



Oral glucose-lowering agents in type 2 diabetes mellitus – an update

Updated:
3 August 2017



Key messages

- 1 Establish patient-centred glycaemic targets.
- 2 Individualise treatment plans based on drug and patient profiles.
- 3 Select metformin as the initial glucose-lowering agent as it has long-term efficacy and safety data.
- 4 Use second generation sulfonylureas when metformin is unsuitable or insufficient in achieving control. Avoid chlorpropamide and glibenclamide as they cause more hypoglycaemia than other sulfonylureas.
- 5 SGLT-2 inhibitors are appropriate for patients who are at risk of hypoglycaemia, are overweight, or with cardiovascular disease.
- 6 Reserve DPP-4 inhibitors for patients with renal impairment.

Manage blood glucose together with other cardiovascular risk factors

A major focus in managing type 2 diabetes mellitus (T2DM) is to maintain glycaemic control while minimising risk of hypoglycaemia and other adverse events. Optimal glycaemic control is paramount in reducing microvascular complications.¹⁻³

T2DM increases risk of cardiovascular disease (CVD). Intensive glycaemic control early in the course of T2DM can reduce the risk of future cardiac events and mortality,⁴ but may not improve cardiovascular outcomes in patients with long-standing diabetes and those with increased hypoglycaemia risk.⁵⁻⁷ Therefore, a comprehensive care plan involving blood pressure and lipid control, smoking prevention or cessation, weight management and healthy lifestyle measures is necessary.

Establish patient-centred glycaemic targets

Establish glycaemic targets with patients, taking into account patient and disease factors (Table 1). Other modifiable factors to consider include patients' attitudes towards therapy and the availability of patient support resources.

For most adults, HbA1c targets of < 7.0% are reasonable. However, lower targets of < 6.5% may be appropriate in some patients if these can be achieved without significant hypoglycaemia.

