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Outcome measures are used to monitor the effects of interventions in clinical practice or in formal clinical trials. They may also be used to assess changes within populations either spontaneously or as a result of public-health measures. They are used to monitor the course of illness as part of a management plan or, for larger groups, to identify changes brought about, for instance, by migration or immunization. The choice of outcome measure depends on the age of the child, the complexity of the outcome (for instance, whether its application is to individuals or populations), and the time scale over which it is necessary to detect changes in outcome. The most commonly used outcome measures are clinical symptoms, which are often compiled into scoring systems. Surprisingly, these are often the least well-validated measures of outcome. Physiologic measures, although well validated, are difficult to apply to infants and pre-school children. The role of inflammatory markers is currently limited to research rather than clinical practice. Other outcome measures such as quality of life, impact-of-asthma instruments, and measures to determine the health-economic aspects of asthma are poorly developed in childhood. The right outcome depends on the question being asked, the age of the subjects, and the time scale and complexity over which measurement is required.

Why measure outcome?

All clinical research involves measurement. In relation to childhood asthma, we often wish to measure those features which determine the nature and severity of disease. These include the genetic background, environmental agents, and

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medical services (Fig. 1). These are all inputs. They are of varying importance in the management of children with asthma. For instance, at the moment, we know little of genetic polymorphisms and their role in predicting patterns or severity of asthma, a little more about the importance of environmental agents such as the concentration of the major house-dust-mite antigen Der p 1, and much about certain aspects of medical care such as the availability of drugs administered by nebulizers. The accurate measurement of outcome is probably of more importance (1), and can be considered on a number of levels, from the small-scale patient/doctor interaction to the large-scale impact of asthma on society in general (Fig. 1, Table 1). There are many reasons for wishing to measure outcome.

Measuring the response to an intervention

The rational management of individual patients demands careful measurement of the outcome of diagnostic and therapeutic interventions. This is difficult and can be likened to a clinical trial in which the number of subjects is 1 and there is no control group. The inherent power of such a trial is of course very small. Another problem is that childhood asthma varies not only from day to day but also from hour to hour. This means that the repeatability of any measures of outcome (such as lung function or symptom scores) is poor, reducing the confidence with which one can identify change. For instance, the response to an inhaled β -agonist is often used to support a diagnosis of asthma. The outcome, however, depends not only on the ability to measure lung function, but also on the prevailing level of airway obstruction. A child whose asthma is well controlled

Table 1. Why measure outcome?

• measure the response to an intervention	• single patient
• public health (population) measures	• diagnostic study
• monitor course of illness	• therapeutic intervention
• management of individual patient	• clinical trial
• therapy (management plan)	• therapeutic trial
• organization of care	• management
	(organizational) study
• epidemiological studies	
• secular trends	
• prevalence	
• recognition of risk factors	

may have little airway obstruction and hence only minimal reversibility on one occasion, while exhibiting severe airway obstruction and marked reversibility on another.

Therapeutic interventions over a longer time scale introduce other variables, and all paediatricians will recognize the difficulty of detecting symptomatic improvement in a child with poorly controlled asthma in response, for instance, to the addition of a long-acting β -agonist. To get round the problem of low power to detect a response in an individual, the methodology for “n=1” clinical trials has been proposed (2).

There are two main types of clinical trial which depend on accurate measurement of outcome: therapeutic trials and management (organizational) studies. In the former, the intervention is in the form of a pharmacologic or environmental manipulation, whereas, in the latter, some form of organizational or health-services research (such as a study of primary versus secondary care or of an educational intervention) is under test. Of course, the relevant outcome measures will differ. In the former example, symptom scores, physiologic measures, or health-service utilization (for instance, acute severe episodes requiring hospitalization) would be appropriate outcome measures. For the latter, health-services utilization, quality-of-life, or health-economic measures might be more appropriate.

On a population level, there are as yet no major interventions on the scale of the “back-to-sleep” campaign to reduce cot death, in the field of asthma. Examples of potential population interventions include traffic-reduction measures and environmental tobacco-smoke control. In the future, it is possible that large-scale interventions affecting the indoor environment (for instance, to reduce house-dust-mite levels) will fall into this category of research.

