15TH CONSENSUS CONFERENCE ON ANTI-INFECTIVE THERAPY

MANAGEMENT OF LOWER RESPIRATORY TRACT INFECTIONS IN IMMUNOCOMPETENT ADULTS

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organized by the *Société de Pathologie Infectieuse de Langue Française*
with the participation of the following scientific societies:

- APNET (Association Pédagogique Nationale pour l'Enseignement de la Thérapeutique)
- APP (Association de Perfectionnement des Pneumologues Libéraux)
- CMIT (Collège des Universitaires de Maladies Infectieuses et Tropicales)
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- SNFMI (Société Nationale Française de Médecine Interne)
- SPLF (Société de Pneumologie de Langue Française)
- SRLF (Société de Réanimation de Langue Française)

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INTRODUCTION

In 1991, the consensus conference organized in Lille by the *Société de Pathologie Infectieuse de Langue Française* (SPILF) on antibiotic therapy for respiratory tract infections was the first conference of this type to be organized in the world. However, in the absence of publication in an English language journal, this conference was ignored by the international medical community in favour of the English conference held in 1993. Since then, so many guidelines on this theme have been proposed that it is difficult to take them all into account, as each country, and in some countries, each society or institution, has defined its own set of guidelines on this subject, sometimes several times each decade. This phenomenon is certainly correlated with the large place occupied by respiratory tract infections in clinical practice, especially general practice, and therefore in health expenditure.

The SPILF, based on its experience of 14 previous consensus conferences, covering a very broad range of infectious diseases, invited its partners, *Association Pédagogique Nationale pour l'Enseignement de la Thérapeutique* (APNET), *Association de Perfectionnement des Pneumologues Libéraux* (APP), *Collège des Universitaires des Maladies Infectieuses et Tropicales* (CMIT), *Société Française de Microbiologie* (SFM), *Société Francophone de Médecine d'Urgence* (SFMU), *Société Nationale Française de Médecine Interne* (SNFMI), *Société de Pneumologie de Langue Française* (SPLF), and *Société de Réanimation de Langue Française* (SRLF) to participate in the organization of a consensus conference on the **management of lower respiratory tract infections in immunocompetent adults.**

The purpose of this conference was not to add yet another set of guidelines to the long list of available guidelines, but rather to try to encourage a change of attitude and to integrate the concept of networking of public and private healthcare structures, to go beyond the limited objective of guidelines for the choice of anti-infective agents in order to define an optimized patient management, to integrate the goal of individual benefit into that of public health management. Another objective was to start the 21st century by taking into account the progress in diagnostic methods, particularly the currently available and future modalities of imaging, molecular biology, and rapid diagnostic tests, whenever they can improve the quality of care for the patient, and a rational management of healthcare for the community: early virological diagnosis, avoiding inappropriate antibacterial therapy in favour of specific antiviral therapy represents a benefit for both the individual and the community. Vaccination extended to groups that are either responsible for diffusion of respiratory tract infectious agents, or suffering from severe forms of infection by these agents is also beneficial for the individual and the community. In the more conventional, but still topical, field of bacteria and antibacterials, we needed to revise bacterial epidemiology and the growth of resistance, by noting the stability of certain data, allowing a certain respite for prescribers of molecules known and monitored for a long time, but also predicting the ecological impact of a possible overuse of a given group of molecules.

QUESTION 1

HOW TO DIAGNOSE LOWER RESPIRATORY TRACT INFECTION?

WHAT CLINICAL AND COMPLEMENTARY DIAGNOSTIC METHODS CAN BE USED TO DISTINGUISH BRONCHIAL INFECTION FROM LUNG INFECTION?

The term "lower respiratory tract infection" (LRTI) refers to three distinct clinical entities: acute bronchitis with a benign course, pneumonia, responsible for a mortality of up to 15%, and acute exacerbation of chronic obstructive pulmonary disease with a variable prognosis; general practitioners ensure the management of 96% to 98% of cases of these infections.

ACUTE BRONCHITIS

Acute bronchitis is a very frequent infection (10 million cases per year in France), usually due to a virus, occurring in an epidemic setting. The diagnosis is clinical: no complementary investigation is useful and chest x-ray is reserved to cases with a doubtful diagnosis. Uncomplicated acute bronchitis usually resolves over about ten days. Complications are rare. No clinical trial has demonstrated the value of antibiotics. Antibiotics are not indicated for acute bronchitis in healthy adults since 1991: (SPILF 1991, AFSSAPS 2005) (Grade A recommendation).

ACUTE PNEUMONIA

Acute pneumonia is an infection of the lung parenchyma with an estimated frequency of 400,000 to 600,000 cases per year in France. Only community-acquired pneumonia (CAP) was considered at this consensus conference. **The diagnosis is difficult**. It is based on a body of clinical and radiological evidence dependent on the examination technique and the examiner's experience. Clinical signs include cough, dyspnoea, lateral chest pain, sputum, fever, tachycardia, tachypnoea, an impression of severity, localized dullness, and zones of crackles, but they are rarely all present.

