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40 years of bedwetting treatment

– what truly makes a difference?

Søren Rittig
Prof. MD, DMSc

Pediatrics and Adolescent Medicine
Aarhus University Hospital
Aarhus, DENMARK
Rittig@clin.au.dk

midt regionmidtjylland

AARHUS UNIVERSITETS HOSPITAL | børn & unge hospital

Disclosures

Advisory board and research collaboration – Ferring Pharmaceuticals

Søren Rittig
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OUTLINE

- Enuresis history
  - ✓ Understanding pathogenesis
  - ✓ The role of genetics
- First-line treatments of nocturnal enuresis
  - ✓ Desmopressin vs. alarm
- Value of bladder diaries when selecting treatment
  - ✓ New prediction tools
- Treatment resistance – what to do?
  - ✓ Multimodal treatment

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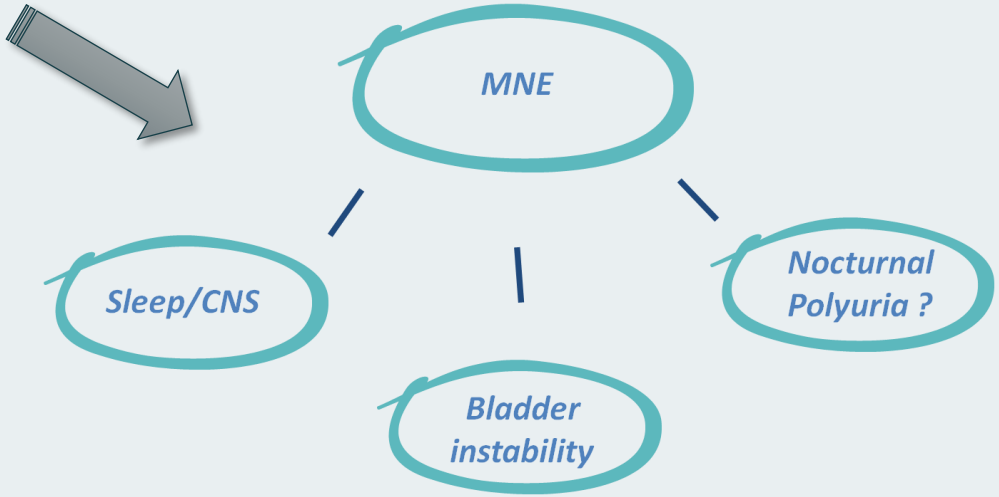
NE pathophysiology – *historical aspects*

Perception during early 1980-ies

- No consensus regarding definitions
- No differentiation between day and night wetting
- Poor understanding of the heterogeneous nature
- Strong belief that psychology/psychiatry played a role
- Many myths and severe social stigmatization



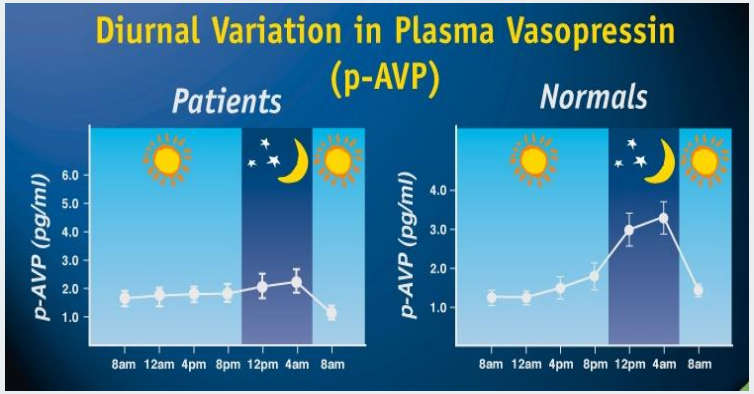
Nørgaard JP: Doctoral Thesis, 1991

NE pathophysiology – *historical aspects*

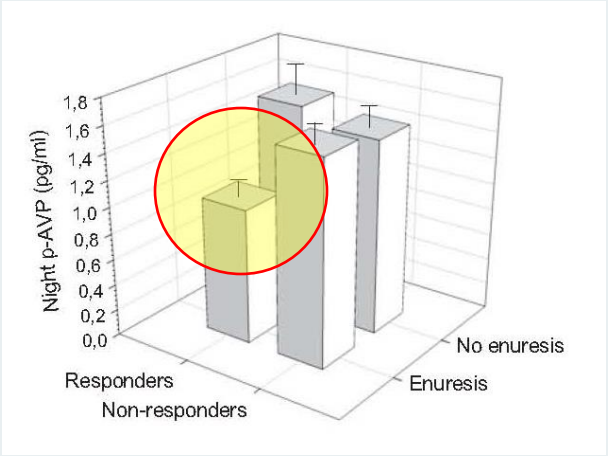
Nocturnal AVP defect

Diurnal anti-diuretic-hormone levels in enuretics.

Norgaard et al, J Urol, 1985



Rittig et al, Am J Physiol, 1989

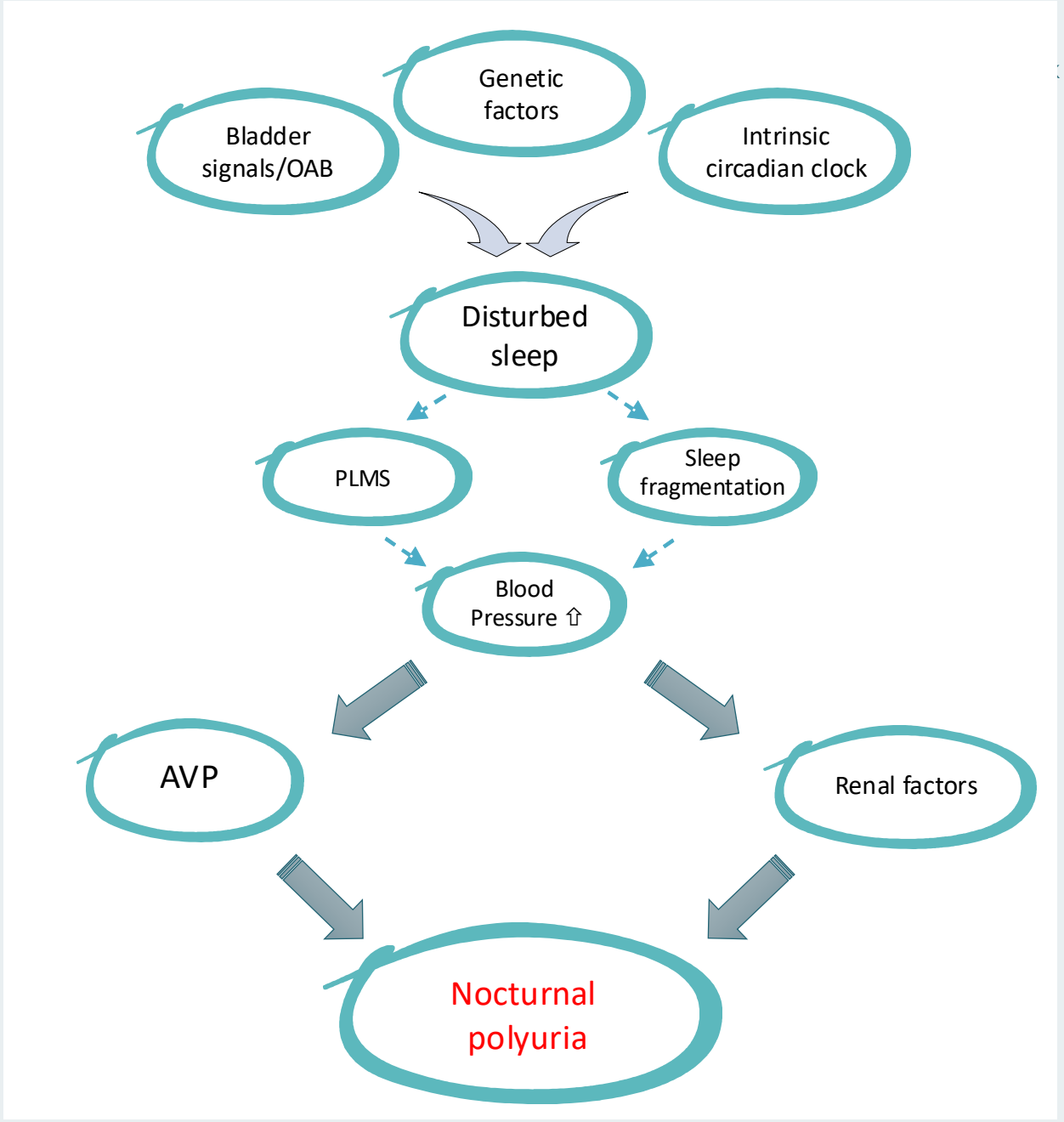


Rittig et al, J Urol, 2010

Conclusion:
Lower p-AVP levels during wet nights in patients with good response to dDAVP.

