The Leeds Teaching Hospitals

NHS Trust

The Challenges of Treating Diabetes in Childhood

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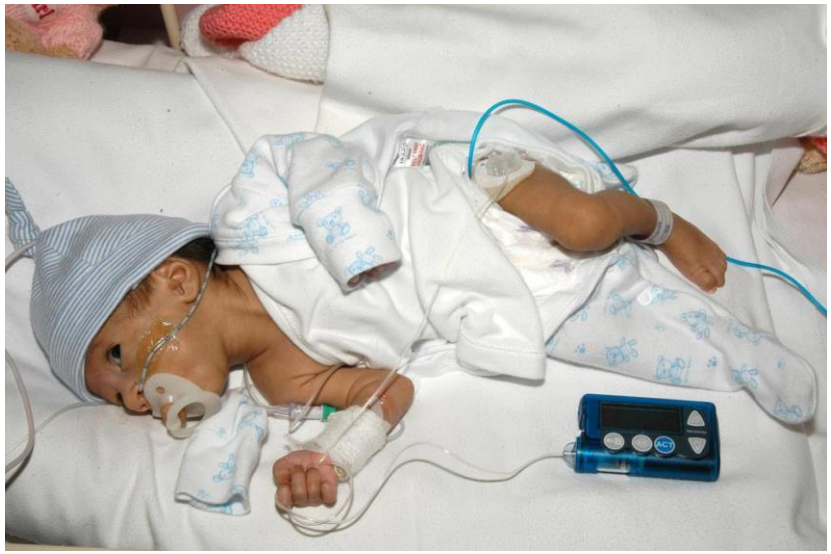
Children are different!!!!



Challenges in Children/Adolescents

- Major differences at various ages
  - infant vs. adolescent / relatively homogeneous adult
  - rapid changes in relatively short period
  - periods possibly having higher risk of complication development (puberty)
- Different consequences of hypoglycaemia
  - physical and mental/psychological
- Different level of compliance
  - patient and parent
- Different lifestyle
  - school, exercise, diet, relationships to others at the same age
- Socio-economic status
  - parental marital status, ethnicity

Facts in Childhood Diabetes

- Type I accounts for the vast majority of diabetes in children
- Type I is increasing in incidence worldwide at 4% per year and especially in under 5's
- Staggering increase in childhood obesity worldwide resulting in earlier onset TypeII
- Molecular genetics identifying increasing number of monogenic types
- Paucity of data in field of diabetes in children
- Data from DCCT and EDIC in Type I and UKPDS in Type II inform the current management of hyperglycaemia

Facts in Childhood Diabetes

- Centre for Disease Control in Atlanta,USA in 2003 reported a loss of almost 20 life years for a 10 yr old children diagnosed with diabetes in 2000
- Majority of children with diabetes world wide are not achieving levels of control to minimise risk of microvascular disease
- 85% of children in UK have HbA1c > 7.5%

Classification

- Neonatal diabetes
  - occurs in 1st month of life and lasts more than 2 weeks
- TypeI
- TypeII
- Genetic defects in insulin action
  - lipoatrophic diabetes
- Diseases of exocrine pancreas
  - CF,pancreatitis haemachromatosis,
- Endocrinopathies
  - Cushings
- Drugs/Chemical induced
  - Steroids
  - Immunosuppressives

Classification

- Infections
  - Congenital rubella
  - Cytomegalovirus
  - Enterovirus
- Immune mediated
  - anti-insulin receptor antibodies
  - autommune polyendocrine syndromes
- Genetic Syndromes
  - Down,Klinefelters,Turners,DIDMOAD,Prader-Willi

Morbidity and Mortality

- DKA is leading cause in Type I in children
- Most cases seen in established diabetes
- DKA usually associated with inadvertent or deliberate insulin omission
- DKA at onset commoner in younger age
- Can occur in 25% of Type II at onset
- Mortality 0.15-0.30% with cerebral oedma accounting for 60-90% of deaths
- Those surviving cerebral oedema 25%-35% have permanent neuro- disability

Hypoglycaemia

- Very common
- Most feared complication of Type I in childhood
- Very common in young children
- 50% of severe episodes occur during sleep
- Day time exercise is huge risk factor for overnight hypoglycaemia

Aims of Therapy

- Obtain the best possible blood glucose control whilst minimising hypoglycaemia
  - age/size of child
  - insulin requirements
  - C peptide reserve
  - absorption and insulin kinetics
  - brittleness
  - nutritional requirements for growth
  - ethnic/family cultural traditions about feeding
  - erratic eating/sleeping patterns
  - more frequent blood sugar monitoring
  - positive behaviour reinforcement

Guidelines, recommendations

- Consensus Guidelines 2000 by ISPAD
- NICE 2004
- ADA Statement, 2005 Diabetes Care

ADA Recommendation:HbA1c aims

Table 4—*Plasma blood glucose and A1C goals for type 1 diabetes by age group*

Values by age	Plasma blood glucose goal range (mg/dl)		A1C	Rationale
	Before meals	Bedtime/overnight		
Toddlers and preschoolers (<6 years)	100–180	110–200	<8.5 (but >7.5) %	• High risk and vulnerability to hypoglycemia
School age (6–12 years)	90–180	100–180	<8%	• Risks of hypoglycemia and relatively low risk of complications prior to puberty
Adolescents and young adults (13–19 years)	90–130	90–150	<7.5%*	• Risk of hypoglycemia • Developmental and psychological issues

Key concepts in setting glycemic goals:

