Research letter

Prescribing preferences and availability of nebulizers and inhalers for inhaled medications in bronchiectasis: results of a specialist survey

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This manuscript has recently been accepted for publication in the ERJ Open Research. It is published here in its accepted form prior to copyediting and typesetting by our production team. After these production processes are complete and the authors have approved the resulting proofs, the article will move to the latest issue of the ERJOR online.

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Prescribing preferences and availability of nebulizers and inhalers for inhaled medications in bronchiectasis: results of a specialist survey

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Supported by: EMBARC3 is funded by the European Respiratory Society through the EMBARC3 clinical research collaboration. EMBARC3 is supported by project partners Armata, AstraZeneca, Boehringer Ingelheim, Chiesi, CSL Behring, Grifols, Insmed, Janssen, Lifearc, and Zambon. J.D.C. is supported by the GlaxoSmithKline/Asthma and Lung UK Chair of Respiratory Research.
To the Editor,

Bronchiectasis clinical practice guidelines advocate several medications to be prescribed by the inhaled route (1, 2). Examples are inhaled saline (isotonic or 3-7% hypertonic) as a mucolytic and inhaled antibiotics for eradication of *Pseudomonas aeruginosa* (PA) or for maintenance treatment of people chronically infected with various organisms (mainly PA) (1). In people with concomitant asthma or chronic obstructive pulmonary disease (COPD), guidelines advocate inhaled corticosteroids, and patients with clinically significant breathlessness are recommended to receive long-acting beta-agonists and/or muscarinic antagonists. Evidence supporting these recommendations is based on randomized controlled trials (RCTs) for inhaled antibiotics (reviewed in (3)) and for hypertonic saline (4). The delivery of a nebulized drug to the bronchi has been estimated to vary 10-fold between nebulizer systems due to factors such as mean mass aerodynamic diameter (MMAD), drug loss to the atmosphere and nebulizer, and nebulization time (5). Consequently, the European Respiratory Society has published guidelines on the choice and care of nebulizers used for acute and chronic airway diseases, including cystic fibrosis (CF) and bronchiectasis (5).

In keeping with the ERS guidelines (5) recommendations, RCTs of inhaled medication often administer the study medication through a uniform and protocol-specified nebulizer device, designed to optimize particle size and delivery as a drug-device combination. Examples are the InnoSpire Deluxe air compressor (Philips Respironics): a jet nebulizer (JN) tested with inhaled Tobramycin solution (6), a vibrating-mesh nebulizer (VMN) for inhaled Tobramycin solution (7), I-Neb (Adaptive Aerosol Delivery VMN) for inhaled colstin (8), PARI LC Sprint (a JN) for inhaled ciprofloxacin (9), and eFlow rapid VMN (PARI Pharma) for inhaled hypertonic saline (4). These are specialized nebulizers powered by jet or vibrating mesh technologies, sometimes with adaptation to the patient’s breathing pattern, designed to optimize particle size and hence drug delivery. To date, no drug has been licensed for bronchiectasis, and inhaled antibiotics are frequently used off-label. A large number of different nebulizer and inhaled devices are available and in the absence of licensed drug-device combinations, off-label treatments may be delivered with widely varying devices. The assurance of optimal drug delivery is therefore unknown.

Our aim in this study was to assess the preferences of specialists and the availability of devices used for inhaled medications in patients with bronchiectasis. For this aim, we conducted an online survey of prescribing preferences of inhaled medications and nebulization devices, which was administered to respiratory health care professionals who treat patients with bronchiectasis. The survey was developed by members of the European Multicenter Bronchiectasis Research and Audit Collaboration (EMBARC) (10) and consisted of 11 items, which were open and multiple-choice questions of single and multiple selection. The survey was administered through email to respiratory professionals caring for patients with bronchiectasis who were recruited from the EMBARC collaboration, and it was available from December 2019 to February 2020. Participation was anonymous and voluntary, and no ethical approval was required. IBM SPSS Statistics 28.0 (IBM, New York, NY) was used for statistical analyses. Descriptive analysis was used and data are reported as frequencies and percentage of the total number of survey respondents. Normality was tested using the Kolmogorov–Smirnov test test. Anova and t-tests were used to assess groups of parametric data. Statistical significance was set at a<0.05.

