2010 French SPILF-AFSSAPS Guiding Criteria for Streptococcus Pneumoniae Acute Community-Acquired Pneumonia: Evaluation in Patients of the PACSCAN-ESCAPED Cohort

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Data collection: YEC, XD.

Statistical analyses and data interpretation: MBH, ST, XD.

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Abstract

Objective. To assess the proportion of patients meeting the 2010 SPILF-AFSSAPS guiding criteria for *Streptococcus pneumoniae* in patients consulting at the emergency departments of four French university hospitals for acute community-acquired pneumonia (CAP) suspicion.

Patients and methods. The PACSCAN study prospectively included 319 patients. Medical history, clinical, biological, and radiological presentations were collected. An adjudication committee retrospectively classified the diagnostic certainty based on the initial chest CT scan data and the follow-up data up to Day 28. *Streptococcus pneumoniae* was looked for according to the clinician's choice of blood culture, pneumococcal urinary antigen test, nasopharyngeal PCR, and/or sputum microbiological examination.

***Results*.** All patients (100%) met at least one criterion for *Streptococcus pneumoniae* CAP and six (2%) met all criteria. The distribution of criteria ranged from 32% (chest pain criterion) to 86% (age ≥40 years criterion). These figures were respectively 100%, 3%, 38%, and 82% when the study population was restricted to the 139 patients with definite or probable CAP, according to the adjudication committee. Taking into account the microbiological results, the criteria taken one by one or combined did not make it possible to differentiate the 19 *Streptococcus pneumoniae* CAP from the other CAPs.

***Conclusion*.** The 2010 SPILF-AFSSAPS guiding criteria for *Streptococcus pneumoniae* CAP are found in very variable proportions and do not, in their current form, make it possible to accurately guide towards a pneumococcal etiology in patients included in the PACSCAN study.

INTRODUCTION

Acute community-acquired pneumonia (CAP) is a common infection, with numerous complications and uncertain prognosis [1]. When microbiological samples are collected, *Streptococcus pneumoniae* is the most common bacterium isolated and is also responsible for most deaths [2]. CAP prognosis depends on the early initiation of the antibiotic therapy. Physicians thus cannot wait for microbiological documentation and must prescribe an empirical antibiotic therapy based on anamnesis and clinical, biological, and radiological findings [3].

Approximately one third of pneumococcal strains is resistant to macrolides in France; no antibiotic is therefore active against all bacterial infectious agents responsible for CAP, except for fluoroquinolones with anti-streptococcal activity. For patients without any risk factors and to avoid antibiotic combinations or the use of extended-spectrum antibiotics (fluoroquinolones active against *Streptococcus pneumoniae)* and their consequences on the emergence of resistant bacteria [4], eight criteria defining *Streptococcus pneumoniae* CAP have been suggested in the 2010 SPILF-AFSSAPS guidelines to guide antibiotic therapy prescription with amoxicillin [5]. These criteria are presented as a list, with no specific priority nor weighting; thus, leading to different interpretations. It is indeed unclear whether a single criterion is enough to suspect pneumococcal CAP and to initiate amoxicillin, or whether a combination of several criteria − or all of them − are needed to favor this antibiotic.

On the basis of a cohort study of patients presenting with CAP suspicion and managed in emergency departments, we evaluated the proportion of patients meeting the 2010 SPILF-AFSSAPS guiding criteria for *Streptococcus pneumoniae* CAP depending on their interpretation. We then compared the proportion of patients meeting several criteria

depending on diagnostic certainty for CAP, as confirmed by a specific committee, and on the microbiological etiology of *Streptococcus pneumoniae* or lack of it.

PATIENTS AND METHODS

Study population and conduct of the study

The present study was performed based on the previously published originator study PACSCAN/ESCAPED [6]. PACSCAN was a prospective, multicenter, interventional study aimed at assessing the diagnostic and therapeutic impact of early and systematic chest computed tomography (CT) scan in patients consulting for pneumonia suspicion in four emergency departments of Parisian university hospitals between November 2011 and January 2013.

