A comparison of the costs of bronchodilator delivery methods in children with asthma exacerbations treated in hospital. The first Polish study in children

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Abstract

Introduction: Recommended methods of administering bronchodilator drugs in children with asthma exacerbations in a hospital include the pressurized metered-dose inhaler (pMDI) and nebulization (NEB). These methods differ in clinical effectiveness, safety and, as some studies indicate, the cost of their use in a child.

Aim: To calculate the direct costs of hospital therapy conducted with the use of short-acting β₂-agonist (SABA) or its combination with short-acting muscarinic antagonist (SAMA) administered via pMDI with valved holding chamber (VHC) versus the same drugs in NEB in children with asthma exacerbation.

Material and methods: A retrospective analysis of the costs of SABA (salbutamol) and SABA + SAMA (fenoterol + ipratropium bromide) inhalation therapy was performed. Based on the data obtained from the financial department, the pharmacy, and the sterilization department of the university hospital, the direct unit cost of the inhalation therapy in the child was calculated.

Results: The results of the analysis indicate that in a hospital setting the cost of one-time SABA or SABA + SAMA administration via pMDI+VHC is 1.5–2.4 times lower compared to NEB. The payer incurred the lowest costs during anti-obstructive treatment using SABA with pMDI + VHC (PLN 9.39 for one inhalation procedure). The working time of medical staff during the inhalation treatment is the component generating the highest cost for the hospital (up to 40% of direct costs).

Conclusions: In hospital conditions, the supply of SABA or SABA + SAMA with the use of pMDI + VHC in a child with asthma exacerbation is more beneficial financially than the supply of the same drugs in NEB.

Key words: nebulization, pressurized metered-dose inhaler, bronchodilator, asthma, children.

Introduction

Short-acting β₂-agonists (SABA) or their combination with short-acting muscarinic antagonists (SAMA) in inhalation are among the most important anti-obstructive drugs. These drugs are used in many diseases with acute bronchial obstruction in children, such as asthma, bronchitis, bronchiolitis, bronchopulmonary dysplasia, and pulmonary exacerbation of cystic fibrosis. They are available in the following inhalation forms: pressurized metered-dose inhaler (pMDI), breath-actuated pressurized metered-dose inhaler (pMDI-BA), metered-dose liquid inhaler (MDLI), dry powder inhaler (DPI) and as solutions for nebulization (NEB) [1–6].

Rational health policy is based on pharmacoeconomic analyses. These analyses help in choosing the method of treatment of a given disease – which one is most cost-effective while maintaining the highest clinical effectiveness. Research to date has shown that SABA as well as the combination of SABA and SAMA used in aerosol therapy of respiratory diseases may differ not only in the method of administration, but also in clinical effectiveness, safety and costs associated with their use in patients [3–9]. Research results indicate that regardless of the calculation method, the use of SABA with pMDI in combination with a valved holding chamber (VHC) instead of NEB is associated with a reduction in total costs in both the emergency department and the hospital ward [10–15]. There has been no similar analysis carried out in Poland.

Aim

The aim of the study was to estimate the total direct costs of bronchial obstruction therapy in children with...
asthma exacerbation using SABA or a combination of SABA and SAMA administered via pMDI + VHC versus the same drugs in NEB in a hospital ward setting.

**Material and methods**

An analysis was carried out of the costs of inhalation therapy SABA (salbutamol) and SABA (fenoterol) in combination with SAMA (ipratropium bromide) conducted in children with asthma exacerbation in a hospital setting from the payer’s perspective. The direct costs of two inhalation therapy methods (pMDI + VHC, NEB) used in the non-invasive treatment wards of the University Children’s Hospital in Lublin were calculated (in accordance with the hospital procedure for the administration of inhaled drugs number PPO7/2018) taking into account direct medical costs (cost of drugs, devices for their administration, remuneration for medical staff) as well as direct non-medical costs (cost of personal protective equipment, sterilization of drug delivery devices) [16, 17]. The sources of data necessary to calculate the above-mentioned costs are presented in Table 1.

