CHEST

Original Research

CHEST INFECTIONS

Nonsteroidal Antiinflammatory Drugs May Affect the Presentation and Course of Community-Acquired Pneumonia

Guillaume Voiriot, MD; Sandra Dury, MD; Antoine Parrot, MD; Charles Mayaud, MD; and Muriel Fartoukh, MD

Background: **Nonsteroidal antiinflammatory drugs (NSAIDs) are commonly used as antipyretics and analgesics and may affect the host response to acute infection. We investigated the potential influence of NSAIDs on the presentation and short-term outcomes of nonimmunocompromised inpatients with community-acquired pneumonia (CAP) admitted to the ICU.**

Methods: **All consecutive patients with CAP admitted to the ICU or step-down unit of a university hospital during a 4-year period were prospectively included, except when receiving long-term NSAIDs or steroids. Drug exposures, presentation, and hospital course were recorded.**

Results: **Of the 90 patients included, 32 (36%) had taken NSAIDs prior to hospital referral. Compared with nonexposed patients, they were younger and had fewer comorbidities but similar severity of disease at presentation, despite a longer duration of symptoms before referral. However, they more often developed pleuropulmonary complications, such as pleural empyema and lung cavitation (37.5% vs 7%; *P* = .0009), and had a trend to more-invasive disease, with a higher frequency of pleural empyema (25% vs 5%, *P* = .014) and bacteremia, especially in those not having received concomitant antibiotics (69% vs 27%, *P* = .009). Nevertheless, the patients in the NSAID group had no more severe systemic inflammation or remote organ dysfunction. In multivariable analyses, NSAID exposure was independently associated with the occurrence of pleuropulmonary complications (OR, 8.1; 95% CI, 2.3-28).**

Conclusions: **Our findings suggest that NSAID exposure at the early stage of CAP is associated with a more complicated course but a blunted systemic response, which may be associated with a delayed diagnosis and a protracted course.** ***CHEST 2011; 139(2):387–394***

Abbreviations: CAP = community-acquired pneumonia; LRTI = lower respiratory tract infection; NSAID = nonsteroidal antiinflammatory drug; PSI = Pneumonia Severity Index; SAPS = Simplified Acute Physiologic Score; SOFA = Sepsis-related Organ Failure Assessment

Community-acquired pneumonia (CAP) is a common and potentially life-threatening disease, especially in elderly patients with comorbidities.[1,2] Guidelines for the management of CAP are regularly updated to provide useful advances in diagnosis and treatment.[1,3] Whereas steroids or other immunomodulators have been suggested to improve the outcome of severe CAP,[4,5] none of the guidelines advised on the use of nonsteroidal antiinflammatory drugs (NSAIDs) in the initial management of CAP. However, NSAIDs are commonly used, available over the counter, and are prescribed often by general practitioners to alleviate symptoms.[6] For example, surveys of the management of lower respiratory tract infections (LRTIs) found that French general practitioners prescribed antiinflammatory drugs (NSAIDs or steroids) in addition to antibiotics to 46% to 72.5% of their patients.[7,8]

Manuscript received January 19, 2010; revision accepted June 28, 2010.

Affiliations: From the Service de Pneumologie et Réanimation (Drs Voiriot, Dury, Parrot, Mayaud, and Fartoukh), Hôpital Tenon, Assistance Publique-Hôpitaux de Paris; and Université Pierre et Marie Curie (Dr Mayaud), Paris, France.

Correspondence to: Muriel Fartoukh, MD, Hôpital Tenon, Assistance Publique-Hôpitaux de Paris, 04 rue de la Chine, 75020 Paris, France; e-mail: muriel.fartoukh@tnn.aphp.fr

DOI: 10.1378/chest.09-3102

Although the administration of NSAIDs may limit inflammation and lung tissue damage,[9-12] some clinical observations suggest that NSAIDs, while blunting the inflammatory response, may mask a developing infection.[13,14] Considering the frequent administration of NSAIDs in outpatient management of LRTIs[7,8] and the relative lack of human data about the consequences of such prescriptions,[15,16] we sought to investigate the potential impact of prehospital treatment with NSAIDs on the initial presentation and course of nonimmunocompromised adults referred to the hospital for pneumonia.

Materials and Methods

Patient Selection and Inclusion Criteria

The study was conducted between November 2002 and November 2006 in Tenon Hospital, a tertiary-care university hospital in Paris, France. All consecutive patients with CAP admitted to the ICU or its affiliated step-down unit (eight and six beds, respectively) were eligible. Pneumonia was clinically suspected in patients with a new infiltrate evidenced on chest radiograph and recent onset of at least one of the following clinical signs suggestive of pneumonia: cough, sputum production, chest pain, crackles, and fever.[1] All radiographs were reviewed by two pulmonary physicians to confirm the presence of a pulmonary infiltrate suggestive of pneumonia. Pneumonia was considered community acquired in the absence of hospitalization for ≥ 2 days in the preceding 90 days and of any other known risk factor for health-care-associated infection. Patients with severe COPD, cystic fibrosis, tracheostomy, cirrhosis, solid or hematologic malignancy, neutropenia, sickle cell disease, AIDS, and aspiration pneumonia were excluded. In addition, patients receiving long-term NSAID therapy or receiving steroids (≥ 20 mg prednisone equivalent per day for > 2 weeks) also were excluded.