The presence of unilateral crackles has a good positive predictive value for CAP (Professional consensus), while a combination of respiratory rate < 30/min, pulse < 100 bpm and temperature < 37.9°C has a good negative predictive value for CAP (Grade B recommendation).

The clinical features are even more misleading in the elderly and may sometimes be limited to confusion, tachypnoea, dyspnoea, or deterioration of a pre-existing chronic disease.

The AP chest x-ray, possibly completed by a lateral film, is essential (Professional consensus). Systematized alveolar opacities are easily recognized. In contrast, interstitial opacities and peribronchial clumped opacities suggestive of "bronchopneumonia" are more difficult to identify. The diagnosis is even more difficult in the elderly due to frequent pre-existing abnormalities, the high prevalence of bronchopneumonia forms, and the technical difficulties of radiography.

Unenhanced CT scan is useful in cases presenting diagnostic difficulties. CT angiography is reserved for the differential diagnosis of pulmonary embolism.

The contribution of **laboratory tests** to the diagnosis of CAP has been poorly evaluated. Marked leukocytosis and high CRP and procalcitonin values are in favour of bacterial CAP. Inversely, low CRP and procalcitonin values confirmed on D2 argue against bacterial infection. At the present time, in outpatient medicine, it appears logical to limit laboratory tests to patients with an uncertain diagnosis.

ACUTE EXACERBATIONS OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

An estimated 2,000,000 cases of acute exacerbations of chronic obstructive pulmonary disease are observed each year in France, responsible for 40,000 to 60,000 hospitalisations. They usually occur in a patient with known COPD, but can sometimes be the first sign of COPD. This slowly progressive chronic disease, essentially caused by smoking, is characterized by partly reversible bronchial obstruction (FEV_1/VC ratio less than 70%). The severity of COPD must be evaluated by a pulmonary function tests after resolution of the acute episode, allowing classification in stages of severity, facilitating optimal patient management.

The diagnosis of acute exacerbation of COPD is difficult because the clinical features are not specific and are continuous with the signs of COPD. Several diagnostic criteria have been defined. For the *Société de Pneumologie de Langue Française* (2003) and AFSSAPS (2005), an acute exacerbation of COPD is defined as the accentuation or appearance of one or several symptoms of the disease (cough, sputum, dyspnoea), regardless of the severity of the episode. A viral or bacterial infection is responsible in only one half of all exacerbations. Fever is inconstant; routine laboratory tests and chest x-ray are poorly contributive. Among Anthonisen's classical criteria (deterioration of dyspnoea, increased purulence of sputum, increased volume of sputum), only frankly purulent sputum constitutes a strong argument in favour of a bacterial cause.

QUESTION 2

LOWER RESPIRATORY TRACT INFECTIONS: INITIAL WORK-UP AND REFERRAL OF PATIENTS WITH ACUTE COMMUNITY-ACQUIRED PNEUMONIA (CAP)

Once the diagnosis of CAP has been established, the next step consists of evaluation of its severity, which, among other things, will determine the choice of the site of management. Severity is systematically assessed by the combination of clinical factors and comorbidities. Evaluation is facilitated by calculation of 4 scores specifically devoted to CAP: Fine's score (Pneumonia Severity Index: PSI), CRB 65, the British Thoracic Society (BTS) score, and the American Thoracic Society (ATS) score **(Table I).**

Table I

ELEMENTS OF CALCULATION OF FINE'S SCORE (PSI)

- Class 1 corresponds to a healthy adult under the age of 50 with no signs of severity and no comorbidity (probability of mortality less than 0.1%). No blood tests.

		Points assigned
- Demographic factor		
Age	Men	= Age (years)
	Women	= Age -10
Nursing-home resident		+ 10
- Co-existing illnesses		
	Neoplastic disease	+ 30
	Liver disease	+ 20
	Congestive heart failure	+ 10
	Cerebrovascular disease	+ 10
	Renal disease	+ 10
- Physical examination findings		
	Altered mental status	+ 20
	Respiratory rate > 30/min	+ 20
	Systolic blood pressure < 90 mmHg	+ 20
	Temperature < 36°C or > 40°C	+ 15
	Pulse 125 bpm	+ 10
- Laboratory and radiographic findings		
	Arterial blood pH < 7.35	+ 30
	Blood urea nitrogen ≥ 11 mmol/l	+ 20
	Sodium < 130 mmol/l	+ 20
	Haematocrit < 30%	+ 10
	PaO_2 < 60 mmHg	+ 10
	Pleural effusion	+ 10

Class	Points	Mortality
II	≤ 70	0.6-0.7%
III	71-90	0.9-2.8%
IV	91-130	8.2-93%
V	> 131	27-31%

BRITISH THORACIC SOCIETY SCORE (CURB 65)

Confusion
Urea > 7 mmol/l
Respiratory rate ≥ 30/min
Blood pressure: systolic < 90 mmHg
or diastolic ≤ 60 mmHg
65 Age ≥ 65

A patient presenting at least 2 of these 4 factors has a 36-fold higher risk of mortality.

