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Review Article

Hyponatremia: Exploring Etiological Insights, Diagnostic Challenges, and Evolving Management Paradigms

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Abstract

Hyponatraemia is a very common electrolyte abnormality seen especially in hospitalized patients. It is associated with increased mortality, morbidity and increased length of hospital stay if not addressed properly. Hyponatremia is defined as serum concentration of sodium as less than 135mmol/L.

Hyponatremia results from relative excess of total body water to sodium content. Serum sodium concentration is determined by serum water content. Serum concentration of water increases by water intake (driven by thirst or by habit), and it is reduced due to insensible losses from the body like sweating and by urine dilution. The underlying pathophysiological mechanisms leading to hyponatremia depend upon underlying pathological cause leading to disturbances in serum ADH level and urinary water excretion.

Hyponatremia can be further divided between mild (Na=130-135 mmol/L). moderate (Na=125-129 mmol/L) and severe (Na <125 mmol/L) hyponatremia especially in hospitalized patients. Secondly, Hyponatremia may develop rapidly with severe symptoms called Acute Hyponatremia (<48 hours' duration) or develop slowly (>48 hours) called Chronic Hyponatremia with no symptoms to minimal symptoms. Acute Hyponatremia (sever) can present with severe CNS symptoms, increased morbidity and mortality and increased ICU admissions. The treatment with hypertonic saline (1.8% and 2.7% NaCl) for severe symptomatic hyponatremia needs careful monitoring in ICU/HDU. Tolvaptan may be considered in patients with high ADH activity, regardless of whether they are euvolemic or hypervolemic. In summary, hyponatremia should be managed according to the underlying etiology, the duration and degree of hyponatremia, symptoms severity and patients' volume status.

Key words: Hyponatremia, ADH (Antidiuretic hormone), ICU (intensive care unit), HDU (high dependency unit), Acute and Chronic

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Introduction

Hyponatremia is defined as serum concentration of sodium less than 135 mmol/L. Normal range of serum sodium is 135-145 mmol/L[1] Hyponatraemia is a very common electrolyte abnormality seen especially in hospitalized patients. It is associated with increased mortality, morbidity and increased length of stay if not addressed properly in hospitalised subgroup of patients,[2,3] and there is an increased risk of re-admission as compared to patients having normal serum sodium levels.

Pathophysiology; Hyponatremia results from relative excess of total body water to sodium content. Serum sodium concentration is determined by serum water content. Serum concentration of water increases by water intake (driven by thirst or by habit), and it is reduced due to insensible losses from the body like sweating and by urine dilution.[4]

Urine dilution is regulated by antidiuretic hormone (ADH) which is secreted by the hypothalamus and stored in posterior pituitary.[5] When it is released appropriately due to low circulating volume and stimulation of baroreceptors, it causes reabsorption of water from the kidneys and prevents water loss from the body, thus

maintaining body homeostasis of water balance. When this ADH is secreted inappropriately, not due to body physiological response, it will cause dilutional hyponatremia. In most cases of hyponatremia, there is an inability to suppress ADH secretion. In few rare conditions like primary polydipsia, ADH is suppressed but there is excessive iatrogenic water intake which will cause dilutional hyponatremia.

The underlying pathophysiological mechanisms leading to hyponatremia depend upon underlying pathological cause leading to disturbances in serum ADH level and urinary water excretion. In certain conditions, the threshold for ADH secretion is reduced leading to impaired water excretion from the kidneys leading to a constant low level of serum sodium; this condition is called Reset Osmo-stat Syndrome.[6]

Classification:

Based upon Symptoms Severity	**Mild**: • gait disturbances • falls • concentration and cognition deficits **Moderate Severe:** • nausea • confusion • headache **Severe:** • vomiting • somnolence • seizures • cardiorespiratory distress • reduced GCS • coma
Based upon duration of Onset[5,7]	**Acute:** • less than 48 hours duration **Chronic:** • greater than 48 hours duration or unknown
Based upon Serum Sodium Level[5,7]	**Mild:** • 130-135 mmol/L **Moderate:** • 125-129 mmol/L **Severe:** • < 125 mmol/L
Based upon Serum Osmolality[6] (Measured)	Hypotonic: < 275 mOsm/kg - true hyponatremia Isotonic: 275-295 mOsm/kg - pseudo hyponatremia Hypertonic: > 295 mOsm/kg - hyperosmolar
Based upon Volume Status (In hypotonic hyponatremia)	• Euvolemic • Hypovolemic • Hypervolemic

Causes of hyponatremia: Causes of hyponatremia are multifactorial. They are broadly classified based upon serum osmolality, which shows the number of solute particles in 1 kg of solvent. The normal serum osmolality ranges between 275-295 mOsm/kg.

