Respiratory Medicine 123 (2017) 28–33

Contents lists available at ScienceDirect

Respiratory Medicine

journal homepage: www.elsevier.com/locate/rmed

Prehospital NSAIDs use prolong hospitalization in patients with pleuro-pulmonary infection

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ARTICLE INFO

Article history:
Received 19 August 2016
Received in revised form
2 December 2016
Accepted 11 December 2016
Available online 12 December 2016

Keywords:
Community acquired pneumonia
Length of hospitalization
Nonsteroidal anti-inflammatory drugs
Pleural empyema
Pleural infection

ABSTRACT

Objective: Nonsteroidal anti-inflammatory drug (NSAID) pre-hospitalization consumption might affect the course of pneumonia. We opted to assess the potential effects of pre-hospitalization use of NSAIDs in patients with pleuropulmonary infection in the context of the duration of hospitalization.
Methods: A prospective observational study of 57 consecutive patients with a diagnosis of pneumonia and parapneumonic pleural effusion was conducted. The exact medication history the previous fifteen days was recorded.
Results: Prehospital use of NSAIDs >6 days was positively associated with prolonged hospitalization extending out for approximately 10 days. Immunosuppression was an independent risk factor for prolonged hospitalization of more than 5 days. This group of patients also had more complicated pleural effusions and difficult to treat management. In the immunocompetent group of patients, there was a negative inverse correlation of duration of NSAIDs use with pleural fluid pH and glucose. The longer medication with NSAIDs correlated with lower values of C–reactive protein, and erythrocyte sedimentation rate. Importantly, the early prehospital antibiotic use significantly prevented the development of empyema.
Conclusion: Our findings highlight the potential complications involved with prehospital use of NSAIDs and especially that prolonged NSAID use which may lead to longer hospitalization duration and more complicated pleural effusions.

1. Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely prescribed in the community; however they are not considered free from complications. Taking into account the overuse of NSAIDs in the absence of medical control it has been estimated that more than 30 million people worldwide use NSAIDs every day [1]. Their use is associated with a spectrum of potential adverse effects and the cost associated with their toxicity is extremely high [2–5]. Excess deaths associated with NSAIDs exceed 16.000 patients per year in USA alone [2], and the costs associated with their side effects reach €59 million in the Netherlands annually [4]. There is an ongoing debate regarding the potential effects of NSAIDs use in the course of community-acquired pneumonia [6,7]. An over prescription of NSAIDs has been observed in the management of lower respiratory tract infections in the general practice [8]. They are routinely administered due to their analgesic and antipyretic properties; however their consumption seems to affect the host immune response to acute infection [6,7,9,10]. Their use in the early stages of community-acquired pneumonia has been recently associated with a blunted presentation, protracted infection course and increased risk of pleuropulmonary complications, especially pleural empyema [6,7]. A significant fraction of patients hospitalized due to pneumonia, have parapneumonic pleural effusions (~20%–40%), and the mortality is higher in those patients [11,12]. Additionally, 10% of those patients develop empyema [11,12]. Along with increased mortality, pleural empyemas often necessitate prolonged treatment, longer hospitalization and more interventions [12–14]. Identifying potential risk factors may lead to better treatment and thus decreased mortality, morbidity and costs. The aim of this study was to investigate the potential effects of pre-hospitalization NSAIDs use in patients with pneumonia and parapneumonic effusion in the context of the duration of hospitalization.

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http://dx.doi.org/10.1016/j.rmed.2016.12.005
0954-6111/

2. Materials and methods

2.1. Study participants

In this prospective observational study 57 consecutive patients that were hospitalized in the University Hospital of Larissa from March 2015 to January 2016 with a diagnosis of pneumonia and parapneumonic pleural effusion were included. The diagnosis of community acquired pneumonia was based on the detection of a new and persistent pulmonary infiltrate involving one or more lobes, or bilateral infiltrates for which there was no other clinical cause and at least two of the following clinical criteria: (1) fever or hypothermia (temperature >38 or < 35.5 °C); (2) leucopenia or leukocytosis (white blood cells $\leq 4 \times 10^9/L^{-1}$ or $\geq 12 \times 10^9/L^{-1}$) or (3a) purulent respiratory secretions and (3b) acquisition of the infection outside a hospital, long-term care facility or nursing home [15–17]. Exclusion criteria were: a) hospital-acquired pneumonia or health-care-associated pneumonia, b) previously known pleural effusion, c) use of cytotoxic, immunosuppressive or steroids drugs (daily doses >40 mg of prednisolone or equivalent for >2 weeks), chronic exposure to NSAIDs. Parapneumonic effusion complicating pneumonia was diagnosed by pleural ultrasonography, chest radiography and CT scanning. The study was approved by the University Hospital of Larissa Ethics Committee. Informed consent for inclusion in the study was given by each patient or their next of kin.

