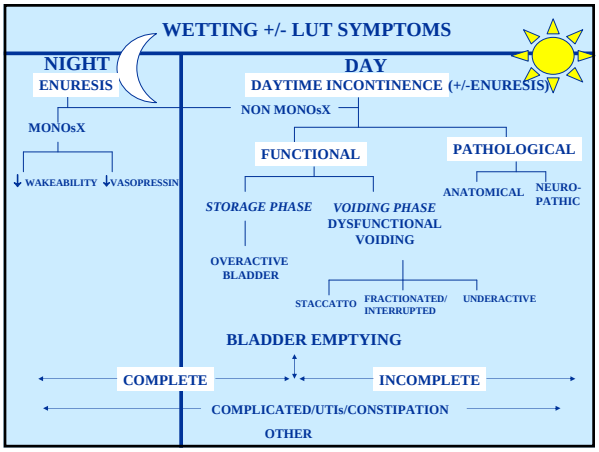
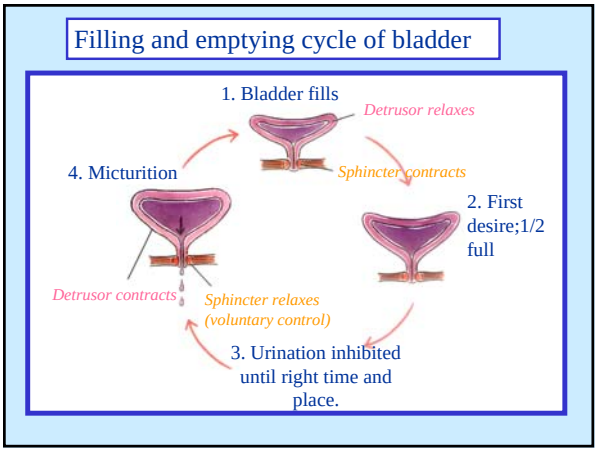
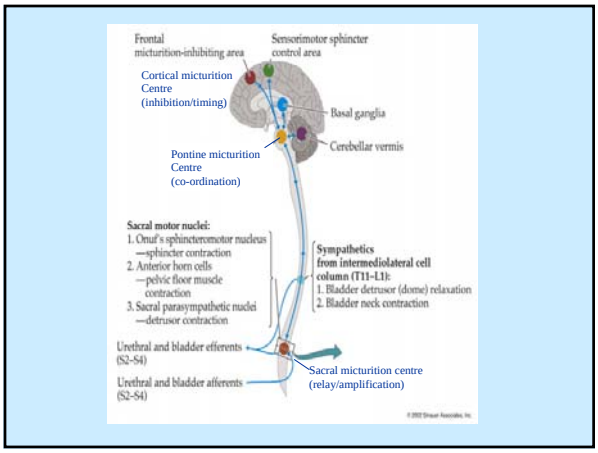
Enuresis and sickle cell disease

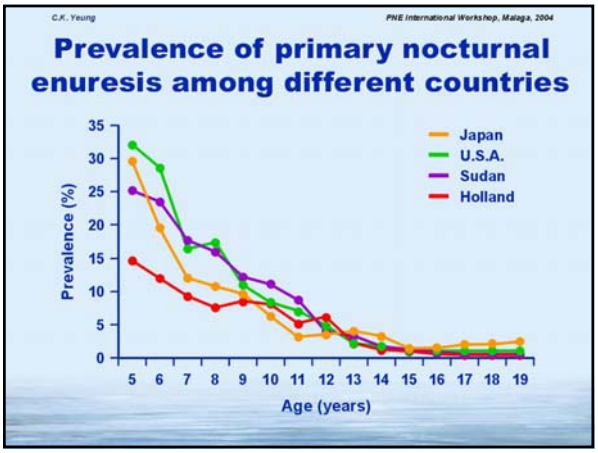
Dr. Anne Wright
Evelina Children's Hospital
Guy's and St Thomas' Hospital Trust
London

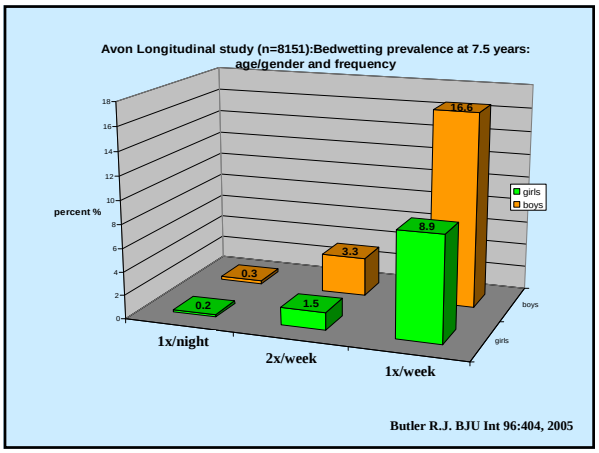
A scheme for thinking about wetting in children

