

Cost-effectiveness of clean air administered to the breathing zone in allergic asthma

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Abstract

Introduction: Airsonett Airshower (AA) is a novel non-pharmaceutical treatment for patients with perennial allergic asthma that uses a laminar airflow directed to the breathing zone of patients during sleep. It has been shown that AA treatment in addition to optimized standard therapy significantly increases asthma-related quality of life among adolescent asthmatics. However, the cost-effectiveness of AA treatment has not yet been assessed. As reimbursement decisions are increasingly guided by results from the cost-effectiveness analysis, such information is valuable for health-care policy-makers.

Objective: The objective of this study was to estimate the cost-effectiveness of adding AA treatment with allergen-free air during night sleep to optimized standard therapy for adolescents with perennial allergic asthma compared with placebo.

Materials and Methods: A probabilistic Markov model was developed to estimate costs and health outcomes over a 5-year period. Costs and effects are presented from a Swedish health-care perspective (QALYs). The main outcome of interest was cost per QALY gained.

Results: The Airshower strategy resulted in a mean gain of 0.25 QALYs per patient, thus yielding a cost per QALY gained of under €35 000 as long as the cost of Airshower is below €8200.

Conclusions: Adding AA treatment to optimized standard therapy for adolescents with perennial allergic asthma compared with placebo is generating additional QALYs at a reasonable cost. However, further studies taking more detailed resource use and events such as exacerbations into account would be needed to fully evaluate the cost-effectiveness of AA treatment.

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Key words

asthma – cost-effectiveness – decision modeling – quality of life

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Authorship

All authors contributed to the conception and design of the study, the interpretation of results and the critical revision of the manuscript. T-HB and GT have developed the model, performed the analysis and completed the initial draft of the manuscript.

Conflict of interest

An initial cost-effectiveness analysis of Airshower as a consultancy, where T-HB and GT got paid from Airsonett, was performed. OZ has received financial support from Airsonett when conducting a clinical trial investigating Airsonett Airshower. However, no financial support was received for the final economic analysis presented in this paper or for the writing of the paper itself. The authors retained full control over the paper's content and over the decision to submit the manuscript, with no influence from Airsonett.

Introduction

In patients with extrinsic allergic asthma and continuing or iterated allergen exposure it is well known that limiting allergen concentration in inhaled air has a beneficial effect. This fact has been clearly shown in studies where patients have moved from the allergen, e.g. by going to the alps in dust mite allergy or in domestic animal allergy when allergen exposure has been stopped (1, 2). However, air cleaning interventions until now have shown little or no effect on patients with perennial allergic asthma (3). A placebo-controlled study (4) investigating a novel treatment, Airsonett Airshower (AA), using a laminar airflow directed to the breathing zone of patients with perennial allergic asthma showed an increase in asthma-related quality of life (AQLQ) and a decrease in exhaled nitric oxide as an indicator of airway inflammation.

However, this demonstrated positive effect of using AA in addition to standard treatment is also associated with increasing treatment costs. Considering this additional effect in relation to the cost incurred to investigate whether or not it represents value for money is therefore natural. This is especially important as cost-effectiveness has become a key criterion for decision-makers when deciding which health-care interventions should be made available in collectively funded health-care systems (5).

The aim of this study is to estimate the cost-effectiveness of adding AA treatment to optimized standard therapy for perennial allergic asthmatic adolescents compared with placebo. In particular, health outcomes are measured in terms of quality-adjusted life years (QALYs).

Materials and methods

The economic analysis was based on the clinical trial of AA by Pedroletti *et al.* (4). Because of the short follow-up time of the patients, the results were extrapolated to a longer time perspective. The

effect of AA vs placebo was in the clinical trial measured in terms of mini-AQLQ. To derive QALY from AQLQ, we employed an algorithm previously reported (6).

Study design

The clinical study of AA has been described in detail in the paper by Pedroletti *et al.* (4). Briefly, the study was designed as a two-center, double-blind, placebo-controlled, crossover trial. Twenty-two patients were randomized into one of two arms starting with either active or placebo treatment. This was followed by a washout period of 2 weeks and ending with a second period of either active or placebo treatment (Fig. 1). Each treatment period was 10 weeks long and all subjects maintained their medication from randomization throughout the study. The AA treatment is designed to reduce the allergen load in the patients' breathing zone by vertically displacing the contaminations, originating from the bed and the room environment, with a laminar, allergen-free airflow during night sleep. The airflow is filtered, slightly cooled and 'Air showered' over the subject. Because of the higher density, the cooled air falls slowly down and displaces the contaminants from the breathing zone. No negative side effects from AA were observed in the clinical trial. The patients included in the clinical study were 12–33 years old with an average age of 18.8 years.