Data Collection

Demographics, comorbidities, recent treatment with NSAIDs alone or in combination with antibiotics before hospital referral, initial clinical and laboratory findings, radiologic and microbiologic investigation, management, hospital length of stay, and vital status at discharge were prospectively collected. A recent use of NSAIDs was defined as the oral intake of NSAIDs either after a general practitioner prescription or by self-medication within the 10-day period preceding referral. The severity of pneumonia was assessed from the Pneumonia Severity Index (PSI)[17] and from generic scores of severity and organ dysfunction, such as the Simplified Acute Physiologic Score (SAPS) II[18] and the Sepsis-related Organ Failure Assessment (SOFA) score.[19] A microbiologic diagnosis of pneumonia was routinely attempted from blood cultures, at least one respiratory tract secretions sample, and urinary antigen tests.

An invasive disease was defined as the presence of bacteremia or empyema.[20] Pneumonia-related complications included organ failure (respiratory, hemodynamic, or renal)[21] and pleural or parenchymal pulmonary complications (pleural empyema or lung cavitation) present within 24 h of admission to the ICU or step-down unit or occurring later. Mortality was defined as death from any cause within 30 days of hospitalization.

Ethical Considerations

This pilot study was conducted in accordance with French law and approved by the ethical review board of the Société de Pneumologie de Langue Française. Each patient was given oral and written information.

Statistical Analysis

Our study first aimed at describing the initial presentation of patients admitted to the ICU for severe pneumonia, with a special focus on NSAID use. Results are expressed as mean ± SD (range). Unless specified, data are reported as NSAID group vs non-NSAID group. Between-group comparisons were determined with the Mann-Whitney *U* test for categorical variables and the χ^2 test or the Fisher exact test for nominal variables. $P < .05$ was statistically significant.

Second, we identified factors associated with the occurrence of invasive disease and complications (pleural empyema or lung cavitation). Variables selected by univariable analysis ($P < .2$) were entered in a stepwise backward logistic regression model to identify predictors of invasive disease or complications. The number of events per variable entered in the multivariate model averaged 10 to avoid overfitting.[22] The results are reported as OR and corresponding 95% CI. All statistical analyses were performed on a personal computer using Statview software (SAS Institute; Cary, North Carolina).

Results

Initial Presentation

During the study period, 107 patients with CAP were admitted to our unit, of whom 17 met exclusion criteria (Fig 1). Of the remaining 90 patients (60 men; age, 52 ± 15 years), 46 (51%) were classified as high risk (PSI risk class IV/V) at hospital referral. Thirty-two (36%) had been taking NSAIDs either alone (n = 18) or together with antibiotics (n = 14) for 5 ± 2 days (range, 1-10 days; median, 5 days) (Fig 2) prior to referral. Five patients taking NSAIDs also were

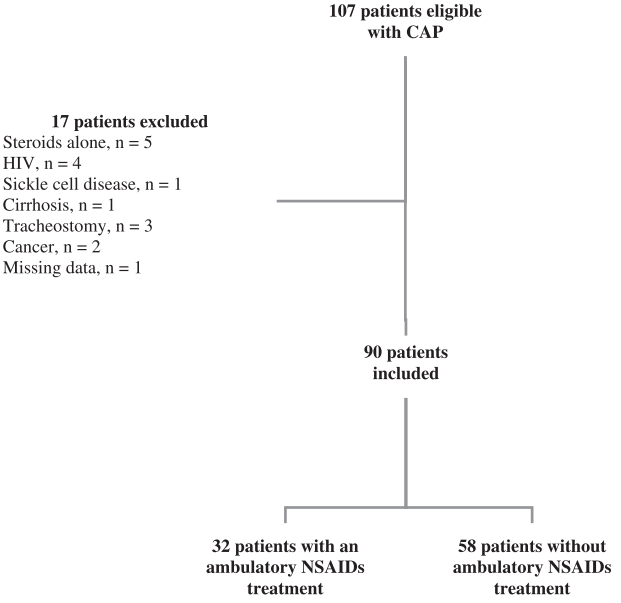

Figure 1. Flowchart. CAP = community-acquired pneumonia; NSAID = nonsteroidal antiinflammatory drug.

receiving low-dose steroids (< 20 mg/d equivalent prednisone). Of the other 58 patients not having taken NSAIDs, 16 (28%) had received antibiotics. Patients exposed to NSAIDs were younger and more often women, had fewer comorbidities, and had a slightly lower mean PSI value (Table 1). The duration of pneumonia-related symptoms prior to hospital referral or ICU admission was longer in the NSAID group.

