CENTRAL DIABETES INSIPIDUS – INPATIENT MANAGEMENT

PRACTICE GUIDELINE ©

INTENDED USE OF THIS DOCUMENT

- This document is intended for use within Sydney Children's Hospital Randwick and The Children's Hospital at Westmead in conjunction with Endocrine team consultation.
- It should be used for patients >4 weeks of age admitted to inpatient wards and Emergency Departments and may be used in ICU and operating theatres/recovery as appropriate, alongside ICU policies. It is not for use in neonates.
- The management protocols in Section 4 of this document are intended to be used after a diagnosis of central diabetes insipidus has been established, and the fluids recommended may not be appropriate when the diagnosis is not yet clear.
- The Paediatric Improvement Collaborative guideline on Diabetes Insipidus is endorsed to be used in NSW and may help inform investigation and diagnosis of DI.
- The following guidelines may also be useful to inform aspects of diagnosis and management not covered in this document:
  - Acute Central Diabetes Insipidus – PICU Management – CHW
  - Argipressin Infusion for Diabetes Insipidus in CICU
  - Water and Electrolyte Management in PICU – CHW
  - Intravenous Fluid and Electrolyte Therapy – SCH Practice Guideline
  - Paediatric Improvement Collaborative guideline: Hypernatraemia
  - Traumatic Brain Injury Management – CICU SCH
  - Severe Traumatic Brain Injury – PICU – CHW

Approved by:	SCHN Policy, Procedure and Guideline Committee	
Date Effective:	1st August 2023	**Review Period:** 3 years
Team Leader:	Paediatric Endocrinologist	**Area/Dept:** Endocrinology

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DOCUMENT SUMMARY/KEY POINTS

- The Endocrinology team should be consulted for all patients with central diabetes insipidus (DI) admitted to hospital wards and should review these patients daily.
- All inpatients with central DI require strict fluid balance to be documented.
- Even when charted as a regular dose, desmopressin may need to be given early or delayed – refer to flowcharts.
- Desmopressin should not be given if serum sodium < 135 mmol/L unless specifically instructed by medical team.
- If a patient with central DI has urine output > 4 mL/kg/hour for 2 hours or more and there is no documented plan for the next dose of desmopressin, contact the medical team immediately as desmopressin is likely required.
- An unexpectedly positive or negative fluid balance in a patient with central DI should prompt clinical review by the medical team and measurement of serum and urine sodium and osmolality.

CHANGE SUMMARY

- N/A – New Document
- **03/12/24** – Minor review. Links to newly published SCH policy "Argipressin Infusion for Diabetes Insipidus in CICU" added.

READ ACKNOWLEDGEMENT

- Medical and nursing staff responsible for the care of SCHN inpatients with diabetes insipidus are to read and acknowledge (sign-off) having read this guideline.

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1 Background

1.1 What is Central Diabetes Insipidus?

Central diabetes insipidus (DI) is a condition affecting water balance, where complete or partial deficiency of secretion of anti-diuretic hormone (ADH), also known as vasopressin, from the posterior pituitary results in the production of very large quantities of dilute urine. Without adequate management, this can result in severe dehydration, hypernatraemia and circulatory shock.

Central DI occurs mainly in the following circumstances:

- Congenital abnormality of pituitary development (congenital hypopituitarism).
- Presence of a pituitary fossa tumour.
- Post-operatively after resection of a pituitary fossa tumour or by damage to the pituitary stalk.
- Head trauma, intracranial haemorrhage or infection, brain death.

Central DI, especially when caused by a pituitary fossa tumour or resection, may be associated with loss of the thirst mechanism. This predisposes patients to severe dehydration and hypernatraemia. Patients with an intact thirst mechanism who are unable to drink to thirst are similarly at risk of dehydration and hypernatraemia (e.g., very young children, altered consciousness, vomiting and diarrhoea, severe illness).

1.2 How does anti-diuretic hormone (ADH) work?

ADH, in coordination with the thirst mechanism, maintains normal plasma osmolality by regulating excretion of free water. It acts on the kidneys, where it stimulates insertion of water channels into the tubular luminal membranes, leading to reabsorption of water and concentration of urine. ADH deficiency therefore results in excretion of free water.

1.3 Clinical definition of diabetes insipidus

- Urine volume > 4 mL/kg/hour for at least 2 hours, AND
- Urine specific gravity ≤ 1.005 or urine osmolality < plasma osmolality, AND
- Serum sodium > 145 mmol/L and plasma osmolality >300 mOsm/kg (if accurate fluid replacement has not occurred).