Pneumonia was suspected by the emergency specialist if patients met the following criteria: 1/ presence of systemic infection (sweat, and/or chills, and/or aches and pain, and/or temperature ≥38°C or <36°C) and symptoms of acute lower respiratory tract infection (at least one among cough, sputum production, dyspnea, chest pain, altered breathing sounds at auscultation). Lung radiography and chest CT scan were successively performed at the emergency department. They were then interpreted under the same conditions by the blinded hospital radiologist. Microbiological tests (sputum cytobacteriological examination [SCBE], blood culture, *Legionella,* and pneumococcal urinary antigen test) were left to the physician's choice based on protocols implemented at the hospital. Nasopharyngeal samples were collected and frozen for nasopharyngeal multiplex PCR and pneumococcal PCR (PCR RespiFinder-19) [7].

Demographic, clinical, biological, microbiological, and radiological data was collected using a standardized method and documented in an electronic form. Taking into consideration

all clinical, biological, microbiological, radiological, and outcome data (phone call to patients on Day 28), but blinded to the nasopharyngeal PCR results, an independent adjudication committee (a radiologist, a pulmonologist, and an infectious disease specialist) retrospectively defined the definite likelihood of CAP based on a four-level Likert scale: confirmed CAP, probable CAP, possible CAP, and CAP excluded (gold standard).

We used the 2010 SPILF–AFSSAPS guiding criteria and applied them to the PACSCAN population. We then selected within the PACSCAN study the sub-population of patients with a high level of CAP diagnostic certainty (confirmed or probable CAP), as defined by the adjudication committee, and for whom microbiological testing by blood culture or pneumococcal urinary antigen test or PCR had been performed.

Identification of Streptococcus pneumoniae CAP

The pneumococcal etiology of CAP was defined based on microbiological documentation (blood culture, pneumococcal urinary antigen test, SCBE, and nasopharyngeal pneumococcal PCR). All patients with at least one positive microbiological sample for *Streptococcus pneumoniae* were considered as having *Streptococcus pneumoniae* CAP. All other patients were considered as having CAP caused by a pathogen other than *Streptococcus pneumoniae*.

2010 SPILF-AFSSAPS diagnostic criteria indicative of Streptococcus pneumoniae CAP

The 2010 SPILF-AFSSAPS guidelines define criteria for *Streptococcus pneumoniae* CAP as follows: 1) age ≥40 years and/or presence of comorbidity(ies), 2) sudden onset, 3) high fever as of the first day, 4) general unease, 5) chest pain, 6) systematized alveolar opacity, 7) hyperleukocytosis with neutrophils [5].

We defined patients with diabetes, homozygous sickle cell anemia, splenectomy, asthma, COPD, or other pulmonary diseases as patients with comorbidity. Sudden onset was considered when this term was documented in the patient's medical file or if the patient had consulted at the emergency department within 24 hours after symptom onset. High fever was defined as temperature ≥38°C from symptom onset. Chest pain was defined as lateral chest pain on admission to the emergency department. Neutrophilic hyperleukocytosis was defined as blood count ≥10,000/mm^3 (performed at the emergency departments of the four hospitals). We did not take into account the "general unease" criterion because of its difficult interpretation in patients consulting at the emergency department.

Criteria were then grouped into four categories: "risk factor" criteria (age ≥40 years and/or with associated comorbidity/comorbidities); "clinical" criteria (sudden onset, high fever as of the first day, general unease, chest pain); "biological" criteria (neutrophilic hyperleukocytosis); or "radiological" criteria (systematized alveolar opacity on frontal chest radiography).

Statistical analyses

Distribution of criteria and categories following grouping was described in the study population and then compared based on the etiology (*Streptococcus pneumoniae* CAP or CAP caused by a pathogen other than *Streptococcus pneumoniae*) by Fisher's exact test. Various criteria and/or category associations were described and compared between the two groups using Fisher's exact test.

Ethics

The French Agency for the Safety of Health Products (French acronym ANSM) and the institutional review board (French acronym CPP) (Paris No. 2011-oct-12749) approved the protocol and the information letter for patients. All patients were asked to read the information letter and sign the study consent form before the start of the study.

