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ORIGINAL RESEARCH

Comparative Impact of C-Reactive Protein Testing in Hospitalized Patients with Acute Respiratory Tract Infection: A Retrospective Cohort Study

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ABSTRACT

Introduction: Evidence-based data on the usefulness of C-reactive protein (CRP) monitoring in patient outcomes are lacking. CRP testing in patients with acute respiratory tract infections (ARTIs) showed wide variability between internal medicine wards in our hospital network. In this study we aimed to investigate whether repetitive CRP tests might influence the switch of antibiotic therapy from intravenous (IV) to oral (PO) route and whether CRP measurements affect the combined outcome of readmission and in-hospital mortality.

Methods: This was a retrospective cohort study conducted in two internal medicine wards selected in a network of five teaching hospitals on the basis of their CRP prescription frequency. Clinical and laboratory data of 296 patients with ARTIs and admitted from 1 January to 31 December 2016 were analyzed.

Results: The mean ± SD of CRP tests/patient and the in-hospital length of antibiotic therapy (days) in the low-CRP (L-CRP) vs the high-CRP (H-CRP) wards were 1.14 ± 0.62 vs 3.43 ± 1.54 ($p < 0.001$) and 7.1 ± 2.6 vs 7.5 ± 3.2 ($p = 0.298$), respectively. The probability of antibiotic switching was higher in the L-CRP ward (HR 2.90, 95% CI 1.69–4.95, $p < 0.001$) correlating with the lower number of CRP determinations (HR 1.20, 95% CI 1.01–1.41, $p = 0.034$). In-hospital readmissions and mortality rates did not significantly differ between the two wards (L-CRP 17.1% vs H-CRP 10.0%, $p = 0.133$). The number of CRP determinations affected the combined outcome (OR 1.38, 95% CI 1.01–1.90, $p = 0.043$).

Conclusions: Repetitive CRP testing in ARTIs offers no added value to either antibiotic switch or patient outcomes in hospitalized patients in internal medicine wards.

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INTRODUCTION

Appropriate use of laboratory tests is an important target for healthcare quality improvement. Unnecessary diagnostic tests increase healthcare costs, lead to unwarranted investigations and therapeutic prescriptions, and may negatively impact patient outcomes [1]. Repetitive laboratory tests in stable patients did not positively affect the clinical outcome with regards to mortality, length of in-hospital stay, and readmission rate [2–4]. The Choosing Wisely Campaign, an initiative launched by the American Board of Internal Medicine, aimed to target unnecessary low-value investigations and treatment [5, 6]. Similarly, the Swiss Society of General Internal Medicine recommends to avoid ordering routine and duplicative laboratory tests in hospital care [4]. C-reactive protein (CRP) is a biomarker considered as one of the most sensitive acute-phase reactants of systemic inflammation and as a strong independent predictor of antibiotic prescription [7].

Serum CRP is also widely used in the follow-up of hospitalized patients with acute respiratory tract infections (ARTIs), which represent one of the most common reasons for adults presenting to primary care settings and for hospitalization worldwide [8].

Evidence-based data on the usefulness of CRP monitoring in improving patient outcomes are lacking.

In 2014, a project was launched that aimed at enhancing adherence to the Choosing Wisely recommendation on laboratory tests in a network of five public teaching hospitals in southern Switzerland (Ente Ospedaliero Cantonale, EOC) [9]. The project was addressed to all healthcare providers of the EOC internal medicine wards and explored the efficacy of a multilevel strategy (educational plus audit and feedback plus web-based open continuous benchmarking), aiming at reducing unnecessary inpatient laboratory testing. The web-based continuous benchmarking, called "Reporting Wisely", consisted of a monitoring system that automatically performed a blood withdrawal benchmarking between hospital wards becoming an open resource available to all healthcare providers in the network. The monitoring started in January 2015, but was opened to all staff members only from January 2016. The web-based clinical support recorded continuously, by updating the data weekly, the number and volume of blood withdrawals for every ward of the network up to the unit level, providing a trend in the evolution of the laboratory prescriptions, and a benchmark for the other units and wards of the network. Thanks to this reporting system we noticed that physicians' attitudes towards prescribing CRP tests showed wide variability across internal medicine wards in our hospital network.

The primary aim of this study was to investigate whether repetitive CRP tests in hospitalized patients with ARTIs might influence the switch of the antibiotic therapy from intravenous (IV) to oral (PO) administration. Secondly, we aimed to estimate if CRP measurements could influence the combined outcome of readmission and in-hospital mortality.