1) Hypertonic Hyponatremia (High Serum Osmolality > 295 mOsm/kg)

It is also called hyper osmolar and happens in hyperglycemia which draws fluid from the intracellular space to extracellular leading to serum dilution and hyponatremia which is not true hyponatremia. It settles down with correction of hyperglycemia.[6,8]

Corrected Serum Sodium with hyperglycemia

Measured Serum Sodium + 2.4 X (Serum Glucose – 5.5 mmol/L / 5.5 mmol/L)

2) Isotonic Hyponatremia (Normal Serum Osmolality)

Serum sodium is falsely low due to:

- o Hyperproteinemia (multiple myeloma most common cause)
- o Hypertriglyceridemia.

This happens due to a laboratory error in measuring serum sodium which can be tackled by using ion-specific electrodes method to measure serum sodium[6,8].

3) Hypotonic Hyponatremia (Low Serum Osmolality < 275 mOsm/kg)

Or (True Hyponatremia)

Hypotonic hyponatremia can result from several conditions that can be categorized based upon their effect on extracellular fluid volume status[5,9].

❖ ***Hypovolemic (volume depletion): H_2O & Na^{++}***

Causes:

- Thiazides diuretics.
- Endocrine disorders (primary adrenal insufficiency – Addison's Disease)
- Cerebral salt wasting syndrome (may happen due to any cerebral insult such as subarachnoid hemorrhage).
- Severe diarrhea and / or vomiting.
- Transdermal sodium Losses (e.g., severe sweating, during exercise, extensive skin burns).
- Salt wasting nephropathies, e.g., tubulopathy after chemotherapy.
- Third space losses (e.g., bowel obstruction, pancreatitis, severe hypoalbuminemia, sepsis, muscle trauma and rhabdomyolysis).

❖ ***Hypervolemic (Volume Overload): H_2O & Na***

This may happen due to.

- Liver cirrhosis
- Congestive heart failure
- Nephrotic syndrome

There is reduced effective arterial blood volume (EABV) which usually can be predicted by resting tachycardia and postural hypotension particularly in nephrotic syndrome and liver cirrhosis due to reduced oncotic pressure and fluid movement from intravascular space to interstitial compartment.

This leads to baroreceptor reflex mediated ADH release, causing water retention and diluting serum sodium. In congestive cardiac failure, ADH is released secondary to reduced cardiac output. Other mechanisms are, increased serum renin concentration due to low EABV, which leads to angiotensin II production along with aldosterone production, all leading to sodium and water retention with a picture of fluid overload.

❖ ***Euvolemic: H_2O but Na***

It usually happens when ADH is added to the serum inappropriately either due to inappropriate secretion from the pituitary gland or due to extra pituitary production, e.g., due to paraneoplastic syndrome associated with malignancies. Common causes in this category are:

- SIADH
- Reset Osmo-stat syndrome
- Hypothyroidism
- Secondary adrenal insufficiency.

Other causes with dilutional hyponatremia with euvolemia could be due to transit rise in serum ADH which may happen under following conditions.

- post-operative
- pain
- stress
- medicines

Medicines

Different medicines can cause hypotonic hyponatremia by affecting homeostasis between sodium and water content by increasing production of ADH or potentiating its effect, causing hyponatremia[8,10]. Hyponatremia may appear within days or even years after starting new medications, but generally improves once the offending medicine is stopped.

- ***Diuretics:*** All types can cause hyponatremia but thiazides or thiazides like medicines are common. Mechanism – inhibit sodium chloride reabsorption in distal renal tubules.[11] Loop diuretics can lower sodium but more common when taking angiotensin converting enzymes inhibitors and spironolactone together.
- ***SSRIs:*** Citalopram is more common than others. Hyponatremia usually may develop after few weeks of starting treatment and usually resolve within two weeks of stopping. Older age and concurrent use of diuretics are risk factors for developing hyponatremia with SSRIs. [10,12]
- ***Antipsychotics:*** Such as Haloperidol and Phenothiazine.
- ***Carbamazepine:*** More common in older age group or taken with concurrent diuretics or with antipsychotics[13].