2.2. Data collection

Information regarding demographic characteristics, medical history, existence of co-morbidities or immunosuppression, smoking history, use of prescribed and/or over the counter chronic medications was collected. Moreover, the exact medication history regarding the previous fifteen days concerning the number, type and duration of pain medication including NSAIDs and analgesics as well as the probable administered antibiotics were recorded. Patient's immunosuppression was defined as active solid or hematologic malignancy, leucopenia, immunodeficiency, alcohol use, injecting drug use, presence of asplenia, HIV infection, pregnancy or neuromuscular disease.

The following clinical values on admission were recorded for each patient: pleural fluid analysis and cultures, initial routine laboratory tests and pO_2 level on admission. Chest radiography was used to estimate the pleural effusions size and they were further categorized into five groups. The size and distribution of the effusion on the posteroanterior and lateral chest radiographs were quantitated using the following cutoffs: 1. blunting of the costophrenic angle, 2. more than blunting of the costophrenic angle but 25% of hemithorax occupied by pleural fluid, 3. pleural fluid occupying 25–50% of hemithorax, 4. pleural fluid occupying 50–75% of hemithorax, 5. pleural fluid occupying 75% of hemithorax [18].

Ultrasound was used to confirm the presence of pleural fluid collection, to determine if pleural effusions are free-flowing versus encapsulated as well as the relative ease of thoracentesis. Thoracentesis was performed under direct ultrasound guidance.

Effusions were classified as exudates according to Light's criteria [12]. We further distinguished them as uncomplicated parapneumonic pleural effusions or empyemas based on the chemistry of the pleural fluid, ultrasound imaging appearance and bacteriology [12]. Indications of chest tube insertion were the presence of empyema, a positive result of gram stain or culture, organised (encapsulated) pleural effusion, a technical difficulty of monitoring pleural cavity for fluid recurrence (for example because of patient's somatotype), or the necessity of repeated thoracentesis [12].

2.3. Statistical analyses

Data were analyzed using the statistical program SPSS v.22 (IBM SPSS, USA). Quantitative variables were presented as mean ± standard deviation (SD) and categorical variables were presented as frequencies with percentages. Chi-square test was used to detect differences between categorical variables. Students' t-test was used in order to detect differences between NSAIDs usage, antibiotic medication, presence of immunosuppression or co-morbidities and quantitative variables. Predictors regarding longer duration of hospitalization were assessed by multivariate linear regression analyses calculating the odds ratios (ORs) and the corresponding 95% confidence intervals. The association between duration of hospitalization and NSAIDs use, duration of NSAIDs use and other variables was evaluated with univariate linear regression. Non-significant variables in multivariate models were dropped from the final model unless they had a confounding effect or significant interaction with another variable. All tests of significance were two-tailed, and a p value ≤ 0.05 was considered significant.

3. Results

3.1. Study participants characteristics

The characteristics of the whole study participants as well as of the subgroups according to prehospital NSAIDs use or no are summarized in Table 1 and Table 2.

From the 57 patients that were included in the study, the majority were males (81% versus 19% females). There was no significant age difference between males and females (49.43 ± 18.17 vs 51.54 ± 15.86 years old respectively, $p = 0.714$). Cigarette smoking was more common in males (78.3% versus 45.5%, $p = 0.030$) as was the smoking severity (28.82 ± 28.16 pys in males versus 6.18 ± 10.06 pys in females, $p = 0.012$). From our study population 26/57 (46%) patients had co-morbidities as shown in Table 3. In Table 3 a comparison between the frequencies of the co-morbidities in patients that received NSAIDs and that did not receive NSAIDs was done. There were no differences in the co-morbidities between the two groups. The 63% of the patients ($n = 36$) received NSAIDs before hospital admission in order to manage symptoms with a mean duration of 4.41 ± 2.99 days. The mean duration of symptoms (productive cough, chest pain, fever) was the same for the patients that used NSAIDs and the patients that did not (7.52 ± 4.48 vs 7.66 ± 5.33 days, $p = 0.917$). There were no significant differences in age, gender, co-morbidities, prehospital use of antibiotics, smoking status and pO_2 levels on admission between the two groups.

