Consensus conference

Management of patients with cystic fibrosis

18-19 November 2002

Palais du Luxembourg - Paris

Topic 1: Pulmonary disease and infection
Guidelines (short version)
SPONSOR

Société Française de Pédiatrie

CO-SPONSORS

Association Française de Pédiatrie Ambulatoire
Association Muco-Kiné
Association Pédagogique Nationale pour l’Enseignement de la Thérapeutique
Club Pédiatrique de Pneumologie et Allergologie
Comité de Nutrition de la Société Française de Pédiatrie
Groupe Francophone d’Hépato-Gastro-Entérologie et Nutrition Pédiatriques
Société de Kinésithérapie de Réanimation
Société de Pneumologie de Langue Française
Société Française de Microbiologie
Société Nationale Française de Gastro-Entérologie
Société Nationale Française de Médecine Interne

WITH THE SUPPORT OF

Vaincre la Mucoviscidose
SOS Mucoviscidose

THE CONFERENCE WAS MADE POSSIBLE BY THE SUPPORT OF

Chiron, GSK, Roche, Solvay Pharma, AstraZeneca, Wyeth-Lederle, Braun Medical Division OPM, MSD Chibret
Schering Plough, Aventis Pharma, Orphan, Nestlé, Vitalaire, Abbott, Baxter, Pari, Bastide Médical
and of two associations of patients and families
Vaincre la Mucoviscidose, SOS Mucoviscidose
STEERING COMMITTEE

C. Marguet, chairman, paediatrician, Rouen

G. Bellon, paediatrician, Lyon
J. de Blic, paediatrician, Paris
E. Bingen, microbiologist, Paris
L. David, paediatrician, Lyon
P. Dosquet, ANAES methodologist, Paris
I. Durieu, specialist in internal medicine, Lyon
B. Housset, chest physician, Créteil
R. Klink, paediatrician, Laon
A. Munck, paediatrician, Paris
C. Paindavoine, ANAES methodologist, Paris
C. Perrot-Minnot, physiotherapist, Reims
G. Reychler, physiotherapist, Woluwe
MD. Touzé, ANAES methodologist, Paris
D. Turck, paediatrician, Lille
D. Vital-Durand, specialist in internal medicine, Lyon
B. Wallaert, chest physician, Lille
TOPIC 1: PULMONARY DISEASE AND INFECTION
(18 NOVEMBER 2002)

JURY 1

B. Housset, chairman, chest physician, Créteil

F. Cambier, paediatrician, Amiens
P. Fainsilber, general practitioner, Gaillon
C. Karila, paediatrician, Massy
M. Joras, journalist, Paris
JF. Lemeland, microbiologist, Rouen
H. Lanier, Vaincre la Mucoviscidose, Paris
B. Quinet, paediatrician, Paris
I. Tillie-Leblond, chest physician, Lille
V. Touzot-Dubrulle, physiotherapist, Lille

EXPERTS 1

P. Althaus, physiotherapist, Bottens
G. Bellon, paediatrician, Lyon
F. Bremont, paediatrician, Toulouse
G. Chabanon, microbiologist, Toulouse
A. Clément, paediatrician, Paris
V. David, paediatrician, Nantes
P. Diot, chest physician, Tours
S. Dominique, chest physician, Rouen
D. Hubert, chest physician, Paris
T. Moreau, statistician, Villejuif
I. Pin, paediatrician, Grenoble
P. Plesiat, microbiologist, Besançon
A. Sardet, paediatrician, Lens
V. Storni, paediatrician, Roscoff

LITERATURE GROUP 1

L. Bassinet, chest physician, Créteil
P. Chatain-Desmarquets, paediatrician, Lyon
M. Le Bourgeois, paediatrician, Paris
L. Lemé, bacteriologist, Rouen
C. Opdekamp, physiotherapist, Brussels
I. Sermet-Gaudelus, paediatrician, Paris
C. Thumerelle, paediatrician, Lille

The organisation and running of the conference complied with the formal method recommended by the French National Health Accreditation and Evaluation Agency (ANAES). The conclusions and guidelines presented in this document were drawn up by the conference jury, who were acting in complete independence. ANAES is not liable in any way for their content.
INTRODUCTION

In cystic fibrosis, mutations of the CFTR protein induce an increase in mucus viscosity, which encourages bacterial growth and attachment to mucins. Inflammation and infection create a vicious circle, leading to lung damage.

