

Review article

GINA guidelines on asthma and beyond*

Clinical guidelines are systematically developed statements designed to help practitioners and patients make decisions regarding the appropriate health care for specific circumstances. Guidelines are based on the scientific evidence on therapeutic interventions. The first asthma guidelines were published in the mid 1980s when asthma became a recognized public health problem in many countries. The Global Initiative on Asthma (GINA) was launched in 1995 as a collaborative effort between the NHLBI and the World Health Organization (WHO). The first edition was opinion-based but updates were evidence-based. A new update of the GINA guidelines was recently available and it is based on the control of the disease. Asthma guidelines are prepared to stimulate the implementation of practical guidelines in order to reduce the global burden of asthma. Although asthma guidelines may not be perfect, they appear to be the best vehicle available to assist primary care physicians and patients to receive the best possible care of asthma.

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Clinical guidelines are systematically developed statements designed to help practitioners and patients make decisions regarding the appropriate health care for specific circumstances (1). Guidelines have existed for decades and hundreds have been published for many diseases (2) including asthma (3–6) and allergic rhinitis (7, 8). Clinicians are being inundated by a tidal wave of guidelines. In addition to numerous clinical guidelines, a number of 'guidelines for guidelines' have been produced (1). The goal of guidelines is their wide dissemination within the medical community to all health care professionals and patients in order to improve patients' care. There are also potential benefits, limitations and harms of clinical guidelines which should be weighted (2). Guidelines need constant updating and revision in order to follow the scientific evidence.

Guidelines are based on the scientific evidence on mechanisms and therapeutic interventions. Bronchial inflammation in asthma was not recognized until the 1980s (9–11) and before 1985, inhaled corticosteroids (ICS) were rarely the first line treatments (12) although their efficacy had been demonstrated (13). Interestingly, combination therapy was found to be the most effective treatment of asthma (14–19). Bronchial remodeling was a later focus of attention (20), but to date there is no treatment convincingly reducing remodeling. Finally, asthma co-morbidities are not sufficiently well embedded in most asthma guidelines whereas most asthmatics have rhinitis (8). There is therefore an evolving concept of asthma (Table 1).

The first asthma guidelines were published in the mid 1980s when asthma became a recognized public health problem in many countries, particularly in Australia and New Zealand (21). Although the prevalence of asthma is still increasing in many but not all countries (22), mortality and morbidity have decreased in countries where asthma guidelines have been published and asthma plans implemented (23). The role of asthma guidelines is apparently important but, due to a new understanding of the disease, the recent updates focus more on control than on severity (24, 25, 26).

Abbreviations: ANAES, Agence Nationale d'Accréditation et d'Evaluation en Santé; ARIA, Allergic Rhinitis and its Impact on Asthma; EMEA, European Agency of the Evaluation of Medicinal Products; EBM, evidence based medicine; IPCRG, International Primary Care Respiratory Group; ISAAC, International Study of Asthma and Allergy in Children; NHLBI, National Heart Lung and Blood Institute; NIH, National Institutes of Health; RCT, randomized controlled trial; SIGN, Scottish Intercollegiate Guideline Network; WHO, World Health Organization.

*In memoriam to Professors Romain Pauwels and Ann Woolcock

Table 1. Evolution of concepts for the treatment of asthma

	First line treatment	Uncontrolled asthma*
1980–85	Short acting β_2	Add ICS
1985–90	ICS	Add short acting β_2
1989–94	ICS	Increase ICS dose
1994–97	ICS	Increase ICS dose consider adding LA β_2
1997–99	ICS	Add LA β_2 if needed increase ICS and/or add LTRA
2000–	ICS if ICS naive ICS + LA β_2 if ICS treated	Add LA β_2 (or LTRA) Increase ICS and/or add LTRA

*: short acting β_2 always used as rescue medications.

ICS: inhaled corticosteroids, LA β_2 : long acting β_2 agonist, LTRA: leukotriene receptor antagonist.

In this table theophylline was not considered.

Moderate persistent asthma is defined according to GINA (6).

Needs for guidelines in the management of asthma

Asthma is one of the most common chronic pathological conditions throughout the world and has been the focus of clinical and public health interventions during recent years. It is estimated that around 300 million people in the world currently have asthma (27).

