PAEDIATRIC HOSPITAL LEVEL ESSENTIAL MEDICINES LIST
CHAPTER 7: ENDOCRINE SYSTEM
NEMLC MEETING 9 DECEMBER 2021

MEDICINE AMENDMENTS

SECTION	MEDICINE	ADDED/DELETED/NOT ADDED
7.2 Adrenal hyperplasia, congenital		
Medicine Treatment	Sodium chloride, oral	Dose amended
7.3 Adrenal insufficiency, acute		
Medicine Treatment, stabilisation – prevention	Hydrocortisone, IV	Doses amended
7.4 Diabetes insipidus		
Medicine Treatment, central diabetes inspidus	oral lyophilisate formulation of desmopressin (MELT)	Not added
7.5 Diabetes Mellitus		
Medicine Treatment, Type 1 Diabetes Mellitus	Long acting insulin analogues	Not added
	Insulin therapy, Two injection basal bolus regimen	Deleted
7.6 Hypoglycaemia in children		
Medicine Treatment, stabilisation – prevention	Hydrocortisone, IV	Deleted
	Glucagon, IM, SC	Added
7.8 Hypocalcaemia in Children	Elemental calcium, oral	Dose amended

7.1 Disorders of Sex Development (DSD)

Diagnostic Criteria

Investigations

It was proposed that the specifics of the test for 17-hydroxyprogesterone level related to maternal extraction be removed as this is no longer conducted[1]. This was supported by the Paediatric Hospital Level Expert Review Committee.

The text was amended as follows:

» Elevated 17-hydroxyprogesterone level to confirm diagnosis of adrenal hyperplasia (to be done after day 3 of life ~~with maternal extraction~~ for an accurate interpretation of the result).

[1] Communication with the National Health Laboratory Services

7.2 Adrenal hyperplasia, congenital

Medicine Treatment

An external comment was received to adjust the dose and frequency of sodium chloride which is supported by a consensus statement on 21-Hydroxylase deficiency[2]. The Paediatric Hospital Level Expert Review Committee agreed to the proposed change.

The text was amended as follows:

For salt losing patients:

- Sodium chloride, oral, ~~0.5–1 g for every 10 kg body weight per day~~ 1-2 g daily divided and given with feeds.

7.3 Adrenal insufficiency, acute

Description

Minor textual changes were suggested by an external commentator with which the Paediatric Hospital Level Expert Review Committee agreed.

The text was amended as follows:

Patients on chronic steroid therapy are at risk for adrenal insufficiency if treatment is abruptly stopped.

~~Consider augmentation of the~~ Increase steroid dose during times of stress (fever, trauma and surgery) to prevent adrenal crisis (see below)

Diagnostic Criteria

Clinical

- It was suggested and agreed by the Committee that mild hypercalcaemia as an uncommon symptom be added.

The text was amended as follows:

» Hypoglycaemia
» Hyponatraemia
» Hypercalcaemia (uncommon)

Stabilisation

Prevention

Minor grammatical changes were suggested and accepted by the Committee.

The text was amended as follows:

Patients on chronic steroid therapy are at risk of adrenal insufficiency during stressful situations e.g. sepsis, trauma, elective or emergency surgery. ~~Augment~~ Increase the dose of steroids for the duration of stressful period.

[2] Joint LWPES/ESPE CAH Working Group.. Consensus statement on 21-hydroxylase deficiency from the Lawson Wilkins Pediatric Endocrine Society and the European Society for Paediatric Endocrinology. J Clin Endocrinol Metab. 2002 Sep;87(9):4048-53. doi: 10.1210/jc.2002-020611. PMID: 12213842.

It was proposed by external commentator that the dose of hydrocortisone for minor and major stress be adjusted to double and treble the dose respectively rather than stipulating a specific dose[3]. The Committee agreed with the proposal.

The text was amended as follows:

For major stress, e.g. > 39°C:
- Treble hydrocortisone replacement until recovery (usually 3 days), IV~~, 2 mg/kg/day for the duration of the stress.~~

For minor stress, e.g. URTI, >38°C:
- Double hydrocortisone replacement until recovery (usually 3 days), oral~~, 1 mg/kg/day for 3 days.~~

7.4 Diabetes Insipidus

Desmopressin: oral retained

Desmopressin: nasal spray retained

Desmopressin: oral lyophilisate formulation of desmopressin (MELT) not added

Medicine Treatment

Central diabetes insipidus (Specialist initiated)

The supplier of desmopressin in South Africa has advised that all formulations (spray, drops and oral tablets) except the oral lyophilisate formulation of desmopressin (MELT) will be phased out. However, a timeline for the phase out nor a potential price of the MELT has been provided. This will be further explored by the procurement team. The Committee agreed that the MELT would not be added to the Paediatric Hospital Level Standard Treatment Guidelines at this stage until further information has been provided and the Section 21 for the spray will continue to be pursued in the interim.

