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SPECIAL ARTICLE

Asthma Management: Evidence Based Studies and Their Implications for Cost-Efficacy

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SUMMARY **This review attempts to infer a cost-effective strategy for the management of bronchial asthma based on evidence from randomized controlled trials. Acute severe asthma should be treated with short-acting inhaled beta-agonists followed by a short course of oral steroids. Decisions on hospital admission should be made within 1 to 2 hours and prolonged treatment in emergency departments avoided. A comprehensive educational and drug optimizing program will prevent chronic illness and relapse. Educational programs should be brief but intensive, supervised by asthma specialists and incorporate self monitoring of symptoms plus written action plans. Peak expiratory flow monitoring should not be mandated for all patients. Inhaled corticosteroids (ICS) are the most cost-effective drugs for the long term prevention of asthma. ICS should be started at low doses. If the symptoms of asthma are not well controlled by moderate doses of ICS, high dose ICS treatment should be avoided and add on medication prescribed instead. Oral bronchodilators are less expensive add on medication than long-acting inhaled beta-agonists.**

Bronchial asthma is a chronic disease with high and ever increasing global prevalence. In Singapore asthma is currently diagnosed in 1:5 children and 1:20 adults.[1] The dramatic increase in prevalence of asthma, especially among children, in recent decades to "epidemic" proportions has been associated with urbanisation and economic development. It imposes a major economic burden on any nation, especially developing ones, and incurs both direct costs from its treatment and indirect costs from loss of school attendance and work productivity.[1,2] The recent economic turmoil in Asia brings this issue into sharp focus.

Several clinical practice guidelines on the management of asthma have been published.[3,4] These consensus statements do not however agree in many important areas and their recommendations are not entirely based upon good evidence.[5] Guidelines therefore should merely serve as frameworks for a rational approach in applying basic principles to individual patient care. Moreover, none of the guidelines have been developed on the basis of cost-efficacy. Cost considerations, however, are imperative for the practising doctor in South East Asia who faces increasing demand for better treatment, rising costs of asthma care and a diminishing economic pie.

There are few studies which directly address cost-efficacy of specific interventions in asthma management.[6,7] In this regard, the American National Asthma Education and Prevention Program (NAEPP) task force has called for more formal economic studies.[7] By contrast, there are a large number of RCT (randomised controlled trials) comparing the efficacy of different drugs and regimens in the pharmacological treatment of asthma. It is possible, therefore, by matching

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the costs of different drugs and regimens with their clinical efficacy, to make a reasonable choice of the most effective yet least expensive regimens in the management of asthma. This approach should not, however, be viewed as a substitute for formal economic studies of different treatment regimes.

Most of the recommendations of "best" or most cost-effective treatment in this review are therefore inferential and based upon (1) direct measure of comparative efficacy from RCT and (2) an estimate of the costs of competitive drugs, regimens and protocols. This process has been facilitated, in recent years, by a growing number of studies which have directly examined the relative cost-effectiveness of different treatment strategies.

Treating acute exacerbations (Table 1)

Treatment of acute asthma is directed at reducing the airways obstruction, improving pulmonary function, relieving symptoms and preventing further progress of disease.[8] Short acting, beta-2 adrenergic agonists administered via inhalation are the most effective drugs in achieving maximal stimulation of β-adrenergic receptors without causing serious side effects.[8,9,10] They may be delivered via wet nebulizers or metered dose inhalers (MDI) plus large-volumed spacers with equal safety and efficacy.[10,11,12,13] They should be administered over the first 30 to 60 minutes either continuously or in repeat doses. There is uncertainty about the exact maximally effective dose of beta-2 drugs. But, on the basis of controlled dose ranging studies, that cumulative doses of salbutamol from 5.0 to 10 mg via wet nebulization or 2.0 to 3.0 mg via MDI and spacer are probably safe and adequate.[12] The MDI with spacer protocol is cheaper, more widely accessible, and thus more cost-effective than wet nebulization. Subcutaneous adrenaline (1:1,000 dilution, 0.5 ml repeated every 15 to 20 minutes) is an equally effective and cheaper alternative to inhaled beta-2 agents.[14,15,16,17,18] But adrenaline injection is associated with higher risk of cardiovascular side effects and should be reserved for patients who fail to respond to initial inhaled beta-2 treatment.[19] Intravenous infusion of beta-2 agonist is not superior to the inhalational route in the initial treatment of severe asthma.