In the 1980s, the severity of asthma had only just become clearly understood. Asthma prevalence, morbidity and mortality were found to increase in all age groups, but particularly in children (28–30). Asthma was found to affect the social life of the patients (31), and to be a leading cause of school (32) and work absenteeism (33). Many asthma deaths were shown to be preventable, due to suboptimal long-term medical care and delay in obtaining help during the final attack. Moreover, it was felt that the majority of asthma sufferers should be able to lead normal or nearly normal lives if properly treated.

These considerations led to an increased awareness of asthma, and guidelines for optimal management were developed first in the areas of the world where the asthma burden was the most severe, and then world-wide.

In 2007, guidelines and their updates will continue to be needed because many patients are still uncontrolled (34–37) and new studies constantly produce either a new treatment or a better understanding of the current treatments.

Development of guidelines

The development of clinical guidelines should follow a strict process which is now well established by several organizations including WHO, NIH, SIGN (<http://www.sign.ac.uk>) and the ANAES (<http://www.anaes.fr>).

The first guidelines were proposed using experts' opinions based on clinical trials and mechanistic

Development of guidelines

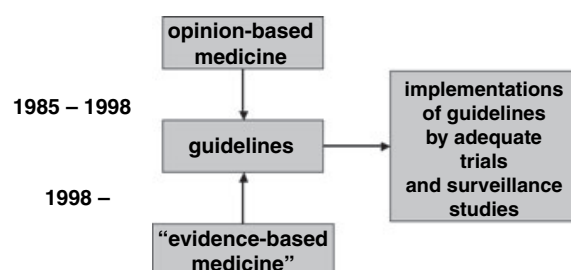


Figure 1. Development of guidelines

approaches (Opinion-based medicine) (Fig. 1). 'Evidence-based-medicine' (EBM) has become an essential component in the preparation of guidelines. This is used to track down, critically appraise (for its validity and usefulness) and incorporate the information obtained from randomized controlled trials (RCT) in order to establish the clinical bases for diagnosis, prognosis and therapeutics (38, 39). Evidence-based medicine attempts to provide a logical and convenient framework from which the quality and relevance of clinical studies may be assessed in an unbiased manner (40). Systematic reviews contribute to the resolution of uncertainty when original research, reviews and editorials disagree (41). The Cochrane Collaboration has led the way in setting new standards for preparing systematic reviews (42) even though some criticisms exist (43, 44). It is also clear that RCTs only study highly selected patients and are far from representing the entire population. An example of this are smoking asthmatics for whom there is little available evidence available to make the best treatment recommendations, as they are often excluded from RCTs in asthma. Moreover, compliance to treatment, a major problem of asthma management, is far better in RCTs than in real life (17). Thus, the conclusions raised from EBM are not applicable to the entire population of asthmatic patients.

Although progress has been made in obtaining reliable evidence on the beneficial effects of interventions, developments in the identification, interpretation and reporting of harmful effects is more challenging (45, 46). RCTs do not sufficiently assess the side effects of treatments, and post-marketing surveillance is required. There is an urgent need for better evidence regarding side effects (risks) (47). The debate on the safety of long-acting β_2 -agonists (48, 49) exemplifies this important issue concerning risk assessment in guidelines.

The recommendations follow criteria which may differ from country to country. In the US, a guide is proposed (50, 51), whereas in Europe and at WHO, an alternative is used (52). More recently, a complex evaluation was proposed. This was based on evidence with a net benefit

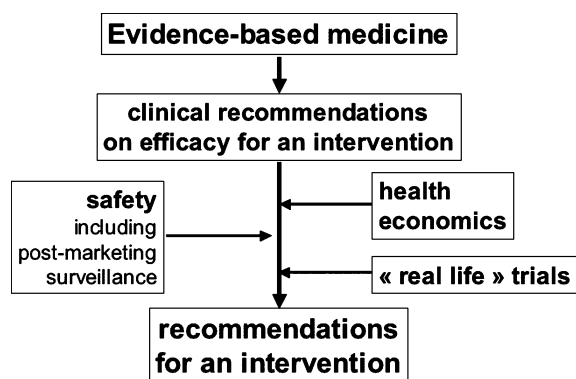


Figure 2. From evidence based medicine to recommendation for an intervention.

for the patient and adjusted for risk (47). However, this proposal is still evolving.

Use of guidelines

Opinion leaders

It is important that guidelines should be accepted by opinion leaders in their respective countries as they have a significant impact on their dissemination. However, certain new information which does not fit with current belief may not be easily accepted. An example of this is the case for the tertiary prevention of allergy which is still promoted at variance with the evidence (53).

