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Cover picture

JOHN HUNTER FOUNDER OF SCIENTIFIC SURGERY

From an untutored Scottish country boy, John Hunter (1728-1793) rose to become eighteenth-century London's foremost surgeon and medical scientist. Combining natural talent, insatiable curiosity, and keen observation, he was one of the greatest comparative anatomists of all time. The skeletons of the now-extinct Great Auk and of the Irish Giant are two of 13,682 specimens which comprised his famous collections, war-spared remants of which still are on exhibit in London's Royal College of Surgeons. Posthumously, Dr. Hunter was honored as "The Founder of Scientific Surgery"

Second steps in managing type 2 diabetes

Summary

In type 2 diabetes, diet, exercise and attaining a healthy weight should be encouraged at every opportunity.

Metformin is the usual first-line drug management.

Sulfonylureas are appropriate as second-line drugs for many patients. Other oral drugs are preferable if weight gain or hypoglycaemia are significant problems.

If a combination of metformin and a sulfonylurea is not suitable, either a dipeptidyl peptidase-4 inhibitor or sodium-glucose cotransporter 2 inhibitor can be prescribed. The patient characteristics and the beneficial and adverse effects of the drug should be considered when selecting second-line therapy.

Due to their adverse-effect profiles, thiazolidinediones and acarbose should be reserved for patients with contraindications to all other oral drugs, and those who will not tolerate injectable drugs.

Keywords: incretin mimetics, metformin, oral hypoglycaemic drugs, sodium-glucose co-transporter 2 inhibitors, sulfonylureas, type 2 diabetes

(Aust Prescr 2018; ***41****: 141-4)*

Introduction

Type 2 diabetes is a common medical condition, with the prevalence increasing to 1 million people in Australia in 2014–15.[1] The goals of therapy should be individualised, based on patient characteristics, including age and comorbidities. Diet, exercise and a healthy weight are important components of the management.

The range of drugs for type 2 diabetes (see Table) has increased in recent years, delaying the need for insulin therapy, but adding complexity to treatment algorithms. Metformin is first line for drug therapy.[2] Sulfonylureas have a major role as second-line drugs, however there are a number of alternative options that should be considered when weight gain and hypoglycaemia are to be avoided. The choice of second-line drug should be individualised, based on the degree and timing of hyperglycaemia, comorbid conditions and the drug's beneficial and adverse-effect profile.

The Pharmaceutical Benefits Scheme (PBS) has placed some limitations on the prescribing of second- and third-line drugs for type 2 diabetes. These restrictions need to be considered when prescribing, especially as they change from time to time.

Treatment targets

The treatment targets relating to overall glycaemic control, glycated haemoglobin (HbA1c) and glucose monitoring for patients with type 2 diabetes are an important consideration when selecting a second-line drug. These should be individualised, with age, comorbidities, diabetes-related complications, and the person's preferences among a number of factors to be considered. The risk of hypoglycaemia should always be balanced against the benefits of tight glycaemic control.

The Australian Diabetes Society has created a website that includes an algorithm for the management of type 2 diabetes and provides case studies to assist with setting targets. Once a target has been set, treatment should be escalated if the concentration of HbA1c is above the target, or has not improved by at least 0.5% after three months.

Monitoring

The recommended frequency of self-monitoring of glucose depends on the drugs prescribed. For people taking insulin, more frequent monitoring is required, compared to drugs that do not pose a significant risk of hypoglycaemia. However, when starting a second-