The immunocompromised group ($n = 11/57$) included patients with malignancy, neuromuscular diseases, drug users and alcoholics, while there were no patients with other types of immunosuppression. In the group of immunocompromised patients the number of patients that used NSAIDs prior to hospitalization was significantly lower than the group of immunocompetent patients (36.4% versus 69.6% respectively, $p = 0.040$). Immunosuppressed patients had received NSAIDS within 4.75 ± 3.59 days before hospital admission. Immunocompromised patients as compared to immunocompetent patients had elevated values of neutrophils on admission (16.682 ± 6.255 versus 11.901 ± 5.635 respectively, $p = 0.016$), more complicated pleural effusions ($p = 0.008$) i.e lower pleural pH (6.91 ± 0.17 versus 7.13 ± 0.23, $p = 0.011$), lower pleural glucose values (10.67 ± 14.10 mg/dL versus 70.65 ± 62.28 mg/dL, $p = 0.007$), and longer duration of chest tube placement (11.63 ± 10.47 days versus 4.89 ± 6.39 days, $p = 0.008$) compared to the immunocompetent group.

Table 1
Participants characteristics of the total study group.

	All patients n = 57	
Gender		
Males	46 (81%)	
Females	11 (19%)	
Age	49.77 ± 17.64	
Smoking		
Yes	41 (72%)	
No	16 (28%)	
PYS	24.45 ± 27.14	
Co-morbidities		
Yes	26 (46%)	
No	31 (54%)	
Immunosuppression		
Yes	11 (19%)	
No	46 (81%)	
NSAIDs		
Yes	36 (63%)	
No	21 (37%)	
Duration of NSAIDs (days)	2.84 ± 3.19	
Antibiotics[a]		
Yes	19 (33%)	
No	38 (67%)	
Localization	Right	26 (46%)
	Left	26 (46%)
	Both	5 (8%)
Size	Costphrenic angle	23 (20%)
	<25%	25 (28%)
	25%–50%	40 (38%)
	50%–75%	9 (10%)
	>75%	2 (4%)
Thoracentesis		
Yes	40 (70%)	
No	17 (30%)	
Type		
Parapneumonic	15 (37.5%)	
Empyema	25 (62.5%)	
Chest tube		
Yes	32 (56%)	
No	25 (44%)	
Chest drainage duration (days)	11.03 ± 7.26	
Duration of hospitalization (days)	12.47 ± 6.96	

Data are expressed as mean ± SD or as frequencies (percentages).
[a] Prehospital use of antibiotics. **Abbreviations**: PYS: pack year smoking.

3.2. Pleural bacteriology as predictor factor

In our study, the causative bacteria were detected in one quarter of the total (predominant was Streptococcus pneumoniae serotype 1). A positive association was identified between a positive pleural culture and chest drainage duration (12.50 ± 8.79 days versus 6.70 ± 5.26 days, p = 0.040). No association was identified between a positive pleural culture and the duration of hospitalization (p = 0.189).

3.3. Comparison of the effects of NSAIDs use in immunocompetent patients

Immunocompetent patients (n = 46/57) that received NSAIDs (n = 32/46) had lower pleural fluid pH (7.08 ± 0.21 versus 7.27 ± 0.24, p = 0.049) and glucose levels (55.53 ± 53.14 mg/dL versus 114.38 ± 69.32 mg/dL, p = 0.018) as compared to the immunocompetent patients that did not use NSAIDS. Moreover, patients that used NSAIDs for more than 6 days (n = 8/32) had significantly lower CRP values on admission than the ones that used NSAIDs for less than 6 days (p = 0.030). Immunocompetent patients free of co-morbidities (n = 26/46) that used NSAIDs (n = 22/26) had significantly lower pleural fluid pH levels than immunocompetent patients free of co-morbidities that did not use NSAIDs (pleural pH value = 7.12 ± 0.15 versus 7.45 ± 0.02, p = 0.012). The immunocompetent patients free of co-morbidities that used NSAIDs (n = 22/26) for more than 3 days (n = 12/22) as compared to the ones that used NSAIDs for less than 3 days had significantly lower ESR values independent of antibiotics use (39.33 ± 15.57 mm versus 56.44 ± 18.68 mm respectively, p = 0.030).