It is important to distinguish appropriate diuresis following administration of large amounts of IV sodium chloride 0.9% from DI, as the former is associated with good hydration status rather than dehydration and does not require treatment. This scenario is most common after surgery. To help make this distinction, quantify intra-operative fluid input and type, and output/losses, and assess hydration status using body weight, blood pressure and heart rate. Measurement of urinary sodium and osmolality can also be helpful as urine sodium is usually not measurable in DI but high after excess IV sodium administration.

2 Post-operative diabetes insipidus

Post-operative DI may be transient, permanent or exhibit a triphasic pattern.

- Transient DI usually has an abrupt onset on the first post-operative day and resolves within several days.
- Triphasic pattern:
  - Early post-operative DI (injury-related neuronal shock, during which no ADH secretion occurs) in first 1-2 days, followed by
  - Recovery period in which inappropriate amounts of ADH may be secreted (leak of hormone from degenerating neurons), which may rapidly cause hyponatraemia if not recognised promptly. This usually lasts several days and is followed by
  - Permanent DI (permanent lack of secretion due to damaged or absent neurons), usually evident after a week or so.

3 Management

3.1 Fluid management

Acute DI can be managed with accurate fluid replacement alone; however, this has potential adverse effects, including hyperglycaemia, intravenous line difficulties due to high infusion rates and urinary catheter leakage.

Fluid type

- IV sodium chloride 0.45% + glucose initially (see below for glucose content).
- If serum sodium > 150 mmol/L: fluid type to be determined after discussion with Endocrinologist or intensivist, and depends on degree of hypernatraemia, time over which this has developed and level of dehydration. See flow charts in Section 4.
- If serum sodium < 135 mmol/L*: sodium chloride 0.9% ± glucose 5% (see below).
- Glucose content:
  - Glucose 5% (in addition to appropriate sodium chloride concentration) is appropriate for fluid rates up to approximately maintenance rate. Lower glucose concentration is required when fluid rate is high.
  - Sodium chloride 0.9% is available with glucose 5% or without glucose as standard ward stock.
  - Sodium chloride 0.45% + glucose 5% is standard ward stock.
  - Sodium chloride 0.45% + glucose 2.5% requires special order from stores.
  - Sodium chloride 0.225% is only available with glucose 3.75% and only stored in ICU.
- Maintenance IV potassium should be given but avoid adding to fluids that will be given at high or variable rates. Please refer to Potassium Management Practice Guideline.

Fluid rate (when managing with fluid replacement alone), calculated hourly as:

- Volume of urine losses in previous hour, PLUS
- Insensible losses, calculated as 17 mL/m^2/hour, PLUS
- Volume of other body fluid losses in previous hour, if applicable, PLUS
- A positive or negative adjustment to correct under- or overhydration over a set time period (often 12-48 hours).
    - Body weight and its change over time accurately reflects hydration status and should always be monitored in conjunction with fluid input and output.
    - Serum sodium > 150 mmol/L suggests underhydration; a positive adjustment may be needed.
    - Serum sodium < 135 mmol/L* suggests overhydration; a negative adjustment/fluid restriction may be needed.

Intravascular volume expansion, if required, should be achieved with sodium chloride 0.9% before commencing the above fluid management.

*Serum sodium < 135 mmol/L only occurs in DI if there has been overzealous fluid and/or desmopressin administration and this needs to be addressed promptly – see Section 3.7 and flowcharts.

3.2 ADH replacement

ADH for therapeutic use is available in two forms:

- Aqueous argipressin (Pitressin®) 20 units/mL for continuous IV infusion
    - Commonly known as vasopressin
    - Requires intensive monitoring and should only be used in ICU and operating theatres.
    - Half-life 30 minutes, clinical duration of action 2-3 hours.
    - Titrate to urine output.
    - Should be used in acute post-operative DI, traumatic brain injury and brain death and with severe intercurrent illness.
    - Refer to ICU policies for vasopressin infusion protocols.
        - CHW policy.
        - SCH Local Work Procedure (LWP).
- Desmopressin (Minirin®)
    - Half-life ~3 hours, duration of action 6-14 hours depending on formulation.
    - Should generally only be used in stable patients.
    - Oral 200 microg tablets most commonly used and are fully soluble in water, so can be dissolved to make smaller doses. Discard remainder and make up fresh for next dose.
    - Has on-off effect, so dose determines duration of action, not degree of response.
    - The diuresis following the offset of action is often referred to as “breakthrough”.

