World Health
Organization

Prevention and Control of Noncommunicable Diseases:
Guidelines for primary health care in low-resource settings

CANCER

HEART DISEASE
& STROKE

DIABETES

CHRONIC
RESPIRATORY
DISEASE

Prevention and Control of Noncommunicable Diseases: Guidelines for primary health care in low resource settings

World Health Organization

Contents

Compact disc content

1. Diagnosis and Management of type 2 diabetes in primary health care in low-resource settings; Systematic reviews and GRADE tables, Benefits and harms of recommendations, Members of the guideline development group

2. Management of asthma and chronic obstructive pulmonary disease in primary health care in low-resource settings; GRADE tables, Search strategies, References, Members of the Guideline Development Group

3. Simplified tools for implementation of the guidelines

3.1 World Health Organization 2008. Prevention of Cardiovascular Disease. Pocket Guidelines for Assessment and Management of Cardiovascular Risk

3.2 WHO/ISH risk prediction charts

3.3 World Health Organization 2010. WHO Package of Essential Noncommunicable disease interventions and protocols

3.4 World Health Organization 2011. Scaling up action against noncommunicable diseases; how much does it cost? and Tool for estimating cost of implementing the Best Buys (with the User Guide)

Other WHO documents on Prevention and Control of Noncommunicable Diseases

I
Diagnosis and management of type 2 diabetes in primary health care in low-resource settings

II
Management of Asthma and Chronic Obstructive Pulmonary Disease in primary health care in low-resource settings

Abbreviations

ABCD	Appropriate Blood Pressure Control in Diabetes
ACCORD	Action to Control Cardiovascular Risk in Diabetes
ACE	angiotensin converting enzyme
ADVANCE	Action in Diabetes and Vascular Disease: preterax and Diamicron Modified Release Controlled Evaluation
ASCOTT-LLA	Anglo-Scandinavian Cardiac Outcomes Trial--lipid-lowering arm
ASPEN	Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in non-insulin-dependent diabetes mellitus
CARDS	Collaborative Atorvastatin Diabetes Study
CVD	cardiovascular disease
DCCT	Diabetes Control and Complications Trial
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HbA1c	glycated haemoglobin
HIV	human immunodeficiency virus
HOT	Hypertension Optimal Treatment
HPS	Heart Protection Study
IDF	International Diabetes Federation
IFG	impaired fasting glycaemia
IGT	impaired glucose tolerance
i.v.	intravenous
NCD	noncommunicable disease
NICE	National Institute for Health and Clinical Excellence
OGTT	oral glucose tolerance test
OHA	oral hypoglycaemic agents
PHC	primary health care
RCT	randomized controlled trial
UKPDS	United Kingdom Prospective Diabetes Study
VADT	Veterans Affairs Diabetes Trial
WHO	World Health Organization

Diagnosis and management of type 2 diabetes in primary health care in low-resource settings

1. Executive Summary

The primary goal of the guideline is to improve the quality of care and the outcome in people with type 2 diabetes in low-resource settings. It recommends a set of basic interventions to integrate management of diabetes into primary health care. It will serve as basis for development of simple algorithms for use by health care staff in primary care in low-resource settings, to reduce the risk of acute and chronic complications of diabetes.

The guideline was developed by a group of external and WHO experts, following the WHO process of guideline development. GRADE methodology was used to assess the quality of evidence and decide the strength of the recommendations.

Recommendations

- Point of care devices can be used in diagnosing diabetes if laboratory services are not available.
  Quality of evidence: not graded
  Strength of recommendation: strong

- Advise overweight patients to reduce weight by reducing their food intake.
  Quality of evidence: very low
  Strength of recommendation: conditional

- Advise all patients to give preference to low glycaemic-index foods (beans, lentils, oats and unsweetened fruit) as the source of carbohydrates in their diet.
  Quality of evidence: moderate
  Strength of recommendation: conditional

- Advise all patients to practice regular daily physical activity appropriate for their physical capabilities (e.g walking).
  Quality of evidence: very low
  Strength of recommendation: conditional

- Metformin can be used as a first-line oral hypoglycaemic agent in patients with type 2 diabetes who are not controlled by diet only and who do not have renal insufficiency, liver disease or hypoxia.
  Quality of evidence: very low
  Strength of recommendation: strong

- Give sulfonylurea to patients who have contraindications to metformin or in whom metformin does not improve glycaemic control.
  Quality of evidence: very low
  Strength of recommendation: strong

- Give a statin to all patients with type 2 diabetes aged ≥ 40 years.
  Quality of evidence: moderate
  Strength of recommendation: conditional

- The target value for diastolic blood pressure in diabetic patients is ≤80mmHg.
  Quality of evidence: moderate
  Strength of recommendation: strong

- The target value for systolic blood pressure in diabetic patients is <130mmHg
  Quality of evidence: low
  Strength of recommendation: weak

- Low-dose thiazides (12.5 mg hydrochlorothiazide or equivalent) or ACE inhibitors are recommended as first-line treatment of hypertension in diabetic patients. They can be combined.
  Quality of evidence: very low for thiazides, low for ACE inhibitors
  Strength of recommendation: strong

- Beta blockers are not recommended for initial management of hypertension in diabetic patients, but can be used if thiazides or ACE inhibitors are unavailable or contraindicated.
  Quality of evidence: very low
  Strength of recommendation: strong

- Give patients health education of patients on foot hygiene, nail cutting, treatment of calluses, appropriate footwear.
  Quality of evidence: low
  Strength of recommendation: strong

- Educate health care workers on assessment of feet at risk of ulcers using simple methods (inspection, pin-prick sensation)
  Quality of evidence: low
  Strength of recommendation: strong

- Persons with type 2 diabetes should be screened for diabetic retinopathy by an ophthalmologist when diabetes is diagnosed and every two years thereafter, or as recommended by the ophthalmologist.
  Quality of evidence: low
  Strength of recommendation: conditional

- Unconscious diabetic patients on hypoglycaemic agents and/or blood glucose ≤2.8 should be given hypertonic glucose intravenously. Food should be provided as soon as the patient can ingest food safely.
  Quality of evidence: strong
  Strength of recommendation: strong

- Unconscious diabetic patients on hypoglycaemic agents and/or blood glucose ≤2.8 mmol/L administer intravenously 20 to 50ml of 50% glucose (dextrose) over 1 to 3 minutes. If not available, substitute with any hypertonic glucose solution. Food should be provided as soon as the patient can ingest food safely.
  Quality of evidence: very low
  Strength of recommendation: strong

- If blood glucose ≥18 mmol (refer to hospital with i.v. drip 0.9% NaCl 1 litre in 2 hours, continue at 1 litre every 4 hours until hospital.
  Quality of evidence: very low
  Strength of recommendation: strong

These recommendations will be the basis for developing simple treatment algorithms for training primary care staff on integrated management of NCDs in low resource-settings.

2. Background

The implementation plan of the Global Strategy for Prevention and Control of Noncommunicable Diseases (NCDs) was endorsed by the World Health Assembly in May 2008. The objective 2 of this NCD Action Plan highlights the need to establish national policies and plans for NCD prevention and control (*1*). As one of the key components of this objective, WHO is called upon to "provide technical guidance to countries in integrating cost-effective interventions against major NCDs into their health systems". Furthermore, the Action Plan proposes that Member States "implement and monitor cost-effective approaches for the early detection of cancers, diabetes, hypertension and other cardiovascular risk factors" and "establish standards of health care for common conditions like CVD, cancers, diabetes and chronic respiratory diseases integrating when ever feasible their management into PHC".

Although there are several national and international guidelines on diabetes management, they are too complex for application in primary care in low-resource settings. The Global status report on noncommunicable diseases 2010 highlights the need for countries to integrate NCD prevention and management into primary health care even in low resource settings (2). WHO has identified an essential package of cost-effective interventions with high impact, feasible for application in resource-poor settings (3).

3. Objectives and target audience

The primary goal of the guideline is to improve the quality of care and the outcome in people with type 2 diabetes in low-resource settings. The guideline provides a basis for development of simple algorithms for management of diabetes with essential medicines and technology available in first-contact health services in low-resource settings. It recommends a set of basic interventions to integrate management of diabetes into primary health care. The recommendations are limited to patients with type 2 diabetes, as the more complex management of type 1 diabetes requires more specialized care.

The target users are health care professionals responsible for developing diabetes treatment protocols which will be used by health care staff in primary care units in low-resource settings.

A guideline development group was constituted, which included external experts and WHO staff (see CD).

4. Funding and declarations of interest

This work was funded by WHO funds.

Every member of the guideline development group and the peer reviewers (See CD for list of peer reviewers), completed a standard WHO declaration of interest forms (see CD).

5. Methodology and process

Scope of the guideline

The guideline development group used the GRADE methodology to formulate relevant questions on diabetes diagnosis and management in primary health care a low-resource context and identify important outcomes related to diabetes diagnosis and management (*4*). There were 12 questions to cover these domains:

■ Use of point-of-care devices (glucose meters) in diagnosing diabetes

■ Lifestyle management of diabetes

■ Use of medicines from the essential medicines list in managing hyperglycaemia

■ Use of medicines from the essential medicines list in reducing the risk of cardiovascular disease and diabetic nephropathy (antihypertensive medication, statins)

■ Screening for diabetic retinopathy for prevention of blindness

■ Interventions to prevent foot ulcers/amputation

■ Interventions in diabetes-related emergencies

The questions and outcomes identified as critical or important were peer reviewed and modified by 4 external experts. The outcomes are presented in the GRADE Tables.

Identification and generation of evidence

The following databases were searched for systematic reviews published up to December 2010:

■ Medline/Pubmed

■ Embase

■ DARE

■ Cochrane Database of Systematic Reviews

Identified systematic reviews were considered suitable if they were up-to-date in 2008 or later, and if they scored 8 or more on the 11-point AMSTAR tool for assessing the quality of systematic reviews (*5*). If more

than one acceptable systematic review was identified, the most recent one was used, unless data on one or more outcomes of interest were available only in the earlier review. The outcomes in the scoping questions matched those defined in the systematic reviews, with very few exceptions.

Systematic reviews of acceptable quality but published or updated before 2008 were updated using the same search strategy and study inclusion criteria as the original review and re-running the meta-analysis including the newly identified study/studies, if any (Table 1).

Where no suitable systematic reviews were identified in the literature search, they were commissioned from Hubert Department of Global Health, Rollins School of Public Health, Emory University, Atlanta, Georgia, USA and Health Management and Policy, and VA Center for Practice Management and Outcomes Research at the University of Michigan, An Arbor, Michigan, USA. Systematic reviews were not commissioned for interventions where no RCTs or observational studies were conducted and for interventions for which the group concluded that currently recognized treatment effects are unlikely to be confused with other effects or biases (e.g. administration of glucose in hypoglycaemia).

The identified and commissioned systematic reviews were used for assessing the quality of the evidence and summarizing the findings in GRADE tables. GRADE tables were not prepared for case series or reports, nor studies of laboratory analytical equivalence.

Existing evidence-based guidelines for diabetes prevention, diagnosis and management were reviewed (NICE (*6*), Canadian Diabetes Association (*7*), American Diabetes Association (*8*), Scottish Intercollegiate Guidelines Network (*9*)), as well as the international guideline developed by the International Diabetes Federation (IDF) for prevention and management of type 2 diabetes (*10*). These guidelines contain a broad range of interventions, and, with the exception of the IDF guideline, appropriate for a high-resource setting. However, some of the interventions are feasible in low-resource settings and were considered for this guideline.