3.4. Prehospital antibiotic use

Antibiotic use at the early stage of community acquired pneumonia compared to no antibiotic therapy led to significantly lower values of neutrophils on admission (10,827 ± 3705 × 10^9/L versus 13,822 ± 6703 × 10^9/L, p = 0.034), elevated pleural fluid pH levels (7.24 ± 0.26 versus 7.02 ± 0.20, p = 0.010), uncomplicated parapneumonic effusions (p = 0.035), smaller size of effusion (i.e ≤25%, >25 p = 0.044). On the other hand, prehospital antibiotic use led to significantly less first chest tube placements (p = 0.008), second catheter insertion or multiple drains to evacuate the pleural spaces (p = 0.001), and total duration of drainage (1.15 ± 2.08 days versus 8.71 ± 8.28 days, p < 0.001). In patients who receive NSAIDs, the prehospital use of antibiotics (n = 10/36) led to significantly lower pleural pH values (7.01 versus 7.26, p = 0.013) and significantly fewer days of chest tube drainage (9.19 versus 1.20, p < 0.001) compared to the patients that did not medicate with antibiotics before admission.

3.5. Multivariate linear regression model regarding the factors that influence the duration of hospitalization

In multivariate linear regression analysis the duration of NSAIDs use >6 days and the presence of immunosuppression were independent predictors of longer hospitalization (Table 4). NSAID use for more than 6 days was considered an independent risk factor for prolonged hospitalization of more than 10 days (B = 10.868, p < 0.001) while the presence of immunosuppression was considered an independent risk factor for prolonged hospitalization of more than 5 days (B = 5.025, p = 0.007).

4. Discussion

In the current study we opted to assess the potential effects of pre-hospitalization use of NSAIDs in patients with pneumonia and parapneumonic effusion in the context of the duration of hospitalization. Our main findings were that:

Prehospital use of NSAIDs >6 days was positively associated with prolonged hospitalization. Immunosuppresion was an independent factor in this context. The group of immunocompromised patients had also significantly more complicated pleural effusions and difficult therapy management with the need for more interventions. In the immunocompetent group, there was a negative inverse correlation of NSAIDs use with pleural fluid pH and glucose. Moreover, the longer the NSAIDs use was the lower the values of serum inflammatory markers were. Specifically, the use of NSAIDS ≥ 3 days resulted in lower ESR values and the use of NSAIDs >6 day resulted in lower serum CRP. Additionally, the early prehospitalization antibiotic treatment significantly prevented the development of empyema even in patients who were receiving NSAIDs.

The study population consisted of patients with pneumonia and parapneumonic effusions that were admitted to the hospital with common clinical presentation in terms of fever, productive cough and chest pain. There were no differences in the age, smoking history, and presence of immunosuppression or co-morbidities between the two groups that we studied (NSAIDs versus non NSAIDs). At this common advanced stage of disease we aimed at

Table 2
Study participant characteristics of the subgroups according to prehospital NSAIDs use or no.

	NSAIDs group n = 36	No NSAIDs group n = 21	p - value
Gender			
Males	8 (22.2%)	3 (14.3%)	0.464
Females	28 (77.8%)	18 (85.7%)	
Age	48.08 ± 16.34	52.67 ± 19.74	0.349
Smoking			
Yes	26 (72.2%)	15 (71.4%)	0.949
No	10 (27.8%)	6 (28.6%)	
PYS	28.53 ± 31.39	45 ± 17.48	0.085
Co-morbidities			
Yes	14 (38.9%)	12 (57.1%)	0.182
No	22 (61.1%)	9 (42.9%)	
Immunosuppression			
Yes	4 (11.1%)	7 (33.3%)	0.040
No	32 (88.9%)	14 (66.7%)	
Antibiotics			
Yes	10 (27.8%)	9 (42.9%)	0.244
No	26 (72.2%)	12 (57.1%)	
Localization			
Right	16 (44.4%)	10 (47.6%)	0.194
Left	15 (41.7%)	11 (52.4%)	
Both	5 (13.9%)	0	
Size			
Costphrenic angle	7 (19.4%)	6 (28.6%)	0.506
<25%	9 (25%)	5 (23.8%)	
25%–50%	16 (44.4%)	7 (33.3%)	
50%–75%	2 (5.6%)	3 (14.3%)	
>75%	2 (5.6%)	0	
Thoracentesis			
Yes	27 (75%)	13 (61.9%)	0.297
No	9 (25%)	8 (38.1%)	
Type			
Parapneumonic	9 (33.3%)	6 (46.2%)	0.433
Empyema	18 (66.7%)	7 (53.8%)	
Chest tube			
Yes	22 (61.1%)	10 (47.6%)	0.322
No	14 (38.9%)	11 (52.4%)	
Chest drainage duration (days)	11.40 ± 8.10	10.20 ± 5.20	0.670
Duration of hospitalization (days)	13.67 ± 6.85	10.42 ± 6.82	0.90

