NHS England

Evidence Review: Temperature-controlled laminar airflow device for persistent allergic asthma (children)

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Contents

1. Introduction

The UK direct healthcare costs for asthma are over £1 billion per year, of which a high percentage is focused on those with the top quartile of severity-related drug requirements. Such patients require specialist tertiary investigation and care. Detailed assessment is required to establish which patients have truly therapy resistant disease compared with those that have potentially avoidable contributors to high morbidity, such as: poor concordance with therapy, significant co-morbidities (obesity, rhinitis etc), avoidable adjuvants such as cigarette smoke, wrong prescription or wrong diagnosis. Having excluded the former, those with severe persistent allergic asthma are considered for treatment with omalizumab.

This policy has considered the clinical evidence available to support the routine commissioning of temperature-controlled laminar airflow devices for children suffering from persistent allergic asthma as a treatment prior to the consideration of omalizumab.

2. Research questions

Are temperature-controlled laminar airflow devices clinically effective in reducing airway inflammation, sustaining improved asthma control, reducing annual exacerbation rates, and improving quality of life patients with persistent allergic asthma compared with no intervention or with other standardised treatments?

Are temperature-controlled laminar airflow devices cost effective in children with persistent allergic asthma?

3. Methodology

Research questions and a search strategy were agreed with key members of the Clinical Reference Group and NHS England Public Health Lead (See Appendix Two). From this a PubMed search was undertaken. In addition, the Cochrane database was searched for systematic reviews. NICE and SIGN were searched for relevant guidance. Relevant papers were identified through abstract review and are summarized in Appendix One. The Clinical Evidence Review has been independently quality assured.

The evidence review did not consider 'grey' literature (i.e., non published, non peer-reviewed) or evidence outside the search strategy.

4. Results

A detailed breakdown of the evidence is included in the Appendix.

5. Summary of evidence

The evidence review looked to consider the following research questions:
Are temperature-controlled laminar airflow (TCLA) devices clinically effective in reducing airway inflammation, sustaining improved asthma control, reducing annual exacerbation rates, and improving quality of life patients with persistent allergic asthma compared with no intervention or with other standardised treatments? Are TCLA devices cost effective in children with persistent allergic asthma?

Based on the inclusion and exclusion criteria detailed in the appendix, 4 studies were selected for full review. This includes a National Institute for Health and Care Excellence (NICE) Medtech Innovation Briefing published in August 2014. There are two Grade 1- studies, including a randomised controlled trial and one cost-effectiveness study which were both funded by Airsonnet AB. There is one Grade 3 case series which addresses clinical effectiveness in addition to quality of life outcomes.

The best current evidence for use of TCLA devices for persistent allergic asthma comes from a single, relatively large, randomised study (Boyle et al 2012). This study was not designed primarily to evaluate the full effects clinical effectiveness of TCLA such as impact on asthma exacerbations, hospitalisation, emergency room visits and use of medication. The history of frequent or severe exacerbations was not an inclusion criterion. In the included study population, the active and placebo groups showed no statistically significant difference in standard asthma medication use and asthma exacerbations. There was no follow-up of the patients post study period to evaluate long term effectiveness. TCLA treatment was associated with a greater decrease in fraction exhaled nitric oxide (FeNO) than placebo during the study period of one year. There was no significant impact on blood eosinophil counts, total IgE level and overall lung function between treatment groups.

Despite the identified limitations in study design, there is some evidence from the study that TCLA can improve quality of life for patients with more severe and uncontrolled asthma. Of those patients who had at least 1 day of treatment with the Airsonett device, there was a significantly greater proportion with increase in AQLQ score of at least 0.5 points and 1 points compared with the placebo group. Statistically significant improvements using this measure were most noticeably reported in those with poor symptom control (ACT<18) who received high intensity treatment. These differences in improvement of quality of life only reach statistical significance in the subgroup of patients aged below 12 years. The study was powered on subgroup> 12 years.

The other study which specifically addressed questions of clinical effectiveness in addition to quality of life (Schauer et al 2015) is a non-randomized uncontrolled pre and post retrospective observational study to investigate the effect of 12 months' TCLA use in a population of 30 patients (27 finished full 12 month follow-up). Due to small number of patients and the observational study design, the findings from the study cannot be generalised to broader patient population.