LESS COMMON MEDICINES

1) Medicines that may increase production or potentiate effect of ADH[8,11]

- o Angiotensin converting enzyme inhibitors (ACEIs)
- o Angiotensin II receptor antagonists
- o Proton pump inhibitors (PPIs)-omeprazole and lansoprazole more common)
- o Anticonvulsants (sodium valproate, lamotrigine, levetiracetam).
- o Amiodarone
- o Theophylline
- o Dopamine antagonist (metoclopramide & domperidone)
- o Antidiabetics (insulins, chlorpropamide, tolbutamide).
- o NSAIDs – particularly in combination with thiazide diuretics or heart failure.
- o MDMA (ecstasy).

2) Medicines can cause loss of ADH Inhibition

- NSAIDs with diuretics.

3) Medicines producing exogenic ADH

- Desmopressin
- Oxytocin

Syndrome of Inappropriate Secretion Of Adh (Siadh)

Excessive unsuppressed release of ADH due to either inappropriate release from pituitary gland or due to increased secretion due to non-pituitary source, leading to state of excessive water content without major sodium retention will lead to dilutional hyponatremia[12].

Causes

- Malignancy: for example small cell lung cancer, bowel cancers.
- CNS disorders: subarachnoid hemorrhage, meningoencephalitis etc.
- Pulmonary diseases: e.g. pneumonia.
- Idiopathic

Diagnostic Criteria

- Serum osmolality < 275 mOsm/kg
- Euvolemia
- Urine osmolality > 100 mOsm/kg
- Spot urinary sodium > 30 mmol/l with normal dietary salt and water intake
- Normal renal and cardiac functions
- Exclusion of hypothyroidism, adrenal insufficiency and diuretics use.

Reset Osmo-Stat Syndrome

- A Subtype of SIADH[14]
- Secretion of ADH at a lower threshold of plasma osmolality which leads to corrective mechanisms to re-establish normal serum sodium level at a lower level, leading to a persistent and stable low sodium.
- It may happen as a cause of chronic hyponatremia in pregnancy, quadriplegic patients, and patients with psychosis.
- Other causes associated with it could be, tuberculosis, encephalitis, and metastatic malignancy[15]

Endocrine Disorders

- Primary adrenal insufficiency (Addison's Disease)
- Hyponatremia occurs due to increased urinary excretion of sodium due to relative mineralocorticoid deficiency.
- Glucocorticoid deficiency may lead to low sodium when associated hypopituitarism.
- Elderly people with secondary adrenal insufficiency are prone to develop hyponatremia.
- Severe hypothyroidism may cause hyponatremia.

Cerebral Salt Wasting Syndrome

- May happen secondary to subarachnoid hemorrhage, traumatic brain injury, intracranial surgery.
- Thought to be due to altered levels of brain and / or arterial natriuretic peptides leading to increased urinary sodium and water excretion.[(16)]
- The patient clinically will demonstrate with signs of volume depletion.
- Responds to sodium chloride 0.9% infusion and fludrocortisone.

Differences between SIADH and Cerebral Salt Wasting Syndrome[17]

	SIADH	Cerebral Salt Wasting
Blood Pressure	Normal	Normal to Orthostatic Hypotension
Central Venous Pressure (CVP)	Normal	low
Urine Volume	Normal to Low	High
Urine Sodium Concentration	>30mmol/l	>>30mmol/l
Serum Urea Concentration	Normal to Low	Normal to High
Serum Uric Acid concentration	Low	low

Heart Failure

- Hyponatremia will happen primarily due to low cardiac output[18].
- Due to heart failure, there is expansion of plasma volume but there is reduction of effective circulating arterial blood volume, which stimulates ADH secretion, increased renin secretion which leads to angiotensin II production.
- All these mechanisms lead to sodium and water retention leading to hypervolemic hypotonic hyponatremia.

Liver Disease

- Hyponatremia appears approximately in 30% of cases of chronic liver disease and established liver cirrhosis[19].
- In chronic liver disease (CLD) there is reduced effective arterial blood volume (EABV) due to arterial vasodilation and AV shunting.
- Reduced EABV leads to baroreceptors mediated stimulation of ADH, which leads to water retention, causing hypervolemic hypotonic hyponatremia.