- Goals should be individualized and lower goals may be reasonable based on benefit–risk assessment
- Blood glucose goals should be higher than those listed above in children with frequent hypoglycemia or hypoglycemia unawareness
- Postprandial blood glucose values should be measured when there is a disparity between preprandial blood glucose values and A1C levels

Diabetes Care 2005 Jan;28(1):186-212

Consensus Guidelines 2000 by ISPAD

Table 5: Target indicators of glycemic control

Level of control	Ideal (non-diabetic)	Optimal	Suboptimal	High risk (action required)
Biochemical assessment[a]				
Preprandial or fasting BG (mmol/l)	3.6–6.1	4.0–7.0[b]	>8.0	>9.0
Postprandial BG (mmol/l)	4.4–7.0	5.0–11.0	11.1–14.0	>14.0
Nocturnal BG[c] (mmol/l)	3.6–6.0	Not <3.6	<3.6 or >9.0	<3.0 or >11.0
HbA_{1c} (%) (DCCT standardized)	<6.05	<7.6	7.6–9.0	>9.0

[a]These population-based target indicators must be adjusted according to individual circumstances. Different targets will be appropriate for various individuals such as young children, those who have experienced severe hypoglycemia or those with hypoglycemic unawareness

[b]If fasting morning BG is <4 mmol/l, consider the possibility of antecedent nocturnal hypoglycemia

[c]These figures are based on clinical studies but no strict evidence-based recommendations are available

NICE 2004

Children and young people with type 1 diabetes and their families should be informed that the target for long-term glycaemic control is an HbA_{1c} level of less than 7.5% without frequent disabling hypoglycaemia and that their care package should be designed to attempt to achieve this.

A

Children and young people with type 1 diabetes and their families should be informed that aiming to achieve low levels of HbA_{1c} can lead to increased risks of hypoglycaemia and that high levels of HbA_{1c} can lead to increased risks of long-term microvascular complications.

A

Children and young people with HbA_{1c} levels consistently above 9.5% should be offered additional support by their diabetes care teams to help them improve their glycaemic control because they are at increased risk of developing diabetic ketoacidosis and long-term complications.

B

Targets and Reality

- UK survey by Novo Nordisk in 2006
- National Paediatric Diabetes Audit 2002
- National Diabetes Audit 2004/5 (England and Wales)
- Scottish National Audit – DIABAUD3
- Italian Audit 2005
- German Paediatric Diabetology Working Group Audit 1996, 2006

Treatment regimens for children with diabetes

findings of a Novo Nordisk survey of UK physicians

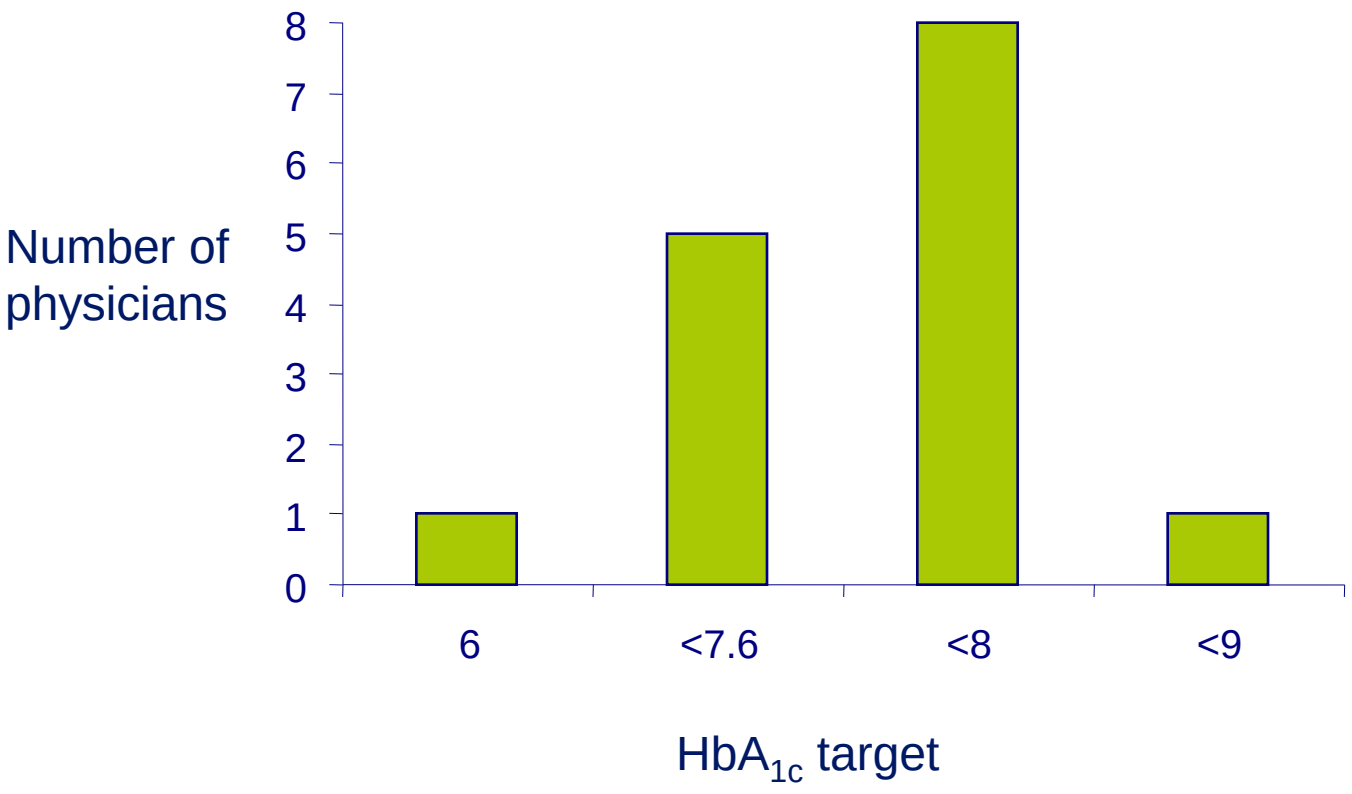
Early 2006

Responder characteristics

Responder locations

Responder characteristics	Mean	Range
Years specialising	14.3	3.5–25
Number of children treated with diabetes (per doctors)	73	26–160

