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RESPIRATORY INFECTIONS

Non-steroidal Anti-inflammatory Drugs may Worsen the Course of Community-Acquired Pneumonia: A Cohort Study

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Abstract
Purpose Non-steroidal anti-inflammatory drugs (NSAIDs) are frequently prescribed or used as self-medication in cases of community-acquired pneumonia (CAP). Nevertheless, the consequences of such medication on the risk of pleuroparenchymal complications are not well known. The aim was to investigate whether exposure to NSAIDs prior to hospital admission among patients suffering from CAP is associated with the development of pleural complications or a lung abscess.
Methods All consecutive non-immunocompromised patients with CAP and admitted to a university hospital were prospectively included (2-year period). The risk of pleuropulmonary complications was analyzed according to previous exposure to NSAIDs.
Results Of the 221 included patients, 40 (18.1%) had developed a pleuropulmonary complication. NSAIDs intake prior to admission was reported for 24 patients (10.9%) who were younger (50.6 ± 18.5 vs. 66.5 ± 16.4 years; $p = 0.001$), had less comorbidities (60 vs. 25.1%; $p = 0.001$), had a longer duration between the first symptoms of CAP and the start of an antibiotic therapy (6.1 ± 7.6 vs. 2.8 ± 3.8 days; $p = 0.001$), and who had a higher incidence of pleuropulmonary complications (33.3 vs. 16.2%; $p = 0.048$). In multivariate analyses, two factors were independently associated with the development of pleuroparenchymal complications: NSAIDs intake [Odds Ratio (OR) = 2.57 [1.02–6.64]; $p = 0.049$] and alcohol abuse (OR = 2.68 [1.27–5.69]; $p = 0.01$).
Conclusions Our findings suggest that NSAIDs, often taken by young and healthy patients, may worsen the course of CAP with delayed therapy and a higher rate of pleuropulmonary complications.

Keywords Non-steroidal anti-inflammatory drug · Community-acquired pneumonia · Empyema · Parapneumonic effusion · Lung abscess

Abbreviations

95% CI	95% Confidence interval
BMI	Body mass index
CAP	Community-acquired pneumonia
CCI	Charlson Comorbidity Index
ICU	Intensive care unit
LOS	Length of stay
MRSA	Methicillin-resistant *Staphylococcus aureus*
MSSA	Methicillin-susceptible *Staphylococcus aureus*
NSAIDs	Non-steroidal anti-inflammatory drugs
OR	Odds ratio
P. aeruginosa	*Pseudomonas aeruginosa*
PPE	Parapneumonic pleural effusion
PSI	Pneumonia Severity Index
SD	Standard deviation
S. pneumonia	*Streptococcus pneumonia*

Introduction

Community-acquired pneumonia (CAP) is a common pulmonary infection caused by bacterial or viral agents. Its incidence in France is estimated at between 400,000 and 600,000

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cases per year [1]. Lower respiratory airway infections, including CAP, are associated with a poor prognosis and represent the second main cause of death worldwide [2]. The CAP mortality rate ranges from <5% in ambulatory patients to >30% in patients admitted into critical care units [3].

Mortality among individuals with CAP is related to acute respiratory failure or shock, whereas morbidity is often related to complications, such as complicated parapneumonic pleural effusion, empyema, or lung abscess. Parapneumonic pleural effusion (PPE) is the most frequent complication, which occurs in 20–40% of CAP cases, whereas empyema is less frequent, occurring in 5–10% [4–6]. The incidence of CAP complications is increasing, and Grijalva et al. reported that the incidence of empyema doubled between 1996 and 2008 [7].

NSAIDs are frequently prescribed or used as self-medication in cases of CAP. Raherison et al. reported that 32–48% of patients suffering from lower respiratory tract infection had taken NSAIDs [8]. More recently, Voiriot et al. found that 32% of patients with CAP and who were admitted to an intensive care unit had taken NSAIDs prior to hospital admission [9]. To the best of our knowledge, only one prospective (90 patients) study and one retrospective (106 patients) study have investigated CAP in adult populations: these studies reported a strong relationship between NSAIDs use and complications (emergence of PPE, empyema, or lung abscess) [9, 10]; these findings are in accordance with the results of such studies conducted among pediatric populations [11–14]. Thus, the first aim of our study was to evaluate the impact of NSAIDs taken prior to hospital admission among patients with CAP and the emergence of complications (i.e., PPE, empyema, or lung abscess). Secondary aims were to evaluate the impact of NSAIDs intake on length of stay (LOS), intensive care unit (ICU) admission, organ failure, and mortality.