Cost-effectiveness analysis

Based on the population from the clinical trial, the costs and health outcomes of treating the patients with AA compared with placebo were determined by using a decision analytic model. We extrapolated the costs and effects to a 5-year time horizon. The analysis was performed from a Swedish health-care perspective, including costs directly associated with the health-care provider. Costs and QALYs were discounted by 3% per annum according to recent guidelines (7).

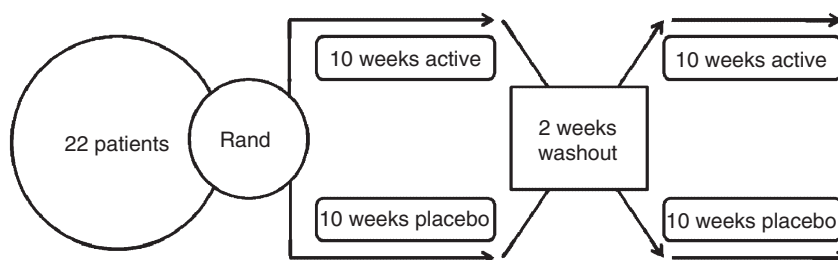


Figure 1. Study design. Rand, randomized.

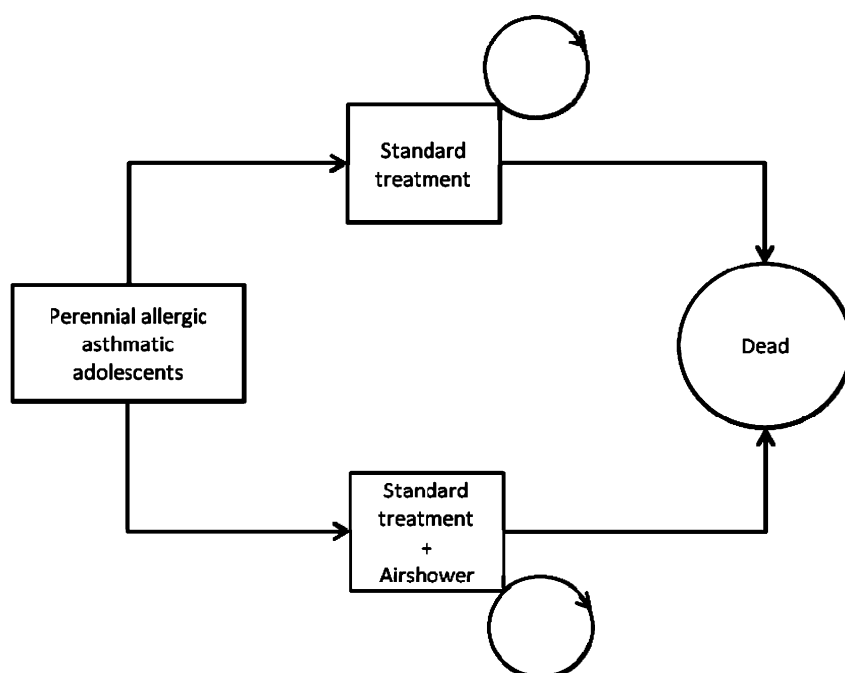


Figure 2. Simplified model structure.

Treatment strategies

The two treatment strategies under investigation were either providing a patient with an AA (Airshower strategy) or a placebo AA (henceforth referred to as placebo strategy). In the AA strategy, patients were assumed to use the Airshower for 5 years, changing the air filter two times per year. The patients were assumed to use the AA for 8 h per night. No changes were made to the standard treatment of asthma, neither during the Airshower strategy nor during the placebo strategy.

However, a sensitivity scenario analyzing a time horizon of 13 years was also performed. This was based on the functional lifetime of AA, given a survival time of 40 000 h and a daily usage of 8 h. This was carried out to examine the consequences of the assumption of using an AA for the maximal functional time vs an investment perspective of the Swedish county council of 5 years.