Nocturnal polyuria

- new pathogenic model

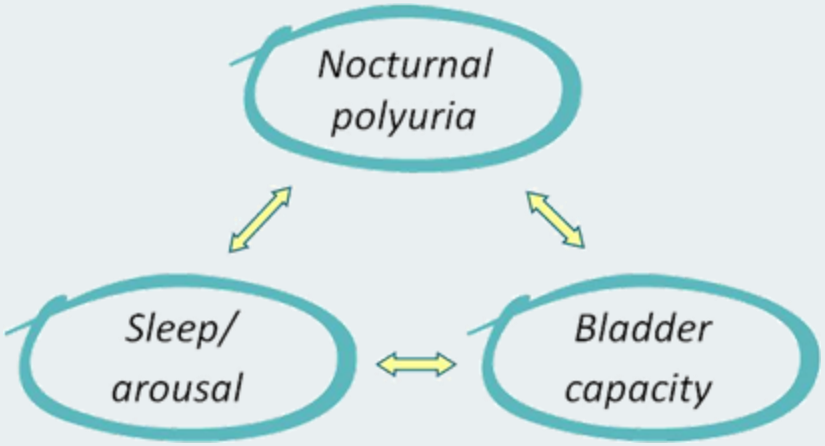


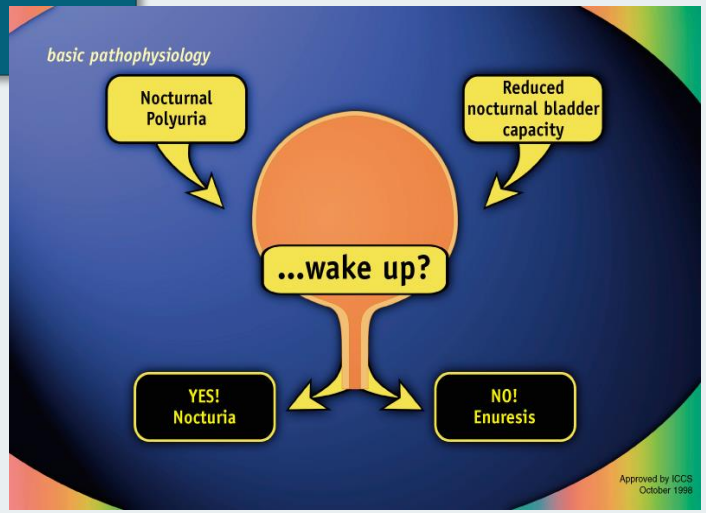
NE pathogenesis
- the three-factor model

Nocturnal enuresis is caused by a mismatch between nocturnal urine volume and nocturnal bladder capacity

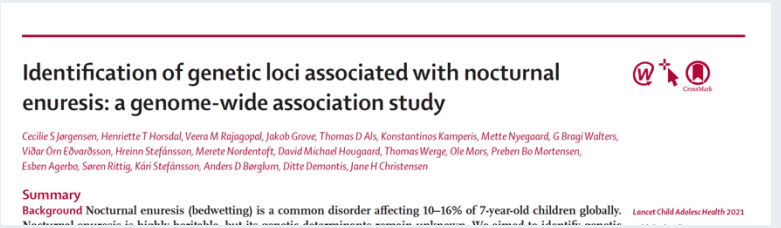
+

Inability to awaken when this occurs





First GWAS study in enuresis



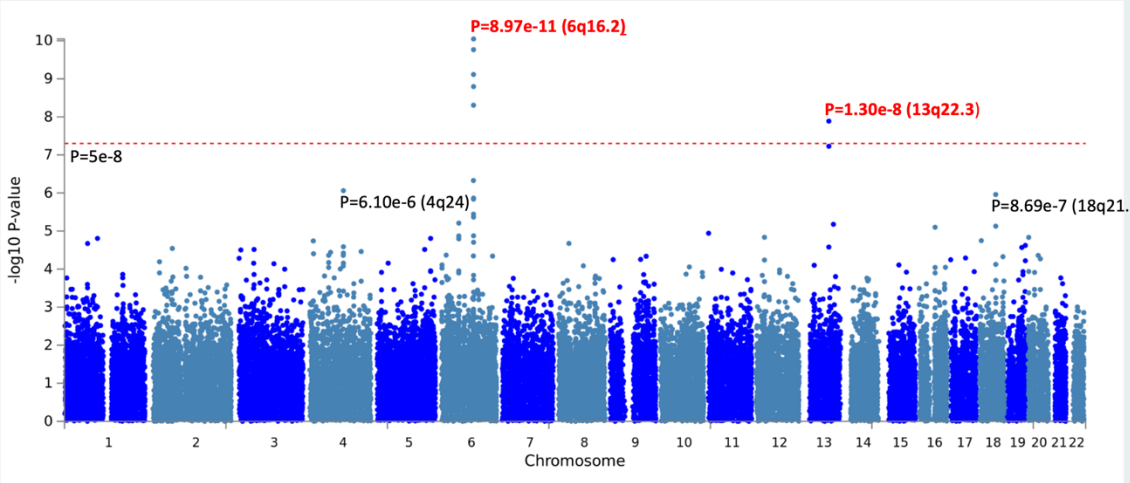
Identification of genetic loci associated with nocturnal enuresis: a genome-wide association study

Cecilie S Jørgensen, Henriette T Horsdal, Veera M Rajagopal, Jakob Grove, Thomas D Als, Konstantinos Kamperis, Mette Nyegaard, G Bragi Walters, Viðar Örn Eðvarðsson, Hreinn Stefánsson, Merete Nordentoft, David Michael Hougaard, Thomas Werge, Ole Mors, Preben Bo Mortensen, Esben Agerbo, Søren Rittig, Kári Stefánsson, Anders D Børglum, Ditte Demontis, Jane H Christensen

Summary

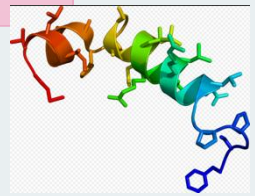
Background Nocturnal enuresis (bedwetting) is a common disorder affecting 10–16% of 7-year-old children globally. Lancet Child Adolesc Health 2021

3882 cases and 31.073 controls in iPSYCH
SNP heritability: 27,79% (± 3,42%)
Replicated at deCODE Genetics



Conclusion:

- Common variants on Chr. 6 and 13 are responsible for a significant proportion of the genetic risk of NE
- The variants identified seems to be involved with known pathogenic factors (sleep, urine production and bladder function)
- Correlation between genetic risk of NE and ADHD
- Pointing towards a drug target related to the hypocretin pathway.



