Prolonged treatment with inhaled ampicillin in children with non-cystic fibrosis bronchiectasis☆

Tratamiento prolongado con ampicilina inhalada en pacientes pediátricos con bronquiectasias no relacionadas con la fibrosis quística

To the Editor:

Non-cystic fibrosis-associated bronchiectasis (NCFB) is a chronic lung disease characterized by frequent exacerbations. In patients with NCFB, inhaled antibiotics provide higher infection site concentrations without systemic side effects. However, little evidence is available on nebulized antibiotic therapy in children[1,2].

This study, based on the work of Máiz et al.[3,4], aimed to analyze the effectiveness and safety of inhaled ampicillin therapy in children with NCFB colonized by ampicillin-sensitive *Haemophilus influenzae* (*H. influenzae*), penicillin-sensitive *Streptococcus pneumoniae* (PSSP), methicillin-sensitive *Staphylococcus aureus* (MSSA), or polymicrobial flora.

Medical records collected between 31/07/2014 and 31/03/2020 were reviewed. We included patients younger than 18 years of age diagnosed with NCFB colonized with any of the respiratory pathogens listed above who had ≥ 3 respiratory exacerbations per year and/or persistent symptoms without meeting respiratory exacerbation criteria[5] (prolonged productive cough, unexplained recurrent fever, qualitative or quantitative change in expectoration). Patients were administered inhaled ampicillin after their parents or guardians gave consent for off-label use of the antibiotic.

The drug was prepared by diluting one vial of intravenous sodium ampicillin in 4 mL of water for injection. The resulting osmolarity was approximately 650 mOsm/kg. The dose used was 500 mg/12 h, and the solution was administered using either a vibrating mesh nebulizer (e-Flow®rapid) or a high-flow nebulizer (Pari Boy® SX), via an oronasal mask or a mouthpiece, depending on patient age and/or collaboration.

The minimum treatment time was 4 months. Rest periods took place in the months of lower circulation of respiratory viruses[6].

Criteria for discontinuation were: resolution of respiratory symptoms; number of respiratory exacerbations ≤ 1 every 6 months; isolation of *Pseudomonas aeruginosa* (PA) or aminopenicillin-resistant pathogens; adverse effects; refusal of treatment.

A total of 6 patients were included, 4 of whom were boys. The median age at baseline was 13 years (IQR 10–13.6). Five patients presented other comorbidities, 3 of whom (patients 1, 5 and 6) were children with highly complex chronic disease[7] (Table 1).

The median duration of treatment and follow-up were 17.5 (IQR 8.75–24) and 25.5 (IQR 10.5–30) months, respectively. Only patient 4 had discontinued ampicillin by the end of the study.

During follow-up, no aminopenicillin-resistant microorganisms or PA were isolated. In patient 2, *Mycobacterium haemophilum* was isolated but this finding was neither confirmed in subsequent cultures nor was it clinically relevant.

After treatment initiation, no admissions were recorded ($p = 0.0003$) and a significant decrease in the median number of exacerbations ($p = 0.027$) from 7 (IQR 7–7.75) to 2.5 (IQR 1.25–3.75) was observed. In the 2 years following drug discontinuation, patient 4 received more than 10 antibiotic cycles for respiratory exacerbations.

In all patients, cultures of secretions became negative during treatment, with a median of 3.92 (IQR 1.49–7.45) months until negativization.

No adverse effects were detected. Table 1 summarizes patient characteristics and outcomes.

Nebulized aminopenicillin therapy in patients with chronic lung diseases has been studied by other authors who reported favorable results[8]. Clinical trials with inhaled amoxicillin-clavulanic acid have also demonstrated the safety and good tolerance of this treatment[9]. However, this is the first study to explore nebulized ampicillin in children with NCFB. In 2009, Maiz et al.[3,4] published a series of 13 patients with bronchiectasis caused by cystic fibrosis and chronic MSSA colonization, showing a decrease in the number of hospital admissions and the use of systemic antibiotics after prolonged treatment with inhaled ampicillin. Although the MSSA isolated in sputum cultures were penicillin-resistant, the efficacy of treatment was probably due to the high lung concentrations achieved by administering the antibiotic by inhalation, levels that were higher than the minimum inhibitory concentration (MIC) for the targeted microorganisms[10,11]. In our study, all ampicillin-sensitive *H. influenzae* isolates in BAL were sensitive to ampicillin, although the MICs for MSSA or PSSP were not reached. However, despite this, and in line with other studies, our patients responded to nebulized ampicillin, probably for the reason stated above[10–12]. In contrast to Maiz's series, none of our patients presented chronic colonization by these pathogens: apart from during exacerbations and in the year before starting ampicillin, mixed polymicrobial flora or a single microorganism were identified in the respiratory samples. Some of these exacerbations may have been initiated by respiratory viruses[6]. However, exacerbations could have declined because, rather than eradicating a single pathogen, prolonged treatment with nebulized ampicillin decreases the pulmonary bacterial load that is probably high in patients with bronchiectasis[13–15]. Furthermore, the pathogens commonly identified in children with NCFB[15] are mostly sensitive to aminopenicillins (more so if higher drug concentrations are achieved by inhalation), which would also explain our patients' improvement.