METHODS

Study Design and Setting

We conducted a retrospective multicenter cohort study in adult patients (older than 16 years) admitted for ARTIs in the internal medicine wards of two teaching hospitals in the Italian-speaking region of Switzerland ("Ospedale Regionale della Beata Vergine", Mendrisio and "Ospedale Regionale Bellinzona e Valli", Bellinzona) during the period from 1 January to 31 December 2016. The two hospital wards are part of a network of five teaching hospitals of the EOC. The two wards were selected on the basis of a preliminary analysis of CRP frequency determination in the "Reporting Wisely" dashboard, which revealed different patterns: low-CRP (L-CRP) and high-CRP (H-CRP) ordering [9].

All clinical and laboratory data of hospitalized patients admitted for ARTIs were collected from patient charts and electronic medical records used for patient clinical management. Cases of ARTIs were collected on the basis of ICD-10 code in the following diagnostic groups: acute upper respiratory infections (J10.0–J10.1), influenza and pneumonia (J11.0–J18.9), bronchitis and other acute lower respiratory infections (J20–J22, J85, J86), chronic obstructive pulmonary disease with acute lower respiratory infection (J44.0–J44.1), Legionnaires' disease (A48.1).

The data collected were anonymized. The study was conducted in accordance with the Declaration of Helsinki. The study was exempt from institutional review board approval by the Swiss Ethics Committee because it involved anonymous secondary data only. Informed consent was not obtained because the data were from de-identified and previously collected administrative data.

Measures and Data Collection

We retrospectively collected data from 296 patients aged 18 years or more hospitalized for ARTIs at the internal medicine wards L-CRP and H-CRP. Patient demographic and anthropometric characteristics and laboratory data were recorded. Data included gender, age, body mass index (BMI), co-existing illnesses (diabetes, hypertension, history of cerebrovascular or cardiovascular diseases, renal failure, heart failure, liver failure, rheumatological diseases, chronic obstructive pulmonary disease, neurological diseases, HIV, immunosuppression, hematologic malignancy, solid malignancy). Clinically relevant parameters were recorded, including temperature, respiratory rate, heart rate, and blood pressure. Laboratory data included white blood cell count and CRP level. Radiological exams such as X-ray radiography, and computed tomography (CT), were recorded.

Characteristics of hospitalization such as length of stay, in-hospital duration of antibiotic therapy, and timing of antibiotic switch from intravenous to oral pathway were also collected.

Outcome Measures

The primary endpoint was to evaluate the added value of CRP measurement in the timing of switching of antibiotic therapy from IV to PO administration in patients hospitalized for ARTIs. The secondary endpoint was a composite measure of mortality and readmission. Mortality was defined as hospital death during the index admission. Readmission was defined as an unplanned admission to the same hospital within 30 days after discharge.

Statistical Analysis

Descriptive statistics are presented mean ± standard deviation for continuous variables, and as numbers and percentages for categorical variables. Continuous and categorical variables were compared using the Kruskal and χ^2 tests, respectively. To assess the associations between CRP testing and timing of antibiotic route switching, the Cox proportional hazards ratio was applied. The hazard ratios (HRs) are presented with 95% confidence intervals (95% CIs) and p values testing the null hypothesis of the HRs being equal to 1. Kaplan–Meier curve analysis was used to estimate antibiotic route switching over time. In the Kaplan–Meier curve analysis of antibiotic route switching, patients were divided into subgroups according to hospitalization in the L-CRP or H-CRP internal medicine ward. Comparisons were performed with the log-rank test. Multivariable logistic models were used for our composite secondary outcome of mortality and readmission to examine the relationship with CRP determination. Multivariate models were adjusted for the following covariates: age, gender, case mix, in-hospital length of stay, and first value of CRP. The Case Mix Index is the relative value assigned to the Swiss Diagnosis-Related Group (DRG) at hospital discharge and corresponds to the cost weights of all hospitalized patients in a limited period divided by the number of admissions. Data analysis was performed using R statistical software (www.r-project.org). Statistical significance for all outcomes was set at $p \leq 0.05$.