CRB 65 (SIMPLIFIED SCORE)

C Mental **C**onfusion
R **R**espiratory rate ≥ 30/min
B **B**lood pressure: systolic < 90 mmHg
or diastolic ≤ 60 mmHg
65 AGE ≥ 65

This score can be used in office practice
(if 0 criterion; outpatient treatment is possible
≥ 1 criterion: assessment in hospital)

AMERICAN THORACIC SOCIETY SCORE (REVISED IN 2001)

3 MINOR CRITERIA

- PaO_2/FiO_2 < 250
- Multilobar involvement
- SBP ≤ 90 mmHg

2 MAJOR CRITERIA

- Need for mechanical ventilation
- Septic shock

The presence of 2 minor criteria or 1 major criterion is predictive of the need for admission to the intensive care unit with a sensitivity of 78%, a specificity of 94%, a PPV of 75% and a NPV of 95%.

These scores were not all constructed with the same objectives: **when used coherently and conjointly, these scores, especially the PSI, help to guide the most appropriate mode of patient management**. The PSI confirms the possibility of community management (Grade A recommendation). The CURB 65, BTS and ATS scores appear to be more relevant to guide the decision for intensive care management. They should be optimally used in a stepwise approach.

- Step 1: **search for pre-existing conditions compromising the success of outpatient treatment**: haemodynamic instability, decompensation of a pre-existing disease requiring hospitalisation, acute hypoxia, psychiatric or social problems, and inability to take oral therapy.
- Step 2: **calculation of the PSI score:** patients in classes I and II not presenting any criteria of the first step, can be treated on an outpatient basis (Grade A recommendation).

Patients with a PSI score > II require inpatient management (Grade A recommendation).

In hospitalised patients, the ATS score can guide the decision for intensive care management (Grade B recommendation).

An example of this approach is illustrated in **Figure 1**.