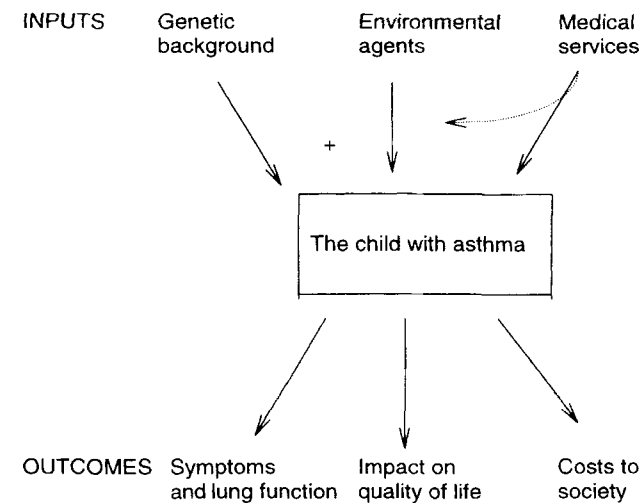


Figure 1. Inputs and outcomes.

Monitoring the course of illness

Variations of the severity of asthma within an individual child may occur in response to therapeutic intervention or may simply represent the “natural history” of disease in that individual. All management guidelines depend on the ability to monitor clinical features within individual patients, responding to change by appropriate alterations in the advice provided through guided self-management plans. Some decisions relate to therapy (i.e., drug management) and others to organization of care (for instance, the decision to manage an individual within primary care, secondary care, or intensive care). Both therapeutic and organizational decisions depend on our ability to distinguish chronic day-to-day symptoms from acute episodes.

Epidemiologic studies are designed to identify secular trends in disease (which may be important in health-service planning), to compare disease prevalence in different groups (whether static or migrant), and to detect early-life risk factors. For these applications, health outcomes may need to be measured over long periods of time and in large numbers of individuals. Much has been learned by the application of standardized questionnaires to repeated cohorts (3) and by repeated examination over long periods of time of individual cohorts (4–6). The International Study of Asthma and Allergy in Childhood (ISAAC) uses standardized methods to compare the prevalence of asthma and wheeze in populations of children throughout the world. By comparing the features of populations with widely disparate prevalences of asthma, clues to the pathogenesis of the disease are likely to emerge (7).

The complexity of outcome measures

Given the wide range of questions for which outcome measures are needed, it is not surprising that the scale of complexity can vary from the molecular to the population (Table 2). Recent evidence that the basis of many of the physiologic features of asthma is to be found in the way in which actin and myosin interact in airway smooth muscle will eventually be translated into direct measurements of smooth-muscle function in response to therapeutic interventions. However, this is an arcane issue beyond the scope of this paper. Examples of some outcome measures at each level of complexity are given in Table 2. Of course, these measures are not independent but interact in all directions. There is no single outcome measure which is appropriate for all clinical or research questions. The appropriate measure

Table 2. Complexity of outcome measure

Scale	Example of outcome measure
Society	Economics of health care
Family	Quality of life
Child	Symptoms
Respiratory system	PaO ₂ or SaO ₂
Airways	Peak flow/spirometry
Cells	Inflammatory markers
Molecules	Smooth-muscle properties

depends on the reason for measuring outcome. For example, from the perspective of the cell biologist, the economics of health care is remote, while, for the clinician, measures which depend on cell or molecular biology are irrelevant to the immediate demands of clinical practice. For the intensivist, the immediate concern is to maintain “vital functions”; thus, the overall function of the respiratory system, represented by measures of gas exchange, is the immediate and overwhelming concern.

Duration of outcome

Interventions operate over a wide range of time scales (Table 3). For instance, the response to a bronchodilator challenge test is determined within minutes, while the response to an intervention in the perinatal period, to reduce allergic sensitization, may not have its full beneficial effects for many years, perhaps not until adult life is reached. In general, studies on individual patients require a relatively short period of observation to detect an outcome, whereas population programmes are likely to require repeated periods of observation, lasting for several years.

The issue of duration of observation introduces several problems, of which the following are commonly met examples. The repeatability of clinical observations tends to deteriorate with time for individual subjects, reducing our ability to evaluate an intervention. For studies over long

Table 3. Duration of outcome

Time scale	Example of intervention
Minutes	Bronchodilator challenge
Hours	Treatment of acute severe asthma
Days/weeks	Guided self-management
Weeks/months	Environmental measures
Years	Trials of early intervention

periods of time, the precise wording of questionnaires and the availability of identical quality-controlled physiologic measurement equipment are important in minimizing measurement error and bias. For very long-term studies, one of the major constraints is funding, since few charitable or government funding bodies will agree to support research over periods longer than 5–7 years, let alone the decades which will be required to determine whether early-life interventions have beneficial (or indeed harmful) long-term effects.