Medtech innovation briefing on the Airsonett temperature-controlled laminar airflow device for persistent allergic asthma (NICE, 2014) advises that the device is non invasive and non pharmaceutical. No treatment related adverse events have been identified. Two trials (Boyle et al 2012, Pedroletti et al. 2009) showed statistically significant improvement in asthma related quality of life in people with severe persistent allergic asthma when Airsonett was compared with a placebo device. There was no statistically significant difference in asthma medication usage or exacerbation rates, which were secondary outcome measures in one randomised controlled trial. The second Randomised Control Trial (Pedroletti et al. 2009) was identified as a crossover study with a very small sample size, and no details were reported on the methods of randomisation or blinding. All other studies reviewed had small sample sizes and provided insufficient information to assess their quality.

There is currently very limited published evidence on how the use of the Airsonett device, or similar TCLA would affect NHS resources by either reducing the use of Omalizumab and other alternative treatment options or reducing asthma exacerbations.

The Medtech review advises that the average cost of long term treatment with Airsonett is £5.72 per patient per day. The estimated cost of an add on therapy currently used in NHS practice, Omalizumab, is £23 per day.

The only study on cost-effectiveness of TCLA (Brodtkorb et al 2010) is based on Markov model of QALYs for next 5 year using data from Pedroletti et al (2011). The study concludes that Airshower strategy could result in a mean gain of 0.25 QALYs per patient in Sweden, thus yielding an approximate cost per QALY gained of under £25,571 as long as the cost of Airshower is below £5991 [Original figures provided in euros and converted to the nearest full pound based on conversion rate on 19/10/2015 of £1 to 1.37 euros and is provided as a guideline for comparison only]. The study does not include comparative cost effectiveness with existing comparator interventions such as Omalizumab, immunosuppressant therapy and bronchial thermoplasty.

The UK LASER Trial (Laminar Airflow in Severe Asthma for Exacerbation Reduction) currently underway could provide conclusive evidence regarding the clinical and comparative cost effectiveness of TCLA in patients with Persistent Allergic Asthma.

Appendix One

de	intervention			Outcomes							Reference	Other		
Grade of evidenc	Study design	Study size	Intervention	Category	Primary Outcome	Primary Result	Secondary Outcome	Secondary Result	Study Endpoint	Study Endpoint Result	Reference	Complications noted	Benefits noted	Comments
1-	RCT	312	Active TCLA device installed in patient 's bedroom	Clinical effectiveness of the intervention	Quality of life assessed by the mini-AQLQ, or in children ≤11 years, the PAQLQ. A change of 0.5 is considered clinically significant.	Of those patients who had at least 1 day of treatment with the Airsonett device, there was a significantly greater proportion with increase in AQLQ score of at least 0.5 points compared with the placebo group (odds ratio [OR] 1.92, 95% confidence interval [CI] 1.09 to 3.38; p=0.02). Statistically significant improvements using this measure were also reported in the following patient subgroups: those aged under 12 years (OR 5.57, 95% CI 1.13 to 27.48; p=0.02); those with high intensity treatment (GINA 4) at baseline (OR 2.42, 95% CI 1.05 to 5.60; p=0.04); those with poor symptom control (ACT<18) at baseline (OR 3.45, 95% CI 1.66 to 7.2; p<0.001); those with both GINA 4 and ACT<18 at baseline (OR 4.47, 95% CI 1.48 to 15.19; p=0.009). Measured as an increase in AQLQ score of at least 1 point, the improvement seen in patients having TCLA compared with placebo was significant only in those patients with ACT<18 (OR 2.78, 95% CI 1.36 to 5.67; p=0.005) and those with both GINA 4 and ACT<18 (OR 8.81, 95% CI 2.14 to 36.32; p=0.003).	1. Airway inflammation (fractional exhaled nitric oxide; FeNO), 2. Systemic allergy (specific IgE levels to indoor aeroallergens and blood eosinophil count), 3.Airflow obstruction (forced expiratory volume in 1 s, FEV1; forced expiratory flow at 50% of vital capacity, FEF50; peak expiratory flow, PEF).	1.TCLA treatment was associated with a greater decrease in FeNO (fraction exhaled nitric oxide) during the study than placebo—mean difference −7.1 ppb (95% CI −13.6 to −0.7; p=0.03; table 3), which was of greater magnitude in patients with abnormally raised FeNO (>45 ppb) at baseline (mean difference −29.7 ppb; 95% CI −47.2 to −12.2; p=0.001). 2.There was no significant difference in blood eosinophil counts and total IgE level change between treatment groups. A rise in cat-specific IgE levels relative to baseline level in the placebo group (mean 35%; 95% CI 18% to 53%) and a significantly smaller rise in the active group (mean 8%; 95% CI 0 to 17%; p=0.01;). Lesser increases in levels of specific IgE to house dust mite and dog allergens were also seen in the active versus the placebo group, but the differences between groups were not statistically significant. 3. There was no significant difference between groups in measures of lung function FEV1, FEF50 or PEF	long term asthma control	NA	Boyle, Robert J.; Pedroletti, Christophe; Wickman, Magnus; Bjermer, Leif; Valovirta, Erkka; Dahl, Ronald; Von Berg, Andrea; Zetterström, Olof; Warner, John O.; 4A Study Group. Nocturnal temperature controlled laminar airflow for treating atopic asthma: a randomised controlled trial. Thorax. 2012,	None	Improvement in quality of life	There is clearer evidence on the impact of TCLA in improving quality of life for patients with more severe and uncontrolled asthma. However, the difference in improvement of quality of life by 0.5 points on AQLQ did not reach statistical significance in the subgroup of patients aged 12 years and over, the group on which the study was powered. A key impact of effective asthma management is reduction in emergencies/ exacerbation and reduction in use of medications. This study was not designed primarily to evaluate effects of TCLA on asthma exacerbations, because a history of frequent or severe exacerbations was not an inclusion criterion. In the study population , no statistically significant difference was demonstrated between active and placebo group in asthma exacerbations and standard medicine use. It should be noted that there was a difference (absolute difference ranging from 14.1 to 14.8%) in responder rate between active and placebo group with greater response in active group. and the difference was greatest in those with both high-treatment intensity (GINA 4) and poor symptom control (ACT<18) at baseline.