Formulation of recommendations

The recommendations were formulated by the WHO secretariat and discussed at a group meeting. They are based on the GRADE evidence tables which also include assessment of the risk of serious side-effects of treatment. The group gave special consideration to the feasibility of the guideline implementation in low-resource settings. Consensus was a priori defined as agreement of at least 4 group members (majority). Any strong

disagreements would have been reported in this document, but consensus was reached on every recommendation and there was no need for voting.

Risks and benefits

The alternative for most of the recommendations in low-resource settings in primary care is usually no intervention. The consequences of untreated type 2 diabetes have been inferred from trials data on patients that did not achieve improvement in established risk factors for complications, and there is no doubt that diabetes substantially increases the risk of premature mortality, limb amputation, blindness and kidney failure (*11*).

There are no data on individual diabetic patient values and preferences in low resource settings, and they could vary between populations. However, the group agreed that early death, heart attacks, strokes, limb amputation, blindness, kidney failure would generally be perceived as important outcomes to be avoided. Overall, although there is some doubt over precision in some interventions, the recommended interventions potentially decrease the risk of these outcomes by 10-40% which was judged to be a treatment effect of relevant size. Furthermore, the interventions have been in widespread use for many years and potential harm of treatment was judged to be acceptable when contrasted with the benefits. More detailed consideration of risks and harms can be found in Annex 2.

Strength of recommendations

For recommendations developed by the GRADE process the strength of the recommendation was based on the quality of evidence, balance between desirable and undesirable effects and cost. The values and preferences are those of the group members as data on the diabetic population in low-resource settings area scarce and likely differ between cultures.

Strong: Moderate or high quality evidence of effectiveness for at least one critical outcome, desirable effects judged to outbalance the undesirable or very low quality evidence on undesirable effects; low cost and feasibility in low-resource settings; can be adopted as policy in most settings.

Weak/conditional: low or very low quality evidence of effectiveness for all critical outcomes, small benefits or harms judged to dominate over benefits, questionable feasibility, lack of follow-up interventions at higher levels of health care.

Peer review

The draft document was sent to 6 peer reviewers (See CD). There was general agreement on the recommendations, but some modifications were suggested. Treatment with sulfonylurea was added at the reviewers' request. The guideline development group accepted the suggestion of one reviewer to draw attention to medication that has known unfavourable interaction with antiretroviral treatment because the guideline is likely to be used in populations with a high prevalence of HIV infection and antiretroviral treatment. Two reviewers had serious reservation over the feasibility of statin treatment initiated at the primary care level, and this is reflected in the weak strength of the recommendation. Use of insulin was also suggested by some peer reviewers for inclusion, but was not included because of general unavailability of insulin in primary care in low-resource settings. While there was general agreement that insulin should be available in primary care for people already on insulin treatment, the guideline group agree that initiating insulin treatment would be too complex for most primary care settings.

Some reviewers suggested recommending aspirin for primary prevention of cardiovascular disease, but the group agreed that this recommendation is insufficiently supported by evidence and that potential harm was not negligible, so it was not included.

6. Adaptation and implementation

WHO will provide technical assistance to national guideline expert groups in developing simple management algorithms based on the guideline (see integrated protocols and other tools for Best Buys and WHO Package of Essential Noncommunicable Disease in CD, to facilitate guideline implementation in primary care). Workshops for training primary health care teams and policy makers on the use of the management protocols will be conducted in every low-income country that decides to integrate NCD prevention and management into primary care services. The proposed interventions present a minimum for improving diabetes care at the primary care level and should be applicable in all countries. However, the treatment protocols based on the guideline might nevertheless need to be specific to the local situation, depending on the availability of technology and medication.

7. Update

The guideline will be updated in 2016, unless made seriously obsolete earlier by breakthrough research.

8. Format and dissemination

The guidelines will be printed and available in pdf format on the WHO website. It will also be disseminated through ministries of health to all participants of workshops that will be organized for training primary care staff on the use of management protocols based on the guideline.

9. Impact and quality of the guideline

Initially, the effect of the guidelines will be assessed through process indicators by the ministries of health and technical help from WHO (e.g. number of low-income countries that introduce diabetes management at the primary care level, people with diabetes diagnosed in primary care, number of referrals for fundus examination, availability of essential medication at primary care level).

Countries will also be given technical assistance to monitor disease outcomes and indicators, depending on availability of resources for NCD surveillance (e.g. proportion of diabetic patients with adequate glycaemic control, incidence of acute complications, rates of limb amputations, etc.).

10. Recommendations and evidence

A. Diagnosing diabetes

Diabetes is diagnosed by laboratory measurement of plasma glucose in a blood sample. Diagnostic cut-off values are presented in Table 1 (*12*). Fasting capillary glucose is likely to be the most feasible measurement in low-resource settings.

The guideline development group agreed that all people 40+ years old should have the following measurements: waist circumference, blood pressure, fasting or random plasma glucose, urine protein, urine ketones in newly diagnosed diabetes, plasma cholesterol if the test is available and testing of foot pulses and sensation if known to have diabetes.

Table 2. Current WHO recommendations for the diagnostic criteria for diabetes and intermediate hyperglycaemia

Diabetes	
Fasting plasma glucose	≥7.0mmol/l (126mg/dl)
2-h plasma glucose*	**or**
	≥11.1mmol/l (200mg/dl)
Impaired Glucose Tolerance (IGT)	
Fasting plasma glucose	<7.0mmol/l (126mg/dl)
2-h plasma glucose*	**and**
	≥7.8 and <11.1mmol/l (140mg/dl and 200mg/dl)
Impaired Fasting Glucose (IFG)	
Fasting plasma glucose	6.1 to 6.9mmol/l (110mg/dl to 125mg/dl)
2-h plasma glucose*#	**and (if measured)**
	<7.8mmol/l (140mg/dl)

*   Venous plasma glucose 2-h after ingestion of 75g oral glucose load

\#   If 2-h plasma glucose is not measured, status is uncertain as diabetes or IGT cannot be excluded

In first-contact health services in low-resource setting laboratory measurement of plasma glucose is not available and patients need to be referred to the next level of care for diagnosis. This is often impractical and costly. The guideline panel considered the use of hand-held devices that measure blood glucose in a capillary blood sample. These devices are

currently widely used for self-monitoring of glycaemia in persons with diagnosed diabetes, but are not routinely used for diagnosing diabetes.

Question: Can point-of-care devices be used for diagnosing diabetes in the absence of laboratory facilities?

Recommendation

> **1.** Point of care devices can be used in diagnosing diabetes if laboratory services are not available.
> Quality of evidence: not graded
> Strength of recommendation: strong

A systematic review evaluating diagnostic accuracy of hand-held devices is the basis for this recommendation (SEE: Systematic review Echouffo Tcheugui JB et al). Two kinds of studies were identified – studies of analytical accuracy and epidemiologic studies of diagnostic performance. Results obtained by hand-held devices showed good agreement with those obtained by laboratory methods on the same sample, but the level of analytical accuracy varied with respect to standards defined by several professional organisations, and there is no single set of assessment criteria.

The epidemiological studies were not suitable to answer the question on the sensitivity and the specificity of measurement by hand-held devices in diagnosing diabetes because none of the studies compared blood glucose values obtained by 2 methods in the same blood sample. Therefore, a GRADE table for the evidence was not produced. The recommendation is based on studies of accuracy of biochemical methods used by currently available point of care devices..

B. Glycaemic control

Lowering of plasma glucose towards normal values relieves symptoms of hyperglycaemia and has a beneficial effect on macrovascular and microvascular complications.

The evidence on improved cardiovascular outcome comes from a meta-analysis of randomized controlled trials designed to estimate the effects of more intensive glucose control compared to less intensive control on the risk of major cardiovascular events in patients with type 2 diabetes (*14*). Various pharmacologic agents were used to lower plasma glucose in these studies.

There is evidence of moderate quality that lowering glycaemia has a modest beneficial effect on cardiovascular disease risk (9% reduction).

This is supported by the follow-up of the UKPDS participants 10 years after the study was closed (*15*). No effect on overall mortality was shown.

The evidence for beneficial effect of glucose lowering on microvascular complications come from several RCTs. The Diabetes Control and Complications Trial (DCCT) has shown that better glycaemic control reduces the risk of microvascular complications in type 1 diabetes (*16*) and subsequent epidemiological follow-up of the trial cohort suggests that the risk of macrovascular complications is reduced as well by intensive glucose control (*17*). In the ADVANCE trial major microvascular outcomes (new or worsening retinopathy or nephropathy) were reduced by 14% in the intensively treated group (*18*).

The VADT trial did not find a reduction of macrovascular and microvascular complications with intensive glucose control, but found a slower progression of albuminuria in the intensively treated group (*19*). The UKPDS found a 25% relative risk reduction in aggregate microvascular endpoints in the intensively treated group (*20*).

The guideline development group consensus was that patients with newly diagnosed diabetes and urine ketones 2+ or with newly diagnosed diabetes in lean persons <30 years should be referred to a higher level of care.

Advice on diet and physical activity

The majority of persons with Type 2 diabetes are overweight or obese, which further increases their risk of macrovascular and microvascular complications through worsening of hyperglycaemia, hyperlipidaemia and hypertension. (*21*)

Questions: Does advice on diet and physical activity improve outcomes in diabetic patients?

Does low glycaemic-index food improve outcomes in diabetic patients?

Recommendations

1. Advise overweight patients to reduce weight by reducing their food intake.
   Quality of evidence: very low
   Strength of recommendation: conditional

2. Advise all patients to give preference to low glycaemic-index foods (beans, lentils, oats and unsweetened fruit) as the source of carbohydrates in their diet.
   Quality of evidence: moderate
   Strength of recommendation: conditional

3. Advise all patients to practice regular daily physical activity appropriate for their physical capabilities (e.g walking).
Quality of evidence: very low
Strength of recommendation: conditional

There is strong evidence that type 2 diabetes can be prevented or delayed in persons at high risk by repeated counselling on weight-loss and increasing physical activity. The evidence on what dietary advice is effective once type 2 diabetes is diagnosed is less clear. The evidence on important outcomes is either very low (glycaemic control, intentional weight loss) or not available (risk of chronic complications and quality of life).

The evidence for these recommendations comes from a Cochrane review of randomised trials that compared different dietary advice and approaches (*22*). Very little data could be integrated with a meta-analysis and none of the studies examined long-term outcomes. There is some indication that better glycaemic control, as measured by glycated haemoglobin (HbA1c) could be achieved when dietary advice is combined with advice on exercise. None of the trials included in the Cochrane review had a control group which received no advice at all, which is the current reality in most low-resource settings. Despite the low quality of the evidence, advice on diet and physical activity is recommended as the intervention is deemed feasible, is low-cost, has a low risk of adverse events and not been proven to be ineffective by high quality evidence. The recommendation on favouring foods with a low glycaemic index is based on a systematic review that found a favourable effect of such a diet on glycaemic control (*23*). However, no studies were conducted in low-resource settings and the concept of the glycaemic index might be too complex for this diet to be feasible in areas of low literacy and basic health services.

Diabetes is a progressive illness. Introduction of oral hypoglycaemic agents (OHA) will often be necessary in patients on diet treatment only, and the dosage further increased to improve glycamic control. In studies of where intensive glycaemic control was compared with less intensive control in patients with type 2 diabetes, there was no glycaemic control threshold effect for complications. However, it was shown that patients who achieved HbA1c values of 7% or below had a significantly lower risk of microvascular complications than did less intensively treated patients who achieved a higher mean HbA1c value (7.9-9.4%) (*18*;*19*;*24*). An HbA1c value of approximately 7% is associated with fasting plasma glucose concentration of approximately 6.5mmol/l (*25*).