Development stage

Outcome measures which are appropriate for infants may not be appropriate for adolescents or adults. The most obvious example, physiologic measurement, is illustrated in Table 4.

Age of subjects

Symptom scores, quality-of-life scales, and health-economic measures are all different for infants, schoolchildren, and adults. Therefore, choice of the right outcome will be determined by the age of the subjects. The pattern of symptoms, the level of cooperation with physiologic measurement techniques, and the role of children in society all vary with age.

The nature of asthma

Of potentially greater importance than age itself is the fact that the nature of wheezing disorders changes substantially with age. Asthma in the first 2 years of life may be an entirely different disorder from asthma in a schoolchild or adult, requiring a different approach, different interventions, and different measures of outcome (8). Even on the level of symptom patterns, there are major differences in the assessment of infants and schoolchildren. The youngest children have mainly episodic symptoms in which cough is a particularly important feature, whereas schoolchildren

with atopic asthma suffer a variable level of day-to-day wheeze and chest tightness, as well as suffering from acute episodes in response to viral respiratory tract infection. Inflammatory markers appropriate to monitor the level of inflammation in a schoolchild with atopic asthma may not be relevant to the asthmatic infant and pre-school child (9, 10).

What types of outcome measure are useful?

Symptoms

In spite of the importance of symptoms in clinical assessment and in the measurement of outcome, they have received relatively little attention compared with the huge research effort which has been focused on physiologic measurement. Symptoms are of primary importance to children and their families. Hence, management plans which have been heavily based on peak-flow measurement have not been generally welcomed in paediatric practice. Quality-of-life scores are heavily symptom-based, and almost all the epidemiologic surveys are dependent on the recognition of a single symptom: wheeze.

Even the meaning of the term “wheeze” differs between individuals within a single society (encompassing, for instance, rattly breathing, upper respiratory tract noises, and, on occasion, inspiratory stridor!), between language groups (as illustrated by the problems experienced by the ISAAC study), and between children and their parents (as indicated by the apparent differences in the prevalence of asthma when children rather than their parents are asked about the occurrence of recent wheezing) (11). Many young children develop transient wheezing associated with colds, and the significance of this in relation to persistent or troublesome daily wheeze in atopic schoolchildren is as yet unclear (13).

Pre-school children develop largely episodic wheeze associated with viral infections. Most scoring systems and questionnaires fail to distinguish clearly between day-to-day variations in the level of wheeze and acute severe episodes. Indeed, it may be impossible to do so in a child with severe chronic asthma in whom the daily symptoms merge imperceptibly into more severe episodes. Thus, the recognition of acute episodes is itself biased by the level of interval symptoms. It is paradoxically easier to recognize acute episodes in pre-school children in the absence of interval symptoms than in older, inherently more severely asthmatic schoolchildren. A technique has been described for identify-

Table 4. Developmental stage

Age of subject	Physiologic measurement technique
Infancy	Rapid thoracic compression
Pre-school child	Rint; oscillation mechanics
Schoolchild	Peak flow
Adolescent/adult	Spirometry

ing acute episodes based on peak-flow measurement, but this has not been tested on daily symptom scores (12). In addition to questions of the validity, repeatability, specificity, and sensitivity of symptoms such as wheeze in cough, there are even greater concerns when symptoms are lumped together to produce overall clinical scores. These have largely been used as outcome measures for therapeutic trials in acute severe asthma in inpatient settings (14).

Poor reproducibility and poor validation of scoring systems mean that they cannot be generally recommended as outcome measures.

In summary, for young children, clinical scores are all that we have. Nevertheless, they have enormous defects. Perhaps only within centres and after careful standardization can symptoms alone be used as valid outcome measures for interventions. Where they are used in epidemiologic studies, particularly for the determination of prevalence of asthma, even well-standardized questionnaires based on the prevalence of wheeze lead to more questions than answers.

Physiologic measures

The measurement of lung function is of secondary importance to most children with asthma, with the exception of individuals whose ability to perceive the level of airway obstruction is poor. The most widely used measure of lung function, peak flow, is appropriate only for children over the age of 6 or 7 years, is very much dependent on device and technique (15), is insensitive to peripheral (small) airway obstruction, and is very insensitive in comparison, for instance, to flow-volume measurement. On the other hand, spirometric measurements which may be appropriate under very carefully controlled conditions in the clinic setting are technically difficult for children to perform and are almost always inappropriate for frequent home monitoring for the measurement of asthma from day to day. Nevertheless, for short-term measurement of the response to bronchodilator or bronchoconstrictor challenge and for therapeutic studies in acute severe asthma in hospital where measurements are taken under controlled conditions, both peak-flow and spirometric indices are valuable.