Bacterial colonisation occurs very early in the natural history of the disease. The first organisms involved are *Haemophilus influenzae* (HI) and *Staphylococcus aureus* (SA). Colonisation by *Pseudomonas aeruginosa* (PA) takes place a few months to a few years later.

There is thus a need to include guidelines on treatment strategies for respiratory problems within overall disease management.

DEFINITIONS

- **PA treatment.** The jury adopted some of the definitions of the European consensus[^1] (see Box).

  European consensus definitions concerning treatment of *P. aeruginosa* (PA)

  **Early colonisation:** Presence of *PA* in the bronchial tree without direct (inflammation, fever, etc.) or indirect (specific antibody response) signs of infection and tissue damage.

  **Chronic lung colonisation:** Presence of *PA* in the bronchial tree for at least 6 months, based on at least three positive cultures with at least one month between them without direct (inflammation, fever etc.) or indirect (specific antibody response) signs of infection and tissue damage.

  **Bronchopulmonary infection:** Early colonisation combined with direct or indirect signs of infection. For *PA*, infection in non-expectorating patients with negative bacterial cultures can also be diagnosed on the basis of antibody detection in two successive tests.

  **Chronic bronchopulmonary infection:** Chronic colonisation combined with direct or indirect signs of infection. For *PA*, chronic infection in non-expectorating patients with negative bacterial cultures can also be diagnosed on the basis of antibody detection in two successive tests.

- **Exacerbation.** The definition adopted by the jury was onset of an **acute episode** of clinical deterioration when the patient is in a stable state:
  - increased cough;
  - increased expectoration (volume and purulence);
  - decreased tolerance to effort or physical activity;
  - loss of weight or loss of appetite;
  - deterioration of respiratory function (forced expired volume in 1 sec (FEV₁), forced vital capacity (FVC));
  - marked increase in airway bacterial load (in CFU/ml) during routine monitoring.

- **Eradication** of an organism is the disappearance, after treatment, of an organism previously detected in a high-quality airway secretion sample.

SAMPLE-TAKING PROCEDURES

The jury recommended routine bacteriological monitoring at each visit (1-3 months) as soon as cystic fibrosis is diagnosed. Monitoring should be adapted to the patient's age and the severity of the respiratory disorder.

There are several ways of collecting airway secretions:

- **Bronchoalveolar lavage (BAL)** is the gold standard bacterial sample, but it is invasive.  
- **In patients with spontaneous expectoration:**  
  - *Sputum induction and culture* was recommended. The sample may be optimised by chest physiotherapy or by using bronchodilators and/or an rhDNAse aerosol (grade \( B \)).
  
- **In the absence of spontaneous expectoration:**  
  - A *throat swab*, which may be taken after coughing, is the only test that has been validated in comparison with BAL (grade B).
  - *Nasopharyngeal aspiration* is frequently used and well tolerated in infants. However, it has not been evaluated.
  - *Nebulisation of hypertonic saline*. Expectoration induced by hypertonic saline is performed after inhalation of beta-2-mimetics and requires monitoring of lung function. Its role has not yet been determined.

Irrespective of the collection method, the jury would like isolation and enrichment methods, and in particular the identification of small-colony variants of SA and mucoid PA, to be standardised as far as possible between laboratories. They could be the subject of written procedures to be distributed to all bacteriology laboratories linked to French Cystic Fibrosis Skills and Resources Centres (CRCM).