Materials and Methods

Patients: Inclusion Criteria

The study was conducted between February 2013 and February 2015 in Amiens University Hospital (France). All consecutive patients with CAP who had been hospitalized in our institution were prospectively included during this period if they fulfilled the following criteria: recent infiltrates on a chest X-ray or appearance of focal pulmonary crackles (major criteria) associated with at least two minor criteria (i.e., temperature >38 or <35 °C, chills and/or sweats, cough, dyspnea, or chest pain) and temporal criteria (first symptoms before hospital admission or within 48 h following admission). Patients were excluded in cases of immunosuppression (HIV infection) and/or immunomodulatory treatment (including steroids at a dose of >20 mg prednisone equivalent per day for more than 2 weeks), and/or chemotherapy.

Data Collection

The following data were collected: demographics, comorbidities (Charlson Comorbidity Index (CCI) [15]), treatments (NSAIDs and antibiotics before hospital admission), date of the first symptoms, initial clinical data and laboratory findings, radiological and microbiological investigations, management, LOS, and outcomes. Use of NSAIDs was defined as the intake of NSAIDs as either prescribed by a general practitioner or as self-medication after the first symptoms of CAP but prior to hospital admission. NSAIDs intake was investigated via systematic questioning of the patient and his/her family members, asking these individuals to recall the use of NSAIDs (generic and trade names). The general practitioner and the pharmacist of the patient were also questioned. The severity of pneumonia was assessed according to the pneumonia severity index (PSI) [16], and microbiological samples were recorded.

Pleural or parenchymal pulmonary complications were recorded from each patient by performing chest radiography (at least at admission, day 2, and discharge) and confirmed if needed by computed tomography or ultrasonography. Pleural complications (defined according to the British Thoracic Society criteria [17]) were PPE with at least one of the following characteristics: loculated PPE, purulent or turbid/cloudy pleural fluid, the presence of organisms identified by a Gram stain and/or culture from a non-purulent pleural fluid sample, pleural fluid pH <7.2, or a large symptomatic non-purulent effusion. Parenchymal complications were defined as a lung abscess recognized either on a chest radiography (cavity with or without air-fluid level) or on a computed tomography scan (homogeneous area of low density surrounded by a markedly enhanced well-formed wall) [18]. Mortality was defined as death from any cause within 30 days following hospital admission.

Ethical Considerations

This study was conducted in accordance to French laws and was approved by the ethical research committee (CPP Nord-Ouest II 2013-54). Oral and written information have been delivered to each eligible patient before inclusion.

Statistical Analyses

Our first aim was to evaluate the association between NSAIDs use before admission and the appearance of a pleural or parenchymal CAP complication. Because prior data indicated that the complication rate among patients

without prior exposure to NSAIDs was 15%, and considering a relative risk of 2.5, a power of 0.9, and that ~25% of the population will be exposed to NSAIDs, 224 subjects were required to reject the null hypothesis that the relative risk of developing a complication was equal to 1 for patients who had taken NSAIDs compared to unexposed patients. The Type-I error probability associated with this null hypothesis test was 0.05. We used Fisher's exact test to evaluate this null hypothesis.

Univariate descriptive analysis of the population was conducted. Results for continuous variables are expressed as their mean ± standard deviation (SD). The results for categorical variables are expressed as frequencies and percentages. Comparative analysis, using Fisher's exact test, was performed by considering exposure to NSAIDs prior to admission. A bivariate analysis was also performed for the other variables potentially associated with the development of complications. Variables selected to be included in the multivariate analyses ($p < 0.1$ and clinically relevant) were entered in a stepwise backward logistic regression model to identify predictors of pleural or parenchymal complications. The number of events per variable entered into the multivariate model averaged 10 to avoid overfitting. We computed the odds ratio (OR) as well as the corresponding 95% confidence interval (95% CI). All statistical analyses were performed using SAS 9.3 (Cary, NC) software.