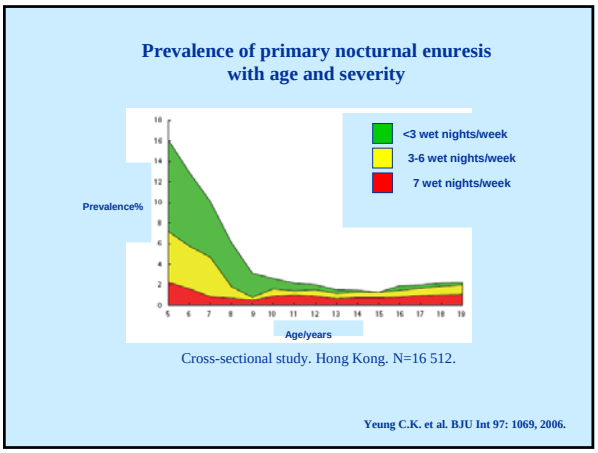


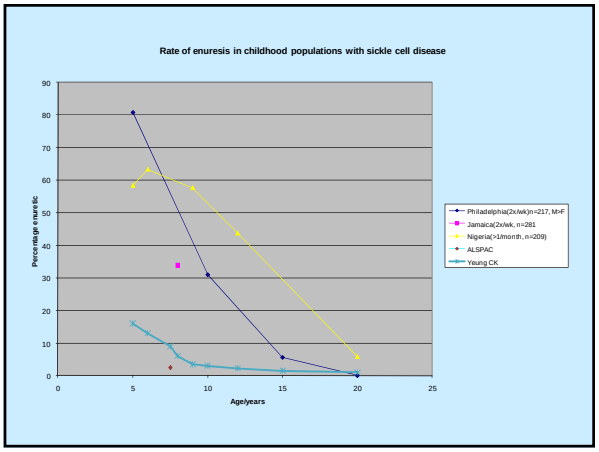


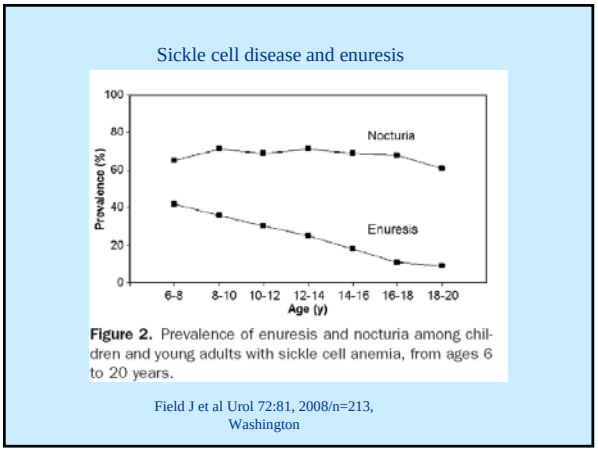


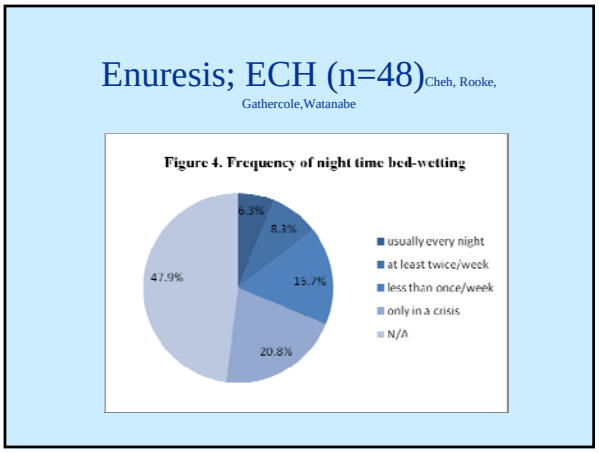


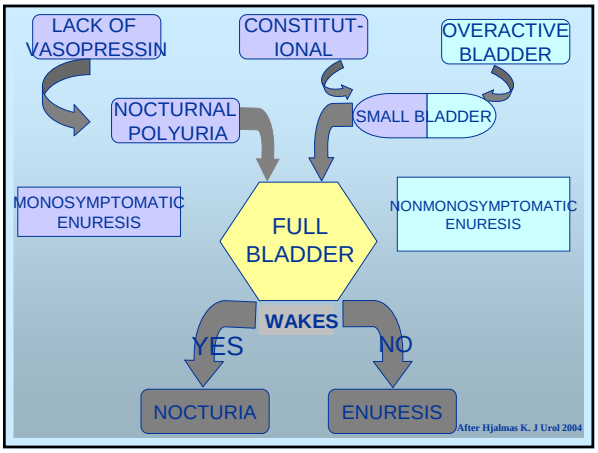




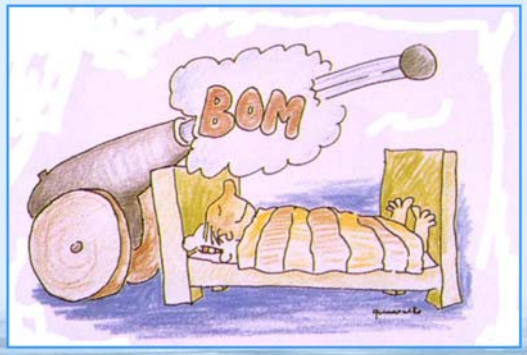








Sleep arousal disturbance underlies all nocturnal enuresis



PNE and Impaired Arousal Response

- Elevated arousal threshold associated with a reduced prepulse inhibition (PPI) of startle in enuretic patients, suggesting a dysfunction in the pontine tegmentum
  - *Ornitz EM, 1999*
  - *Wolfish N, 1999*
  - *von Gontard, 2001*
- Arousal disturbance and reduced ability to inhibit bladder activities and micturition during sleep may both originate from a common dysfunction in the brainstem

Other sleep components

Table 1 Differences between enuretic and healthy children in sleep evaluation with SDSC scales

	Enuretic $N=270$	Nonenuretic $N=274$	P
DIMS	14.92±4.25	11.31±3.51	<.001
SBD	8.0±3.32	4.2±2.03	<.001
DA	6.43±3.05	3.91±1.78	<.001
SWTD	14.63±4.36	9.3±3.55	<.001
DOES	10.36±3.45	8.02±3.33	<.001
SHY	5.16±1.92	2.857±1.53	<.001
Total score	59.51±12.05	39.67±11.33	<.001

DIMS disorders in initiating and maintaining sleep, *SBD* sleep breathing disorders, *DA* disorders of arousal, *SWTD* sleep–wake transition disorders, *DOES* disorders of excessive somnolence, *SHY* nocturnal hyperhydrosis

