

Levofloxacin, amoxicillin-clavulanate and piperacillin-tazobactam, as a consequence of their very common use in CAP (amoxicillin-clavulanate, levofloxacin) and HCAP (piperacillin-tazobactam), were the drugs most frequently included in therapies. Since levofloxacin was highly used in recent years in FVG and, consequently, it has a high potential of selection of MDR bacteria, the reduction of its prescription and consumption showed the positive impact of the FVG Regional AMS program.

In most of the available evidence (10, 19, 21), only one of the parameters considered in our study (usually type of drug) was evaluated, mainly in combination with other types of variables (time of treatment start, patients' outcome, etc.): the choice to include drug, dosage and duration of therapy in our evaluation was driven not only by the need to ensure a more reliable and accurate assessment of every single treatment, but also to identify more clearly the critical issues and practices about antibiotic prescriptions, in order to define targeted areas for improvement.

The data analysis on the duration of therapy in the two types of pneumonia showed, for both CAP and HCAP, a more than 50% non-compliance degree with Regional Recommendations. In detail,

for CAP we registered a tendency for an excessive duration. Conversely, in most cases, therapy for HCAP resulted shorter than in the recommended duration, possibly suggesting that a substantial proportion of these pulmonary infections were unrecognized and managed as CAP by physicians.

Last but not least, a slight improvement in compliance for the variable drug dosage was observed in post-stewardship interventions group for CAP and HCAP, even though in CAP the adherence degree to recommendations remained below 50%.

Differences in treating CAP and HCAP could suggest that the differential diagnosis between CAP and HCAP could be better promoted among clinicians since the lack of compliance could be partially justified with the lack of knowledge. In our study, reasons for the poor agreement with Regional Recommendations in HCAP could be similar to those pointed out by others (23, 26): HCAP has been recognized as a new type of pneumonia recently (IDSA-ATS Guidelines 2005), and the lack of awareness/knowledge by physicians on its epidemiologic, etiologic and diagnostic-therapeutic features could explain the wrong categorization of HCAP as CAP and consequently the poorer compliance. According to what suggested

Table 4 - Multivariate analysis of therapeutic compliance (Odds Ratio Estimates and Wald Confidence Intervals).

Independent variable	Compliant drug		Compliant dosage		Compliant duration		Compliant therapy					
	OR	95%	OR	95%	OR	95%	OR	95%				
Stewardship Intervention POST vs PRE	2.109	1.240	3.586	1.378	0.868	2.187	1.241	0.768	2.004	1.445	0.721	2.897
Age continuous years	0.978	0.961	0.996	0.994	0.978	1.011	1.002	0.985	1.019	0.976	0.955	0.997
Sex F vs M	0.874	0.520	1.469	1.504	0.953	2.375	0.922	0.571	1.488	0.770	0.388	1.532
Sepsis No vs yes	0.800	0.479	1.337	1.199	0.762	1.885	1.434	0.893	2.302	1.103	0.560	2.175
Renal failure No vs yes	1.034	0.579	1.847	1.251	0.755	2.073	0.824	0.488	1.393	1.190	0.532	2.660
Beta-lactam allergy No vs yes	1.502	0.417	5.418	0.845	0.296	2.411	0.671	0.230	1.954	0.924	0.193	4.432
Risk factors <i>P. aeruginosa</i> No vs yes	3.754	1.743	8.084	2.221	1.218	4.049	4.238	1.985	9.048	-	-	-
Type of pneumonia CAP vs HCAP	6.832	3.358	13.899	0.701	0.426	1.152	0.620	0.373	1.031	1.661	0.720	3.830

by some Authors (27, 28), a more specific definition of HCAP could help clinicians to identify it and to follow the right therapeutic approach. However, as room for improvement has been highlighted, a specific training on the therapeutic management of HCAP emerged as a need.

Administering drugs without adjusting to patient's renal function is one of the first causes of dosage inadequacy in both types of pneumonia: more than 50% of patients with renal impairment included in our study were treated with at least one antibiotic at an inappropriate dosage (always higher than recommended). The issue is of great concern if we consider population ageing and, consequently, the rate of patients with chronic diseases; thus, specific training on this topic addressed to healthcare professionals should be considered a priority for healthcare organizations that aim to promote a safer drugs usage. Similarly, room for improvement is clearly highlighted in 72 hours re-evaluation of the empiric antibiotic treatment.

As emerged in other similar studies (19, 25, 29-30), prescribers could be influenced by factors as a conscious rejection of the use of clinical guidelines based on belief that they are not appropriate and/or do not provide the most suitable therapeutic options for the type of patient, the choice of limiting the use of broad spectrum and too expensive antimicrobials, the lack of knowledge and/or awareness of antimicrobials use. Thus, specific training on a proper use of antimicrobials to all professionals, with reference to the prescription practice in all its phases (drug selection, dosage definition, duration of therapy), represents a cornerstone to optimize the therapeutic management of pneumonia. Several factors could explain the differences in compliance highlighted by our study and by similar studies in literature (31). In Regional Recommendations, one single drug was allowed as first line choice for CAP and HCAP: so, a higher compliance degree

was registered with International Guidelines (e.g. IDSA (11-12)) for the treatment of CAP, where alternatives to penicillins (e.g. cephalosporins and quinolones) were included as a first-choice treatment. Conversely, the presence of renal impairment and peculiarities of epidemiological pattern could not be considered as contributing factors to the lack of compliance. First of all, the appropriate dosage adjustments in patients with renal failure were specified in the Regional Recommendations and were therefore easily accessible to the clinician; secondly, the guidelines were produced on the basis of local epidemiological data and with regard to the regional antibiotic resistance patterns.