Table **Second-line drugs for type 2 diabetes**

Class	Approximate HbA1c reduction*	Benefits in addition to glucose-lowering	Adverse effects	Precautions
Sulfonylureas	0.5–1.3%	Nil	Hypoglycaemia, weight gain	Kidney impairment (dose reduction may be required), severe liver disease, elderly
Dipeptidyl peptidase-4 inhibitors	0.7–1%	Minimal hypoglycaemic risk	Pancreatitis	Pancreatic disease, kidney impairment (dose reduction may be required)
Glucagon-like peptide-1 analogues	0.8–0.9%	Weight loss	Nausea and vomiting	Kidney impairment (contraindicated if CrCl <30 mL/min), pancreatic disease, gallbladder disease, pre-existing gastrointestinal symptoms, family or personal history of thyroid cancer (based on animal models)
Sodium-glucose co-transporter 2 inhibitors	0.5–0.7%	Lowering of blood pressure, cardioprotection, weight loss	Genitourinary infections, euglycaemic ketoacidosis	Fasting or peri-operative state, acute intercurrent illness, taking loop diuretics, kidney impairment (contraindicated if CrCl <45 mL/min)
Insulin	Superior to other diabetes drugs	Nil	Hypoglycaemia, weight gain	Inability to safely administer insulin or monitor glucose
Acarbose	0.8%	Nil	Gastrointestinal symptoms	Gastrointestinal disease, kidney impairment (contraindicated if CrCl <25mL/min), note glucose (not sucrose) must be administered to treat hypoglycaemia
Thiazolidinediones	0.7–0.8%	Nil	Worsening of heart failure, increased fracture risk, macular oedema, cardiac ischaemia, bladder cancer	Osteoporosis, macular oedema, heart failure, liver disease

CrCl creatinine clearance

* The approximate glycated haemoglobin (HbA1c) reduction is based on studies using the class of drug as adjuvant therapy to metformin.

line drug, it is important to be able to both assess the efficacy of the treatment, as well as ensure that there is no significant hypoglycaemia. Glucose should be monitored at least daily and at varied times across the day to provide a picture of the overall glycaemic profile, in particular the effect of meals and activity on glycaemic control. Once someone is stable on a new drug, with the exception of insulin, monitoring frequency can be reduced.

Management

It is essential to counsel people on the importance of diet, exercise and a healthy weight for improving control of type 2 diabetes. These should be discussed regularly to optimise glycaemic control and minimise the dose or number of drugs required to maintain control. Non-drug management is of equal importance in people of healthy weight, as it is in those who are overweight or obese.

Metformin

Metformin is typically prescribed as the first-line drug for type 2 diabetes.[2] It improves insulin sensitivity and is effective in improving glycaemic control. There is no weight gain and a limited risk of hypoglycaemia.

There are some situations in which metformin is contraindicated, such as end-stage kidney disease (creatinine clearance <15 mL/min), or not tolerated, for example, because of gastrointestinal adverse effects. If metformin was not used as the initial drug to manage type 2 diabetes, and no contraindications or previous intolerance exist, then it could be considered as a second-line drug. A dose reduction is required for metformin if the patient's creatinine clearance is less than 90 mL/min. Conditions that alter kidney function may increase the risk of lactic acidosis.

Sulfonylureas

Sulfonylureas such as gliclazide and glibenclamide have traditionally been used as second-line oral drugs, as add-on therapy to metformin. They are effective drugs that should be considered when metformin therapy does not achieve the target for glycaemic control. The reduction in HbA1c is 0.5–1.3% when used in addition to metformin.[3] Sulfonylureas are particularly recommended as second-line drugs if it is anticipated that the patient is likely to need a glucagon-like peptide-1 (GLP-1) analogue as a third-line drug in the relatively near future, for example in an overweight or obese person whose HbA1c is significantly above target.

Sulfonylureas act as insulin secretagogues, so there is a risk of hypoglycaemia and weight gain. Hypoglycaemia is a significant risk in patients with kidney impairment and the elderly, particularly because of the long duration of action.

Incretin mimetics

Incretins are neuroendocrine hormones produced by the gastrointestinal tract in response to food. They are involved in stimulating insulin secretion and suppressing glucagon secretion. Incretins also suppress appetite and inhibit gastric emptying. The major incretin hormones are glucagon-like peptide and glucose-dependent insulinotropic polypeptide (GIP). These hormones are metabolised by dipeptidyl peptidase-4 (DPP-4).

There are currently two types of incretin mimetic drugs that are effective in the management of type 2 diabetes. These are the oral DPP-4 inhibitors and the injectable GLP-1 analogues. The choice between a DPP-4 inhibitor and a GLP-1 analogue may be influenced by a number of factors including patient preference regarding route of administration, desired weight loss (more likely with GLP-1 analogue), and the magnitude of improvement needed for glycaemic control (tends to be greater with GLP-1 analogue when weight loss and appetite effects are also factored in).