Cartenuto M et al Sleep Breath. 2010 Jul 6.
Facial patterns and primary nocturnal enuresis in children

Other sleep components

- Adenotonsillectomy improves symptoms of nocturnal enuresis (n=107) in children with OSA
  - Cure 61.4%
  - Improvement 22.8%
    - Basha S Laryngoscope. 2005 Jun;115(6):1101-3
- Children with SCD have high rates of disordered sleep including high rates of OSA (10-79%)
  - Rogers V J Clin Sleep Med. 2010 Aug 15;6(4):374-81.
  - Daniel LC Pediatr Blood Cancer. 2010 Sep;55(3):501
  - Salles C J Bras Pneumol. 2009 Nov;35(11):1075-83

Mechanisms of action: alarms

- Alarm is triggered when urine comes into contact with sensor
- Body-worn and bedside systems
- Behavioural conditioning mostly based on reward (operant) but also negative effects (aversive)

Mechanisms contd

- In successful alarm treatment
  - 2/3 achieve dryness whilst sleeping through the night
  - 1/3 have nocturia as a means of achieving dryness
- Alarms increase
  - Nocturnal bladder capacity
  - Daytime bladder capacity
    - Taneli C Scand J Urol Nephrol. 2004;38(3):207-10
    - Hvistendahl GM J Urol. 2004 Jun;171(6 Pt 2):2611
    - Hansen AF Scand J Urol Nephrol Suppl. 1997;183:59-60