- Doses **are not calculated by weight or BSA**, as there is significant dose variability between individuals, but there is a general relationship to body size.
- Generally, a small dose is given initially, with subsequent doses and frequency adjusted according to response. See Table 1.
- The decision to start desmopressin and the initial dose should always be discussed with the endocrinologist or intensivist.
- The aim is to titrate doses to achieve twice or three times daily dosing with a neutral fluid balance at an appropriate fluid intake and 2 or 3 periods of 1-2 hours diuresis per day, without interrupting sleep.
- Overdose may cause fluid overload and hyponatraemia. Serum sodium should be monitored, and fluid restriction is required until offset of the antidiuretic effect.
- A high degree of caution is required when using desmopressin in patients with cardiac or renal failure.

Table 1: Desmopressin formulations, dose equivalence and suggested doses[1,2]

Form of desmopressin	Dose equivalent to 1 microgram parenteral	Age group	Starting dose	Common long-term dose ranges
Oral 200 microg tablet	200 microg	<1 month 1 month-2 years 2-12 years >12 years	1-4 microg 10 microg 50 microg 100 microg	5-50 microg/day 30-150 microg/day 100-800 microg/day 100-1200 microg/day
One tablet can be dissolved in 20 mL water to make 10 microg/mL solution. A standard dilution should be used consistently in individual patients.				
Intranasal 100 microg/mL spray or drops	10 microg (1 spray)	<1 month 1 month-2 years 2-12 years >12 years	0.1-0.5 microg 0.5-1 microg 1-2.5 microg 2.5-4 microg	1.25-10 microg/day 1.25-10 microg/day 5-20 microg/day 5-20 microg/day
May need 1:10 dilution for small doses of nasal drop				
Parenteral (IV, IM or subcut) 4 microg/mL	1 microg	<1 month 1 month-2 years 2-12 years >12 years	0.1 microg 0.1-0.4 microg 0.1-0.4 microg 0.5 microg	0.2-1 microg/day 0.5-2 microg/day 0.5-2 microg/day 1-4 microg/day
Can be administered using an insulin syringe to enable accuracy with small doses				
Sublingual 120 or 240 microg wafer	120 microg	Generally only used temporarily if impaired enteral absorption. Use dose equivalent to effective oral dose. Smallest dose 60 microg (half wafer).		
Not PBS-listed for DI				

3.3 Low solute diet/thiazide diuretic

Given that infants are fluid-dependent for nutrition, an endocrinologist may choose to manage central DI in an infant with a low-solute diet (such as breastmilk) and a thiazide diuretic rather than with desmopressin. This approach may result in fewer fluctuations in serum sodium. This decision should only be made by the treating endocrinologist.

Starting doses:[3-5]

- Chlorothiazide: 5-10 mg/kg/DAY in 2-3 divided doses per day
- Hydrochlorothiazide: 1-2 mg/kg/DAY in 2-3 divided doses per day

3.4 Aims of treatment in immediate post-operative period and unstable patients

- Normal circulating blood volume with mildly decreased total body water.
  - The aim is to maintain cerebral perfusion pressure but minimise risk of cerebral oedema. Overhydration and rapid changes in blood volume are to be avoided.
- Serum sodium 140-150 mmol/L, avoid rapid changes.
- The CHW PICU policy addresses the specifics of management at CHW.

3.5 Aims of treatment for stable patients

- Normal hydration status.
- Effective control of diuresis to minimise interruption to sleep and daily activities.
- Serum sodium 135-150 mmol/L.

3.6 Treatment of hypernatraemia

If serum sodium > 160 mmol/L, hypernatraemia should be corrected slowly, unless there is clear evidence that hypernatraemia has developed acutely (within 24 hours).

- Fall in serum sodium should not exceed 0.5 mmol/L/hour.
- Correction of dehydration over 48 hours is likely to achieve this.
- Sodium chloride 0.9% is often the most appropriate rehydration fluid to achieve a safe rate of correction while serum sodium > 160 mmol/L.
- Frequent serum sodium levels are required initially to establish a safe rate of correction.

If serum sodium is falling too rapidly, fluid rate should be decreased and/or sodium content increased.

3.7 Treatment of hyponatraemia

Serum sodium < 135 mmol/L in the context of DI only occurs if there has been excess fluid intake and/or desmopressin/vasopressin administration. Fluid intake and desmopressin doses should therefore be reviewed if there is hyponatraemia.