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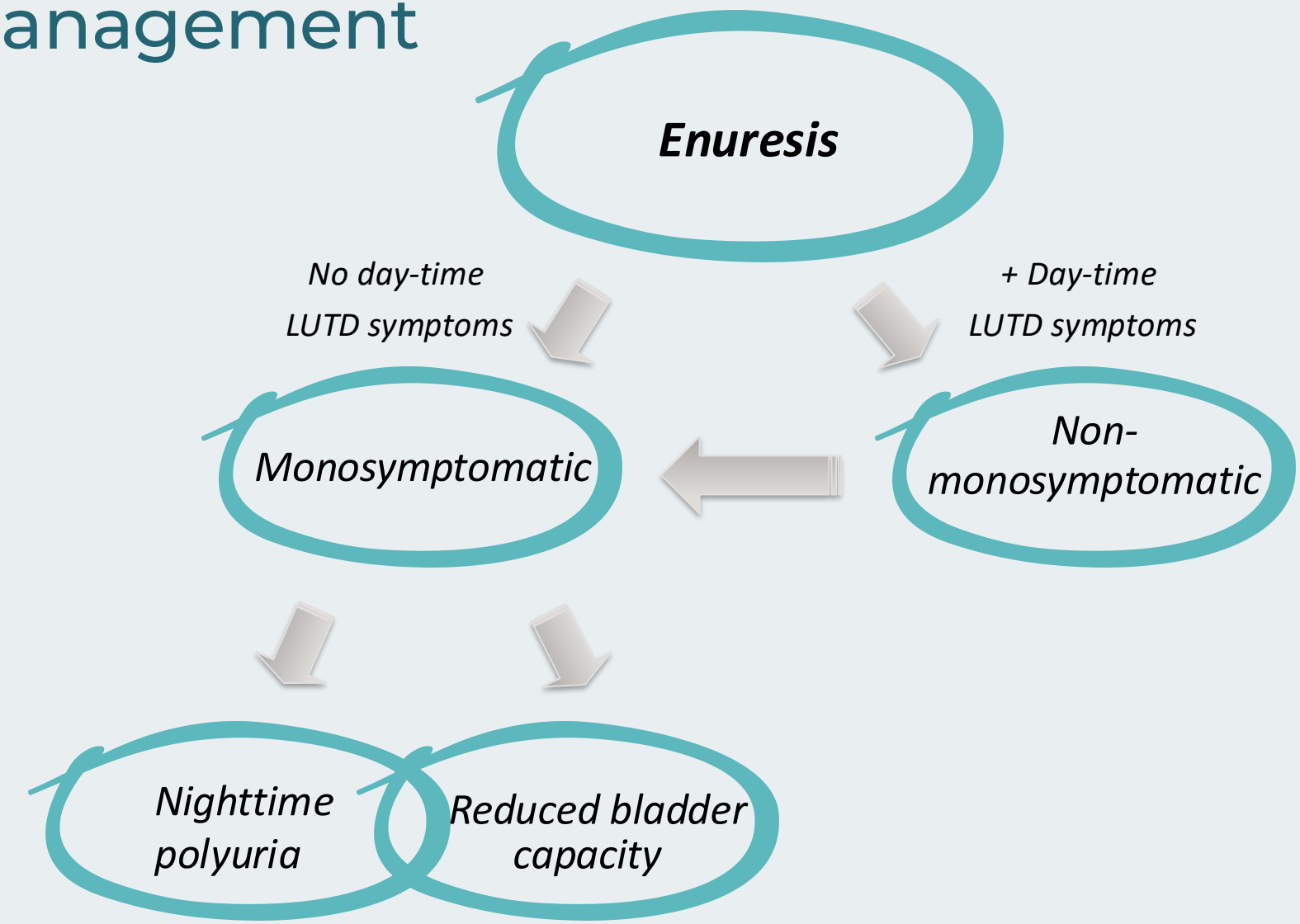
Enuresis management

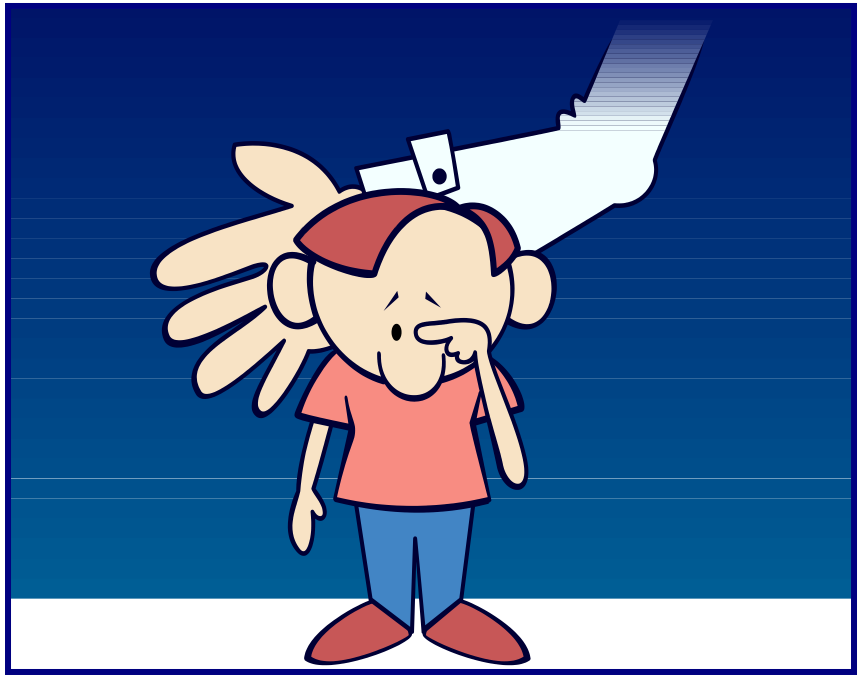


Austin et al, J Urol; 2014;191(6):1863-1865.
Neveus et al, J Ped Urol; 2020; (16):10-19.

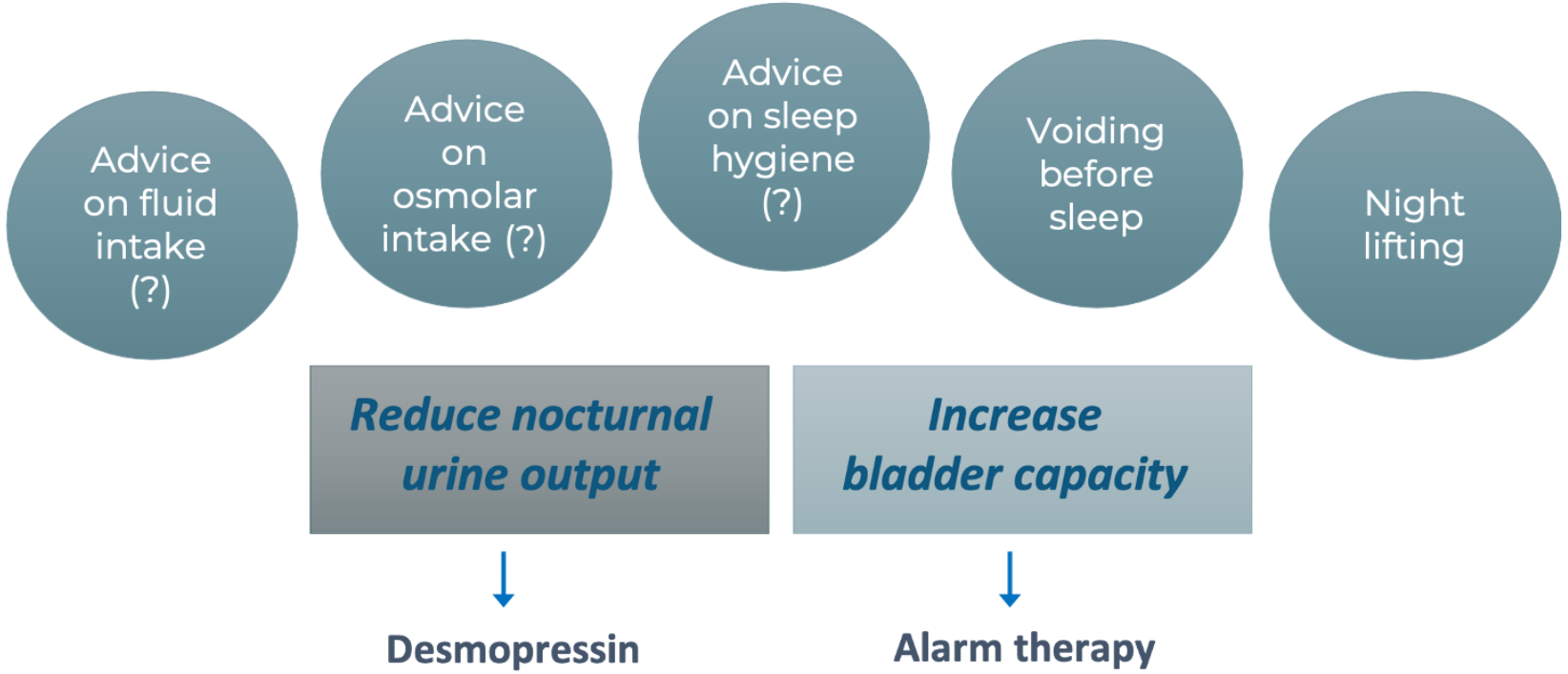
A common 'treatment'