Do alarms work? Cochrane review

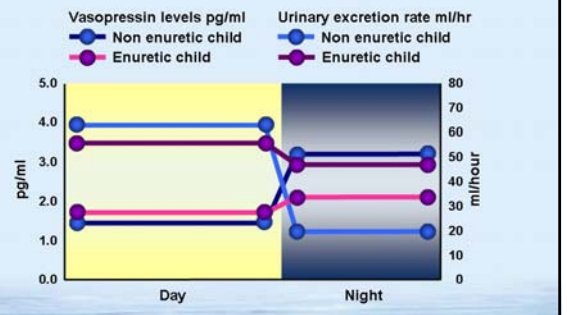
- Alarms are more effective than control in RCTs
- Two thirds of children become dry during alarm use
- One half remain dry after treatment

Glazener CMA. Cochrane Review, Feb 2003

Nocturnal polyuria

- Nocturnal urine volume > 130% x Expected Bladder capacity (EBC)
- EBC = Age (years) x 30mls + 30mls
  - (Age/years +1) X 30mls
  - Hjalmas formula

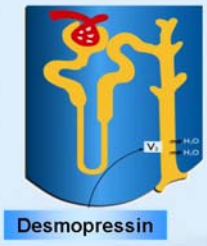
Diurnal variation in plasma vasopressin and urine production



Rittig S et al. *Am J Physiol* 1989;256:F664–71

Desmopressin

- Analogue of vasopressin (antidiuretic hormone)
- Potent antidiuretic
- Concentrates urine
- No direct bladder effect
- No direct cardiovascular action



Using Desmopressin

DesmoMelt	1 x 120 mcg Melt at bedtime, increasing to 2 only if necessary
Desmotabs 0.2 mg desmopressin tablets	1 x 0.2 mg tablet at bedtime, increasing to 2 only if necessary

- Desmospray; licence for enuresis removed.
- Desmopressin can be used for as long as symptoms persist - reassess every 3 months (minimum one week off treatment)
- Desmopressin does not suppress endogenous vasopressin after 24/52 tmt Knudsen UB Urol Res 1991

Desmopressin safety; clinically sig hyponatraemia

- Medline search 1972-2006
- Post marketing safety data Ferring 1972-2005
- Ten million children used desmopressin world wide
  - Approx 5 million intranasal (intro 1972)
  - Approx 5 million oral formulation (intro 1987, melt 2005)
- Sig hyponatraemia= headache, nausea, vomiting, altered consciousness, seizure due to water intoxication

Clinically sig hyponatraemia; desmopressin

- Intranasal preparation
- 172 reports
  - 145 PMS
  - 27 additional Medline
- Pharmacokinetics
  - 6-24 hours (prolonged effect in some children) Dehoorne J Urol 2006

- Oral preparation
- 6 reports
- Duration of action is dose dependent with optimal dose giving 8-10 hours duration

Robson J Urol 2007

Safe use of desmopressin

- Fluid restriction before bed
  - Sporting activity at night
- Caution coexistent conditions
  - Cystic fibrosis
  - D&V
  - ADHD
  - Prader Willi
- Supervision of younger children
- Caution with prodromal symptoms; headache, nausea, vomiting

» Thumfart J Urol 2005

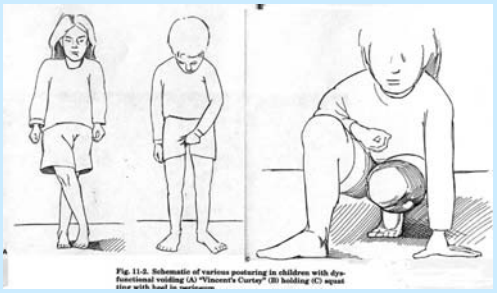
Desmopressin in SCD

- Only one study comments on its use in very small numbers; in six out of ten patients it was successful
  - Figueroa T. J Urol Vol. **153, 1987-1989, June 1995**
- No contraindication to it's use as long as child can adhere to fluid restriction limitations

Reduced nocturnal bladder capacity

- Small bladder (monosymptomatic)
- Overactive bladder (OAB/non-monosymptomatic)
  - Daytime LUT symptoms in addition to enuresis
  - Nocturnal OAB

Urgency: overwhelming desire to pass urine +/- incontinence. Counteracted by various *holding manoeuvres* including Vincents Curtsey.