One hundred thirty specialists answered the survey: 94 (72.3%) identified as respiratory physicians and the rest were nurses (23, 17.7%), physiotherapists (8, 6.2%) and 5 (3.8%) other professions.
Respondents came from 25 countries (in and outside Europe) with the majority (53, 40.7%) from the UK, and 10 (7.7%) from France and from Germany.

Table 1 presents the prevalence of medication use, preferred delivery mode per type of medication and preferred nebulizer devices. For inhaled antibiotics, specialists were less likely to allow ‘any nebulizer’ compared to when using other inhaled medications (27.8% vs. 45.3-55.3%, p<0.001 for comparisons with inhaled saline, both isotonic and hypertonic). Specialists reported that they often recommend using a mouthpiece (n=77, 59.2%) when nebulizing. The most important factors when choosing a nebulizer were suitability of prescribed medication (n=79, 60.8%), ease of use and cleaning (n=68, 52.3%), compliance with standards for particle size (n=56, 43.1%), and cost (n=49, 37.7%). There was no significant difference in the consideration for the choice of nebulizers between regions (p>0.05 for comparisons between regions: UK, Eastern Europe, Western Europe, and non-Europe). In response to an open-ended question regarding the choice of nebulizers, availability and cost considerations were often limiting in choice of nebulizers.
Availability of inhaled medications (isotonic/hypertonic saline or antibiotics) for people with bronchiectasis does not necessarily ensure the availability of the specialized nebulizer which was tested with the drug in a clinical trial. Our findings show that while specialists in bronchiectasis care have an appreciation of the importance of the quality and suitability of the nebulizer device, availability is often limited. However, no study to our knowledge has compared the efficacy of drug delivery, or clinical outcomes, of different nebulizers, and so the choice of a nebulizer device is largely driven by cost and availability. Therefore, patients use available devices (usually low-cost jet nebulizers) which may affect drug deposition into the airways as well as nebulization time, and in turn may impair adherence and effectiveness. The use of simple jet nebulizers will become increasingly hard to justify when the evidence base for drug plus advanced device emerges. Our findings indicate that specialists place more importance on the nebulizer system when prescribing inhaled antibiotics than isotonic or hypertonic saline. The preference of many experts for pressurized meter-dose inhalers (pMDI) inhalers is surprising given the impact on carbon emission by propellants used in these inhalers (11), and the availability of dry-powdered inhalers (DPIs) for most types of inhaled medication. Likewise, the heterogeneity of the responses regarding nebulizer choices may reflect both lack of standards but also could stem from inadequate knowledge of specialists regarding different nebulizers and their drug suitability. For example, the use of ultrasonic nebulizers may not comply with some antimicrobials due to excessive heating of the solution (12), however, ultrasonic nebulizers were the chosen nebulizers for inhaled antibiotics among 8 (8.9%) of the specialists.

It is important to acknowledge and address the availability of specialized nebulizers in the future-when inhaled drugs are registered, and currently when prescribing inhaled antibiotics, and when assessing efficacy in ‘real life’ studies.
Bibliography


Table 1: Use of inhaled medications and preferred mode of delivery

<table>
<thead>
<tr>
<th>Pharmacologic class (N using)</th>
<th>Choice of device for medication delivery</th>
<th>Type of nebuliser for nebulised medications</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nebulisers</td>
<td>Meter-dosed inhalers</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>-----------</td>
<td>----------------------</td>
</tr>
<tr>
<td>Bronchodilators (N=115)</td>
<td>47 (41.2)</td>
<td>26 (22.8)</td>
</tr>
<tr>
<td>Inhaled corticosteroids* (N=106)</td>
<td>15 (14.2)</td>
<td>19 (17.9)</td>
</tr>
<tr>
<td>Isotonic saline (N=86)</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Hypertonic saline (n=108)</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Inhaled antibiotics (N=99)</td>
<td>76 (78.4)</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Respondents were asked whether they prescribe each of the pharmacological classes. For those answering ‘yes’ or ‘sometimes’, questions regarding mode of delivery and choice of nebulizers were available. For each pharmacological class, numbers indicate respondents who replied ‘yes’ or ‘sometimes’. Data presented as Numbers (percent).

* Inhaled corticosteroids ± long-acting beta agonists. ** Either nebulizer or dry-powdered inhalers: 16.5%. †p<0.001 for comparisons between inhaled antibiotics and inhaled saline, both isotonic and hypertonic

N/A: not applicable.
Percentages do not add up to 100%, as respondents could select more than one answer.