The actual cost of one inhalation procedure was estimated for the doses of drugs recommended for an average child aged 6 years with bronchial obstruction, in whom bronchodilators were administered via pMDI + VHC (with a mouthpiece) or via a nebulizer through the mouthpiece according to current recommendations [5]. At the University Children’s Hospital in Lublin, bronchodilator drugs are mainly delivered by VHC, such as Aero-Chamber Plus Flow-Vu® and Respichammer Hospital® as well as by the OMRON A3 Complete® jet nebulizer and the Intec Twister Mesh® nebulizer. The technical characteristics of the tested inhalation devices are summarized in Table 2. The calculations also took into account drug losses during filling residual volume of nebulizers (RV). The average duration of the inhalation procedure was based on data from the Mason et al. study (Table 1), while the lifespan of inhalation drug delivery devices was adopted according to the manufacturer’s recommendations [18].

**Table 1. Output sources**

| Variables and model parameters | Data sources |
|--------------------------------|-------------|
| Drug costs                     | Data obtained from the Pharmacy of the University Children's Hospital in Lublin (price list as of 21.04.2020) |
| The cost of valved holding chambers | The offer obtained from NZ Techno on 21.04.2020* |
| The cost of nebulizers         | Data based on the purchase invoice of the OMRON A3 Complete® and Intec Twister Mesh® for the needs of one of the departments at the University Children's Hospital in Lublin (January 2020) |
| Sterilization cost             | Data obtained from the Sterilization and Disinfection Department of the University Children's Hospital in Lublin (price list as of 21.04.2020) |
| Nurse’s remuneration          | Announcement of the Speaker of the Sejm of the Republic of Poland of 28 June 2019 regarding the publication of the consolidated text of the act on the method of determining the lowest basic salary of certain employees employed in health care entities |
| Time needed to complete the drug delivery procedure with the use of pMDI + VHC or NEB | Time and motion study by Mason et al. [18] and the measured real time needed to perform the inhalation procedure (3 min. for pMDI + VHC, 7 min. for NEB with a mesh nebulizer, 20 min. for NEB with a constant-output jet nebulizer) |
| The cost of additional materials necessary during the inhalation procedure (gloves, disinfectant, syringes, needles) | Data obtained from the hospital's financial department. Guidelines for the use of personal protective equipment in accordance with the in-hospital procedure "Inhalation medication using various aerosol therapy techniques" (procedure number: PPO7/2018) |

pMDI – pressurized metered-dose inhaler, VHC – valved holding chamber, NEB – nebulization; * main distributor of Trudell Medical International products in Poland.

**Table 2. Characteristics of tested devices used during the aerosol therapy**

| Device                                      | Characteristics |
|---------------------------------------------|-----------------|
| AeroChamber Plus Flow-Vu®                  | Dual-valve, low-resistance, small-volume (149 ml), antistatic system, fitted to all pMDI, visual and acoustic control of the inspiratory flow rate |
| Respichamber Hospital®                      | Dual-valve, low-resistance, small-volume (149 ml), antistatic system, fitted to all pMDI, possibility of high-temperature sterilization |
| OMRON A3 Complete®                         | Constant-output jet nebulizer, RV = 0.7 ml nebulization rate 0.3–0.7 ml/min MMAD of the aerosol cloud 3–10 µm |
| Intec Twister Mesh®                         | Active mesh nebulizer, membrane reverse cleaning system, RV = 0.1 ml, MMAD of the aerosol cloud 4.8 µm, battery powered |

pMDI – pressurized metered-dose inhaler, RV – residual volume, MMAD – mass median aerodynamic diameter.
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All costs were expressed in PLN and compared after converting the currencies with other analyses available in the literature.