Metformin

Question: Can metformin be used as first-line oral hypoglycaemic agent in patients with type 2 diabetes?

Recommendation

> **1.** Metformin can be used as a first-line oral hypoglycaemic agent in patients with type 2 diabetes who are not controlled by diet only and who do not have renal insufficiency, liver disease or hypoxia.
> Quality of evidence: very low
> Strength of recommendation: strong

The evidence for this recommendation comes from a Cochrane review of randomised-controlled trials (RCT) (*26*). The daily dose of metformin was 1-3g and titrated clinically. The results for the comparison between metformin and diet or metformin and placebo were presented and analysed separately for the United Kingdom Prospective Diabetes Study (UKPDS) (*27*) because of its considerably longer follow-up and differences in reporting primary outcomes compared to the other included trials that compared metformin to diet or placebo.

Only a small number of studies reported patient-important outcomes such as death, major morbid events (e.g. stroke, myocardial infarction, amputation, blindness, renal failure) and quality of life. The majority of studies reported surrogate outcomes that indicate increased risk for important outcomes (e.g. HbA1c, cholesterol, retinopathy or nephropathy progression) or laboratory outcomes (e.g. C-peptide levels). The data on morbidity and mortality come largely from the UKPDS.

Data on lactic acidosis, a serious side-effect of fenformin use and by analogy feared to be caused by metformin as well come from a Cochrane review of RCTs and observational studies (28). It provides high quality evidence that the risk of this complication is low and not higher than with other hypoglycaemic agents. However, although 97% of the studies included in the systematic review did include patients with at least one of the standard contraindications for metformin (renal insufficiency, cardiovascular diseases, liver diseases, pulmonary disease), the review was not able to quantitatively assess the safety of metformin treatment in the presence of each of these hypoxic co-conditions. More research on the risk of lactic acidosis with metformin use in these particular populations is needed. If in doubt over the presence of contraindications, the patient should be referred to the next level of care. Metformin should be discontinued during acute severe illness such as pneumonia, severe infection, dehydration, myocardial infarction and the patient referred to the next level of care.

Metformin vs diet only

One arm of UKPDS (UKPDS 34) allocated overweight and obese patients to either metformin or diet only (*27*). Patients allocated to metformin had a significantly lower risk of any diabetes-related death and macrovascular and microvascular outcome (RR 0.74, 95% CI 0.60-0.90). All-cause mortality was also significantly lower in patients in the metformin arm of the trial (RR 0.68, 95% CI 0.49-0.93). The only other RCT that compared metformin to diet only and reported morbidity and mortality found a higher but statistically nonsignifant risk of ischaemic heart disease in patients treated with metformin (RR 3.0, 95% CI 0.13-71.92) (*29*). Three RCTs comparing metformin with diet reported glycated haemoglobin (HbA1c) (*27;29;30*). Metformin-treated patients had a significantly lower mean HbA1c value (Standardised mean difference -1.06, 95% CI -1.89 to -0.22). Data on adverse events was available only for hypoglycaemia which was recorded in two RCTs and the risk was found to be increased.

Metformin vs placebo

Six RCTs recorded adverse events (hypoglycaemia, diarrhoea, gastrointestinal disturbances). Diarrhoea was found to be more frequent with metformin than with placebo, but was not life-threatening. Hypoglycaemia and gastrointestinal does not appear to be more frequent with metformin.

Overall, this recommendation is based on moderate quality evidence that metformin lowers blood glucose, as measured by HbA1c. The evidence on other, potential, beneficial effects of metformin on long-term microvascular and macrovascular complications is of low or very low quality, or not available.

Sulfonylureas

Question: Can sulfonylurea be used as first-line oral hypoglycaemic agent in patients with type 2 diabetes?

Recommendation

> **1.** Give a sulfonylurea to patients who have contraindications to metformin, or in whom metformin does not improve glycaemic control.
> Quality of evidence: very low
> Strength of recommendation: strong

This recommendation is derived from a systematic reviews of RCTs that compared effectiveness and safety of metformin and sulfonylureas (*31*).

There were 17 trials that compared glycaemic control and overall metformin and sulfonylureas were shown to perform similarly in lowering HbA1c. The evidence on similar levels of glycaemic control (HbA1c) achieved with metformin and sulfonylureas is of high quality.

There are fewer trials that compared metformin and sulfonylurea and examined important long-term outcomes such as cardiovascular disease and microvascular complications. The systematic review did not pool the results for some of the outcomes because of substantial methodological diversity (e.g. different dosage and definitions of outcomes), or lack of trial data to combine. Five RCTs reported on all-cause mortality and found a small effect that favours metformin (*32-36*), but the evidence is of low quality.

Two RCTs reported on cardiovascular outcomes, but they were not a primary outcome in either (*33;37*). The evidence of low quality does not favour either drug. No RCT evaluated the progression of retinopathy. One RCT examined the effect of metformin and sulfonylurea on the glomerular filtration rate and progression of microabluminuria, but did not compare the two treatment groups directly (*38*).

There is high quality evidence from nine RCTs that the risk of hypoglycaemia is higher with sulfonylureas than with metformin (*32;34;39-45*).

Table 2: Sulfonylureas used in clinical trials included in the systematic review (*31*)

Sulfonylurea	Daily dosage (mg)	Duration of action
Glibenclamide	2.5-15	Intermediate to long
Glipizide	2.5-20	Short to intermediate
Gliquidone	15-180	Short to intermediate
Gliclazide	40-320	Intermediate
Glimepiride	1-6	Intermediate

First generation sulfonylureas (tolbutamide, chlorpropamide) were not included in the systematic review.

Glibenclamide is a second generation sulfonylurea and the only sulfonylurea on the WHO Essential Medicine List. Thus it is most likely to be available in low-resource settings. As precaution against severe hypoglycaemia, glibenclamide should be started with a small dose of 2.5-5 mg once daily with breakfast, and adjusted according to response to a maximum of 15 mg daily (*46*).

The guideline development group consensus was that patients with fasting plasma glucose >14 mmol/l despite maximal doses of metformin and sulfonylurea should be referred to the next level of care.

C. Reducing the risk of cardiovascular disease and diabetic nephropathy

Nephropathy

Morbidity and mortality from cardiovascular disease (CVD) are two to five times higher in persons with diabetes compared to people without diabetes (*47*), and diabetes confers about a two-fold excess risk for a wide range of vascular diseases, independently from other conventional risk factors (*48*). Treatment recommendations are based on the level of CVD risk as estimated by the WHO CVD risk-assessment tool (*49*).

Diabetic nephropathy occurs in about 25% of people with type 2 diabetes (*50*), and a substantial proportion progresses to end-stage renal disease (*51*).

Statins

Question: Should statins be given to patients with type 2 diabetes for primary prevention of CVD?

Statins (3-hydroxymethyl-3-methylglutaryl coenzyme A reductase inhibitors) have been found to reduce CVD risk in persons at high risk. A recent meta-analysis combining the results of 76 randomized trials of statins in primary and secondary prevention of CVD concluded that statins have a beneficial effect on all-cause mortality, revascularisation, risk of myocardial infarction and stroke, and cause relatively mild adverse events (*52*). Much of statins' therapeutic effect is believed to come from its lowering of low-density lipoprotein, but there is some evidence of other, possibly lipid-independent, beneficial effects on blood vessels (*53*).

Recommendation

> **1.** Give a statin to all patients with type 2 diabetes aged ≥ 40 years.
> Quality of evidence: moderate
> Strength of recommendation: conditional

Table 3. Statins used in clinical trials with diabetic patients included in the systematic review (*54*)

Statin	Daily dosage (mg)
Lovastatin*	20-40
Simvastatin*	40
Pravastatin	10-40
Atorvastatin	10
Glimepiride	1-6

* Contraindicated in HIV positive patients receiving protease inhibitors or ritonavir (*55;56*).

Despite the availability of generic statins, their cost could still make their availability in low-resource settings uncertain, or their introduction into primary health care could reduce the population coverage by more affordable essential medication such as antihypertensives and metformin. Therefore, the recommendation is conditional on availability of resources for statins, after complete coverage by metformin, sulfonylureas and antihypertensives.

The evidence for this recommendation comes from a meta-analysis of randomized controlled trials of statins in the primary prevention of CVD in people without established cardiovascular disease but with CVD risk factors, one of which is diabetes (*54*). The meta-analysis was conducted for major patient-important outcomes such as total mortality, major coronary heart disease events, stroke and serious adverse events such as cancer and did not include studies with surrogate outcomes such as vascular changes. The meta-analysis included large trials that included diabetic patients only (CARDS) (*57*), ASPEN (*58*), HPS (*59*), and data from a large diabetic subgroup of the ASCOT-LLA study, a trial of statins in people with different CVD risk factors such as hypecholesterolaemia, hypertension and high LDL- cholesterol (*60*). There were two trials with diabetic patients only that reported all cause mortality, one reported a statistically insignificant reduction (CARDS), while the other reported a non-significant increase (ASPEN). All the trials included patients aged 40 years and older, predominantly male and of European origin, although some ethnic groups were also included.

Trials which reported the outcome of major coronary events in diabetic patients showed a 17- 36% reduction in the odds in people receiving statins (CARDS, ASCOT-LLA, HPS). Separate synthesis was not presented for people with diabetes, but the meta-regression analysis found no heterogeneity

of statin effect in subgroups dichotomised by sex, age and presence of diabetes (*54*). A subsequent meta-analysis of controlled trials of statins in both primary and secondary prevention of CVD confirmed the findings that statins offer benefits in people at high risk of CVD, including people with diabetes and that the effect of several currently available statins was similar (*61*). The meta-analysis also demonstrated an increased risk of elevated liver enzymes but not an increased risk of important clinical events, except for an increased risk for diabetes (*52*). However, if available, liver function laboratory testing should be performed before introducing statin treatment.

In the GRADE evidence profile pooled data from studies conducted on diabetic patients without cardiovascular disease provide moderate quality evidence that administration of statins to people with diabetes reduces mortality, the risk of coronary events and stroke and is unlikely to substantially affect the short-term risk of cancer and death due to all causes.

Antihypertensive treatment

Blood pressure lowering in diabetic patients reduces the risk of microvascular and macrovascular complications (11;62;63).

Question: What are the target blood pressure targets to improve outcomes in patients with type 2 diabetes?

Recommendations

Target blood pressure values

1. The target value for diastolic blood pressure in diabetic patients is ≤80mmHg.
   Quality of evidence: moderate
   Strength of recommendation: strong

2. The target value for systolic blood pressure in diabetic patients is <130mmHg
   Quality of evidence: low
   Strength of recommendation: weak

The evidence for the recommended target for diastolic blood pressure comes from two randomized controlled trials. The diabetes arm of the Hypertension Optimal treatment (HOT) Trial showed clinically important reductions in cardiovascular mortality and major cardiovascular events in the group with diastolic blood pressure ≤80 mmHg, compared to those with ≤90 mmHg. (*64*). The UKPDS found a reduction in progression of

microvascular disease, risk of stroke and risk of any diabetes related end-point in the group assigned to tight blood pressure control which achieved a mean diastolic blood pressure of 82 mmHg. (*65*). The GRADE table shows a meta-analysis of the study results which provides high quality evidence that tighter diastolic blood pressure control reduces overall mortality, and moderate quality evidence that it reduces the risk of myocardial infarction, stroke and progression of microvascular complications in people with type 2 diabetes.