Kidney Disease

- Polycystic kidney disease and chronic pyelonephritis may lead to sodium losing nephropathies, leading to increased urinary excretion of sodium and water, causing hypovolemic hypotonic hyponatremia[16].
- Nephrotic Syndrome, there is reduction of EABV due to significant low oncotic pressure which causes increased ADH secretions and water retention, leading to hypervolemic hypotonic hyponatremia.

Third spacing

- When too much fluid moves from blood vessels into interstitial compartment due to increased vascular permeability, there are baroreceptors mediated

ADH secretions causing water retention and diluting serum sodium.

- Causes are bowel obstruction, pancreatitis, sepsis, muscle trauma (rhabdomyolysis).

Diagnostic work up

Take a detailed history & establish duration of hyponatremia, whether acute or chronic.

- Detailed history of medications, any new medication added, and new symptoms developing.
- History of dizziness suggesting orthostatic hypotension & hypovolemia.
- Detailed physical examination, especially look for resting tachycardia, evidence of postural hypotension, dry mucus membranes, reduced skin turgor, all indicating signs of hypovolemia.
- Any sign of fluid overload raised JVP, evidence of pulmonary congestion, ascites, ankle, and sacral oedema.

Diagnostic Tests; (Basic work up)

- Repeat serum sodium level, to compare with initial reading, to know how fast sodium is dropping.
- Check serum osmolality, urine osmolality, spot urine sodium at the same time.
- Serum potassium, blood glucose, liver function tests, urea, creatinine.
- Chest x-ray to find any evidence of fluid overload, lung infection or any mass.
- TSH and 9 am Cortisol level

Management Strategies

General Management

Management is determined by;

1) Severity of symptoms
2) Chronicity of hyponatremia (Acute or Chronic)
3) Patient's volume status

In all patients;

1) Stop any non-essential offending medications.
2) Review IV fluids, e.g., stop any ongoing hypotonic fluids like dextrose infusions.
3) Consider whether patient meets criteria for referral to ICU/HDU
4) Limit rise in serum sodium in first 24 hours to < 10 mmol/l and < 8 mmol/l in each following 24 hours.

1) Admit the patient if;

- Acute onset, i.e., duration < 48 hours
- Acute severe hyponatremia < 125 mmol/L
- Symptomatic patients
- Signs of severe hypovolemia or fluid overload.

2) Referral to Endocrine team;

- If the cause of hyponatremia remains unclear after the initial workup.
- Refractory hyponatremia when sodium levels fail to improve after initial management.
- If there is suspicion of SIADH or any other endocrine abnormality associated.
- Clinical suspicion of reset osmo-stat syndrome or cerebral salt wasting syndrome.

3) Referral Criteria to Intensive care;

- All referrals should be in accordance with patient treatment escalation plan e.g., a patient with ward-based care as ceiling of treatment would not be appropriate for referral.
- Critical symptomatic hyponatremia < 110 mmol/L and or serum osmolality < 240 mOsm/kg.
- Evidence of cerebral oedema or raised intracranial pressure (on clinical assessment and / or CT brain).
- Evidence of significant hemodynamic instability not responding to initial treatment.
- Patients need multi-organ support.
- Refractory or severe symptomatic hyponatremia needing hypertonic saline through central line.

4) Management of Severe Symptomatic Hyponatremia;

(e.g., ongoing seizures, deep coma, low GCS due to severe hyponatremia)

Society for Endocrinology guideline states that patients with severe symptomatic hyponatremia need immediate Hypertonic Saline treatment, irrespective of knowing the cause.

- Hypertonic saline, 3% or 2.7% sodium chloride 150 ml IV bolus over 20 minutes, through central line.
- Check serum sodium concentration after 30 minutes.
- In severe symptomatic patients, an initial increase in serum sodium 5 mmol/L is expected in the first few hours of starting treatment with hypertonic saline.
- Aim of correction 10 mmol/L during first 24 hours, and up to 18 mmol/L in 48 hours to avoid complications of overcorrection.
- In emergency situations, it may start with sodium chloride 0.9% infusion especially in volume depleted patients.
- Stop ongoing treatment if symptoms improve or reach target of 10 mmol/L or serum sodium of 130 mmol/L, whichever comes first.
- Pursue diagnostic approach and to treat specific

causes.