**Results**

Based on the obtained data, the cost of inhalation drugs used in asthma exacerbation therapy and devices for their administration was calculated. According to the hospital price list of 21 April 2020, the payer paid PLN 0.08 for SABA and PLN 0.26 for SABA + SAMA administered via pMDI per inhalation procedure. The same drugs used in NEB cost the hospital PLN 0.71 and PLN 0.70 respectively (without taking into account the cost of the drug needed to fill the RV of nebulizer) and were 8.9 and 2.7 times more expensive than drugs administered by pMDI. Considering the lifetime of inhalation drug delivery devices, it was calculated that the cost of using VHC per treatment together with the costs of sterilization was PLN 7.96 (identical for both analysed VHC). When using nebulizers, these costs were lower and amounted to: PLN 7.50 for a jet nebulizer and PLN 5.38 for a mesh nebulizer (Table 3).

### Table 3. The cost of the drug and the device for its supply per inhalation procedure

| Drug/medical device | Dose of the drug per inhalation procedure (excluding RV of the nebulizer)* | The cost of buying 1 pack of the drug or 1 medical device | Cost of the drug/medical device for one inhalation procedure (excluding the cost of the drug needed to fill the RV of the nebulizer) |
|---------------------|--------------------------------------------------------------------------------|----------------------------------------------------------|------------------------------------------------------------------------------------------|
| Berodual® (NEB)     | 0.38 mg + 0.19 mg (0.75 ml = 15 drops)                                       | PLN 18.53 (20 ml)                                         | PLN 0.70                                                                                  |
| Berodual N® (pMDI)  | 100 µg + 21 µg/puff (2 puffs)                                                | PLN 25.86 (200 puffs)                                     | PLN 0.26                                                                                  |
| Ventolin® (NEB)     | 2.5 mg (1 ampoule)                                                           | PLN 14.18 (20 ampoules)                                   | PLN 0.71                                                                                  |
| Ventolin® (pMDI)    | 200 µg (2 puffs)                                                             | PLN 7.81 (200 puffs)                                      | PLN 0.08                                                                                  |
| AeroChamber Plus Flow-Vu® | NA                           | PLN 60.48 (100 gas sterilizations)                       | PLN 0.61 + PLN 7.35 (gas sterilization)                                                   |
| RespiChamber Hospital® | NA                           | PLN 61.02 (100 gas sterilizations)                       | PLN 0.61 + PLN 7.35 (gas sterilization)                                                   |
| OMRON A3 Complete®  | NA                           | PLN 190 (1500 inhalations)                               | PLN 0.13 + PLN 5.25 (gas sterilization)                                                   |
| Intec Twister Mesh® | NA                           | PLN 150 (1000 inhalations)                               | PLN 0.15 + PLN 7.35 (gas sterilization)                                                   |

pMDI – pressurized metered-dose inhaler, NEB – nebulization, RV – residual volume, NA – not applicable. *Based on the characteristics of the medicinal products (as of 20.04.2020).

### Table 4. Total direct cost of the inhalation procedure using a combination of short-acting β₂-agonists with short-acting muscarinic antagonists depending on the type of the inhalation device (in PLN)

| Fenoterol + ipratropium bromide | Cost of the dose of medicine to be given to the patient | Cost of the drug needed to fill the RV of the nebulizer | Cost of one use of the medical device | Cost of additional materials (gloves, disinfectant) | Cost of nurse’s work | Cost of sterilization, packaging, hospital transport | Total direct cost of one inhalation procedure |
|---------------------------------|--------------------------------------------------------|--------------------------------------------------------|--------------------------------------|-----------------------------------------------------|---------------------|-----------------------------------------------------|---------------------------------------------|
| OMRON A3 Complete® (RV = 0.7 ml) Drug: Berodual® (NEB) | 0.70                                                   | 0.65*                                                  | 0.15                                 | 4.95                                                | 8.97                | 7.35                                                | 22.77                                       |
| Intec Twister Mesh® (RV = 0.1 ml) Drug: Berodual® (NEB) | 0.70                                                   | 0.09**                                                 | 0.13                                 | 4.95                                                | 3.14                | 5.25                                                | 14.26                                       |
| pMDI + AeroChamber Plus Flow-Vu® Drug: Berodual N® (pMDI) | 0.26                                                   | NA                                                     | 0.61                                 | 0                                                  | 1.35                | 7.35                                                | 9.57                                        |
| pMDI + RespiChamber Hospital® Drug: Berodual N® (pMDI) | 0.26                                                   | NA                                                     | 0.61                                 | 0                                                  | 1.35                | 7.35                                                | 9.57                                        |