Model structure

The model employed to estimate cost and health outcomes of the two strategies under consideration consisted of a simple two-state Markov structure (Fig. 2). Markov models are well-recognized methods for analyzing clinical and economic consequences of medical decisions, particularly in long-term diseases characterized by repeating risks of events over time (8). In a Markov model, hypothetical patients reside in one of a

set of mutually exclusive health states at each and every point in time. During intervals of equal length, referred to as Markov cycles, patients can make transitions from one state to another, with the probability of moving between health states being determined by transition probabilities (8). In our model we only considered one state transition, from treated with AA (or placebo) to death. The probability of transition to the death state was, in both strategies, based on the age-adjusted probability of death from the Swedish general population (9).

The cycle length in the model was set to 1 year. This is a compromise between the increased detail the model would offer regarding the disease if utilizing a shorter cycle length and the increased complexity of the model. Thus, given the progression of the current patients and the detail of the material available, 1 year seemed appropriate. In future models based on new data, taking, e.g. exacerbations into account, a shorter cycle length of 2 weeks could be implemented, as has been used in previous publications regarding asthma treatment with omalizumab (10, 11).

Data

The effect of AA vs placebo was in the clinical trial measured in terms of mini-AQLQ. This measurement is not directly suitable to calculate QALYs, which are needed to perform a cost-utility analysis. When calculating QALYs, the time spent in a health state is

weighted by a quality-adjustment weight, or utility, between 0 (dead) and 1 (full health), representing the quality of life associated with the health state. This utility weight is however possible to derive from the mini-AQLQ by employing an algorithm previously reported (6). To account for the fact that each and every patient has experienced both AA and placebo treatments because of the crossover design of the clinical trial, the treatment effect in the model was incorporated as the mean of the individual incremental treatment effects. Of the 22 patients included in the clinical study, only 20 completed the mini-AQLQ, and only these 20 could be included in our analysis. This resulted in a mean difference in utility of 0.054 [standard error (SE) 0.04] between the Airshower strategy and the placebo strategy, and was incorporated in the model as a normal distribution. In accordance with the clinical trial, we also explored the results of only analyzing the data for the patients entering the study with an AQLQ value of equal or below 5. This resulted in a mean difference in utility of 0.26 (SE 0.08).

The cost included in the model was only the cost of AA. Because of the novel nature of this intervention, the cost of the AA is still not set. This is mainly because of the uncertainty for which categories of patients the AA will be prescribed to. The marginal cost of AA will be lower if AA is prescribed to a large group of asthma patients compared with a smaller subgroup of patients with a mini-AQLQ score equal or below 5. To account for this uncertainty regarding the cost of AA, we have performed the analysis over a large spectrum of costs and identified a cost threshold for a willingness to pay of €35 000. However, to account for the statistical uncertainty in the analysis, we have specifically performed the probabilistic sensitivity analysis for the fixed costs of AA of €5000 and €15 000. During the lifetime of the Airshower, the only extra cost acquired was the cost of the installation of two new filters per year at a total of €190 per year.

Analysis

The results were calculated as the cost per QALY gained for the Airshower strategy compared with the placebo strategy, which is known as the incremental cost-effectiveness ratio (ICER). The ICER is the ratio of the difference in costs between the two alternatives to the difference in health outcome (in this instance QALYs) between the two alternatives given by the formula below. Thus, the ICER shows the mean incremental cost of gaining an extra QALY by employing a strategy with an Airshower rather than a strategy with a placebo. Consequently, a low ICER value indicates

greater cost-effectiveness compared with a high ICER value.

$$ICER = \frac{\text{cost airshower} - \text{cost placebo}}{\text{effect airshower} - \text{effect placebo}} \quad (1)$$

According to recent guidelines, the model was analyzed using second-order Monte Carlo simulation in order to reflect uncertainty in the model inputs (12). With this approach, values are drawn randomly from the defined probability distributions in the model, and costs and QALYs are established for both strategies. This process is repeated 10 000 times and thus providing 10 000 estimates of the ICER, reflecting the uncertainty in the outcome. The uncertainty surrounding the estimated ICER also reflects the uncertainty in the decision of employing a Airshower strategy rather than a placebo strategy. The proportion of the 10 000 simulations that resulted in an ICER below the threshold value that decision-makers are willing to pay for a QALY is the probability of AA treatment being cost-effective. As there is no single true willingness to pay for a QALY, this probability can be presented for a range of willingness-to-pay values in so-called cost-effectiveness acceptability curves (13), making it possible for the decision-maker to establish the willingness to pay in a specific application and then assess the probability that the treatment strategy is cost-effective.