7.5 Diabetes Mellitus

7.5.1 Type 1 Diabetes Mellitus

General and Supportive Measures

Constant carbohydrate meal plan

It was proposed by an external commentator that further detail be added under constant carbohydrate meal plan section, which was agreed to by the Paediatric Hospital Level Expert Review Committee.

[3] Bornstein, S. R., Allolio, B., Arlt, W., Barthel, A., Don-Wauchope, A., Hammer, G. D., Husebye, E. S., Merke, D. P., Murad, M. H., Stratakis, C. A., & Torpy, D. J. (2016). Diagnosis and Treatment of Primary Adrenal Insufficiency: An Endocrine Society Clinical Practice Guideline. The Journal of clinical endocrinology and metabolism, 101(2), 364–389. https://doi.org/10.1210/jc.2015-1710

The text was amended as follows:

Consistency is the key. The amount of insulin, usually two or three doses per day, is kept relatively constant from day-to-day. Carbohydrates should be manipulated to match the relatively constant insulin dose. **If able to count carbohydrates, ~~give~~ 1 unit of insulin per 15g of carbohydrate should be given during the day, 1.5 - 2.5 units per 15 g carbohydrates for breakfast, 1.2 units per 15 g carbohydrates for supper and 0.5 units per 15 g carbohydrates during the night.**

Glycaemic Targets

A comment was received highlighting that glycaemic targets for children are moving towards being as strict for children as adults. It was thus agreed by the Committee that the line stating that targets are not as strict for children should be removed.

The text was amended as follows:

Glycaemic targets

» ~~Glycaemic targets for young children should not be as strict as for adults~~. Balance the ability of the family to avoid recurrent hypoglycaemia. A paediatrician should assist in setting practical goals. See table "Monitoring, control and adjustments".

An amendment to acceptable target ranges before meals was suggested in an external comment aligned with recommended tighter glycaemic control for all patients (not differentiating by age) to avoid long term microvascular complications. The values are supported by the International Society for Pediatric and Adolescent Diabetes (ISPAD) Clinical Practice Consensus Guidelines 2018[4].

The text was amended as follows:

- Acceptable target range before meals:
  - > Acceptable target range before meals: 4-8 mmol/l
  - > Acceptable target range after meals: 5-10 mmol/l

	~~**Blood glucose levels**~~
~~> Infants and toddlers~~	~~6– 12 mmol/L~~
~~> School-age children and some young adolescents~~	~~4– 10 mmol/L~~
~~> Most adolescents and young adults~~	~~4– 8 mmol/L~~

- Monitor HbA1c levels 3 monthly. The aim is to maintain HbA1C as close as possible to the recommended range, i.e. 6.5 - 7.5%. Aim for a ~~lower~~ HbA1C ~~in~~ at the lower end of range in patients who are adherent to home glucose monitoring.

Medicine Treatment

Long-acting insulin analogues – see Medicine Review.

[4] Danne T, Phillip M, Buckingham BA, Jarosz-Chobot P, Saboo B, Urakami T, Battelino T, Hanas R, Codner E. ISPAD Clinical Practice Consensus Guidelines 2018: Insulin treatment in children and adolescents with diabetes. Pediatr Diabetes. 2018 Oct;19 Suppl 27:115-135. doi: 10.1111/pedi.12718. PMID: 29999222.

Insulin Therapy

Duration of Action of Standard Insulins

A comment was received suggesting slight amendments to timeframes for duration of action which are aligned with the South African Medicines Formulary. Changes were made to the timeframes of short acting insulins and timeframes retained for intermediate acting accordingly.

The text was amended as follows:

Duration of action of standard insulins

Insulin	Onset of action	Peak action	Effective duration
Regular/short acting	30–60 minutes	2~~–3~~ 4hours	~~8–10~~ 5-8 hours
Intermediate acting	2–4 hours	4–12 hours	12–20 hours

Choice of insulin regimen

It was asserted in an external comment and supported by the Committee that instead of stating that the twice-daily regimen is suboptimal and still including the details thereof, the three injections daily regimen be actively recommended, and the details of the twice-daily regimen be accordingly removed.

The text was amended as follows:

» Multiple daily injections provide for the best glycaemic control in young people with type 1 diabetes. If manageable, the basal bolus regimen should be the regimen of choice. ~~A twice-daily injection regimen is suboptimal.~~ A twice daily injection regimen is not recommended, but 3 injections a day is a good alternative.

Basal Bolus Regimen

Two Injection Daily

The specifications for the Two Injection Daily regimen were removed as agreed above and the following text deleted:

~~**OR**~~

~~Two Injections daily~~

- ~~A mixture (premixed combination) of short and intermediate acting insulins (before breakfast and the main evening meal).~~
- ~~The total daily dose is divided so that $^{2}/_{3}$ is given in the morning and $^{1}/_{3}$ in the evening.~~
- ~~The morning or evening dose is then again split between the intermediate-acting and the short-acting insulin in a 70:30 ratio which is pre-mixed~~
- ~~This regimen is less flexible but easier to instruct.~~

~~**Two injections daily: Premixed 70/30**~~		
~~Breakfast~~	~~intermediate acting (70% of morning dose)~~ ~~+~~ ~~short acting insulin (30 % of morning dose)~~	~~$^{2}/_{3}$ of total daily dose in units~~
~~Supper~~	~~intermediate acting (. 70% of evening dose)~~ ~~+~~ ~~short acting insulin (30% of **evening** dose)~~	~~$^{1}/_{3}$ of total daily dose in units~~

None of these regimens can be optimised without frequent assessment of blood glucose monitoring.

