Early Dysnatremia and its association with mortality & Acute Kidney Injury
Results from the AWAKEN Study

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Background

- Incidence of dysnatremia in critically ill neonates during the first week of life and its association with mortality and AKI is not well described.
- Few studies describe associations between sodium aberrations in early life and poor outcomes (neurologic, developmental, respiratory).
- Most studies are single center and/or focus on a specific population within the NICU.
- We hypothesized:
  (1) Early dysnatremia will be associated with increased risk of mortality
  (2) Early dysnatremia will be associated with increased risk of AKI by postnatal day 7.

Methods

AWAKEN Cohort:

- Multinational, retrospective study of critically ill neonates admitted to 24 neonatal intensive care units
- **Inclusion Criteria:**
  - born or admitted to a level 2-4 NICU
  - received intravenous fluids for ≥48 hours
- **Exclusion criteria:**
  - admission >14 days of age
  - congenital heart disease requiring surgical repair within 7 days of life
  - lethal chromosomal anomaly
  - death within 48h of admission
  - inability to determine AKI status
  - severe congenital kidney abnormalities

Ancillary Study:

- **Inclusion Criteria:**
  - GA ≥24 w
  - At least 1 serum sodium (sNa) value within DOL 2-7
- **Primary Exposure**

Hyponatremia : sNa <135meq/mL (mild: 130-134; moderate: 125-129; severe: <125)

Hypernatremia: sNa >145meq/L (moderate: 146-155, severe: ≥156)

- **Primary Outcome**

Mortality: Death prior to 36 weeks post-GA or hospital discharge.

- **Secondary Outcome**

AKI: rise in serum creatinine > or = to 0.3 mg/dl or urine output <1 ml/kg per hour by postnatal day 7

- **Statistical Methods**

Multivariable logistic regression models were created separately to evaluate association with outcomes

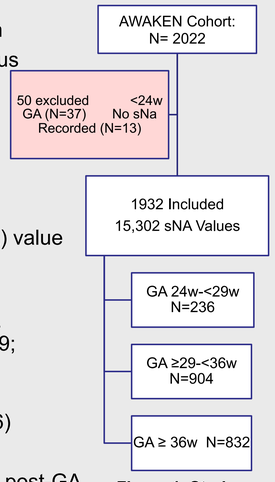

Figure 1. Study Design Flowchart

Results

1) Early Dysnatremia is Associated with Increased Odds of Mortality (Table 2)

- Hyponatremia and hypernatremia was associated with over 2.5 time the odds of death.
- Greater odds of mortality for infants who developed both hypo and hypernatremia

-2) Early Hypernatremia was associated with AKI on postnatal day 7

-In adjusted models, infants with hypernatremia had 1.6 times odds of AKI

-May be related to fluid losses and or provision strategies

Table 1. Baseline Demographics and Clinical Characteristics of Infants With Dysnatremia

	Eunatremia N=986	Hyponatremia N=531	Hypernatremia N=304	Hypo & Hypernatremia N=151	P value
Median GA (IQR) -w[a]	35 (32-38)	36 (32-39)	32 (28-35)	32 (27-37)	<0.001
GA Group (w)- n(%)					<0.001
24-<29	47 (4.8)	51 (9.6)	89 (29.3)	49 (32.5)	
29-<36	514 (52.1)	188 (35.4)	148 (48.7)	54 (35.8)	
≥36	425 (43.1)	292 (55.0)	67 (22.0)	48 (31.8)	
Sex					0.44
Female	415 (42.1)	240 (45.2)	133 (43.8)	53 (35.1)	
Male	569 (57.7)	290 (54.6)	170 (55.9)	98 (64.9)	
Race – *n(%)*					0.008
Black	186 (18.9)	104 (19.6)	66 (21.7)	24 (15.9)	
White	552 (56.0)	332 (62.5)	171 (51.5)	102 (67.5)	
Other/Unknown	248 (25.2)	95 (17.9)	67(22.0)	25 (16.6)	
Maternal Characteristics- n(%)					
Pre-eclampsia/eclampsia	174 (17.6)	86 (16.2)	39 (12.8)	15 (9.9)	0.036
Diabetes	147 (14.9)	67 (12.6)	41 (13.5)	14 (9.3)	0.24
Antenatal steroid treatment	345 (35.0)	137 (25.8)	167 (54.9)	64 (42.4)	<0.001
Birth History					
Median Birthweight (IQR) – *g*	2235 (1681-3075)	2540 (1695-3230)	1787 (1138-2568)	1664 (990-2841)	<0.001
C-Section Delivery – *n(%)*	593 (60.5)	309 (59.0)	170 (57.0)	89 (58.9)	0.74
Median 5-minute Apgar Score (IQR)	9 (8-9)	8 (6-9)	8 (7-9)	7 (5-8)	<0.001
Compression in the delivery room	17 (1.7)	32 (6.0)	8 (2.6)	21 (13.9)	<0.001
Admission Diagnoses					
Seizures	24 (2.4)	17 (3.2)	13 (4.3)	9 (6.0)	0.078
Respiratory Failure	366 (37.1)	233 (43.9)	195 (64.1)	114 (75.5)	<0.001
Hypoxic Ischemic Encephalopathy	34 (3.4)	45 (8.5)	14 (4.6)	21 (13.9)	<0.001
Necrotizing Enterocolitis	3 (0.3)	6 (1.1)	0 (0.0)	3 (2.0)	0.012
Medications – *n(%)*					
Antimicrobials					
Vancomycin	11 (1.1)	28 (5.3)	18 (5.9)	9 (6.0)	<0.001
Piperacillin/Tazobactam	24 (2.4)	15 (2.8)	10 (3.3)	3 (2.0)	0.81
Aminoglycoside[b]	677 (68.7)	403 (75.9)	264 (86.8)	128 (84.8)	<0.001
Vasopressor[c]	53 (5.4)	75 (14.1)	49 (16.1)	39 (25.8)	<0.001
Diuretic[d]	25 (2.5)	54 (10.2)	14 (4.6)	16 (10.6)	<0.001
Caffeine	191 (19.4)	111 (20.9)	136 (44.7)	74 (49.0)	<0.001
Indomethacin	11 (1.1)	14 (2.6)	25 (8.2)	18 (11.9)	<0.001
Median Fluid Balance D7 (IQR) – % [e]	-3.13 (-6.5-0.75)	-.62 (-5.9-3.2)	-4.25 (-8.1-0)	-4.35 (-8.79-3.12)	<0.001
Discharge Diagnoses					
Endocrine	13 (1.3)	18 (3.4)	8 (2.6)	5 (3.3)	0.045
Neurological Disease	82 (8.3)	96 (18.1)	50 (16.4)	57 (37.7)	<0.001
Intraventricular Hemorrhage	37 (3.8)	38 (7.2)	26 (8.6)	39 (25.8)	<0.001
Hypoxic Ischemic Encephalopathy	25 (2.5)	47 (8.9)	10 (3.3)	19 (12.6)	<0.001
Necrotizing Enterocolitis	16 (1.6)	18 (3.4)	13 (4.3)	11 (7.3)	<0.001
Renal Disease	58 (5.9)	73 (13.7)	36 (11.8)	37 (24.5)	<0.001
Death – n(%)[f]	11 (1.1)	24 (4.5)	16 (5.3)	14 (9.3)	<0.001