Dipeptidyl peptidase-4 inhibitors

DPP-4 inhibitors, also known as gliptins, are effective in reducing postprandial glucose, without a risk of hypoglycaemia. DPP-4 inhibitors are weight neutral, and are generally well tolerated. As adjuvant therapy to metformin, they result in a modest reduction in HbA1c, in the order of 0.7–1%.[4-7] They have been associated with pancreatitis, so should not be prescribed to people with a previous history of pancreatic disease. Regular monitoring of pancreatic function is

not required, however the drug should be stopped if people develop symptoms consistent with pancreatitis and this is confirmed on blood tests.

Glucagon-like peptide-1 analogues

GLP-1 analogues are given by subcutaneous injection. These drugs predominantly target postprandial glucose, without a risk of hypoglycaemia. They have the beneficial effects of increasing satiety, thereby reducing dietary intake and causing weight loss. The expected HbA1c reduction from GLP-1 analogues is 0.8–0.9%.[8,9]

An expected adverse effect is nausea and vomiting, in particular triggered by certain food types and large portion sizes. Like DPP-4 inhibitors, GLP-1 analogues have an increased risk of pancreatitis and pancreatic malignancy, but no routine monitoring of pancreatic function is required.

Several GLP-1 analogues are approved by the Therapeutic Goods Administration, however only exenatide and dulaglutide are currently listed on the PBS. Exenatide is available in a standard-release formulation administered as a twice-daily injection and an extended-release formulation injected weekly. Dulaglutide is administered as a weekly injection. Current PBS authority criteria restrict GLP-1 analogues to use as third-line drugs, prescribed in combination with both metformin and a sulfonylurea, or with either metformin or a sulfonylurea if there is a contraindication to a combination of both oral drugs.

Sodium-glucose co-transporter 2 inhibitors

Sodium-glucose co-transporter 2 (SGLT2) inhibitors, or gliflozins, are the latest class of oral hypoglycaemic drugs. They work by blocking the renal sodium-glucose co-transporter, resulting in an increase in urinary glucose excretion. In combination with metformin they reduce HbA1c by 0.5–0.7%. SGLT2 inhibitors, such as dapagliflozin and empagliflozin, have the beneficial effect of mild weight and blood pressure reduction, due to the diuretic action. Another significant benefit is the cardioprotective effect reported in the EMPA-REG trial,[10] which makes the drugs a good choice for people with or at high risk of cardiovascular disease.

SGLT2 inhibitors can cause a number of adverse effects, which may make them intolerable. The glycosuria results in an increased risk of genital candidiasis and urinary tract infections, which can be severe and recurrent. SGLT2 inhibitors can cause kidney impairment, which is often transient. It is usually due to hypovolaemia as a consequence of the diuretic effect of the SGLT2 inhibitor, and those with pre-existing kidney impairment are at particular risk. There is also a small but clinically significant risk of euglycaemic ketoacidosis,[11] particularly in the perioperative period, when it is recommended that SGLT2 inhibitors are withheld for three days pre- and postoperatively.

Insulin

The role of insulin as a second-line drug is predominantly in people with hyperglycaemia who do not respond adequately to oral hypoglycaemic drugs or incretin mimetics, or in those who have significant symptomatic hyperglycaemia requiring immediate glucose-lowering. Insulin comes in a number of forms, with the frequency of subcutaneous injections ranging from once daily to five times a day. A variety of regimens can be prescribed. These include:

- basal insulin alone
- a basal-plus regimen (basal insulin with a rapid-acting insulin analogue with one meal)
- a basal-bolus regimen (rapid-acting insulin analogue administered with each meal)
- pre-mixed insulins injected one to three times daily.

When insulin is prescribed in type 2 diabetes, it is usually taken in addition to, not instead of, the other hypoglycaemic drugs, minimising the insulin doses required. In particular, metformin should always be continued. Sulfonylureas are an exception, however, and should be stopped once rapid-acting or pre-mixed insulin is commenced, as they will not provide any additional improvement in glycaemic control. They can, however, provide ongoing benefit in those taking only long-acting insulin. The other exception relates to PBS prescribing – the extended-release formulation of exenatide, and dulaglutide are not currently PBS-approved in combination with insulin. If appropriate, these can be switched to the immediate-release

formulation of exenatide, which is approved for use in combination with insulin.