The recommended target of <130 mmHg for systolic blood pressure is based on evidence from two randomized controlled trials (*66;67*) and one prospective cohort study (*62*). The recommendation is based on moderate quality evidence that systolic blood pressure <130 mmHg offers some protection against stroke. The evidence on the beneficial effect of blood pressure <130mmHg on mortality and myocardial infarction is of low quality. In an epidemiological analysis of the UKPDS trial, lowest risk of death, coronary heard disease and microvascular complications was observed in study participants with a systolic blood pressure <120 mmHg (*62*). In the normotensive Appropriate Blood Pressure Control in Diabetes (ABCD) randomized controlled trial the participants in the moderate treatment arm achieved mean systolic blood pressure of 137 mmHg and those in the intensive treatment arm achieved 128 mmHg. The primary outcome was creatinine clearance and no difference between the two treatment arms was seen in this outcome. However, there was statistically significant reduction in risk of retinopathy progression and stroke (*67*). The Action to Control Cardiovascular Risk in Diabetes (ACCORD) was a randomized trial designed to test the effect of a target systolic blood pressure <120 mmHg on major cardiovascular events. The mean systolic blood pressure was119.3 mmHg in the intensive intervention group and 133.5 mmHg in the standard treatment group. No significant difference between the two intervention groups was found in all-cause death rates, nor in a composite outcome of nonfatal myocardial infarction, nonfatal stroke or death from cardiovascular causes. The intensive treatment group had a significantly lower risk of stroke (*66*). Serious events that necessitated hospitalization, are life-threatening or cause permanent disability were recorded. The intensively treated group had a higher incidence of hypotension, bradycardia or arrhythmia and hyperkalaemia, but the absolute risk of these adverse events was low (*68*). In the HOT study systolic blood pressure was consistently underestimated in the measurement and it is therefore difficult to use the data. In the UKPDS, the mean systolic blood pressure in the group with tight blood pressure control was 144 mmHg, and 154 mmHg in the group with less tight control. (*69*)

The guideline development group consensus was that patients with diabetes proteinuria or blood pressure >130/80 mmHg despite treatment with 2 or 3 blood pressure lowering agents should be referred to the next level of care.

Choice of antihypertensive agent

Question: Can low-dose thiazides/inhibitors of angiotensin-converting enzyme (ACE-inhibitors)/beta blockers be used to improve outcomes in patients with type 2 diabetes and hypertension?

Recommendations

1. Low-dose thiazides (12.5 mg hydrochlorothiazide or equivalent) or ACE inhibitors are recommended as first-line treatment of hypertension in diabetic patients. They can be combined.
   Quality of evidence: very low for thiazides, low for ACE inhibitors
   Strength of recommendation: strong

2. Beta blockers are not recommended for initial management of hypertension in diabetic patients, but can be used if thiazides or ACE inhibitors are unavailable or contraindicated.
   Quality of evidence: very low
   Strength of recommendation: strong

Table 4. Antihypertensive agents used in clinical trials included in systematic reviews (*70*;*71*)

Agent	Daily dosage (mg)
Thiazides	
hydrochlorothiazide	12.5-25
chlorthiazide	500-1000
trichlormethiazide	1-4mg
ACE inhibitors	
enalapril	5-40
lisinopril	10-20
ramipril	2.5-20
captopril	50-100
cilazapril	2.5-10
fosinopril	20-40
trandolapril	2-4
perinodopril	2-4
Beta-blockers	
atenolol	50-100
propranolol	2-4

The evidence for these recommendations comes from a Cochrane review of randomized placebo- or untreated group - controlled trials of at least one year duration (*70*), and is supported by the results of a RCT not included in the review (*72*). The Cochrane review did not separately analyse data from diabetic patients, but some of the included trials were on diabetic patients only and diabetes was not an exclusion criterion in any of the RCTS included in the meta-analysis. The recommendations are graded as "strong" because the moderate quality evidence is supplemented by a trial not included in the review because it was a head-to-head comparison of thiazides and ACE inhibitors and showed no significant difference between these two drug groups in the incidence of coronary heart disease. (*72*) There is moderate quality evidence that beta-blockers compared to placebo did not reduce all-cause mortality nor coronary heart disease, but did reduce the risk of stroke. Thus priority is given to low-dose thiazides and ACE inhibitors. In a Cochrane review of the effect of blood pressure lowering agents on pregression of renal complications, ACE inhibitors have additionally been shown to reduce the progression to microalbuminuria in normoalbuminuric diabetic patients (*71*), but this effect has not been examined for thiazides. Although the risk of adverse events was significantly higher with these antihypertensive agents than with placebo, the adverse events were judged to be relatively mild. The choice of antihypertensive medication in low-resource settings is likely to be influenced by local availability and cost. Priority should be given to thiazides and ACE inhibitors.

D. Prevention of lower limb amputations

Diabetes is the leading cause of non-traumatic lower limb amputations (*73*). The lifetime risk of developing foot ulcers in persons with diabetes is about 15% (*74*). These lesions may become infected and ultimately result in amputation because of gangrene.

Question: Does multifactorial intervention with educating patients on foot care and education of health staff to asses risk of foot ulcers reduce the incidence of foot ulcers in patients with type 2 diabetes?

Recommendations

1. Give patients health education on foot hygiene, nail cutting, treatment of calluses, appropriate footwear.
   Quality of evidence: low
   Strength of recommendation: strong

2. Educate health care workers on assessment of feet at risk of ulcers using simple methods (inspection, pin-prick sensation).
Quality of evidence: low
Strength of recommendation: strong

A high value is placed on avoiding lower limb gangrene and need for amputation.

The evidence used in formulating these recommendations comes from a systematic review (*75*). The review included individual and cluster-randomized clinical trials of combined interventions that included at least two levels of care (the patient, the health care provider, the health care system). Due to heterogeneity between studies in study interventions, control interventions and health care settings, no synthesis of outcome data was attempted.

The recommendations are supported by low quality evidence from 5 RCTs, none of them conducted in low-resource settings. The recommended interventions were judged to be feasible and low-cost, and are recommended despite the lack of evidence of their effectiveness, as the evidence of no effect was also of low quality. The guideline group judged that the evidence of no effect was insufficient and that research is recommended to increase the body of evidence, particularly in low-resource settings.

The guideline development group consensus was that patients with severe foot infection and/or foot ulcers should be referred to the next level of care.

E. Prevention of blindness

Diabetic retinopathy is a major cause of vision loss worldwide (*76*).

The disease evolves through recognizable stages in its progression to blindness, is an important public health problem and there are effective and accepted screening tests. Timely laser photocoagulation therapy can prevent progression of vision loss (*77*).

Question: What is the recommended frequency of screening for retinopathy to reduce the incidence of vision loss in type 2 diabetic patients by at least 50%?

Recommendation

> **1.** Persons with type 2 diabetes should be screened for diabetic retinopathy by an ophthalmologist when diabetes is diagnosed and every two years thereafter, or as recommended by the ophthalmologist.
> Quality of evidence: low
> Strength of recommendation: conditional

This recommendation is based on data from developed countries which show that a substantial proportion of newly diagnosed diabetic patients already have diabetic retinopathy (*78*). The recommended frequency of screening is based on a systematic review of cohort studies, modelling and cost-effectiveness analyses (see systematic review by Echouffo Tcheugui) that examined the effect of different screening intervals on risk of vision loss and costs. The studies were too heterogeneous for quantitative synthesis, and the recommended screening interval ranged from one to four years. A one-year screening interval is unlikely to be feasible in low-resource settings.

Authors of studies that compared a 2-year interval with a 1-year interval are largely in agreement that a 2-year interval is acceptable as the risk of missing sight-threatening retinopathy is low. The largest cohort study, conducted in the United Kingdom and following 20,778 diabetic patients for 17 years found an odds ratio of 0.93 (95%CI: 0.82–1.05) when comparing incidence of sight-threatening retinopathy in patients screened every 1 year to the incidence in patients screened every 2 years (*79*). An interval of more than 24 months was associated with an increased risk (OR=1.56, 95% CI: 1.14-1.75) However, all the cohort studies were conducted in developed countries.

Unfortunately, many low-resource settings do not have the laser equipment for photocoagulation of retinal/macular lesions for treating sight-threatening retinopathy, hence the weak/conditional recommendation.

The guideline development group consensus was that diabetic patients with recent deterioration of vision or no retinal exam in 2 years should be referred to the next level of care.

F. Severe hypoglycaemia

Hypoglycaemia (low blood glucose) is a frequent complication in diabetic patients receiving medication to lower blood glucose, particularly sulfonylurea and insulin. The brain requires a continuous supply of glucose and this is dependent on arterial plasma glucose concentrations (*80*).

Severe hypoglycaemia is defined as hypoglycaemia where the patient is unable to self-treat (*81*). It can cause loss of consciousness and coma, lead to neuronal death and is potentially life-threatening (*82*). The functional brain failure caused by hypoglycaemia is corrected after blood glucose concentration is raised. This can be accomplished by ingestion of carbohydrates, if that is feasible or parenteral glucose if not feasible.

Question: What is the recommended intervention in severe hypoglycaemia?

Recommendations

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1. Unconscious diabetic patients on hypoglycaemic agents and/or blood glucose ≤2.8 should be given hypertonic glucose intravenously. Food should be provided as soon as the patient can ingest food safely.
   Quality of evidence: strong
   Strength of recommendation: strong

2. Unconscious diabetic patients on hypoglycaemic agents and/or blood glucose ≤2.8 mmol/L administer intravenously 20 to 50ml of 50% glucose (dextrose) over 1 to 3 minutes. If not available, substitute with any hypertonic glucose solution. Food should be provided as soon as the patient can ingest food safely.
   Quality of evidence: very low
   Strength of recommendation: strong

The evidence for this recommendation is derived from animal studies, clinical observations and case reports (*83*;*84*). Although there are no RCTs or observational studies to support this recommendation, the group concluded that there is vast clinical experience that shows a very strong effect of oral or parenteral glucose administration to justify the strength of the recommendation (*81*). Parenteral therapy is necessary when the patient is unable or unwilling to ingest glucose or sucrose orally. However, evidence on the recommended oral or parenteral dosage and frequency is of very low quality, as the effects of various doses have not been investigated systematically.

G. Hyperglycaemic emergencies

Diabetic ketoacidosis (DKA) and hyperosmolar hyperglycaemic state are life-threatening conditions with somewhat different features that require treatment in hospital by experienced staff. Even there, the case-fatality rate can be quite high (*85*). Both conditions are characterised by fluid and electrolyte depletion and hyperglycaemia. In a primary care setting it will usually not be possible to diagnose diabetic ketoacidosis, but it should

be suspected in patients with extreme hyperglycaemia. Hyperglycaemia slows gastric emptying, therefore oral rehydration might not be effective, even in patients who are notvomiting (*86*).

Question: What is the optimal fluid replacement regimen in persons with extreme hyperglycaemia?

Recommendation

> **1.** If blood glucose ≥18 mmol(l refer to hospital with i.v. drip 0.9% NaCl 1 litre in 2 hours, continue at 1 litre every 4 hours until hospital.
> Quality of evidence: very low
> Strength of recommendation: strong

A separate GRADE table was not prepared for this recommendation. While it is reasonable to attempt rehydration in hyperglycaemic dehydrated individuals suspected of having diabetic ketoacidosis, the rate and quantity of fluid in hyperglycaemia have not been extensively investigated. The recommendation is based on early physiological studies and one randomized clinical trial that compared two rates of physiologic saline infusion on a small sample of patients and favours a slower rate of infusion in achieving electrolyte balance and rehydration in patients without extreme volume deficit (*87*).