- Monitor serum sodium 4 hourly until serum sodium > 125 mmol/L, then can monitor every 6 hours until 130 mmol/L.

5) Management of Moderate to Severe Hyponatremia;

- Diagnostic assessment and treat the cause specified.
- Consider hypertonic saline (as for severe).
- Aim of correction 8-10 mmol/L during first 24 hours, and up to 18 mmol/l in 48 hours to avoid complications of overcorrection.
- Aim to reach serum sodium of 130 mmol/L (over an acceptable period of recommended correction).
- Monitor serum sodium 4-6 hours in first 24 – 48 hours.

6) Management of Mild Hyponatremia;

- Check for any obvious errors and stop precipitating factors, for example any medicine specified or diuretics or hypotonic fluids like dextrose water.
- Diagnostic assessment and treatment of the cause.
- Aim of correction 8-10 mmol/L during first 24 hours, and up to 18 mmol/L in 48 hours to avoid complications of overcorrection.
- Aim to reach serum sodium of 130 mmol/L (over an acceptable period of recommended correction).

What to do if overcorrecetd or rapidly corrected?

- Stop ongoing treatment, for example hypertonic saline or normal saline infusion.
- Can start 5% dextrose infusion at 10 ml/kg over one under strict monitoring of serum sodium and urine output, until you achieve target level.

  Target; 10 mmol/L in first 24 hours and up to 18 mmol/L in 48 hours.
- Can use Desmopressin 1-2 micrograms IV, maximum frequency to give every 8 hours, and monitor serum sodium and urine output, to stop as soon as you reach required target.

Fluid restriction and use of diuretics

- Recommended in SIADH as first line therapy.
- Also recommended if congestive cardiac failure or liver cirrhosis with signs of fluid overload.
- Generally, less than one liter including all oral liquids (including tea, coffee, milk, juices, or free water).
- Apply FURST formula by dividing the sum of urinary cations (urine sodium & urine potassium) by plasma sodium, to calculate the effectiveness of fluid restriction and electrolyte free water clearance.
- If a urine osmolality is > 350 mOsm/kg, a loop diuretic can be added as this will cause increase in renal free water clearance.

Correction of hypokalemia

(If hypokalemia co-exists simultaneously)

- Hypokalemia drives sodium into the cell to maintain electroneutrality.
- Exogenous oral potassium supplements directly enter cells and causes sodium efflux, thus raising serum sodium concentration. Hypokalemia correction should be given priority over severe hyponatremia correction.
- Sodium is reabsorbed in the distal and collecting tubule for the exchange of potassium (aldosterone dependent).

Patients with reduced circulatory volume

(i.e., low effective arterial blood volume (EABV)

- Do not use hypertonic saline in volume depleted patients.
- Monitor serum sodium and urine output especially in very dehydrated patients.
- If there is sudden increase in urine volume after starting IV crystalloids, check serum sodium concentration immediately, as in volume depleted patient once you restore intravascular volume with IV fluids, it will stop secretion of ADH as negative feedback, so risk of free water urinary clearance is increased, and patient will develop polyurea. Serum sodium concentration may rise sharply because of free water clearance from the body and infused sodium. If this happens, stop ongoing IV fluids, and keep monitoring urine output and serum sodium.

Patients with siadh

1) Fluid restriction is the first line treatment.
2) Stop any offending medicine.
3) Increase oral solute intake.

- Oral urea intake of 0.25 – 50 g/kg per day (or)
- Combination of loop diuretics and oral salt (sodium chloride)
- Slow sodium tablets (600mg / tablet): usual dose is 1-4 grams orally three times per day.
- Slow sodium tablets may be given hourly as a substitute for hypertonic saline in non-urgent situations.
  - Demeclocycline and vasopressin receptor antagonists are NOT recommended
  - If there is suspicion of underlying malignancy, investigate further by CT chest, abdomen and pelvic.

