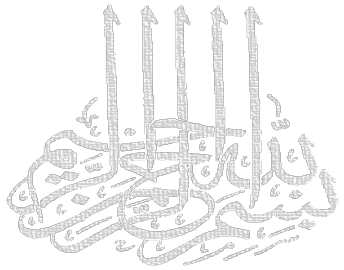


Electrolytes, Renal and Diabetes Insipidus Management

Outline

- Kidney management factors
- Effect of hypernatremia on graft function
- Diagnosis of diabetes insipidus
- Differential diagnosis of hypernatremia
- Management of diabetes insipidus
- Conclusion

Kidney Donors

- General Principles:
  - Maintain euvolemia – 'flooding' not necessary
  - Recognize and treat DI
  - Crystalloids or colloids can be used for resuscitation (avoid HES)
  - When performing contrast studies – adequately hydrate and use minimal amount of contrast necessary

Kidney Donors

- Vasopressor use:
  - 'Good vasopressors' – Dopamine, Vasopressin
- Avoid use of epinephrine

Imppact of ICU on Renal Functions

- What ICU interventions are associated with rise in s cr prior to graft harvesting?

Research

Open Access

Impact of intensive care on renal function before graft harvest: results of a monocentric study

Valéry Blasco[1], Marc Leone[1], Julien Bouvenot[2], Alain Geissler[1], Jacques Albanèse[1] and Claude Martin[1]

[1]Département d'Anesthésie et de Réanimation, Hôpital Nord, Assistance Publique Hôpitaux de Marseille, Chemin des Bourrely, 13915 Marseille cedex 20, Université de la Méditerranée, Faculté de Médecine, 13005 Marseille, France
[2]Service de Biostatistique, Faculté de Médecine, Université de la Méditerranée, Bd Jean Moulin, 13005 Marseille, France

Corresponding author: Marc Leone, marc.leone@ap-hm.fr

Received: 14 Jul 2007 Revisions requested: 20 Aug 2007 Revisions received: 30 Aug 2007 Accepted: 14 Sep 2007 Published: 14 Sep 2007

Critical Care 2007, 11:R103 (doi:10.1186/cc6120)
This article is online at: http://ccforum.com/content/11/5/R103

Blasco V, et al. Impact of intensive care on renal function before graft harvest: results of a monocentric study. Crit Care. 2007;11(5):R103

Imppact of ICU on Renal Functions

- What ICU interventions are associated with rise in s cr prior to graft harvesting?
    - 6 year retrospective study – 143 brain-dead donors

- Independent risk factors
    - Brain death > 24 hours (OR: 2.64, 95% CI: 1.25 to 5.59; p = 0.011)
    - Volume of mannitol (OR: 2.08, 95% CI: 1.03 to 4.21; p = 0.041)

Blasco V, et al. Impact of intensive care on renal function before graft harvest: results of a monocentric study. Crit Care. 2007;11(5):R103

Hypothermia and kidney graft fx

- Question:
  - Is hypothermia conducive to improved renal graft function

Therapeutic Hypothermia in Deceased Organ Donors and Kidney Graft Function

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 30, 2015 VOL. 373 NO. 5

Therapeutic Hypothermia in Deceased Organ Donors and Kidney-Graft Function

Claus U. Niemann, M.D., John Feiner, M.D., Sharon Swain, M.S.N., R.N., Scott Bunting, R.R.T., Melissa Friedman, M.S.N., R.N., Megan Crutchfield, M.P.H., Kristine Broglio, M.S., Ryutaro Hirose, M.D., John P. Roberts, M.D., and Darren Malinoski, M.D.

Therapeutic Hypothermia in Deceased Organ Donors and Kidney-Graft Function

- Prospective RCT
- Donor Hypothermia (34 to 35 C) [N=180] vs Normothermia (36.5 to 37.5 C) [N=190]
- Outcomes:
  - delayed kidney graft function
    - rates of individual organs transplanted in each treatment group
    - the total number of organs transplanted per donor

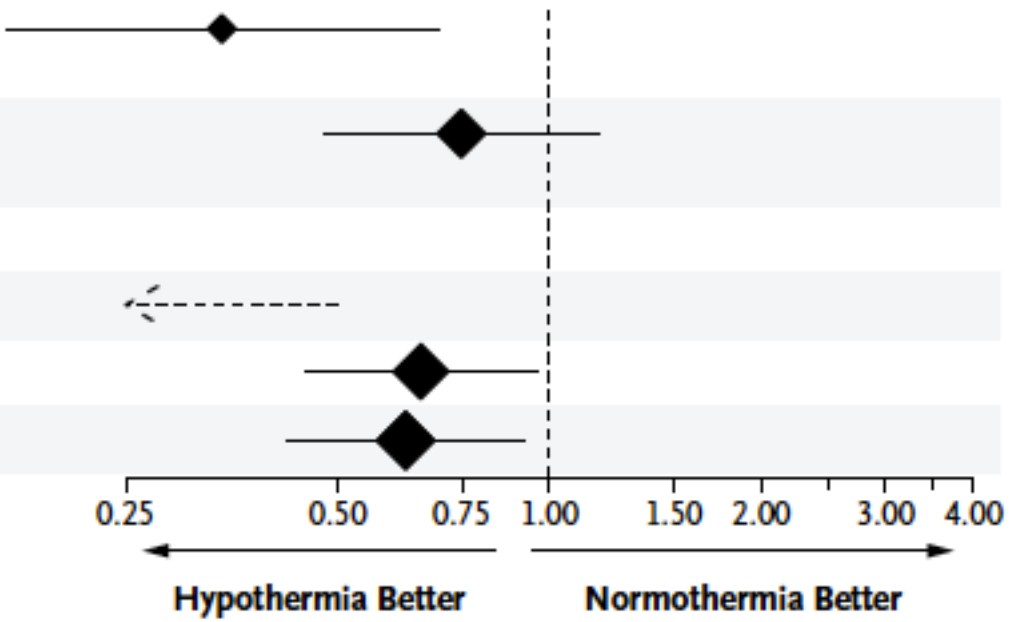
Niemann C, Feiner J, Swain S et al. Therapeutic Hypothermia in Deceased Organ Donors and Kidney-Graft Function N Engl J Med 2015;373:405-14.