Most UK physicians aimed for an HbA_{1c} target of 7.5–8%



The charity for people with diabetes

The National Paediatric Diabetes Audit

Results from the audit year 2002

HbA1c

National average and range of latest result

	Number	Average	Min	Max	± Standard deviation
England (excluding Jersey)	N=9,336	8.98	3.95	20.0	1.69
Northern Ireland	N=526	8.72	5.20	16.7	1.56

Table 13 Average HbA_{1c} in England and Northern Ireland

Age group	Boys	Girls	Total
0-5	8.42	8.57	8.48
6-10	8.57	8.71	8.64
11-16	9.16	9.22	9.19

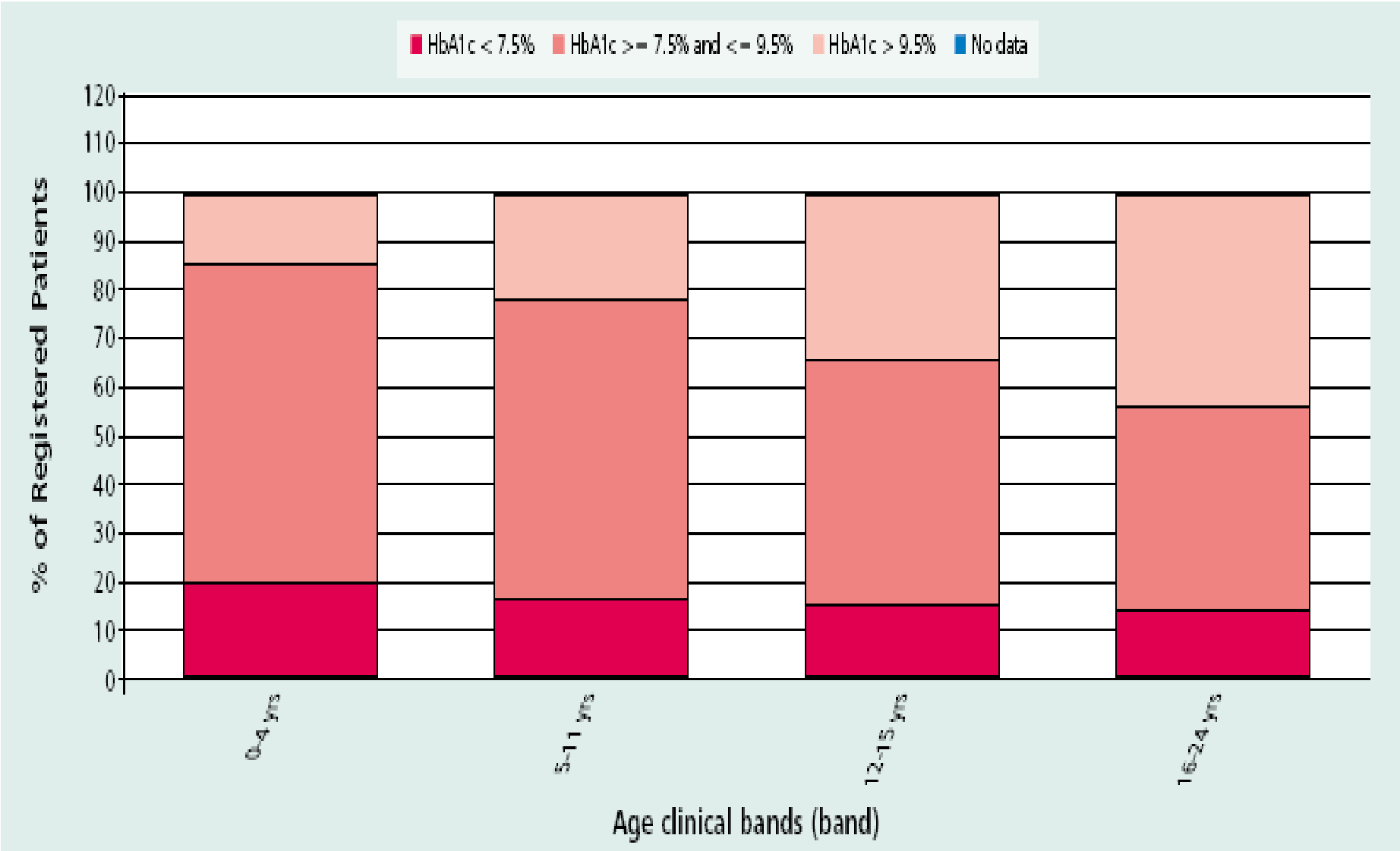
Target level	<7.5%			<=9%		
Age group	Boys	Girls	Total	Boys	Girls	Total
0-5	21%	19%	20%	72%	62%	69%
6-10	19%	16%	18%	67%	64%	65%
11-16	14%	15%	14%	53%	51%	52%

National Diabetes Audit

Report for the audit period 2004/05

Part of National Clinical Audit Support Programme

HbA1c targets by age band



DIABAUD 3

GLYCAEMIC CONTROL IN CHILDREN AND ADOLESCENTS UNDER 15 YEARS OF AGE WITH TYPE 1 DIABETES IN SCOTLAND

HbA1c

Results: DIABAUD 3 confirmed that glycaemic control remains unsatisfactory in children and adolescents with a high percentage of subjects falling outside the targets described in accepted guidelines, placing the majority at a high risk of future micro-vascular complications. The overall mean HbA_{1c} was 9.2% (SD 1.54). Only 9.7% of subjects achieved the NICE recommended target of an HbA_{1c} equal to or < 7.5%.