RESULTS

A total of 296 patients hospitalized for ARTIs in the L-CRP ($N = 134$) and H-CRP ($N = 162$) internal medicine wards were analyzed. The demographic and clinical characteristics of the study population are shown in Table 1. The two internal medicine wards significantly differ in the number of CRP tests performed per patient. The mean (± SD) of CRP tests/patient/hospitalization was 1.14 (± 0.62) in the L-CRP and 3.43 (± 1.54) in the H-CRP ward, respectively ($p < 0.001$). The two wards did not significantly differ in their case mix (L-CRP 0.90 ± 0.27 vs H-CRP 0.84 ± 0.25, $p = 0.074$) or for in-hospital length of stay (L-CRP 7.9 ± 3.4 vs H-CRP 8.0 ± 3.2 days, $p = 0.891$). There was significant difference in patient age (L-CRP 74 ± 16.8 vs H-CRP 69.8 ± 17.5 years, $p = 0.011$).

The cases diagnosed as ARTIs presented the following distribution in the study cohort (*n*, %): pneumonia associated or not to influenza infection 235, 79.4%; bronchitis and other acute lower respiratory infections 38, 12.8%; acute upper respiratory infection 8, 2.7%; Legionnaires' disease 15, 5.1%. Cases of chronic obstructive pulmonary disease with acute lower respiratory tract infection were not analyzed. The sub-analysis of the considered diagnosis according to ward (L-CRP vs H-CRP) showed no significant differences in the incidence of pneumonia (75.4% vs 82.7%, $p = 0.158$), acute bronchitis (14.4% vs 12.4%, $p = 0.917$), and upper RTIs (2.24% vs 3.1%, $p = 0.930$).

The in-hospital length of antibiotic therapy (L-CRP 7.1 ± 2.6 vs H-CRP 7.5 ± 3.2 days, $p = 0.298$) was the same in the two wards, while significant differences were found in the timing of antibiotic route switching from IV to PO (log-rank difference between groups $p < 0.001$). Kaplan–Meier estimates of the cumulative probability of antibiotic route switching are shown in Fig. 1. The risk factors associated with probability of antibiotic route switching are shown in Table 2. In the multivariable Cox proportional model the probability of antibiotic route switching significantly increased in the L-CRP ward (HR 2.90, 95% CI 1.69–4.95, $p < 0.001$) and with the lower number of CRP

Table 1 Characteristics of the study population according to internal medicine services (low-CRP ward and high-CRP ward) ($n = 296$)

Demographic	L-CRP ward ($n = 134$)	H-CRP ward ($n = 162$)	*p* value
Age (years)	74 ± 16.8	69.8 ± 17.5	0.011
Gender, female (%)	43.3	41.9	0.913
BMI, kg/m^2	25.7 ± 4.8	25.6 ± 5.9	0.693
Main co-morbidities			
Case mix	0.90 ± 0.27	0.84 ± 0.25	0.074
Arterial hypertension (%)	70.9	54.9	0.007
Congestive heart failure (%)	17	21.6	0.417
Diabetes (%)	27.6	24.7	0.662
COPD and asthma (%)	34.3	27.7	0.276
Neurological disease (%)	32	29	0.741
Liver disease (%)	14	17	0.570
Chronic kidney disease(%)	19.4	29	0.076
HIV, rheumatic disease, organ transplant (%)	21.6	8	0.001
Hemato-oncological disease	15.7	15.4	0.999
Clinical data			
Temperature (°C)	37.6 ± 0.1	37.5 ± 0.1	0.319

Table 1 continued

Demographic	L-CRP ward (n = 134)	H-CRP ward (n = 162)	p value
Systolic blood pressure (mmHg)	129.0 ± 19.0	127.0 ± 25.0	0.181
Diastolic blood pressure (mmHg)	74.1 ± 11.1	73.0 ± 13.7	0.441
Heart rate (beats/min)	87.3 ± 15.8	92.5 ± 19.9	0.016
Oxygen saturation (%)	94 (90–96)	94 (92–96)	0.363
Oxygen treatment requirement DH (%)	5.2	17.3	0.002
Systemic steroids (%)	11.2	21.0	0.036
Antibiotic prescription (%)	42.5	43.9	0.916
Antibiotic length DH (days)	7.1 ± 2.6	7.5 ± 3.2	0.298
Chest radiography DH	1.1 ± 0.48	1.1 ± 0.53	0.959
Pleural effusion (%)	17.9	13.6	0.388
Chest CT DH (%)	0.1 ± 0.30	0.1 ± 0.32	0.961
In-hospital length of stay (days)	7.9 ± 3.4	8.0 ± 3.2	0.891
Mortality/ readmission, n (%)	23 (17.1)	17 (10)	0.133
Laboratory data			
CRP tests/patient/ DH	1.14 ± 0.62	3.43 ± 1.54	< 0.001
CRP, first value (mg/L)	124 ± 121	118 ± 105	0.658
Neutrophil tests/patient/ DH	1.1 ± 0.46	1.67 ± 1.14	0.153
Neutrophil first value (10^9/l)	8.63 ± 4	9.41 ± 5.16	0.153

BMI body mass index, *COPD* chronic obstructive pulmonary disease, *CVD* chronic kidney disease, *CRP* C-reactive protein, *DH* during hospitalization, *L-CRP* low-CRP, *H-CRP* high-CRP

tests performed (HR 1.20, 95% CI 1.01–1.41, p = 0.034), while it decreased with higher numbers of hospitalization days (HR 0.85, 95% CI 0.78–0.92, p < 0.001).