GENERAL PRINCIPLES OF ANTIBIOTIC THERAPY

The dose and duration of antibiotic treatment should be adjusted according to bacterial sensitivity to antibiotics and to pharmacokinetic characteristics in individuals with cystic fibrosis. In cystic fibrosis, the volume of distribution per kg of bodyweight is increased and elimination half-life is decreased. Increased renal and non-renal clearance means that high doses of antibiotics are needed (grade A). Pharmacokinetic characteristics are further modified by the patient's nutritional status and disease severity.

The doses recommended by most specialist teams have still not been clearly defined, and rarely correspond to a product’s marketing authorisation (AMM) in France. During the conference, the jury produced a summary of treatment practices which have been published or discussed, mentioning wherever possible whether they comply with the marketing authorisation. Full responsibility for their prescription therefore lies with the practitioner. The doses and treatment period proposed are for subjects - adults and children - with normal renal and hepatic function; they are not for pregnant women, newborns or infants.

---

3 A grade A guideline is based on scientific evidence established by a high level of evidence. A grade B guideline is based on presumption of a scientific foundation derived from studies of an intermediate level of evidence. A grade C guideline is based on studies of a low level of evidence. In the absence of specific scientific evidence, guidelines are based on agreement among professionals expressed by the jury. See: ANAES, *Guide d'analyse de la littérature et gradation des recommandations*. Janvier 2000. (Guide to literature analysis and grading of guidelines, January 2000).
Adjustment of the dose and methods for monitoring possible treatment-related toxicity are not discussed in this document, but the prescriber must be familiar with them. In cystic fibrosis, repeated courses of antibiotics over many years mean that hepatic and renal toxicity and ototoxicity should be monitored. Regular assessment of good aerosol technique is needed.

For further information on antibiotic therapy in patients with cystic fibrosis, the reader should consult specialist works and textbooks.

QUESTION 1
What are the diagnostic criteria for bronchopulmonary infection with *Staphylococcus aureus (SA)*?

*SA* is a commensal bacterium of the nasopharynx. It is found in 66% of patients with cystic fibrosis. There are different types:
- methicillin-sensitive *SA (MSSA)* and methicillin-resistant *SA (MRSA)*. In France, 9.2% of patients with cystic fibrosis are *MRSA* carriers;
- small-colony variant *SA* are intracellular microbial agents and are partly responsible for chronic colonisation of the bronchial airways by *SA*.

**Exacerbation, together with *SA* detection in an airway secretion sample, indicates *SA* infection.**

I. Clinical criteria

The clinical criteria are those given above for exacerbation. They are essential to a diagnosis of *SA* infection and the treatment decision.

II. Microbiological criteria

Bacteriological testing is performed on bronchial secretions collected by a non-invasive method.

- **Early colonisation with *SA*** is difficult to diagnose because of the commensal nature of the bacterium. The jury recommended using a *SA* detection threshold of $10^2$ CFU/ml in cultures and routine use of culture media selective for *SA* and small-colony variants.
- **SA infection** is defined by clinical criteria and *SA* detection in successive samples. No threshold could be recommended, but a level $>10^5$ CFU/ml should trigger investigation of signs of exacerbation.

PCR and serum anti-*SA* antibody determination were not recommended.

QUESTION 2
What strategy should be adopted for antibiotic therapy for *Staphylococcus aureus*, irrespective of the route of administration?

Implementation of strict hygiene measures is crucial because of the increasing prevalence of *MRSA*.

Published data on treatment for exacerbations and secondary prophylaxis is too scant to be able to recommend specific protocols.