Results

Populations

During the study period, 224 patients with CAP were prospectively included in the study. Three patients had to be excluded because first symptoms date back to more than 21 days. Only 29% of the patients had no comorbidities (CCI = 0). Patients were 64.8 years old on average and were mostly male (71%). During the follow-up period, 40 patients (18.1%) presented with a pleural and/or a parenchymal complication: 24 patients with a pleural complication, 8 patients with a pulmonary abscess, and 8 patients with both complications. The mean LOS was 17.2 ± 24.1 days. For the whole population, the mortality rate was 8.6%. Admission to an ICU was required for 35.7% of patients, with a 30-day mortality rate of 13.9%. The characteristics of the population, according to the main outcomes, are reported in Table 1.

Characteristics of the Patients Exposed to NSAIDs

Twenty-four patients (10.9%) had taken NSAIDs prior to admission. These patients were younger than those who had not received NSAIDs (50.6 ± 18.5 vs. 66.5 ± 16.4 years; $p < 0.001$), with fewer comorbidities ($p = 0.001$), and had more frequently received an adapted antibiotic therapy (defined as an antibiotic therapy adapted to the documented pathogen or in accordance to French guideline for the treatment of CAP) [19] prior to admission (37.5 vs. 16.2%; $p = 0.022$). The duration between the first symptoms and admission was significantly longer in the NSAIDs subgroup (8.2 ± 5.3 vs. 4 ± 4.7 days; $p = 0.01$). Alcohol abuse and tobacco use were similar in the two groups. NSAIDs intake was not correlated with mortality or the emergence of organ failure, but seemed to be associated with a more frequent need for thoracic surgery (16.7 vs. 4.6%). Characteristics of the population according to NSAIDs intake are shown in Table 2.

Bivariate and Multivariate Analyses

In bivariate analysis, the occurrence of a CAP complication was associated with tobacco use (OR = 2.3 [1.00–5.27]; $p = 0.029$), alcohol abuse (OR = 2.69 [1.28–5.66]; $p < 0.001$), NSAIDs intake prior to admission (OR = 2.58 [1.02–6.53]; $p = 0.048$), a longer delay between the first symptoms and admission (6.4 ± 6.1 vs. 4 ± 4.5 days; $p = 0.027$), a longer delay in the initiation of adequate antibiotic therapy (5 ± 5.1 vs. 2.8 ± 3.8 days; $p = 0.014$), and a longer LOS (27.9 ± 19.1 vs. 14.9 ± 24.4 days; $p = 0.002$). Moreover, we also found a significant positive correlation between CAP complications and the biologic criteria for malnutrition (serum albumin level <20 g/L and/or serum prealbumin level <50 mg/L). These criteria were observed in 51.5% of complicated CAP versus 9.9% of non-complicated CAP cases ($p < 0.001$). However, it must be noted that the serum albumin and/or prealbumin data were available for only 154 of our 221 patients, and mainly for patients with a CAP complication ($p = 0.04$). No significant relationships were found between CAP complications and isolated pathogens, PSI score, mortality, or organ failure.

We built two multivariate analysis models (Table 3). Five variables were entered in the first model (history of alcohol abuse, delay in adequate antibiotic therapy, NSAIDs intake prior to admission, CCI (CCI ≥ 1, reference), and age (categorized into <60 and ≥60 years)). Two factors appeared independently associated with CAP complications: alcohol abuse (OR = 2.85 [1.32–6.16]; $p = 0.01$) and delay to adequate antibiotic therapy (1.10 [1.03–1.20]; $p = 0.005$). Then, considering the possibility that delay in the initiation of antibiotic therapy could be an intermediate factor in the relationship between NSAIDs intake and complicated CAP, we used a second model without this variable; two factors appeared independently associated with CAP complications: alcohol abuse (OR = 2.68 [1.27–5.69]; $p = 0.01$) and NSAIDs intake prior to admission (OR = 2.57 [1.02–6.64]; $p = 0.049$).

Table 1 Characteristics of patients with CAP according to the development of a pleural or parenchymal complication