Table 3. Results of the Primary Efficacy Analysis.*

Variable	Odds Ratio for Delayed Graft Function (95% CI)	P Value
Hypothermia vs. normothermia	0.62 (0.43–0.92)	0.02
Organ-procurement organization, A vs. B	0.85 (0.57–1.28)	0.43
Standard-criteria donor vs. expanded-criteria donor	1.21 (0.69–2.13)	0.50
Creatinine level at enrollment, per 1-mg-per-deciliter increase	1.99 (1.42–2.80)	<0.001
Donor age, per 1-yr increase	1.04 (1.02–1.05)	<0.001
Kidney cold-ischemia time, per 1-hr increase	1.03 (1.00–1.05)	0.04

Therapeutic Hypothermia in Deceased Organ Donors and Kidney-Graft Function

Subgroup	Hypothermia	Normothermia
	no. of events/total no. (%)	
Donor criteria		
Expanded-criteria donation	22/71 (31)	39/69 (56)
Standard-criteria donation	57/209 (27)	73/217 (34)
Donation procedure		
Dual-kidney donation	0/5	5/6 (83)
Single-kidney donation	79/275 (29)	107/280 (38)
Overall	79/280 (28)	112/286 (39)



Niemann C, Feiner J, Swain S et al. Therapeutic Hypothermia in Deceased Organ Donors and Kidney-Graft Function N Engl J Med 2015;373:405-14.

Donor Factors Affecting Liver Transplant Outcome

Not Amenable to Change

- Age
- Sex
- ABO Blood Type
- Cause of Death
- Macrosteatosis
- Endotoxins and Cytokines

Amenable to Change

- ICU LOS
- Ischemia Times
- **Hypernatremia**
- Nutrition and Liver Glycogen
- Hypotension/Vasoactive Drugs
- Preconditioning for I/R

Powner et al: Prog Transplantation 2004;14:241-249

Clinical Variables Affecting Short-term Graft Function

	Odds Ratio
Donor Sodium > 155	3.03
Cold Ischemia Time > 12 hours	1.20
Warm Ischemia Time > 45 minutes	1.06

Totsuka et al: Transpl Proc, 2004; 36: 2215-2218

What factors are associated with graft dysfx?

- 168 consecutive liver transplantations

- Factors independently predictive of early post-op graft dysfx:
  - Donor serum sodium concentration
  - Total ischemia time
  - Platelet transfusion during surgery
  - Recipient prothrombin activity

González FX, et al. Predictive factors of early postoperative graft function in human liver transplantation. Hepatology. 1994 Sep;20(3):565-73.

How high is too high?

- Retrospective review of 649 OLTs
  - Donor plasma sodium > 155 mmol/L (RR = 2, 95% CI = 1.1-3.6)

Figueras J, et al. The deleterious effect of donor high plasma sodium and extended preservation in liver transplantation. A multivariate analysis. Transplantation. 1996 Feb 15;61(3):410-3.

Does correction of donor Na make a difference?

- 181 OLTs

- 3 donor groups:
  - A Na ≤155 mEq/L
  - B Peak Na >155 mEq/L but final ≤155 mEq/L
  - C Peak Na >155 mEq/L and final >155 mEq/L

Totsuka E, et al. Influence of high donor serum sodium levels on early postoperative graft function in human liver transplantation: effect of correction of donor hypernatremia. Liver Transpl Surg. 1999 Sep;5(5):421-8.