The main antistaphylococcal antibiotics used in cystic fibrosis are shown in Tables 1 and 2.
### Table 1. Main antistaphylococcal antibiotics used orally in cystic fibrosis

<table>
<thead>
<tr>
<th></th>
<th>Proposed dose mg/kg/day</th>
<th>Times taken/day</th>
<th>Maximum dose mg/day</th>
<th>Compliance with AMM*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxycillin + clavulanic acid</td>
<td>80 (C)**</td>
<td>2-3</td>
<td>3000 (C) (A)</td>
<td>=</td>
</tr>
<tr>
<td>Cephalexin</td>
<td>50 (C) 100 (A)</td>
<td>3</td>
<td>&gt;</td>
<td></td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>30 (C)</td>
<td>2-3</td>
<td>1500 (C) (A)</td>
<td>=</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>50 (C)</td>
<td>2</td>
<td>3000 (C) (A)</td>
<td>=</td>
</tr>
<tr>
<td>Fusidic acid in a combination (see text)</td>
<td>30 - 60 (C)</td>
<td>2-3</td>
<td>1500 (C) 1000-1500 (A)</td>
<td>=</td>
</tr>
<tr>
<td>Linezolid (AMM* if age &gt; 18 yrs)</td>
<td>1 200 mg/day</td>
<td>2</td>
<td>=</td>
<td></td>
</tr>
<tr>
<td>Minocycline</td>
<td>4 (if age &gt; 8 yrs) 100-200 mg/day (A)</td>
<td>2</td>
<td>=</td>
<td></td>
</tr>
<tr>
<td>Oxacillin, cloxacillin</td>
<td>100 - 150</td>
<td>3-4</td>
<td>&gt;</td>
<td></td>
</tr>
<tr>
<td>Pristinamycin</td>
<td>50 (C) (A)</td>
<td>2</td>
<td>4000</td>
<td>=</td>
</tr>
<tr>
<td>Rifampicin in a combination (see text)</td>
<td>20 - 30</td>
<td>2</td>
<td>20/kg (A)</td>
<td>=</td>
</tr>
</tbody>
</table>

* AMM, marketing authorisation, = dose complies with dose given in AMM; > dose higher than that given in AMM.
** (A): adults; (C): children.

### Table 2. Main antistaphylococcal antibiotics used intravenously in cystic fibrosis

<table>
<thead>
<tr>
<th></th>
<th>Proposed dose (mg/kg/day)</th>
<th>Injections/day (N)</th>
<th>Maximum dose (mg/day)</th>
<th>Compliance with AMM*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin</td>
<td>20-30</td>
<td>1-3</td>
<td>20 /kg (A) Total cumulative dose &lt; 15g</td>
<td>&gt;</td>
</tr>
<tr>
<td>Amoxycillin + clavulanic acid</td>
<td>200 (C) 2-12 g/day (A)</td>
<td>3-4</td>
<td>1200 mg clav. acid /day and 200 mg/injection (A)</td>
<td>=</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>30 (C) 400-1200 mg/day (A)</td>
<td>2-3</td>
<td>1200 (C) (A)</td>
<td>=</td>
</tr>
<tr>
<td>Linezolid (AMM* if age &gt;18 yrs)</td>
<td>1200 mg/day (&gt;18 yrs)</td>
<td>2</td>
<td>=</td>
<td></td>
</tr>
<tr>
<td>Oxacillin</td>
<td>300</td>
<td>3-4</td>
<td>&gt;</td>
<td></td>
</tr>
<tr>
<td>Rifampicin</td>
<td>20-30</td>
<td>2</td>
<td>Max 20/kg (A)</td>
<td>=</td>
</tr>
<tr>
<td>Teicoplanin</td>
<td>20</td>
<td>1-2</td>
<td>&gt;</td>
<td></td>
</tr>
<tr>
<td>Tobramycin</td>
<td>8-10</td>
<td>1-3</td>
<td>&gt;</td>
<td></td>
</tr>
<tr>
<td>Vancomycin</td>
<td>40 (C) 2 000 mg/day (A)</td>
<td>4</td>
<td>=</td>
<td></td>
</tr>
</tbody>
</table>

* AMM, marketing authorisation, = dose complies with dose given in AMM; > dose higher than that given in AMM.
** (A): adults; (C): children.