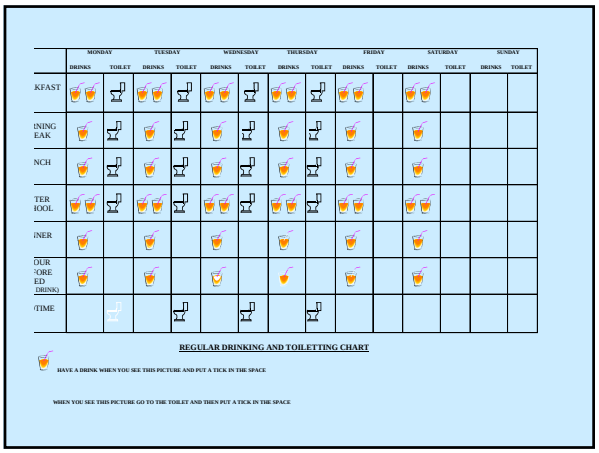
Management of OAB

Bladder retraining

- **Regular fluid intake**
- **Timed regular voiding**
- **Correct toiletting position**
- **Charts**

Drug therapy

- **Anticholinergics**
  - **Oxybutynin**
    - **`2.5-5mg tds**
    - **XL formulation**
  - **Tolterodine**
    - **1-2mgbd**
    - **XL prep**
  - **Titrate slowly**
  - **R constipation first**



Bladder capacity in SCD

- Only one study addresses bladder capacity in SCD +/- enuresis n=31
  - Two matched groups all with SS, Jamaica
  - 8-13 years
  - Overnight urinary osmolality and volumes not statistically different
  - Enuretics had smaller FBC (ave 291 vs 395)p 0.005
    - Readett D Archives of Disease in Childhood 1990; 65: 615-618

Causative factors

- Attribution by parents:

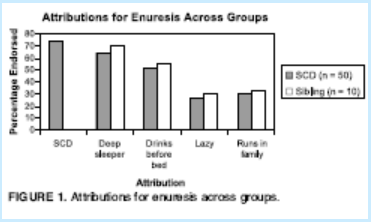


FIGURE 1. Attributions for enuresis across groups.

Jordan SS; Mississippi 2005

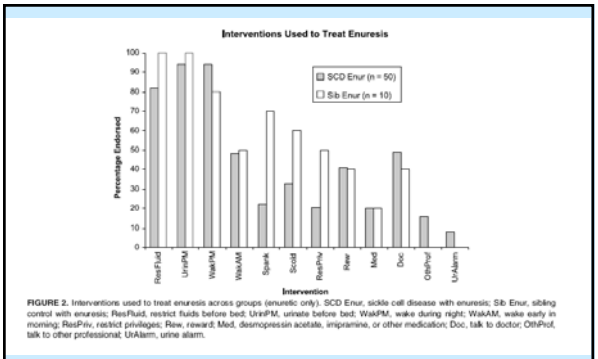
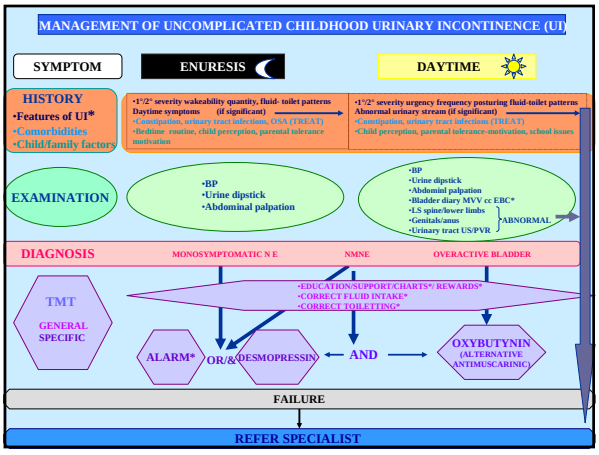


FIGURE 2. Interventions used to treat enuresis across groups (enuretic only). SCD Enur, sickle cell disease with enuresis; Sib Enur, sibling control with enuresis; ResFluid, restrict fluids before bed; UrinPM, urinate before bed; WakPM, wake during night; WakAM, wake early in morning; ResPriv, restrict privileges; Rew, reward; Med, desmopressin acetate, imipramine, or other medication; Doc, talk to doctor; OthProf, talk to other professional; UrAlarm, urine alarm.

Jordan SS; Mississippi 2005



New challenges in managing enuresis in SCD

- Establish epidemiology including severity and current classifications
- Establish underlying mechanisms specific to SCD
  - Sleep disorders
  - Polyuria
  - Bladder parameters
- Establish effective management pathways for SCD + enuresis
  - Desmopressin sensitivity
  - Alarm response
  - Combinations

Thank you