Aim to correct the serum sodium level by no more than 0.5 mmol/L/hour to reduce the likelihood of osmotic demyelination.

- This is usually achieved by fluid restriction.
- Frequent serum sodium levels are required initially to establish a safe rate of correction.

4 Protocols

Patients with central DI after pituitary fossa surgery, traumatic brain injury or brain death, or who have severe intercurrent illness require ICU management and vasopressin infusion. Refer to respective ICU policies for vasopressin infusion protocols. CHW policy, SCH LWP.

4.1 Patients with significant sodium or fluid imbalance or on transition from vasopressin infusion

ICU care with hourly fluid balance and urine replacement

For patients with significant sodium or fluid imbalance but otherwise stable, and for patients transitioning from vasopressin infusion, the following protocol should be used. This requires ICU management, usually in consultation with Endocrinology.

Fluid type
- If sodium 135-150 mmol/L: sodium chloride 0.45% + glucose 5% or 2.5% depending on fluid rate*
- If sodium < 135 mmol/L#: sodium chloride 0.9% + glucose 5%. Fluid restriction likely required
- If sodium > 150 mmol/L: IV fluid choice must be discussed with Endocrine or ICU team before commencement
  - Sodium chloride 0.225% + glucose 3.75% may be appropriate if hypernatraemia has developed within 24 hours
  - Sodium chloride 0.9% or 0.45% are often more appropriate for correction of hypernatraemia of longer or unclear duration
  - Refer to Section 1.7 regarding safe correction of hypernatraemia
- Oral fluids can be included if IV fluid rates are adjusted appropriately

Hourly fluid rate calculation
- Volume of previous hour's urine loss, PLUS
- Insensible losses (17 mL/m^2/hr), PLUS
- Volume of any non-urinary fluid losses (if applicable), PLUS
- If patient is under- or overhydrated, a positive or negative adjustment calculated as total volume required divided by desired period of correction

Monitoring
- Continuous HR, SaO2 and cardiac monitoring, hourly BP, cap refill and neurological monitoring
- Daily or twice daily weight
- Hourly measurement of fluid intake
- Urinary catheter, hourly urine volumes & specific gravity usually necessary; otherwise strict fluid balance essential
- Serum electrolytes & glucose 2-hourly initially, decreasing frequency if stable
- Urine electrolytes and osmolality twice daily and as needed – helpful at initial presentation and when interpreting unexpected serum electrolyte results and fluctuations in urine output
- Calculate serum osmolality and fractional excretion of sodium twice daily

Desmopressin

Patient with established diabetes insipidus:
- Chart usual doses as regular doses
- Adjust as necessary to achieve 1-2 hour diuresis between doses

New diagnosis of diabetes insipidus:
- Chart PRN, starting with conservative initial dose (see Table 1)
- Adjust doses to achieve 1-2 hour diuresis, 2 or 3 times per day