Results

The result of the base-case analysis showed that the Airshower strategy resulted in a mean gain of 0.25 QALYs per patient and having an ICER below €35 000 as long as the cost of the AA was below €8200. The sensitivity scenario with a 13 years perspective led to a gain of 0.59 QALYs and having an ICER below €35 000 as long as the cost of the AA was below €18 760. The scenario only analyzing the data of the patients with mini-AQLQ values of equal or below 5, i.e. more severe asthma, resulted in a mean gain of 0.594 QALYs. In this scenario the ICER will not be higher than €35 000 before the cost of AA exceeds €20 100 (Fig. 3).

When performing the analysis for fixed costs for AA of €5000, the ICER was €22 418, €11 670 and €10 007 for the base case, the 13 years and the mini-AQLQ values of equal or below 5 scenario, respectively. Corresponding results for the €15 000 cost resulted in ICERs of €62 644, €26 619 and €26 847. The results of the probabilistic sensitivity analysis are shown in the cost-effectiveness acceptability curve (Fig. 4), thus showing the probability that AA treatment is cost-effective over a range of willingness-to-pay values for both the €5000 and the €15 000 alternate.

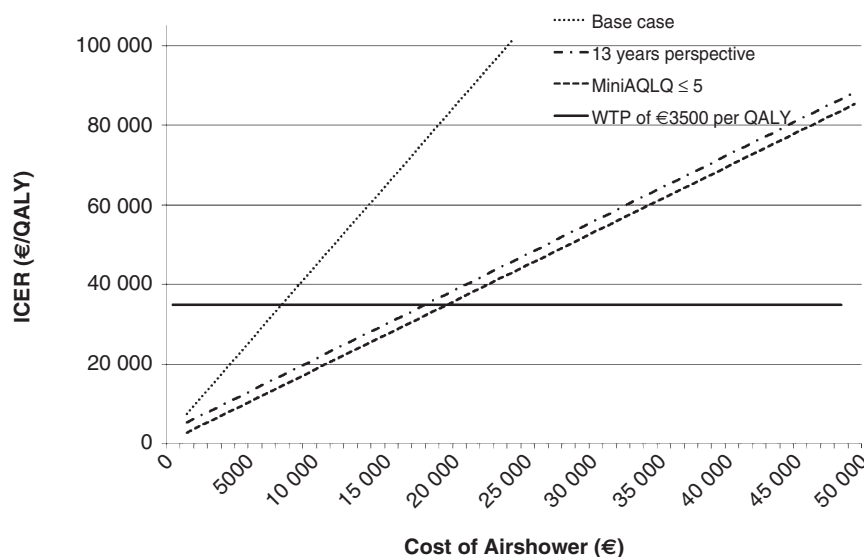


Figure 3. Relationship between cost of Airsonett Airshower and incremental cost-effectiveness ratio (ICER). AQLQ, asthma-related quality of life; QALY, quality-adjusted life year; WTP, willingness to pay.

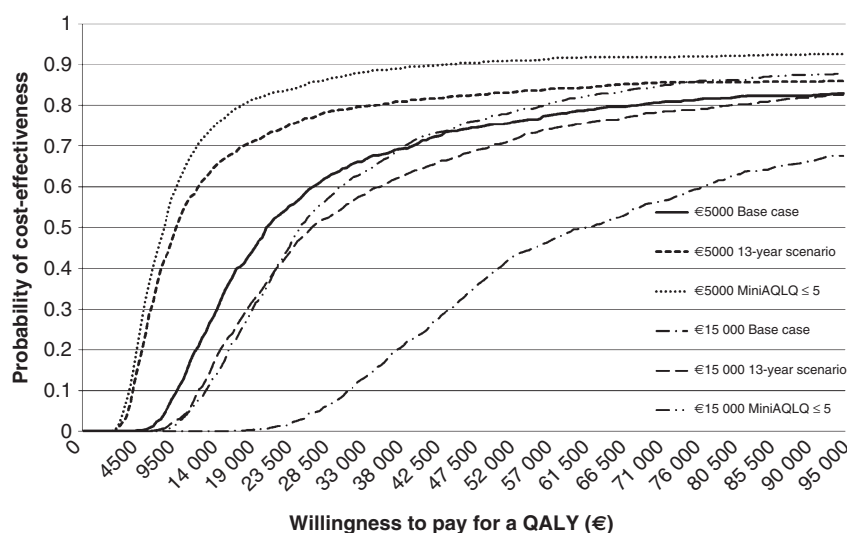


Figure 4. Cost-effectiveness acceptability curve. AQLQ, asthma-related quality of life; QALY, quality-adjusted life year.