1-	Other	312	Active TCLA device installed in patient's bedroom	Clinical effectiveness of the intervention	Quality of life assessed by the mini-AQLQ, or in children ≤11 years, the PAQLQ. A change of 0.5 is considered clinically significant.	Of those patients who had at least 1 day of treatment with the Airsonett device, there was a significantly greater proportion with increase in AQLQ score of at least 0.5 points compared with the placebo group (odds ratio [OR] 1.92, 95% confidence interval [CI] 1.09 to 3.38; p=0.02). Statistically significant improvements using this measure were also reported in the following patient subgroups: .those aged under 12 years (OR 5.57, 95% CI 1.13 to 27.48; p=0.02) • those with high intensity treatment (GINA 4) at baseline (OR 2.42, 95% CI 1.05 to 5.60; p=0.04) • those with poor symptom control (ACT<18) at baseline (OR 3.45, 95% CI 1.66 to 7.2; p<0.001) • those with both GINA 4 and ACT<18 at baseline (OR 4.47, 95% CI 1.48 to 15.19; p=0.009). Measured as an increase in AQLQ score of at least 1 point, the improvement seen in patients having TCLA compared with placebo was significant only in those patients with ACT<18 (OR 2.78, 95% CI 1.36 to 5.67; p=0.005) and those with both GINA 4 and ACT<18 (OR 8.81, 95% CI 2.14 to 36.32; p=0.003).	1. Airway inflammation (fractional exhaled nitric oxide; FeNO), 2. Systemic allergy (specific IgE levels to indoor aeroallergens and blood eosinophil count), 3.Airflow obstruction (forced expiratory volume in 1 s, FEV1; forced expiratory flow at 50% of vital capacity, FEF50; peak expiratory flow, PEF).	1.TCLA treatment was associated with a greater decrease in FeNO (fraction exhaled nitric oxide) during the study than placebo—mean difference −7.1 ppb (95% CI −13.6 to −0.7; p=0.03; table 3), which was of greater magnitude in patients with abnormally raised FeNO (>45 ppb) at baseline (mean difference −29.7 ppb; 95% CI −47.2 to −12.2; p=0.001). 2.There was no significant difference in blood eosinophil counts and total IgE level change between treatment groups. A rise in cat-specific IgE levels relative to baseline level in the placebo group (mean 35%; 95% CI 18% to 53%) and a significantly smaller rise in the active group (mean 8%; 95% CI 0 to 17%; p=0.01;). Lesser increases in levels of specific IgE to house dust mite and dog allergens were also seen in the active versus the placebo group, but the differences between groups were not statistically significant. 3. There was no significant difference between groups in measures of lung function FEV1, FEF50 or PEF	long term asthma control	NA	Brodtkorb, Thor-Henrik; Zetterström, Olle; Tinghög, Gustav. Cost-effectiveness of clean air administered to the breathing zone in allergic asthma. Clin Respir J. 2010	None	Improvement in quality of life	There is clearer evidence on the impact of TCLA in improving quality of life for patients with more severe and uncontrolled asthma. However, the difference in improvement of quality of life by 0.5 points on AQLQ did not reach statistical significance in the subgroup of patients aged 12 years and over, the group on which the study was powered. A key impact of effective asthma management is reduction in emergencies/ exacerbation and reduction in use of medications. This study was not designed primarily to evaluate effects of TCLA on asthma exacerbations, because a history of frequent or severe exacerbations was not an inclusion criterion. In the study population , no statistically significant difference was demonstrated between active and placebo group in asthma exacerbations and standard medicine use. It should be noted that there was a difference (absolute difference ranging from 14.1 to 14.8%) in responder rate between active and placebo group with greater response in active group. and the difference was greatest in those with both high-treatment intensity (GINA 4) and poor symptom control (ACT<18) at baseline.