RESULTS

Study population and Streptococcus pneumoniae CAP

The PACSCAN study included 319 patients who consulted at the emergency department for CAP suspicion: 155 men (48.6%); mean age of 64.7 +/-20.0 years; 195 (61.1%) had comorbidities. The adjudication committee classified 163 patients (51%) as having confirmed or probable CAP and 139 of them (44%) had undergone microbiological testing (blood culture or pneumococcal urinary antigen test) (Figure I). The characteristics of the 139 included patients did not differ from those of the 24 patients of the PACSCAN cohort with confirmed or probable CAP diagnosis without microbiological documentation (data not shown). The proportion of women among these 139 patients was 45.3% and the mean age was 62 years (+/-19.1); 69 patients (50%) had one comorbidity, including 26 (18.7%) with diabetes, 26 (18.7%) with COPD, and 17 (12.2%) with asthma.

Among these 139 patients, 113 (81%) had undergone blood culture, 105 (76%) pneumococcal urinary antigen test, and 79 (56%) both of these microbiological examinations. Other microbiological examinations performed were nasopharyngeal pneumococcal PCR (103 patients, 74%) and SCBE (53 patients, 38%). Of the 139 patients, 19 (14%) were considered as having *Streptococcus pneumoniae* CAP.

2010 SPILF-AFSSAPS diagnostic criteria indicative of Streptococcus pneumoniae CAP

Table I details the proportion of patients meeting each 2010 SPILF-AFSSAPS criterion for *Streptococcus pneumoniae* CAP within the overall study population (n=319 patients). All patients (n=319, 100%) met at least one criterion and 6/319 patients (2%) met all criteria. Criterion distribution ranged from 32% for the chest pain criterion (n=103/319) to 86% for the age ≥40 years criterion (n=275 patients) (Table I). These figures were respectively 100%, 3%, 38%, and 82% when limiting the study population to the 139 patients with confirmed or probable CAP as per the adjudication committee's conclusion and microbiological documentation (Table 2).

In these 139 patients and considering the pneumococcal etiology of CAP or lack of it, the sudden onset criterion was more frequent in patients with *Streptococcus pneumoniae* CAP (63%, n=12) than in those with CAP caused by a pathogen other than *Streptococcus pneumoniae* (41%, n=49). However, the difference was not significant (p=0.08). When separately considering all other criteria, the distribution difference between both groups was not significant (Table II).

Comparison of the various 2010 SPILF-AFSSAPS diagnostic criteria indicative of Streptococcus pneumoniae CAP, either assessed separately or together

Table III details various grouping techniques for the "risk factors", "clinical criteria", "biological criteria", and "radiological criteria" categories in the 139 patients with confirmed or probable CAP; 33 (24%) patients met at least one criterion of each of the four categories and 114 patients (82%) met at least one criterion of the "risk factors" category. The association of clinical and biological criteria was more frequent in the group of patients with *Streptococcus pneumoniae* CAP (n=11, [58%] versus 41 [34%]; p=0.07). Similarly, the association of clinical,

biological, and radiological criteria was more frequent in the group of patients with *Streptococcus pneumoniae* CAP (n=9, [47%] versus 31 [26%]; *p*=0.06).

Further analyses

Tables IV and V compare the proportion of patients meeting each of the 2010 SPILF-AFSSAPS guiding criterion for *Streptococcus pneumoniae* CAP or their association in the 300 patients managed in the four hospitals for CAP suspicion but for whom *Streptococcus pneumoniae* CAP diagnosis was not confirmed, and in the 19 patients with *Streptococcus pneumoniae* CAP. All criteria combined were significantly more frequent in the group of patients with *Streptococcus pneumoniae* CAP. The same goes for criteria such as high fever as of the first day, systematized alveolar opacity, or neutrophilic hyperleukocytosis.

DISCUSSION

Use of the 2010 SPILF-AFSSAPS guiding criteria for pneumococcal CAP in this prospective cohort of 319 patients with CAP suspicion led to considering this microbial etiology and to favoring a beta-lactam-based treatment, although with various proportions based on interpretation of these criteria. Besides, comparing these criteria with the later microbiological documentation − including the latest PCR techniques − did not allow for identifying the optimal association of criteria.

The study population was made of consecutive patients managed for CAP at the emergency departments of four Parisian university hospitals, located in four non-neighboring administrative districts of Paris, for 12 consecutive months. Our sample representativeness is therefore optimal. As reported by other hospital studies, the proportion of patients with comorbidities (especially respiratory disorders) is high. Diagnostic and microbiological

processes are therefore more difficult during their management for CAP suspicion. This is why we believe that the present findings can be extrapolated to all patients managed for CAP in French hospitals.