The HbA1c reduction varies depending on dosage and regimen, but it is superior to all other drugs for diabetes.[11] Adverse effects include hypoglycaemia and weight gain. Access to refrigeration is needed to store insulin before use.

Acarbose

Acarbose is an oral hypoglycaemic drug, which has a limited role in the management of type 2 diabetes. It acts by delaying the intestinal absorption of carbohydrates, which causes the undesirable adverse effects of flatulence and other gastrointestinal symptoms. As an adjuvant to metformin, acarbose lowers HbA1c by 0.7%,[11] however this was based on only a few studies with small numbers of patients. Acarbose is generally considered to be less effective at improving glycaemic control than other oral hypoglycaemic drugs, which should be prescribed in preference.

Thiazolidinediones

Thiazolidinediones, also known as glitazones, act as insulin sensitisers, and reduce HbA1c by 0.7–0.8% when used with metformin.[11] These drugs are no longer commonly used because of their adverse effects. Rosiglitazone was associated with an increase in the risk of cardiac ischaemia, and pioglitazone with an increase in the risk of bladder cancer. Both these thiazolidinediones are associated with worsening heart failure, increasing the risk of fracture in people with osteoporosis, and worsening diabetic macular oedema.

Conclusion

There are a number of drugs that are suitable for use as second-line therapy in the management of type 2 diabetes. However, there is no single drug that is consistently superior as adjuvant therapy to metformin and, as a result, treatment algorithms are complex. The choice of second-line therapy should be based on the individual, considering the treatment goals, comorbidities, degree and timing of hyperglycaemia, and the beneficial and adverse effects of each class of drug.

Many people will progress to require more than two drugs to adequately manage their type 2 diabetes. There are a number of possible combinations, the most common being metformin, a sulfonylurea and one of a DPP-4 inhibitor, SGLT2 inhibitor or GLP-1 analogue. The combination of metformin, a DPP-4 inhibitor and an SGLT2 inhibitor has recently gained PBS approval, and is also an effective management option. Specialist advice should be sought if appropriate glycaemic control is unable to be achieved with these combinations, if hypoglycaemia is preventing overall adequate glycaemic control, or if there are significant diabetes-related complications.

Conflict of interest: none declared

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Management of anaphylaxis

Definitions

1. Any acute onset illness with typical skin features (urticarial rash or erythema/flushing, and/or angioedema), plus involvement of respiratory and/or cardiovascular and/or persistent severe gastro-intestinal symptoms.
2. Any acute onset of hypotension or bronchospasm or upper airway obstruction where anaphylaxis is considered possible, even if typical skin features are not present.

Signs and symptoms of allergic reactions

Mild or moderate reactions

* Swelling of lips, face, eyes
* Hives or welts
* Tingling sensation in mouth
* Abdominal pain, vomiting (these are signs of anaphylaxis for insect allergy)

Anaphylaxis

Watch for any one of the following signs of anaphylaxis:

* Difficult/noisy breathing
* Swelling of tongue
* Swelling or tightness in throat
* Difficulty talking or hoarse voice
* Wheeze or persistent cough
* Persistent dizziness or collapse
* Pale and floppy (young children)
* Vomiting abdominal pain for insect stings or bites

Immediate action

1. Remove allergen (if still present).
2. Call for assistance.
3. Lay patient flat. Do not allow patient to stand or walk. If breathing is difficult, allow them to sit.
4. Give intramuscular injection (IMI) of adrenaline (epinephrine) without delay using an adrenaline autoinjector if available or adrenaline ampoules and syringe.

* 1:1000 IMI into outer mid-thigh – 0.01mg per kg up to 0.5mg per dose

Table 1. Adrenaline (epinephrine) dosages chart

Age (years)	*Weight (kg)*	*Adrenaline 1:1000*	*Adrenaline autoinjector*
<1	5-10	0.05-0.1 ml	
1-2	10	0.1 ml	10-20 kg (~1-5yrs) 0.15mg (green labelled device)
2-3	15	0.15 ml	
4-6	20	0.2 ml	
7-10	30	0.3 ml	>20kg (~>5yrs) 0.3mg (yellow labelled device)
10-12	40	0.4 ml	
>12 and adults*	>50	0.5 ml	

* For pregnant women, a dose of 0.3mg should be used.