Subjects 10 years and over had a mean HbA_{1c} of 9.5% (SD 1.6) compared with all other ages 8.9%. HbA_{1c} increased with age and is significantly worse during adolescence. There was no association between HbA_{1c} and sex. The mean HbA_{1c} was 9.2% for both males and females.

Nationwide cross-sectional survey of 3560 children and adolescents with diabetes in Italy

Journal of Endocrinological Investigation.
28(8):692-9, 2005 Sep.

Summary

- Multicenter (n=53) cohort evaluation of 3560 children and adolescents (age:1.6-17.1 yrs) with T1DM
- HbA_{1c} (centralized measure, DCCT standardized): 8.87±1.77 %
- 32 % of patients had HbA_{1c} < 8.0 %
- HbA_{1c} correlated with: puberty, disease duration and inversely with frequency of blood glucose monitoring

German Paediatric Diabetology Working Group Audit 1996[1], 2006[2]

[1]Journal of Pediatric Endocrinology. 12(1):31-8, 1999 Jan-Feb.
[2]Diabetes Care. 29:218-225, 2006.

Summary

- Multicenter (n=23) cohort evaluation of 2407 children and adolescents with T1DM
- HbA_{1c} : 7.8 %

1996

Table 1—*Clinical and laboratory characteristics per age-group in patients with type 1 diabetes* 2006

Characteristic	Total number of patients	Frequency of complete records (%)	Age-group 1	Age-group 2	Age-group 3	*P* value*
Age (years)	27,358	100.0	7.5 ± 2.5	13.7 ± 1.4	18.5 ± 2.3	<0.0001
Age range (years)	27,358	100.0	0.25–11	12–16	17–26	
Male sex (%)	27,358	100.0	51.7	51.7	52.5	NS
Age at diagnosis (years)	27,358	100.0	5.0 ± 2.5	8.8 ± 3.6	10.4 ± 4.4	<0.0001
Diabetes duration (years)	27,358	100.0	2.5 ± 2.3	4.9 ± 3.6	8.2 ± 4.8	<0.0001
A1C (%)†	26,308	96.2	7.8 ± 1.5	8.5 ± 1.8	8.6 ± 2.0	<0.0001

Conclusion

- Although published guidelines are similar,no such universal definition of optimal control exists as we have in case of adults
- Achieving glycaemic targets is a definite challenge all over the world
- Challenge becomes more difficult when facing certain child-specific factors
- ***UK results are not merely different from what other European countries can achieve, but definitely far from any defined targets***

Can we do better by choosing a specific treatment regimen ?

Current Available Regimens

- Premix (2x, 3x daily)
  - human
  - analogue
- Basal-bolus
  - human (soluble and intermediate-acting)
  - analogue (rapid-acting and basal)
  - mixed regimens
- CSII via pumps

ADA Recommendation: insulin/regimen

INSULIN MANAGEMENT OF DIABETES— Insulin type, mixture of insulins in the same syringe, site of injection, and individual patient response differences can all affect the onset, peak, and duration of insulin activity. In general, insulins used in children are rapid-acting insulin analogs, short-acting insulin, intermediate-acting insulin (NPH and Lente), and long-acting insulin analogs. These insulins are used in combination or individually and are delivered by syringe or, in some cases, a pen or pump.

Recommendations

- Insulin requirements are usually based on body weight, age, and pubertal status.
- A basal-bolus insulin regimen using either and MDI regimen or an insulin pump should be considered.

Diabetes Care 2005 Jan;28(1):186-212

Consensus Guidelines 2000 by ISPAD

Many formulations of insulin are available; most have some role in the management of type 1 diabetes *(Table 6)*.

Table 6: Types of insulin preparations and suggested action profiles

Insulin type	Onset of action (h)	Peak of action (h)	Duration of action (h)
Rapid-acting analogs	0.15–0.35	1–3	3–5
Short-acting			
Regular/soluble	0.5–1	2–4	5–8
Intermediate-acting			
Semi-lente (pork)	1–2	4–10	8–16
Isophane NPH	2–4	4–12	12–24
IZS lente type	3–4	6–15	18–24
Long-acting			
Ultralente type	4–8	12–24	20–30
Analog	2–4	none	24

NPH, neutral protamine Hagedorn insulin; IZS, insulin zinc suspension

Consensus Guidelines 2000 by ISPAD

- no preferred regimen in the guideline
- individualized choice recommended on the basis of several patient-related factors
- some advantages of rapid-acting analogues are mentioned
  - "not only reduces postprandial hyperglycemia but that postprandial and nocturnal hypoglycemia may also be reduced"
  - "offer the useful option of being given after food to toddlers"
- some disadvantages of pre-mixed preparations are mentioned
  - "they remove the flexibility "
  - "some evidence of poorer metabolic control in adolescents"
  - "may be useful when compliance …is a problem"

NICE 2004

RECOMMENDATIONS

Children and young people with type 1 diabetes should be offered the most appropriate insulin preparations (rapid-acting insulin analogues, short-acting insulins, intermediate-acting insulins, long-acting insulin analogues or biphasic insulins) according to their individual needs and the instructions in the patient information leaflet supplied with the product with the aim of obtaining an HbA_{1c} level of less than 7.5% without frequent disabling hypoglycaemia and maximising quality of life.

