

which should be confirmed by CT scans with contrast medium or magnetic resonance imaging.

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### Pleural Effusion After Intravesical Administration of Bacillus Calmette-Guérin\*



#### *Derrame pleural tras tratamiento intravesical con bacilo de Calmette-Guérin*

To the Editor,

Intravesical instillation of bacillus Calmette-Guérin (BCG), a live attenuated strain of *Mycobacterium bovis*, has been shown in numerous studies to be an effective treatment for superficial *in situ* bladder cancer. However, this procedure is not free of complications.<sup>1–3</sup>

We report the case of a patient diagnosed with pleural effusion due to *M. bovis* after treatment with intravesical BCG instillation.

This was an 85-year-old man, former smoker, with mild chronic obstructive pulmonary disease, atrial fibrillation, and pacemaker implantation due to sick sinus syndrome, diagnosed with multifocal transitional cell carcinoma of the bladder treated by transurethral resection and 6 BCG instillations. One year later, he presented in the emergency department with pleuritic chest pain and increased dyspnea. Chest radiograph (Fig. 1) revealed right pleural effusion. Empirical antibiotic therapy began with amoxicillin/clavulanic acid and the patient was admitted to the respiratory medicine department for further examination with chest computed tomography (CT) and diagnostic thoracentesis. The CT revealed extensive right pleural effusion with passive atelectasis of the ipsilateral lower lobe, subpleural calcified granuloma in the left lower lobe, and prevascular and hilar lymphadenopathies, suggestive of a previous granulomatous process. Thoracentesis was performed, yielding cloudy pleural exudate with elevated adenosine deaminase (ADA) (63.9 U/l), and a predominance of mononuclear cells (85%). We did not perform a pleural biopsy due to the high probability that this was a *Mycobacterium* infection, given the characteristics of the pleural fluid. Culture of the fluid was positive for *M. bovis*, leading to a diagnosis of pleural effusion due to *M. bovis* caused by intravesical instillation of BCG. The patient was treated for 6 months with isoniazid, rifampicin, and ethambutol with good clinical response and resolution of the pleural effusion, with no adverse drug effects.

Although intravesical instillation of BCG is usually well tolerated, local (1%) and systemic (4.8%) complications have been described. Among the systemic events, pulmonary complications

account for 1%–3% and 5 forms of presentation have been described: interstitial pneumonitis, empyema, diffuse alveolar damage, pneumonia with or without cavitation, and miliary tuberculosis (TB). The latter is the most common form of infection due to BCG in the literature and accounts for one third of cases.<sup>1,2</sup> Some authors argue that the underlying cause of systemic involvement is hypersensitivity to the BCG, while others believe that it is due to systemic dissemination after hematogenous seeding from the bladder.<sup>3,4</sup>

No evidence is available to show that prophylaxis with isoniazid protects against systemic dissemination after intravesical BCG administration.<sup>5</sup> Complications may take months or even years to appear after the first instillation.<sup>2</sup>

In our patient, culture was positive for *M. bovis*. The chest CT showed residual lesions suggestive of an old untreated TBC. Complications occur more often in patients with a history of TBC than in patients without previous tuberculous disease.<sup>6</sup>

Our case was an unusual presentation of bacilli in the pleural fluid, prompting a diagnosis of pleural effusion due to BCG dissemination after intravesical instillation, 1 year after receiving this treatment. It is also uncommon for this complication to present as pleural effusion. We could only find 1 similar case of pleural



Fig. 1. Posteroanterior chest radiograph. Large right pleural effusion. Intracavitary pacemaker.

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effusion 6 years after administration of BCG treatment, although in that patient, no mycobacteria could be isolated from pleural fluid.<sup>7</sup>

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## In Vitro and In Vivo Evaluation of the Combination of Oscillating Positive Expiratory Pressure and Nebulization: A Randomized Cross-Over Study



### Evaluación in vitro e in vivo de la combinación de presión espiratoria positiva oscilante y nebulización: estudio aleatorizado cruzado

To the Editor:

Positive expiratory pressure (PEP) as airway clearance technique prevents airway closure during expiration, reduces gas trapping in the lung,<sup>1</sup> increases collateral ventilation<sup>2</sup> and improves spatial ventilation distribution.<sup>3</sup> The addition of oscillations promotes mucus mobilization based on the reduced mucus viscosity<sup>4</sup> and distributed flows in more airways.<sup>5</sup> Oscillating PEP devices have been proposed in cystic fibrosis.<sup>6</sup> Simultaneous use of PEP and nebulization is sometimes performed in cystic fibrosis patients even if its clinical benefits are still not well established.