Influence of High Donor Serum Sodium Levels on Early Postoperative Graft Function in Human Liver Transplantation: Effect of Correction of Donor Hypernatremia

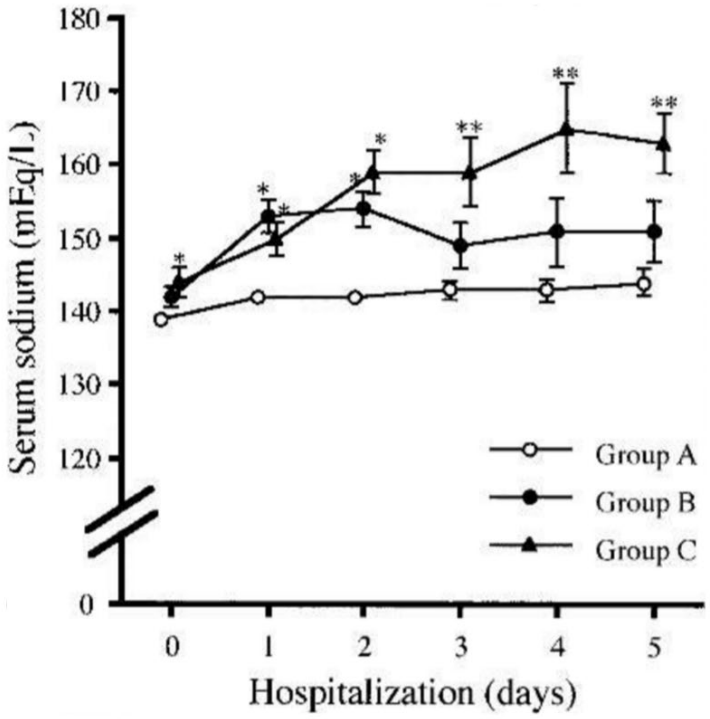


Figure 1. Changes in donor serum sodium concentration during hospitalization. *$P < .05$ *v* group A. **$P < .05$ *v* groups A and B.

Totsuka et al. Liver Transplantation and Surgery, Vol 5, No 5 (September), 1999:pp 421-428

Does c

Table 2. Recipient Characteristics, OLT Procedure, and Early Graft Outcome

	Total (n = 181)	Group A (n = 118)	Group B (n = 36)	Group C (n = 27)	*P*
Age (yr)	51.1 ± 0.9	50.4 ± 1.1	50.4 ± 2.3	55.6 ± 1.8	NS
Sex (M/F)	108/73	68/50	19/17	21/6	NS
Previous OLT	26 (14.4%)	14 (11.9%)	9 (25.0%)	3 (11.1%)	NS
UNOS status 1	59 (32.6%)	36 (30.5%)	13 (36.1%)	10 (37.0%)	NS
Preoperative liver function tests					
AST (U/L)	283.1 ± 74.4	292.8 ± 102.4	380.8 ± 171.2	113.3 ± 23.5	NS
PT (s)	16.36 ± 0.38	16.59 ± 0.52	16.27 ± 0.71	15.34 ± 0.54	NS
T-Bil (mg/dL)	8.15 ± 0.77	8.25 ± 0.95	7.90 ± 1.59	8.31 ± 2.49	NS
OLT procedure					
CIT (h)	11.29 ± 0.27	11.59 ± 0.36	10.24 ± 0.53	11.55 ± 0.54	NS
WIT (min)	45.5 ± 0.9	45.3 ± 0.4	43.9 ± 1.6	48.7 ± 3.4	NS
Operating time (h)	10.15 ± 0.19	10.07 ± 0.21	9.55 ± 0.43	11.35 ± 0.73	NS
Intraoperative transfusion (U)†	36.2 ± 2.5	34.6 ± 2.8	38.0 ± 6.3	46.5 ± 8.2	NS
Early graft loss	28 (15.5%)	15 (12.7%)	4 (11.1%)	9 (33.3%)*	
Cause of graft loss					
Primary nonfunction	9 (5.0%)	4 (3.4%)	0 (0%)	5 (18.5)*	
Preservation injury	6 (3.3%)	4 (3.4%)	1 (2.8%)	1 (3.7%)	
Hepatic arterial thrombosis	3 (1.7%)	1 (0.8%)	1 (2.8%)	1 (3.7%)	
Multiple organ failure due to sepsis	7 (3.9%)	4 (3.4%)	2 (5.6%)	1 (3.7%)	
Other‡	3 (1.7%)	2 (1.7%)	0 (0%)	1 (3.7%)	

Abbreviations: OLT, orthotopic liver transplantation; UNOS, United Network for Organ Sharing; AST, aspartate aminotransferase; PT, prothrombin time; T-Bil, total bilirubin; CIT, cold ischemia time; WIT, warm ischemia time; NS, not significant.

*$P < .05$ *v* groups A and B.

†Red blood cell and fresh-frozen plasma.

‡Other causes of graft failure were graft-versus-host disease, intra-abdominal bleeding, and unknown death.

Totsuka E, et al. Influence of high donor serum sodium levels on early postoperative graft function in human liver transplantation: effect of correction of donor hypernatremia. Liver Transpl Surg. 1999 Sep;5(5):421-8.

Influence of High Donor Serum Sodium Levels on Early Postoperative Graft Function in Human Liver Transplantation: Effect of Correction of Donor Hypernatremia

	Group A serum sodium of 155 mEq/L or less before organ procurement (n = 118);	Group B peak sodium greater than 155 mEq/L and final sodium 155 mEq/L or less (n = 36)	Group final sodium greater than 155 mEq/L (n = 27)
Graft Loss (90 days)	12.7%	11.1%	33%

Recipients of hepatic allografts from donors with uncorrected hyperna- tremia had a significantly greater incidence of graft loss compared with recipients of hepatic allografts from normonatremic donors. However, the differences in graft survival were abrogated by the correction of donor hypernatremia before procurement.