Although the prevalence of organ failures and requirement for organ support on ICU admission did not differ between groups (Table 1), patients in the NSAID group tended to have a lesser overall severity at initial presentation, as illustrated by a trend to lower SAPS II and SOFA scores. With regard to the initial presentation (Table 2), patients in the NSAID group had a higher prevalence of chest pain and pleural syndrome. Additionally, they more often had multilobar infiltrates and pleural effusion on the admission chest radiograph.

Microbiologic Documentation

Pneumonia was microbiologically documented in 68 (75%) patients. The documentation rate did not differ between groups (NSAID group, 23/32, 72%; non-NSAID group, 45/58, 78%; $P = .73$) and was not influenced by prehospital administration of antibiotics (with antibiotics, 21/30, 70%; without antibiotics, 47/60, 78%; $P = .54$). It should be noted that 21 of the 30 patients (70%) having received antibiotics had a microbiologically documented pneumonia and that the antibiotics regimens were appropriate in only eight (38%) of them according to the definite etiologic diagnosis (NSAID group, 4/8, 50%; non-NSAID group, 4/13, 31%; $P = .65$).

Streptococcus pneumoniae (n = 43) was the predominant microorganism recovered in both groups (47% vs 48%, NSAID vs non-NSAID, respectively); Penicillin-susceptible or intermediate strains (penicillin minimum inhibitory concentration, < 2 μg/mL) were equally distributed between the two groups. Eight patients (seven not receiving NSAIDs) had *Legionella* pneumonia, two from each group had *Pseudomonas aeruginosa*, and four had polymicrobial pneumonia (two patients from each group).

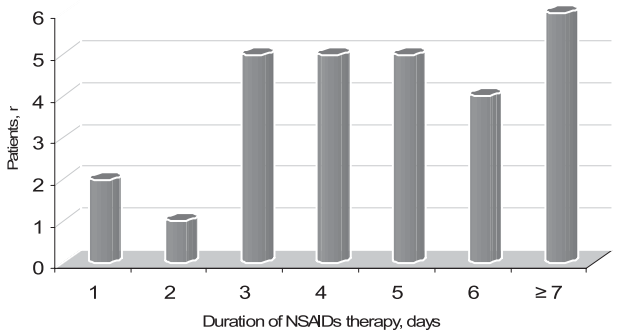

FIGURE 2. Distribution of the duration of NSAID therapy before hospital referral in 90 patients with CAP. NSAID therapy of at least 1-day duration was considered for eligibility. No minimal daily dosage was required. The duration of NSAID exposure was 5 ± 2 days (range, 1 to 10 days; median, 5 days; interquartile range, 3-6 days). Only two patients had been taking NSAIDs for just 1 day. See Figure 1 legend for expansion of abbreviations.

Bacteremia was documented in nearly one-third of our patients, with 24 of 27 bacteremic episodes caused by *S pneumoniae*. The bacteremia rate was comparable in the two groups (34% vs 28%, NSAID vs non-NSAID, respectively; $P = .56$) (Table 3). However, in patients not having received prior antibiotics, the bacteremia rate was significantly higher in the NSAID group (69% vs 27%; $P = .009$). Pleural empyema also was more common in the NSAID group (25% vs 5%; $P = .014$). Four patients, all in the NSAID group, had both positive pleural fluid and blood cultures. Overall, an invasive disease (ie, bacteremia or empyema) occurred in 38% of the patients (Table 3) and was more common in the NSAID group, especially in those patients not administered concomitant antibiotics.

Course During the ICU and Hospital Stay

All the patients with a microbiologically documented pneumonia, except one in each group (66/68; 97%), received an appropriate antimicrobial regimen within the first 24 h of admission to our unit. Overall, pneumonia-related organ failures, including respiratory, hemodynamic, or renal failure, were not more frequently observed in the NSAID group (Table 4). However, pleural empyema and lung cavitation were more frequent in the NSAID group (12/32, 37.5%) than in the non-NSAID group (4/58, 7%; $P = .0009$). In univariable analysis, female sex and NSAID exposure were significantly associated with such complications. In multivariable analysis, NSAID exposure remained the only variable independently associated with the occurrence of pleuropulmonary complications (OR, 8.1; 95% CI, 2.3-28) (Table 5). Likewise, NSAID exposure was the only variable associated with invasive disease, but only in the subgroup of patients not having received prehospital antibiotics (OR, 3.8; 95% CI, 1.2-11.9, $P = .02$). Finally, the duration of antimicrobial therapy administered for pneumonia was 10 days longer in the NSAID group ($P = .003$), and there was a trend to longer ICU and hospital lengths of stay in the NSAID group (Table 4). The overall mortality rate was similar in the two groups (Table 4).