– Let's wait and see

– "Time to take action"

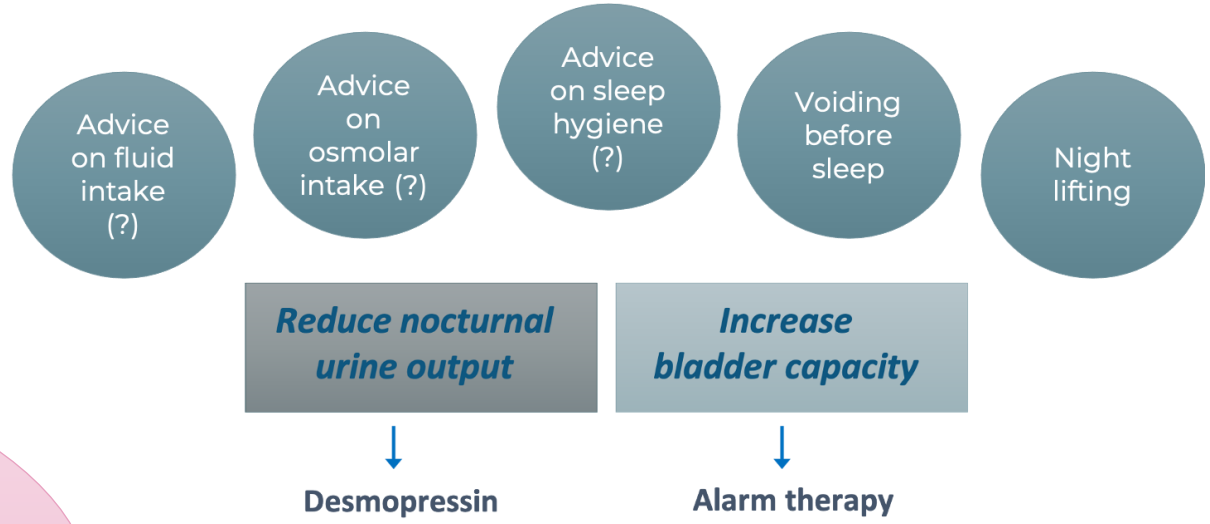


Management approach – before first line



Other aspects:
Family motivation, availability of alarm, cost issues

Management approach – before first line

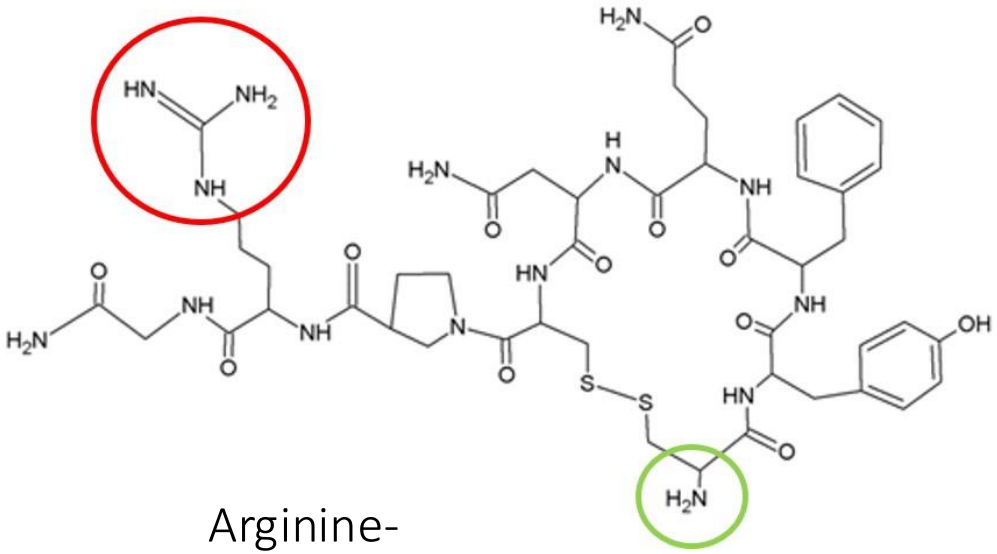


New advice:

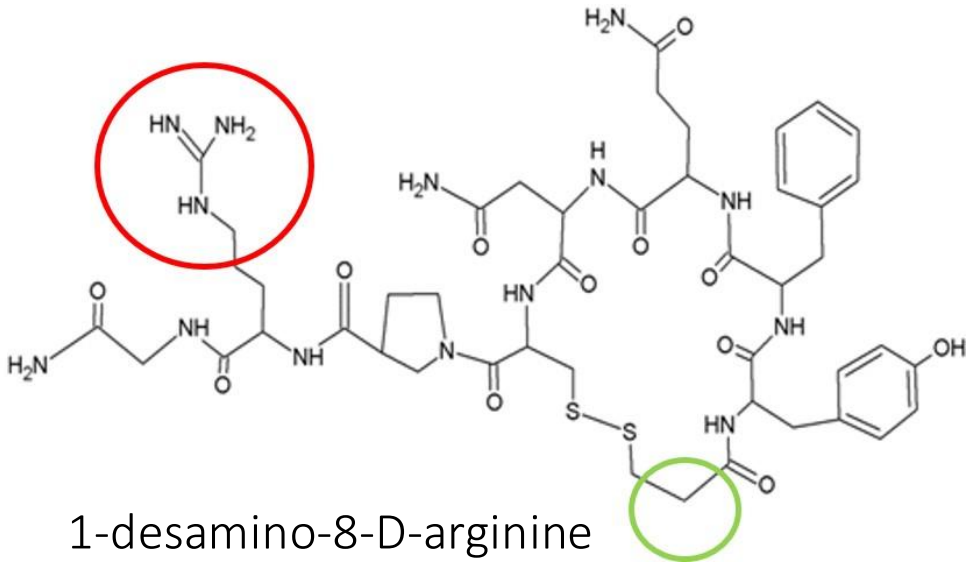
- If the child use disposable diapers/garments try to discontinue for 1-2 weeks.
- If no effect restart.