Characteristics	All patients ($n = 221$)	Complicated CAP ($n = 40$)	Non-complicated CAP ($n = 181$)	p-value*
Age <60 (years)	85 (38.5)	21 (52.5)	64 (35.4)	0.05
Male	156 (70.6)	30 (75)	126 (69.6)	0.569
Charlson score = 0	64 (29)	16 (40)	48 (26.5)	0.099
Duration of pneumonia symptoms (days)				
Before hospital admission	4.4 ± 4.9 (0–21)	6.4 ± 6.1 (0–21)	4 ± 4.5 (0–21)	0.027
Before adequate antibiotic therapy	3.2 ± 4.1 (0–21)	5 ± 5.1 (0–20)	2.8 ± 3.8 (0–21)	0.014
Adequate antibiotic therapy prior to admission	41 (18.6)	7 (17.1)	33 (18.3)	0.85
Corticosteroid use prior to admission	9 (4,1)	1 (2.5)	8 (4.4)	
PSI score at admission	96 ± 34.4 (21–219)	93.5 ± 35 (21–181)	96.6 ± 34.3 (22–219)	0.61
PSI class				0.247
I	22 (10)	7 (17.5)	15 (8.3)	
II	32 (14.5)	4 (10)	28 (15.5)	
III	54 (24.4)	8 (20)	46 (25.4)	
IV	76 (34.4)	17 (42.5)	59 (32.6)	
V	37 (16.7)	4 (10)	33 (18.2)	
ICU admission	79 (35.7)	21 (52.5)	58 (32)	0.018
Length of stay (days)	17.2 ± 24.1 (2–295)	27.9 ± 19.1 (5–94)	14.9 ± 24.4 (2–295)	0.002
Mortality	19 (8.6)	3 (7.5)	16 (8.8)	1
Organ failure	87 (39.4)	19 (47.5)	68 (37.6)	0.284
NSAIDs intake	24 (10.9)	8 (20)	16 (8.8)	0.05
Alcohol	48 (21.7)	15 (37.5)	33 (18.2)	0.011
Tobacco	147 (66.5)	32 (80)	115 (63.5)	0.032
Biological criteria for malnutrition (154 patients)[a]	29/154 (18.8)	17/33 (51.5)	12/121 (9.9)	<0.001
BMI ($kg/m^{2)}$	25.7 ± 6.7 (11.4–49.6)	23.8 ± 6.2 (14.7–39.5)	26.1 ± 6.8 (11.4–49.6)	0.053
Documented pathogen	105 (47.5)	24 (60)	81 (44.8)	0.115
Influenza virus	2 (0.9)	0 (0)	2 (1.1)	
S. pneumoniae	34 (15.4)	4 (10)	30 (16.6)	0.47
H. influenzae	13 (5.9)	2 (5)	11 (6.1)	
MRSA	7 (3.2)	3 (7)	4 (2.2)	
MSSA	9 (4.1)	3 (7.5)	6 (3.3)	
P. aeruginosa	13 (5.9)	2 (5)	11 (6.1)	

Data are presented as their mean ± SD (range) for qualitative data or as no. (%) for quantitative data, unless otherwise indicated

CAP community-acquired pneumonia, *NSAIDs* non-steroidal anti-inflammatory drugs, *PSI* pneumonia severity index, *BMI* body mass index, *ICU* intensive care unit, *S. pneumonia Streptococcus pneumonia*, *MRSA* methicillin-resistant *Staphylococcus aureus*, *MSSA* methicillin-susceptible *Staphylococcus aureus*, *P. aeruginosa Pseudomonas aeruginosa*

* *P*-values refer to the differences between the complicated CAP group and the non-complicated CAP group

[a] Biological criteria for malnutrition were defined as a serum albumin level <20 g/L or a serum prealbumin level of <50 mg/L

To specify the role of NSAIDs in the occurrence of CAP complications, a subgroup analysis was performed after exclusion of the 24 patients who had already presented with a pleural or parenchymal complication at admission. Among the 197 patients hospitalized for non-complicated CAP, 16 patients developed a pleural and/or parenchymal complication during hospitalization and NSAIDs use still appeared to be a significant risk factor in this subgroup (OR = 4.69 [1.45–15.18]; $p = 0.01$). No correlations were observed between CAP complications and alcohol abuse in this subgroup analysis ($p = 0.51$).

Discussion

In this prospective study, we found that NSAIDs intake prior to hospital admission was a strong independent factor that favored pleural and/or parenchymal

