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Special Article

Spanish Consensus on the Prevention and Treatment of *Pseudomonas aeruginosa* Bronchial Infections in Cystic Fibrosis Patients☆

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ABSTRACT

Pseudomonas aeruginosa is the main pathogen in bronchopulmonary infections in cystic fibrosis (CF) patients. It can only be eradicated at early infection stages while reduction of its bacterial load is the therapeutic goal during chronic infection or exacerbations. Neonatal screening and pharmacokinetic/pharmacodynamic knowledge have modified the management of CF-patient. A culture based microbiological follow-up should be performed in patients with no infection with *P. aeruginosa*. At initial infection, inhaled colistin (0.5–2 MU/tid), tobramycin (300 mg/bid) or aztreonam (75 mg/tid) with or without oral ciprofloxacin (15–20 mg/kg/bid, 2–3 weeks) are recommended. In chronic infections, treatment is based on continuous administration of colistin or with a 28-day on–off regimen with tobramycin or aztreonam. During mild-moderate exacerbations oral ciprofloxacin (2–3 weeks) can be administered while serious exacerbations must be treated with intravenous combination therapy (beta-lactam with an aminoglycoside or a fluoroquinolone). Future studies will support rotation and/or new combination therapies. Epidemiological measures are also recommended to avoid new *P. aeruginosa* infections and cross transmission of this pathogen.

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Consenso español para la prevención y el tratamiento de la infección bronquial por *Pseudomonas aeruginosa* en el paciente con fibrosis quística

Palabras clave:
Fibrosis quística
Pseudomonas aeruginosa
Infección bronquial
Tratamiento antibiótico

RESUMEN: Pseudomonas aeruginosa es el patógeno más importante en la infección broncopulmonar en fibrosis quística (FQ). Solo se erradica en la infección inicial, mientras que la reducción de su carga bacteriana es el objetivo terapéutico en la infección crónica y exacerbaciones. El cribado neonatal y la farmacocinética/farmacodinámica han cambiado el manejo del paciente con FQ. Se debe realizar un seguimiento microbiológico en los pacientes sin infección por *P. aeruginosa*. En la infección inicial se recomienda tratamiento inhalado (28 días) con colistina (0,5-2 MU/8 h), tobramicina (300 mg/12 h) o aztreonam (75 mg/8 h) con o sin ciprofloxacino oral (15-20 mg/kg/12 h, 2-3 semanas). En la infección crónica se recomienda solo vía inhalada en tratamiento continuo con colistina, o en ciclos *on-off* de 28 días con tobramicina o aztreonam. Durante las exacerbaciones leves-moderadas se recomienda tratamiento oral (ciprofloxacino, 2-3 semanas) y en las graves tratamiento intravenoso (β-lactámico asociado a un aminoglicósido o una fluoroquinolona). Estudios futuros sustentarán la rotación y nuevas combinaciones de antimicrobianos. Se deben establecer también medidas epidemiológicas que eviten nuevas infecciones y la transmisión cruzada de *P. aeruginosa*.

Introduction

The management and evolution of cystic fibrosis (CF) patients are directed by the presence of *Pseudomonas aeruginosa* (PA) bronchial colonization. In 2005, the Spanish Consensus Group for Antimicrobial Therapy in the CF Patient published a consensus document on the use of antibiotics to treat *P. aeruginosa* colonization in CF.[1] It was the first report to consider the pharmacokinetics (PK) and pharmacodynamics (PD) of treatment strategies and the dynamics of bacterial infection in CF. The publication of additional recommendations,[2–6] neonatal screening programs,[7] the authorization of new antibiotics for CF[8,9] and new scientific developments[10–19] have prompted us to update our earlier report. Recommendations have been graded according to their level of evidence[20] based on studies published in PubMed and weighted according to clinical experience (Table 1).

Clinical Evaluation

PA can be detected early by frequent bacterial culture of respiratory secretions.[21–24] This is particularly useful in children screening positive for CF, as these patients are usually asymptomatic (III-A). Other useful strategies include monitoring patients for PA antibodies (III-B),[25,26] polymerase chain reaction (III-B),[27] and study of sputum for volatile organic compounds (III-C).[28]

The prevalence of PA colonization increases with age, and can be as high as 80% in patients aged >18 years.[29–36] Persistently high bacterial load and the change from a non-fucoid to a mucoid morphotype correlate with more exacerbations, pulmonary decline and mortality.[29,32,36] Exacerbations (Table 2) are characterized by changes in existing symptoms and the appearance of new symptoms.[35,37,38]

Lung function can be normal in patients with primary PA infection. Initially, changes are observed in hyperinflation markers, such as residual volume (RV), RV/total lung capacity, and mesoexpiratory flows. Lung clearance index, a measure of inert gas washout using multiple-breath tests, detects minimal abnormalities, and is higher in patients with PA infection. Test results within normal limits have an excellent negative predictive value (93%) for ruling out PA infection (III-B).[33,39–41]

Reduced forced expiratory volume in 1 s (FEV1) shows progression of the infection and is a good measure of the severity of exacerbations (III-A).[42] Chest computed tomography (HRCT) provides early detection of airway decline and is useful in estimating severity (III-A).[43–46] Lung infection is associated with increased air trapping and greater structural damage, including bronchiectasis.[47] HRTC scores are worse in PA colonization[29,48,49] and during exacerbations.[50]

Patterns of Infection and Microbiological Evaluation

Pulmonary infection in CF can be classified into 3 phases[1]:

- *Initial colonization (primary colonization)*. Detection of the first positive PA culture in which non-mucoid, antibiotic-sensitive strains are usually isolated. A negative culture after the first positive culture can indicate an aborted initial colonization, cryptic colonization, or eradication of PA following antibiotic therapy. PA is considered eradicated when negative results are obtained from at least 2 cultures: 1 taken 1–2 weeks following completion of treatment and another 2–4 weeks later.[51]
- *Intermittent colonization*. This is indicated by intermittent positive and negative results from consecutive cultures after an initial infection. It can indicate permanent low-grade colonization, sample heterogeneity (different origins), or apparently transient eradication with colonization persisting in the sinuses, causing intermittent reinfection.[3,52] Different strains are isolated, including mucoid morphotypes.
- *Chronic infection*. Common in CR patients with advanced disease. Mucoid colonies with a variety of other morphotypes are found as a result of specialization and adaptation of PA to the endobronchial environment. The causes of exacerbations are still unclear, but they usually coincide with increases in bacterial load or the emergence of antigenic variants.

Table 3 shows the patterns of infection defined in 2005[1] and updated according to the Leeds criteria and correlated with clinical parameters (II-A).[53,54]

Basic Antimicrobial Treatment Strategies

Treatment of PA infection is essential for controlling progression of respiratory disease. PA is rarely eradicated once chronic infection has set in, so the best treatment strategy is early prevention (I-A). Inhaled antibiotics are the treatment of choice in PA colonization in view of the particular niche in which it thrives, its tendency to form biofilms, and the inability of some oral or intravenous antibiotics to reach effective concentrations in the respiratory mucosa.[9,18,55–58] This strategy can also help prevent the development of drug resistance, although it is important to