DISCUSSION

In this prospective observational study, we investigated the potential impact of NSAIDs during prehospital

Table 1—*Demographics and Severity at Presentation of Patients With CAP, According to Prior Receipt of NSAID Use*

Characteristic	All Patients (N = 90)	NSAID Group (n = 32)	Non-NSAID Group (n = 58)	*P* Value[a]
Age, y	52 ± 15 (17-80)	47 ± 15 (18-77)	55 ± 15 (17-80)	.017
Sex, male (female)	60 (30)	18 (14)	42 (16)	.16
Comorbid condition[b]	36 (40)	6 (19)	30 (52)	.003
Duration of symptoms of pneumonia, d				
Before hospital referral	4 ± 2.5 (0-12)	4.7 ± 2.5 (1-10)	3.5 ± 2.5 (0-12)	.03
Before ICU admission	4.6 ± 2.6 (0-12)	5.5 ± 2.4 (2-10)	4.1 ± 2.5 (0-12)	.009
Time between hospital referral and ICU admission, d	0.6 ± 1.2 (0-5)	0.8 ± 1.4 (0-5)	0.5 ± 1 (0-5)	.77
Antibiotics ongoing for at least 24 h	30 (33)	14 (44)	16 (28)	.18
Initial severity and management during the first 24 h of ICU admission				
PSI score at hospital referral	91 ± 36 (17-173)	87 ± 35 (28-153)	94 ± 37 (17-173)	.35
PSI class IV and V at hospital referral	46 (51)	14 (44)	32 (55)	.41
SAPS II score	33 ± 23 (6-116)	26 ± 17 (6-85)	36 ± 25 (6-116)	.051
SOFA score	4.4 ± 3.5 (0-15)	4.0 ± 3.3 (0-13)	4.6 ± 3.6 (0-15)	.37
Mechanical ventilation	28 (31)	8 (25)	20 (34)	.49
Acute renal failure	45 (50)	15 (47)	30 (52)	.83
Hemodialysis	1 (1)	0	1 (2)	…
Severe sepsis/septic shock	36 (40)	10 (31)	26 (45)	.30
Vasopressors or inotropes	17 (19)	3 (9)	14 (24)	.15

Data are presented as mean ± SD (range) or No. (%), unless otherwise indicated. Two-thirds of the patients (n = 60; 67%) were directly admitted from the ED to the ICU (n = 45) or to the step-down unit (n = 15). The other 30 patients were secondarily referred from the medical wards within 48 h of hospital admission (19 and 11 to the ICU or the step-down unit, respectively). CAP = community-acquired pneumonia; NSAID = nonsteroidal antiinflammatory drug; PSI = Pneumonia Severity Index; SAPS = Simplified Acute Physiologic Score; SOFA = Sepsis-related Organ Failure Assessment.

[a]*P* values refer to the differences between the NSAID and non-NSAID groups.

[b]Comorbid conditions were defined as pulmonary disease, cardiac failure, renal disease, CNS disorder, hepatic disease, and diabetes mellitus.

care on the presentation and course of nonimmunocompromised adults referred to the hospital for severe CAP. Patients receiving NSAIDs accounted for 35% of our series. Compared with patients not exposed to NSAIDs, the NSAID group had a longer duration of symptoms before referral and developed more often pleuropulmonary complications. In addition, the NSAID group had a trend to more-invasive disease, as illustrated by more frequent bacteremia, which was significant only in those not having received antibiotics. However, NSAID recipients had no more severe systemic inflammation or remote organ dysfunction. These findings suggest that NSAID use at the early stage of CAP can be associated with a less-effective compartmentalization of infection, but a blunted systemic response, which may result in delayed diagnosis and management, and a protracted course.

It is noteworthy that the patients in the NSAID group differed from their counterparts in terms of

Table 2—*Initial Clinical and Radiologic Presentation of Patients With CAP According to Prior Receipt of NSAIDs*

Presentation	All Patients (N = 90)	NSAID Group (n = 32)	Non-NSAID Group (n = 58)	*P* Value[a]
Initial clinical signs and symptoms				
Respiratory rate > 30 breaths/min	33 (37.5)	12 (40)	21 (36)	.91
Cough	64 (71)	24 (75)	40 (69)	.63
Sputum production	42 (48)	15 (50)	27 (47)	.82
Dyspnea	77 (87)	28 (90)	49 (85)	.53
Pleural syndrome	21 (23)	13 (41)	8 (14)	.009
Chest pain	44 (49)	20 (63)	24 (41)	.08
Crackles	68 (76)	24 (75)	44 (76)	.9
Body temperature, °C	38.2 ± 1.2	38.0 ± 1.1	38.3 ± 1.3	.15
Initial radiologic patterns				
Unilateral infiltrate	54 (60)	17 (53)	37 (64)	.78
Multilobar infiltrate (> 2 lobes)	53 (59)	24 (75)	29 (50)	.04
Pleural effusion[b]	30 (33)	17 (53)	13 (22)	.006
Lung cavitation	2 (2)	1 (3)	1 (2)	1

Data are presented as No. (%) or mean ± SD. See Table 1 for expansion of abbreviations.