Breinbjerg et al, Eur J Pediatr. 2024 May;183(5):2443-2453

Desmopressin (dDAVP)



Arginine-vasopressin (AVP)



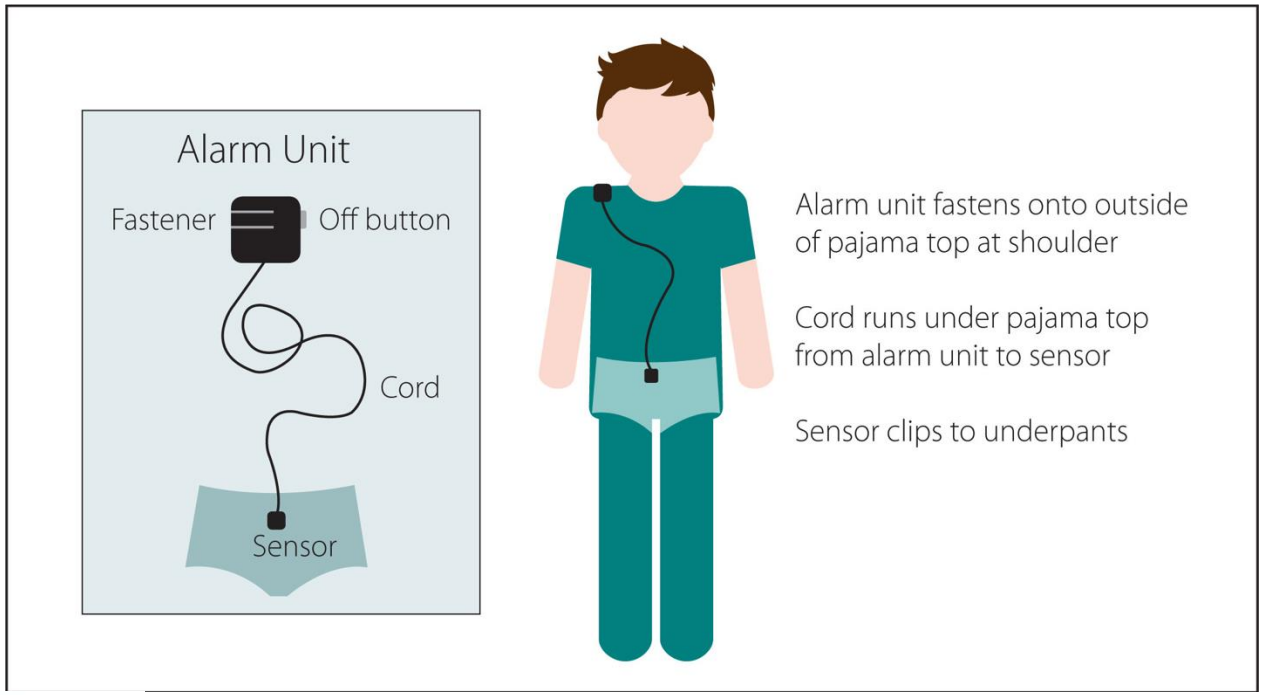
1-desamino-8-D-arginine vasopressin
= DESMOPRESSIN (dDAVP)

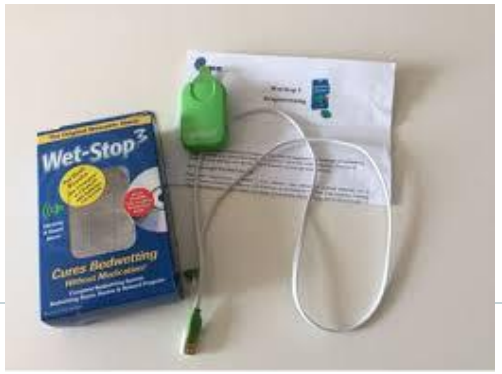
⇩ URINE PRODUCTION

Tablet: 0,2 - 0,6 mg

Lyophilisate: 120 - 360 µg

Enuresis alarm





Treatment of enuresis

- in practice

General advice given to all children:
Explanation, demystification, removal of guilt

Active treatment with the enuresis alarm or desmopressin offered to children age 6 years or older who are bothered by their condition

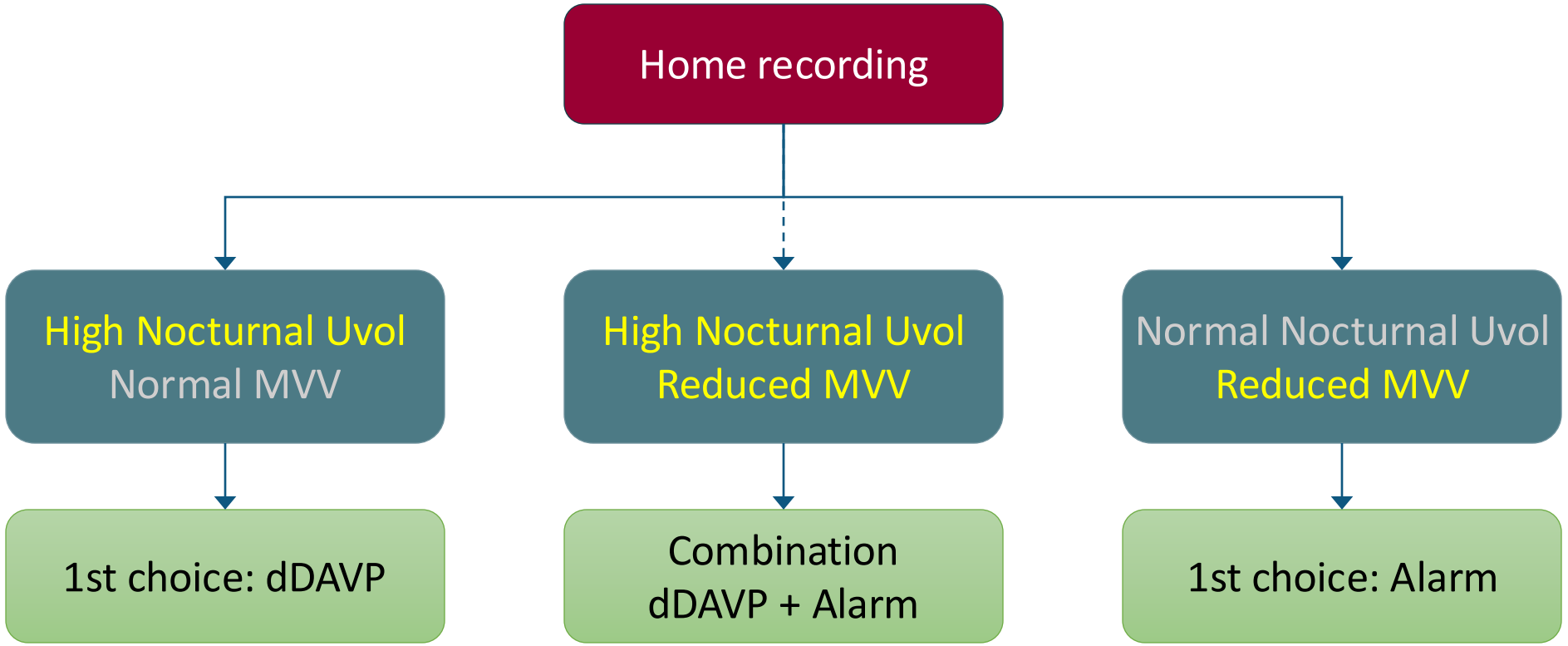
Alternative strategies for the choice of the first therapy

Simple strategy	Extended strategy
Present the assets and draw-backs of the alarm and desmopressin and let the family choose	Perform voiding diary. Offer desmopressin to children with nocturnal polyuria + normal voided volumes. Offer the alarm to children with low voided volumes.