Anti-cholinergics such as ipratropium bromide are often administered together with beta-agonists for acute exacerbations.[20,21] Rodrigo, in a yet unpublished meta-analysis of 9 studies in 1,416 patients showed that the addition of ipratropium bromide to beta-agonists in emergency room asthma offers a small but statistically significant improvement in pulmonary function plus a reduction in hospital admissions.[22] This report has not undergone peer review and moreover, there is no information on the cost-efficacy of this combined treatment approach

All patients treated for acute severe asthma should receive supplemental oxygen which may be used directly to drive nebulization. Other additional drugs and adjunctive modalities are of no proven benefit and should not be used in initial treatment. They include theophyllines,[23,24] inhaled steroids,[25] magnesium,[26,27,28] mucolytics, antibiotics, helium-oxygen mixtures,[29,30,31] aggressive intravenous hydration, airway lavage, chest physiotherapy and mask applied

Table 1 Initial treatment of acute severe asthma

Drug	Device/route	Each Dose (for adults)	Frequency
Salbutamol	MDI + spacer	100 μg	5 doses every 10 minutes, 3-5x
Sabutamol	Wet nebulizer	2.5 mg	1 dose every 15-20 minutes, 2-3x
Adrenaline	Subcutaneous	1:1,000, 0.5 ml	1 dose every 15-20 minutes, 2-3x

The 3 treatment regimens are equally effective. Adrenaline is the cheapest but associated with the highest risk of systemic side effects. Salbutamol via the metered dose inhaler (MDI) with spacer is cheaper than wet nebulization but requires more supervision.

continuous positive airway pressure.

Two thirds of patients will show rapid subjective and objective improvement following inhalation of beta-2 drugs.[11,32,33] A decision to either admit or discharge patients should be made within 2 hours.[32,33] Protocols which retain patients who do not respond promptly to initial treatment in the emergency department for further therapy may not be cost effective. Straus *et al.*[11] and Rodrigo *et al.*[33] have shown that these patients can be identified early (~30 minutes of starting treatment) by measurement of the Peak expiratory flow rates (PEFR), are unlikely to respond to even more intensive treatment over the next few hours and will require hospitalization and systemic corticosteroid therapy for 4 to 5 days before resolution of the signs and symptoms of severe asthma.

Objective assessment of lung function during the treatment of acute asthma is recommended by all guidelines and most experts. The cost-efficacy of protocols which mandate pulmonary function measurements may depend, however, on the state of current practice. McFadden *et al.*[32] have shown that, in a North American hospital where patients with acute asthma are generally kept for a longer period in the emergency department than most developing countries, protocol directed treatment was more cost-effective than usual care. However, the role of serial PEFR measurements was not rigorously tested in this study from Cleveland since in nearly 50% of cases patients were discharged despite failure to achieve a target PEFR of > 60% predicted. By contrast, we have found that, in Singapore, strict adherence to a PEFR guided protocol resulted in prolonged and more intensive treatment with higher admission rates but not better pulmonary function.[34] This is an area which needs further investigation.

Patients who have been treated successfully for an acute exacerbation continue to have airway inflammation which may persist for days to weeks. They experience relapse rates of between 15% to 20% in the first week. Rowe *et al.*[35] showed, in a meta-analysis, that this relapse rate may be reduced by 58% with a course of oral corticosteroids. Systemic corticosteroid treatment does not have an immediate effect on pulmonary function and its commencement may be delayed for up to 6 hours with negligible effects on clinical outcome in acute asthma.[36] Moreover, oral steroids are as effective as steroid injections. Thus, a 7 to 10 day course of oral prednisolone (~0.5 mg per kg body weight per day) should be prescribed to most patients following emergency treatment of acute severe exacerbations at the time of release from hospital or clinic. The steroid course may be stopped abruptly with no significant effect on symptoms or risk of relapse.[37]

Preventing asthma relapse

The largest direct cost of asthma care is hospital treatment.[1,2] This is incurred mostly by patients with severe and chronic relapsing disease.[2] Intervention programs directed at reducing long term disease severity and preventing relapse have generally followed practice guideline recommendations and focused on (a) patient education, (b) self-management protocols and (c) optimization of drug treatment.[3] The results of controlled studies suggest that both patient-education-self management programs and drug optimisation can be cost effective. The most successful interventions however, are comprehensive programs which incorporate patient education and self management with best drug treatment regimens directed by asthma specialists in conjunction with primary care doctors.[38]

(a) Education and action plans (Table 2)

Gibson *et al.*[39] have shown, in a meta-analysis of 22 randomized controlled studies, that asthma self-management education improves health outcomes for adults with asthma. Greater improvements were noted when education was

Table 2 Education and self monitoring

1.	An intense but abbreviated educational program.
2.	Self management according to symptoms.
3.	Written action plan.
4.	Consider peak flow monitoring only if ≥ 2 hospital admissions per year.
5.	Drug optimization supervised by asthma specialists.

supplemented by written action plans. Taitel *et al.*,[40] in a study which controlled for medical treatment and Weinstein *et al.*[41] in a study on children with severe asthma have confirmed that self-management programs can be cost-beneficial. Ronchetti *et al.*[42] and Kauppinen *et al.*[43] have also shown that abbreviated, and therefore less expensive, educational programs are as effective as elaborate and intensively structured programs. This is consistent with the findings of Cote *et al.*[44] that structured educational programs improve knowledge but may add little to an intensive phase of treatment optimisation supervised by asthma specialists. Furthermore, in an economic analysis which compared two educational programs, Neri *et al.*[45] was unable to show that a complete program was more cost-effective than a reduced program.