Practicing clinicians

The development of sound guidelines does not ensure their use in practice. This has often been demonstrated for the management of asthma (54–59). Systematic reviews of strategies for changing professional behavior show that relatively passive methods of disseminating and implementing guidelines (by publication in professional journals or mailing to targeted healthcare professionals) rarely lead to changes in professional behavior (60). An intrinsic gap exists between the publication of guidelines and clinical practice (61). The role of EBM and guidelines is not to discount expert opinion (62) but, wherever possible, to require that recommendations be based on the results of rigorous and controlled scientific study. Barriers to the use of guidelines include lack of relevant evidence, newness of the concept, impracticality for use in day-to-day practice and negative impact on traditional medical skills and ‘the art of medicine’.

Patients

Patients now have access to evidence-based, online health information leading to a new dimension of EBM and guidelines (63, 64). Many patients bring health

information from the internet to the consultation (63). Moreover, involving patients in the planning and development of health care has contributed to changes in the provision of services across a range of different settings (65). Patients were involved in the development of the ARIA guidelines (8).

Education of health professionals

It is widely believed that the education of health professionals should be more evidence based (66) and that some benefits can be gained (67). Evidence in education should include not only formal, research-derived knowledge but also tacit knowledge (informal knowledge, practical wisdom and shared representations of practice) (68). However, EBM is not generally fully implemented in graduate and postgraduate education.

Policy makers

Guidelines are also needed to inform policy- and decision-makers about the organization and delivery of health and social care (69–71). A distinction should be made between practice policies (use of resources by practitioners), service policies (resource allocation, pattern of services) and governance policies (organizational and financial structures) (72).

Regulatory authorities

Guidelines are also used by regulatory authorities for the registration of treatments. This was the case for omalizumab which was specifically approved for uncontrolled severe asthmatics (GINA step 4) by the EMEA (73). Although it is important to target patient groups in the development of anti-asthmatic treatment, this may have some negative effects since guidelines are constantly evolving.

From opinion-based to evidence-based guidelines: 15 years of asthma guidelines

The first guidelines on asthma

Guidelines prepared in Australia and New Zealand were among the first asthma guidelines, probably because of the asthma death epidemic of the 1980s (74). These guidelines were based on the opinion of experts and their goal was to reduce asthma deaths and morbidity (21). It is interesting to note that they were also published in nurse journals (75).

An international meeting was held in Toronto (Canada) in May 1989 to develop a standardized approach to the assessment and treatment of asthma (76).

These guidelines were based on severity and attempted to achieve asthma control.

Table 2. Assessment of control in the NHLBI/GINA and UK guidelines

Control of asthma	
BTS/SIGN: GOALS (77)	GINA/NHLBI: GOALS (4, 6, 50)
<ul style="list-style-type: none"> • Minimal symptoms during day and night • Minimal need for reliever medication • No exacerbations • No limitation of physical activity • Normal lung function (in practical terms FEV₁ and/or PEF \geq 80% predicted or best) 	<ul style="list-style-type: none"> • Minimal (ideally no) chronic symptoms, including nocturnal symptoms • Minimal (ideally no) use of <i>prn</i> β_2 agonist • Minimal (infrequent) exacerbations • No emergency visits • No limitations on activities, including exercise • PEF circadian variation of less than 20% • (Near) normal PEF • Minimal (or no) adverse effects from medicine

UK and National Heart, Lung, and Blood Institute (NHLBI) guidelines on asthma

In 1990–1991, two major guidelines were published (4, 77). These were well referenced and, for many years, represented up-to-date documents due to their publication in important journals. They had a great impact on the management of asthma. Both were opinion-based and graded according to severity based on the following: the level of symptoms, reliever medications, airflow limitation and its variability. Although there were some variations between them (4 or 5 steps), they both aimed at the control of asthma (Table 2) and proposed an early controller treatment based on inhaled corticosteroids. These documents were updated using the opinion of experts (78, 79).

International consensus on asthma and the Global Initiative for Asthma (GINA)

To enhance health professional education around the world, the USA's National Heart, Lung and Blood Institute (NHLBI), under the direction of Dr Claude Lenfant, initiated an International Asthma project in 1991 and culminated in early 1992 with *The international consensus report on the diagnosis and management of asthma* (5). This report was widely distributed, reprinted and translated into many languages.