### STRATEGIES FOR ANTISTAPHYLOCOCCAL ANTIBIOTIC THERAPY IN CYSTIC FIBROSIS

#### I. Primary antibiotic prophylaxis

The issue of primary prophylaxis is becoming particularly acute in regard to the French neonatal screening programme. **Primary prophylaxis is not recommended (grade A) in infants and children with cystic fibrosis as it exposes the patient to earlier and more frequent colonisation by PA.**
II. Treatment of exacerbations

Antibiotic administration was recommended to treat exacerbations (grade A), but no specific treatment protocol could be recommended on the basis of available trial results.

- **MSSA infection.** MSSA is sensitive to most antibiotics (see Table 1).
  - **The first step in treatment is an oral beta-lactam** for at least 14 days. **This may be combined with fusidic acid.**
  - Patients allergic to penicillin may receive fusidic acid and rifampicin as an alternative. Neither of these antibiotics should be given as monotherapy (grade A).
  - In cases of infection with both *SA* and *HI*, the combination of amoxycillin and clavulanic acid was proposed.
  - If MSSA colonisation persists beyond 14 days, treatment with a beta-lactam may be considered (see Table 1) - account being taken of the patient's clinical status - and extended for 1-3 months. However, no specific rule could be established.

- **MRSA.** The most efficient antibiotics are pristinamycin and rifampicin. Their combination was recommended as first choice treatment. The alternatives include glycopeptides (vancomycin and teicoplanin) and, more recently, linezolid (marketing authorisation if age > 18 years). For severe disease, two-drug intravenous (IV) therapy may be preferred.

- **Infection with small-colony variants.** Treatment of small-colony variants is indicated if there are clinical signs. In the absence of validated data, the jury proposed administration of rifampicin, which has better cell penetration, in combination with fusidic acid.

- **Mixed infection with SA + PA.** Antibiotic therapy should be directed against both organisms.

III. Secondary antibiotic prophylaxis

Maintenance treatment or secondary prophylaxis should be considered to avoid early recurrence of respiratory symptoms. There is insufficient information in the literature to determine the best prophylactic treatment.

- **MSSA infection.** Monotherapy for 1-3 months (oxacillin, cloxacillin or minocycline in adults and children aged over 8 years) was recommended. Linezolid may also be indicated (marketing authorisation if age > 18 years).

- **MRSA infection**
  - Nebulised vancomycin (outside marketing authorisation) was not recommended.
  - Sequential alternating antibiotic therapy has not been validated.
  - Combination of rifampicin and fusidic acid for 6 months seems to be useful, but confirmation is needed.
  - Linezolid trials are ongoing in this indication.

**QUESTION 3**
What are the diagnostic criteria for bronchopulmonary infection with *Pseudomonas aeruginosa*?
Repeated and severe *PA* infection is characteristic of cystic fibrosis.

### I. Clinical criteria

Clinical exacerbation, although not a specific criterion, is an essential element in the diagnosis of *PA* infection. Even mild clinical signs raise the question of exacerbation.

### II. Bacteriological criteria

- **Early colonisation.** *PA* colonisation may start very early in childhood. The first identification of *PA* in airway secretions defines early colonisation. This was the basis for recommending routine bacterial culture of specimens every 1-3 months.

- **Chronic colonisation** with a nonmucoid strain is to be expected after a period of transient colonisation with various strains. However, once a mucoid phenotype has been isolated, currently available antibiotics will fail to eradicate the bacteria. Colonisation with a mucoid strain is commonly associated with more rapid deterioration of lung function.

- **Infection.** The $10^5$ CFU/ml threshold for BAL cultures may differentiate between chronic colonisation and infection. The invasive nature of BAL collection means that it cannot be recommended as a routine test. It should be reserved mainly for two situations – when there is a discrepancy between clinical signs and bacteriological results, or when there is no clinical improvement under treatment.