Achieving a balance between food intake, insulin levels and energy expenditure is an essential pre-requisite for achieving glycaemic control.

Adjustment of insulin dosage for 3 injection regimen ~~and 2 injection regimen~~

The insulin dose should not be changed after a single abnormal blood glucose reading.

Adjust the dose only once a pattern has been established. The dose to be adjusted depends on the time of abnormal glucose readings, as indicated in the table below:

	Timing of the unsatisfactory blood glucose level			
	Before breakfast	**Before lunch**	**Before supper**	**At ± 21h00**
~~Two injections daily/ t~~Three injections daily regimens				
Insulin dose to be **increased** if *glucose too high* Insulin dose to be **decreased** if *glucose too low*	~~Supper (in case of premixed insulin) or~~ 21h00 dose: intermediate acting insulin	Breakfast dose: short acting insulin	Breakfast dose: intermediate acting insulin	Supper dose: short acting insulin
	Timing of the unsatisfactory blood glucose level			
	Before breakfast	**2 hours after breakfast**	**2 hours after lunch**	**At ± 21h00**
Basal-bolus regimen				
Insulin dose to be **increased** if *glucose too high* Insulin dose to be **decreased** if *glucose too low*	21h00 dose: intermediate acting insulin	Breakfast dose: rapid (or short acting) insulin	Lunch dose: rapid (or short acting) insulin	Supper dose: rapid (or short acting) insulin

7.5.1.1 Guidelines for management of diabetics on sick days

General and Supportive Measures

Insulin Therapy

It was suggested that the section under general guidelines when giving extra insulin be reworded with more specifics included, which was agreed upon by the Paediatric Hospital Level Expert Review Committee.

The text was amended as follows:

General guidelines when giving extra insulin:

~~» If the blood glucose is rising or if ketones in the urine, the patient must seek urgent medical attention.~~

~~Moderate urine ketones~~

~~» The extra dose of insulin is usually 10–20% of the total daily dose.~~

~~This extra insulin is given as short (or rapid) acting insulin every 3 hours.~~

~~If the blood glucose drops < 8.3 mmol/L, it may be necessary to sip regular juice or other sugar-containing drinks. This is done to raise the blood glucose before giving the next insulin injection.~~

~~Large amount of urine ketones~~

~~» Give 20% of the total daily insulin dose.~~

~~Repeat as above if necessary.~~

» **If the blood glucose is > 14 mmol/l and capillary beta-hydroxybutyrate ≥ 1.5 mmol/l or if ketones > 1+ in the urine, the patient must seek urgent medical attention.**

» **If no ketonaemia/ketonuria:**

> **Blood glucose 14-22 mmol/l**: Add 5% of total daily dose (TDD) of insulin or 0.05 u/kg to ordinary bolus.

> **Blood glucose > 22 mmol/l**: Add 10% TDD or 0.1u/kg to ordinary bolus, drink sugar-free fluids

Check blood glucose and ketones every 2 hours, repeat additional insulin if needed every 2-4 hours.

Extra Fluids

Minor amendments were recommended and accepted by the Committee under the extra fluids section.

The text was amended as follows:

In addition to taking extra insulin, extra sugar-free fluids, ~~e.g. water and fruit juices~~ are important to prevent dehydration ~~acidosis~~. If blood glucose < 10 mmol/l (if intake is poor), sugar-containing fluid should be given (to prevent ketosis). ~~These fluids replace the fluids lost in the urine and prevent dehydration.~~

7.5.2.2 Diabetic Ketoacidosis

Diagnostic Criteria

Minor edits were suggested by an external commentator under diagnostic criteria and were accepted by the Paediatric Hospital Level Expert Review Committee.

The text was amended as follows:

DIAGNOSTIC CRITERIA

» Heavy glycosuria (~~2~~3+ or more)

» Hyperglycaemia, i.e. blood glucose ~~usually~~ > 11 mmol/L, ketonuria 2+

» Blood gas: pH < 7.3, ~~B~~bicarbonate < 15 mmol/L ~~**and** patients who are clinically dehydrated.~~

» Polyuria, polydipsia and dehydration

» Kussmaul respiration, nausea, vomiting, abdominal pain, depressed level of consciousness are all late signs

~~» May be vomiting.~~

~~» May be drowsy.~~

Medicine Treatment

Fluids

It was suggested that the calculation of fluid replacement be reformatted into tables, which the Committee agreed upon.