GPP

RECOMMENDATIONS

Pre-school and primary school children with type 1 diabetes should be offered the most appropriate individualised regimens to optimise their glycaemic control.

C

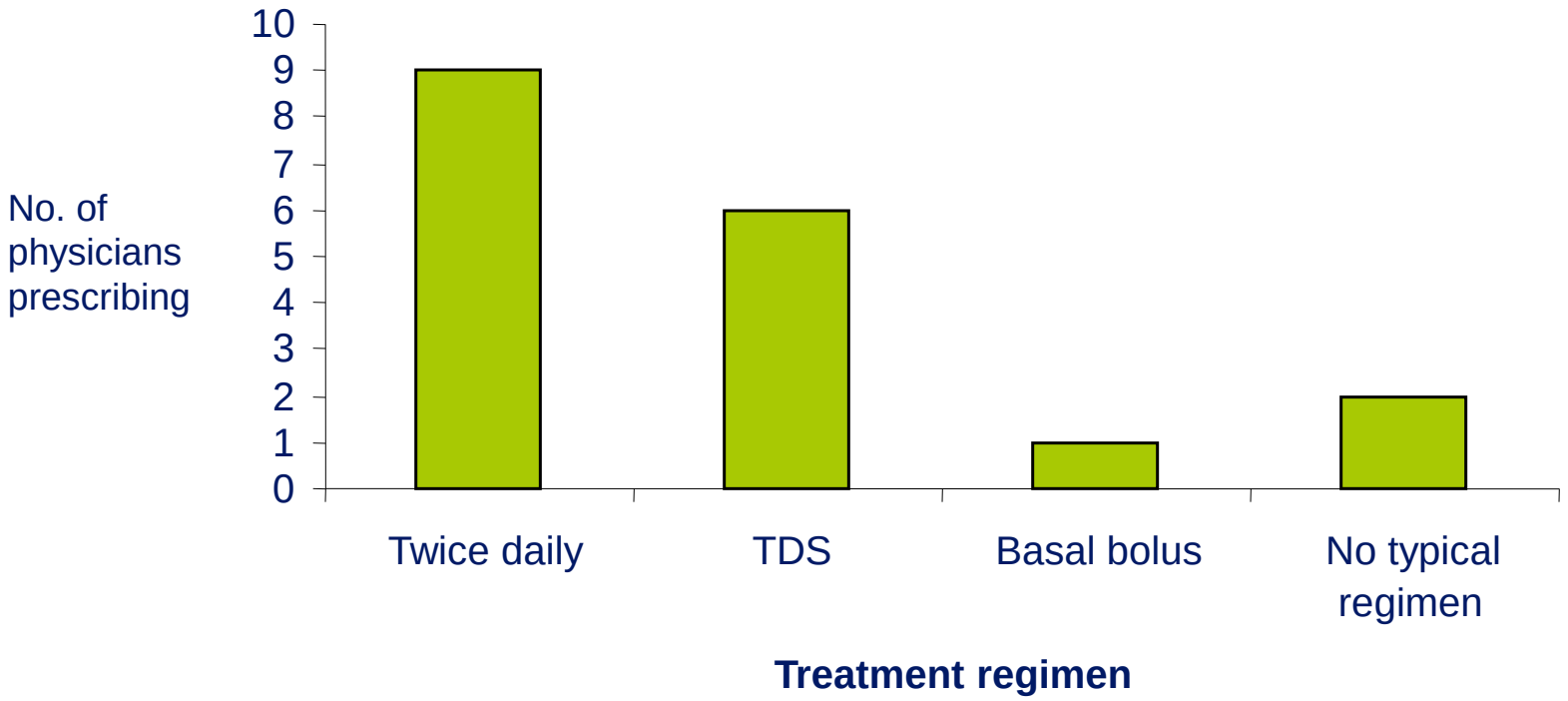
Young people with type 1 diabetes should be offered multiple daily injection regimens to help optimise their glycaemic control.

A

Multiple daily injection regimens should be offered only as part of a package of care that involves continuing education, dietary management, instruction on the use of insulin delivery systems and blood glucose monitoring, emotional and behavioural support, and medical, nursing and dietetic expertise in paediatric diabetes, because this improves glycaemic control.