### III. Detection of specific antibodies

Chronic colonisation and chronic infection may be distinguished by the presence of more than 2 lines of precipitation in immuno-electrophoresis. This prompted the recommendation of serological monitoring every 3-4 months. The jury recommended that this type of test should be coordinated on a national basis, with the setting up of reference centres, if possible, to ensure standardisation and quality control.

**QUESTION 4**

What strategy should be adopted for antibiotic therapy for *Pseudomonas aeruginosa*, irrespective of the route of administration?

To delay early colonisation as much as possible, primary prophylaxis should focus on hygiene measures.

### I. Antibiotics used

Available antibiotics are used either alone or in combination, orally (Table 3), IV (Table 4) or by inhalation (Table 5), depending on the stage and severity of *PA* infection, and may be administered at higher doses than those recommended in the marketing authorisation.

### II. Antibiotic treatment strategy

1. **Early colonisation**

There is no question that treatment is required, but there is no best protocol which has been validated by international consensus.
### Table 3. Main antibiotics used orally in PA infection

<table>
<thead>
<tr>
<th>Proposed dose</th>
<th>Times taken/day</th>
<th>Compliance with AMM*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azithromycin (outside AMM in children) 250-500 mg/day</td>
<td>1</td>
<td>&gt;</td>
</tr>
<tr>
<td>Ciprofloxacin (AMM if age &gt;5 yrs) 40 mg/kg/day (C) 1-1.5 g/day (A) Max 1500 mg/day (C) (A)</td>
<td>2</td>
<td>=</td>
</tr>
</tbody>
</table>

* AMM, marketing authorisation, = dose complies with dose given in AMM; > dose higher than that given in AMM. ** (A): adults; (C): children.

### Table 4. Main antibiotics used intravenously in PA infection

<table>
<thead>
<tr>
<th>Proposed dose (mg/kg/day)</th>
<th>Injections/day (N)</th>
<th>Compliance with AMM*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin 20-30</td>
<td>1-3</td>
<td>&gt;</td>
</tr>
<tr>
<td>Max 20 mg/kg/day (A) Total dose &lt; 1.5g</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aztreonam (marketing authorisation in adults) 150-200 Max 12 g/day</td>
<td>3</td>
<td>&gt;</td>
</tr>
<tr>
<td>Ceftazidime 200-250 Max 12 g/day</td>
<td>3 or continuous infusion (loading dose)</td>
<td>&gt;</td>
</tr>
<tr>
<td>Ciprofloxacin (marketing authorisation if age &gt; 5 yrs) 30 (C) 400-1 200 mg/day (A) Max 1 200 mg/day (C) (A)</td>
<td>2-3</td>
<td>=</td>
</tr>
<tr>
<td>Colistin 0.1-0.15 million units/kg/ day</td>
<td>2-3</td>
<td>&gt;</td>
</tr>
<tr>
<td>Imipenem 75-100</td>
<td>3</td>
<td>&gt;</td>
</tr>
<tr>
<td>Max 4 g/day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meropenem (indication outside marketing authorisation in children) 120-160 Max 6 g/day</td>
<td>3-4</td>
<td>&gt;</td>
</tr>
<tr>
<td>Piperacillin (± tazobactam; marketing authorisation if age &gt;12 yrs) 300 (C) 200 (A) Max 12 g/day (A)</td>
<td>3-4</td>
<td>=</td>
</tr>
<tr>
<td>Ticarcillin (± clavulanic acid) 250 (C) 400 (A) Max 15 g/day (A) (Max 20/kg/day clav acid (C) Max 1 200 mg/day clav acid (A))</td>
<td>3-4</td>
<td>= (A) &gt; (C)</td>
</tr>
<tr>
<td>Tobramycin 8-10</td>
<td>1-3</td>
<td>&gt;</td>
</tr>
</tbody>
</table>

* AMM, marketing authorisation, = dose complies with dose given in AMM; > dose higher than that given in AMM. ** (A): adults; (C): children.