3	Case series	30 patients completing 4 months and 27 patients completing 12 months	Night time TCLA	Clinical effectiveness of the intervention	Intraindividual change in asthma control after 12 months of TCLA use: 1) the number of exacerbations; 2) the need of asthma-related emergency care; 3) the need of asthma related hospital admissions; 4) the need of asthma-related intensive care; 5) the use of oral corticosteroids; 6) changes in asthma control according to ACT index and GINA classification	1) During the 12 months of TCLA use, the exacerbation frequency diminished from an average of 3.6 (range 1-12) to an average number of exacerbations of 1.3 for the whole period (range 0-5; p<0.001). The proportion of patients without any exacerbations increased from 13 to 33% (p<0.05) during the TCLA period. Within the first 4 months of TCLA use, 60% of the participants were free of exacerbations (p<0.001).2)During the 12 months of TCLA use, the patient proportion needing asthma-related emergency room visits was reduced from 72 to 23% (p=0.001). 4) The proportion of patients requiring asthma-related inpatient hospitalization declined from 45 to 20% (p<0.05). No patient needed intensive care treatment after TCLA was introduced as compared with 14% during the previous year, but this difference was statistically not significant.5) The proportion of patients treated with oral steroids decreased during the study from 33 to 22% but the decline was not significant. After 12 months, the number of patients requiring oral steroids was reduced from 10 to 6 individuals. There were no significant changes in the use of inhaled corticosteroids (ICS) or other regular controller medications including the omalizumab dosing. The need for rescue medication, regular short-acting bronchodilators diminished during the 12-month TCLA period but was not statistical significant. 6)After 12 months of TCLA use, the proportion of patients with uncontrolled disease had diminished from 55 to 0%, and the ratio with controlled disease increased from 10 to 34%. The outcome after 4 months approached statistical significance (p=0.0503) but was highly significant (p<0.001) after 12 months TCLA use . The mean ACT score increased significantly during TCLA use, at 4 months from 14.1 to 17.8 (p,0.01) and after 12 months a score of 18.5 was recorded (p<0.0001). The proportion of patients with symptoms of BHR declined significantly during the study, from 73% at baseline to 33% after 12 months (p<0.01).	Lung function, use of relievers, ability to work (or go to school, symptoms of bronchial hyperactivity (coughing etc), frequency of daily and nightly symptoms	There was a trend for daytime symptoms to decline, but this was not significant (p 0.09 after 12 months). However, the frequency of night time symptoms was significantly (p<0.05) lower after 4 months of TCLA use; the difference approached statistical significance after 12 months (p=0.074). The proportion of patients reporting an asthma-related inability to work (or go to school) was lower but did not reach significance. Lung function tests FEV1 values after 12 months of TCLA improved significantly (p<0.01). Changes to other values (PEF, FEV1/FVC) were reported to show numerical changes toward a normalization of lung function but are not significant.	long term asthma control	NA	Schauer, Uwe; Bergmann, Karl-Christian; Gerstlauer, Michael; Lehmann, Sylvia; Gappa, Monika; Brenneken, Amelie; Schulz, Christian; Ahrens, Peter; Schreiber, Jens; Wittmann, Michael; Hamelmann, Eckard; and all members of the German Asthma Net (GAN). Improved asthma control in patients with severe, persistent allergic asthma after 12 months of nightly temperature-controlled laminar airflow: an observational study with retrospective comparisons. 0. 2015	None	See outcomes	This is a non-randomized uncontrolled pre and post retrospective observational study to investigate the effect of 12 months' TCLA use during real-life conditions. While this is the only study which analyses the detailed impact on TCLA on overall asthma management and utilisation of other medication, its limitations in the study design and the small number of patients significantly limit its usefulness.