The text was amended as follows:

Calculation of fluid requirement during the subsequent phase of rehydration

Maintenance (over 24hrs)

≤ 10 kg	100ml/kg/24 hrs
11-20 kg	1000 ml + 50ml/kg/24hr for each kg from 11-20
> 20 kg	1500 ml + 20 ml/kg/24hr for each kg > 20

Obese children: Use ideal body weight for height

+

Rehydration (over 48 hours)

5% dehydrated	50ml/kg/48hrs
10% dehydrated	100ml/kg/48hrs

Review at least 2 hourly.

+/- Ongoing losses

Replace urine loss in excess of 2ml/kg/hour	= urine output in ml/kg/hr – 2 ml/kg/hr

Review at least **2 hourly**

~~Calculation of fluid requirement during the subsequent phase of rehydration (see table below for the calculations determined for different weights)~~	
~~Fluid requirement = deficit + maintenance~~	
~~Calculate deficit = estimated % dehydration x body weight (kg and equivalent in mL)~~	
~~Calculate maintenance (mL):~~	
~~≤1 year:~~	~~120 mL/kg/24 hours~~
~~All children older than 1 year – the sum of the following:~~	
~~• first 10 kg body weight:~~	~~100 mL/kg/24 hours~~
~~• second 10 kg body weight:~~	~~50 mL/kg/24 hour~~
~~• additional weight > 20 kg body weight:~~	~~20 ml/kg/24 hours~~
~~Add deficit to 48 hour maintenance and replace this volume evenly over 48 hours, initially with sodium chloride 0.9%. When blood glucose falls to 12–15 mmol/L change the infusion to a dextrose-containing maintenance fluid, e.g. dextrose 5% in sodium chloride 0.45%.~~	
Assess hydration status and repeat VBG every 4–6 hours	

An additional comment was proposed and agreed upon by the Committee. The following line was added to the text accordingly.

Note: Sodium chloride 0.9% is preferred for resuscitation and the initial phase of rehydration. However, to prevent the occurrence of hyperchloraemic acidosis switch to sodium chloride 0.45%/dextrose 5% after blood glucose has fallen to 12 mmol/L or less. Monitor sodium and chloride (on VBG) 4-6 hourly and adjust maintenance fluids as necessary.

It was proposed and agreed by the Committee that an infusion rate range be added for short acting insulin in line with the International Society for Pediatric and Adolescence Diabetes guidelines[5]. It was also agreed that blood glucose levels be aligned. An external comment suggested minor rewording under the section, which was agreed upon by the Committee.

The text was amended as follows:

Insulin

- Insulin short acting, 0.05-0.1 unit/kg/hour as a continuous IV infusion.
  - Add insulin, 50 units (0.5 mL) to 50 mL sodium chloride 0.9% in a syringe pump to get a solution of 1 unit/mL.
  - Use a separate canula and line for insulin administration.
  - Do not add insulin to the vacolitres administering maintenance and rehydration fluids.
  - ~~Attach this using a Y-connector to the IV fluids already being administered.~~
  - ~~Do not add insulin directly to the fluid bags.~~
  - ~~The solution should be administered at a rate of 0.1 mL/kg/hour~~
  - ~~(0.1 unit/kg/hour).~~

  If the rate of blood glucose fall exceeds 5 mmol/ L/hour or the blood glucose falls to 147 mmol/L:
  - Add a dextrose-containing fluid.
  - Do not stop the insulin infusion while dextrose is being infused.

  If the blood glucose falls below ~~4~~5 mmol/L:

7.5.2.3 Hypoglycaemia in Diabetes

Medicine Treatment

It was proposed in external comment that blood glucose level be aligned with ISPAD guidelines with which the Paediatric Hospital Level Expert Review Committee agreed.

The text was amended as follows:

Mild or moderate hypoglycaemia:

Immediate oral rapidly absorbed simple carbohydrate, e.g.:

- Glucose, oral, 5–15 g or 1-3 level teaspoons of sugar (depending on child's age) in a small amount of water.
  - Wait 10–15 minutes.
  - If blood glucose has not risen by 3-4 ~~to 6-8~~ mmol/L, repeat above.
  - As symptoms improve, the next meal or oral complex carbohydrate should be ingested, e.g. fruit, bread, cereal, milk, etc.

[5] Wolfsdorf et al. 2018. ISPAD Clinic Practice Consensus Guidelines 2018: Diabetic ketoacidosis and the hyperglycemic hyperosmolar state. Available: https://www.ispad.org/page/ISPADGuidelines2018

7.5.2.5 Dyslipidaemia

Diagnostic Criteria

The safety of statins in children under 8 years was discussed specifically related to demyelination. This was explored and limited data was found. The current text does not recommend statins for children under 8 years and cases of homozygous familial hypercholesterolaemia are referred. It was asserted that the screening should be amended from 5 years to 8 years, and this was agreed by the Paediatric Hospital Level Expert Review Committee.