The most cost-effective educational program would thus appear to be brief (a single day or session) but intensive (including multi-media presentations and one-to-one hands-on practice) one. It should incorporate a written action plan with treatment guided by self-monitoring of symptoms.

(b) Self monitoring of peak flow

The use of an objective measurement of pulmonary function such as PEFR to guide self management plans is recommended by most guidelines.[3,4] Eight RCT have examined the efficacy of integrating PEFR into self management plans.[44,46-52] The results are inconclusive with 5 out of 8 studies showing no additional benefit from PEFR monitoring (Table 3). In general, PEFR-guided self monitoring appears to have little or no impact among primary care patients with a low level of asthma activity. Objective monitoring may have a role however in patients with frequent severe exacerbations requiring hospital admission (≥ 2 per year).

The problems with home PEFR charting in accordance with current guidelines include poor compliance,[53] lack of agreement on treatment boundaries,[54] failure to consistently predict exacerbations before symptoms[55,56] and over treatment if action plans are strictly adhered to.[57] No cost studies have been conducted with regards to PEFR monitoring. There is little justification in the basis of current evidence to recommend the routine use of PEFR charts in self management programs.[58,59]

(c) Drug optimization (Table 4)

Optimisation of drug treatment is a key element of all intervention programs. Several long term cohort studies have shown that preventive treatment with inhaled corticosteroids (ICS) can improve, often dramatically, the clinical outcomes of patient with chronic persistent asthma.[60,61] With ICS patients experience less symptoms,[60] better pulmonary function,[60,61] superior quality of life,[61] up to 80% fewer hospital admissions[61] and need less rescue medication.[60,61]

Concern about the cost of drugs is the main reason for inadequate treatment of asthma in developing countries.[62] It also partly accounts for the over dependence on

Table 3 Effect of peak flow monitoring on the outcome of asthma: randomized controlled trials

Authors	N	Country	Setting	Exacerbations (per year)	Duration (months)	Outcome
Charlton *et al.*[46]	115	UK	P	not stated	12	no difference
GRASSIC[47]	562	UK	P	< 1.0	12	no difference
BTS[48]	72	UK	P	Not stated	6	no difference
Ignacio *et al.*[49]	70	Spain	H	4	6	improved
Lahdensuo *et al.*[50]	115	Finland	P	"rare"	12	improved
Cote *et al.*[44]	149	Canada	H	2.0	12	no difference
Cowie *et al.*[51]	139	Canada	H	3.5	6	improved
O'Turner *et al.*[52]	92	Canada	P	< 1.0	6	no difference

Exacerbations: number of acute episodes needing emergency care or hospital admission per patient per year before the study;
UK: United Kingdom, P: Primary care, H: Hospital, GRASSIC: Grampian study, BTS: British Thoracic Society.

Table 4 Cost effective preventive treatment

		Adult doses
1.	Start with a low dose ICS	200-400 μg
2.	Wait 6-8 weeks	
3.	Step up to moderate dose ICS	800-1000 μg
4.	Add on oral slow release theophylline	200-300 mg BD
5.	Switch from theophylline to inhaled salmeterol	25-50 μg BD
6.	Alternatively to inhaled formoterol	9-12 μg BD

The patient should proceed gradually from one level to the next (in a "stepped up" approach) should the symptoms of asthma fail to remit. Remission may be defined as fewer than 2 symptomatic episodes per week which require acute relief medication (usually with short acting beta-2 via MDI).

intermittent use of symptom relieving drugs rather than long term preventive medication. We found that only one third of patients who were treated for acute severe exacerbations in an emergency department in Singapore were receiving preventive treatment.[63] And at the primary care level, 40% of patients who had regular nocturnal symptoms (≥ 2 times per week) were not receiving preventive medication. (TK Lim & NC Tan unpublished data). This is not a rational approach as economic analyses conducted among medicaid patients in North America[64] and children in Sri Lanka[65] have shown the cost benefits of introducing ICS. Thus, ICS is cost effective long term therapy in both developed and developing countries. Andersson *et al.*[66] showed in children with newly diagnosed asthma, that inhaled budesonide resulted in 36% lower failure rates and 27% lower health care costs than cromoglycate.