Table 2 Characteristics of the population according to prior receipt of NSAIDs

Characteristics	All patients ($n = 221$)	NSAIDs group ($n = 24$)	Non-NSAIDs group ($n = 197$)	p-value*
Age (years)	64.8 ± 17.3 (19–103)	50.6 ± 18.5 (22–89)	66.5 ± 16.4 (19–103)	<0.001
Age <60 years	85 (38.5)	16 (66.7)	69 (35)	0.004
Male	156 (70.6)	21 (87.5)	135 (68.5)	0.06
Charlson score = 0	64 (29)	15 (62.5)	49 (24.9)	<0.001
Duration of pneumonia symptoms (days)				
Before hospital admission	4.4 ± 4.9 (0–21)	8.2 ± 5.3 (0–21)	4 ± 4.7 (0–21)	<0.001
Before adequate antibiotic therapy	3.2 ± 4.1 (0–21)	5.4 ± 4.7 (0–15)	3 ± 4 (0–21)	0.008
Adequate antibiotic therapy prior to admission	41 (18.6)	9 (37.5)	32 (16.2)	0.022
PSI score at hospital	96 ± 34.4 (21–219)	76.6 ± 33.4 (33–140)	98.4 ± 33.8 (21–219)	0.003
Pleuroparenchymal complications[a]	40 (18.1)	8 (33.3)	32 (16.2)	0.048
ICU admission	79 (35.7)	8 (33.3)	71 (36)	0.827
Length of stay (days)	17.2 ± 24.1 (2–295)	17.9 ± 16.7 (2–72)	17.1 ± 24.8 (2–295)	0.879
Mortality	19 (8.6)	1 (4.2)	18 (9.1)	
Organ failure	87 (39.4)	11 (45.8)	76 (38.6)	0.513
Need for surgery	13 (5.9)	4 (16.7)	9 (4.6)	
Alcohol	48 (21.7)	6 (25)	42 (21.3)	0.793
Tobacco	147 (66.5)	15 (62.5)	132 (67)	0.819

CAP community-acquired pneumonia, *NSAID* non-steroidal anti-inflammatory drugs, *PSI* pneumonia severity index, *ICU* intensive care unit

* *P*-values refer to the differences between the complicated CAP group and non-complicated CAP group

[a] Pleuroparenchymal complications are defined by the development of a complicated parapneumonic pleural effusion, empyema, or a lung abscess

Table 3 Bivariate and multivariate analyses of variables associated with the development of a pleural or parenchymal complication

Variable	Complicated CAP ($n = 40$)	Non-complicated CAP ($n = 181$)	Bivariate analysis		Multivariate analysis	
			OR (95% CI)	p-value	OR (95% CI)	p-value
Model N°1						
Age <60 years	21 (52.5)	64 (35.4)	2.02 (1.01–4.03)	0.046		
Charlson score = 0	16 (40)	48 (26.5)	1.85 (0.91–3.77)	0.092		
Alcohol	15 (37.5)	33 (18.2)	2.69 (1.28–5.66)	0.009	2.85 (1.32–6.16)	0.01
Delay to adequate antibiotic therapy (days)	5 ± 5.1	2.8 ± 3.8	1,10 (1.03–1.2)	0.004	1,10 (1.03–1.20)	0.005
NSAIDs intake	8 (20)	16 (8.8)	2.58 (1.02–6.53)	0.048		
Model N°2						
Age <60 years	21 (52.5)	64 (35.4)	2.02 (1.01–4.03)	0.046		
Charlson score = 0	16 (40)	48 (26.5)	1.85 (0.91–3.77)	0.092		
Alcohol	15 (37.5)	33 (18.2)	2.69 (1.28–5.66)	0.009	2.68 (1.27–5.69)	0.01
Tobacco	32 (80)	115 (63.5)	2.3 (1.00–5.27)	0.050		
NSAIDs intake	8 (20)	16 (8.8)	2.58 (1.02–6.53)	0.048	2.57 (1.02–6.64)	0.049

CAP community-acquired pneumonia, *NSAIDs* non-steroidal anti-inflammatory drugs

complications during CAP. This result is of major importance, given the high morbidity and mortality associated with such complications. The strength of the association described in this study appears consistent with previous pediatric [11, 12, 14] and adult findings [9, 10]. This association is further supported by studies which report complications of skin and soft-tissue infection or in cases of pharyngitis [20, 21].

The role of NSAIDs in the occurrence of CAP complications remains unclear due to a possible protopathic bias. Because NSAIDs intake remains correlated to CAP complications, when considering the subgroup of 197 patients

without a complication at admission, this result suggests that NSAIDs intake may be a causal factor of CAP complications in adults. NSAIDs intake was not the only significant factor we found associated with CAP complications: in our multivariate analysis, alcohol abuse was also independently associated with CAP complications, as previously shown by Charmers et al. [22]. and Falguera et al. [4].