a. *w*- week *GA*- Gestational Age
b. Treatment with gentamicin/amikacin/tobramycin/netilimicin
c. Treatment with at least one of the following: Dopamine, Norepinephrine, Epinephrine, Milrinone, Hydrocortisone
d. Treatment with furosemide and/or spironolactone and/or chlorthalidone
e. *D7*- postnatal day 7. Fluid balance was calculated based on comparison of daily weight with birthweight: % change = [(dailyweight-birthweight)/birthweight] x 100
f. A total of 65 deaths are reported however 4 deaths occurred prior to postnatal day 3 were not included in adjusted analyses

Figure 2. Incidence of Dysnatremia within the Cohort

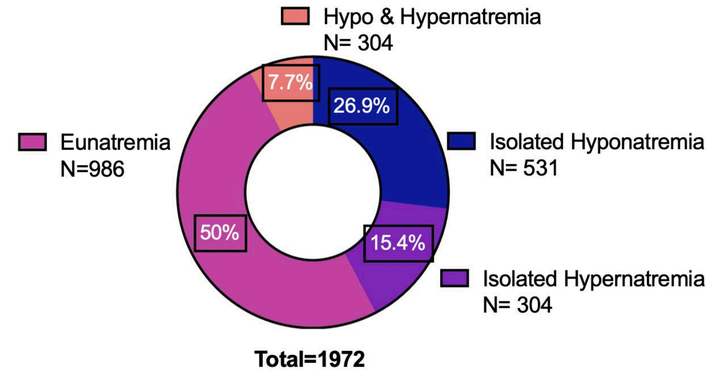

Table 2. Models of the Association of Early Dysnatremia and Mortality (N=1968)

	Model A OR (95% CI)	Model B OR (95% CI)	Model C OR (95% CI)
Hyponatremia	3.67 (1.60-7.67)	3.36 (1.60-7.09)	2.54 (1.19-5.46)
Hypernatremia	4.61 (2.10-10.16)	3.37 (1.47-7.72)	2.41 (1.02-5.69)
Hypo & Hypernatremia	9.05 (4.03-20.35)	6.40 (2.73-14.94)	3.48 (1.42-8.34)

Model A: Unadjusted association of dysnatremia with mortality
Model B: Model A + adjustment for gestational age, birthweight and site
Model C: Model B with adjusted for compressions at birth, vasopressor use (at least one of the following: Dopamine, Norepinephrine, Epinephrine, Milrinone, Hydrocortisone) and acute kidney injury.

Table 3. Models of the Association of Early Dysnatremia and AKI on postnatal day 7 (N=1731)

	Model A OR (95% CI)	Model B OR (95% CI)	Model C OR (95% CI)
Hyponatremia	1.53 (1.05-2.23)	1.52 (1.04-2.21)	2.54 (0.93-2.04)
Hypernatremia	1.57 (1.03-2.39)	1.71 (1.11-2.64)	1.62 (1.03-2.54)
Hypo & Hypernatremia	2.7 (1.53-4.77)	2.95 (1.65-5.27)	2.67 (1.42-8.34)

Model A: Unadjusted Model
Model B: Adjusted for gestational age and site
Model C: Model B adjusted for vasopressor use (at least one of the following: Dopamine, Norepinephrine, Epinephrine, Milrinone, Hydrocortisone), diuretic treatment (furosemide and/or spironolactone and/or chlorthalidone), aminoglycoside treatment and vancomycin treatment.

Conclusions

- Almost half of neonates who met inclusion criteria developed dysnatremia in the first week of life.
- Hyponatremia and/or hypernatremia within the first week of life are significantly associated with mortality.
- Hypernatremia may be associated with neonatal AKI.
- Further prospective studies are necessary to evaluate if sodium management in combination with fluid provision strategies improve neonatal AKI and mortality.

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