The recommendation of the 2010 SPILF-AFSSAPS guidelines to favor a narrow spectrum antibiotic therapy for CAP patients (excluding ICU patients) in order to limit the resistance selection pressure of antibiotics, is based on the careful analysis of risk factors, clinical presentation, biological and radiological findings, and outcome evaluation after 48 hours of antibiotic therapy. Considering the lack of clear application guidelines for these criteria, using this initial analysis that is based on “guiding criteria” is prone to interpretation by prescribers. Thus, the proportion of the 319 patients with one or more suggestive criteria for pneumococcal infection and who would thus rather receive a beta-lactam antibiotic therapy than a macrolide treatment, ranges from 2% to 100% depending on whether or not we believe that all criteria should be met or if only one criterion is enough. This wide range does not take into consideration whether the adjudication committee agreed to the confirmed or probable nature of the pneumonia (irrespective of microbiological documentation), because of the high frequency of risk factors (advanced age and comorbidities) in this population of patients consulting at the emergency departments for CAP. These risk factors probably reflect the characteristics of patients consulting at the emergency departments of French hospitals, irrespective of the consultation reasons.

We also assessed how the presence of these suggestive criteria depended on the probable pneumococcal nature of CAP using current microbiological documentation techniques, including PCR to look for viruses and bacteria with respiratory tropism. Although the identification of the pneumococcal genome in the respiratory tract of patients cannot be

considered as confirmation of the pneumococcal origin of CAP, the use of pneumococcal PCR makes up for prior prescription of antibiotics − reported in one third of patients included in the present study − that can negate SCBE and blood culture results in these patients. As previously mentioned, risk factor characteristics were equally distributed in the two groups, irrespective of the microbiological origin. The association of clinical and biological or clinical, biological, and radiological criteria was more frequently observed in patients with pneumonia considered as definitely or probably pneumococcal, although statistically non-significant. However, sensitivity of these associations was poor as they were respectively observed in 58% and 47% of patients with pneumococcal CAP.

Our study has several limitations. As it was not initially designed to assess the SPILF-AFSSAPS criteria, all criteria were not documented as such in the data collection form. Sudden onset of episodes was thus not documented as such, and physicians had to look back in the patients' files and make an estimation. All patients did not have blood culture systematically collected at the emergency department; we thus had to limit the analysis of criteria distribution to the subgroup of the PACSCAN patients with microbiological documentation. In this population, the proportion of patients considered as having *Streptococcus pneumoniae* CAP (16%) was small and limits the possibility to assess the performance of diagnostic criteria. However, this proportion is similar to that reported in recent studies, and mainly by Rosanel Amaro in a 2016 prospective cohort study of 5,791 patients consulting for CAP at the emergency department of Barcelona hospital, Spain. The authors reported 16% of patients with *Streptococcus pneumoniae* CAP [8]. This small proportion is believed to be explained by the decreased tobacco consumption and by the effectiveness of anti-pneumococcal conjugated vaccines [9, 10]. We also considered patients with negative microbiological results for *Streptococcus pneumoniae* as not presenting with pneumococcal pneumonia. We could

have identified some of them as *Streptococcus pneumoniae* carriers had we performed further tests.

Because of the non-unequivocal presentation of the 2010 SPILF-AFSSAPS guiding criteria for *Streptococcus pneumoniae* CAP, such criteria are open to various interpretations. This is why these criteria are found in a highly varied proportion of patients managed at the emergency department for CAP suspicion. As such, these criteria do not guide with precision towards *Streptococcus pneumoniae* or atypical germs. To spare antibiotics and to use targeted antibiotic therapies, clinical studies are required to define and approve a diagnostic score combining various criteria (risk factors, clinical presentation, biological results available at the emergency department) to help physicians diagnose *Streptococcus pneumoniae* CAP, especially in populations with a higher risk of morbi-mortality in case of such infection. In the meantime, using the Japanese score − that has not been validated for use in the French population − could be suggested to physicians to guide the antibiotic therapy choice in patients presenting with acute community-acquired pneumonia [11].