0	Systematic	NA	NA	Clinical effectiveness of the intervention	NA	NA	NA	NA	NA	NA	National Institute for Health and Care Excellence. The Airsonett temperature-controlled laminar airflow device for persistent allergic asthma. 0. 2014	-	-	Medtech innovation briefings summarise the published evidence and information available for Airsonett TCLA device for use in persistent allergic asthma. Clinical effectiveness: Two relevant randomised controlled trials using the Airsonett device and 4 relevant abstracts of conference proceedings were identified in the clinical evidence review. Airsonett AB also provided data from 2 small case series reports. The trial by Boyle et al. (2012) has been included in this review as it falls within the agreed timeline. Overall, the study was of reasonable methodological quality and reporting quality. The second Randomised Control Trial Pedroletti et al. (2009) was identified as a crossover study with a very small sample size, and no details were reported on the methods of randomisation or blinding. All other studies reviewed had small sample sizes and provided insufficient information to assess their quality. There were also 4 registered trials which, despite being completed, had no associated publications. No studies have yet directly compared the Airsonett device with omalizumab. Cost effectiveness: The cost and resource savings will be realised if the device were shown to reduce the number of severe asthma exacerbations that need medical attention. There is currently no published evidence on how the use of the Airsonett device would affect NHS resources by either reducing omalizumab use or reducing asthma exacerbations. The actual breakdown of the cost /patient is included in the Medtech review.

Appendix Two

Literature search terms

Assumptions / limits applied to search:	
Original search terms:	None
Updated search terms - Population	Asthma*
Updated search terms - Intervention	Airsonett Airshower Protexo Temperature-Controlled Laminar Airflow Temperature Controlled Laminar Airflow TLA device
Updated search terms - Comparator	Oral steroids Omalizumab Xolair Bronchial thermoplasty
Updated search terms - Outcome	None
Inclusion criteria	General inclusion criteria In order of decreasing priority, the following are included: 1. All relevant systemic reviews and meta-analysis in the last 5 years and those in 5-10 years period which are still relevant (e.g. no further updated systematic review available) 2. All relevant RCTs and those in the 5-10 years period which are still relevant (e.g. not superseded by a next phase of the trial/ the RCT is one of the few or only high quality clinical trials available) >>>> If studies included reached 30, inclusion stops here 3. All relevant case control and cohort studies, that qualify after exclusion criteria >>>> If studies included reached 30, inclusion stops here 4. All relevant non analytical studies (case series/ reports etc.) that qualify after exclusion criteria >>>> If studies included reached 30, inclusion stops here 5. Expert opinion

	Specific inclusion criteria
	English language <5 years, <10 years RCTs, SRs, MAs Title/Abstract The following article that is not available on PubMed but has been included for review based on clinician Adam Fox's suggestion, based on its relevance and publication in a reputable journal: Schauer U., Bergmann, K, Gerstlauer, M. Improved asthma control in patients with severe, persistent allergic asthma after 12 months of nightly temperature-controlled laminar airflow: an observational study with retrospective comparisons. 2015. European Clinical Respiratory Journal. 2: 28531.
Exclusion criteria	**General exclusion criteria**
	Studies with the following characteristics will be excluded: 1. Do not answer a PICO research question 2. Comparator differs from the PICO 3. < 50 subjects (except where there are fewer than 10 studies overall) 4. No relevant outcomes 5. Incorrect study type 6. Inclusion of outcomes for only one surgeon/doctor or only one clinical site
	Specific exclusion criteria
	-