The cumulative incidence of mortality and hospital readmission rates did not significantly differ between the two services (L-CRP 23% vs H-CRP 17%, p = 0.133), as reported in Table 1. A multivariable logistic regression model was developed to examine variables associated with the combined secondary outcome of mortality and hospital readmission. The number of CRP determinations, the first value of CRP, and the patients' case mix significantly affected the combined outcome (OR 1.38, 95% CI 1.01–1.90, p = 0.043; OR 0.99, 95% CI 0.98–0.99, p = 0.043; OR 5.89, 95% CI 1.20–29.5, p = 0.029, respectively) (Table 3).

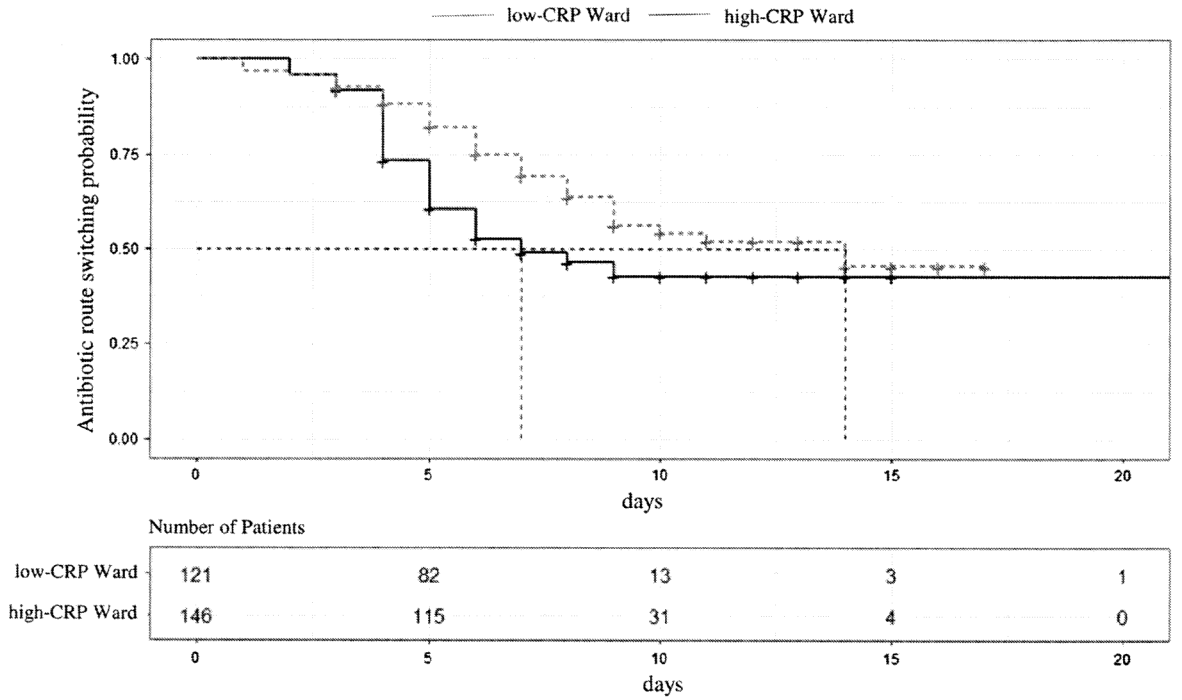

Fig. 1 Kaplan–Meier curve of antibiotic route switching over hospitalization time in the two internal medicine wards. Continuous black line represents H-CRP ward, dotted red line represents L-CRP ward, x-axis represents length of hospitalization in days, y-axis represents probability of antibiotic route switching

Table 2 Risk factors for antibiotic route switching during hospitalization (IV vs PO)