[a]*P* values indicate the differences between the NSAID and non-NSAID groups.

[b]A thoracentesis was performed in 26 patients, including 16 in the NSAID group and 10 in the non-NSAID group.

Table 3—*Prevalence of Bacteremia and Empyema*

Positive Sample	All Patients (N = 90)	NSAID Group (n = 32)	Non-NSAID Group (n = 58)	*P* Value	No Prior Antibiotics: NSAID Group (n = 16)	No Prior Antibiotics: Non-NSAID Group (n = 41)	No Prior Antibiotics: *P* Value[a]
Pleural fluid, blood cultures, or both	34 (38)	15 (47)	19 (33)	.273	11 (69)	13 (32)	.025
Blood cultures	27 (30)	11 (34)	16 (28)	.56	11 (69)	11 (27)	.009
Pleural fluid	11 (12)	8 (25)	3 (5)	.014	4 (22)	2 (5)	.046
Pleural fluid + blood cultures	4 (4)	4 (12)	0	…	4 (22)	0	…

Data are presented as No. (%). Two NSAID patients and one non-NSAID patient without antibiotics did not have blood cultures obtained. An invasive disease was defined as the presence of bacteremia or empyema (positive pleural fluid, positive blood cultures, or both). Pleural fluid culture was positive for 11 (42%) of the 26 patients with pleural effusion in whom a thoracentesis was performed (NSAID, 8/16; non-NSAID, 3/10). See Table 1 legend for expansion of abbreviation.

[a]Significant differences between the NSAID and non-NSAID groups were observed for positive blood and pleural fluid cultures for the subgroup of patients not having received prior antibiotics before referral (see text).

demographics and clinical characteristics, being more often women and younger and having fewer comorbid conditions, resulting in a relatively low proportion (44%) of patients in high-risk classes of pneumonia severity at referral. The higher proportion of women in the NSAID group might reflect a higher propensity for self-medication or more regular use of these drugs than in men. Conversely, those not exposed to NSAIDs more closely match those described in a large series of inpatients with CAP,[17,23,24] with a similar proportion (55%) of high-risk patients. Thus, the overall severity in this series was in the low range compared with series of ICU patients with severe CAP.[25] Similarly, the duration of pneumonia-related symptoms until admission to our unit was similar to that described in these series; however, the NSAID group was characterized by a longer time to admission and more often presented with pleural involvement and multilobar infiltrates than other series of severe CAP.[24] Thus, it is tempting to speculate that the NSAID group had a disproportionately high rate of ICU admission despite its younger age and fewer associated comorbid conditions because of a longer delay to hospital referral and a higher frequency of pleuropulmonary complications, with a trend to more invasive disease.

Table 4—*Complications During ICU Stay and Outcomes*

Complication	All Patients (N = 90)	NSAID Group (n = 32)	Non-NSAID Group (n = 58)	*P* Value[a]
Pleural or pulmonary				
Pleural empyema or lung cavitation	16 (18)	12 (37.5)	4 (7)	.0009
Organ failure and support				
At least one organ failure and support[b]	16 (18)	6 (19)	10 (17)	.91
ARDS	12 (13)	6 (19)	6 (10)	.33
Mechanical ventilation	5 (6)	3 (9)	2 (3)	.34
Renal failure	10 (11)	3 (9)	7 (12)	1
Dialysis	5 (6)	1 (3)	4 (7)	.65
Septic shock	4 (4)	1 (3)	3 (5)	1
Vasopressors or inotropes	4 (4)	1 (3)	3 (5)	1
Hospital-acquired infection				
Nonpulmonary	10 (11)	6 (19)	4 (7)	.16
Pulmonary	11 (12)	5 (16)	6 (10)	.51
Other outcome measures, d				
Length of ICU stay	13.9 ± 17.6 (1-103)	18.4 ± 22 (1-103)	11.3 ± 14.2 (1-87)	.1
Length of hospital stay	20.8 ± 21.3 (1-124)	23.2 ± 21.8 (2-124)	19.6 ± 21 (1-106)	.07
Duration of antimicrobial therapy	18.7 ± 11.3 (1-55)	24.5 ± 14 (3-55)	15.4 ± 8 (1-45)	.003
Mortality				
ICU	3 (3)	0	3 (5)	.55
Hospital	4 (4)	1 (3)	3 (5)	1

Data are presented as No. (%) or mean ± SD (range). Pneumonia-related complications included organ failure (respiratory, hemodynamic, or renal failure) and pleural or parenchymal pulmonary complications (pleural empyema or lung cavitation) present within 24 h of admission to the unit or occurring later. Respiratory failure was defined as a room air oxygen saturation of < 90% or a respiratory rate of > 30 breaths/min or a requirement for mechanical ventilation. Shock was defined as a sustained decrease in systolic BP of ≥ 40 mm Hg from baseline or a systolic BP < 90 mm Hg despite adequate fluid infusion. Renal failure was defined as a urinary output < 20 mL/h or the need for hemodialysis. Mortality was defined as death from any cause within 30 d of hospitalization. See Table 1 legend for expansion of abbreviation.