Note:

* Repeat every 5 minutes as needed.
* If multiple doses are required for a severe reaction (e.g. 2-3 doses), consider adrenaline infusion if skills and essential equipment are available.
* For emergency treatment of anaphylaxis, ampoules of adrenaline 1:1000 should be used for both IM doses and infusion if required.

Positioning of patient

* Laying the patient flat will improve venous blood return to the heart.
* By contrast, placing the patient in an upright position can impair blood returning to the heart, resulting in insufficient blood for the heart and low blood pressure.
* The left lateral position is recommended for patients who are pregnant to reduce the risk of compression of the inferior vena cava by the pregnant uterus.
* Fatality can occur within minutes if a patient stands or sits suddenly.
* For mainly respiratory reactions, the patient may prefer to sit and this may help breathing and improve ventilation. Beware that even sitting may trigger hypotension. Monitor closely. Immediately lay the patient flat again, if there is any alteration in conscious state or drop in blood pressure.
* If vomiting, lay the patient on their side (recovery position).
* Patients must not walk to the ambulance, even if they appear to have recovered.

Supportive management – when skills and equipment are available

* Check pulse, blood pressure, ECG, pulse oximetry, conscious state.
* Give high flow oxygen if available and airway support if needed.
* Obtain IV access in adults and in hypotensive children.
* If hypotensive, give IV normal saline 20ml/kg rapidly and consider additional wide bore IV access.

Additional measures – IV adrenaline infusion in clinical setting

If inadequate response after 2-3 adrenaline doses, or deterioration of patient, start IV adrenaline infusion, given by staff trained in its use or in liaison with an emergency or critical care specialist.

IV adrenaline infusions should be used with a dedicated line, infusion pump and anti-reflux valves wherever possible.

If no infusion pump is available:

* Mix 1 ml of 1:1000 adrenaline in 1000 ml of normal saline.
* Start infusion at 5 ml/kg/hour (~0.1 µg/kg/minute).
* Titrate rate up or down according to response and monitor continuously.

CAUTION: IV boluses of adrenaline are not recommended without specialised training as they may increase the risk of cardiac arrhythmia.

Table 2. Additional measures to consider if IV adrenaline infusion is ineffective

For upper airway obstruction	* Nebulised adrenaline (5ml i.e. 5 ampoules of 1:1000). * Consider intubation if skills and equipment are available.
For persistent hypotension or shock	* Give normal saline (maximum of 50ml/kg in first 30 minutes). * Glucagon (1-2mg IMI or IV as starting dose) especially for patients on beta blockers or has heart failure. * In adults, selective vasoconstrictors metaraminol (2-10mg) or vasopressin (10-40 units) only after advice from an emergency medicine/critical care specialist.
For persistent wheeze	**Bronchodilators:** * Salbutamol 8-12 puffs of 100µg using a spacer or 5mg salbutamol by nebuliser. Note: Bronchodilators do not prevent or relieve upper airway obstruction, hypotension or shock. **Corticosteroids:** * Oral prednisolone 1mg/kg (maximum of 50mg) or intravenous hydrocortisone 5mg/kg (maximum of 200mg). Note: Steroids must not be used as a first line medication in place of adrenaline.

Antihistamines and corticosteroids

The standard treatment of anaphylaxis should also include administration of antihistamines and corticosteroids. Corticosteroids have no immediate effect on anaphylaxis. However, administer them early to prevent a potential late-phase reaction.

Antihistamines

* Antihistamines have no role in treating or preventing respiratory or cardiovascular symptoms of anaphylaxis.
* Do not use oral sedating antihistamines as side effects (drowsiness or lethargy) may mimic some signs of anaphylaxis.
* Injectable promethazine should not be used in anaphylaxis as it can worsen hypotension and cause muscle necrosis.