Discussion

Although there is no single true value of a willingness to pay for a QALY, our results show that as long as the cost of AA is below €8200, the ICER is below the €35 000 threshold used by the National Institute of Clinical Excellence (14). Also, it has a substantially lower cost per QALY than presented for pharmaceuticals currently in use in Sweden for asthma treatment (11). In addition, AA treatment of patients with more severe asthma (mini-AQLQ < 5) would result in an even lower cost per QALY. Although based on a small sample, the probabilistic sensitivity analysis showed that there is a high probability for the AA treatment to be cost-effective for a wide range of willingness to pay

for a QALY. The gain of QALYs with AA should be compared to gain of QALYs in with other treatments of asthma. Gains of QALY and cost-effectiveness for asthma treatment are, however, to the authors' knowledge, not widely available. Two studies assessing the cost-effectiveness of omalizumab have previously been reported (10, 11). In their base-case analysis, they found that with a 5-year treatment with omalizumab, the patient gained 0.76 and 1.08 QALYs, respectively, over a lifetime perspective. This was however in a population with severe asthma and should therefore primarily be compared with our sensitivity scenario for patients with more severe asthma with a QALY gain of 0.594 over 5 years. In addition, the studies of omalizumab have been questioned for exaggerating the

mortality pertaining to exacerbations (15). So comparing the results from the sensitivity scenario of the study by Brown *et al.* (10) excluding motility because of exacerbations could seem more appropriate. In this scenario they reported a gain of 0.47 QALY (10), and thus a smaller gain than shown in our results for AA.

The study is however subject to a number of limitations, which might have an impact on our analysis. First, it should be noticed that these results are not taking potential effects of exacerbations into account. Earlier publications evaluating the cost-effectiveness of asthma treatments have relied heavily on the treatment effect with regard to the reduced occurrence of exacerbations, leading to a large positive impact on the effect (10, 11). However, these studies, as earlier noted, have been questioned for exaggerating the mortality pertaining to exacerbations (15). In our study, exacerbations were not specifically monitored in the clinical trial. This means that our cost-effectiveness estimates are based on a conservative assumption. If the study had included data regarding exacerbations, then it would most probably result in an even more favorable cost-effectiveness ratio for AA. Second, the choice of time horizon of the use of AA for 5 years is also an assumption introducing some structural uncertainty. However, we would argue that we have taken a conservative approach. The functional lifetime of an AA would be 13 years under normal use. The sensitivity scenarios investigating the impact of the time horizon of 13 years showed that when the cost of AA is below €18 760, the ICER is under conventional values of willingness to pay for a QALY. Also it could be argued that the analysis should be performed with a lifetime horizon capturing the full potential of treating the patients (16). Given the current evidence, and follow-up time of the patients, extrapolating the results to a lifetime perspective does however seem dubious. This means that our estimates are based on a conservative choice as we are not assuming any long-term effects of the AA for the patients' asthma status. Third, to truly reflect the impact on costs, it would be of interest to include not only costs pertaining to the medical treatment but also societal costs in general, capturing factors such as sick leave, travels, etc. Our approach is conservative also in this respect, as applying a societal perspective would most likely make the ICER value for AA treatment even more attractive. In addition, our analysis is based on a rather small sample of patients. This is however accounted for in the probabilistic sensitivity analysis as the small sample leads to wider distributions for the parameters and is thus propagated to the final result as shown in the cost-effectiveness acceptability curve (CEAC) (Fig. 4).

Finally, it should be remembered that our analysis is based on a study population with a specific phenotype of asthma and that the results of this cost-effectiveness analysis can therefore not be automatically generalized to other asthma populations.

From a policy perspective, AA represents a type of non-pharmaceutical treatment that may be used to substitute the more costly pharmaceutical treatment. However, many regulatory bodies, e.g. the Pharmaceutical Benefit Board in Sweden, consider pharmaceutical treatments isolated, not taking alternate non-pharmaceutical treatments into account. Society therefore risks wasting financial resources as well as not maximizing aggregate health if non-pharmaceutical treatments have no opportunities to gain reimbursement. AA is an illustrative example of such a treatment that is regularly overlooked as a treatment alternative since the existing framework regarding reimbursement only considers pharmaceutical treatments.

In conclusion, adding AA treatment to optimized standard therapy for young adults with perennial allergic asthma is generating additional QALYs at a reasonable cost. However, further studies taking more detailed resource use and events such as exacerbations into account would be needed to fully evaluate the cost-effectiveness of AA.

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