We observed a longer LOS than reported in the REACH study (13.6 ± 11.5) [23, 24]. We assume that this difference could be partially explained by the elevated proportion of patients admitted into the ICU in our study which is associated with higher LOS [25]. The proportion of cases of complicated CAP was 18.1% in our study, which agrees with the literature [4–6]. As others have reported, longer hospital stay and more frequent ICU admissions are observed in cases of complicated CAP [22]. Twenty-four of our patients (10.9%) had received NSAIDs through medical prescription or by self-medication. This rate is lower than in previous studies, which reported NSAIDs exposure ranging from 14 to 45% [8, 9, 26]. However, given the systematic collection of the data regarding NSAIDs use in our study, we can assume that the exposure prevalence in our study is accurate. The low NSAIDs exposure observed in our study could be explained by the characteristics of our population, where our study population presented with a high prevalence of comorbidities was, on average, older, compared to previous studies where patients were, overall, younger with fewer comorbidities and had a lower PSI score at admission [9, 10].

Delayed hospital referral and delayed antibiotic therapy were strongly correlated to complicated CAP in bivariate analysis. Because those two variables are linked, as indicated by their collinearity, we decided to include only the delay in adequate antibiotic therapy in our first multivariate analysis model; this factor appeared to be independently associated with CAP complications. On the other hand, a longer delay between the first symptoms and either the start of an adequate antibiotic therapy or admission into hospital was found in cases of NSAIDs intake, despite higher adequate antibiotic therapy. This result suggests that CAP complications were partly due to delayed therapeutic care. This delay might be caused by the well-known effects of NSAIDs, which reduce warning signs (i.e., fever and chest pain) [9, 10, 27]. According to these findings, we concluded that delayed hospital referral or delayed antibiotic therapy should be considered as intermediate factors in the association between NSAIDs intake and the development of pleuropulmonary complications. Therefore, these variables were not included in our second multivariate model. Moreover, NSAIDs are known to interfere with responses mediated by the prostaglandin and leukotriene pathways, and many studies have demonstrated that aspirin, the most studied NSAID, exerts multiple effects on different components of innate and adaptive immunity. Aspirin can induce apoptosis of different immune cells, modulate their proliferation/maturation process, and regulate their cytokine production [28].

Experimental models of infection, that have focused on the direct effect of the immunological response after NSAIDs exposure, have found discordant results, with some studies reporting a reduction and others reporting an increase in the host's defenses [29, 30]. These results vary according to the drug studied and the dose administered [31]. These conflicting data and the lack of controlled randomized studies in humans have prevented us from concluding a direct effect of NSAIDs in the development of these complications of CAP.

Potential confounding factors must also be considered when evaluating the results of our observational study, such as time to clinical stability (not prospectively collected), seasonality, or day and time of admission. Given the limited number of events, we could not adjust for more than four confounding variables as this would inhibit the convergence of the model. Considering this, only the main statistically and clinically relevant variables (according to bivariate analysis) were included.

Malnutrition is a common risk factor for CAP complications, as observed by Charmers et al. [22] We were not able to include biological data for malnutrition in our model because of the high proportion of missing data, and because albumin and prealbumin were mainly measured in cases of prolonged hospitalization or in complicated CAP, indicating that this variable may have been subjected to differential misclassification bias.

Concerning the secondary outcomes, we did not observe any difference in terms of LOS in hospital, ICU admission, organ failure, or mortality between NSAIDs patients and non-NSAIDs patients. These results are consistent with the studies of Messika et al. and Voiriot et al. [9, 10].

Conclusion

We found strong evidence for the imputability of NSAIDs taken prior to admission and the occurrence of CAP complications, particularly in young and healthy patients who are most exposed to these medications. Regarding the worldwide use of NSAIDs, either by prescription or by self-medication, general practitioners and pharmacists should be aware of the risk of providing NSAIDs in cases of respiratory infectious symptoms.

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Author's Contribution DB had the initial idea for the research, designed the study, obtained and analyzed the data, interpreted findings, and wrote the first draft of the manuscript. NP, CT, PD, CA, and VJ contributed to development of the study's methods and data interpretation, and commented on successive drafts of the manuscript. All authors have seen and approved the final version of the manuscript for publication.

Compliance with Ethical Standards

Conflict of interest No potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

Ethical Approval A favorable ethical opinion was obtained from the ethical research committee (reference CPP Nord-Ouest II 2013-54).

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