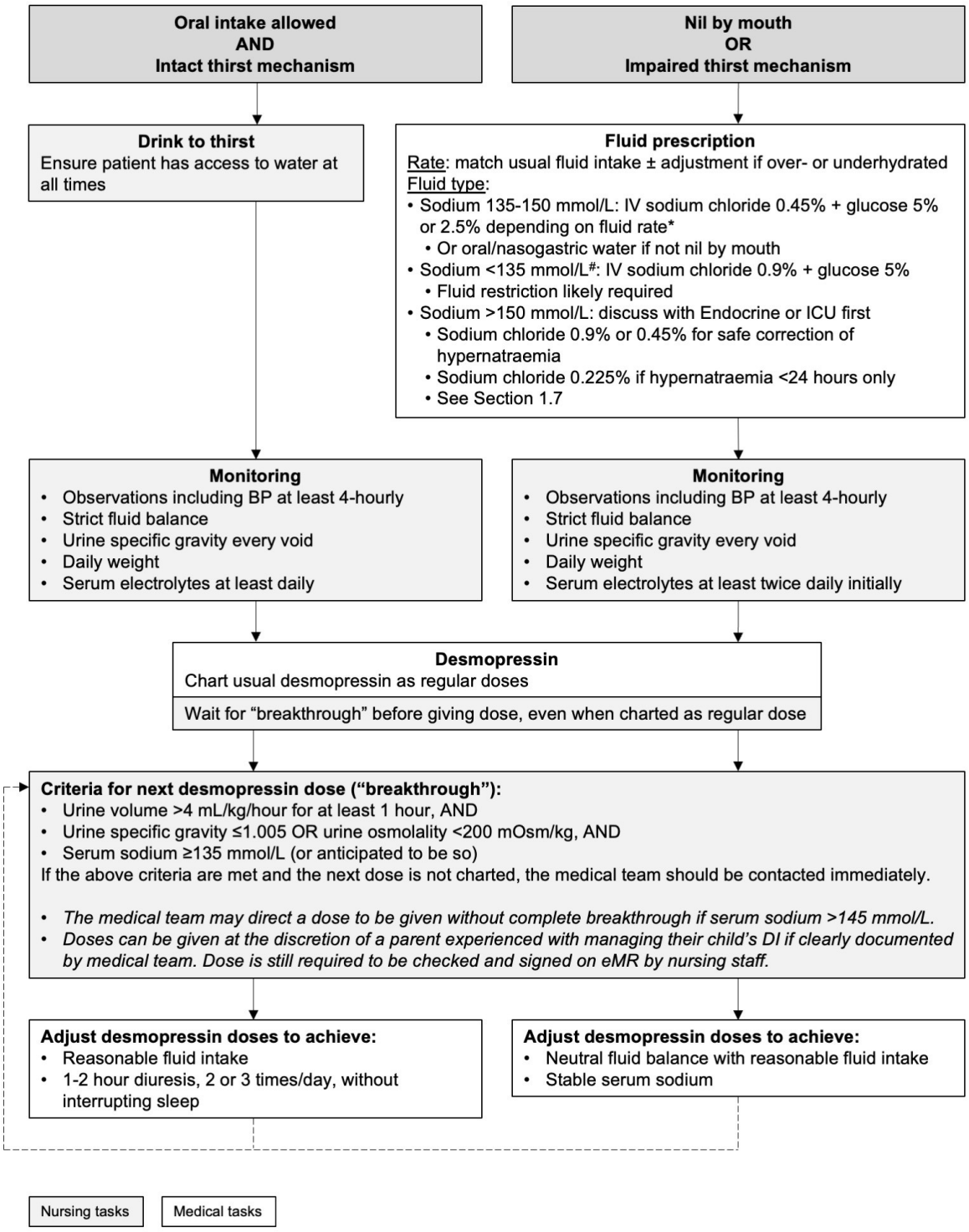
Criteria for next desmopressin dose ("breakthrough"):
- Urine volume >4 mL/kg/hour for 2 hours, AND
- Urine specific gravity ≤1.005 OR urine osmolality <200 mOsm/kg, AND
- Serum sodium ≥140 mmol/L (or anticipated to be so)

Once patient is euvolaemic with serum sodium 140-150 mmol/L and has been on desmopressin for at least 24 hours for initial dose titration, they can transition to Protocol 4.2 or 4.3

*Use glucose 2.5% if fluid rate significantly higher than maintenance rate is required (see Section 3).
#Serum sodium <135 mmol/L only occurs in DI if there has been overzealous fluid and/or desmopressin administration.

4.2 Patients with ESTABLISHED diabetes insipidus with normal or mildly abnormal sodium and fluid balance (sodium <160 mmol/L)