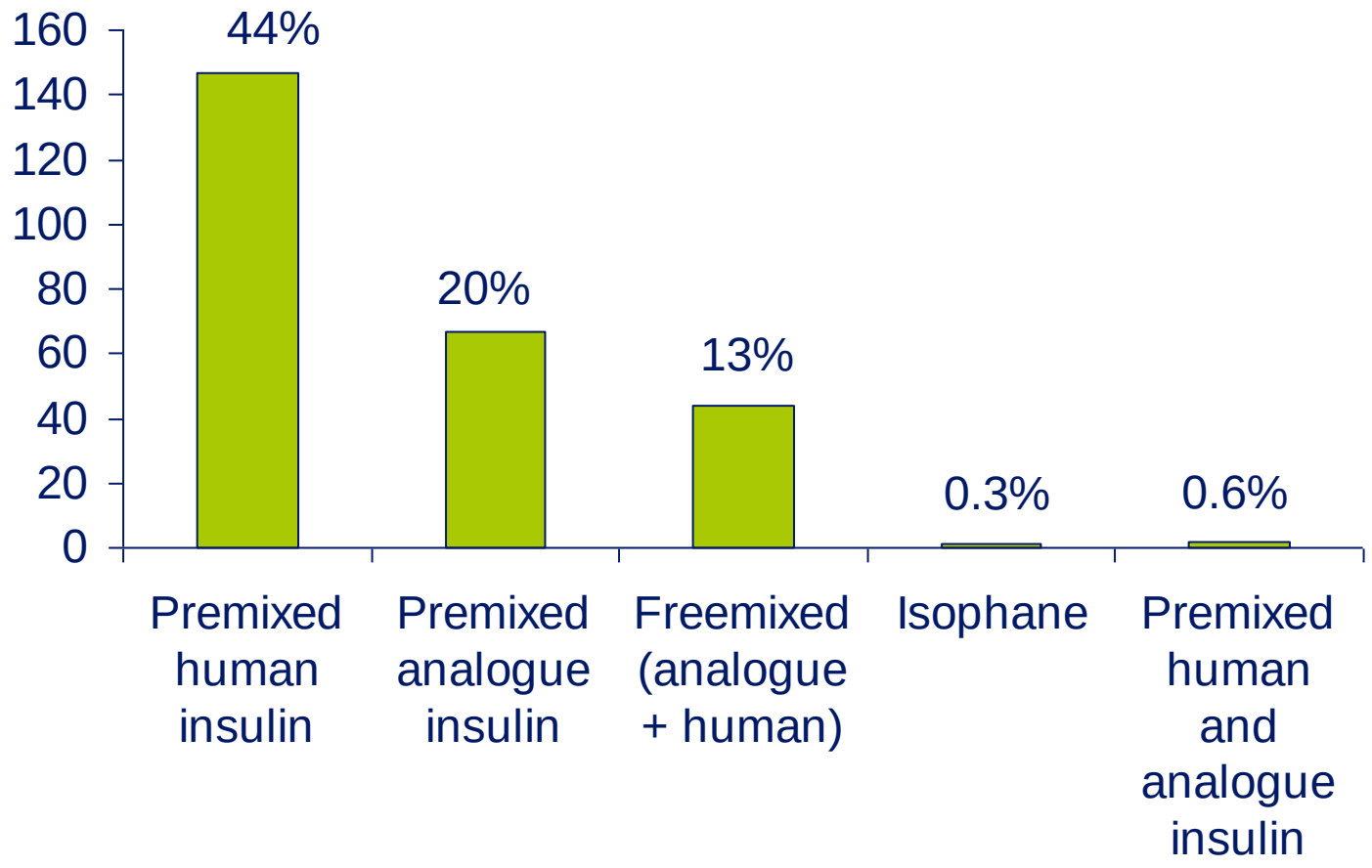
C

Twice daily regimens are the most often prescribed in the UK



Note: some physicians stated more than one typical regimen

Twice-daily regimens



The Belief in Intensification (UK)

- Given the choice, 85% of physicians who responded would like to use more intensive regimens
- 73% intensified regimens as child aged
- More intensive regimens are introduced as soon as the child is mature enough to cope; usually at age 11

Analogue use (UK)

- All physicians used analogues in children
  - 87% used analogues frequently
- 73% of respondents stated that an evidence-based study may alter treatment practices
- Good study would consider:
  - Glycaemic control
  - Psychosocial factors

DIABAUD 3

GLYCAEMIC CONTROL IN CHILDREN AND ADOLESCENTS UNDER 15 YEARS OF AGE WITH TYPE 1 DIABETES IN SCOTLAND

- analyse the effect of ‘conventional’ insulin regimen

Scottish Study Group for the Care of the Young with Diabetes
Diabetic Medicine 23 1216-1221

Treatment regimens

While the majority of subjects were on two injections per day (51%), there had been a significant increase in patients treated with three injections per day (split evening dose) in DIABAUD 3 compared with DIABAUD 2 (D3, 43% versus D2, 2%). In DIABAUD 2, 94% of subjects were on two injections per day. Less than 10% of patients in DIABAUD 3 were on multiple insulin therapy (MDI- i.e. 4 or more injections per day). There was no significant association found between HbA_{1c} and number of injections per day. Only four (2.5%) subjects were recorded as using an insulin pump.

German Paediatric Diabetology Working Group Audit 1996[1], 2005[2]

[1]Journal of Pediatric Endocrinology. 12(1):31-8, 1999 Jan-Feb.
[2]Eur. J. Pediatr. 164:73-79, 2005

Regimens in practice

- 80 % of patients were on intensive insulin therapy
- HbA_{1c} : 7.8 %

1996

Table 2 Insulin regimen and metabolic control according to age-groups 2005

	All patients (n = 6309)	Age-group < 5 years (n = 782)	Age-group 5–< 7 years (n = 1053)	Age-group 7–< 9 years (n = 4474)	P -value for age-groups
Insulin dose (IU) per kg body weight	0.71 ± 0.23	0.65 ± 0.24	0.69 ± 0.24	0.72 ± 0.24	< 0.0001
Daily number of injections (n)	3.14 ± 0.86	3.13 ± 0.91	3.20 ± 0.87	3.13 ± 0.85	0.07
Patients on 1 injection/day (%)	1.4	3.2	1.8	1.0	< 0.0001
Patients on 2 injections/day (%)	28.5	25.8	25.0	29.7	< 0.005
Patients on 3 injections/day (%)	29.1	31.9	30.7	28.3	< 0.01
Patients on 4+ injections/day (%)	39.1	35.0	39.4	39.8	< 0.05
Patients on pump therapy (%)	1.9	4.1	3.1	1.2	< 0.0001
Mean $HbA1_c$ (DCCT-standardised)	7.6 ± 1.5%	7.6 ± 1.5%	7.5 ± 1.4%	7.6 ± 1.5%	Not significant

Premix bd or MDI or Pump ?