Totsuka et al. Liver Transplantation and Surgery, Vol 5, No 5 (September), 1999:pp 421-428

The Effect of Pre-transplant Serum Sodium Concentration on Outcome Following Liver Transplantation

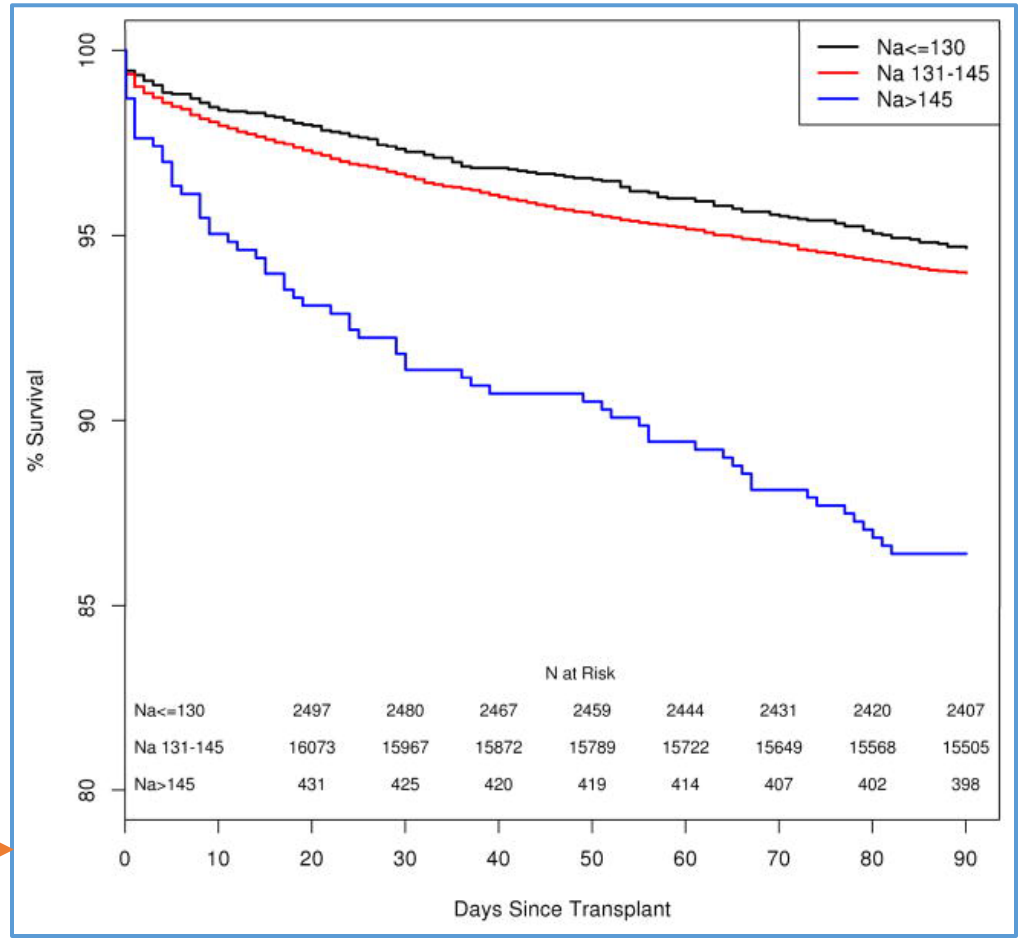
19,537patients with serum Na that was available immediately before LTx from 2003–20010.

Three groups:

- Hyponatremic (Na ≤ 130 mEq/L)
- Normonatremic (Na=131–145mEq/L)
- Hypernatremic (Na >145 mEq/L)

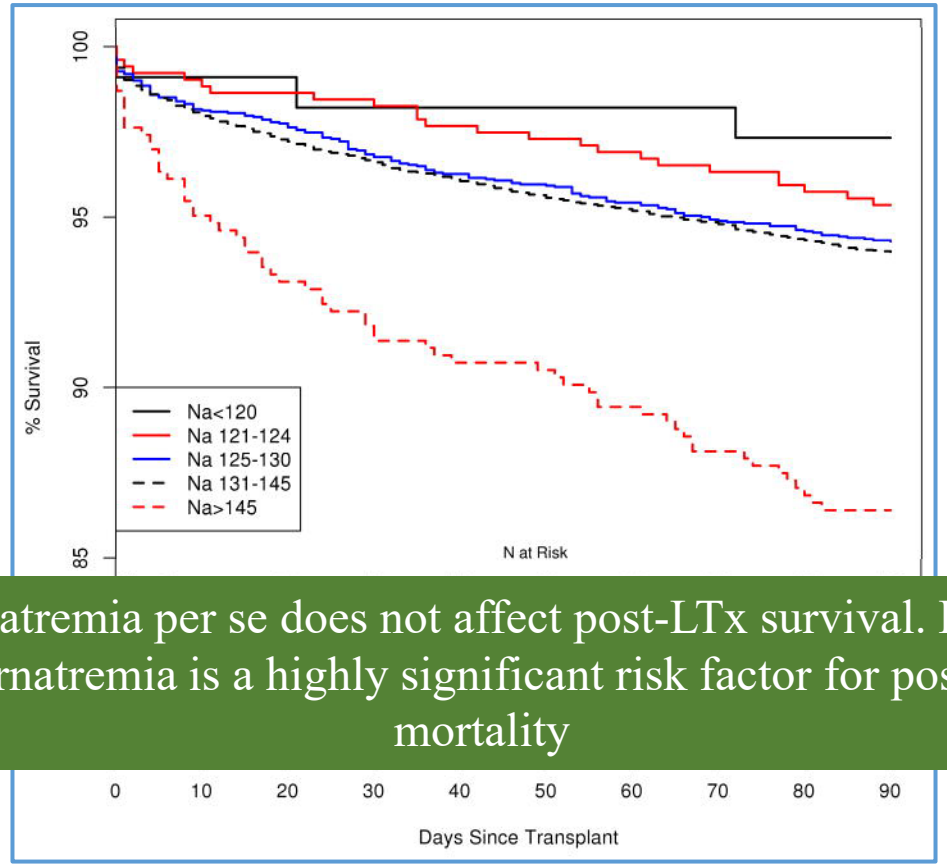
Outcome: 90 day mortality:

Kaplan-Meier curve compares patient survival after LTx by the serum sodium level



Leise, M., D. et al. Liver Transpl. 2014 Jun; 20(6): 687–697.

Kaplan-Meier curve compares patient survival after LTx by mild (Na 125–130), moderate (121–124), and severe hyponatremia (Na < 120) compared to normonatremia and hyponatremia



Hyponatremia per se does not affect post-LTx survival. Pre-LTx hypernatremia is a highly significant risk factor for post-LTx mortality

Leise, M., D. et al. Liver Transpl. 2014 Jun; 20(6): 687–697.

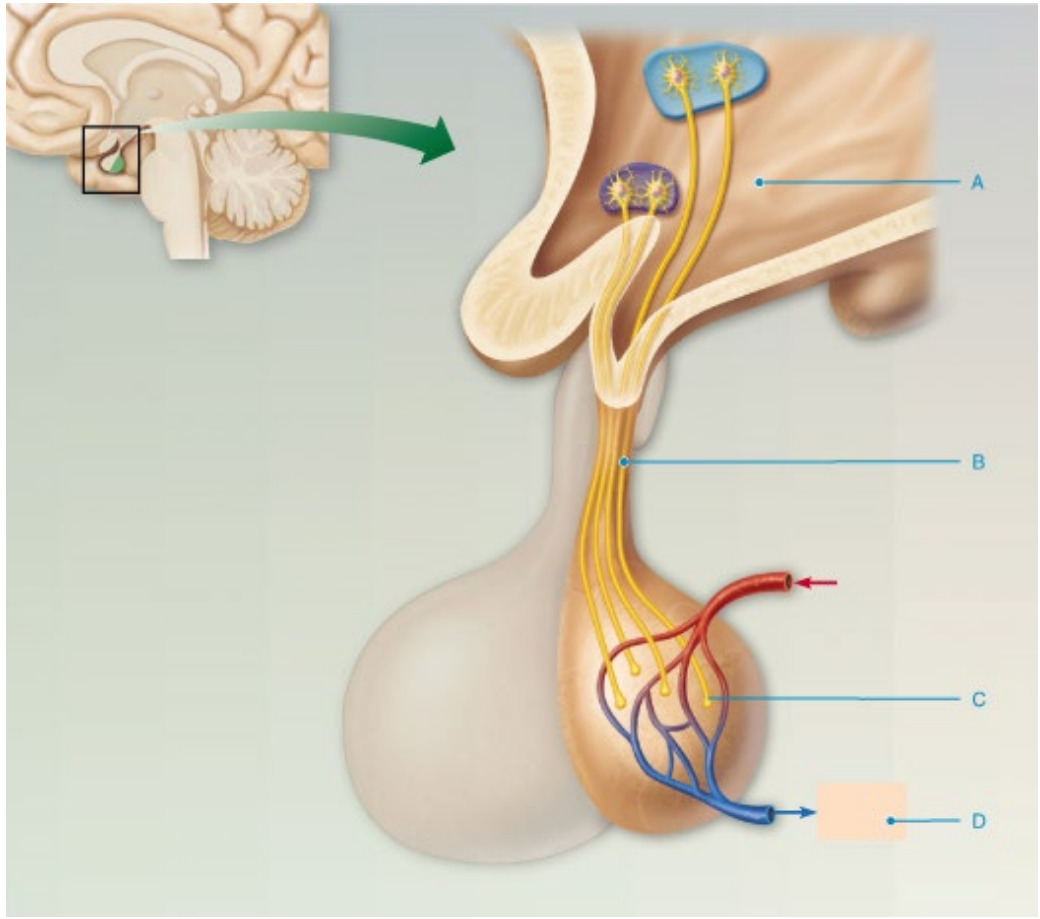
From the SCCM…..

- Sodium:
  - It is not known if further correction of Na below 155 leads to improved outcomes.