[a]*P* values indicate differences between the NSAID and non-NSAID groups.

[b]At least one organ failure, among respiratory, hemodynamic, or renal failure, developed after 24 h of admission to our unit.

Table 5—*Univariable Analysis of Variables Associated With Pneumonia Complicated by Pleural Empyema or Lung Cavitation in 90 Patients With CAP*

Variable	No.	Pneumonia Complicated by Empyema or Cavitation, No. (%)	Univariable Analysis	
			OR (95% CI)	*P* Value
Age, y	…	…	0.97 (0.94-1.007)	.12
Sex				
Female	30	9 (30)	1	…
Male	60	7 (12)	0.31 (0.1-0.9)	.04
Comorbid conditions				
No	54	11 (20)	1	…
Yes	36	5 (14)	0.6 (0.2-2)	.04
PSI IV/V				
No	44	7 (16)	1	…
Yes	46	9 (20)	1.3 (0.4-3.8)	.6
NSAID exposure				
No	58	4 (7)	1	…
Yes	32	12 (37.5)	8.1 (2.3-28)	.001
Antibiotics prior to referral				
No	60	8 (13)	1	…
Yes	30	8 (27)	2.4 (0.8-7.1)	.13

Pneumonia-related complications were defined as pleural empyema or lung cavitation present within 24 h of admission to the ICU or occurring later. See Table 1 legend for expansion of abbreviations.

Antimicrobial therapy was administered to one-third of the patients before hospital referral, in keeping with previous reports.[24,26] Only 38% of the antibiotics received during the prehospital period were adequate, with a similar proportion in the NSAID and non-NSAID groups. Altogether, pneumonia was microbiologically documented in 75% of our patients, a rate somewhat higher than that reported (50%-72%) in other studies of CAP requiring ICU admission.[5,24] The etiologies were similar, however, with a predominance of *S pneumoniae*, followed by *Legionella pneumophila*, *Staphylococcus aureus*, and *P aeruginosa*.[5,24] The higher proportion of *Legionella* pneumonia in the non-NSAID group was an unexpected finding. It should be noted that patients taking NSAIDs were younger women without comorbidities compared with patients in the group not taking NSAIDs. On the contrary, patients having *L pneumophila* pneumonia are more likely to be men with comorbidities. Thus, it is quite possible that the higher proportion of *L pneumophila* in the non-NSAID group may reflect these differences in population between the two groups.

Overall, pleural fluid culture was positive in 12% of our patients, similar to previous series.[24,27] However, pleural fluid culture was more often positive in the NSAID group, supporting a role for NSAIDs in favoring invasive disease. Bacteremia was evidenced in one-third of our patients overall, a rate again in the high range of that reported in other series of severe CAP.[5,23,28] It is noteworthy that patients receiving NSAIDs and no antibiotics had a strikingly high bacteremia rate (69%), again suggesting noncontainment of the infection. As mentioned previously, the rate of antibiotic use during prehospital care and their adequacy were similar between the NSAID and non-NSAID groups, suggesting that bacteremia and empyema were likely related to the ambulatory NSAID therapy.

Finally, a radiographic pattern of cavitation was recorded in an unexpectedly high proportion (10%) of patients, especially in the NSAID group (7/32). Specifically, the only two patients with pneumococcal pneumonia and cavitation had received NSAIDs. Lung cavitation is distinctly uncommon in immunocompetent adults with CAP[23,24,27] and has been identified as an independent risk factor of treatment failure.[26,29] The longer duration of antimicrobial therapy administered for pneumonia and the trend toward a longer ICU and hospital length of stay in the NSAID group likely reflect the more frequent occurrence of pulmonary-related complications, as previously suggested.[23,26,27]

Despite their more complex initial presentation and more invasive disease, the NSAID group had no more systemic inflammatory response and organ dysfunction. These patients actually had a lower mean generic score of severity (SAPS II) than the patients not taking NSAIDs (Table 1), which is likely related to the between-group imbalance of age and comorbidities. Nevertheless, the SOFA score, which only reflects sepsis-related organ dysfunctions, also tended to be lower in NSAID recipients, suggesting a role of NSAIDs for limiting the systemic inflammatory response and associated organ dysfunctions, as previously reported in experimental studies.[11]

Resident alveolar macrophages and circulating polymorphonuclear neutrophils constitute the first-line defense of the lung against invading pathogens

through phagocytosis and intracellular killing, thus avoiding their systemic dissemination and the development of multiorgan failure.[29] Arachidonic acid derivatives, including prostaglandins, thromboxanes, leukotrienes, and platelet-activating factor, play a critical role in the pulmonary inflammatory response.[30] NSAIDs interfere with the response mediated by the prostaglandin and leukotriene pathways, but their overall effects on the course of infection remain controversial. In experimental in vivo studies, NSAIDs administered before or during a bacterial or chemical pulmonary challenge both reduced neutrophil migration and recruitment to the lung and decreased lung bacterial clearance, with controversial results regarding mortality.[9,12] On the other hand, there are conflicting data of NSAID effects on phagocytosis and bacterial killing of monocytes and macrophages, which were found to be either enhanced or decreased in experimental models of pneumonia.[31,32] Indeed, the balance between the leukotriene or prostaglandin pathways during acute inflammation and infection in humans is not well understood, and cyclooxygenase inhibitors may result either in enhanced or in decreased bacterial host response.