Table 1. Patient-centred glycaemic targets

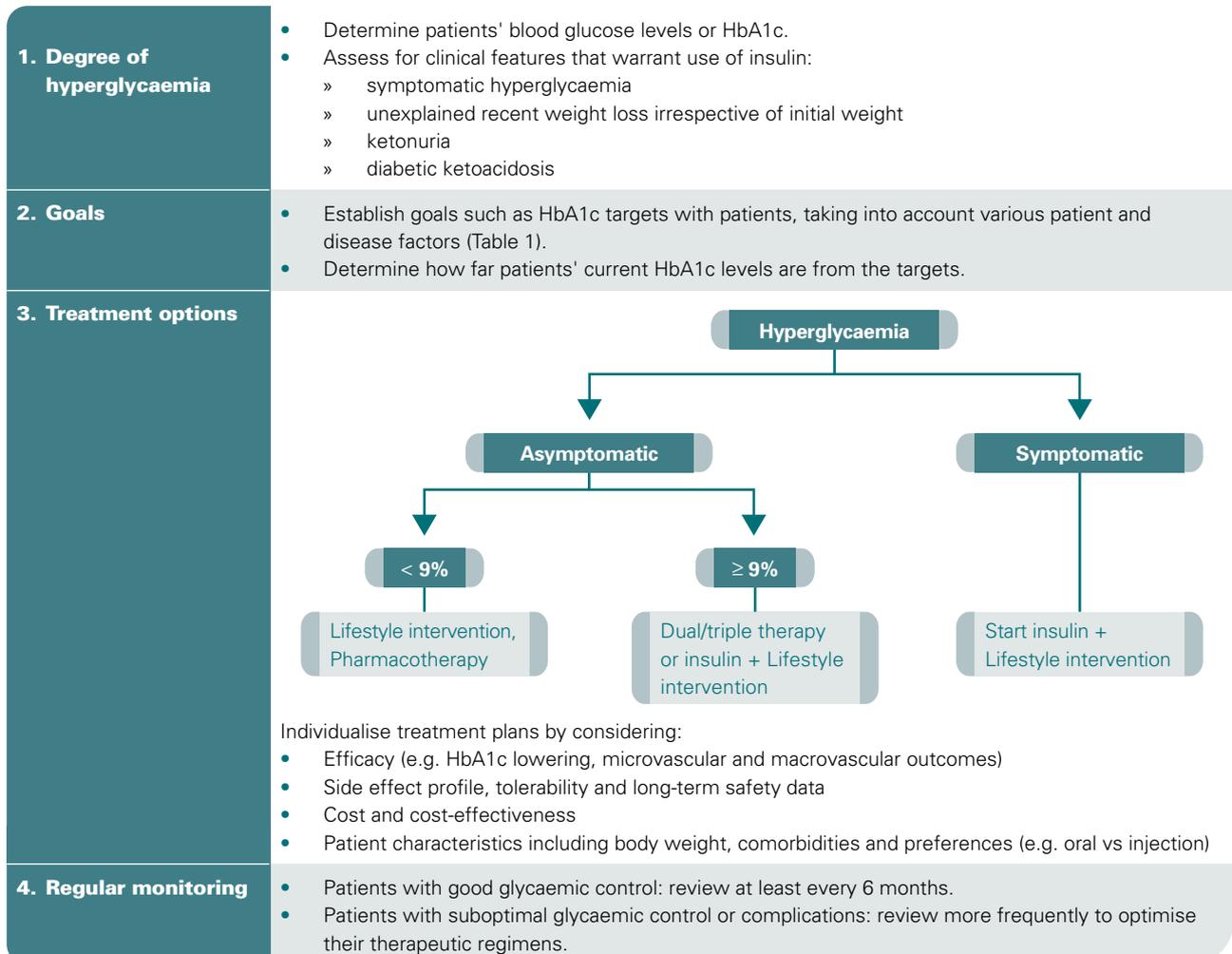
Patient and disease factors	HbA1c 7.0%	
	← More stringent	→ Less stringent
Risk of hypoglycaemia and adverse effects	Low (e.g. younger age)	High (e.g. elderly or frail)
Disease duration	Short	Long-standing
Life expectancy	Long	Short
Comorbidities	Absent few/mild Present	

Adapted from the American Diabetes Association, *Standards of Medical Care in Diabetes, 2017*.⁸

Individualise treatment plans

Individualise treatment plans by considering drug and patient profiles (Figure 1).

Figure 1. Achieving glycaemic control in adults with T2DM



Oral glucose-lowering agents

When lifestyle intervention (i.e. healthy diet, physical activity, weight control) is insufficient in achieving glycaemic control, initiate glucose-lowering agents whilst continuing lifestyle intervention.

Oral agents are preferred over injections due to convenience and acceptability. However, do not delay insulin therapy in patients with symptomatic hyperglycaemia, unexplained recent weight loss irrespective of initial weight, ketonuria or diabetic ketoacidosis.

As the duration of diabetes increases, insulin resistance develops and pancreatic β -cell function progressively declines. Multiple glucose-lowering agents are required to achieve and maintain glycaemic control. Combining agents with different mechanisms of action and side effects can enhance glycaemic control and tolerability.

Metformin (MET) – Preferred initial glucose-lowering agent

Metformin has good HbA1c lowering (1 – 1.5%) and long-term safety data. Titrate the dose gradually and advise patients to take metformin with or after meals to reduce gastrointestinal side effects, such as nausea, vomiting and diarrhoea.

Use metformin with caution in patients with renal impairment and those at risk of lactic acidosis (e.g. patients with hepatic impairment or heart failure).

Long-term use of metformin may be associated with vitamin B12 deficiency. In patients with established anaemia or peripheral neuropathy, monitor B12 levels as part of routine care.⁸

Sulfonylureas (SU) – Use second generation sulfonylureas

Sulfonylureas are typically the next class of drugs used when metformin is unsuitable or insufficient in achieving control. Sulfonylureas lower HbA1c by 1 – 1.5%, are affordable and have long-term safety data.