As the drug amount reaching the lungs is essential for the clinical response of drug with a dose-dependent effect, this study aims at evaluating the effect of a new oscillating PEP device combined to a nebulizer on the drug delivery to the lungs.

We connected a jet nebulizer (Sidestream<sup>®</sup>, Philips-Respironics) (NEB) at the distal end of an oscillating PEP device (Aerobika<sup>®</sup>, Trudell-Medical) (NEB-OPEP) with a T-piece blocking the extra vent. Each nebulizer was filled with 250 mg of amikacin diluted with 3 mL of normal saline.

In the in vitro part, a dual-chamber test lung (5600i Dual Adult Test Lung; Michigan Instrument Inc.) driven by a ventilator (Servo-i<sup>®</sup>, MAQUET) (Fig. 1) simulated an adult breathing pattern ( $V_t = 500$  mL-RF = 12 breaths/min-I/E ratio = 1:2-breath-hold time = 0.25 s). An absolute bacterial/viral filter (Air Safety Ltd, Lancashire) was placed between the lung model and NEB-OPEP/NEB to measure the inhaled dose (IND). Another filter placed on the expiratory port collected the exhaled dose (ExD). The mass of amikacin collected on filters during nebulization was quantified using the residual gravimetric method.<sup>7</sup> The nebulizer output was calculated by dividing the IND by the nebulization duration. The residual volume was quantified.

In the in vivo part, after ethical approval (B40320107908) and registration of the trial (NCT02535130), six non-smoker healthy

males were recruited. They signed a written informed consent form. They were excluded if they received any antibiotic or aerosolized drug during the month preceding the experiments, for history of cardiovascular and/or pulmonary disease, for allergy to aminoglycosides and for abnormal pulmonary function.

After (1) selection visit, spirometry and medical examination and (2) training to inhale correctly, (3) inhalation and (4) urine sampling were performed. Each subject repeated the steps 3 and 4 in similar conditions using a randomized crossover setting ([www.randomizer.org](http://www.randomizer.org)) with a one-week washout period between the two configurations (NEB or NEB-OPEP). The subjects breathed spontaneously through mouthpiece wearing a noseclip.

Just before the experiments, the urinary bladder of the subjects was emptied. Then, urine samples were collected at each spontaneous micturition during the 24 h following the nebulization. The volume and timing of micturition were recorded.

After sampling by fluorescence polarization immuno-assay, the total daily amount of amikacin excreted in the urine (Cu max) reflecting lung deposition and the elimination rate constant was calculated using the Michaelis-Menten kinetic model from cumulating amikacin amount measured at each micturition (Cu) and represents the lung dose (LD) ( $Cu\ max = Cu \times (1 - e^{-Ke \cdot x \cdot t})$ ).

The residual amount of drug was calculated by multiplying residual volume and its final concentration.

In vitro, no difference was found between NEB and NEB-OPEP for IND (34.4% (30.0–38.0) vs 29.6% (26.8–32.0)) and ExD (20.8 (19.6–23.2) vs 25.2% (22.4–28.4)). Nebulizer output was higher for NEB than for NEB-OPEP ( $1.49 \pm 0.14$  vs  $1.10 \pm 0.12$  mL min<sup>-1</sup>;  $p = 0.032$ ).

Six subjects completed the study ( $21.8 \pm 1.0$  y –  $179.2 \pm 8.8$  cm –  $76.5 \pm 11.7$  kg – FEV1:  $97 \pm 7\%$ ). The lung dose was reduced by 40% and the time required to finish the nebulization was 1.2 min longer with NEB-OPEP than with NEB (Table 1).

Lung delivery around 5% of the ND with NEB confirmed previous results.<sup>8</sup> In addition, our results showed that interposing this new OPEP device between the nebulizer and the patient's mouth reduced the efficiency of the nebulization similarly to results found with other PEP devices under different conditions.<sup>9,10</sup> This is clinically important when dose-dependent drugs are administered. The reduced lung delivery could be explained by the impaction of particles in the PEP device that filters the larger particles.<sup>9,11</sup> However, this hypothesis was neither verified in our study (similar IND and ExD) nor in a previous study.<sup>12</sup>