Data are expressed as mean ± SD or as frequencies (percentages).
*Prehospital use of antibiotics. **Abbreviations**: PYS: pack year smoking.

Table 3
Comparison of co-morbidities according to prehospital NSAIDs use.

Co-morbidities n = 26	NSAIDs group n = 14	No NSAIDs group n = 12	p - value
AH	10 (38.5)	4 (15.4)	0.343
COPD	6 (23.0)	2 (7.7)	0.372
Diabetes	3 (11.5)	3 (11.5)	0.387
Dyslipidemia	5 (19.2)	1 (3.8)	0.272
Coronary	3 (11.5)	0	0.244

Data are expressed as mean ± frequencies (percentages). Percentages are calculated based on the total number of patients that had co-morbidities (n = 26).

identifying independent risk factors that could influence the duration of hospitalization.

In our study, patients that used NSAIDs had the same mean duration of symptoms with the patients that did not use NSAIDs (approximately 8 days). The patients included in our study that received NSAIDs prior to hospitalization used them for a mean of 4.44 (1–7) days, which is comparable to what was reported in a previous study by Messika et al. (approximately 4 days) [7]. One difference between our study and previous studies was that it was reported that patients with pneumococcal pneumonia who had received NSAIDs prior to hospitalization were significantly younger

Table 4
Multivariate linear regression model of hospitalization duration.

Model	Unstandardized coefficients		Standardized coefficients	Sig.	95,0% Confidence interval for B		Collinearity statistics	
	B	Std. error	Beta		Lower bound	Upper bound	Tolerance	VIF
(Constant)	14.322	0.809		<0.001	12.700	15.944		
Immunosuppression	−10.868	1.625	−0.680	<0.001	−14.127	−7.609	0.966	1.036
NSAIDs use >6 days	5.025	1.791	0.285	0.007	1.433	8.618	0.966	1.036

a. Predictors: (Constant), immunosuppression, NSAIDs use>6 days.
b. Dependent Variable: Duration of hospitalization.
c. Excluded variables: age, co-morbidities, prehospital use of antibiotics, ultrasound image of encapsulation, serum C–reactive protein on admission, pleural pH on first thoracentesis.
$R = 0.687$, $R^2 = 0.471$, adjusted $R^2 = 0.452$.

(almost 20 years) and had less co-morbidities [6,7].

Recent studies, both in children and young adults, support the notion that there is an association between NSAIDs use and increased risk of infection [6,7,9,19–21], and more severe presentation of pneumonia with more frequent pleuropulmonary complications such as complicated pleural effusions [6,7,19]. These observations support the results of our study that suggest that the prehospitalization use of NSAIDs in previously healthy individuals resulted in more complicated pleural effusions and potential changes in the host immune response. These findings may be attributed to the potential blunting of the initial symptoms by the use of NSAIDs that could mask the severity of the infection and delay the use of antibiotics and hospital admission [6,7]. Recently, it has been reported that prolonged onset of symptoms may have an impact on clinical outcome among hospitalized patients with community acquired pneumonia, as it was associated with a higher rate of suppurative complications [22].

It is generally accepted that the timely initiation of antibiotic treatment in bacterial infections is of utmost importance for prognosis [6,7,23,24]. Our study also indicates that early antibiotic treatment is critical for a favorable outcome as it reduces inflammation, restrains pleural disease progression to empyema and limits pleural interventions.