However, sulfonylureas cause weight gain and pose a risk of hypoglycaemia, especially in the elderly and those with renal or hepatic impairment.

Use second generation sulfonylureas, such as glipizide and gliclazide, which are less likely to cause hypoglycaemia as compared to other sulfonylureas. Avoid chlorpropamide and glibenclamide which have higher hypoglycaemia risks.⁹

Modified-release (MR) gliclazide and glimepiride are taken once daily and may improve patient adherence. However, these tablets are costlier compared to glipizide or immediate-release (IR) gliclazide.

SGLT-2 inhibitors

– For patients who are at risk of hypoglycaemia, are overweight, or with cardiovascular disease

Consider sodium-glucose cotransporter-2 (SGLT-2) inhibitors in patients who cannot tolerate sulfonylureas or when hypoglycaemia is a concern. They lower HbA1c (0.6 – 0.9%), body weight and blood pressure, and may benefit those who are overweight or obese.

SGLT-2 inhibitors have been shown to improve cardiovascular outcomes in T2DM patients. EMPA-REG and CANVAS results show a reduction in heart failure hospitalisations in T2DM patients with established CVD.^{10,11} Results from CVD-REAL suggest that these cardiovascular benefits are a class effect and extend to patients at the lower end of the cardiovascular risk spectrum.¹² Completion of DECLARE TIMI-58 trial (dapagliflozin) will provide more clarity on this.

SGLT-2 inhibitors have been associated with an increased risk of urinary and genital tract infections, diabetic ketoacidosis (DKA) and lower limb amputations (canagliflozin).¹¹ As of 3rd January 2017, thirteen DKA cases have been reported locally (eight with canagliflozin, two with dapagliflozin and three with empagliflozin. Note different utilisation rates for each agent).¹³

Avoid SGLT-2 inhibitors in patients at risk of DKA (e.g. suspected T1DM, severe hyperglycaemia, recent surgery, infection, low caloric or carbohydrate intake, long-standing T2DM or pancreatic insufficiency).

Always counsel patients to seek urgent medical attention if they have symptoms of DKA and pain in their lower limbs. Patients on SGLT-2 inhibitors should also observe good genital hygiene.

SGLT-2 inhibitors work by blocking renal glucose reabsorption and are not recommended for patients with severe renal impairment (Table 2). Consider them as a class and choose the lowest cost option.

DPP-4 inhibitors

– For patients with renal impairment

Dipeptidyl peptidase-4 (DPP-4) inhibitors have similar HbA1c lowering (0.5 – 0.8%) as SGLT-2 inhibitors. They are weight neutral, well tolerated and rarely cause hypoglycaemia. Local cost-effectiveness analyses have shown that MET + DPP-4 inhibitor is not cost-effective compared to MET + SU or MET + SGLT-2 inhibitor. However, consider DPP-4 inhibitors for patients unable to use sulfonylureas (i.e. hypoglycaemia or weight gain) or SGLT-2 inhibitors (i.e. renal or other side effects).

Long-term cardiovascular outcome trials suggest no significant differences in composite cardiovascular endpoints. However, saxagliptin and alogliptin¹⁴ may increase heart failure hospitalisations, particularly in patients with heart or renal disease. The United States Food and Drug Administration (FDA) has issued safety warnings on heart failure with the use of these drugs.¹⁵

DPP-4 inhibitors are suitable for patients with renal impairment with dose adjustments as shown in Table 3. Linagliptin does not require dose adjustments for patients with declining renal functions.

Other glucose-lowering agents

Other oral glucose-lowering agents include meglitinides, thiazolidinediones and alpha-glucosidase inhibitors. Their safety and cost limit their widespread use. Table 4 lists all the oral glucose-lowering agents registered in Singapore while Table 5 lists their efficacy, safety and cost.

Using fixed-dose combinations, such as a sulfonylurea, SGLT-2 inhibitor or DPP-4 inhibitor with metformin, reduce pill burden and improve patient adherence. However, they are less flexible for dose titration.