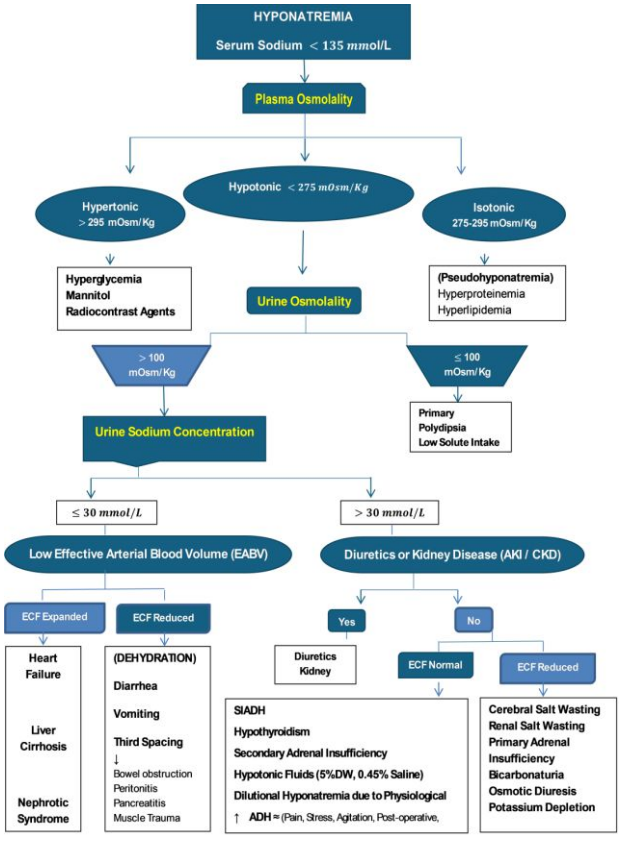
- Head Imaging CT/MRI if clinically indicated.=

Tolvaptan in SIADH:

- Not recommended in mild to moderate symptomatic patient
- Can be given in chronic hyponatremia (duration > 48 hours) with severe symptoms.
- Monitor serum sodium after 8 hours of 1st dose, then daily until it is stopped.
- Contraindicated in patients with hypovolemia, AKI, and liver disease.
- Discontinue demeclocycline while on tolvaptan.
- Discontinue fluid restriction while on tolvaptan.
- Do not use along with hypertonic sodium chloride.
- Tolvaptan is metabolized via the cytochrome p450 pathway therefore enzyme inducers/inhibitors should be avoided or used with caution, and dose adjustments made where required.
- 15 mg daily initially, but better to start 7.5 mg to avoid rapid rise in serum sodium.
- The dose should be titrated down if serum Na >145 mmol/L or an increase in serum Na >12 mmol/day is seen20.

Diagnostic Algorithm For Acute Hyponatremia

Calculations



Adrogue-Madias Formula

The degree to which one litre of a given solution would be expected to initially raise the serum sodium concentration in a hyponatraemic patient, without any evidence of sodium losses in the urine, can be estimated from the following formula.

Formula based calculation should only be guide and should not be replaced as a replacement for clinical judgement. In clinical practice, the predictive accuracy of formulae is limited. Formula-based prescription of fluid has been associated with inadvertent overcorrection of sodium.

➢ **Increase in serum sodium: (infusate Na – serum Na) ÷ (TBW + 1)**

TBW is the estimated Total Body Water: {Lean Body Weight in kg x (0.5 women & 0.6 men)}

For example, one litre of normal saline 0.9% infusion (containing 154 mmol/L of sodium) is given to a 60 kg woman with a serum sodium of 110 mmol/L.

Estimated TBW: (60 x 0.5) →30 Litres.

Expected increase in serum sodium = (154 – 110) ÷ 31 = 1.4 mmol/L.

➢ **TBW is the estimated Total Body Water = litres**

{Lean Body Weight in kg x (0.5 women & 0.6 men)}

➢ **Total Na Deficit = mmol**

TBW × {desired serum Na mmol/L – current serum Na mmol/L}

➢ **Rate of infusion in 1 litre bag of fluid = ml/hour**

{Na requirement (mmol) × 1000} ÷ {Infusate Na (mmol/L) x Time (hrs)}

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Authors' Contribution

KA: Conception

ASA, ZA: Design of the work

ZA: Data acquisition, analysis, or interpretation

ASA, ZA: Draft the work

KA: Review critically for important intellectual content

KA, ASA, ZA: Approve the version to be published

KA, ASA, ZA: Agree to be accountable for all aspects of the work

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