Similar to our observations, it has been suggested that NSAID use during the initial stage of skin and soft tissue infection—notably in the absence of concomitant antibiotics—may be hazardous.[13] Thus, NSAID use might impede the timely recognition and delay the diagnosis and treatment of streptococcal necrotizing fasciitis, although an impact on outcome was not apparent.[16]

Despite our study being prospective, it has important limitations. The most obvious one is related to its observational, uncontrolled design. Our series included a diverse group of patients, and its design resulted in differing demographic characteristics of our two study groups. Additionally, because this study involved a single center, its generalizability is unknown; a larger, multicenter study is necessary to confirm our results. In addition, the frequency of the administration of (or self-medication with) NSAIDs in patients with LRTI is unknown. Studies from Europe suggest that NSAIDs are widely used, particularly in the younger age groups.[6-8] It is also possible that their effects may vary according to the duration of therapy and specific drug used. Finally, we did not record the exact reason of NSAID use. The potential impact of these variables should be best explored within the context of a prospective study.

Altogether, our results suggest that NSAID use during the early phase of CAP resulted in a more subacute initial presentation characterized by a delayed hospital referral, a local noncontainment of the infectious process, and a complicated course but no more or possibly less systemic inflammatory response. Our findings provide another piece of evidence that NSAIDs might alter the course of infection and result in more-invasive disease and complications, potentially leading to increased hospital and ICU admission rates and a protracted hospital course, especially in patients not receiving antibiotics.

Acknowledgments

Author contributions: *Dr Voiriot:* contributed to the acquisition, analysis, and interpretation of data; statistical analysis; and drafting of the manuscript.
Dr Dury: contributed to the acquisition, analysis, and interpretation of data.
Dr Parrot: contributed to the acquisition, analysis, and interpretation of data.
Dr Mayaud: contributed to the interpretation of data.
Dr Fartoukh: contributed to the study concept and design; acquisition, analysis, and interpretation of data; statistical analysis; drafting of the manuscript; critical revision of the manuscript for important intellectual content; and study supervision.
Financial/nonfinancial disclosures: The authors have reported to *CHEST* that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.
Other contributions: We thank Prof Christian Brun-Buisson (University Paris Val de Marne, Créteil, France) for his useful advice and critical revision of the manuscript.

References

1. Mandell LA, Wunderink RG, Anzueto A, et al; Infectious Diseases Society of America; American Thoracic Society. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis*. 2007;44(2 suppl 2):S27-S72.
2. Mortensen EM, Coley CM, Singer DE, et al. Causes of death for patients with community-acquired pneumonia: results from the Pneumonia Patient Outcomes Research Team cohort study. *Arch Intern Med*. 2002;162(9):1059-1064.
3. British Thoracic Society Standards of Care Committee. BTS Guidelines for the Management of Community Acquired Pneumonia in Adults. *Thorax*. 2001;56(suppl 4):IV1-IV64.
4. Confalonieri M, Urbino R, Potena A, et al. Hydrocortisone infusion for severe community-acquired pneumonia: a preliminary randomized study. *Am J Respir Crit Care Med*. 2005;171(3):242-248.
5. Laterre PF, Garber G, Levy H, et al; PROWESS Clinical Evaluation Committee. Severe community-acquired pneumonia as a cause of severe sepsis: data from the PROWESS study. *Crit Care Med*. 2005;33(5):952-961.
6. Aronoff DM, Neilson EG. Antipyretics: mechanisms of action and clinical use in fever suppression. *Am J Med*. 2001;111(4):304-315.
7. Raherison C, Peray P, Poirier R, et al. Management of lower respiratory tract infections by French general practitioners: the AIR II study. Analyse Infections Respiratoires. *Eur Respir J*. 2002;19(2):314-319.
8. Taytard A, Daures JP, Arsac P, et al. Management of lower respiratory tract infections by general practitioners in France [in French]. *Rev Mal Respir*. 2001;18(2):163-170.
9. Esposito AL. Aspirin impairs antibacterial mechanisms in experimental pneumococcal pneumonia. *Am Rev Respir Dis*. 1984;130(5):857-862.
10. Konstan MW, Vargo KM, Davis PB. Ibuprofen attenuates the inflammatory response to Pseudomonas aeruginosa in a rat