II
Management of Asthma and Chronic Obstructive Pulmonary Disease in primary health care in low-resource settings

Abbreviations

AMSTAR	Assessment of Multiple Systematic Reviews
AQoL	asthma-specific quality of life
CFC	chlorofluorocarbon
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CRD	chronic respiratory disease
CRQ	Chronic Respiratory Questionnaire
FEV1	forced expiratory volume in 1 second
FVC	forced expiratory vital capacity
GINA	Global Initiative for Asthma
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HFA	hydrofluoroalkane
HIV	human immunodeficiency virus
HQ	headquarters
HRQol	health-related quality of life
IUATLD	International Union Against Tuberculosis and Lung Disease
kg	kilogram
LMIC	low- and middle-income country
MD	mean dose
MDI	metered-dose inhaler
MeSH	Medical Subject Headings
mg	milligram
ml	milliliter
NCD	noncommunicable disease
OR	odds ratio
PEF	peak expiratory flow
PEFR	peak expiratory flow rate
PICOT	population/intervention/comparator/outcome/time
prn	pro re nata (as needed)
QoL	quality of life
RCT	randomized controlled trial
RR	relative risk
SGRQ	St George's Respiratory Questionnaire
SMD	standardized mean difference
ug	microgram
WHO	World Health Organization

Management of Asthma and Chronic Obstructive Pulmonary Disease in primary health care in low-resource settings

1. Executive summary

Chronic respiratory diseases (CRDs), particularly bronchial asthma and chronic obstructive pulmonary disease (COPD), are major public health problems accounting for a considerable share of the disease burden in low- and middle-income countries (LMICs). In 2004, 6.8% of deaths in women and 6.9% in men in LMICs were caused by CRDs, according to the *WHO Global burden of disease report: update 2004*.

Prevention and control of CRDs need to be addressed through a public health approach, including the implementation of key interventions at a primary health care level. It is particularly important to give due consideration to the limited resources available in LMICs where the use of essential medicines and equipment and the availability of health workers need to be prioritized.

According to the World Health Organization (WHO) 2008–2013 Action Plan for the Global Strategy for Prevention and Control of Noncommunicable diseases (WHO Global NCD Action Plan), endorsed by the World Health Assembly in 2008, WHO is called upon to provide technical guidance to countries for the integration of cost-effective interventions against major NCDs in their health systems. This guideline is a tool that provides such assistance.

The care offered at present to patients with CRDs is not always based on evidence or best practice and this is the first time WHO has produced a guideline for the management of asthma and COPD through a primary care approach in resource-limited settings. This guideline is designed for easy access and implementation in busy community clinics and small hospitals and is intended to complement other evidence-based guidelines such as the International Union Against Tuberculosis and Lung Disease (IUATLD)

and the Global Initiative for Asthma (GINA) guidelines. These guidelines should be referred to if more information is required; for example, on classification of disease severity.

The main purpose of this guideline is, therefore, to provide evidence-based recommendations on management of asthma and COPD in primary health care in low-resource settings. The target users are physicians and health workers. The main objectives are to reduce avoidable death and morbidity related to asthma and COPD and to improve health outcomes in resource-limited settings where management facilities are limited in terms of availability of diagnostic facilities and medicines.

The guideline is concerned with the management of asthma and COPD by:

- focusing at a primary health care level in low-resource settings;
- assisting the users who will be physicians and health workers in primary care, and staff in government health departments concerned with procuring drugs[*];
- safeguarding affordability by organizing drug treatment around four major groups of medicines on the WHO Essential Medicines List (salbutamol, beclometasone, prednisolone, antibiotics) – other drugs are mentioned only if they have been shown to be helpful and if they are sometimes available and used in resource-poor countries, e.g. oral theophylline;
- assuring that all complicated or severe cases are referred to the next level of care.

The strength of the recommendations for the management of asthma and COPD that are developed, summarized and presented in this guideline reflects the degree of confidence that the desirable effects of adherence to the recommendations outweigh the undesirable effects. As described in the guideline, the following factors were considered during the recommendation making process: (i) quality of evidence; (ii) uncertainty of balance between desirable and undesirable effects; (iii) variability in values and preferences of outcomes by different individuals; and (iv) cost effectiveness.

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[*]   See integrated protocols and other tools for Best Buys and WHO Package of Essential Noncommunicable Disease in CD, to facilitate guideline implementation in primary care)

2. Recommendations

* Strength of recommendation/Quality of evidence

Management of stable asthma

REC 1: In order to determine the best management approach, asthma control should be assessed using severity and frequency of symptoms. (Particularly nocturnal symptoms, exercise induced wheezing, the use of beta agonists and absence from work/school due to symptoms, the frequency of exacerbations and peak expiratory flow (PEF) if available.) *** (***Strong recommendation, low quality evidence***) Annex 4.1; 4.2**

REC 2: Inhaled corticosteroids (beclometasone) should be given to all patients with chronic persistent asthma. If their use needs to be prioritized in resource-constrained settings, the highest priority group should be those with life-threatening attacks and attacks requiring hospital admission where the use of a regular inhaled steroid is likely to save money by reducing hospital admissions. Patients with frequent exacerbations are also a high priority group, as are those with persistent troublesome symptoms, those using high doses of beta agonists and those losing time from work or school.

Numerous studies have demonstrated that inhaled steroids reduce asthma exacerbations and improve lung function, although they vary in terms of dosage used, type of steroid and mode of delivery, including the use of a spacer. Low doses (e.g. beclometasone 100ug once or twice daily for children and 100ug or 200ug twice daily for adults) are adequate for most patients with mild or moderate asthma; patients with more severe asthma require higher doses.

The lowest dose of beclometasone that controls symptoms should be determined for maintenance treatment. Any deterioration in symptom control should be treated with an increase in dose. A spacer should be used with a metered-dose inhaler (MDI) to reduce candidiasis and increase drug deposition in the lung.

Ensuring that low-cost, good quality generic preparations of inhaled beclometasone are readily available for all patients with persistent asthma is the highest priority.
* (*Strong recommendation, moderate quality evidence***) Annex 4.3; 4.4**

REC 3: A stepwise approach to treatment is recommended:

- Step 1. Inhaled beta agonist (salbutamol) as required (prn)

- Step 2. Continue inhaled salbutamol prn and add inhaled beclometasone 100ug or 200ug twice daily, or 100ug once or twice daily in children

- Step 3. Continue inhaled salbutamol prn and increase the dose of beclometasone to 200ug to 400ug twice daily

- Step 4. Add low-dose oral theophylline (assuming that long-acting beta agonists are not available), or increase dose of inhaled beclometasone

- Step 5. Add oral prednisolone in the lowest dose possible to control symptoms

At each point it is important to check patients' adherence to their medications and that their inhaler technique is correct. For patients requiring regular prednisolone referral to a specialised centre should be considered.
* Annex 7

Management of exacerbation of asthma

REC 1: Oral prednisolone should be given for all acute exacerbations of asthma. For adults, a dose of 30–40mg daily is appropriate, while for children (<16 years) a dose of 1mg per kg daily has fewer adverse effects on behaviour than 2mg per kg, so a dose of 1mg per kg (up to 30mg daily) is recommended. Patients should have easy access to oral corticosteroids for exacerbations. In children, prednisolone tablets can be crushed and given with sugar. The usual duration of treatment is three days for children and five days for adults though it may need to be extended if the patient has not recovered fully.
* (*Strong recommendation, low-quality evidence***) Annex 4.6**

REC 2: Inhaled salbutamol: higher doses of inhaled salbutamol should be given to all patients with acute severe exacerbations; salbutamol may be given by nebulizers or spacers (commercial or homemade). The evidence suggests no important advantages of nebulizers over spacers in children over the age of 2 (or adults) although these studies did not include patients with life-threatening asthma. Other considerations may be relevant in making the choice between nebulizers and spacers such as the availability of nebulizers, the need to prevent cross-infection and whether the patient will use a spacer at home. Steps must be taken to keep nebulizers and spacers clean (sterile) and to prevent transmission of infections.

Following treatment with salbutamol, patients should have repeat clinical assessments at intervals (e.g. 15–20 minute intervals) to ensure that

they are responding to treatment. Failure to respond requires further doses or more intensive treatment.

Once the patients have recovered, their usual maintenance treatment should be reviewed and altered if indicated to prevent recurrent exacerbations.

* (_Strong recommendation, low-quality evidence_**) Annex 4.7; 4.8; 4.15**

REC 3: Oxygen: if available, oxygen should be administered to patients with acute severe asthma. This is in keeping with normal practice in high-resource settings where the decision to use oxygen is based on low oxygen saturation readings.

* (_Strong recommendation, very low-quality evidence_**)**

REC 4: Second-line drugs: if patients do not respond to salbutamol and prednisolone, then second-line drugs may need to be considered. If a nebulizer and ipratropium bromide are available and a second-line treatment is required, nebulized ipratropium bromide is recommended for children with acute asthma.

* (_Weak recommendation, very low-quality evidence_**)**

REC 5: Intravenous magnesium: at present, there is insufficient evidence to recommend intravenous magnesium as a routine second-line drug.

* (_Weak recommendation, very low-quality evidence_**)**

REC 6: Intravenous salbutamol: on the basis of the balance between benefits and risks, intravenous salbutamol is NOT recommended for use as a second-line drug.

* (_Strong recommendation, very low-quality evidence_**)**

REC 7: Intravenous aminophylline: on the basis of the balance between benefits and risks, intravenous aminophylline is NOT recommended for routine use as a second-line drug. When taken in addition to beta agonists and steroids there is no significant benefit for adults and only marginal benefit for children. There is evidence of adverse effects for children and adults. The risks are seen as outweighing the benefits in settings where monitoring is not feasible.

* (_Weak recommendation, very low-quality evidence_**)**

Management of stable COPD

REC 1: When given as required short-acting beta-agonists are effective in improving symptoms in patients with stable COPD. Patients should be prescribed beta agonists as required. There are no data from which to assess the optimum frequency of administration, or the effect of regular

administration. Inhaled beta agonists are recommended rather than oral preparations because oral preparations have more pronounced undesirable effects that may be of particular relevance in view of common co-morbidities with COPD, e.g. arrhythmias in patients with coronary heart disease.

* (*Weak recommendation, very low-quality evidence*) **Annex 4.11; 4.12**

REC 2: Theophylline: as it is unlikely that blood levels can be monitored in resource-constrained settings, only low doses of theophylline are recommended. Patients should be advised to stop treatment and consult a doctor if adverse effects are experienced.

* (*Weak recommendation, very low-quality evidence*) **Annex 4.14**

REC 3: Oral corticosteroids (prednisolone) are ineffective in stable COPD except possibly in high doses when there are important side effects. On the basis of the balance between benefits and risks, oral steroids are NOT recommended for use in stable COPD.

* (*Strong recommendation, very low-quality evidence*) **Annex 4.13**

REC 4: Inhaled steroids (beclometasone): when given in high doses there may be a small benefit from inhaled steroids; however, high doses are expensive for resource-poor countries and high doses have more adverse effects, including pneumonia. The risks are unknown in areas where the prevalence of HIV and tuberculosis are high. Since the benefit is modest, the risk/benefit ratio is much higher than it is for asthma. The use of inhaled steroids for patients with stable COPD therefore cannot be justified. NOT recommended.