The text was amended as follows:

Children should be screened for dyslipidaemia if any of the following are present:

- Family history of premature cardiac disease or dyslipidaemia
  > Children should be screened ~~at 5 years and again at~~ from 8 years. Children should be screened earlier than ~~5~~ 8 years if homozygous familial hypercholesteremia is suspected.
- A medical condition associated with dyslipidaemia: diabetes mellitus, nephrotic syndrome, liver disease, obesity.

7.6 Hypoglycaemia in Children

Medicine Treatment

It was suggested and agreed by the Committee that hydrocortisone should be removed under treatment as this is currently not being practised, and glucagon should be added at the standard dose under stabilisation. Furthermore, an external comment was received proposing an increase in the dextrose water concentration if required under stabilisation.

The text was amended as follows:

MEDICINE TREATMENT

After collection of initial blood samples:

- Dextrose 10%, IV, 2–5 mL/kg.
  - Dilute dextrose 50% solution before use to 10% strength.

  (1 mL/kg of dextrose 50% plus 4 mL/kg of water for injection, gives 10% dextrose solution).

~~If hypoglycaemia persists or the serum glucose is difficult to maintain in the normal range, consider adrenal insufficiency:~~

~~ADD~~

- ~~Hydrocortisone, IV, 2–3 mg/kg, immediately.~~

Stabilisation

- Sodium chloride 0.9%/dextrose 5%~~, or a 10% dextrose IV infusion if needed.~~
- Increasing the dextrose concentration in the fluid to 7.5% or 10% may be necessary:
  - To increase from 5% to 10% dextrose concentration in 1 L of fluid, add 100 ml 50% dextrose water
  - 10 ml 50% DW increases dextrose concentration of 100ml of fluid by 5%

~~If hypoglycaemia persists, consider adrenal insufficiency or hyperinsulinism. Hyperinsulinism is likely in the neonate if the rate of glucose infusion required to maintain normoglycaemia is above 8mg/kg/min.~~ For persistent hypoglycaemia consider the underlying cause, e.g. hyperinsulinism or

adrenal insufficiency (refer to section). For persistent hypoglycaemia in the neonate, see Chapter 19 Prematurity and Neonatal Conditions.

An inappropriately high insulin or C-peptide level at the time of the confirmed hypoglycaemia is also strongly suggestive of hyperinsulinism.

If hyperinsulinism is suspected, administer:

- Glucagon, IM/SC.
  - If < 12 years of age: 0.5 mg.
  - If > 12 years of age: 1.0 mg.

AND

- Diazoxide, orally, 5 mg/kg/day in three divided doses, may increase to 15 mg/kg/day.

7.7 Growth Disorders

Diagnostic Criteria

Several minor changes were recommended which were accepted by the Paediatric Hospital Level Expert Review Committee.

The text was amended as follows:

» A child is regarded as short if his/her height for age z-score is below –2 for ~~gender~~ age and sex
» To further evaluate short stature, assess parental height. Target height:
  > for a boy = (father's height + (mother's height + 13 cm)) ÷ 2, range 10cm above and below target height.
  > for a girl = ((father's height – 13 cm) + mother's height) ÷ 2, range 9 cm above and below target height.
» If the child's predicted final height is ~~> 10 cm~~ below the target height range, monitor growth velocity over 6 months to 1 year.

7.8 Hypocalcaemia in children

Description

An external comment suggested adding hyperventilation as a cause of hypocalcaemia upon which the Paediatric Hospital Level Expert Review Committee agreed.

The text was amended as follows:

The main causes of hypocalcaemia in children are:
» vitamin D deficiency,
» calcium deficiency,
» magnesium deficiency,
» reduced parathyroid hormone production or resistance,
» impaired renal function.,
» hyperventilation.

7.8 Hypocalcaemia in Children

Medicine Treatment

Chronic Therapy

It was proposed and accepted by the Paediatric Hospital Level Expert Review Committee that the dose of calcium be changed to a range in line with the South African Medicines Formulary.

The text was amended as follows:

- Calcium, elemental, oral, 45-65~~50~~ mg/kg/day until normal calcium level is achieved (given with meals).
  - Maintenance dose: 30 mg/kg/day.

7.11 Hypopituitarism

Description

Suggestions were proposed and accepted by the Paediatric Hospital Level Expert Review Committee under the description section.

The text was amended as follows:

The deficiency may be due to:

» congenital abnormalities with/without midline structural abnormalities of the brain,

» central nervous system tumours, e.g. craniopharyngioma, histiocytosis

» ~~histiocytosis,~~

» complications of radiation therapy.

Diagnostic Criteria

Clinical

Suggestions were proposed and accepted by the Committee and the text was amended as follows:

Clinical

» Neonates with hypopituitarism may present with:
  > persistent hypoglycaemia,
  > cholestatic jaundice (related to low cortisol),
  > micropenis.

» ~~Growth failure with immature body proportions~~ Short stature with normal or high BMI.

» Polydipsia, polyuria, nocturia, enuresis in the case of panhypopituitarism.