It was recognized, however, that the mere existence of such guidelines would not necessarily improve the outcome for those with asthma. The Global Initiative on Asthma (GINA) was therefore launched as a collaborative effort between the NHLBI and the World Health Organization (WHO). The first phase of this initiative was the production of a report that reflected the most up-to-date clinical practice in relation to asthma. This report, *The global strategy for asthma management and*

prevention, was published at the beginning of 1995 and covered more issues than the previous international report (6). *The global strategy* contains important sections on epidemiology, the pathogenesis and prevention of asthma, as well as chapters on treatment and education. The international panel appreciated the difficult financial situation prevailing in many countries. Although preferred treatments were highlighted, the report covered all acceptable therapies and included a well-referenced review of complementary therapies as well as sections on health economics, implementation of guidelines and organization of care.

The second phase of the GINA project was to produce materials to help improve the delivery of care to those with asthma. The following short documents based on the report were published:

- Asthma Management and Prevention: A Practical Guide for Public Health Officials and Health Care Professionals, highlights from the workshop report (6).
- Pocket Guide for Asthma Management and Prevention, a summary of patient care information for primary health care professionals.
- What You and Your Family Can Do About Asthma, a patient information booklet. Technical discussions on asthma and asthma management as well as specific citations from the scientific literature are included in the complete report.

These landmark GINA documents, which present guidelines for asthma management, take into account the new scientific and sociologic understanding of asthma in different settings.

Other opinion-based guidelines

Pediatric guidelines. Asthma often starts in infancy and childhood and there are specific problems related to this condition in pre-school children as well as in adolescents (80, 81). Many pediatricians felt that guidelines for asthma did not sufficiently cover these aspects and proposed guidelines specific to children (82–86).

International consensus of asthma and GINA-based guidelines. These two guidelines raised considerable interest and were adapted by several countries, one of the first being Japan (87). An interesting initiative was the development of asthma guidelines in a region such as the Caribbean, where asthma prevalence is very high (88).

Practice parameters. In the US, several practice parameters have been published (89, 90).

Guidelines for developing countries. One of the important questions was whether asthma guidelines were applicable to developing countries (91). In 1992, guidelines were proposed in South Africa (92), but they were not totally

devised for developing countries. This is why the International Union against Tuberculosis and Lung Diseases (IUATLD, now renamed the UNION) has published guidelines derived from the first GINA document and specifically targeted to developing countries (93). In particular, these guidelines were focused on the WHO essential list of drugs.

Guidelines for deprived populations. It appeared that guidelines were difficult to apply in deprived populations (94, 95). In the NAEPP inner city asthma plan (96), appropriate asthma care was delivered to deprived populations and asthma morbidity decreased considerably (97).

Evidence-based updates and new guidelines. An important question in the development of guidelines is when they should be updated (98). Many deficiencies were identified in early guidelines, especially those using an opinion-based format (99). It was therefore important to update guidelines using EBM.

GINA guidelines (50), NHLBI guidelines (100), guidelines from the UK (101), Canada (102–105) or the UNION (106) were updated using the EBM format.

All of these guidelines only consider asthma alone whereas the vast majority of asthmatics have rhinitis and/or rhinosinusitis (107). The ARIA guidelines were developed using the EBM model and approached the patient more globally integrating the management of asthma and rhinitis (8). Primary care physicians and patients participated in the development of ARIA. The ARIA guidelines have been extensively disseminated and the pocket guide was translated into over 50 languages. Moreover, the ARIA guidelines had a specific target towards pharmacists (108) who represent a very important group of health care workers due to the fact that many asthmatic patients do not consult physicians.

In the first documents, primary care physicians were not included and there was a lack of communication (109, 110). IPAG (111) and IPCRG developed guidelines for use in primary care (112–117). The interest of the IPAG guidelines is that they combine asthma, rhinitis and COPD diagnosis and treatment tracks (111). In the IPAG guidelines, assessment and therapy recommendations

were developed from the GINA, GOLD and ARIA evidence-based practice guidelines for asthma, rhinitis and COPD.

However, all these guidelines used asthma severity as a guide for the management of the disease.