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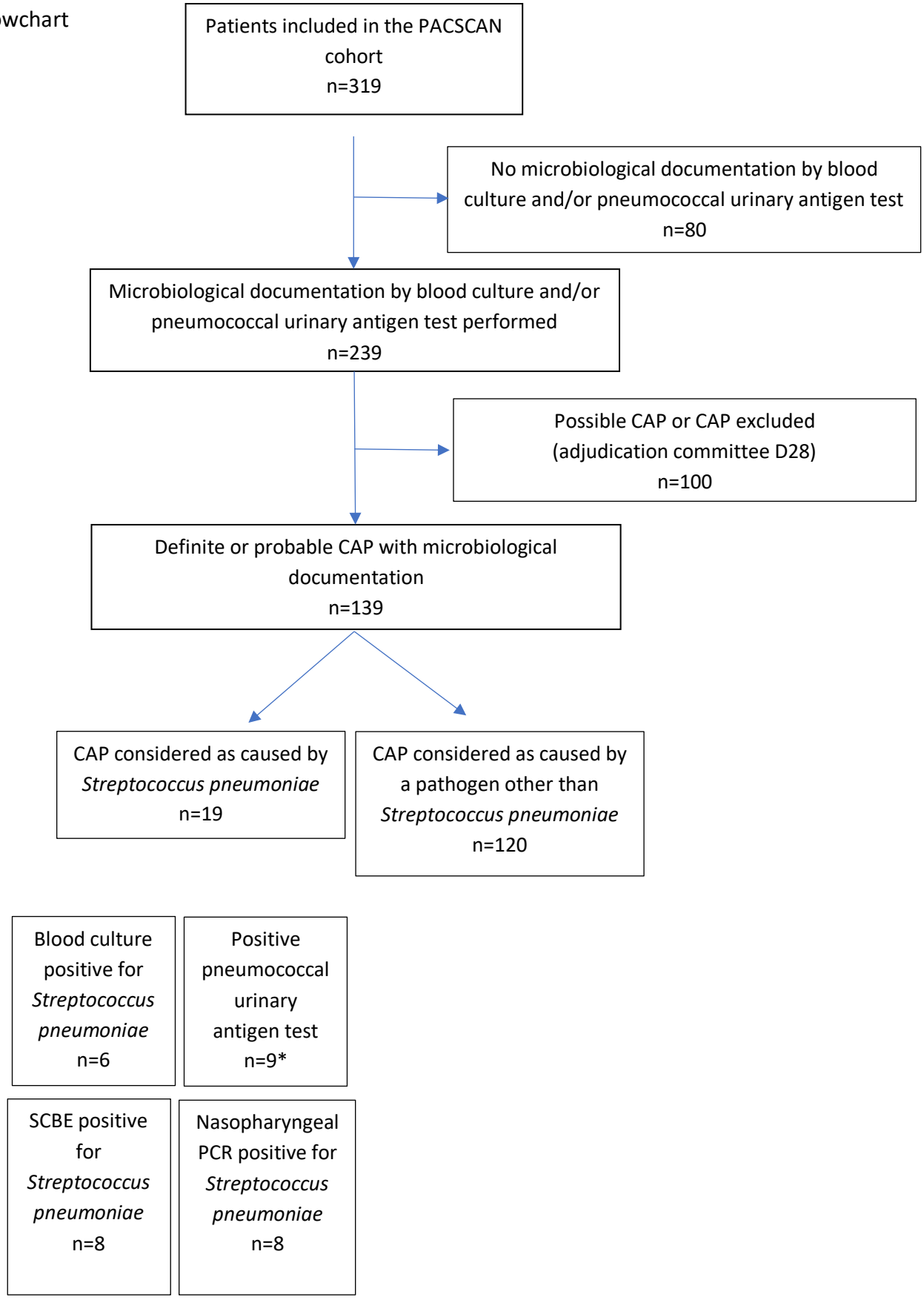
Figure. Flowchart



*including six with negative nasopharyngeal PCR

Table I. 2010 SPILF-AFSSAPS guiding criteria for community-acquired *Streptococcus pneumoniae* pneumonia in 319 patients included in the PACSCAN study

2010 SPILF-AFSSAPS guiding criteria for *Streptococcus pneumoniae* CAP	**PACSCAN population n=319**
All criteria met	6 (2%)
At least 1 criterion met	319 (100%)
Details of criteria	
"Risk factors" criteria	
Aged >40 years	275 (86%)
Associated comorbidities[(a)]	225 (70%)
"Clinical" criteria	
Sudden onset[(b)]	142 (45%)
High fever, as of the first day[(c)]	173 (54%)
Chest pain[(d)]	103 (32%)
"Radiological" criteria	
Systematized alveolar opacity	165 (52%)
"Biological" criteria	
Neutrophilic hyperleukocytosis[(e)]	163 (51%)