Variables	HR	CI (95%)	*p* value
Age	1.00	0.99–1.02	0.370
Gender	1.26	0.86–1.83	0.233
Ward (L-CRP vs H-CRP)	2.90	1.69–4.95	< 0.001
Case mix	0.76	0.34–1.69	0.497
CRP value	1.00	0.99–1.00	0.081
In-hospital length of stay	0.85	0.78–0.92	< 0.001
CRP tests/patient/DH	1.20	1.01–1.41	0.034

Table 3 Risk factors for the combined outcome of mortality and readmission

Variables	OR	CI (95%)	*p* value
Age	1.01	0.99–1.04	0.358
Gender	1.48	0.67–3.37	0.336
Ward (L-CRP vs H-CRP)	0.93	0.32–2.79	0.890
Case mix	5.89	1.20–29.5	0.029
CRP first value	0.99	0.98–0.99	0.043
In-hospital length of stay	0.91	0.79–1.05	0.210
CRP tests/patient/DH	1.38	1.01–1.90	0.043

DISCUSSION

This study shows that repeated CRP testing for hospitalized patients with ARTIs delays physicians' decision for antibiotic route switching and does not affect mortality and readmission outcomes.

The present findings highlight, moreover, wide differences in CRP prescriptions in hospitalized patients between internal medicine wards of the same hospital network, confirming the large variability in laboratory prescriptions, previously revealed by the web-based monitoring system "Reporting Wisely" [9]. In particular,

the average number of CRP tests/patient was found to be almost three times higher in the H-CRP ward than in the L-CRP ward.

Unexpected differences in prescribing behavior arise, even though patients were hospitalized in a hospital network that shares the same guidelines and were comparable for clinical characteristics such as comorbidities, case mix, and length of hospital stay. Interestingly, patients of the L-CRP ward were older and had a higher prevalence of immunosuppressive therapy than those of the H-CRP ward.

Previous studies showed that laboratory test utilization is higher in teaching than in non-teaching hospitals, a finding consistent with the fact that residents are less confident and tend to resort to lab use significantly more often than senior physicians [10]. To the best of our knowledge, these are the first data showing that there is a variance in laboratory prescriptions between internal medicine wards within the same teaching hospital network.

The reasons underlying the different physician behaviors are not clearly identifiable. On one hand, in the two wards analyzed, laboratory tests are ordered mainly by residents without differences in the level of in-service training and with the same number of patients cared for by an individual physician. Moreover, it is important to underline that CRP measurements were performed as part of pragmatic routine monitoring and blood test panels. H-CRP and L-CRP wards showed a similar trend in ordering other usually requested blood tests (1.16 vs 0.82, $p < 0.001$ blood withdrawals per patient per day of hospital stay), suggesting different, ward-specific, prescription behavior.

On the other hand, the training target of the residents and the training characteristics between the wards could be of relevance. Physicians who trained in lower-use regions of the country and who are presumed to favor the choice for generalist fields were better at recognizing appropriate conservative management than those who trained in regions of the country associated with higher intensity medical management, and had probably chosen to specialize, as described previously [11, 12]. Nevertheless, although we can speculate that differences in training objective between physicians could partially explain different prescribing behaviors, this aspect was not investigated in this study and consequently we were unable to confirm this hypothesis.

In our study we observed not only different attitudes of the clinicians towards the use of CRP tests as a diagnostic marker but also differences in antibiotic prescriptions. Indeed, physicians of the L-CRP ward not only prescribed fewer laboratory tests to their patients but also prescribed an earlier switching of the antibiotic route from IV to PO, demonstrating that the number of CRP tests is inversely associated with the probability of antibiotic route switching. The usefulness of CRP as a surrogate for response to antibiotic therapy has been widely studied, and in particular the failure of CRP levels to fall within 5 days of the beginning of antibiotics should prompt clinicians to further investigate inadequate antibiotic therapy, unrevealing resistant infection, new infection, or serious non-infection pathology, such as thrombosis or cancer [13]. Delayed normalization of CRP within the first 3–7 days of follow-up is suggestive of inappropriate empirical antibiotic therapy [14]. Other authors demonstrated that daily CRP measurement is useful in assessing clinical severity in patients with community-acquired or nosocomial pneumonia and poor outcome, and can be helpful in the identification of patients with inappropriate antimicrobial therapy [15, 16]. Correct use of CRP tests should be applied to shorten the duration of antibiotic therapy, thus reducing toxicity, adverse events, and the risk of emergence of resistant strains, and finally lowering the costs [15–17].