Nevéus T, Eggert P, Evans J, Macedo Jr A, Rittig S, Tekgül S, Vande Walle J, Yeung CK, Robson L. 2010

Treatment strategy in MNE

- Based upon bladder diary



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The DRYCHILD study

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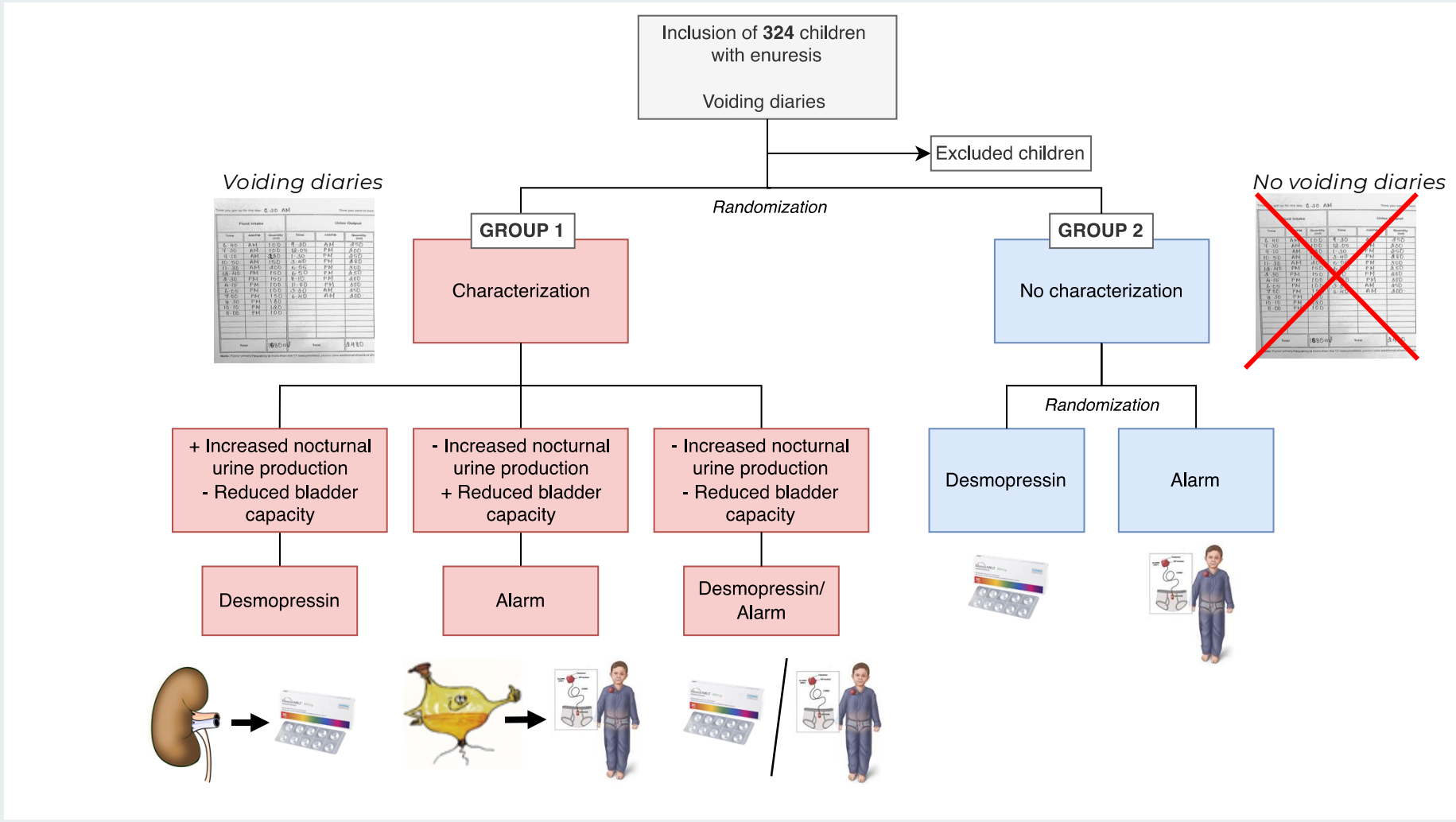
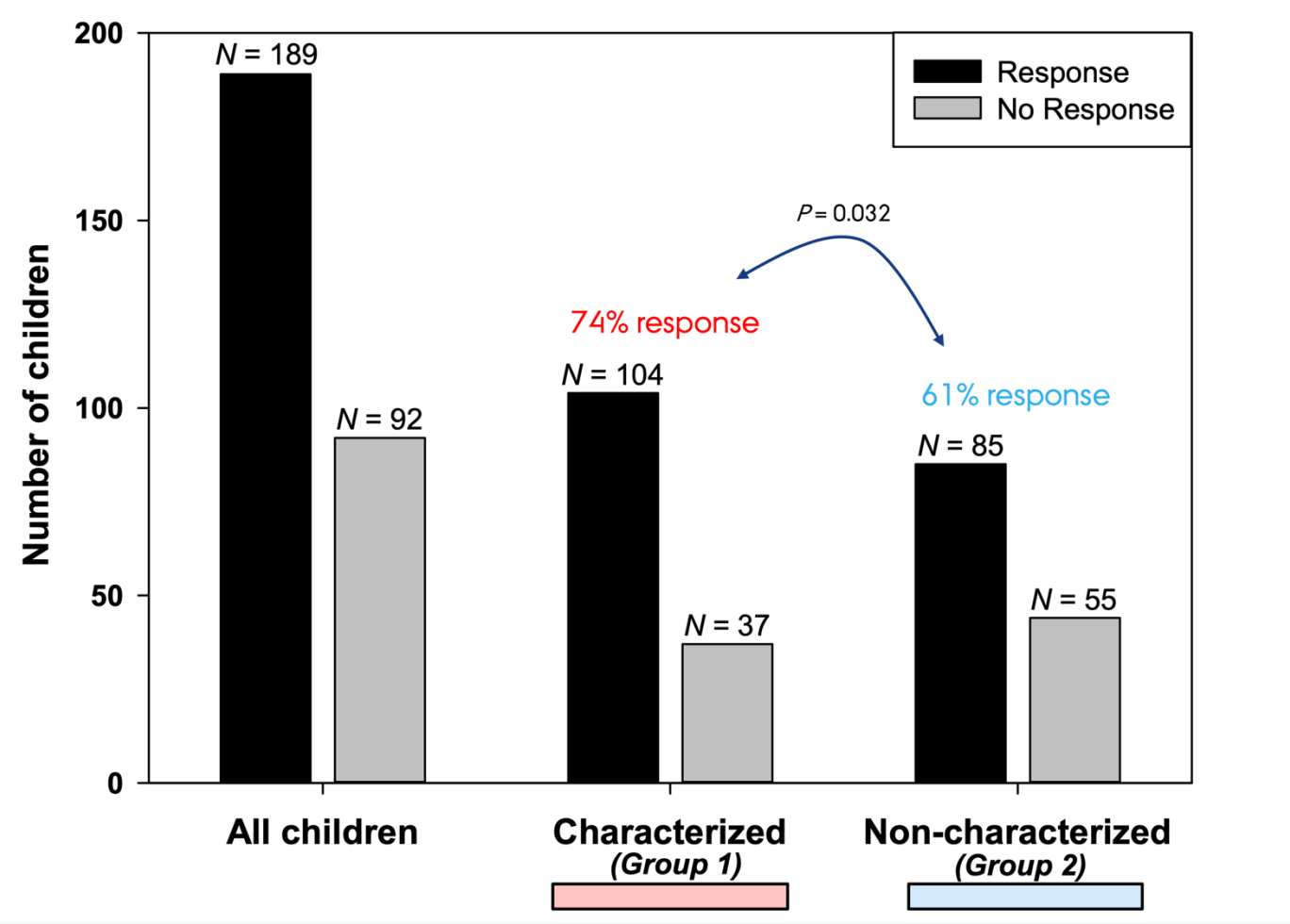
JU Insight

Development of a Novel Prediction Tool for Response to First-Line Treatments of Monosymptomatic Nocturnal Enuresis: A Randomized, Controlled, International, Multicenter Study (DRYCHILD)

Cecilie Siggaard Jørgensen, Lien Dossche, Rongqun Zhai, et al.