Corticosteroids

* The benefit of corticosteroids in anaphylaxis is unproven.
* It is common practice to prescribe a 3-day course of oral steroids (e.g. oral prednisolone 1 mg/kg, maximum 50 mg daily) to hopefully reduce the risk of symptom recurrence after a severe reaction or a reaction with marked or persistent wheeze.

Observe patient for at least 4 hours after last dose of adrenaline

Relapse, protracted or biphasic reactions may occur. Patients require overnight observation if:

* They had a severe or protracted anaphylaxis (e.g. required repeated doses of adrenaline or IV fluid resuscitation), or
* Have a history of asthma or severe and protracted anaphylaxis, or
* Have other concomitant illness (e.g. asthma, history of arrhythmia), or
* Live alone or are remote from medical care, or
* Presented for medical care late in the evening.

True biphasic reactions are estimated to occur after 3-20% of anaphylactic reactions.

Follow up treatment including advice for hospital discharge

Adrenaline autoinjector

* If there is a risk of re-exposure (e.g. stings, foods, unknown cause) then prescribe an adrenaline autoinjector before discharge, pending specialist review.
* Teach the patient how to use the adrenaline autoinjector using a trainer device.

Allergy specialist referral

* Refer all patients who present with anaphylaxis for specialist review
* The allergy specialist will:

  Identify or confirm cause.

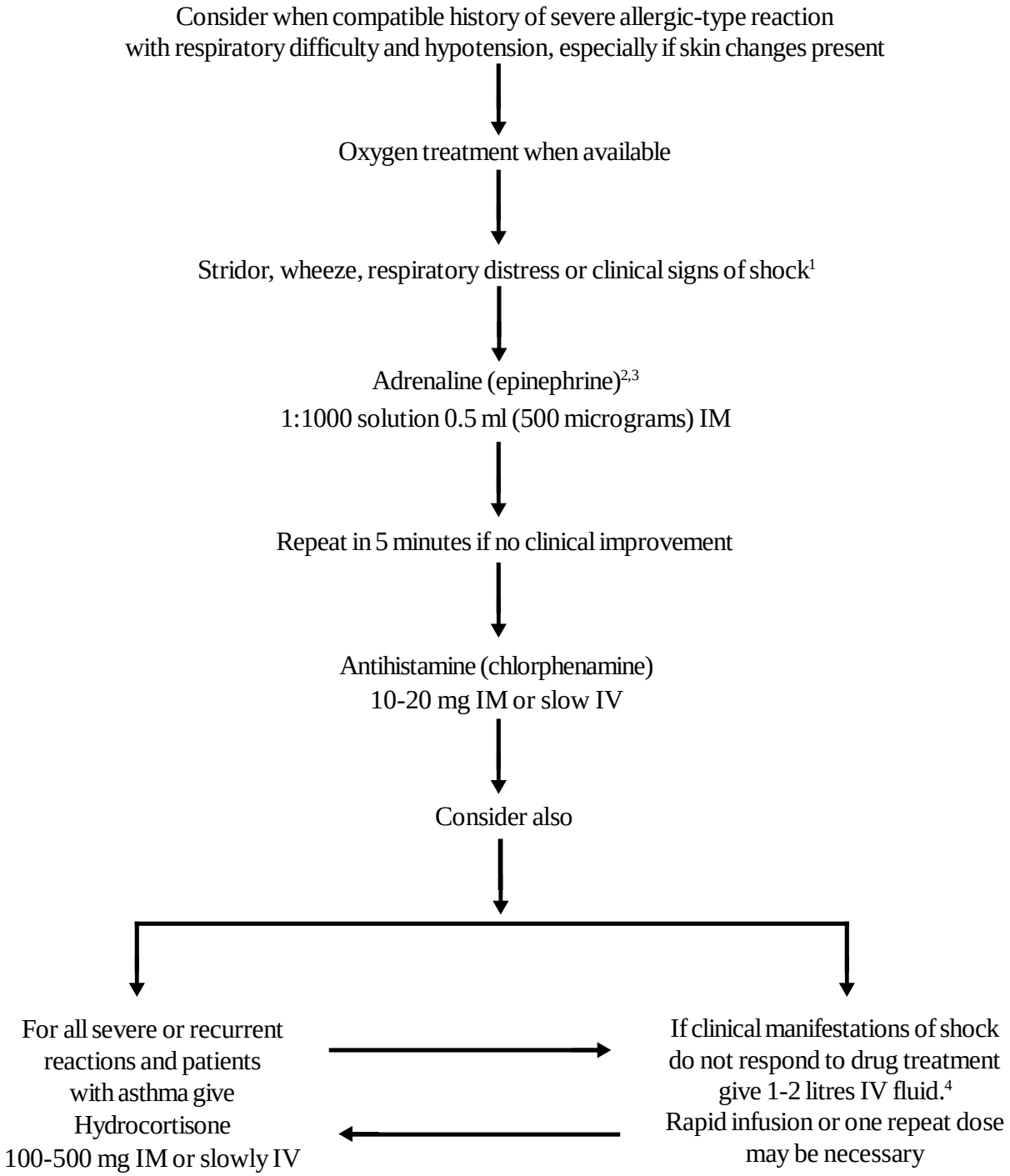
  Educate regarding avoidance and prevention strategies, and management of comorbidities.