* (*Strong recommendation, very low-quality evidence*)

REC 5: Ipratropium bromide: when compared to regular short-acting beta agonists, short-term inhaled ipratropium bromide has small benefits with regard to reducing symptoms and improving lung function. Currently, ipratropium bromide preparations are more expensive than beta agonists and there are no data to assess risk versus benefits of regular use over longer periods to recommend long-term regular use of ipratropium bromide. NOT recommended.

* (*Weak recommendation, very low-quality evidence*) **Annex 4.12**

Management of exacerbation of COPD

REC 1: **Antibiotics** should be given for COPD exacerbations.
* (*Strong recommendation, very low-quality evidence***) Annex 4.10**

REC 2: Oral steroids: a short course of prednisolone is recommended for acute severe exacerbations of COPD (e.g. prednisolone 30–40mg for about seven days).
* (*Strong recommendation, very low-quality evidence***) Annex 4.14**

REC 3: Inhaled beta agonists: higher doses of inhaled salbutamol should be administered via a nebulizer or spacer.
* (*Strong recommendation, very low-quality evidence***) Annex 4.12**

REC 4: Oxygen: if available, oxygen should be administered by a device that controls concentration to 24%–28%.
* (*Strong recommendation, very low-quality evidence***)**

REC 5: Intravenous aminophylline: based on the available evidence, intravenous aminophylline is NOT recommended for routine use in acute exacerbations of COPD. Although there are data from only four studies, these show little evidence of benefit; any beneficial effect is likely to be small and is likely to be outweighed by potential adverse effects.
* (*Strong recommendation, very low-quality evidence***)**

The summaries of the considerations of benefits/risks, values, cost and feasibility for the recommendations listed in the following table were discussed by the guideline expert panel based on the experience of its members, consideration of the systematic reviews, moderated discussion and consensus.

Recommendation	Benefits/risks; values and acceptability; cost; feasibility
Management of stable asthma	
REC 1	Standard diagnostic recommendations to assess asthma control should be used in accordance with standard clinical practices, as agreed by the guideline expert panel members.
REC 2	**Benefits:** Highly effective treatment for control of stable asthma as well as significant reduction of exacerbations and improvement of lung function. **Risks:** Risks of side effects are minimal since only the lowest dose that controls symptoms is recommended for maintenance treatment. A spacer should be used with an MDI to reduce candidiasis with beclometasone and increase drug deposition in the lung. **Values and acceptability:** Numerous studies have demonstrated that inhaled steroids reduce asthma exacerbations and improve lung function, although they vary in terms of dosage used, type of steroid and mode of delivery, including the use of a spacer. **Cost:** The regular use of inhaled steroids is likely to save money by reducing hospital admissions of patients with life-threatening attacks and frequent exacerbations. Low-cost, good quality generic preparations of inhaled steroids are recommended. **Feasibility:** Particularly recommended in resource-constrained settings where access to medical care is often restricted.
REC 3	A stepwise approach is a commonly accepted way of managing asthma patients and basically comprises all the other treatment recommendations, as agreed by the guideline expert panel members.

Recommendation	Benefits/risks; values and acceptability; cost; feasibility
Management of exacerbation of asthma	
REC 1	**Benefits/risks:** Benefits far outweigh the risks. For all acute exacerbations of asthma, short-term courses of oral steroids in the recommended doses are effective and carry minimal risk of side effects, e.g. weight gain, fluid retention, high blood pressure, elevated blood sugar. **Values and acceptability:** The efficiency in acute exacerbations of asthma is demonstrated in numerous studies. In the recommended doses, a significant benefit is derived with little risk of side effects. **Cost:** Affordable for resource-constrained settings. **Feasibility:** There should be easy access to oral corticosteroids for patients with exacerbations of asthma.
REC 2	**Benefits/risks:** Effective for improving lung function in patients with acute exacerbations of asthma. For short-term administration of high doses, benefits outweigh the risk of potential side effects. Generally, the evidence suggests no important advantages of nebulizers over spacers. **Values and acceptability:** Based on the severity of asthma exacerbations, prompt treatment can be vital. Following treatment with salbutamol, the patient should have repeated clinical assessments at intervals (e.g. 15–20 minute intervals) to ensure that they are responding to treatment. Failure to respond requires further doses or more intensive treatment. **Cost:** There are no data available directly assessing the cost effectiveness, although, the cost is lower where good quality generic preparations are available. **Feasibility:** Higher doses of inhaled beta agonists should be given to all patients with acute severe exacerbations where available.
REC 3	**Benefits/risks:** In the absence of evidence from randomized controlled trials (RCTs) in asthma, the recommendation is based on observational evidence and strong consensus belief that oxygen is beneficial. **Values and acceptability:** If oxygen is available, it should be administered to all patients with acute severe asthma in keeping with normal practice in high-resource settings where the decision to use oxygen is based on low oxygen saturation readings (pulse oximetry). **Cost:** Short-term use in exacerbations as recommended should be affordable.

Recommendation	Benefits/risks; values and acceptability; cost; feasibility
REC 4	If a nebulizer and ipratropium bromide are available and a second-line treatment is required, adding ipratropium bromide can be recommended for children with acute asthma but ONLY as a second-line treatment. Side effects are rare; paradoxical bronchoconstriction is a recognised though rare problem. **Cost:** There are no data available directly assessing the cost effectiveness, although the cost is lower where good quality generic preparations are available.
REC 5	**Negative recommendation.** At present, there is insufficient evidence to recommend intravenous magnesium as a routine second-line drug and is NOT recommended. However, if it is available, it may be worth trying if the patient continues to deteriorate despite other recommended treatment.
REC 6	**Negative recommendation.** On the basis of the balance between benefits and risks, intravenous salbutamol is NOT recommended for use as a second-line drug.
REC 7	**Negative recommendation.** On the basis of the balance between benefits and risks and because the risks outweigh the benefits in settings where monitoring of blood drug levels is not feasible, intravenous aminophylline is NOT recommended for routine use as a second-line drug.
Management of stable COPD	
REC 1	**Benefits/risks:** When given as required beta agonists are effective in improving symptoms in patients with COPD. The effect of regular administration is unknown. **Values and acceptability:** Inhaled beta agonists are recommended rather than oral preparations because oral preparations have more pronounced undesirable effects that may be of particular relevance in view of common co-morbidities with COPD, e.g. arrhythmias in patients with coronary heart disease. **Cost:** There are no data available directly assessing the cost effectiveness, although the cost is lower where good quality generic preparations are available. It is feasible with an MDI.

Recommendation	Benefits/risks; values and acceptability; cost; feasibility
REC 2	**Benefits/risks:** Theophylline can cause serious adverse effects, particularly if therapeutic blood concentrations are exceeded. Only low-dose slow-release theophylline can be recommended as being relatively safe and providing some efficacy. **Values and acceptability:** Low-dose, slow-release oral theophylline can be effective and well tolerated in the long-term treatment of stable COPD. **Cost:** No data available. **Feasibility:** As it is unlikely that blood levels can be monitored in resource-constrained settings, only low doses of theophylline are recommended. Patients should be advised to stop treatment and consult a doctor if adverse effects are experienced.
REC 3	**Negative recommendation.** Oral corticosteroids (prednisolone) are ineffective in stable COPD except possibly in high doses when there are important side effects. On the basis of the balance between benefits and risks, oral steroids are NOT recommended for use in stable COPD.
REC 4	**Negative recommendation.** When given in high doses, there may be a small benefit from inhaled steroids. However, high doses have more adverse effects and are more expensive, while any benefit is small. Their use for patients with stable COPD cannot be justified when resources are limited.
REC 5	**Negative recommendation.** Compared to regular short-acting beta agonists, short-term inhaled ipratropium bromide has small benefits with regard to reducing symptoms and improving lung function. Currently, ipratropium bromide preparations are more expensive than beta agonists and there are no data to assess risk versus benefits of regular use over longer periods to recommend long-term regular use of ipratropium bromide, thus they are NOT recommended.
Management of exacerbation of COPD	
REC 1	**Benefits/risks:** Since benefits significantly outweigh side effects, antibiotics should be given for all COPD exacerbations with purulent sputum and signs of systemic infection. **Values and acceptability:** Antibiotics are commonly prescribed empirically. Which antibiotic should be prescribed needs to be decided locally according to likely organisms, cost and availability. **Cost:** The cost depends on the antibiotic used.

Recommendation	Benefits/risks; values and acceptability; cost; feasibility
REC 2	**Benefits/risks:** Benefits usually outweigh the risks. Short-term courses of oral steroids in the doses recommended are of benefit for acute exacerbations of COPD and usually have few side effects. **Values and acceptability:** A short course of oral steroids is beneficial and with the doses recommended is associated with minimum risk. However, it is important to weigh potential benefits against side effects for each patient. **Cost:** Affordable for resource-constrained settings. **Feasibility:** There should be easy access for patients with exacerbations of COPD.
REC 3	**Benefits/risks:** Effective for improving lung function in patients with acute exacerbations of COPD. For short-term administration for exacerbations, the benefits of high doses outweigh the risk of potential side effects. The evidence suggests no important advantages of nebulizers over spacers. **Cost:** There are no data available directly assessing the cost effectiveness, although the cost is lower where good quality generic preparations are available. **Feasibility:** Higher doses of inhaled beta agonists should be given to all patients with acute severe exacerbations of COPD where available. Administration either by MDI and spacer or by nebulization is acceptable.
REC 4	**Benefits/risks:** This recommendation is based on observational evidence and strong consensus belief that oxygen is beneficial. High concentrations of supplemental oxygen can lead to the accumulation of carbon dioxide and respiratory acidosis for some people with severe COPD. It is very important, therefore, that when oxygen is administered it is given in a low concentration (24%–28%) using a controlled oxygen delivery device. Patients clearly should not smoke if using or close to an oxygen supply. **Values and acceptability:** If oxygen is available, it should be administered for exacerbations of COPD, as long as a low concentration can be given as prescribed. **Cost:** Short-term use in exacerbations as recommended should be affordable.
REC 5	**Negative recommendation.** Based on the available evidence, intravenous aminophylline is NOT recommended for routine use in acute exacerbations of COPD. Although there are data from only four studies, they show little evidence of benefit; thus any beneficial effect is likely to be small and the risks outweigh benefits.

3. Methodology used to prepare the guideline

The WHO Guideline for Management of Asthma and COPD through a Primary Care Approach in Resource-constrained Settings was prepared according to the WHO Handbook for Guideline Development. The scope in the format of PICOT questions was defined by WHO and circulated to the guideline expert panel members for comments in advance of the guideline expert panel meeting (Annex 3).

The Cochrane Airways Group was consulted to design the search strategy for the finalized scoping questions. A methodologist was contracted to assess the quality of evidence using the Assessment of Multiple Systematic Reviews (AMSTAR) tool and to prepare evidence summaries according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology. The AMSTAR instrument is a validated tool for critically appraising the methodological quality of systematic reviews. It consists of an 11-item questionnaire with each item receiving a score of 1 if the specific criterion was met or a score of 0 if the information was not reported or was unclear or the criterion was not applicable. After applying AMSTAR, the review that scored the highest was selected. Systematic reviews were assessed rather than single studies.

The evidence was assessed according to the GRADE methodology. In this system evidence is classified as high, moderate, low or very low and is defined as follows:

- High: further research is very unlikely to change our confidence in the estimate of effect.

- Moderate: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

- Low: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

- Very low: any estimate of effect is very uncertain.