From severity to control: 2004–2007

The classification of asthma by severity raised concerns (118, 119). It is important to recognize, however, that asthma severity involves both the severity of the underlying disease and its responsiveness to treatment. Thus, the first update of the GINA guidelines defined asthma severity depending on the clinical features, pulmonary function as well as the current treatment of the patient (50). In addition, severity is not an unvarying feature of asthma, but may change over months or years, whereas the classification by severity suggests a static feature. Responsiveness to treatment is heterogeneous however, even among asthmatic patients with asthma of similar severity. Moreover, the use of severity as an outcome measure has limited value in predicting which treatment will be required and what the response to that treatment might be (120). These considerations suggest that the classification of asthma severity is no longer recommended as the basis for treatment decisions and call attention to the importance of assessing asthma control and adjusting treatment accordingly (121, 122).

Two guidelines, already published using asthma control, proposed that a periodic assessment of asthma control is relevant (24, 25). The GINA 2006 revision (26) is also based on control (Table 3 and Fig. 3).

GINA guidelines and beyond

Implementation and application of asthma guidelines

As for any guideline (123), the ultimate goals of GINA are (1) to translate evolving science on asthma into recommendations for the management and prevention of asthma and (2) to stimulate the implementation and evaluation of practical guidelines in order to reduce the global burden of asthma (124).

Table 3. Levels of asthma control in the GINA revision (2006) (26):

Characteristic	Controlled	Partly controlled (any measure present in any week)	Uncontrolled
Daytime symptoms	None (or minimal)	More than twice/week	Three or more features of partly controlled asthma present in any week
Limitations of activities	None	Any	
Nocturnal symptoms/awakening	None	Any	
Need for reliever/rescue treatment	None (or minimal)	More than twice/week	
Lung function (PEF or FEV ₁)	Normal or near-normal	<80% predicted or personal best (if known) on any day	One in any week†
Exacerbations	none	One or more/year*	

* Exacerbations occurring more than once a year should prompt review of maintenance treatment to ensure that it is adequate.

† By definition, an exacerbation in any week makes that an uncontrolled asthma week.

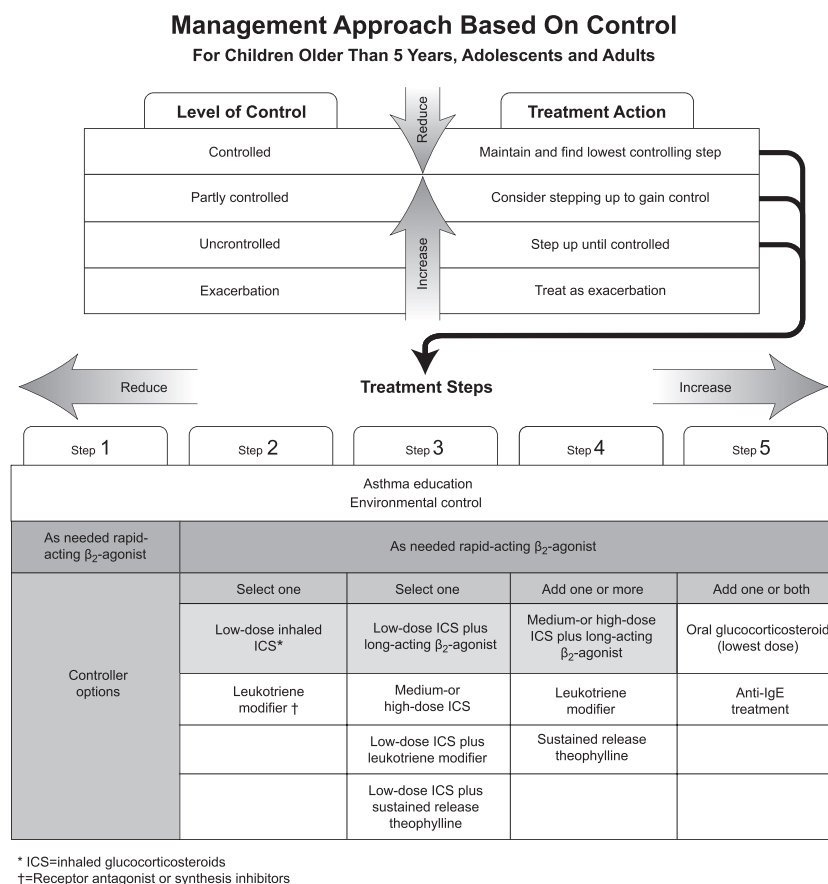


Figure 3. From evidence based medicine to recommendation for an intervention.