Glucagon-like peptide-1 (GLP-1) analogues are not widely used as they are only available as injections and are expensive. They activate GLP-1 receptors, increase insulin secretion, decrease glucagon secretion, slow gastric emptying and promote satiety. Liraglutide has been shown to improve cardiovascular outcomes.¹⁶

Figure 2 provides an algorithm for glucose-lowering.

Table 2. Dosing recommendations for SGLT-2 inhibitors in renal impairment

Creatinine clearance (mL/min)	Canagliflozin (Invokana)	Dapagliflozin (Forxiga)	Empagliflozin (Jardiance)
≥ 60	100 mg or 300 mg once daily	10 mg once daily	10 mg or 25 mg once daily
≥ 45 to < 60	100 mg once daily	Not recommended	10 mg once daily
< 45	Not recommended	Not recommended	Not recommended

Table 3. Dosing recommendations for DPP-4 inhibitors in renal impairment

Creatinine clearance (mL/min)	Alogliptin (Nesina)	Linagliptin (Trajenta)	Saxagliptin (Onglyza)	Sitagliptin (Januvia)	Vildagliptin (Galvus)
≥ 50	25* mg once daily	5 mg once daily	2.5 mg or 5 mg once daily	100 mg once daily	50 mg once or twice daily
≥ 30 to < 50	12.5* mg once daily	No dose adjustment needed	2.5 mg once daily	50 mg once daily	50 mg once daily
< 30†	6.25 mg once daily	No dose adjustment needed	2.5 mg once daily	25 mg once daily	50 mg once daily

*Dosing recommendations for alogliptin are creatinine clearance ≥ 60 mL/min: 25 mg once daily, ≥ 30 to < 60 mL/min: 12.5 mg once daily.

†Including end-stage renal disease on haemodialysis

Table 4. Oral glucose-lowering agents registered in Singapore

Drug class	Single agent (Brand)	Fixed-dose combinations (Brand)
1. Biguanides	<ul style="list-style-type: none"> Metformin 	As listed below
2. Sulfonylureas*	<ul style="list-style-type: none"> Gliclazide Glimepiride (Amaryl) Glipizide Tolbutamide 	Glimepiride + MET (Amaryl M)
3. SGLT-2 inhibitors	<ul style="list-style-type: none"> Canagliflozin (Invokana) Dapagliflozin (Forxiga) Empagliflozin (Jardiance) 	Dapagliflozin + MET (Xigduo XR) Empagliflozin + MET (Jardiance Duo)
4. DPP-4 inhibitors	<ul style="list-style-type: none"> Alogliptin (Nesina) Linagliptin (Trajenta) Saxagliptin (Onglyza) Sitagliptin (Januvia) Vildagliptin (Galvus) 	Alogliptin + pioglitazone (Oseni) Linagliptin + MET (Trajenta Duo) Saxagliptin + MET (Kombiglyze XR) Sitagliptin + MET (Janumet, Janumet XR) Vildagliptin + MET (Galvus Met)
5. Meglitinides	<ul style="list-style-type: none"> Nateglinide (Starlix) Repaglinide (Novonorm) 	
6. Thiazolidinediones	<ul style="list-style-type: none"> Pioglitazone (Actos) Rosiglitazone (Avandia) 	Alogliptin + pioglitazone (Oseni)
7. Alpha-glucosidase inhibitors	<ul style="list-style-type: none"> Acarbose (Glucobay) 	

Active ingredients in **BOLD** denote availability on government subsidy list.

*Chlorpropamide and glibenclamide are not included as they should be avoided due to their risk of hypoglycaemia.

List updated as of 3rd May 2017.