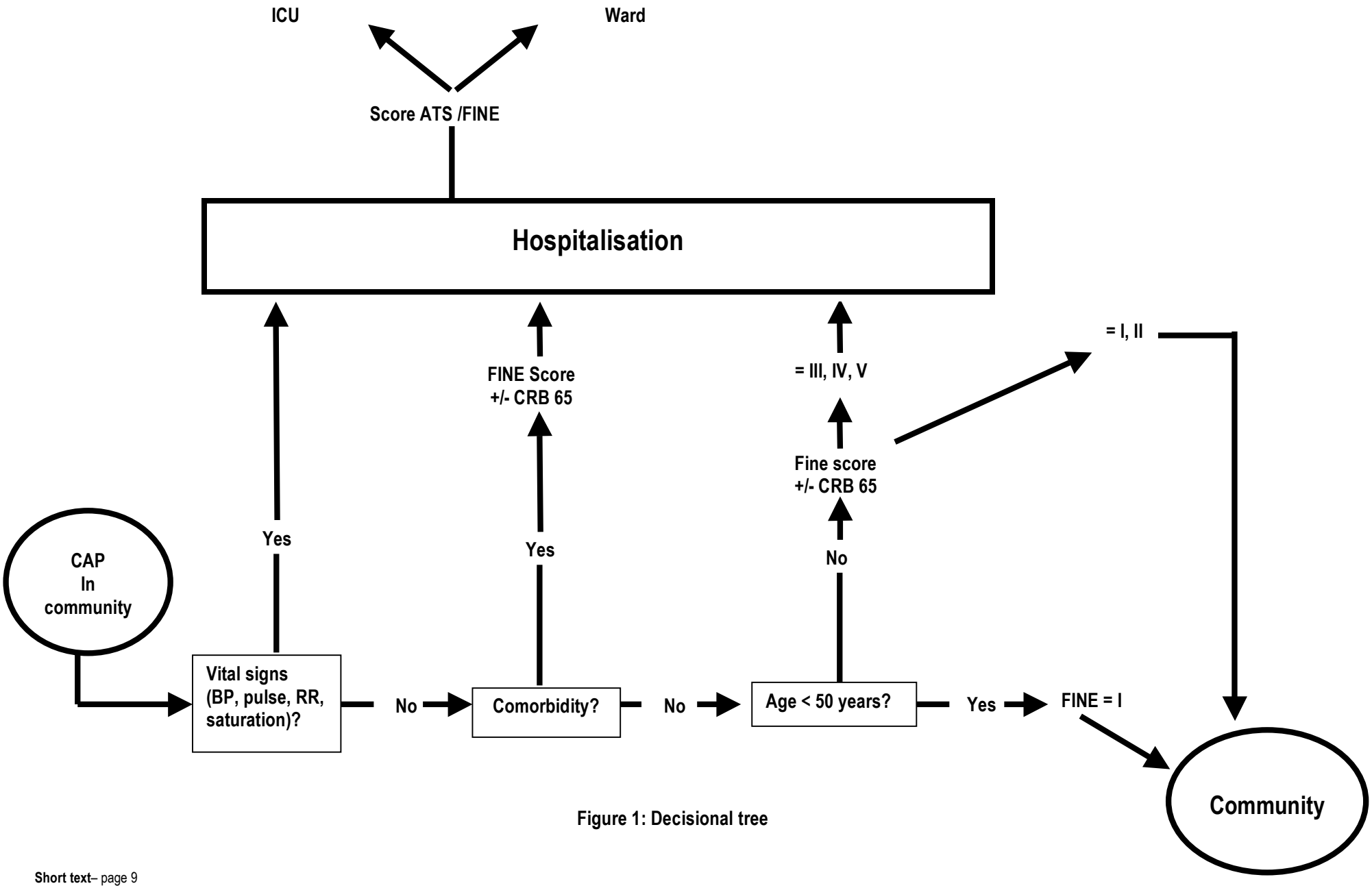

Figure 1: Decisional tree

INITIAL MICROBIOLOGICAL DIAGNOSIS

TESTS

Sputum culture

When performed correctly in a patient without antibiotic therapy, sputum culture has a good sensitivity and a good specificity in pneumococcal CAP: the sensitivity and specificity are higher when pneumonia is more severe, i.e. with bacteraemia.

This examination only has a diagnostic relevance when direct examination is positive.

Urinary *Streptococcus pneumoniae* antigen

The sensitivity of this test ranges from 77% to 89% in bacteraemic CAP and 44% to 64% in non-bacteraemic CAP.

False-positives are rare in adults, even in acute exacerbation of COPD.

This test allows a rapid aetiological diagnosis, which is not suppressed by one week of antibiotics and a positive result persists for several weeks.

Urinary *Legionella pneumophila* antigen

About 80% of patients with *L. pneumophila* serogroup 1 infection excrete antigens in their urine. This excretion appears 1 to 3 days after onset of the disease and can last for 1 year.

The sensitivity and specificity are 86% and 93%, respectively.

MICROBIOLOGICAL DIAGNOSTIC STRATEGY (PROFESSIONAL CONSENSUS)

- **For community-acquired pneumonia, except in nursing homes**, it appears useless to propose a microbiological work-up for patients presenting low severity criteria (PSI: I and II);
- **For hospitalised patients in wards other than intensive care** (PSI: III and IV):
  - blood cultures and sputum culture can be recommended;
  - screening tests for urinary pneumococcus and/or Legionella antigen are not recommended immediately. Tests for urinary Legionella antigens may be justified:
    - in patients with symptoms suggestive of Legionnaire's disease;
    - or presenting haemodynamic instability and/or hypoxia;
    - or in an epidemic setting for all cases of CAP.
- **For patients admitted to the intensive care unit**, blood cultures, culture of tracheobronchial secretions taken during intubation, screening tests for urinary pneumococcus and Legionella antigens are recommended.

MODALITIES OF FOLLOW-UP

AT 48-72 HOURS, FOLLOW-UP REQUIRES CLINICAL REVIEW OF EVERY CASE (GRADE C RECOMMENDATION)

The absence of clinical response, particularly resolution of fever, 48-72 hours after starting treatment, is an indication for chest imaging, looking for a complication, or an argument in favour of a modification of the initial diagnosis. Chest CT scan occupies a central place in investigation strategies.

In the case of clinical failure after 48 to 72 hours of treatment, microbiological investigations must be performed (Grade C recommendation):

- To identify the micro-organism responsible, when it is unknown:
  - sputum culture, if sputum remains purulent;
  - blood cultures;
  - test for urinary pneumococcus and Legionella antigens.

- Possibly to detect a microbial modification (resistance, superinfection) if the microbial cause is known:
  - sputum culture, if sputum remains purulent;
  - blood cultures

LONG-TERM FOLLOW-UP

Chest radiography is recommended 2 months after resolution of the clinical signs in every case (Professional consensus).

AECOPD

The very great majority of cases of AECOPD must be managed on an outpatient basis. Early review, between 24 and 72 hours depending on the case, is essential to verify the efficacy of treatment and the absence of deterioration.

(Grade C recommendation)

Hospitalisation is **recommended** for all patients presenting one of the following criteria (Grade C recommendation):

- major modification of usual symptoms, such as onset of dyspnoea at rest;
- severe COPD (**Table II);**
- appearance of new clinical signs, such as cyanosis or peripheral œdema;
- presence of comorbidities;
- appearance of arrhythmia;
- uncertain diagnosis;
- age greater than 70 years;
- lack of resources at home.