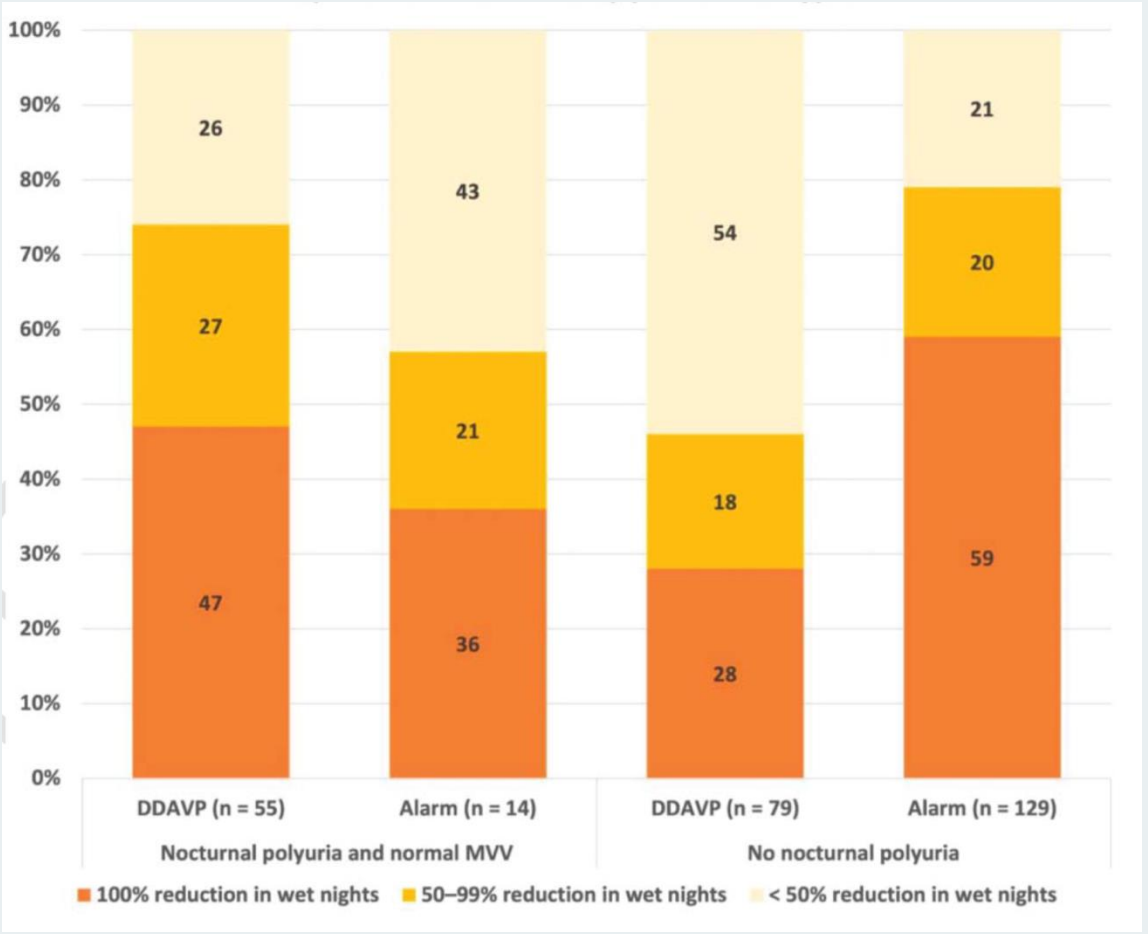
DRYCHILD results



Overall, we observed better effect if children were characterized (home recordings).

DRYCHILD results

The difference in treatment response to first line treatments depends on patient subgroup (up to 50% difference).



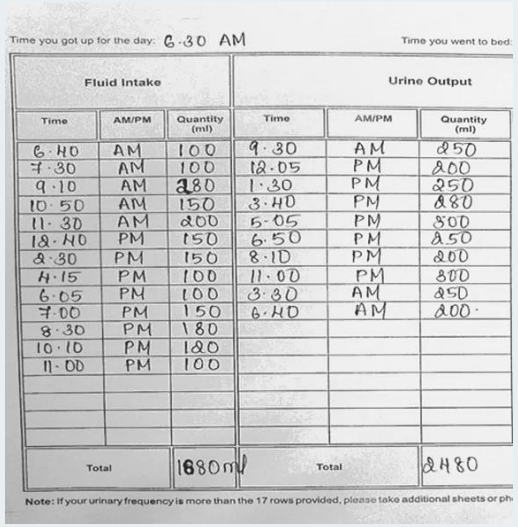
Effect of desmopressin

	Responders (n = 77)	Non-responders (n = 59)	*P* value
Gender (male, n)	58 (75%)	37 (63%)	0.11
Age (years)	8.8 ± 2.3	7.4 ± 1.2	< 0.0001
BMI (kg/m²)	17.3 ± 3.2	16.1 ± 2.1	0.012
Urine production (% of expected for age)	122.3 ± 27.5	104.3 ± 33.2	< 0.001
Bladder capacity (excl. first morning void, % of expected for age)	87.2 ± 23.9	86.5 ± 33.0	0.89
Bladder capacity (incl. first morning void, % of expected for age)	104.3 ± 30.0	91.8 ± 34.7	0.027
Nocturnal bladder capacity (% of expected for age)	83.6 ± 22.4	63.3 ± 25.6	< 0.0001
Enuresis frequency (per week)	5.7 ± 1.5	6.3 ± 1.2	0.0097

Jorgensen et al, J Urol, Vol. 212, 1-9, October 2024

Data-driven treatment

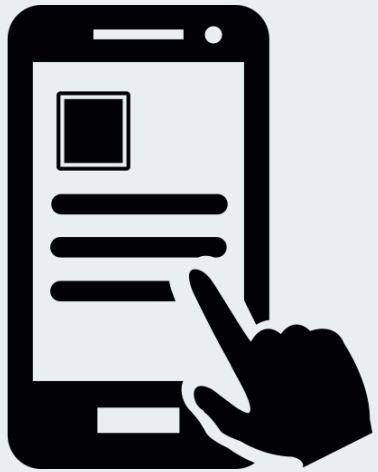
- Positive predictive value: 80%
- Negative predictive value: 75%

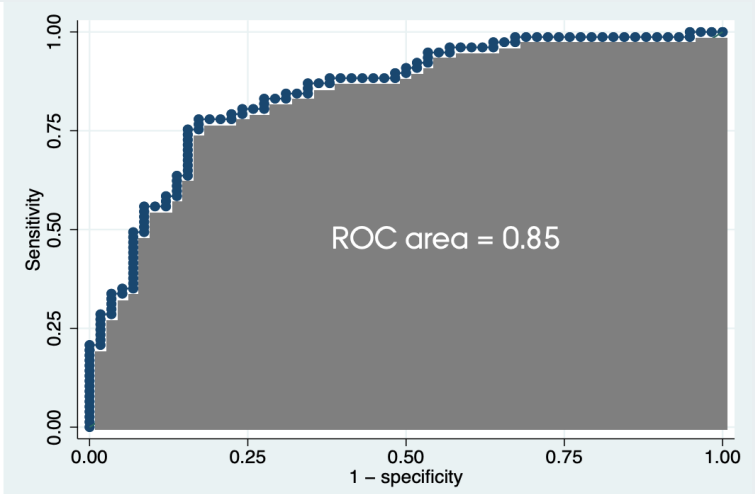


Time you got up for the day: 6.30 AM — Time you went to bed:

Fluid Intake			Urine Output		
Time	AM/PM	Quantity (ml)	Time	AM/PM	Quantity (ml)
6.40	AM	100	9.30	AM	250
7.30	AM	100	12.05	PM	200
9.10	AM	180	1.30	PM	250
10.50	AM	150	3.40	PM	180
11.30	AM	200	5.05	PM	300
12.40	PM	150	6.50	PM	250
2.30	PM	150	8.10	PM	200
4.15	PM	100	11.00	PM	300
6.05	PM	100	3.30	AM	250
7.00	PM	150	6.40	AM	200
8.30	PM	180			
10.10	PM	120			
11.00	PM	100			
Total		1680ml	Total		2480

Note: If your urinary frequency is more than the 17 rows provided, please take additional sheets or ph





Log(ods) = - 6.78 + 0.39 x 1 (*if male*) + 0.47 x age *(years)* + 0.094 x BMI (kg/m^2) + 0.0026 x NUP of MVV_{age} (*%*)
- 0.051 x $MVV_{excluding}$ of MVV_{age} (*%*) + 0.051 x $MVV_{including}$ of MVV_{age} (%) + 0.027 x eNBC of MVV_{age} (*%*) - 0.22 x NE frequency (*per week*)

NUP = nocturnal urine production, MVV_{age} = maximum voided volume for age [21]; MVV = maximum voided volume (excluding/including first morning void), eNBC = nocturnal bladder capacity, NE = nocturnal enuresis

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Nocturnal enuresis
Why do children fail treatment?