- Audits provide conflicting results
  - adolescents tend to switch to MDI more frequently → HbA1c shows deterioration with age, especially around puberty
  - patients usually having the worst metabolic control are tending to switch to MDI
    - due to unstable metabolic control
    - due to non-compliance

- RCTs show consistent benefit of MDI/Pump as opposed to bd

Advantages of Basal/Bolus Therapy

- With rapid-acting analogues better postprandial control after breakfast and dinner without increasing the risk of late morning/evening hypoglycaemia
- Possibility of suggesting more individualised therapy
  - pre-meal/post-meal dosage
  - flexibility in timing of diet
  - flexibility in case of variable amounts of meals
  - flexibility in case of different physical activity patterns day by day
- Easy to add a pre-lunch injection if patient requires
- With basal analogue, no need for fixed early morning injection
- Synergistic beneficial effect on hypoglycaemic risk

Advantages and disadvantages of human premixes

- Advantages:
  - Twice daily is simple and seems to be convenient
  - Have a variety in strength (possible to individualize the therapy in some extent)
  - Could control postprandial period after morning snack and lunch
- Disadvantages:
  - require rigid diet (both in terms of timing and quantity)
  - no real possibility to adjust doses according to daily activity/ blood glucose results
  - postprandial control not comparable with similar effect of rapid-acting analogues
  - significant risk of late morning/early night hypoglycaemia, when premix higher than 30 % used pre-breakfast/dinner

Conclusion

- No clear guideline on preferred insulin preparations and regimens
- There seems to be a consensus that with basal-bolus therapy better glycaemic control can be achieved if patient suitable for this kind of therapy
- Clinical paediatric practice in the UK seems to stay on the conservative side (preferred use of 2x daily premix)
- At the same time there is interest in using modern insulin analogues among UK specialists

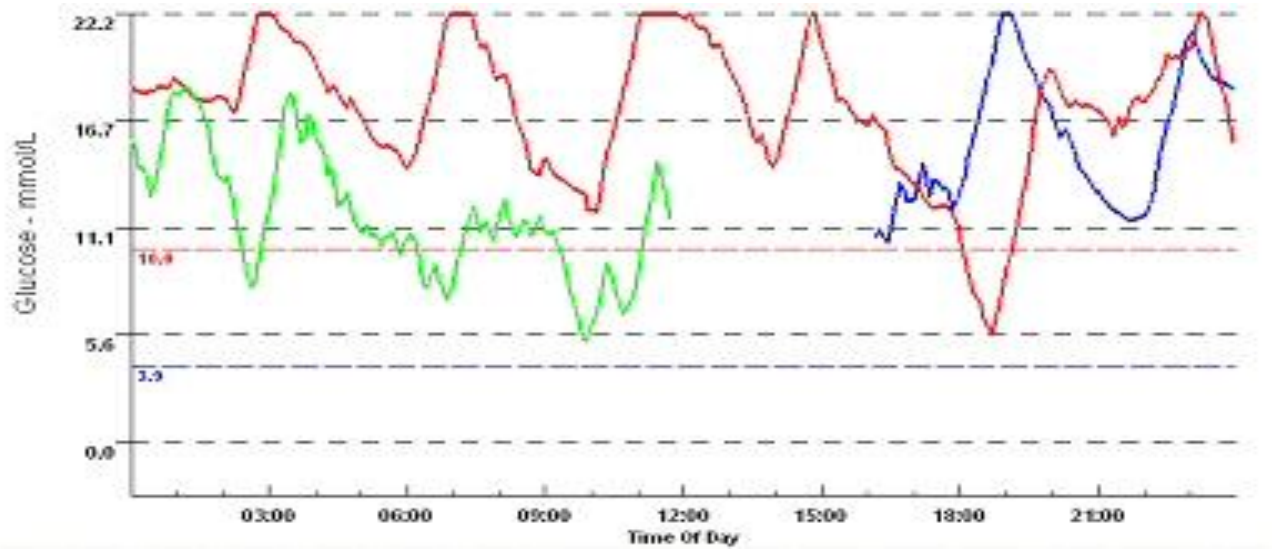

PEPSI

- Four months old
- Weight 6.9kg
- Hyperinsulinism
- Partial then Total pancreatectomy
- Impaired pancreatic endocrine/exocrine function
- Gastrostomy feeds – foregut dysmotility and gastroesophageal reflux
- Poor suck, swallow, wretching and vomiting

- Sliding scale insulin for several weeks
- Basal bolus regime – 7 injections!!
- CSII and CGMS 2 weeks later
- Training aimed at mum
- In-patient therefore ward staff also needed training.
- Mum completely new to diabetes not just pumps – BUT home within 2 weeks

- Daily CGMS downloads in the first week
- 2 hourly blood glucose monitoring
- Optium meter to facilitate checking for ketones as difficult to test urine when not toilet trained
- Target blood glucose at present