Table II: Classification of COPD in stages of severity

STAGE	CHARACTERISTICS
0: At risk	Chronic symptoms: cough, sputum $FEV_1/VC \geq 70\%$
I: Mild COPD	$FEV_1/VC < 70\%$ $FEV_1 \geq 80\%$ of predicted value with or without chronic symptoms (cough, sputum)
II: Moderately severe COPD	$FEV_1/VC < 70\%$ $30\% \leq FEV_1 < 80\%$ of predicted value IIA $50\% \leq FEV_1 < 80\%$ of predicted value IIB $30\% \leq FEV_1 < 50\%$ of predicted value with or without chronic symptoms (cough, sputum, dyspnoea)
III: Severe COPD	$FEV_1/VC < 70\%$ $FEV_1 < 30\%$ of predicted value or $FEV_1 < 50\%$ of predicted value in the presence of respiratory insufficiency ($PaO_2 < 60$ mmHg) or clinical signs of right heart failure

In hospital, the presence of signs of immediate severity requires admission to a **continuous surveillance structure, or intensive care unit.**

Signs of immediate severity adopted by the SPLF for the management of AECOPD are:

- **respiratory signs**: dyspnoea at rest, cyanosis, SpO_2 < 90%, use of accessory respiratory muscles, paradoxical abdominal breathing, respiratory rate > 25/min, ineffective cough;
- **cardiovascular signs:** tachycardia > 110 bpm, arrhythmias, hypotension, mottled skin, peripheral œÒdema;
- **neurological signs**: agitation, confusion, obtundation, coma, asterixis;
- **blood gases**: hypoxia < 55 mmHg on room air, hypercapnia > 45 mmHg, ventilatory acidosis (pH < 7.35).

The presence of profound hypoxia may be sufficient to justify continuous surveillance or intensive care.

The NHLBI/WHO Global initiative for Obstructive Lung Disease (GOLD) proposes the following combination of **hospital discharge criteria**:

1. an interval of at least 4 hours between each dose of inhaled bronchodilator;
2. patient able to walk across the room (if previously ambulant);
3. patient able to eat and sleep without being interrupted by episodes of dyspnoea;
4. patient clinically stable for 12 to 24 hours;
5. arterial blood gases stable for 12 to 24 hours;
6. good understanding of treatment by the patient or care-giver;
7. follow-up and management at home (oxygen therapy, home nurse, etc.) organized, the patient, the family and the doctor consider that management at home is reasonable (Grade C recommendation).

The exacerbation, **regardless of its severity**, must be an opportunity to activate or reactivate the patient's respiratory management according to SPLF guidelines (Grade C recommendation).

Home hospitalisation is an alternative to conventional hospitalisation. The risk of readmission or mortality does not appear to be significantly different between the two modes of management.

The GOLD group proposes **a follow-up visit 4 to 6 weeks** after discharge from hospital in order to evaluate the following parameters, in addition to the usual follow-up of COPD (smoking cessation, vaccinations, patient education to rapidly detect an exacerbation):

- level of independence in the patient's usual environment;
- FEV_1 (follow-up by the general practitioner and respiratory physician);
- verification of inhalation techniques, good understanding of treatment;
- need for home oxygen therapy or nebulized treatment for patients with severe COPD;
- repeat arterial blood gases if the patient presented hypoxia during the exacerbation.

Radiographic assessment may be useful at this stage.

QUESTION 3

HOW TO CHOOSE ANTIBIOTIC THERAPY FOR ACUTE COMMUNITY-ACQUIRED PNEUMONIA? WHAT EPIDEMIOLOGICAL, MICROBIOLOGICAL, PHARMACOLOGICAL (PK-PD), EXPERIMENTAL AND CLINICAL CRITERIA CAN BE USED TO OPTIMIZE THE CHOICE, MODALITIES OF ADMINISTRATION, AND DURATION OF TREATMENT?

CAP is a medical emergency that is usually treated empirically. The aetiological diagnosis is established during hospitalisation in only one half of cases. Pneumococcus is still the main micro-organism to be considered in the choice of treatment. However, in the elderly, the incidence of Gram-negative bacilli and Staphylococci is not negligible. The place of viruses is probably underestimated and should benefit from progress in the field of molecular biology.

- At the present time, about one half of **pneumococc**i present decreased susceptibility, or are resistant to penicillin, but amoxicillin can be used and remains perfectly effective in *S. pneumoniae* pneumonia, even in the case of decreased susceptibility to penicillin G. No clinical strains responsible for pneumonia are resistant to cefotaxime and ceftriaxone.

  There is no indication to use macrolides to treat pneumococcal CAP, because of the high prevalence of resistant strains. Telithromycin has a favourable profile with a low level of resistance in relation to pneumococcus.

  Antipneumococcal fluoroquinolones (APFQ) (levofloxacin and moxifloxacin) possess interesting *in vitro* characteristics, with a broad spectrum and few resistant strains of pneumococcus. However, the extensive use of APFQs could lead to the emergence of resistant pneumococcal strains. The prescription of antipneumococcal fluoroquinolones should therefore be avoided during the 3 months following the use of any other fluoroquinolone (Grade A recommendation).
- 98% of ***H. influenzae*** strains remain susceptible to amoxicillin-clavulanic acid.
- **Legionellas** are constantly susceptible to fluoroquinolones, macrolides, telithromycin and rifampicin.

Optimization of the treatment of CAP must take into account the pharmacokinetic and pharmacodynamic parameters of antibiotics. Over the last 5 years, no randomized, prospective therapeutic trial has demonstrated any difference in terms of clinical efficacy between the various tested molecules. Amoxicillin therefore remains the reference molecule for presumed pneumococcal CAP, because of a better cost/efficacy ratio and a good safety profile (Grade A recommendation).