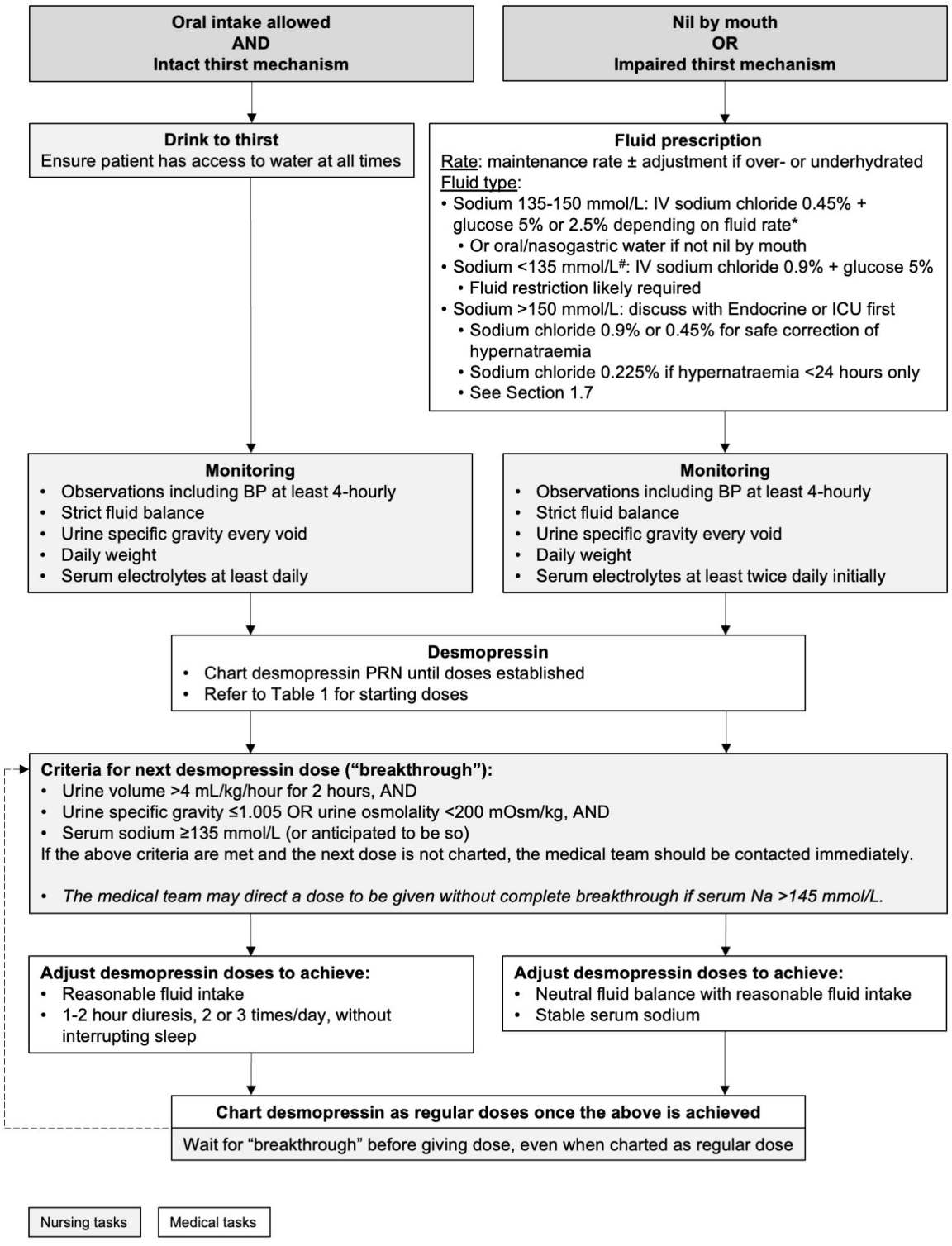
Ward-based care



*Use glucose 2.5% if fluid rate significantly higher than maintenance rate is required (see Section 3).
#Serum sodium <135 mmol/L only occurs in DI if there has been overzealous fluid and/or desmopressin administration.

4.3 Patients with a NEW diagnosis of diabetes insipidus with normal or mildly abnormal sodium and fluid balance (sodium <160 mmol/L)

Ward-based care



*Use glucose 2.5% if fluid rate significantly higher than maintenance rate is required (see Section 3).
#Serum sodium <135 mmol/L only occurs in DI if there has been overzealous fluid and/or desmopressin administration.

4.4 Fasting and surgery in patients with established diabetes insipidus

For procedures less than 4 hours duration not involving the pituitary

- The patient should be first on the operating list.
- Allow to drink to thirst (or their usual fluid intake) *clear fluids* until 1 hour before the procedure.
- Give usual morning dose of desmopressin at least 1 hour before the procedure.
- Maintain strict fluid balance measurement intra- and post-operatively.
- Limit intra-operative IV fluids to replacement of insensible losses (17 mL/m^2/hour) plus accurate replacement of surgical fluid losses.
- Give the next dose of desmopressin after “breakthrough” diuresis post-operatively.
- If procedure is unexpectedly delayed or prolonged, insert urinary catheter and monitor urine output.
    - If diuresis occurs pre-anaesthetic, an oral dose of desmopressin may be given
    - If diuresis occurs intra-operatively, vasopressin infusion should be started
- If further fasting is required post-operatively, protocol 4.2 can be used for ongoing management.

For procedures greater than 4 hours duration or involving the pituitary, vasopressin infusion should be used. This may be commenced pre-operatively in ICU or intra-operatively once diuresis occurs and will require a urinary catheter for strict urine output monitoring either way. Refer to separate respective ICU policies for vasopressin infusion protocols.

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