MET, metformin

Table 5. Properties of oral glucose-lowering agents

	Biguanides	Sulfonylureas	SGLT-2 inhibitors	DPP-4 inhibitors	Meglitinides	Thiazolidinediones	Alpha-glucosidase inhibitors
How do they work?	Decrease hepatic glucose production	Increase insulin secretion	Inhibit SGLT-2 in the proximal tubules, block glucose reabsorption, ↑ glucosuria (act independent of insulin)	Inhibit DPP-4 activity, prolong incretin action, ↑ insulin secretion & ↓ glucagon secretion (glucose-dependent)	Increase insulin secretion	Increase insulin sensitivity	Slow intestinal carbohydrate absorption
HbA1c lowering*	1 – 1.5%	1 – 1.5%	0.6 – 0.9%	0.5 – 0.8%	0.5 – 1.0%	0.5 – 1.5%	0.5 – 0.8%
Patient affordability†	\$	\$	\$\$	\$\$\$	\$\$\$	\$\$\$	\$\$\$
What to watch out for?							
Hypoglycaemia	Neutral	Moderate	Neutral	Neutral	Mild	Neutral	Neutral
Weight	Neutral or loss (mild)	Gain	Loss	Neutral	Gain (mild)	Gain	Neutral
Cardiovascular	↓ CVD events	–	↓ CVD events & mortality	↑ HF hospitalisations (saxagliptin, alogliptin) ¹⁴	–	<ul style="list-style-type: none"> • HF, oedema • ↑ LDL-C (rosiglitazone) • ↓ CVD events (pioglitazone)¹⁷ 	–
Renal	Avoid if eGFR < 30, reduce dose if eGFR < 45	Hypoglycaemia risk	Not recommended in severe impairment	Dose adjustment (except linagliptin)	Hypoglycaemia risk	Fluid retention	–
Other considerations	GI effects, vitamin B12 deficiency, lactic acidosis (rare), avoid in hypoxic states	–	DKA (rare), volume depletion or hypotension (especially with patients on diuretics, ACE-Is, ARBs), ↑ genitourinary infections, lower limb amputations (canagliflozin)	Skin reactions, joint pain, caution in patients with history of pancreatitis	<ul style="list-style-type: none"> • Improve postprandial control • Do not use with SUs 	<ul style="list-style-type: none"> • 6 - 12 weeks required for maximal effect • Avoid in HF, liver failure (rare hepatotoxicity), ↑ fracture risk 	<ul style="list-style-type: none"> • Improve postprandial control • GI effects - flatulence, diarrhoea

*HbA1c lowering values for monotherapy. The efficacy in dual and triple therapy is not additive and may be impacted by dose, duration of disease and baseline glycaemia.