CAP: acute community-acquired pneumonia

a/ Associated comorbidities: history of diabetes, of homozygous sickle cell anemia, of splenectomy, of asthma, of COPD or other pulmonary diseases.

b/ Sudden onset: term used in the patient's medical file and/or if the patient had consulted at the emergency department within 24 hours after symptom onset.

c/ High fever, as of the first day: temperature ≥38°C from symptom onset.

d/ Chest pain: lateral chest pain on admission to the emergency department.

e/ Neutrophilic hyperleukocytosis was defined as blood count ≥10,000 /mm^3

Table II. Proportion of patients meeting the 2010 SPILF-AFSSAPS guiding criteria for *Streptococcus pneumoniae* CAP in the population of 139 patients with definite or probable pneumonia included in the PACSCAN study and microbiological documentation

2010 SPILF-AFSSAPS guiding criteria for *Streptococcus pneumoniae* CAP	**Overall population n=139**	***Streptococcus pneumoniae* CAP, n=19**	**Other CAP n=120**	*p*
All criteria met	4 (3%)	2 (11%)	2 (2%)	0.09
At least 1 criterion met	139 (100%)	19 (100%)	120 (100%)	>0.99
Details of criteria:				
"Risk factors" criteria				
Aged >40 years	114 (82%)	14 (74%)	100 (83%)	0.34
Associated comorbidities[(a)]	80 (58%)	11 (58%)	69 (57%)	>0.99
"Clinical" criteria				
Sudden onset[(b)]	61 (44%)	12 (63%)	49 (41%)	0.08
High fever, as of the first day[(c)]	94 (68%)	15 (79%)	79 (66%)	0.30
Chest pain[(d)]	53 (38%)	9 (47%)	44 (37%)	0.45
"Radiological" criteria				
Systematized alveolar opacity	102 (73%)	15 (79%)	80 (67%)	0.4
"Biological" criteria				
Neutrophilic hyperleukocytosis[(e)]	83 (60%)	14 (74%)	69 (57%)	0.21

CAP: acute community-acquired pneumonia

a/ Associated comorbidities: history of diabetes, of homozygous sickle cell anemia, of splenectomy, of asthma, of COPD or other pulmonary diseases.

b/ Sudden onset: term used in the patient's medical file and/or if the patient had consulted at the emergency department within 24 hours after symptom onset.

c/ High fever, as of the first day: temperature ≥38°C from symptom onset.

d/ Chest pain: lateral chest pain on admission to the emergency department.

e/ Neutrophilic hyperleukocytosis was defined as blood count ≥10,000 /mm^3

Tableau III. Proportion of patients meeting the 2010 SPILF-AFSSAPS combined criteria for *Streptococcus pneumoniae* CAP in the population of 139 patients with definite or probable pneumonia included in the PACSCAN study and microbiological documentation

SPILF-AFSSAPS combined criteria for *Streptococcus pneumoniae* CAP, at least one criterion met	**Overall population n=139**	***Streptococcus pneumoniae* CAP, n=19**	**Other CAP n=120**	***p***
Presence of one criterion of the category				
Risk factors	114 (82%)	14 (73%)	100 (83%)	0.3
Clinical criteria	90 (65%)	15 (79%)	75 (62%)	0.2
Radiological criteria	102 (73%)	15 (79%)	87 (73%)	0.7
Biological criteria	83 (60%)	14 (73%)	69 (57%)	0.2
Combination of two criteria				
Presence of one criterion in each of these two categories				
Risk factors + clinical signs	72 (52%)	10 (53%)	62 (52%)	>0.99
Risk factors + radiological signs	83 (60%)	11 (58%)	72 (60%)	>0.99
Risk factors + biological signs	69 (50%)	10 (53%)	59 (49%)	0.8
Clinical signs + radiological signs	65 (47%)	11 (58%)	54 (45%)	0.3
Clinical signs + biological signs	52 (37%)	11 (58%)	41 (34%)	0.07
Biological signs + radiological signs	66 (47%)	12 (63%)	54 (45%)	0.2
Presence of one criterion in each of these three categories				
Risk factors + clinical signs + radiological signs	52 (37%)	7 (37%)	45 (45%)	1
Risk factors + clinical signs + biological signs	43 (31%)	7 (67%)	36 (30%)	0.6
Risk factors + radiological signs + biological signs	55 (40%)	9 (47%)	46 (38%)	0.4
Clinic signs + biological signs + radiological signs	40 (29%)	9 (47%)	31 (26%)	0.06
Presence of one criterion in each of these four categories	33 (24%)	6 (32%)	27 (23%)	0.3