7.12 Hypothyroidism, congenital

Description

A minor change was recommended and accepted by the Paediatric Hospital Level Expert Review Committee and the text was amended as follows:

Congenital deficiency of thyroid hormone due to:
» aplasia/hypoplasia or ectopia of the thyroid gland,
» Thyroglobulin defects,
» defects in thyroid hormone biosynthesis, or
» intrauterine exposure to antithyroid medicines.

Medicine Treatment

It was recommended that the range stipulated under TSH value for oral levothyroxine be deleted.

The text was amended as follows:

- Levothyroxine, oral, 10-15 mcg/kg as a single daily dose on an empty stomach.
  - Adjust dosage to blood levels of T4 (in the upper half of the reference range) and normalise the TSH ~~(between 0.5–2 mU/L)~~, especially in the first 3 years of life. Check TSH only 6 weeks after adjusting the thyroxine dose.
  - Continue treatment indefinitely.

MEDICINE AMENDMENTS

SECTION	MEDICINE	ADDED/DELETED/NOT ADDED
7.2 Adrenal Hyperplasia, Congenital		
Medicine treatment	Hydrocortisone	Dosing retained
Medicine treatment	Fludrocortisone acetate	Dosing retained
7.3 Adrenal insufficiency, acute		
Medicine treatment	Hydrocortisone	Dosage form amended from IV to oral
7.4 Diabetes insipidus		
Central diabetes insipidus (Specialist initiated)	Desmopressin	Oral retained
	Desmopressin	Nasal spray retained
	Desmopressin	Solution not added
7.5. Type 1 Diabetes		
Medicine Treatment	Analogue insulins	Not added
7.5.2.5 Dyslipidaemia		
Medicine Treatment	Statins	Retained as a class recommendation
7.6 Hypoglycaemia in Children		
Hypoglycaemia not responding to available treatments	Diazoxide	Dosing retained

7.1 Disorders of Sex~~ual~~[6] Development (DSD)

Description

The text was amended as follows:

The current terminology for neonates or children presenting with incomplete differentiation of the external genitalia is “disorder of sex~~ual~~ development”.

[6] Hughes IA. Disorders of sex development: a new definition and classification. Best Pract Res Clin Endocrinol Metab. 2008 Feb;22(1):119-34. doi: 10.1016/j.beem.2007.11.001. PMID: 18279784.

Diagnostic Criteria

Clinical

The text was amended as follows:

» DSDs present with one or more of the following:
  > varying degrees of hypospadias~~, sometimes with chordee~~

It was highlighted by an external commentator and agreed by the Paediatric Hospital Level Expert Review Committee (ERC) that the below text is very important and thus it was inserted into a text box.

» Suspect congenital adrenal hyperplasia in an infant with non-palpable gonads and DSD.

Investigations

It was agreed by the Paediatric Hospital Level ERC that some investigation may be conducted in discussion with a referral centre.

The text was amended as follows:

» Further investigations ~~done in the referral centre.~~ (in discussion with referral centre):
  > Genitourinary imaging (e.g. ultrasound).
  > Genetic evaluation.

7.2 Adrenal hyperplasia, congenital

Hydrocortisone: *Dosing retained*

Fludrocortisone acetate: *Dosing retained*

General and supportive measures

An external commenter added the following text: "Surgical correction of genital abnormalities if the parents request." The Committee noted that mentioning surgical correction should not be considered for this level of care and recommended that this be removed. It was noted that all these patients should be referred.

Medicine Treatment

External comment was received regarding dosing hydrocortisone and fludrocortisone acetate. Both to be initiated with a sub-specialist thus dosing remains unchanged and is aligned with the South African Medicines Formulary[7]. Where possible it is preferable to prescribe by weight rather than body surface area.

[7] South African Medicines Formulary 13th Edition, 2019.

Diagnostic Criteria

The text was amended as follows:

- Neonates with disorder of sex~~ual~~ development (ambiguous genitalia).

7.3 Adrenal insufficiency, acute

Hydrocortisone: *Dosage form amended from IV to oral*

The Paediatric Hospital Level ERC agreed that hydrocortisone in oral form would be more appropriate for minor stress rather than admitting the child into hospital.

The text was amended as follows:

For minor stress, e.g. URTI:

- Hydrocortisone, ~~IV~~ oral, 1 mg/kg/day for 3 days.

7.4 Diabetes Insipidus

Desmopressin: oral retained
Desmopressin: nasal spray retained
Desmopressin: solution not added

Medicine Treatment
Central diabetes insipidus (Specialist initiated)

An external comment was received regarding inclusion of desmopressin solution. The solution is however no longer registered in South Africa.

The text was amended as follows:

Older children:

- Desmopressin, oral, 50–300 mcg/day 8 hourly.
    - Start at the lowest dose and titrate up ~~Titrate~~ according to response. Use the lowest dose at which an antidiuretic effect is obtained.
    - Maximum dose: 1200 mcg daily.

Younger children ~~Infants or where oral administration is not feasible~~:

- Desmopressin, nasal spray, 10 mcg/day (0.1 mL), starting dose.

- Titrate according to response. Use the lowest dose at which an antidiuretic effect is obtained.
- Maximum daily dose: 30 mcg/day once or twice daily.