For these purposes, the following points are essential:

- GINA guidelines should be implemented at all levels from the asthma specialist to the health care worker. Whereas the guidelines should only be based on scientific evidence, it is clear that their application at country level should follow other considerations including barriers (125, 126), health priorities, health care systems and resources of the country.
- Treatment availability and affordability (cost-effectiveness studies are of paramount importance at the country level) are essential. The Asthma Drug Facility is a new mechanism that will provide access to affordable good quality essential asthma drugs (127).
- The number of countries in which GINA guidelines are implemented should be increased.
- The awareness of asthma world-wide should be developed.
- Asthma should be regarded as an important disease by health care planners.
- The GINA initiative on asthma should provide an effective treatment to all asthmatics whatever the socio-economic status of the country.

- There is a need for the development of more effective procedures to communicate key information to both caregivers and patients, and to promote appropriate health behaviors. A symposium in Canada contributed to the initiation of what could become the 'Canadian Asthma and COPD Campaign', aimed at improving care and, hence, the quality of life of those suffering from these diseases (128).

These requirements are sound since guidelines have been shown to significantly reduce the severity and mortality of asthma in countries or areas where management plans have been implemented (97, 129, 130).

An example is the implementation of GINA guidelines in Latin America and in Brazil (131). Asthma hospitalizations are very common in children living in some countries and lead to high costs for the health systems of those countries. Unfortunately, Latin America has limited resources for the payment of appropriate treatment. The main goals of the international guidelines for asthma treatment are not being met. However, in Brazil, asthma programs have shown a considerable reduction in asthma hospitalizations among children living in deprived areas. The local adaptation of inter-

national guidelines has now been implemented in order to decrease costs and optimize outcomes.

Implementation is largely discussed in the new GINA guidelines (26) as it is of great importance for the benefit to the patients.

From guidelines to asthma plans

An asthma action plan based on current guidelines has been proposed by the Health Ministry in some countries such as Brazil, Finland (132), France (133), Portugal and the NAEP in the USA (<http://www.nhlbi.nih.gov/guidelines/asthma/>). The main goal of this plan is to lessen the burden of asthma to individuals and society. The results of the Finnish asthma plan were recently published (23). There was a considerable reduction in mortality, disability pensions and hospitalizations due to asthma. Although the prevalence of asthma increased, costs were contained.

Assessment of the efficacy of guidelines

Guidelines should be implemented and tested for their accuracy and friendly use. The International Consensus of Rhinitis (134) was tested in patients with seasonal allergic rhinitis using an innovative protocol (cluster-randomized trial) which may be the basis for other tests (135). It was found that patients treated by physicians using the consensus treatment had a significantly improved quality of life and reduced symptoms by comparison to those treated by physicians who used a free-treatment choice. Unfortunately, for asthma, although it is suggested that guideline-based treatment is beneficial to the patient (130, 136), there is no direct comparison of treatment strategies, one of which used the GINA guidelines.

There is an urgent need for the development of a matrix which will enable the measurement of the effectiveness of asthma plans such as those which were proposed in Finland.

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GARD

Asthma is only one of the major preventable CRDs which also include respiratory allergies, chronic obstructive pulmonary disease (COPD), occupational lung diseases, sleep apnea syndrome and pulmonary hypertension. The Fifty-Third World Health Assembly recognized the enormous human suffering caused by CRD and requested the WHO Director General to give priority to the prevention and control of CRD, with special emphasis on developing countries (*WHA resolution 53.17*, May 2000, endorsed by all 191 WHO Member States). This led to the formation of the WHO Global Alliance against Chronic Respiratory Diseases (GARD) which considers all CRDs together taking into account co-morbidities and risk factors.

The objectives of GARD are:

- To develop a standard procedure of obtaining relevant data on CRD and risk factors.
- To encourage countries to implement health promotion and CRD prevention policies.
- To propose recommendations of simple strategies for CRD management.

Health priorities, geographic variability in risk factors and the prevalence of different forms of CRD, the diversity of national health care service systems and variations in the availability and affordability of treatments all require all that any recommendation should be adapted to ensure their appropriateness in the community in which they are applied.

Conclusion

Although asthma guidelines may not be perfect, they appear to be the best vehicle we have to assist primary care physicians and patients to receive the best possible care of asthma.

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