Our data address the question why, despite this knowledge and recommendations, attitudes of clinicians towards utilizing CRP testing and prescribing antibiotics is so diverse. If we look at the prescriptions in detail, the antibiotic length during hospitalization was exactly the same in the two wards, in accordance with the international and internal guidelines [18, 19]. The difference we noticed in antibiotic prescriptions was significant only for the withdrawal and the switch from IV to PO prescription. The risk factors that influence physicians' decisions to switch from IV to PO

antibiotics in our teaching hospitals appear to lie in the number of CRP prescriptions, making CRP a sort of curb on the decision-making process of the young residents. In the L-CRP ward instead, clinical factors such as fever or respiratory parameters seem to gain the most consideration. Of note, the different attitudes of the clinicians do not impact the combined outcome of readmission and in-hospital mortality in the two wards. The in-hospital length of stay is also equal in the two wards, although the delayed switch is considered by other authors as one of the major factors influencing length of stay for patients with community-acquired pneumonia [20].

Although the present study was not designed to analyze the cost-effectiveness of CRP determination in the context of ARTIs, some points should be highlighted. Previous studies have evaluated this aspect in trials focused on clinical management of respiratory tract infections, showing the absence of any significant effect on outcomes and the cost-effectiveness of CRPs [21–23]. Of note, most of these studies evaluated the cost-effectiveness of point-of-care CRP tests performed with capillary blood samples, in primary care. Studies on the utility of CRP determinations for acute respiratory infections in hospitalized patients are, on the contrary, lacking.

In recent years, the role of procalcitonin has emerged as a safe and effective tool for the clinical management (decisions about starting and/or stopping and duration of antibiotic therapy) of acute respiratory infections in different patient populations and in different clinical settings [24]. However, in our study we did not perform any sub-analysis of this biomarker, because procalcitonin is not part of routine evaluation of hospitalized patients in our hospital network, and there was no procalcitonin measurement in the sample population.

We have to acknowledge some important methodological issues, which limit the postulated cause–effect relationship between CRP measurement and clinical outcome. This is mainly due to biases, which arise in clinical practice, on both patient and physician level, and potentially compromise the interpretation of retrospective data. At both levels the benefit of serial CRP may go beyond clinical outcomes: patients who ask for more exams to reassure themselves about their illness, and clinicians who strive to demonstrate evidence of clinical improvement though serial CRP measurements. These biases, in a retrospective study, are intangible and difficult to quantify, but could be avoided with a prospective patient satisfaction study aimed at exploring whether frequent CRP measurements lead to better patient awareness about the course of the illness and to better doctor–patient communication.

Moreover, several limitations in our study should be acknowledged. A main limitation is its retrospective design, which implies that some important clinical characteristics were not available. We acknowledge that the impact of CRP on clinical management of ARTIs should be investigated prospectively in groups of patients defined by clinical criteria rather than reimbursement codes. Moreover, the cross-sectional nature of our study does not allow us to infer a causal relationship between CRP testing and our outcomes of interest. In addition, although we adjusted for a number of potential confounding factors, we cannot exclude the possibility that other unknown confounding factors might influence the results of the risk factor analysis. Therefore, prospective observational studies or trials are expected to clarify the causal relationship between CRP determination for ARTIs and hospital readmission/mortality. The H-CRP ward also significantly differed in the oxygen treatment requirement and systemic steroids used, and we cannot exclude that it could at least in part affect the outcome. Nevertheless, our results provide evidence that different physician behaviors in patient management could exist, and that structured education is advocated also in a hospital network sharing the same internal clinical guidelines. A patient-centered approach to ARTIs could have potential benefits in clinical practice and patient outcome. A continuous effort with educational programs associated with stewardship strategy, such as the introduction of electronic laboratory utilization systems, is required to effectively reduce unnecessary laboratory tests and costs without compromising patient care [2].

CONCLUSION

Repeated CRP testing for ARTIs offers no added value to either antibiotic switch or patient outcomes in a hospital network sharing the same guidelines. Clinical decision-making seems to remain challenging in the diagnosis and treatment of patients, and clinical evaluation seems to be more useful than the instrumental approach in the treatment of ARTIs.

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Disclosures. Olivier Giannini, Rosaria Del Giorno, Anna Zasa and Luca Gabutti declare that they have no conflicts of interest.

Compliance with Ethics Guidelines. The study was conducted in accordance with the Declaration of Helsinki. The study was exempt from institutional review board approval by the Swiss Ethics Committee because it involved anonymous secondary data only. Informed consent was not obtained because the data were from de-identified and previously collected administrative data.

Data Availability. The dataset analyzed during the current study is available from the corresponding author on reasonable request.

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