### Table 5. Main antibiotics used by inhalation in PA infection

<table>
<thead>
<tr>
<th>Dose/day</th>
<th>Times taken/day</th>
<th>Compliance with AMM*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colistin 1-6 million units</td>
<td>1-3</td>
<td>Outside AMM</td>
</tr>
<tr>
<td>Tobramycin (if age &gt; 6 years) 600 mg</td>
<td>2</td>
<td>=</td>
</tr>
</tbody>
</table>

* AMM, marketing authorisation, = dose complies with dose given in AMM.
• **Protocol used by most French teams.** The jury recommended this protocol which combines 2 bactericidal antibiotics (beta-lactam + aminoglycoside) given IV for 14-21 days. This treatment may be prolonged by nebulisation using colistin aerosols for 3-6 months. Use of the beta-lactam ceftazidime administered as a continuous infusion is based on satisfactory clinical efficacy and safety results (especially with regard to vein status). The most widely used aminoglycoside is tobramycin given as a single daily dose (grade B). In children aged under 5-6 years, the first course of IV treatment is commonly given during a hospital stay. Treatment efficiency should be monitored closely, monthly if possible, by sputum culture. A further course of IV antibiotic therapy is indicated in the event of a positive culture.

- **Danish 3-stage protocol.** This protocol has not been validated but published results, despite their methodological bias, suggest that it may be an alternative:
  - **step 1:** oral ciprofloxacin (30 mg/kg a day b.i.d) and nebulised colistin (1 million units b.i.d) for 21 days;
  - **step 2:** if PA is isolated more than once within 6 months, oral ciprofloxacin at the same dose and nebulised colistin (2 million units 3 times a day) for 21 days;
  - **step 3:** if PA is isolated for a 3rd time within 6 months, oral ciprofloxacin at the same dose and nebulised colistin (2 million units 3 times a day) for 3 months.

2. Chronic infection

Treatment aims to reduce the bacterial inoculum, delay exacerbations and slow down deterioration in lung function.

- **Treatment of exacerbations.** Exacerbations should be treated (grade A), preferably by IV antibiotics. The choice of antibiotics is based on the last set of microbiological sensitivity tests and on previous response to treatment.
  - Using beta-lactams in order of increasing *in vitro* bactericidal activity is logical but has not been validated.
  - Alternating antibiotics has not been validated.
  - Combining a beta-lactam and tobramycin for at least 14 days (duration not validated) was recommended.
  - Oral ciprofloxacin was not recommended because of its lower bacteriological efficacy (grade B).
  - In the case of multiresistant strains, it was proposed that oral ciprofloxacin be added to the beta-lactam and tobramycin combination (not validated). IV colistin is an option.
  - Inhaled colistin during IV antibiotic therapy is not justified.

- **Scheduled routine treatment for chronic infection.** Maintenance therapy with inhaled antibiotics is an alternative to routine 3-monthly courses of IV antibiotics. Maintenance therapy with tobramycin, inhaled every other month using a suitable nebuliser, has been validated (evidence level 1 trial). It can be used from the age of 6 years; the dose is 300 mg twice a day; the treatment validated by the marketing authorisation is 96 weeks. A course of IV antibiotics should be given at the slightest sign of clinical aggravation or deterioration in lung function.
  - Courses of IV therapy every 3 months were nevertheless recommended in the event of problems of compliance with inhaled treatment, or in patients responding better to repeated courses of IV therapy. No rules have been established.
  - Oral ciprofloxacin may be given between courses when intervals between courses of IV therapy are shorter. There was no evidence to support the combination of co-trimoxazole and ciprofloxacin.
- Macrolides, including azithromycin, seem to have a place in the treatment of chronic infection (indication outside marketing authorisation – evidence level 1 trial). Continuation of treatment should be reassessed at 3 months.
- Treatment at home should be encouraged as often as possible. The availability of auto-diffusers and ready-to-use infusion sets makes outpatient treatment easier.