7.5 Diabetes Mellitus

7.5.1 Type 1 Diabetes Mellitus

External comment was received regarding the limited medicines available which is noted by the Paediatric Hospital Level ERC however it was agreed that the cost impact would be large and thus the addition of medicines such as analogue insulins cannot be considered at this time.

General and Supportive Measures
Constant Carbohydrate Meal Plan

The text was amended as follows:

The amount of ~~carbohydrates~~ carbohydrate (types can vary) is kept about the same for each meal and each snack from one day to the next.

Glycaemic targets

The text was amended as follows:

Monitor HbA1c levels 3 monthly. The aim is to maintain HbA1C as close as possible to the recommended range, i.e. 6.5 - 7.5%. Aim for a lower HbA1C in patients who are adherent ~~with regard~~ to home glucose monitoring.

~~Blood or~~ Urine ketone testing

Availability of tests for capillary beta-hydroxybutarate level at regional hospital level was a concern thus the Paediatric Hospital Level ERC proposed that testing pertain to urine only.

The text was amended as follows:

~~Blood or~~ Urine ketone testing

» ~~Hyperglycaemia and a capillary beta-hydroxybutarate level > 3 mmol/l Lindicates that DKA is present. At levels of 0.6-0.3.0 mmol/lL a mild DKA may still be diagnosed.~~

» ~~If capillary beta-hydroxybutarate strips are not available, significant ketonuria (+++) and hyperglycaemia may also indicate that a DKA is present.~~

» Test ~~capillary blood or~~ urine for ketones in the following circumstances:

> if vomiting occurs,

> any time the blood glucose > 15 mmol/L, especially if the child is unwell and particularly if the blood glucose has been high for more than 24 hours,

> if unusual drowsiness is present,
> in the presence of high temperature, vomiting or diarrhoea, even when the glucose is < 15 mmol/L,
> if abdominal pains occur,
> if the breathing is deep and rapid or smells of acetone.

Medicine Treatment
Insulin therapy

The text was amended as follows:

Principles of insulin therapy:
» To provide sufficient insulin throughout the 24-hour period to cover basal requirements.
» To deliver ~~higher~~ boluses of insulin in an attempt to match the glycaemic effect of meals.

The text was amended as follows:

Adjust the dose only once a pattern has been established. The dose ~~which is~~ to be adjusted depends on the time of abnormal glucose readings, as indicated in the table below:

7.5.1.1 Guidelines for management of diabetics on sick days

Diagnostic Criteria

The text was amended as follows:

» Unstable blood glucose measurements ~~as a result of~~ because of illness, stress or starvation.

7.5.2.3 Hypoglycaemia in diabetics

Medicine Treatment
Severe hypoglycaemia

It was outlined that the glucagon dose is recommended both by weight and by age. It was proposed that one recommendation should be included, and the age recommendation is the simpler of the two.
The text was amended as follows:

Outside hospital
- Glucagon, IM/SC~~, 0.1–0.2 mg/10 kg body weight.~~
  - If < 12 years of age: 0.5 mg.
  - If > 12 years of age: 1.0 mg.

7.5.2.5 Dyslipidaemia

The Paediatric Hospital Level ERC agreed that the section on Dyslipidaemia should primarily be included in the Endocrine chapter with a cross-reference included in the Cardiovascular chapter to the section in the Endocrine Chapter rather than the section falling primarily under the Cardiovascular Chapter, as it is in the current edition of the Paediatric Hospital Level Standard Treatment Guidelines (STGs) and Essential Medicines List (EML). It was asserted that the condition is most often attended to by endocrinologists rather than cardiologists.

Diagnostic Criteria

It was agreed by the ERC that the screening for dyslipidaemia be more detailed in particular in relation to familial dyslipidaemia. A reference for familial hypercholersteraemia was utilised to source recommended ages for screening[8].

The text was amended as follows:

Children should be screened for dyslipidaemia if any of the following are present:

- Family history of premature cardiac disease or dyslipidaemia.
  - > Children should be screened at 5 years and again at 8 years. Children should be screened earlier than 5 years if homozygous familial hypercholesteremia is suspected.
- A medical condition associated with dyslipidaemia: diabetes mellitus, nephrotic syndrome, liver disease, obesity.

Medicine Treatment

The Paediatric Hospital Level ERC discussed whether the recommendation of statins as a class should remain or if a specific molecule be recommended. It was agreed that it should remain as a class with dosing for simvastatin as an example as there is dosing for all the statins in children provided in the British National Formulary[9].

Some minor text changes were made in the section.

The text was amended as follows:

If LDL-C remains above 4.1 mmol/L in children with 2 or more risk factors, or above 4.9 mmol/L regardless of the presence of risk factors, refer to a paediatric specialist for consideration of statins:
Risk factors: smoking, hypertension, BMI >= 95th centile (z-score +1.96), HDL-C < ~~35mg/d~~ 1 mmol/L, diabetes mellitus, renal disease, male sex.