  Initiate immunotherapy where available (some insect venoms).

Documentation of episodes

Patients should be advised to document the circumstances of episodes of anaphylaxis to facilitate identification of avoidable causes (e.g. food, medication, herbal remedies, bites and stings, and co-factors such as exercise) in the 6-8 hours preceding the onset of symptoms.

Management Flowchart for Anaphylaxis



1. An inhaled beta-agonist such as salbutamol may be used as an adjunctive measure if bronchospasm is severe and does not respond rapidly to other treatment.
2. If profound shock is judged, consider giving slow IV adrenaline (epinephrine) 1:10,000 solution. This is hazardous and is recommended only for an experienced practitioner. Note the different strength of adrenaline (epinephrine) that may be required for IV use.
3. If adults are treated with an adrenaline autoinjector, 300 micrograms will usually be sufficient. Half doses of adrenaline (epinephrine) may be safer for patients on amitriptyline, imipramine, or beta blocker.
4. A crystalloid may be safer than a colloid.

Supportive management (when skills and equipment available)

* Monitor pulse, blood pressure, respiratory rate, pulse oximetry, conscious state.
* Give high flow oxygen (6-8 l/min) and airway support if needed.
* Supplemental oxygen should be given to all patients with respiratory distress, reduced conscious level and those requiring repeated doses of adrenaline.
* Supplemental oxygen should be considered in patients who have asthma, other chronic respiratory disease, or cardiovascular disease.
* Obtain intravenous (IV) access in adults and in hypotensive children.
* If hypotensive give intravenous normal saline (20 ml/kg rapidly under pressure), and repeat bolus if hypotension persists.

Consider additional wide bore (14 or 16 gauge for adults) intravenous access.

Summary

Patients with severe anaphylaxis should be given immediate treatment with adrenaline.

Addition of a parenteral antihistamine such as chlorphenamine maleate and a corticosteroid such as hydrocortisone may decrease the duration and severity of symptoms and prevent relapse.

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Current information about drug registration

New chemical entities registered

Generic name	Brand name	Dosage form	Manufacturer	Importer	Therapeutic class /use(s)
Cilnidipine	Cilacar- 5	Tablet, 5 mg	Unique Pharmaceutical Laboratories, India	George Steuart	Calcium channel blocker
Cilnidipine	Cilacar- 10	Tablet, 10 mg	Unique Pharmaceutical Laboratories, India	George Steuart	Calcium channel blocker
Azacitidine	Azac	Injection, 100 mg	Shilpa Medicare Ltd, India	Slim Pharmaceuticals	Antineoplastic
Abacavir	Abamune	Tablet, 300 mg	Cipla Ltd, India	Breath Free Lanka (Pvt) Ltd	Nucleoside reverse transcriptase inhibitor
Deflazacort	Yescort	Tablet, 6 mg	Yash Pharma, India	Avenir Pharma Pvt Ltd	Corticosteroid
Febuxostat	Uric-40	Tablet, 40 mg	Alice Pharma, India	ABC Pharma Services	Antigout agent
Colestyramine	-	Powder for oral suspension, 4 g/sachet	Rubio, Spain	Slim Pharmaceuticals	Bile acid sequestrant

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