Factors that were considered in classifying the evidence were: (i) the study design and rigour of its execution; (ii) the consistency of results and how well the evidence can be directly applied to patients; (iii) interventions; (iv) outcomes; and (v) comparator. Other important factors were whether the data were sparse or imprecise and whether there was potential for reporting bias.

The recommendations were drafted according to the GRADE methodology for assessing the quality of evidence and strength of recommendations. The guideline expert panel, comprising clinical experts and scientists in the area of CRDs, guideline methodology, research, pharmacology and policy-making, was convened on 20–21 December 2010 at WHO headquarters in Geneva (see Annex 1 for the list of participants). The meeting was preceded by several teleconference discussions and e-mail consultations. The priority questions and scope of the guideline were discussed and finalized based on the comments provided by the expert panel members during these discussions preceding the meeting.

The guideline expert panel members were involved in the following:

- advising on the priority of questions and scope of the guideline;

- advising on the choice of important outcomes for decision-making;

- commenting on the evidence used to inform the guideline;

- advising on the interpretation of the evidence, with explicit consideration of the overall balance of risks and benefits of each particular intervention for asthma and COPD patients;

- formulating recommendations, taking into account the scope of the guideline, its target audience and resource-constrained settings.

At the guideline expert panel meeting, the members were asked to identify critical clinical outcomes for the purposes of making the recommendations. The expert panel reviewed the available evidence summaries and made recommendations. All recommendations were based on consensus and in accordance with the assessed evidence.

All declarations of interests of the guideline expert panel members were reviewed before the guideline expert panel meeting (Annex 2). None of the members declared any potential conflict of interests relevant to the discussion and recommendations, either personal or institutional. The GRADE tables (Annex 4) were prepared by the members of the guideline expert panel and the methodologist.

Formulating the recommendations included explicit consideration of the quality of evidence, benefits, harms, burdens, costs and values, and preferences. Recommendations were classified as strong or weak, as recommended in the GRADE methodology.

For each recommendation, the final agreement was based on group consensus by the guideline expert panel members using a combination of the following factors:

- evidence balanced for benefits/risks of the intervention;
- costs, values and feasibility of each particular intervention in resource-constrained settings;
- quality of evidence itself (high, moderate, low, very low);
- preferences of the group based on clinical experience of the expert panel members.

Each recommendation was formulated only when full consensus was reached among the expert panel members based on all of the above-mentioned points. As a result, each recommendation was classified either as strong or weak according to the GRADE methodology.

Strong recommendations can be interpreted as:

- most individuals should receive the intervention;
- most well-informed individuals would want the recommended course of action and only a small proportion would not;
- could unequivocally be used for policy-making.

Weak recommendations can be interpreted as:

- majority of well-informed individuals would want the suggested course of action, but an appreciable proportion would not;
- widely varying values and preferences;
- policy-making will require extensive debates and involvement of many stakeholders.

After the guideline expert panel meeting, the WHO Secretariat revised the draft guideline according to the recommendations from the guideline expert panel. Comments are reviewed by the WHO Secretariat and are being incorporated into the final version.

Identification of important outcomes

Summaries of the best available evidence were prepared to inform scoping questions. A list of potential outcomes to be considered by the guideline expert panel was developed both for asthma and COPD scoping questions. The panel members ranked these outcomes and were requested to identify any relevant critical outcomes not included on the list. The panel members were also asked to identify which outcomes they felt were critical, important but not critical, and not important.

The panel members were then asked to score the outcomes, using numbers corresponding to the GRADE importance of outcomes where 7–9 indicated the outcome was critical for a decision, 4–6 indicated it was important, and 1–3 indicated it was not important. Both the average scores for each outcome and the range of scores were considered. The individual scores were discussed and disagreements were resolved by consensus. Outcomes were included roughly in order of their relative importance in the GRADE tables (Annex 4).

Outcomes (asthma)	Outcomes (COPD)
Mortality	Mortality
Quality of life (QoL)	Quality of life (QoL)
Mechanical ventilation	Breathlessness
Cough	Cough
Wheeze	Wheeze
Dyspnoea	Sputum production
Distance walked	Distance walked
Drop-out	Drop-out
Adverse effects	Serious adverse events
PEFR	PEFR
FEV1	FEV1
FVC	FVC

Search strategy, selection criteria, data collection and judgement

The search strategy was to identify systematic reviews relevant to the scoping questions. Once systematic reviews were identified, searches were also conducted for RCTs in order to identify any additional trials not included in the reviews. Summaries of all identified systematic reviews were shared with members of the guideline expert panel before the December 2011 meeting.

For systematic reviews, an advanced search with Medical Subject Headings (MeSH) was conducted. The comprehensive search strategies designed by the Cochrane Airways Group based on approved PICOT questions are described in Annex 5 (in addition, the Cochrane Airways Group Asthma and COPD registers of RCTs were searched). The limits that were applied to the search included: published in the last 10 years; human being only; English language; systematic reviews.

As a result of the AMSTAR quality assessment of the found systematic reviews, nine systematic reviews for asthma and 14 systematic reviews for COPD PICOT questions were selected (Annex 6).

Evidence profiles based on the systematic reviews were created using the GRADE methodology (Annex 4). Using this approach, assessments of the quality of evidence for each important outcome took into account the study design, limitations of the studies, consistency of the evidence across studies, directness of the evidence with respect to the populations, interventions and settings, and the precision of the summary estimate of effect. If there were several relevant systematic reviews, the most recent one of the highest quality was used. The GRADE evidence profiles have been prepared with footnotes that explain the judgements that were made.

In the majority of cases, the quality of evidence for various outcomes ranged from *very low quality to moderate quality.* The primary reason for this is a lack of availability of evidence for the setting for which the recommendations were made, i.e. patient population from LMICs. In all cases, the quality of evidence was downgraded due to indirectness.

The draft recommendations have been sent for external peer review, which are analysed by WHO. The peer reviewers were asked to comment primarily on the comprehensiveness and accuracy of the interpretation of the evidence base supporting the recommendations in the guideline. The document received positive appraisal; however, the comments of peer reviewers are then sent to the guideline expert panel members for their consideration and discussion. Based on the comments received, the WHO writing team will produce the final product. Comments and suggestions from peer reviewers will be addressed to the responsible officer for reply. Responses will be documented and made available upon request. The summary of peer reviewer comments from four independent experts with no conflict of interest is presented below; the full text is available upon request.

All peer reviewers were asked to submit a signed WHO Declaration of Interests form. Where interest was declared, legal advice was sought on whether the expert would be eligible for reviewing the document (Annex 2). The guideline development group is grateful to these reviewers for their contribution to the guideline.

Major comments of peer reviewers:

■ The guideline is focused mainly on treatment and does not address the issue of non-drug prevention such as tobacco or overweight control.

Advice regarding these risk factors would be beneficial. (*Response: provided in the treatment flowcharts*.)

■ Advice on patient education and establishing a partnership "physician–patient" is important to mention. (*Response: provided in the treatment flowcharts*.)

■ Inhaled corticosteroids should include any other inhaled corticosteroids and not only beclometasone. (*Response: see summary decision-making tables*.)

■ Regarding stable COPD recommendations 1 and 4: the lack of studies for short-acting beta agonists >8 weeks appears to be the issue regarding the inability to recommend them regularly. It should be stated that there are no trials – it is not that the trials exist and demonstrate that there is no effect. The search is only up to 2002; in view of the importance of this and the probability of long-term benefits as described for trials >8 weeks, the guideline should make a clear interpretative comment about likely long-term benefits for symptoms and lung function. (*Response: see summary decision-making tables*.)

It is planned initially to introduce the guideline (English printed version as well as an electronic version on the WHO web site) at regional and subregional workshops that will be organized with country support in close consultation with regional WHO representatives. Implementing partners will be invited to these workshops for wider incorporation. The indicators used to evaluate the impact of interventions will be discussed and selected at the workshops. WHO headquarters will provide technical support at the country level for local adaptation of the guideline. Staff from headquarters and regional and country offices will be familiarized with the guideline in order to assist the countries. It is expected that this guideline will be reviewed in 2016.

4. Annex 3. PICOT questions

Asthma

1. How does PEF monitoring compare to symptoms alone?

Population	children ≤16 years of age adults >16 years of age suffering from asthma
Indicator/Intervention	PEF monitoring
Comparator	symptoms monitoring
Outcomes	FEV1 (level and rate of change) or PEF variability, symptoms improved, exacerbations, morbidity (hospitalization, emergency department visits, unscheduled doctor visits, lost days from work and school)
Recomendations	No important differences found between PEF and symptom monitoring.

2. What evidence is there on prn salbutamol versus placebo for mild asthma?

Population	children ≤16 years of age presenting with symptoms of asthma and on no treatment adults >16 years of age
Indicator/Intervention	treatment with salbutamol as required
Comparator	no treatment or placebo
Outcomes	FEV1 (level and rate of change) or PEF variability, symptoms improved, exacerbations, morbidity (hospitalization, emergency department visits, unscheduled doctor visits, lost days from work and school)
Time	Short-term
Recomendations	Use as required for all patients with symptomatic asthma starting with mild intermittent asthma as short-term reliever therapy. No more than 10–12 puffs per day.

3. What evidence is there on when to add beclometasone?

Population	children ≤16 years of age
	adults >16 years of age suffering from asthma treated with prn salbutamol alone or no treatment
Indicator/Intervention	treatment with regular beclometasone at any dose twice daily
Comparator	regular placebo twice daily
Outcomes	FEV1 (level and rate of change) or PEF variability, symptoms improved, exacerbations, morbidity (hospitalization, emergency department visits, unscheduled doctor visits, lost days from work and school and relief medication use)
Time	more than 12 weeks, preferably at least six months
Recomendations	Use as a regular preventer therapy drug for patients with any of the following features:
	■ exacerbations of asthma requiring oral corticosteroids in the last two years;
	■ using inhaled beta2 agonists three times per week or more;
	■ symptomatic three times per week or more;
	■ waking one night per week (or more).
	The reasonable starting daily dose is 400ug per day (200ug in children). Titrate the dose to the lowest dose at which effective control of asthma is maintained.

4. What evidence is there that oral prednisolone should be given in all cases of acute asthma?

Population	children ≤16 years of age
	adults >16 years of age suffering from acute asthma exacerbation
Indicator/Intervention	use of oral prednisolone
Comparator	oral prednisolone not used
Outcomes	FEV1 or PEF, symptoms (diaries), morbidity (hospitalization, emergency department duration, lost days from work and school), mortality due to exacerbations
Time	short-term
Recomendations	Oral prednisolone 40–50mg daily should be given in all cases of acute asthma.
	Continue oral prednisolone 40–50mg daily for at least five days or until recovery.

5. What evidence is there that supplementary oxygen should be given to all hypoxaemic patients with acute severe asthma?

Population	children ≤16 years of age
	adults >16 years of age suffering from acute severe asthma
Indicator/Intervention	use of oxygen
Comparator	oxygen not used
Outcomes	FEV1 or PEF, symptoms (diaries), morbidity (hospitalization, emergency department duration, lost days from work and school), mortality due to exacerbations
Time	short-term
Recomendations	If available, give supplementary oxygen to all hypoxaemic patients with acute severe asthma (to maintain SpO2 level of 94%–98%).
	Lack of pulse oximetry should not prevent the use of oxygen.

6. What is the evidence that salbutamol administered by nebulizer is more efficacious than salbutamol administered by spacer and MDI in acute asthma?

