

# Over- and underfill: not all nephrotic states are equal

Detlef Bockenhauer



Great Ormond Street  
Hospital for Children  
NHS Trust



# Objectives

- Review pathophysiology of oedema: under- vs overfill
- Treatment options

# The clinical setting: case 1

- A 6-y old girl with known steroid-sensitive nephrotic syndrome relapses in the context of a diarrhoeal illness. She is brought to A&E because of painful legs.
- Examination: BP: 74/46, HR: 158/min, cap refill: 4s. Gross oedema with marked ascites. Both legs are cool, pale and no palpable femoral or pedal pulses.  
US: bilateral femoral arterial thrombi

## Case 2

- 12-y old girl with 1-y history of steroid –resistant nephrotic syndrome is admitted because of severe oedema.
- Examination: BP: 124 mmHg, HR: 84/min, brisk cap. refill. Pitting oedema and palpable ascites.
- She receives daily 20% albumin infusions with diuretics with little improvement
- During one of the albumin infusions, she experiences respiratory difficulties and then has cardiovascular collapse with severe pulmonary oedema. Admitted to PICU, intubated & ventilated. Has remained anuric since

# Intravascular volume in nephrotics

- “underfill”, i.e. severe intravascular depletion with risk of thrombosis (arterial, sinus venous)



- “overfill”, i.e. intravascular excess with risk of pulmonary oedema
- Treatment is obviously critically different

# The Underfill Hypothesis

Urinary protein loss leads to

- => hypoproteinaemia
- => decreased intravascular oncotic pressure,
- => extravasation of sodium and water
- => decreased circulating volume
- => activation of Renin-Angiotensin-Aldo
- => increased tubular salt reabsorption

That all makes perfect sense !

So what is the problem?

# Some clinical observations

What happens, when a child with nephrotic syndrome goes into remission?

1. A dramatic increase in urine output with high urinary sodium

followed by

2. Slow normalisation of serum albumin



# More clinical observations

- Neurohumoral markers for volume depletion (renin, aldosterone) are often NOT elevated in nephrotic patients
- Infusion of albumin leads to hypertension, CHF or pulmonary oedema in some patients
- Infusion of albumin often does not lead to increased urinary sodium
- Analbuminaemic patients (and rats) do not have oedema

# Experimental observations

- Blood volume (measured as red cell volume plus plasma volume) in nephrotic patients is normal or elevated in the majority of patients.
- Extracting albumin from subjects by plasmapheresis does not lead to oedema.

Melzer et al, Annals of Internal Medicine, 1979;91(5)688-96

# Animal Experiments

- Classic experiment by Ichikawa, using rat model of minimal change disease (PAN- nephritis): selectively perfuses only left kidney with PAN. 2 weeks later, left kidney has albuminuria and decreased sodium excretion despite controlled systemic albumin levels.
- Moreover, right (control) kidney (living in same systemic environment) has no reduction in salt excretion.

Ichikawa et al, JCI 91:1295-1300, 1993

# The Overfill Hypothesis

A renal lesion leads to:

1) proteinuria and

2) **primary** sodium retention

=> salt and water “spill over” from the  
overfilled vasculature into the interstitial  
flood plains

# Proteases in nephrotic syndrome

- ENaC, key channel in collecting duct for sodium reabsorption (stimulated by aldosterone, blocked by amiloride...)
- Nephrotic urine contains proteases (plasmin) and these activate ENaC in vivo and in vitro (Svenningsen, P. et al. JASN 2009;20:299-310)
- Corin, a renal protease converting pro-ANP into active ANP is suppressed in NS (Polzin et al, Kidney Int. 2010 Oct;78(7):650-9)

# Arguments against the Overfill hypothesis – clinical observations

- Many patients with nephrotic syndrome have clinical signs of poor perfusion and biochemical evidence of haemoconcentration (elevated haemoglobin, thrombocytosis) and improve with albumin infusion (i.e. improved perfusion, no signs of volume overload)
- Neurohumoral markers are elevated in some nephrotics.

# Clinical reality

- In nephrotic syndrome, patients can be under-or overfilled and convert quickly from one extreme to the other!
- Those with extra-renal volume losses (e.g. case 1, diarrhoea) are at very high risk of underfill
- Some data suggest that patients with minimal change disease are more prone to underfill and those with a “nephritic” component to overfill  
(Meltzer et al, 1979, Ann Int Med 91: 688-696)

# Clinical assessment is key

- Assessment of volume status is critical:  
is the patient underfilled and at risk for  
thrombosis?  
Or overfilled and at risk for pulmonary  
oedema?
- - peripheral perfusion, cap. refill  
- blood pressure, heart rate



# Investigations

	Case 1	Case 2
Hgb g/dl	18.8	9.4
Plateles /nl	980	344
Na mmol/l	142	141
urea mmol/l	6.9	10.5
Creatinine umol/l	58	66
Albumin g/l	6	7
Urine Na mmol/l	5	6
Urine Crea mmol/l	24.5	30.6
FENa %	<0.1	<0.1

# Treatment of underfill

- Albumin!
- Very careful and judicious use of diuretics  
(only with/after albumin)

# Treatment of overfill

- diuretics!
- Usually large doses of furosemide (2-3 mg/kg) are needed
- Critical role of ENaC suggests use of amiloride could be beneficial
- Emerging case reports of successful use of AVPR2 antagonists (Vaptans) in severe oedema

# Vasopressin receptor antagonists?

- Case reports of successful treatment of edema in nephrotic syndrome with oral AVPR2 antagonist (Tolvaptan)

Nephrology (Carlton). 2015 Feb;20(2):103-6

Pediatr Nephrol. 2014 May;29(5):915-7.

- Risk of hypovolemia!

# Treatment in general

- Nephrotic patients can be very challenging!
- Patients can change from underfilled to overfilled and vice versa!
- Careful clinical observation is key!

# Conclusions

- Kidneys are responsible for maintenance of volume homeostasis
- In nephrotic syndrome, this critical task is disturbed
- Patients are at risk for both “underfill” and “overfill”
- Clinical examination is key for volume assessment
- Laboratory parameters can only give additional hints (?haemoconcentration)
- AVPR2 blockers may be useful in treatment of oedema



*"By God, for a minute there it suddenly all made sense!"*