TREATMENT OPTIONS

1- NON-SEVERE CAP IN AN OUTPATIENT

1-a Presumed viral CAP

During the period of circulation of influenza viruses, a SPILF working party recommends treatment with a neuraminidase inhibitor in adults and children over the age of 1 year with a risk of complicated influenza. This treatment must be started as early as possible, within 48 hours after onset of the first symptoms.

1-b Presumed bacterial CAP

No microbiological examination is recommended. Treatment is empirical.

- **For subjects with no comorbidity**: amoxicillin 1 g x 3/day orally **or** pristinamycin 1 g x 3/day orally **or** telithromycin 800 mg/day orally
- **For subjects with comorbidity**: amoxicillin-clavulanic acid 1 g x 3/day orally
- **For elderly patients in a nursing home**: amoxicillin-clavulanic acid 1 g x 3/day orally **or** ceftriaxone 1 g/day IM/I.V./subcutaneous **or** APFQ (levofloxacin 500 mg/day orally **or** moxifloxacin 400 mg/day orally).

Treatment must be reviewed clinically on the 2nd or 3rd day. If fever has not resolved, but with no clinical deterioration after initial treatment with a ß-lactam antibiotic, it is recommended to replace treatment by:

- a macrolide **or** pristinamycin in patients with no comorbidity;
- APFQ (levofloxacin **or** moxifloxacin) in patients with comorbidity.

2- NON-SEVERE CAP IN HOSPITAL (EMERGENCY ROOM OR MEDICAL WARD)

- **Arguments in favour of pneumococcus**: amoxicillin 1 g x 3/day orally/I.V. infusion
- **No arguments in favour of pneumococcus**:
  - **For subjects with no comorbidity**: amoxicillin 1 g x 3/day orally/I.V. infusion **or** pristinamycin 1 g x 3/day orally **or** telithromycin 800 mg/day orally
  - **For elderly subjects or patients with comorbidity**: amoxicillin-clavulanic acid 1 g x 3/day orally/I.V. **or** cefotaxime 1 g x 3/day I.V. infusion **or** ceftriaxone 1 g/day I.V. **or** APFQ (levofloxacin 500 mg x 1 to 2/day orally **or** moxifloxacin 400 mg/day orally)

In the absence of microbiological documentation and after an initial treatment with a ß-lactam, if fever fails to resolve but without any clinical deterioration, it is recommended to add a macrolide or replace by pristinamycin **or** telithromycin.

3- SEVERE CAP IN HOSPITAL (CONTINUOUS CARE OR INTENSIVE CARE UNIT)

Antibiotics must be started before H+4 of admission, as any delay can be detrimental. Aetiological investigations are essential, as inappropriate treatment can compromise the prognosis. An empirical broad-spectrum antibiotic that can be administered by IV and that is active on pyogenic bacteria, Legionella and atypical bacteria, must therefore be used.

- **For young subjects with no comorbidity**:
  (cefotaxime 1-2 g x 3/day I.V. infusion **or** ceftriaxone 1-2 g/day I.V.)
  plus macrolides I.V. **or** APFQ I.V.
- **For elderly subjects or patients with comorbidity**:
  (cefotaxime 1-2 g x 3/day I.V. infusion **or** ceftriaxone 1-2 g/day I.V.)
  plus APFQ (levofloxacin 500 mg x 2/day) I.V.
  More rarely (elderly subjects with comorbidities who have received ß-lactam antibiotics during the previous 30 days), *Pseudomonas aeruginosa* may need to be taken into account in empirical treatment: piperacillin-tazobactam 4 g x 3/day I.V. **or** imipenem 1 g x 3/day I .V . in combination with an aminoglycoside and an antibiotic active on intracellular bacteria (macrolide or fluoroquinolone).

Treatment simplification procedure as soon as microbiological documentation is obtained

- For pneumococcal CAP: amoxicillin 1 g x 3-6/day by I.V. infusion
- For Legionnaire's disease: APFQ **plus** macrolide or rifampicin. The combination should be administered for 5 days.

In the presence of 2 negative urinary Legionella antigen tests at an interval of 48 h, the third-generation cephalosporin can be maintained alone, except in the presence of clinical features suggestive of Legionnaire's disease. In the absence of microbiological documentation, it is preferable to continue the initial combination.

Duration of treatment: the classical duration of treatment is 7 to 14 days (average of 10 days), but this duration can be decreased with the use of new molecules such as ketolides or antipneumococcal fluoroquinolones.

Extensive and systematic use of new molecules in situations in which old molecules are still effective is not recommended (Professional consensus). The development and marketing of new antibiotics have become rare, indicating the need for cautious management of the available antibiotics.

This situation reinforces **the value of respiratory vaccines (influenza and pneumococcus) for high-risk subjects or nursing home residents. Influenza vaccination must be actively encouraged for all healthcare personnel**.

NB: when several equivalent treatment options are available, the molecules are indicated in alphabetical order.