Treatment not directed towards underlying mechanism

Poor adherence

Poor parental support

Comorbidity
ADHD

Constipation

Decreased *nocturnal* bladder capacity

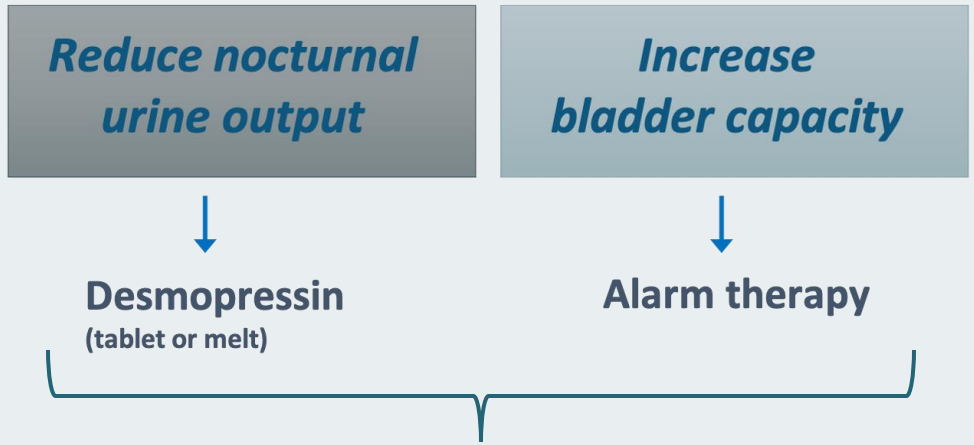
Increased nocturnal Solute excretion

Increased fluid intake during evening

Obstructive sleep apnea (?)

Underlying neuropathic or anatomical pathology

Nocturnal enuresis
Outcome of first line treatments



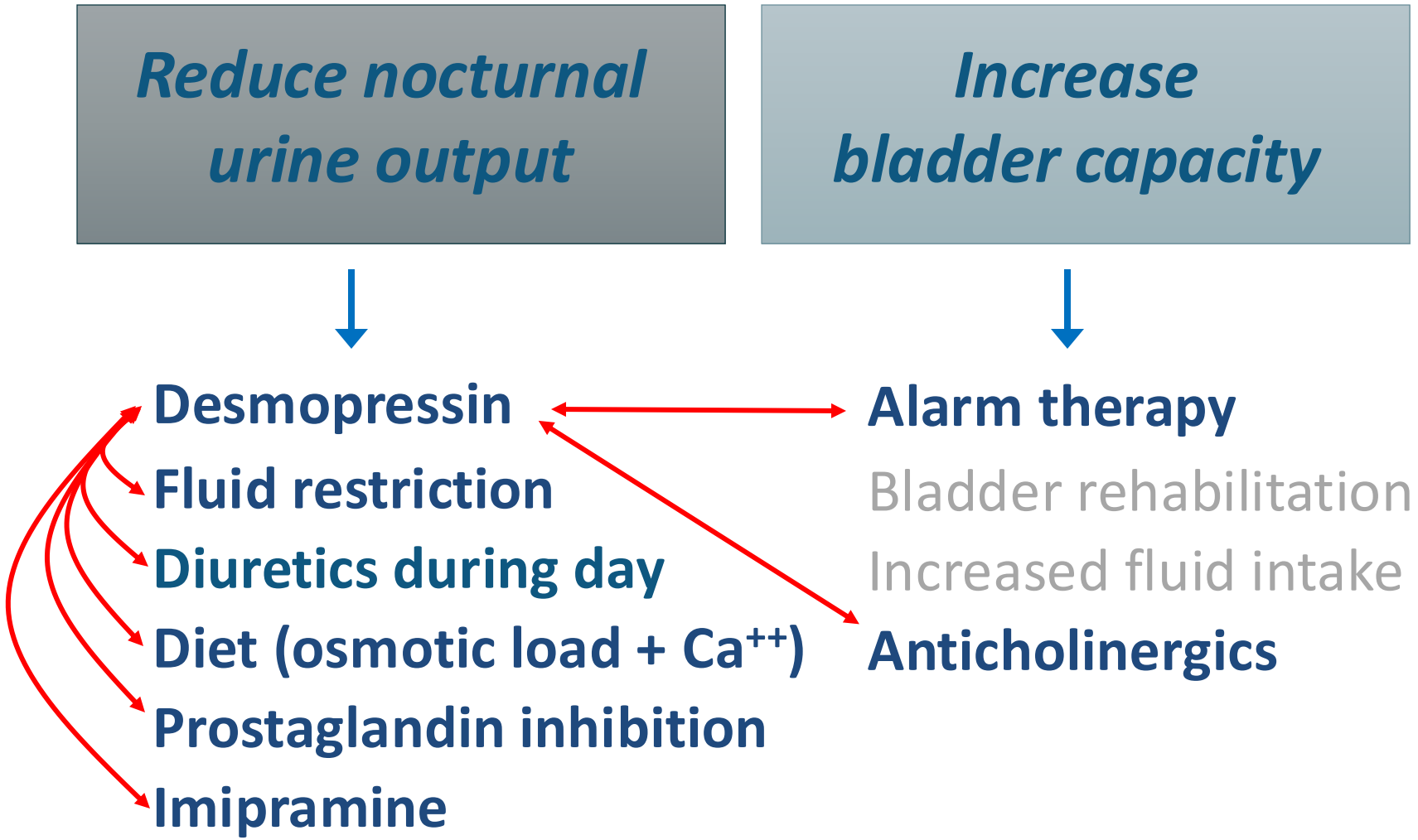
Note:
How do we define failure to treatment? (<50% or completely dry)

With prior characterization: 26% no-response
No prior characterization: 39% no-response

App. 1/3 of all patients fail first line Tx

Therapy-resistant enuresis

- Multimodal therapy for treatment resistant patients



Therapy-resistant enuresis

- Multimodal therapy

Efficacy and safety of multimodal treatment in nocturnal enuresis - A retrospective cohort study

Sonja Izquierdo Riis Meyer, Cecilie Siggaard Jørgensen, Konstantinos Kamperis, René Frydensberg Andersen, Malthe Jessen Pedersen, Mia Faerch, Søren Rittig

- Retrospective design
- N=59 (30 MNE, 29 non-MNE)
- Age: 6-15 yrs, avg. 9,6 yrs
- Severe enuresis (avg >6 wet nights/week)
- Resistant to ddavp/alarm or ddavp+alarm
- Choice of treatment dependent on diary
- Up to 4 concurrent treatment modalities

- 61 % showed full effect of multimodal therapy
- 15 % showed partial effect
- Desmopressin-imipramine was the most common combination
- Use of solifenacin and mirabegron more common in non-MNE
- Recorded side effects were minor and only 1.4% stopped multimodal therapy
- Important to stress that multimodal therapy has low evidence level

Meyer et al. J Pediatr Urol, 2021

Conclusions – 40 years milestones

Removing myths – the three-factor model of pathogenesis.

Creating evidence behind two first line treatments: alarm and desmopressin (NB 1/3 non-response).

Unravelling the genetic background (GWAS) – on the road to a deeper understanding of NE.

Towards an individualized approach – prediction tools, multimodal tx. and new drug targets.

AARHUS UNIVERSITY
DEPARTMENT OF CLINICAL MEDICINE

Thank you for your attention!

Soren Rittig
Prof. MD, DMSc

Pediatrics and Adolescent Medicine
Aarhus University Hospital
Aarhus, DENMARK

Rittig@clin.au.dk