Our study also highlighted room for improvement in the treatment of patients with documented risk factors for infection/colonization due to *P. aeruginosa*; in over 70% of them, the administered antibiotic treatment did not include drugs active against this pathogen. Possible reasons for under-treatment could lie in the underestimation of the risks at the initial patient's assessment (poor collection of medical data at admission) and, when the presence of predisposing factors was documented, in lack of knowledge about epidemiological, etiological and clinical aspects of the infectious diseases related to these underlying conditions. Multivariate analysis confirmed the significantly higher likelihood to be treated with the most appropriate drug(s) in patients with CAP than in HCAP. The presence of risk factors for *P. aeruginosa* infection/colonization was significantly associated with increased risk of non-adherence to the Regional Recommendations. Multivariate analysis confirmed that local AMS intervention based on training of prescribers and booklets with therapeutic suggestions significantly improved the likelihood of being treated with one or more antimicrobials in agreement with local Recommendations keeping

unchanged the adherence to International Guidelines.

The good size of the population in the study, the small number of wards where pneumonia were selected from pre- and post-stewardship interventions phases (that allowed a better comparability of data homogeneity in diagnostic and therapeutic management of patients with pneumonia), the data reliability guaranteed by the involvement of a small number of trained researchers (a model validation study was done) and the evaluation of three variables to assess the appropriateness of antibiotic prescriptions (higher accuracy) should be listed as the main strength points of our study.

Finally, this study stresses once more the need to monitor the results when implementing an AMS program at a local level. In addition to assessing the ability of the program to modify the practice in the desired direction, monitoring provides an opportunity to better understand different aspects of the problem. In our case, we urge better training of professionals not only on the appropriate use of antibiotics but also on their safe use in patients with specific problems (*P. aeruginosa* infections, renal failure).

Conclusions

Our study provided a state of the art on antimicrobials use and compliance degree to Regional Recommendations for the treatment of patients with bacterial pneumonia in an Italian Academic Hospital; it clearly highlighted that some critical issues and rooms for improvements currently exist. Our study stresses, also, the need to systematically adopt evaluation schemes when implementing AMS programs, taking into account antibiotic dosage, duration of therapy, assessment after 72 hours and renal impairment. Specific professional

training on a proper use of antimicrobials, with particular reference to the prescription practice in all its phases (drug selection, dosage definition, duration of therapy), represents a priority in order to promote a more rational and evidence-based clinical practice and to improve patients' outcomes (32).

Conflict of interest: The authors declare that they have no competing interests

Riassunto

Valutazione d'impatto delle raccomandazioni cliniche sull'uso degli antibiotici nelle CAP e nelle HCAP: risultati dell'implementazione di un programma di antimicrobial stewardship in un ospedale universitario

Premesse. Le linee guida e le raccomandazioni locali per il trattamento delle comuni patologie infettive sono un elemento fondamentale della maggior parte dei programmi di Antimicrobial Stewardship. La valutazione dell'aderenza alle linee guida costituisce un metodo efficace di valutazione della qualità di questi programmi; il presente modello di valutazione si propone nello specifico di valutare il trattamento antibiotico delle polmoniti.

Disegno dello studio. Uno studio retrospettivo di confronto pre-post intervento è stato condotto in un Ospedale Universitario italiano del Nord-Est.

Metodi. 231 pazienti con Community-Acquired Pneumonia e 95 con Healthcare-Associated Pneumonia sono stati divisi in due gruppi, pre- e post- intervento (rispettivamente composti da 188 e 138 pazienti). Un corso di formazione e un libretto tascabile sulle raccomandazioni regionali per il trattamento delle polmoniti sono state le strategie di Antimicrobial Stewardship adottate. Il grado di aderenza delle prescrizioni alle raccomandazioni regionali è stato valutato in termini di *molecola*, *dose* e *durata* della terapia in entrambi i gruppi, sia per Community-Acquired Pneumonia che per Healthcare-Associated Pneumonia; è stato effettuato anche un confronto della terapia prescritta con le linee guida internazionali.

Risultati. Un miglioramento significativo è emerso nell'adesione alle raccomandazioni regionali per la variabile *molecola* per il trattamento delle Community-Acquired Pneumonia (38.8% vs 52.2%), ma non per

le Healthcare-Associated Pneumonia; non si sono registrate variazioni significative per quanto riguarda la *dose* o la *durata* di terapia. La riduzione significativa di prescrizione della levofloxacina ha dimostrato l'impatto positivo del programma regionale di Antimicrobial Stewardship. Inoltre, è emerso un elevato livello di adesione alle linee guida internazionali per la variabile *molecola* per il trattamento delle Community-Acquired Pneumonia in entrambi i gruppi (rispettivamente 75.5% and 77.2%).

Conclusioni. Questo studio evidenzia la persistenza di margini di miglioramento nella prescrizione della terapia antibiotica per Community-Acquired Pneumonia e Healthcare-Associated Pneumonia. Per il miglioramento dell'aderenza alle raccomandazioni regionali è necessario individuare nuove strategie per un miglior utilizzo degli strumenti già adottati e per l'individuazione di nuove iniziative di Antimicrobial Stewardship.

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