- BP Goal:
  - Keep MAP >60-70 mm Hg
  - Vasopressor use does not preclude organ use

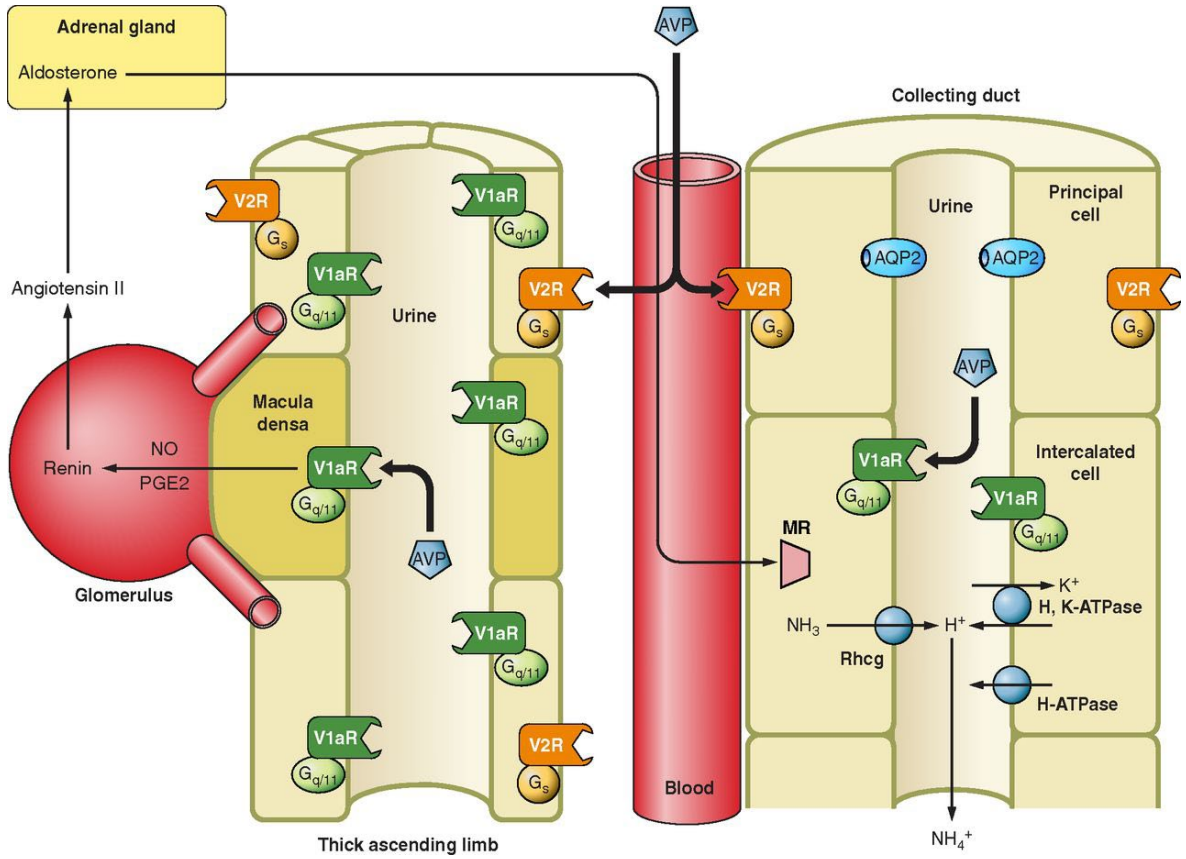
Diabetes Insipidus

- Diabetes insipidus (DI) is caused by decreased secretion (central/neurogenic DI) or action (nephrogenic DI) of antidiuretic hormone (ADH, vasopressin).
- ADH is produced by the hypothalamic neurons in the supraoptic and paraventricular nuclei
- It migrates along their axons to the posterior pituitary gland where it is stored in secretory granules and is secreted in the circulation when stimulated (by increased plasma osmolality—osmoregulation or by decreased arterial blood pressure—baroregulation).