NEB – nebulization, pMDI – pressurized metered-dose inhaler, RV – residual volume, NA – not applicable. *The cost of 0.7 ml of Berodual. **The cost of 0.1 ml of Berodual.
Table 5. The total direct cost of the inhalation procedure using short-acting β₂-agonists depending on the type of the inhalation device (in PLN)

| Salbutamol | Cost of the dose of medicine to be given to the patient | Cost of the drug needed to fill the RV of the nebulizer | Cost of one use of the medical device | Cost of additional materials (gloves, disinfectant) | Cost of a nurse’s work | Cost of sterilization, packaging, hospital transport | Total direct cost of one inhalation procedure |
|------------|--------------------------------------------------------|--------------------------------------------------------|-------------------------------------|-----------------------------------------------|-----------------------|-----------------------------------------------|---------------------------------------------|
| OMRON A3 Complete® (RV = 0.7 ml) Drug: Ventolin® (NEB) | 0.71 | 0.71 | 0.15 | 4.95 | 8.97 | 7.35 | 22.84 |
| Intec Twister Mesh® (RV = 0.1 ml) Drug: Ventolin® (NEB) | 0.71 | 0.71 | 0.13 | 4.95 | 3.14 | 5.25 | 14.89 |
| pMDI + AeroChamber Plus Flow-Vu® Drug: Ventolin® (pMDI) | 0.08 | NA | 0.61 | 0 | 1.35 | 7.35 | 9.39 |
| pMDI + RespiChamber Hospital® Drug: Ventolin® (pMDI) | 0.08 | NA | 0.61 | 0 | 1.35 | 7.35 | 9.39 |

NEB – nebulization, pMDI – pressurized metered-dose inhaler, RV – residual volume, NA – not applicable. *The cost of 1 ampoule of Ventolin®, of which 0.1 ml will be used to fill the RV of the nebulizer (drug loss = 1.8 ml). **The cost of 1 ampoule of Ventolin®, of which 0.7 ml will be used to fill the RV of the nebulizer (drug loss = 2.4 ml).

Tables 4 and 5 present the actual costs of one inhalation procedure, taking into account the cost of the drug needed to fill the RV of the nebulizer, the cost of additional materials used, and the remuneration of medical staff. The cost of SABA + SAMA supply varied depending on the choice of the inhalation method. The hospital incurred the lowest expenses related to drug supply with pMDI + VHC – PLN 9.57. The cost of SABA+SAMA nebulization was 1.5-2.4 times higher (mesh nebulizer – PLN 14.26, jet nebulizer – PLN 22.77). The analysis of expenses related to SABA inhalation showed that regardless of the type of VHC, the cost of one inhalation procedure with the use of pMDI was 1.6–2.4 times lower compared to NEB and VHC, the cost of one inhalation procedure with the use of SABA+SAMA nebulization amounted to PLN 9.39. The most expensive method of SABA administration for the payer was NEB using a constant-output jet nebulizer (PLN 22.84) (Tables 4 and 5).

Discussion

Short-acting β₂-agonists and their combinations with short-acting muscarinic antagonists (SAMA) are, next to corticosteroids (ICS), the most commonly used inhaled drugs in children [1, 2, 19–21]. They are used in the therapy of various diseases, although for many years they have been mainly used in the treatment of asthma [1–3]. According to the recommendations of GINA and the Polish Inhalation Guide, these drugs should be used when necessary in the event of an exacerbation of the disease and administered using pMDI + VHC or alternatively in NEB in both outpatient and hospital treatment [1, 2, 5, 22].