model of chronic pulmonary infection. Implications for anti-inflammatory therapy in cystic fibrosis. *Am Rev Respir Dis*. 1990;141(1):186-192.
11. Michie HR, Manogue KR, Spriggs DR, et al. Detection of circulating tumor necrosis factor after endotoxin administration. *N Engl J Med*. 1988;318(23):1481-1486.
12. Sordelli DO, Cerquetti MC, Fontán PA, García VE. *Pseudomonas aeruginosa* pneumonia. Treatment with nonsteroidal anti-inflammatory agents to prevent lung tissue damage. *Antibiot Chemother*. 1989;42:247-253.
13. Brun-Buisson CJ, Saada M, Trunet P, Rapin M, Roujeau JC, Revuz J. Haemolytic streptococcal gangrene and non-steroidal anti-inflammatory drugs. *Br Med J (Clin Res Ed)*. 1985;290 (6484):1786.
14. Legras A, Giraudeau B, Jonville-Bera AP, et al. A multicentre case-control study of nonsteroidal anti-inflammatory drugs as a risk factor for severe sepsis and septic shock. *Crit Care*. 2009;13(2):R43.
15. Bernard GR, Wheeler AP, Russell JA, et al; The Ibuprofen in Sepsis Study Group. The effects of ibuprofen on the physiology and survival of patients with sepsis. *N Engl J Med*. 1997; 336(13):912-918.
16. Aronoff DM, Bloch KC. Assessing the relationship between the use of nonsteroidal antiinflammatory drugs and necrotizing fasciitis caused by group A streptococcus. *Medicine (Baltimore)*. 2003;82(4):225-235.
17. Fine MJ, Auble TE, Yealy DM, et al. A prediction rule to identify low-risk patients with community-acquired pneumonia. *N Engl J Med*. 1997;336(4):243-250.
18. Le Gall JR, Lemeshow S, Saulnier F. A new simplified acute physiology score (SAPS II) based on a European-North American multicenter study. *JAMA*. 1993;270(24):2957-2963.
19. Vincent JL, Moreno R, Takala J, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med*. 1996;22(7):707-710.
20. Whitney CG, Farley MM, Hadler J, et al; Active Bacterial Core Surveillance Program of the Emerging Infections Program Network. Increasing prevalence of multidrug-resistant *Streptococcus pneumoniae* in the United States. *N Engl J Med*. 2000; 343(1917):1924-1924.
21. Bone RC, Balk RA, Cerra FB, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Chest*. 1992;101(6):1656-1662.
22. Peduzzi P, Concato J, Kemper E, Holford TR, Feinstein AR. A simulation study of the number of events per variable in logistic regression analysis. *J Clin Epidemiol*. 1996;49(12):1373-1379.
23. Rosón B, Carratalà J, Dorca J, Casanova A, Manresa F, Gudiol F. Etiology, reasons for hospitalization, risk classes, and outcomes of community-acquired pneumonia in patients hospitalized on the basis of conventional admission criteria. *Clin Infect Dis*. 2001;33(2):158-165.
24. Moine P, Vercken JB, Chevret S, Gajdos P; The French Study Group of Community-Acquired Pneumonia in ICU. Severe community-acquired pneumococcal pneumonia. *Scand J Infect Dis*. 1995;27(3):201-206.
25. Marrie TJ, Shariatzadeh MR. Community-acquired pneumonia requiring admission to an intensive care unit: a descriptive study. *Medicine (Baltimore)*. 2007;86(2):103-111.
26. Menéndez R, Torres A, Zalacaín R, et al; Neumofail Group. Risk factors of treatment failure in community acquired pneumonia: implications for disease outcome. *Thorax*. 2004;59(11): 960-965.
27. Arancibia F, Ewig S, Martinez JA, et al. Antimicrobial treatment failures in patients with community-acquired pneumonia: causes and prognostic implications. *Am J Respir Crit Care Med*. 2000;162(1):154-160.
28. Leroy O, Santré C, Beuscart C, et al. A five-year study of severe community-acquired pneumonia with emphasis on prognosis in patients admitted to an intensive care unit. *Intensive Care Med*. 1995;21(1):24-31.
29. Menendez R, Torres A. Treatment failure in community-acquired pneumonia. *Chest*. 2007;132(4):1348-1355.
30. Chouaib S, Bertoglio JH. Prostaglandins E as modulators of the immune response. *Lymphokine Res*. 1988;7(3):237-245.
31. Aronoff DM, Canetti C, Peters-Golden M. Prostaglandin E2 inhibits alveolar macrophage phagocytosis through an E-prostanoid 2 receptor-mediated increase in intracellular cyclic AMP. *J Immunol*. 2004;173(1):559-565.
32. Serezani CH, Chung J, Ballinger MN, Moore BB, Aronoff DM, Peters-Golden M. Prostaglandin E2 suppresses bacterial killing in alveolar macrophages by inhibiting NADPH oxidase. *Am J Respir Cell Mol Biol*. 2007;37(5):562-570.