**QUESTION 5**

**What is the place of other respiratory therapies in the treatment of cystic fibrosis?**

**ORAL CORTICOSTEROIDS**

Two indications were recognised for oral corticosteroids:
(i) allergic bronchopulmonary aspergillosis;
(ii) lack of clinical and/or functional improvement of an exacerbation after a 14-day course of antibiotics (experts’ opinion). It is useful to monitor postprandial blood glucose throughout treatment.

There are no indications for long-term oral corticosteroid therapy in cystic fibrosis patients.

**INHALED CORTICOTHERAPY**

Current results do not support recommending routine prescription of inhaled corticosteroids. Concomitant asthma is an indication for using inhaled corticosteroids.

**BRONCHODILATORS**

There was little scientific evidence that bronchodilators are useful in cystic fibrosis. Their routine use was therefore not recommended. Anticholinergics were not recommended (grade B).

There was evidence to support the use of beta-2-mimetics in three situations:
(i) for exacerbations;
(ii) during the stable state of the disease. The indication is clinical. Short- and/or long-acting beta-2-mimetics may be prescribed (grade C);
(iii) before the start of physiotherapy sessions.

**rhDNase**

rhDNase reduces mucus viscosity and facilitates clearance by coughing. There are no factors which can predict response to treatment. Long-term efficacy is assessed mainly on the basis of improvement in FEV1 at 3 months.

rhDNase (1-2 daily nebulisations) was recommended in patients aged over 5 with FVC of ≥40%. There are no significant differences between the various compatible nebulisers (marketing authorisation).

It was recommended that the rhDNase aerosol should be preceded by proximal bronchial drainage. Nebulised rhDNase should be followed by a session of chest physiotherapy 30 minutes later.
PHYSIOTHERAPY IN INFANTS DIAGNOSED DURING SCREENING

The aim of chest physiotherapy is to mobilise bronchial secretions and facilitate their clearance. The recent techniques based on control of expiratory flow, provoked cough and mechanical methods should be distinguished from conventional chest physiotherapy methods.

In asymptomatic infants diagnosed with cystic fibrosis during screening, monthly physiotherapy optimises collection of airway secretions and helps early education of families. So far, no trials have shown that chest physiotherapy is an effective preventive measure in these infants. The jury recommended that daily chest physiotherapy be started as soon as respiratory symptoms appeared.

In symptomatic infants, a daily session was recommended during stable periods, with two daily sessions during exacerbations. The jury emphasised the importance of complying with hygiene procedures.

MECHANICAL METHODS IN THE TREATMENT OF CYSTIC FIBROSIS

The use of mechanical methods is justified when they improve compliance or facilitate clearance of excessive airway secretions. The jury drew on guidelines of the international symposium of mechanical respiratory physiotherapy.

The methods used are:
- drug aerosol therapy and isotonic serum humidification;
- incentive spirometry, which has been validated for bronchial drainage (grade B);
- nasal suction;
- positive expiratory pressure systems;
- external mechanical vibration which increases the volume of expectoration.

Overall, mechanical means can improve the mechanics of respiration, optimise distal airway ventilation and facilitate expectoration. They should be individualised for each patient, and should be simple to use while restricting the patient as little as possible. Finally, they have yet to be validated by multicentre clinical trials which would provide clearer definitions of the indications for each method.

The full French text of these guidelines is available on written request to:
Agence Nationale d’Accréditation et d’Évaluation en Santé
Service communication
2 avenue du Stade de France – 93218 Saint-Denis La Plaine Cedex
or it is available on the ANAES website: www.anaes.fr under “Publications”

1 http://membres.lycos.fr/jikri/