Polish research results indicate that hospital treatment of asthma exacerbation in adults is 7.6 times more expensive than outpatient treatment. Moreover, it has been shown that the cost of pharmacotherapy constitutes only 20% of the direct costs associated with hospital treatment [23]. It is important to look for diagnostic and therapeutic methods that, with high efficiency, will enable the reduction of hospital treatment costs. A cost analysis was carried out for inhalation pharmacotherapy of airway obstruction in children with asthma exacerbation conducted in the non-invasive treatment ward of one of the university children’s hospitals in Poland. For the administration of inhalation drugs, dual-valve, small-volume and low-resistance VHC are used, as well as nebulizers with high clinical efficiency (a constant-output jet nebulizer with mass median aerodynamic diameter (MMAD) regulation function, and an active mesh nebulizer). There are many VHCs available on the Polish market with various parameters, applications and prices. However, only a few meet the criteria of a modern VHC recommended by experts for children. One of them is AeroChamber Plus Flow-Vu® – the most thoroughly tested in vitro and in vivo VHC, and the most commonly used one in the world [4, 5, 24].

The development of technology enabling the precise dosing of inhaled drugs has contributed to the increasingly frequent selection of NEB as aerosol therapy methods. This applies especially to newborns and infants. The role of mesh nebulizers, which generate homogeneous aerosol particles (monodisperse aerosol) and are characterized by low drug losses, short nebulization time and high predicted lung deposition, is becoming increasingly important [25–27].

Pollock et al.’s summary of the systematic reviews to date of the use of bronchodilators in children with asth-
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Table 5: Differences in the cost of inhalation using pMDI + VHC vs. NEB

| Drug Type      | Cost of Inhalation (PLN) | Cost of Additional Materials (PLN) | Estimated Annual Cost of Drug Supply (PLN) |
|---------------|-------------------------|-----------------------------------|------------------------------------------|
| pMDI VHC      | 3.35                    | 0.01                              | 860                                      |
| NEB           | 4.52                    | 0.61                              | 2800                                     |

Researchers also note that the duration of drug administration has the greatest impact on the total cost of the inhalation procedure. Salyer et al. indicated that the time needed to prepare and administer the drug by pMDI + VHC was estimated at 13.2 min, while in NEB at 20.4 min [11]. In turn, in the work of Mason et al., whose data were used in our analysis, the administration of the drug via pMDI took less time (2–3 min) and the duration of NEB was estimated at 20 min [18].

Researchers also note that the duration of drug administration by replacing NEB with drug supply via pMDI + VHC is associated with a reduction in total costs by up to 21% [11]. In Staggs et al. study it was shown that replacing SABA supply in NEB with pMDI + VHC shortened the child’s stay in the emergency department by over 30 min (faster relief of asthma exacerbation, reduction in the number of procedures performed), which resulted in savings of $213,532 per year [12].

The analysis also showed differences in the scope of direct NEB costs depending on the type of the nebulizer used. It has been estimated that the real cost of NEB using a mesh nebulizer is 1.5 times lower versus NEB using a constant-output jet nebulizer (Tables 4 and 5). These differences result from: (i) shorter working time of medical staff when performing NEB with a mesh nebulizer versus a jet nebulizer (7 min vs. 20 min), (ii) 7 times smaller RV of the mesh nebulizer (0.1 ml vs. 0.7 ml), which translates into a lower cost of the drug needed to fill this space, (iii) lower cost of sterilizing the mesh nebulizer versus a jet nebulizer (smaller dimensions of the elements of the mesh nebulizer, which are gas sterilized).

In the University Children’s Hospital in Lublin, inhalation procedures using SABA or SABA + SAMA are performed in 5 wards (neonate pathology ward, infant pathology ward, pulmonology, allergology, and intensive care unit). Assuming that about 6000 inhalation proce-
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Conclusions

In hospital treatment of asthma exacerbations, the direct cost of SABA or SABA + SAMA inhalation by pMDI + VHC is lower compared to the cost of the same drugs carried out with a constant-output jet nebulizer. The actual cost of the inhalation procedure consists of direct medical costs (prices of drugs, devices for their administration, remuneration for medical staff) as well as direct non-medical costs (cost of personal protective equipment, sterilization of drug delivery devices). The working time of medical staff during the inhalation procedure is the component generating the highest cost for the hospital.

Conflict of interest

The authors declare no conflict of interest.

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