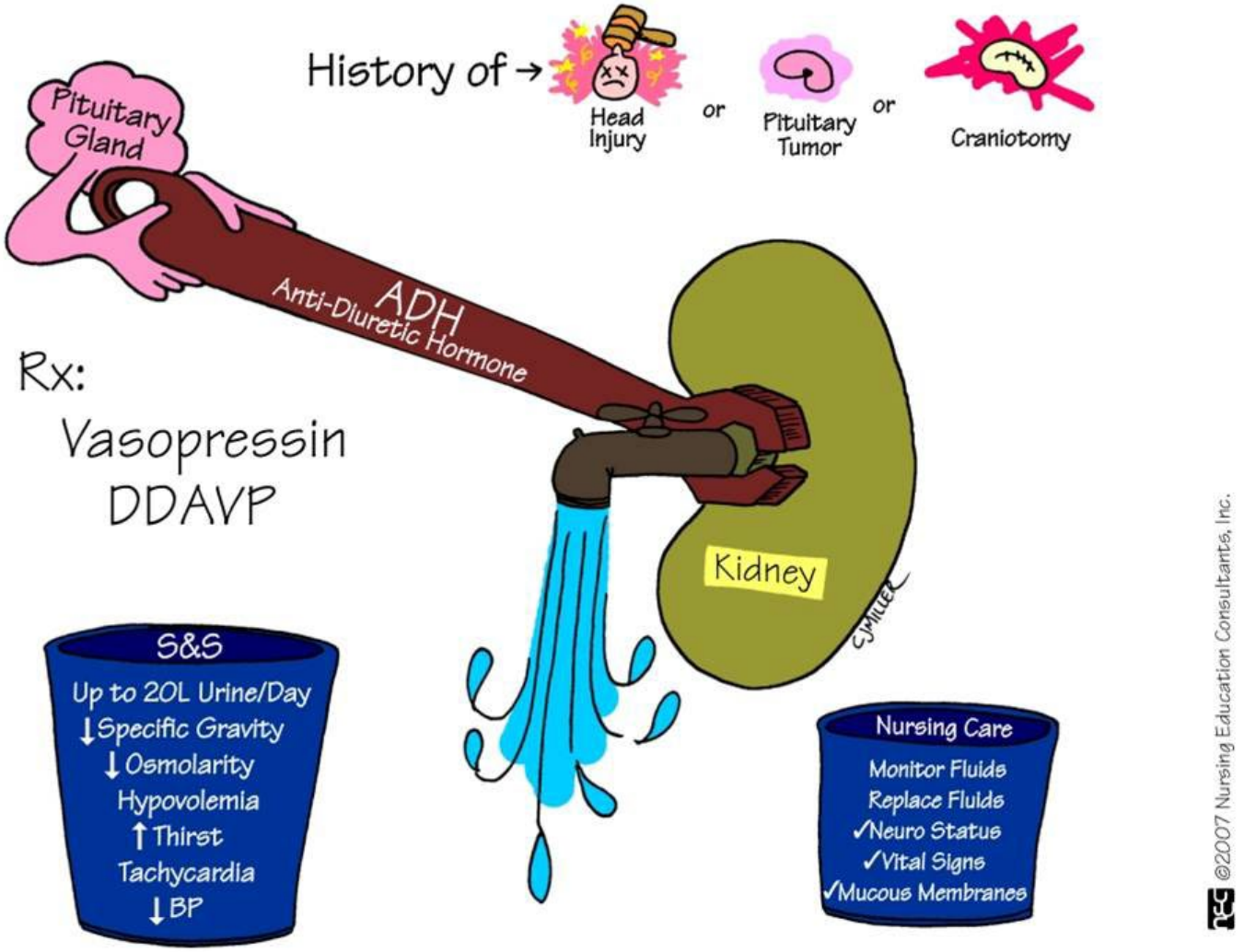


Diabetes Insipidus

- ADH acts on specific receptors (vasopressin receptors; three subtypes V1a, V1b and V2 have been identified).
- Its main physiological effect (increase of water absorption in the distal nephron) requires the stimulation of local V2 receptors promoting the expression of specific water channel proteins (aquaporins) on the luminal surface of the collecting duct.