The prolonged duration of hospitalization increases the economic burden related to the treatment of these patients, thus, identifying potential risk factors that lead to decreased mortality, morbidity and costs is of great significance. Indeed, according to our results immunosuppression and NSAIDs use for more than 6 days was found to be independent predictive factors of prolonged hospitalization. The immunocompromised group of our study included patients with malignancy, neuromuscular diseases, drug users and alcoholics. In this group we observed significantly more complicated pleural effusions and longer duration of chest tube placement. The underlying immunosuppression has already been described in the literature as an independent risk factor for developing empyema [20]. It was reported that immunosuppression including corticosteroid use, gastro-oesophageal reflux, alcohol misuse and intravenous drug abuse, are potential risk factor for pleural infection occurrence [23,24].

Many studies supported that greater co-morbidity was associated with a prolonged hospital stay [14,25,26]. Diabetes mellitus was described as a predisposing factor for pleural effusion development through capillary basement membrane thickening which is a hallmark of long-standing insulin-dependent diabetes mellitus, being related to the duration of the hyperglycemia. The alterations of capillary basement membrane thickening have been reported to increase the leakage of fluid into the pleural cavity, resulting in persistent and refractory effusions [27]. Additionally, it has been reported that in patients with community-acquired pneumonia, diabetes mellitus is associated with a poor prognosis, increasing the rate of pleural effusion and mortality [23,28].

Furthermore, NSAIDs use may suppress the host immune response by *i*nhibiting cyclooxygenase activity, and thereby, the synthesis of prostaglandins and thromboxanes resulting in perturbations of leukocyte adhesion, phagocytosis, and bactericidal activity [10,14,19]. According to recent studies NSAIDs are considered to play an important role in the progression of exudates by inducing alterations in their volume, leukocyte migration and pleural vascular permeability [29]. NSAIDs interfere with the mesothelial permeability of the pleura mainly via prostaglandin production alteration, which seems to influence pleural fluid recycling [29,30]. NSAIDs were shown to hinder pleural permeability *ex vivo*, by inhibiting prostaglandin synthesis and eventually blocking the epithelial sodium channel ENaC and the Na^{+}/K^{+-}ATPase activity normally operating in the pleura [30]. In vivo experiments also demonstrated that NSAIDs limited the absorption of provoked hydrothoraces, by reducing the acute and late absorption rate and thus the volume of the hydrothorax eventually absorbed [29,31]. Additionally, NSAIDs induced increased white cell migration within the pleural cavity with a higher percentage of neutrophils present, indicating the initiation of an inflammatory response in the remaining hydrothorax [29,31]. It is highly likely that NSAIDs have a similar effect in parapneumonic effusions; their effects on ENaC and $Na+-K+$ ATPase decrease the absorption rate of the pleural fluid and pathogen clearance allowing potential pathogens to lead to complicated pleural effusion [32]. However, the exact underlying pathophysiological mechanism remains unclear so far.

In this study, for the first time we described that the prolonged prehospitalization NSAIDs use had a significant impact on the inflammatory markers that were evaluated upon admission and in the duration of hospitalization. This observation supported the notion that prolonged NSAID use may suppress host immune response directly, as this was reflected indirectly through its statistically significant impact on the inflammatory markers evaluated on patient's admission. It was shown that the use of NSAIDs $\geq$3 day positively correlated with lower ESR values and the use of NSAIDs >6 day with lower serum CRP values. In other words, prolonged NSAIDs use may led to hampered patient immune response as we noted before. In addition, NSAID use for more than 6 days was considered an independent risk factor for prolonged hospitalization (of more than 10 days).

A limitation of the study was that although prospective it demonstrates results from one medical center with a uniform population, so further studies are needed in order to demonstrate the global applicability of these results. A larger multicenter prospective study would be ideal in order to confirm our results. A previous study reported a probable association between NSAID use and worse outcomes in young patients with pneumococcal pneumonia [7]. Because of the lack of causative bacteria identification, it was not possible to investigate such an association.

5. Conclusion

In conclusion, our findings highlight the potential danger of prehospital use of NSAIDs and especially of prolonged NSAID use which lead to longer hospitalization duration and more complicated pleural effusions. The early prehospital antibiotic treatment significantly prevented the development of empyema. Immunocompromised patients had often more complicated pleural effusions responsible for more interventions and difficult therapy management. Chest physicians should have these observations in mind when treating pneumonia patients in order to improve management and patient selection as per the severity of the disease.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflicts of interest

None.

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