The outcomes mentioned in previous studies were favorable[3,4,8,9], although it must be said that they were conducted in adults with diseases other than those presented by our patients. We must remember that the main reason for the off-label use of a drug that has only been tested in adults was the shortage of therapeutic options: our patients mostly had multiple conditions and no option for curative treatment, despite having tried other treatments administered according to the recommendations of the latest clinical practice guidelines[1,2,12,16].

This study has limitations: it was a retrospective, before-and-after study without a control group, conducted in a small, heterogeneous group of cases with varying lengths of follow-up. Even so, we observed a statistically significant decrease in admissions and respiratory exacerbations.

Therefore, we conclude that long-term inhaled ampicillin therapy appears to be a safe and effective option in children with NCFB colonized by common pathogens who have frequent exacerbations. However, more extensive, randomized, homogeneous studies are needed to confirm these results and determine the optimal duration and regimen of inhaled ampicillin therapy.

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Table 1
Descriptive summary of the main variables collected and study results.

Variables	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Median, IQR
Demographic data							
Sex	Male	Female	Female	Male	Male	Male	NA
Age at diagnosis of lung disease (years)	10.5	2.5	0.9	8.1	4.6	3.5	4,05 (IQR 2.75–7.23)
Etiology of bronchiectasis	Aspiration syndrome	Post-infectious	Vasculitis, immune dysregulation (low Treg cells)	Idiopathic	Post-infectious	Post-infectious	NA
Comorbidity	HCCP Rett syndrome, GERD, dysphagia	Down syndrome, PHT	Interstitial lung disease, PHT	No	HCCP GERD, operated Tetralogy of Fallot, complete AVB, PM carrier	HCCP ICP, dysphagia, GERD	NA
Microbiology							
Isolates in the year prior to starting inhaled ampicillin (sputum/pharyngeal swab)	Mixed flora, AS Hib, MSSA	Mixed flora, AS Hib, PSSP	Mixed flora, AS Hib, PSSP	Mixed flora, AS Hib	Mixed flora	Mixed flora, AS Hib	NA
BAL isolates in the 2 months prior to starting inhaled ampicillin	MSSA	MSSA, PSSP, AS Hib	AS Hib	AS Hib	AS Hib	AS Hib	NA
Ampicillin MIC (μg/mL) in BAL sample	Not applicable	0.5	0.75	0.75	0.38	0.75	0.75 (IQR 0.5–0.75)
Treatment-related data							
Age at start of treatment (years)	14.6	13.8	7.6	13	13	9	13 (IQR 10–13.6)
Years from diagnosis to start of treatment (n)	4.1	11.3	6	5	7.4	6.5	6.25 (IQR 5.25–7.18)
Months of treatment (n)	26	35	21	17	5	6	19 (IQR 8.75–24.75)
Months off (n)	5	8	19	7	0	0	6 (IQR 1.25–7.75)
Months follow-up (n)	31	43	40	24	5	6	27.5 (IQR 10.5–37.75)
Macrolide therapy	Yes	Yes	Yes	Yes	Yes	Yes	NA
Microbiological isolates during follow-up (sputum/pharyngeal smear)	*PSSP*	*Mycobacterium haemophilum*	*AS Hib*	Mixed flora	Mixed flora	Mixed flora	NA
Outcomes Pre-treatment (12 months)							
Admissions (n)	3	3	1	1	2	2	2 (IQR 1.25–2.75)
Days of admission to the ward (n)	10	7	2	2	4	2	3 (IQR 2–6.25)
Respiratory exacerbations (n)	7	8	6	8	7	7	7 (IQR 7–7.75)
During follow-up							
Admissions (n)	0	0	0	0	0	0	0
Respiratory exacerbations (n)	3	2	4	4	0	1	2.5 (IQR 1.25–3.75)
Negativization of BAL culture	Yes	Yes	Yes	Yes	Yes	Yes	NA
Months until negativization of the BAL culture (n)	7.97	8.93	5.87	1.33	1.3	1.97	3.92 (IQR 1.49–7.45)

AVB: Atrioventricular block; AS Hib: ampicillin-sensitive *Haemophilus influenzae;* BAL: bronchoalveolar lavage; BCH: Bronchiectasis; GERD: gastroesophageal reflux; HCCP: highly complex chronic patient; ICP: infantile cerebral palsy; MIC: Minimum inhibitory concentration; MSSA: methicillin-sensitive *Staphylococcus aureus*; PM: pacemaker; PSSP: penicillin-sensitive *S. pneumoniae*; Treg: regulatory T cells.