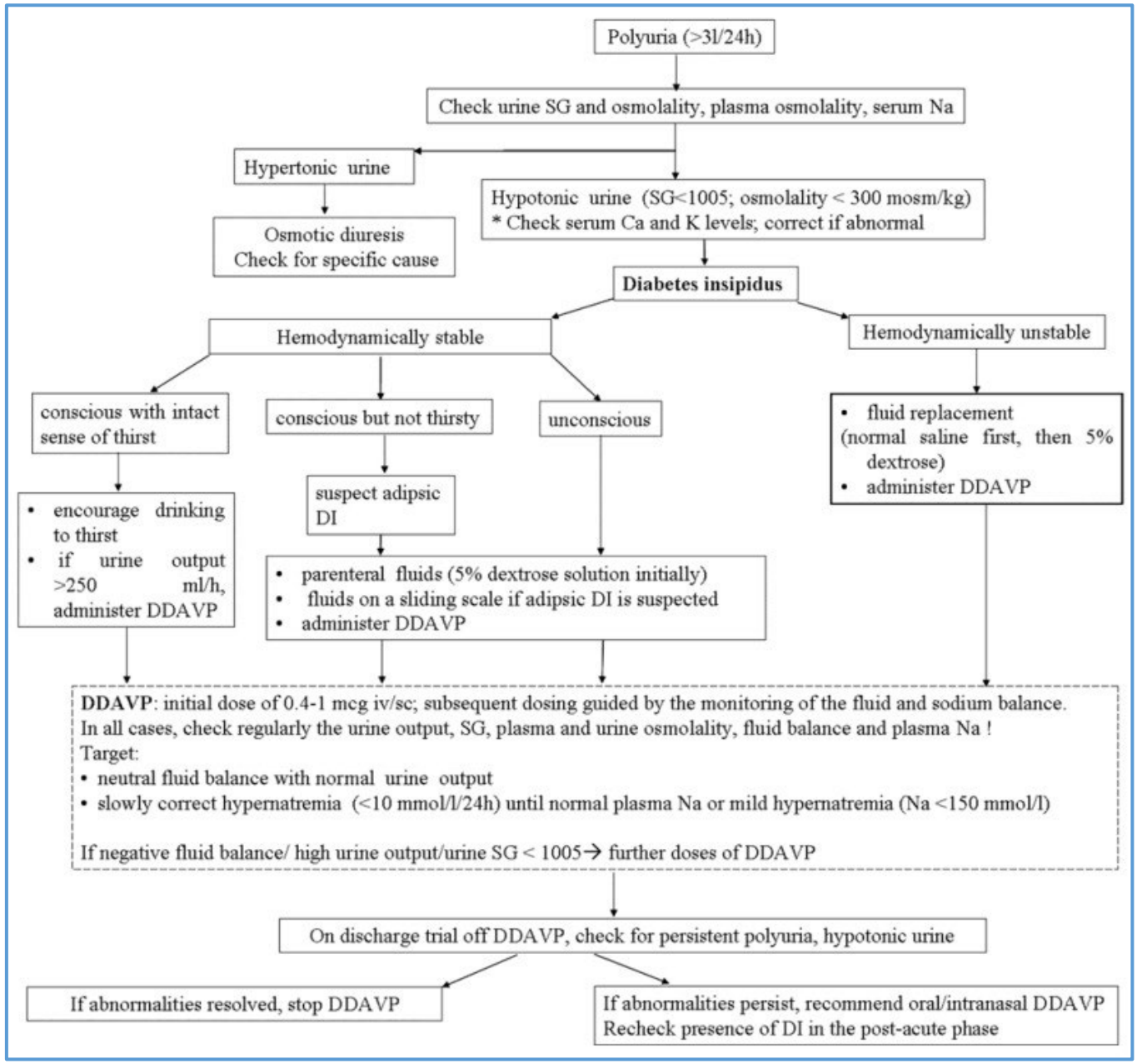
DIABETES INSIPIDUS



Diabetes Insipidus

- Typical Clinical picture:
  - Polyuria: output > 4ml/kg/h
  - Rule of thumb – 500 ml UOP per hour x 2 hours is DI
  - ~~Polydipsia~~
  - ~~Nocturia~~
- Hypovolemia
- Hypernatremia

Laboratory Findings
Na >145 mEq/L
Posm > 285 mOsm/kg
Uosm < 300 mOsm/kg
UNa low
Urine Spec. Grav. < 1.005
UOP > 3ml/kg/h


Polyuria (>3l/24h)
Check urine SG and osmolality, plasma osmolality, serum Na
Hypertonic urine
Osmotic diuresis
Check for specific cause
Hypotonic urine (SG<1005; osmolality < 300 mosm/kg)
* Check serum Ca and K levels; correct if abnormal
Diabetes insipidus
Hemodynamically stable
Hemodynamically unstable
conscious with intact sense of thirst
conscious but not thirsty
unconscious
• fluid replacement (normal saline first, then 5% dextrose)
• administer DDAVP
• encourage drinking to thirst
• if urine output >250 ml/h, administer DDAVP
suspect adipsic DI
• parenteral fluids (5% dextrose solution initially)
• fluids on a sliding scale if adipsic DI is suspected
• administer DDAVP
DDAVP: initial dose of 0.4-1 mcg iv/sc; subsequent dosing guided by the monitoring of the fluid and sodium balance.
In all cases, check regularly the urine output, SG, plasma and urine osmolality, fluid balance and plasma Na !
Target:
• neutral fluid balance with normal urine output
• slowly correct hypernatremia (<10 mmol/l/24h) until normal plasma Na or mild hypernatremia (Na <150 mmol/l)
If negative fluid balance/ high urine output/urine SG < 1005→ further doses of DDAVP
On discharge trial off DDAVP, check for persistent polyuria, hypotonic urine
If abnormalities resolved, stop DDAVP
If abnormalities persist, recommend oral/intranasal DDAVP
Recheck presence of DI in the post-acute phase

Diabetes Insipidus Management

- Early depletion of ADH Characterized by inappropriate diuresis leading to severe hypovolemia hemodynamic and electrolyte instability
- Treatment is aimed at correcting hypovolemia, avoiding hypernatremia and hypokalemia
- Management includes replacing free water loss with hypotonic saline or dextrose in water and electrolytes as needed

Differential Diagnosis

	SIADH	CSW	DI
Serum Na+	< 135 mEq/L	< 135 mEq/L	> 145 mEq/L
Urine Na+	> 25 mEq/L	> 40 mEq/L	< 25 mEq/L
Serum Osm	< 270 mOsm/kg	< 270 mOsm/kg	> 285 mOsm/kg
Urine Osm	> 300 mOsm/kg	> 300 mOsm/kg	< 300 mOsm/kg
Urine O/P	oliguria	polyuria	polyuria
CVP	normal/high	low	normal/low
Plasma ADH	high	normal	low
Rx	Fluid restrict, give Na+, vaprisol, demeclocycline	Give volume, give Na+, fludrocortisone	Drink to thirst, DDAVP (central), HCTZ (nephrogenic)

Central Diabetes Insipidus: Management

- Goal UOP 100-200 ml/hr (output 0.5 – 2.0 ml / kg / h)
- Vasopressin:
  - Low dose shown to reduce inotrope use
  - Plays a critical role in restoring vasomotor tone
    - 4 unit bolus
    - 1- 4 u/hour – titrate to keep SBP >100 or MAP >60
- Desmopressin (DDAVP) 1 mcg IV, may repeat x 1 after 1 hour.
- Replace hourly U.O. on a volume per volume basis with MIVF to avoid volume depletion

Conclusion

- Hypernatremia affects graft function negatively
- Correction of hypernatremia is associated with graft survival similar to normonatremia
- Treat DI aggressively with volume, vasopressin, and DDAVP