Population	children ≤16 years of age suffering from acute asthma exacerbation
	adults >16 years of age suffering from acute asthma exacerbation
Indicator/Intervention	use of nebulizer
Comparator	use of commercial spacer and MDI delivery of salbutamol
Outcomes	FEV1 or PEF, symptoms (diaries), morbidity (hospitalization, emergency department duration, lost days from work and school), mortality due to exacerbations
Time	short-term

7. What is the evidence that salbutamol administered by commercial spacers is better than salbutamol administered by homemade spacers in acute asthma?

Population	children ≤16 years of age suffering from acute asthma exacerbation
	adults >16 years of age suffering from acute asthma exacerbation
Indicator/Intervention	use of commercial spacer and MDI delivery of salbutamol
Comparator	use of homemade spacer and MDI delivery of salbutamol
Outcomes	FEV1 or PEF, symptoms (diaries), morbidity (hospitalization, emergency department duration, lost days from work and school), mortality due to exacerbations
Time	short-term

8. What evidence is there that nebulized ipratropium bromide should be added to salbutamol for patients with acute severe or life-threatening asthma?

Population	children ≤16 years of age
	adults >16 years of age suffering from acute asthma exacerbation
Indicator/Intervention	treatment with nebulized ipratropium bromide in addition to salbutamol
Comparator	nebulized salbutamol alone
Outcomes	FEV1 or PEF, symptoms (diaries), morbidity (hospitalization, emergency department visits, lost days from work and school), mortality due to exacerbations
Time	short- to long-term
Recomendations	Add nebulized ipratropium bromide 0.5mg 4–6 hourly to salbutamol treatment for patients with acute severe or life-threatening asthma or those with a poor initial response to beta2 agonist therapy.

COPD

1. What evidence is there regarding salbutamol as required for stable COPD treatment?

Population	adults >18 years of age with COPD
Indicator/Intervention	treatment with salbutamol up to two puffs four times daily by MDI (with or without spacer)
Comparator	placebo
Outcomes	quality of life (SGRQ), exacerbations (hospitalization, courses of oral corticosteroids, lost days from work)
Time	minimum of 12 weeks

2. What evidence is there regarding ipratropium as required for stable COPD treatment?

Population	adults >18 years of age with COPD
Indicator/Intervention	treatment with ipratropium up to two puffs four times daily by MDI (with or without spacer) in addition to inhaled salbutamol or alone
Comparator	placebo (when used in addition to inhaled salbutamol in both groups) or inhaled salbutamol alone (when compared to inhaled salbutamol)
Outcomes	quality of life, exacerbations (hospitalization, courses of oral corticosteroids, lost days from work)
Time	minimum of 12 weeks

3. What evidence is there on when to add theophylline?

Population	adults >18 years of age with COPD
Indicator/Intervention	treatment with theophylline in addition to salbutamol or ipratropium
Comparator	salbutamol or ipratropium alone
Outcomes	quality of life (SGRQ), exacerbations (hospitalization, courses of oral corticosteroids, lost days from work)
Time	minimum of 12 weeks

4. What evidence is there on when to add beclometasone (inhaled corticosteroids) and in what dose?

Population	adults >18 years of age with COPD
Indicator/Intervention	treatment with beclometasone by MDI (with or without spacer) in addition to inhaled salbutamol or ipratropium (but not long-acting beta2 agonists or tiotropium)
Comparator	salbutamol or ipratropium alone
Outcomes	quality of life (SGRQ), exacerbations (hospitalization, courses of oral corticosteroids, lost days from work)
Time	minimum of 12 weeks

5. What evidence is there on giving oral prednisolone in COPD exacerbations?

Population	adults >18 years of age COPD patients with acute exacerbation
Indicator/Intervention	treatment with oral prednisolone for exacerbations
Comparator	placebo
Outcomes	hospitalization rate and duration, mortality due to exacerbations and complications, reconvalescence rate
Time	short- to medium-term

6. What are the indications for prescribing antibiotic therapy in COPD exacerbations?

Population	adults >18 years of age COPD patients
Indicator/Intervention	antibiotic therapy
Comparator	placebo
Outcomes	hospitalization rate and duration, mortality due to exacerbations and complications, reconvalescence rate
Time	short- to medium-term

Annex 7:
Summary of recommendations

Diagnosis and management of asthma

Stable asthma

Diagnosis

Asthma and COPD can both present with cough, difficult breathing, tight chest and/or wheezing. If uncertainty exists, the following features make a diagnosis of asthma more likely:

- previous diagnosis of asthma;
- symptoms since childhood or early adulthood;
- history of hayfever, eczema;
- intermittent symptoms with asymptomatic periods in between;
- symptoms worse at night or early morning;
- symptoms triggered by respiratory infection, exercise, weather changes or stress;
- symptoms respond to salbutamol.

Measuring PEF before and 15 minutes after two puffs of salbutamol may also help. If the PEF improves by 20%, a diagnosis of asthma is very probable. However, in practice, most patients with asthma have a smaller response to salbutamol.

Assess asthma control

Asthma is considered to be well controlled if the patient has:

- no more than two occasions a week when asthma symptoms occur and require a beta-agonist;
- asthma symptoms on no more than two nights a month;
- no or minimal limitation of daily activities;
- no severe exacerbation (i.e. requiring oral steroids or admission to hospital) within a month;

■ a PEF, if available, above 80% predicted.

If any of these markers is exceeded, the patient is considered to have uncontrolled asthma.

Treatment

Treatment should be increased or decreased according to how well asthma is controlled and by using the stepwise approach described below. It is useful to start initially with a high step to achieve control and to show the patient that treatment can help, and then reduce the dose to the lowest dose to maintain control. Doses of beclometasone refer to those from an HFA fine dose inhaler; for equivalent doses from other inhalers, the dose may need to be doubled.

Stepwise approach

Step 1. Inhaled salbutamol prn

Step 2. Inhaled salbutamol prn plus low-dose inhaled beclometasone, starting with 100ug twice daily for adults and 100ug once or twice daily for children

Step 3. Same as step 2, but give higher doses of inhaled beclometasone, 200ug or 400ug twice daily

Step 4. Add low-dose oral theophylline to Step 3 treatment (assuming long-acting beta agonists and leukotriene antagonists are not available)

Step 5. Add oral prednisolone, but in the lowest dose possible to control symptoms (nearly always less than 10mg daily)

At each step, check the patient's adherence to treatment and observe their inhaler technique. A spacer normally should be used with MDIs since they increase drug deposition and reduce oral candidiasis with inhaled steroids.

Inhaled beclometasone should be available for all patients with persistent asthma, but if supplies are limited priority should be given to patients with life-threatening attacks and/or frequent exacerbations requiring hospitalization and those losing time from work or school.

Review asthma control

Patients with other than very mild asthma should have regular reviews every three or six months and more frequently when treatment has been changed or asthma is not well controlled. This should always include observation of inhaler technique.

Referral for specialist advice should, depending on facilities available, be considered:

■ when asthma remains poorly controlled;

■ when the diagnosis of asthma is uncertain;

■ when regular oral prednisolone is required to maintain control.

Advice to patients and families

Regarding prevention:

■ avoid cigarette smoke and trigger factors for asthma, if known;

■ avoid dusty and smoke-filled rooms;

■ reduce dust as far as possible by using damp cloths to clean furniture, sprinkling the floor with water before sweeping, cleaning blades of fans regularly and minimizing soft toys in the sleeping area;

■ It may help to eliminate cockroaches from the house (when the patient is away) and shake and expose mattresses, pillows, blankets, etc. to sunlight.

Regarding treatment, ensure that the patient or parent:

■ knows what to do if asthma deteriorates;

■ understands the benefit from using inhalers rather than tablets, and why adding a spacer is helpful;

■ is aware that inhaled steroids take several days or even weeks to be fully effective.

Management of exacerbation of asthma

Assess severity

Assess the severity of asthma by analysing symptoms (ability to complete sentences), signs (e.g. heart rate) and PEF and oxygen saturation, if equipment is available.

Treatment

First-line treatment:

■ prednisolone 30–40mg for five days for adults and 1mg per kg for three days for children, or longer, if necessary, until they have recovered;

- salbutamol in high doses by MDI and spacer (e.g. four puffs every 20 minutes for one hour) or by nebulizer;

- oxygen, if available, and if oxygen saturation levels are low (below 90%).

  Reassess at intervals depending on severity.

  Second-line treatment – to be considered if the patient is not responding to first-line treatment:

- Increase frequency of dosing via an MDI and spacer or by nebulizer, or give salbutamol by continuous nebulization at 5–10mg per hour, if appropriate nebulizer available;

- for children, nebulized ipratropium, if available, can be added to nebulized salbutamol.

  Although the evidence for benefits from intravenous magnesium, intravenous salbutamol and intravenous aminophylline is poor, they may be worth trying, if available, when the patient has not responded to standard treatment and is at risk of dying from asthma.

Diagnosis and management of COPD

Stable COPD

Diagnosis

Both asthma and COPD can present with cough, difficult breathing, tight chest and/or wheezing.

  If there is diagnostic uncertainty, the following features favour COPD:

- previous diagnosis of COPD;

- history of heavy smoking, i.e. >20 cigarettes per day for >15 years;

- history of heavy and prolonged exposure to burning fossil fuels in an enclosed space, or high exposure to dust in an occupational setting;

- symptoms started in middle age or later (usually after age 40);

- symptoms worsened slowly over a long period of time;

- long history of daily or frequent cough and sputum production often

- starting before shortness of breath;

- symptoms that are persistent with little day-to-day variation.

Measuring PEF before and 15 minutes after two puffs of salbutamol may also help. If the PEF improves by 20%, a diagnosis of asthma is very probable. A small response makes COPD more likely although a small response often occurs in asthma.

Assessing severity

Assess severity by symptoms (i.e. as moderate if breathless with normal activity and as severe if breathless at rest), and by PEF and oxygen saturation, if possible.

Treatment

■ inhaled salbutamol, two puffs as required, up to four times daily;

■ if symptoms are still troublesome, consider low-dose oral theophylline;

■ if ipratropium inhalers are available, they can be used instead of, or added to, salbutamol, but they are more expensive.

Advice to patient and family

■ ensure they understand that smoking and indoor air pollution are the major risk factors for COPD. Patients with COPD must stop smoking and avoid dust and tobacco smoke;

■ keep the area where meals are cooked well ventilated by opening windows and doors;

■ cook with wood or carbon outside the house, if possible, or build an oven in the kitchen with a chimney that vents the smoke outside;

■ stop working in areas with occupational dust or high air pollution – using a mask may help, but it needs to have an appropriate design and provide adequate respiratory protection.

Exacerbation of COPD

Management

■ Antibiotics should be given for all exacerbations with evidence of infection.

■ For severe exacerbations, give oral prednisolone 30–40mg for around seven days.

■ Give high doses of inhaled salbutamol by nebulizer or MDI with spacer.

■ oxygen, if available, should be given by a mask that limits the concentration to 24% or 28%.

Prevention and Control of Noncommunicable Diseases:
Guidelines for primary health care
in low-resource settings

Why do we need these guidelines?

■ Noncommunicable diseases (NCDs) affect the poor as well as the affluent.

■ Strokes, heart attacks, complications of diabetes and chronic lung disease entrench people in poverty as a result of catastrophic health expenditure and loss of gainful employment. Early detection and treatment can prevent these NCD complications.

■ Universal coverage is necessary for essential NCD interventions that can be delivered in primary health care even in low resource settings.

■ These evidence based guidelines and tools facilitate implementation of the WHO Package of Essential Noncommunicable Disease interventions (WHO PEN) and WHO Best Buys.

World Health Organization