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References

1. Chang AB, Bush A, Grimwood K. Bronchiectasis in children: diagnosis and treatment. Lancet. 2018;392:866–79, http://dx.doi.org/10.1016/S0140-6736(18)31554-X.
2. Poeta M, Maglione M, Borrelli M, Santamaria F. Non-cystic fibrosis bronchiectasis in children and adolescents: neglected and emerging issues. Pediatr Neonatol. 2020;61:255e262. Available from: https://www.pediatr-neonatol.com/article/S1875-9572(19)30522-4/fulltext
3. Máiz L, Del Campo R, Castro M, Gutiérrez D, Girón R, Cantón Moreno R. Maintenance treatment with inhaled ampicillin in patients with cystic fibrosis and lung infection due to methicillin-sensitive *Staphylococcus aureus*. Arch Bronconeumol. 2012;48:384, http://dx.doi.org/10.1016/j.arbres.2012.04.002. Epub 2012 May 21.
4. Máiz L, Lamas A, Fernández-Olmos A, Suárez L, Cantón R. Unorthodox long-term aerosolized ampicillin use for methicillin-susceptible *Staphylococcus aureus* lung infection in a cystic fibrosis patient. Pediatr Pulmonol. 2009;44:512–5, http://dx.doi.org/10.1002/ppul.20983.
5. Kapur N, Masters IB, Morris PS, Galligan J, Ware R, Chang AB. Defining pulmonary exacerbation in children with non-cystic fibrosis bronchiectasis. Pediatr Pulmonol. 2012;47:68–75, http://dx.doi.org/10.1002/ppul.21518.
6. Chen C-L, Huang Y, Yuan J-J, Li H-M, Han X-R, Martinéz García MA, et al. The roles of bacteria and viruses in bronchiectasis exacerbation: a prospective study. Arch Bronconeumol. 2020, http://dx.doi.org/10.1016/j.arbres.2019.12.010.
7. Climent Alcalá FJ, Fernández de Villalta M, Escosa García L, Rodríguez Alonso A, Albajara Velasco LA. Unidad de niños con patología crónica compleja. Un modelo necesario en nuestros hospitales. An Pediatr (Barc). 2018;88:12–8, http://dx.doi.org/10.1016/j.anpedi.2017.04.002.
8. Stockley RA, Hill SL, Burnett D. Nebulized amoxicillin in chronic purulent bronchiectasis. Clin Ther. 1985;7:593–9. PMID: 4053147.

9. Nijdam LC, Assink MDM, Kuijvenhoven JC, de Saegher MEA, van der Valk PDLPM, van der Palen J, et al. Safety and tolerability of nebulized amoxicillin-clavulanic acid in patients with COPD (STONAC 1 and STONAC 2). COPD. 2016;13:448–54, http://dx.doi.org/10.3109/15412555.2015.1107893.
10. Aspa J1, Rajas O, de Castro FR. Pneumococcal antimicrobial resistance: therapeutic strategy and management in community-acquired pneumonia. Expert Opin Pharmacother. 2008;9:229–41, http://dx.doi.org/10.1517/14656566.9.2.229.
11. Geller DE, Pitlick WH, Nardella P, Tracewell WG, Ramsey BW. Pharmacokinetics and bioavailability of aerosolized tobramycin in cystic fibrosis. Chest. 2002;122:219–26, http://dx.doi.org/10.1378/chest.122.1.219.
12. Al-Jahdali H, Alshimemeri A, Mobeireek A, Albanna AS, Al Shirawi NN, Wali S, et al. The Saudi Thoracic Society guidelines for diagnosis and management of noncystic fibrosis bronchiectasis. Am Thorac Med. 2017;12:135–61, http://dx.doi.org/10.4103/atm.ATM_171_17.
13. Ishak A, Everard ML. Persistent and recurrent bacterial bronchitis—a paradigm shift in our understanding of chronic respiratory disease. Front Pediatr. 2017;5:9, http://dx.doi.org/10.3389/fped.2017.00019.
14. Rogers GB, van der Gast CJ, Cuthbertson L, Thomson SK, Bruce KD, Martin ML, et al. Clinical measures of disease in adult non-CF bronchiectasis correlate with airway microbiota composition. Thorax. 2013;68:731–7, http://dx.doi.org/10.1136/thoraxjnl-2012-203105.
15. Flume PA, Chalmers JD, Olivier KN. Advances in bronchiectasis: endotyping, genetics, microbiome, and disease heterogeneity. Lancet. 2018;392(10150):880–90, http://dx.doi.org/10.1016/S0140-6736(18)31767-7.
16. Martínez-García M, Máiz L, Olveira C, Girón MR, Blanco M, Catón R, et al. Normativa sobre el tratamiento de las bronquiectasias en el adulto. Arch Bronconeumol. 2018;54:88–98, http://dx.doi.org/10.1016/j.arbres.2017.07.016.