Published guidelines differ regarding the optimal starting dose of ICS. For example, the British Thoracic Society[4] recommends a "step down" approach while the NAEPP work group[3] was equivocal. The "step down" strategy involves starting treatment at a higher dose of ICS in order, presumably, to achieve faster control of symptoms and enhance the patients confidence in the regimen. When symptoms have resolved, usually after 6 to 8 weeks, the dose of ICS can then be reduced. This may not be the most cost effective strategy. Several RCT which compared different start doses of ICS have shown that the asthma may not get better faster with higher starting doses of ICS.[67] Moreover, after 4 to 6 weeks of treatment, all ICS regimens achieve the same quality of symptom control. It may therefore be more cost effective, in the long term, to start with a lower dose of ICS (200-400 μg of budesonide or equivalent) and explain to the patient that it may take up to 2 months for symptoms to subside. For patients with very active disease, it is simpler and cheaper to combine low dose ICS with a 7 to 10 day course of oral corticosteroids.

Should low doses of ICS fail to control asthma symptoms (following at least 6 to 8 weeks of regular administration), the dose of ICS may be increased (in a "stepped up" strategy) to moderate levels (~1,000 μg budesonide or equivalent per day). If the asthma remains poorly controlled despite treatment with moderate doses of ICS, should the ICS be increased to high doses (> 1,000 μg per day) or should another drug be added to the regimen instead? Results from several RCT have been very consistent on this question. They show that it is more effective to add another drug (long-acting bronchodilator) than to administer high dose ICS.[68] Thus, adding a long-acting inhaled beta-agonist (either salmeterol or formoterol) would result in better control of asthma than doubling the dose of ICS.[69] Andersson *et al.*[70] calculated that adding formoterol to budesonide generated marked improvements in asthma control at only a marginal net increase in cost.

Adding a slow-release oral theophylline to ICS results in a comparable degree of symptom control but is cheaper (and therefore also more cost effective) than doubling the dose of ICS. Davies *et al.*[67] in a meta-analysis of 8 RCT studies of add on therapy, concluded that salmeterol (and probably also formoterol) is more effective and associated with fewer side

effects than theophylline. But oral theophyllines, are cheaper than inhaled long acting beta agonists and would therefore be the preferred drug in a cost conscious strategy despite their lower therapeutic index and poorer patient tolerance. Crompton *et al.*[71] have shown in a RCT that bambuterol, an oral long acting beta agonist, was more convenient and less expensive but equally effective in comparison with inhaled salmeterol. Thus, long-acting oral bronchodilators (either theophyllines or beta-agonists) may be more cost-effective add on drugs than inhaled long-acting bronchodilators.

All inhalational drugs should be delivered either via an MDI plus large volume spacer or a dry powder device. Adding a spacer to the MDI may increase drug delivery by up to 100% and, in the long term, more cost–effective than using the MDI alone. After good control of symptoms have been achieved, every attempt should be made to gradually reduce the number and dose of maintenance drugs in order to determine empirically the lowest maintenance dose and therefore least expensive treatment for each patient. Prospective studies have suggested that up to 40% of patients with adult onset asthma may not need long term maintenance treatment.

Leukotriene blockade

Drugs which modify the leukotriene (LT) pathway are the first new class of anti-asthma medication to be introduced in over 20 years.[72] This is a major breakthrough which had arisen from understanding basic pathogenic mechanisms of the disease. Leukotriene inhibitors are administered conveniently as oral tablets to prevent asthma relapse. Placebo controlled studies have documented clinical efficacy and safety in patients with a wide spectrum of disease activity: from mild recent onset to chronic corticosteroid dependent asthma. The clinical role of these new drugs is best defined in direct comparison with current "optimal" treatment regimens. In mild to moderate asthma, low dose ICS have greater clinical efficacy than LT antagonists.[73] With regards to add on therapy, RCT have shown that zafirlukast was less effective than salmeterol[74] while zileuton was comparable to theophylline.[75] Moreover, LT antagonists are more expensive than conventional drugs and their long term effect on the natural history of asthma remains unknown. It is not cost effective therefore to consider LT antagonists as first choice drugs in the long term treatment of asthma.[76,77]

Conclusion

Current practice guidelines and most controlled trials on the treatment of asthma do not provide adequate economic information. But cost-efficacy is the primary concern during therapeutic decision making in a chronic illness such asthma. Economic outcome is emergent area of research in asthma. In the meantime, however, a most cost-effective strategy for the management of asthma may be inferred from results of RCT which compare the clinical effectiveness of different treatment regimens.

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