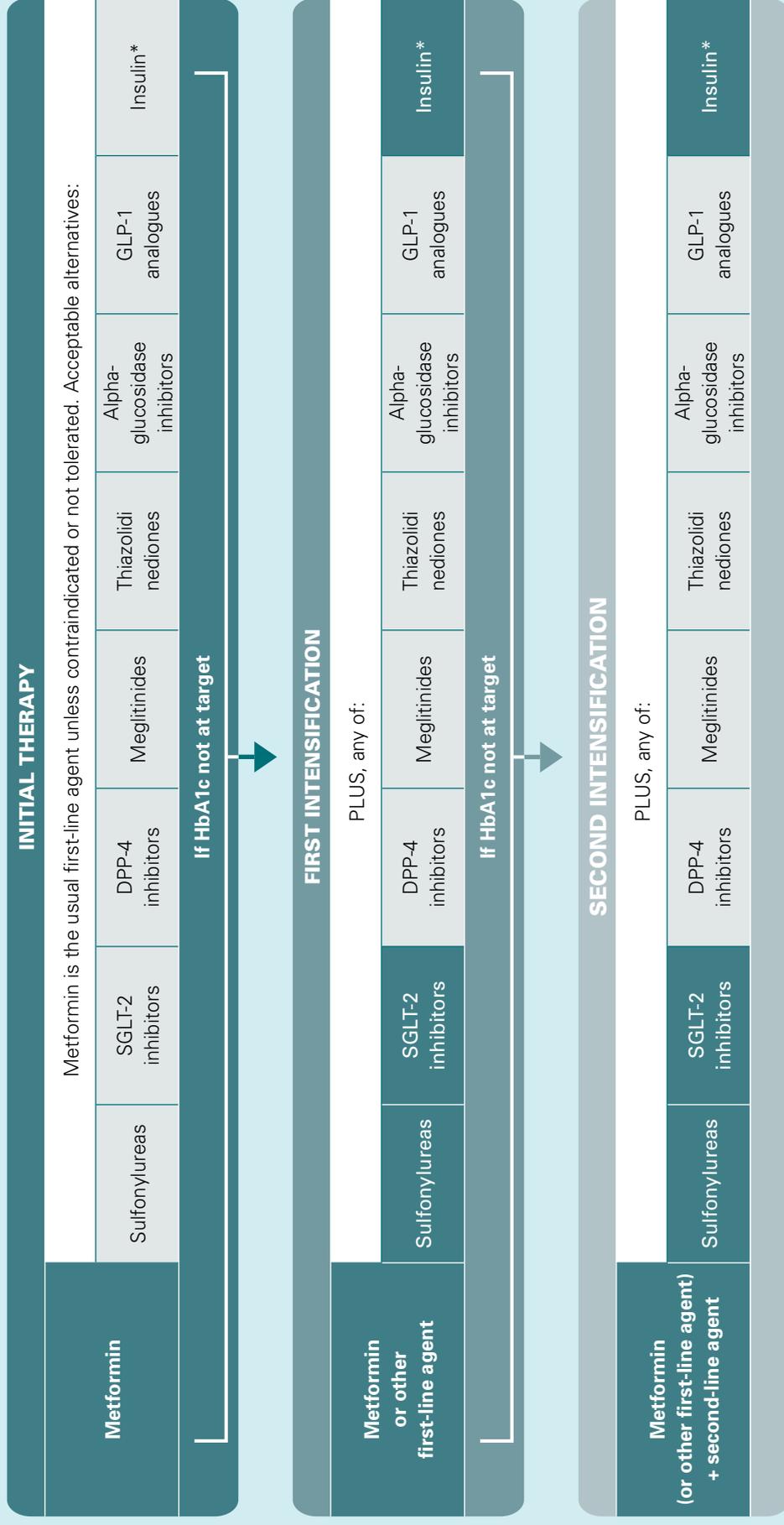
†Price range is indicative for the drug class factoring in subsidy. At the time of publication, dapagliflozin is the only SGLT-2 inhibitor listed on Medication Assistance Fund (MAF).

ACE-Is, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; CVD, cardiovascular disease; DKA, diabetic ketoacidosis; eGFR, estimated glomerular filtration rate; GI, gastrointestinal; HF, heart failure; SU, sulfonylurea.

Note: Table provides a list of some of the common and/or more serious adverse effects. Refer to the product insert for full list of side effects.

Figure 2. Glucose-lowering algorithm

LIFESTYLE INTERVENTION SHOULD BE CARRIED OUT AT ALL STAGES



■ Indicates usual therapy (based on effectiveness, safety or cost-effectiveness)

*Insulin has the greatest glucose-lowering efficacy. It should be initiated for patients:

- with marked hyperglycaemia and/or who are symptomatic.
- who failed to reach, or are unlikely to reach their HbA1c targets with existing treatment or with the addition of another agent.

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Correction added after publication on 3 July 2017: the affiliation for A/Prof. Joyce Lee was corrected to NUS.

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The Agency for Care Effectiveness (ACE) is the national health technology assessment agency in Singapore residing within the Ministry of Health (MOH). ACE develops evidence-based "Appropriate Care Guides" or ACGs to guide a specific area of clinical practice. ACGs are aimed at complementing MOH Clinical Practice Guidelines when these are available, by providing additions and updates as reflected in the evidence at the time of development, and incorporating cost-effectiveness considerations where relevant. The ACGs are not exhaustive of the subject matter. When using the ACGs, the responsibility for making decisions appropriate to the circumstances of the individual patient remains with the healthcare professional. This ACG will be reviewed 3 years after publication, or earlier, if new evidence emerges that requires substantive changes to the recommendations.

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