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Clinical course of patients with bronchiolitis obliterans following hematopoietic stem cell transplantation☆

Evolución de los pacientes con bronquiolitis obliterante secundario a trasplante de progenitores hematopoyéticos

To the Editor:

Chronic graft-versus-host disease (cGVHD) is a multisystemic disease with high morbidity and mortality that develops as a complication in 30%–70% of allogeneic hematopoietic stem cell (HSCT) transplants[1]. Bronchiolitis obliterans (BO) is the pulmonary manifestation of cGVHD, and usually presents as fibrosis and scarring of the small distal airway and fixed airflow obstruction[1,2]. Its clinical presentation includes dyspnea, exercise intolerance, and non-productive cough[1,3]. Clinical manifestations are non-specific, and many patients are initially asymptomatic, so this disease can be diagnosed late. The incidence in patients receiving allogeneic HSCT is estimated to be 2%–5% and 6% in patients already diagnosed with cGVHD[1,4,5], but recent publications suggest that the incidence is on the rise. Thus, the study by Chien et al. showed a prevalence of BO of 5.5% in general, 10% in patients who survived at least one year, and 16% in patients already diagnosed with cGVHD[6,7].

The aim of this study was to describe the prevalence, clinical and spirometric characteristics, and survival of patients with GVHD who developed BO in the previous 10 years. The Hematology and Respiratory Medicine Departments of the Hospital de la Princesa have been collaborating for years in the joint follow-up of these patients. We conducted a retrospective observational study of the 289 HSCTs performed at the Hospital de la Princesa between January 2009 and June 2018, and finally selected 42 patients who were diagnosed with BO. The following variables were collected: age at the time of transplantation, sex, baseline hematological disease, lung function at diagnosis of BO and pre- and post-transplant, microbiological isolates, radiological findings, clinical course, involvement of other organs, and mean survival. Differences in survival by sex, microbiological isolates, or involvement of the lung only or of the lung and other organs were evaluated.

Of the 42 patients with BO, 23 were men and 19 were women. The prevalence of BO was 14.8%. The mean age of the patients at transplantation was 48.39 ± 12.74 years. The HSCT was performed mainly for acute myeloblastic leukemia (34.8%), myelodysplastic syndrome (28.3%), and acute lymphoblastic leukemia (13%). In total, 52.4% of the patients were former smokers with a pack/year index of 22.26 ± 13.52. Mean FEV_1% was 96.28% ± 11.55 before transplantation; 64.6% ± 24.43 at diagnosis of BO; 66.86% ± 31.08 at 6 months; and 69.37% ± 25.94 at 12 months. Sputum culture was carried out in 19 patients: 10 cases were positive for *Aspergillus fumigatus*, 7 for *Pseudomonas aeruginosa* and 2 for *Haemophilus influenzae* and *Stenotrophomonas maltophilia.* The findings on chest computed tomography (CT) were: ground glass and bronchiectasis in 56.4%; alveolar infiltrates in 30.8%; air trapping in 15.4%, and peribronchial thickening and peribronchial nodules in 12.8%. No patient showed images consistent with pleuropulmonary fibroelastosis.

In 11 patients, cGVHD was exclusively pulmonary, while involvement of both the lungs and other organs was observed in the remaining patients (74.4%). The most frequently affected organ was the skin, in 24 cases, followed by ocular (20 cases), oral (17 cases), and hepatic (17 cases) manifestations.

Seventeen patients died, 4 were lost to follow-up, and 24 were still alive at the time of the study. The causes of death were respiratory in 76.4% of the patients, and neurological and digestive in 11.7% each. Fig. 1 shows that the median survival of these patients was 175 months. There were no differences in survival according to sex, microbiological isolates or organ involvement.

In this study, we analyzed the prevalence and clinical characteristics of BO in HSCT. The prevalence of BO in our hospital was 14.8%, which is slightly higher than described in other studies, perhaps due to earlier diagnosis. In previous studies, FEV_1% at diagnosis ranged from 40% to 59%, whereas in ours it was 64.6%, suggesting that we may be diagnosing and treating patients with milder involvement. However, mortality was high, and median survival was 175 months. Limitations of our study include particularly the number of patients and the patient inclusion timeline, so it was difficult to analyze all factors that could influence mortality.

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