Particular problems beset those who wish to study infants and pre-school children. Here the range of physiologic measurement is restricted, experience is limited, and physiologic outcome measures are appropriate only within carefully conducted research protocols (16).

Inflammatory markers

Anti-inflammatory interventions in childhood asthma are often based on assumptions about the nature of inflammation which have yet to be verified. It is only recently, for instance, that we have had conclusive evidence that the inflammatory processes accompanying transient episodic viral wheeze in young children differ from those which are found in persistent asthma (9). Nevertheless, it is possible to obtain direct cellular evidence of inflammation from nasal samples, induced sputum, or bronchial lavage in children, and indirect samples of inflammatory mediators from airway secretions, blood, or urine in children. All but bronchial lavage would appear to be feasible and ethically justifiable as means of investigating the outcome of anti-inflammatory interventions in children in general. The ideal means of monitoring airway inflammation has yet to be developed. A urinary dipstick distinguishing pulmonary inflammation from inflammation elsewhere, and providing the spectrum of inflammatory mediators involved in the inflammatory process would be an ideal solution of the problems in making direct measurements of lower airway inflammation in young children. Such a device has yet to be invented but would facilitate the identification of subsets of asthma, leading to targeted interventions and specific measures of outcome.

Impact scores (quality of life)

Health-related quality-of-life instruments measure the impact of asthma on the daily life of patients. The concept of "domains" demonstrates that quality-of-life scores are not simply fashionable alternatives to symptom diaries. They record aspects of life such as the emotional impact of disease and its effect on daily activities which are not generally recorded in symptom diaries. Although little used in a formal sense in clinical practice, there is increasing awareness of their role in pragmatic clinical trials in particular, because it seems possible that the impact of an intervention on the quality of life will determine the likely adherence to therapy and the use of health resources. While these have not been of much interest to hospital-based paediatricians in the past, they are clearly important in the wider context.

A number of well-validated measurement tools have been developed and recently reviewed (17). They are least well established for pre-school children.

Quality of life should not be used as an outcome measure alone. Only by measuring the impact of asthma in

Table 5. Questions for which answers are sought

	Individual	Group
Prediction	Will my child outgrow asthma?	Can children at high risk of pre-school wheezing be identified?
Preventive intervention	How much has removing the family cat reduced the severity of this child's illness?	How, when and for how long should the outcome of allergen avoidance in infancy be measured?
Therapy	How can we monitor the response to this child's treatment?	How and when should the outcome of a therapeutic trial be measured?

conjunction with other important outcome measures (such as symptoms, lung function, and evidence of continued inflammation) can a complete picture be developed. It is usually inappropriate to measure any one of these alone. If, for instance, it is felt to be important to minimize airway inflammation because the long-term outcome for airway function might thereby be improved, with little or no short-term gain, quality of life early in childhood might possibly deteriorate. Under these circumstances, quality of life could not be an outcome measure but would merely be a means of identifying potential causes of poor compliance with early intervention. On the other hand, a form of treatment which had little effect on "objective" measures of lung function or on symptoms could significantly improve the quality of life (perhaps by reducing the frequency of treatment during the day). Quality of life might be a very valuable and positive measure of the outcome of a change in treatment.

On a population scale, the impact of intervention on provision of health service is an important issue for planners and politicians. The means of measuring the health-economic aspects of childhood asthma have barely been

tackled. In particular, for pre-school children, these include not only direct health costs but also the indirect effects of disease on parents' fitness for work and earning capacity.

Conclusions

Whether measuring clinical outcome in any single individual or determining the result of an intervention within a group of subjects, the first question to be asked is "Why is a measure of outcome required?" (Table 5). Only then is it possible to decide how to measure outcome, when to make the measurements, and how long to continue to record outcome. The dimensions of asthma (duration, complexity, and the age of the subjects) provide the answer to the question, "How should we measure outcome?" For some types of outcome measure and for certain age groups (in particular, pre-school children), not all forms of outcome are currently measurable. This is an important item on the agenda for future research in the field of childhood asthma.

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