[8] Wiegman A, Gidding SS, Watts GF, Chapman MJ, Ginsberg HN, et al. European Atherosclerosis Society Consensus Panel. Familial hypercholesterolaemia in children and adolescents: gaining decades of life by optimizing detection and treatment. Eur Heart J. 2015 Sep 21;36(36):2425-37. doi: 10.1093/eurheartj/ehv157. Epub 2015 May 25. PMID: 26009596; PMCID: PMC4576143.

[9] British National Formulary for Children 2020-2021

The text was amended as follows:

REFERRAL
» Children with homozygous familial hypercholesterolaemia.
» Children under 10 years of age with dyslipidaemia unresponsive to appropriate lifestyle interventions.
» Children with ~~or~~ inadequate response to statins.

The original text in the Endocrine chapter was deleted and replaced with the text from the Cardiovascular Chapter (as amended above). The section will be cross-referenced in the Cardiovascular chapter accordingly.

The text deleted was as follows:

~~DIAGNOSTIC CRITERIA~~
~~Refer to Chapter 4: Cardiovascular system - section 4.10 Dyslipidaemia.~~

~~GENERAL AND SUPPORTIVE MEASURES~~
~~» Optimise diabetes control.~~
~~» Refer to a dietician.~~
~~» Increase physical activity.~~
~~» Members of household who smoke to stop smoking.~~

~~MEDICINE TREATMENT~~
~~If no improvement in LDL levels after 6 months of exercise and dietary interventions, commence statins (Refer to Chapter 4: Cardiovascular system - section 4.10 Dyslipidaemia).~~

7.5.3 Diabetes Mellitus in Adolescents

General and Supportive Measures

The text was amended as follows:

Promote:
» normal growth and pubertal development,
» psychological development,
» maintenance of glycaemic control and adherence,
» ~~normal lifestyle,~~
» avoidance of risk-taking behaviours (smoking, substance abuse),
» sex education.

7.6 Hypoglycaemia in Children

Diazoxide: *Maximum dose retained*

A comment was received regarding increasing the maximum dose of diazoxide however the ERC agreed to retain the maximum dose which is aligned with the South African Medicines Formulary[7] and the British National Formulary[9].

Referral

The text was amended as follows:

- All patients with confirmed hypoglycaemia not explained by intercurrent illness, drugs.
- All neonates with p~~P~~ersisting or recurrent hypoglycaemia.
- Suspected hyperinsulinism.

7.7 Growth Disorders

Description

The text was amended as follows:

Constitutional delay in growth is defined by short stature with a disproportionately short trunk and a bone age that is significantly delayed ~~a bone age~~ relative to chronological age

7.12 Hypothyroidism, congenital

Description

The text was amended as follows:

Congenital hypothyroidism is one of the common treatable causes of preventable ~~mental retardation in~~ intellectual disability in children.

7.13 Hypothyroidism in older children and adolescents

Description

The text was amended as follows:

Acquired hypothyroidism in childhood and adolescents may be due to:
» chronic lymphocytic auto-immune thyroiditis,
» goitrogen induced,
» iodine deficiency,
» post surgery,
» radioactive iodine,
» infiltrations, or
» medicines ~~., e.g. antiretrovirals~~.

7.15 Obesity

An external comment was received the placement of obesity within the Endocrine chapter. It was agreed by the ERC that this is a disorder of metabolism, and thus the Endocrine chapter would be the most appropriate place for this section.

Diagnostic Criteria
Clinical

The text was amended as follows:

» The BMI varies with age. Use sex-specific BMI charts for accurate ~~identification~~ diagnosis ~~of~~. ~~o~~Obesity is defined by a Z-score > +2; overweight by a Z-score of +1. Contrary to WHO teaching, the same cut-offs should be used at all ages of obesity.
» In general obesity is likely if BMI:
> 19 kg/m2 at age 5 years,
> ~~20~~ 23 kg/m2 at age 10 years, and
> 25 kg/m2 at age 18 years.

General and Supportive Measures

The text was amended as follows:

~~> psychological support, e.g. parental guidance in managing abnormal behaviour.~~
> parental guidance in managing abnormal behaviour e.g. temper tantrums

7.17 Polycystic Ovary Syndrome

Several chapter additions were considered by the ERC and it was agreed that a section on polycystic ovary syndrome be included.

The text was included as follows:

Description

Characterised by excessive androgen activity, with many having abnormal insulin activity.

Diagnostic criteria

Clinical

- Hirsutism
- Acne
- Oligomenorrhoea or amenorrhoea due to chronic anovulation
- Female pattern alopecia
- Overweight or obese

Investigations

- Polycystic ovaries on ultrasound

General and supportive measures

- Assess and monitor for long term health complications, including:
  - impaired glucose tolerance
  - insulin resistance
  - type 2 diabetes
  - dyslipidaemia
  - obesity
  - fatty liver
  - depression
  - infertility
- Lifestyle changes in nutrition and exercise to reduce weight

Referral

All suspected cases for assessment and management