Table III: Empirical antibiotic therapy for outpatient management of CAP

	1st choice	Failure of amoxicillin after 48 h
Subjects *with no comorbidity*	amoxicillin 1 g x 3/day orally **Or** pristinamycin 1 g x 3/day orally **Or** telithromycin 800 mg/day orally	macrolide **Or** pristinamycin 1 g x 3/day orally **Or** telithromycin 800 mg/day orally
Subjects *with comorbidity*	amoxicillin 1 g x 3/day orally **Or** pristinamycin 1 g x 3/day orally **Or** telithromycin 800 mg/day orally	macrolide **Or** pristinamycin 1 g x 3/day orally **Or** telithromycin 800 mg/day orally
Elderly subjects *in nursing home*	amoxicillin-clavulanic acid 1 g x 3/day orally **Or** ceftriaxone 1 g/day IM/I.V./SC **Or** APFQ = levofloxacin 500 mg/day orally moxifloxacin 400 mg/day orally	APFQ levofloxacin 500 mg/day orally **Or** moxifloxacin 400 mg/day orally

Table IV: Empirical antibiotic therapy for non-severe CAP in hospital (emergency room, medical ward)

	Arguments in favour of pneumococcus	No arguments in favour of pneumococcus	
		1st choice	**If failure of ß-lactam after 48 h**
Young subjects *with no comorbidity*	amoxicillin 1 g x 3/day orally/I.V. infusion	amoxicillin 1 g x 3/day orally/I.V. infusion **Or** pristinamycin 1 g x 3/day orally **Or** telithromycin 800 mg/day orally	Add a macrolide **Or** replace by telithromycin or pristinamycin
Elderly subjects *with no comorbidity*	amoxicillin 1 g x 3/day orally/I.V. infusion	amoxicillin-clavulanic acid 1 g x 3/day orally/I.V. infusion **Or** cefotaxime 1 g x 3/day I.V. infusion **Or** ceftriaxone 1 g/day I.V. **Or** APFQ (levofloxacin 500 mg x 1 to 2/day orally or moxifloxacin 400 mg/day orally	Add a macrolide **Or** replace by telithromycin or pristinamycin
Subjects *with comorbidity*	Amoxicillin 1g x 3/day orally/I.V. infusion	amoxicillin-clavulanic acid 1 g x 3/day I.V. infusion **Or** cefotaxime 1 g x 3/day I.V. infusion **Or** ceftriaxone 1 g/day I.V. **Or** APFQ (levofloxacin 500 mg x 1 to 2/day orally or moxifloxacin 400 mg/day orally)	Add a macrolide **Or** replace by telithromycin or pristinamycin

Table V: Empirical antibiotic therapy for severe CAP (Intensive Care Unit)

	1st choice
Young subjects *with no comorbidity*	(cefotaxime 1-2 g x 3/day I.V. infusion **or** ceftriaxone 1-2 g/day I.V.) **plus (**macrolides I.V. **or** APFQ I.V.: levofloxacin 500 mg 2/day I.V.)
Elderly subjects *with no comorbidity*	(cefotaxime 1-2 g x 3/day I.V infusion **or** ceftriaxone 1-2 g/day I.V.) **plus** APFQ (levofloxacin 500 mg x 2/day I.V.)
Subjects *with comorbidity*	(cefotaxime 1-2 g x 3/day I.V. infusion **or** ceftriaxone 1-2 g/day I.V.) **plus** APFQ (levofloxacin 500 mg x 2/day I.V.) **if suspicion of *Pseudomonas aeruginosa:*** (piperacillin-tazobactam 4 g x 3/day I.V. or cefepime 2 g x 2/day I.V. or imipenem 1 g x 3/day I.V.) **in combination with** an aminoglycoside **and** an antibiotic active on intracellular bacteria (macrolide or fluoroquinolone)

QUESTION 4
WHAT ARE THE INDICATIONS AND OPTIONS FOR ANTIBIOTIC THERAPY OF AN EXACERBATION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)?

Acute exacerbations of COPD are due to multiple, sometimes interrelated causes. They are due to an infectious agent (viral or bacterial) in only 50% of cases. Bacterial infections are essentially due to *H. influenzae*, *S. pneumoniae*, *Moraxella catarrhalis*, and more rarely *Pseudomonas aeruginosa* in longstanding COPD.

The various stages of severity of COPD are presented in **Table VI** and are determined by the degree of obstruction. However, this classification is not always operational, especially when the patient does not know his/her baseline FEV_1 value, which is all too frequently the case. For this reason, an approximate correspondence that can be easily used in clinical practice between the usual severity of dyspnoea and the stage of severity of obstruction based on pulmonary function tests PFTs) is currently proposed.