CAP: acute community-acquired pneumonia

Table IV. Proportion of patients meeting the 2010 SPILF-AFSSAPS guiding criteria for *Streptococcus pneumoniae* CAP in the PACSCAN population (n=319) according to the pneumococcal or non-pneumococcal origin of CAP

2010 SPILF-AFSSAPS guiding criteria for *Streptococcus pneumoniae* CAP	**PACSCAN population, except for patients with *Streptococcus pneumoniae* CAP n=300**	***Streptococcus pneumoniae* CAP n=19**	***p***
All criteria met	3 (1%)	3 (16%)	**0.003**
At least 1 criterion met	300 (100%)	19 (100%)	1
Details of criteria:			
"Risk factors" criteria			
Aged >40 years	260 (87%)	14 (74%)	0.1
Associated comorbidities[(a)]	213 (71%)	11 (58%)	0.2
"Clinical" criteria			
Sudden onset[(b)]	129 (43%)	12 (63%)	0.09
High fever, as of the first day[(c)]	158 (53%)	15 (79%)	**0.03**
Chest pain[(d)]	94 (31%)	9 (47%)	0.2
"Radiological" criteria			
Systematized alveolar opacity	153 (51%)	15 (79%)	**0.01**
"Biological" criteria			
Neutrophilic hyperleukocytosis[(e)]	149 (50%)	14 (74%)	**0.05**

CAP: acute community-acquired pneumonia; a/ Associated comorbidities: history of diabetes, of homozygous sickle cell anemia, of splenectomy, of asthma, of COPD or other pulmonary diseases; b/ Sudden onset: term used in the patient's medical record and/or if the patient had consulted at the emergency department within 24 hours after symptom onset; c/ High fever, as of the first day: temperature ≥38°C from symptom onset; d/ Chest pain: lateral chest pain on admission to the emergency department; e/ Neutrophilic hyperleukocytosis was defined as blood count ≥10,000/mm^3

Table V. Proportion of patients meeting some 2010 SPILF-AFSSAPS combined criteria for *Streptococcus pneumoniae* CAP in the PACSCAN population (n=319) according to the pneumococcal or non-pneumococcal origin of CAP

Combinations of the 2010 SPILF-AFSSAPS guiding criteria for *Streptococcus pneumoniae* CAP	**PACSCAN population, except for patients with *Streptococcus pneumoniae* CAP n=300**	***Streptococcus pneumoniae* CAP n=19**	***p***
Presence of one criterion of the category			
Risk factors	261 (87%)	14 (73%)	0.15
Clinical criteria	161 (54%)	15 (79%)	**0.03**
Radiological criteria	153 (51%)	15 (79%)	**0.01**
Biological criteria	149 (50%)	14 (73%)	**0.05**
Combination of two criteria			
Presence of one criterion in each of these two categories			
Risk factors + clinical signs	135 (45%)	10 (53%)	0.6
Risk factors + radiological signs	149 (50%)	11 (58%)	0.6
Risk factors + biological signs	136 (45%)	10 (53%)	0.6
Clinical signs + radiological signs	79 (26%)	11 (58%)	0.006
Clinical signs + biological signs	80 (27%)	11 (58%)	0.006
Biological signs + radiological signs	84 (28%)	12 (63%)	0.003
Presence of one criterion in each of these three categories			
Risk factors + clinical signs + radiological signs	77 (26%)	7 (37%)	0.2
Risk factors + clinical signs + biological signs	73 (24%)	7 (67%)	0.2
Risk factors + radiological signs + biological signs	83 (28%)	9 (47%)	0.07
Clinic signs + biological signs + radiological signs	41 (14%)	9 (47%)	**<0.001**
Presence of one criterion in each of these four categories	41 (14%)	6 (32%)	**0.04**