Table VI: Classification of the COPD by stages of severity based on PFTs and in clinical equivalence in routine clinical practice

STAGE	CHARACTERISTICS	CLINICAL EQUIVALENCE[1] evaluated in the absence of exacerbation
0: Chronic bronchitis, not yet obstructive, but at high risk of becoming obstructive	• $FEV_1/VC \geq 70\%$	• Inconstant chronic symptoms (cough, sputum) • **No dyspnoea**
I: Mild COPD	• **$FEV_1/VC < 70\%$** • $FEV_1 \geq 80\%$ of predicted value	• Inconstant chronic symptoms (cough, sputum • **No dyspnoea**
II: Moderately severe COPD[2]	• **$FEV_1/VC < 70\%$** • $30\% \leq FEV_1 < 80\%$ of predicted value	• Frequent chronic symptoms (cough, sputum • **Dyspnoea on exertion**
III: Severe COPD	• **$FEV_1/VC < 70\%$** • $FEV_1 < 30\%$ of predicted value.. • or presence of chronic respiratory insufficiency ($PaO_2 < 60$ mmHg or 8 kPa) or clinical signs of right heart failure	• Almost constant chronic symptoms (cough, sputum • **Dyspnoea at the slightest effort or dyspnoea at rest**

[1] This dyspnoea scale is not strictly correlated with the reference classification based on PFTs.

[2] Sub-stages IIA ($50\% \leq FEV_1 < 80\%$) and IIB ($30\% \leq FEV_1 < 50\%$) are not shown in this table because they have no impact on the indication for antibiotic therapy.

WHAT ARE THE CRITERIA OF THE INDICATION FOR ANTIBIOTIC THERAPY?

The indication for antibiotic therapy depends on the stage of severity of COPD, evaluated in the absence of exacerbation, **on a dyspnoea scale (Table VII):**

- **No dyspnoea**: no antibiotic (Grade A recommendation)
- **Dyspnoea on exertion**: antibiotic only if frankly purulent, greenish sputum (Grade C recommendation)
- **Dyspnoea at the slightest effort or dyspnoea at rest**: systematic antibiotic (Grade A recommendation)

WHICH ANTIBIOTIC SHOULD BE PRESCRIBED WHEN ANTIBIOTICS ARE INDICATED?

The choice of antibiotic is based on this same dyspnoea scale, always evaluated in the absence of exacerbation (**Table VII**) (Professional consensus).

Table VII: Indication and choice of antibiotic therapy for the treatment of acute exacerbations of COPD

CLINICAL STAGE OF SEVERITY OF COPD evaluated in the absence of exacerbation	**INDICATION**	**CHOICE**
No dyspnoea	No antibiotics	
Dyspnoea on exertion	Antibiotics only if frankly purulent, greenish sputum	amoxicillin 3 g/day Second generation oral cephalosporin (cefuroxime-axetil) Third generation oral cephalosporin (cefpodoxime-proxetil, cefotiam-hexetil) macrolide pristinamycin telithromycin
Dyspnoea at the slightest effort or dyspnoea at rest	Systematic antibiotics	amoxicillin-clavulanic acid (3 g/day of amoxicillin) Third generation parenteral cephalosporin (cefotaxime I.V. or ceftriaxone I.V/, IM or SC) Antipneumococcal fluoroquinolone (levofloxacin, moxifloxacin)

Antipneumococcal fluoroquinolones must not be prescribed if the patient has received treatment with a fluoroquinolone, regardless of the indication, during the previous 3 months (Grade A recommendation). These fluoroquinolones must also be used cautiously in institutions (risk of transmission of resistant strains) **and in the elderly receiving systemic steroids** (increased risk of tendinitis) **(Grade A recommendation).**

WHAT EPIDEMIOLOGICAL, MICROBIOLOGICAL, PHARMACOLOGICAL (PK-PD) AND CLINICAL CRITERIA CAN BE USED TO OPTIMIZE THE CHOICE, MODALITIES OF ADMINISTRATION, AND DURATION OF TREATMENT?

- Oral cephalosporins, which present an unfavourable relationship between bioavailability and intrinsic antibacterial activity on pneumococcus, especially in the case of decreased susceptibility to penicillin, must no longer be used in severe forms of exacerbation of COPD (Professional consensus).
- PFTs must be systematically performed in the absence of exacerbation to define the prescription criteria for subsequent episodes (**Table VI**). The "dyspnoea on exertion" stage is then replaced by stage II of the current COPD classification. The "dyspnoea at the slightest effort or dyspnoea at rest" stage is then replaced by stage III. This spirometric assessment should allow more accurate detection of COPD with referral to a respiratory physician in order to optimize patient education and prevention.
- Several recent studies demonstrate the efficacy of a 5-day course of antibiotics for various families of antibiotics (ß-lactams, macrolides, ketolide, fluoroquinolones); a 5-day course of antibiotics is recommended in mild forms (stage 2) (Professional consensus). Marketing Authorisations indicate a duration of treatment of 5 days for sustained-release clarithromycin, telithromycin and moxifloxacin and 4 days for pristinamycin (Grade A recommendation). The duration of antibiotic therapy can be prolonged for a maximum of 7 to 10 days in certain severe cases (Grade A recommendation).
- Patients with recent antibiotic therapy or recent hospitalisation are probably at greater risk of presenting resistant bacteria. In the case of failure of first-line therapy, it is recommended to perform sputum culture and chest x-ray. Antibiotic therapy may need to be modified on the basis of the sputum culture in the case of modification of the bacterial flora, especially with the presence of *Pseudomonas*.