  7-13mmol/l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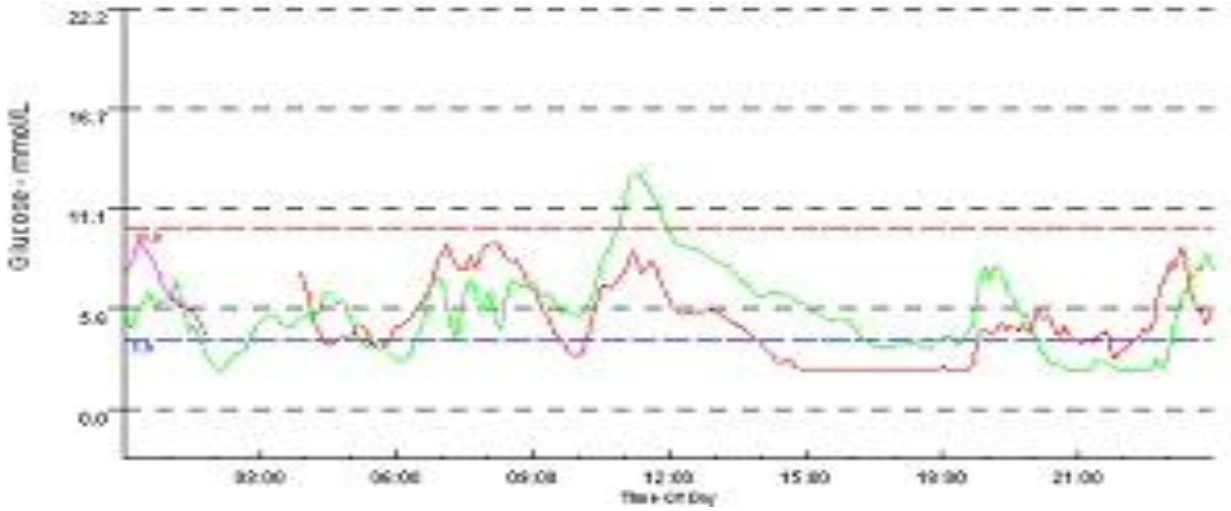
Time Of Day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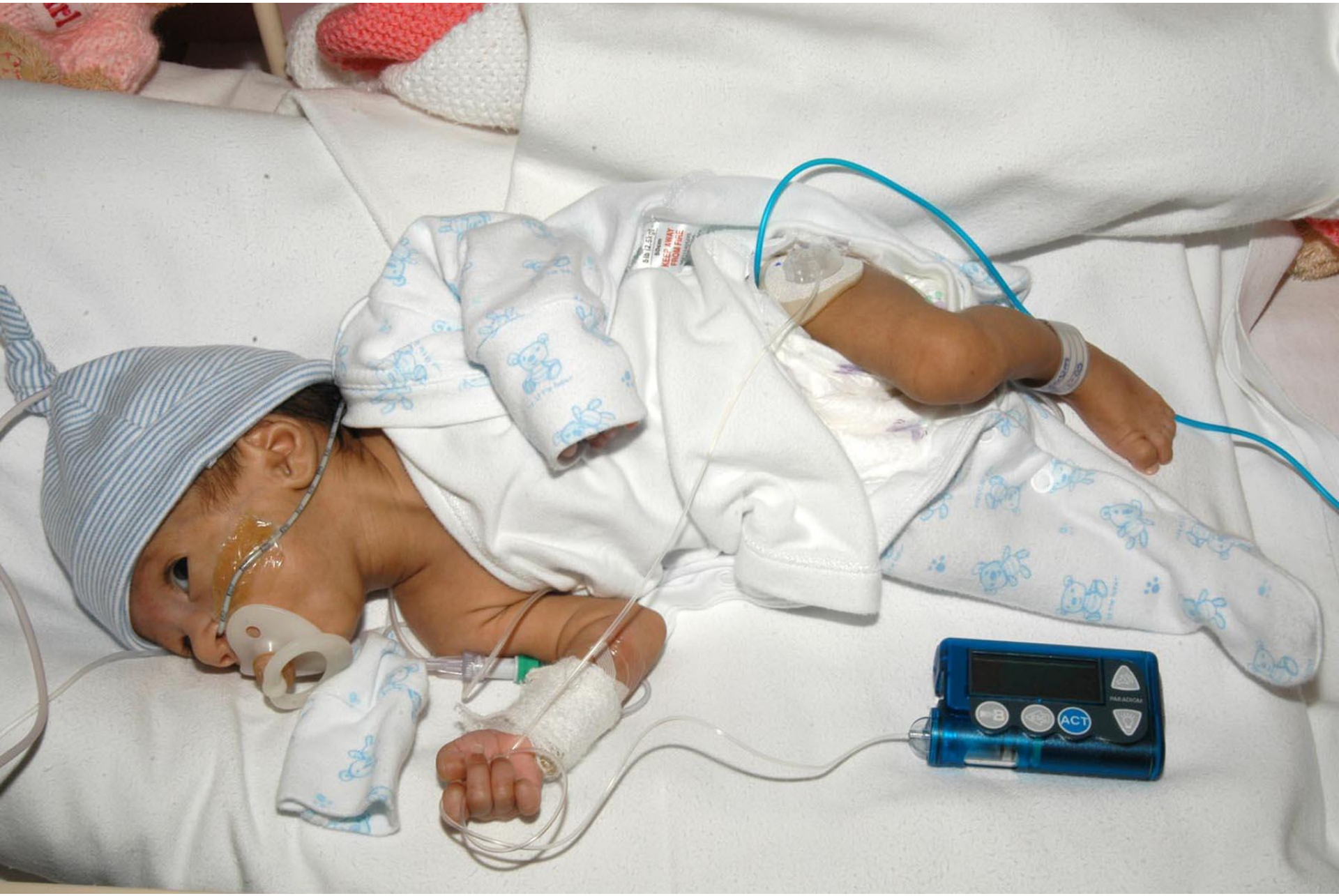
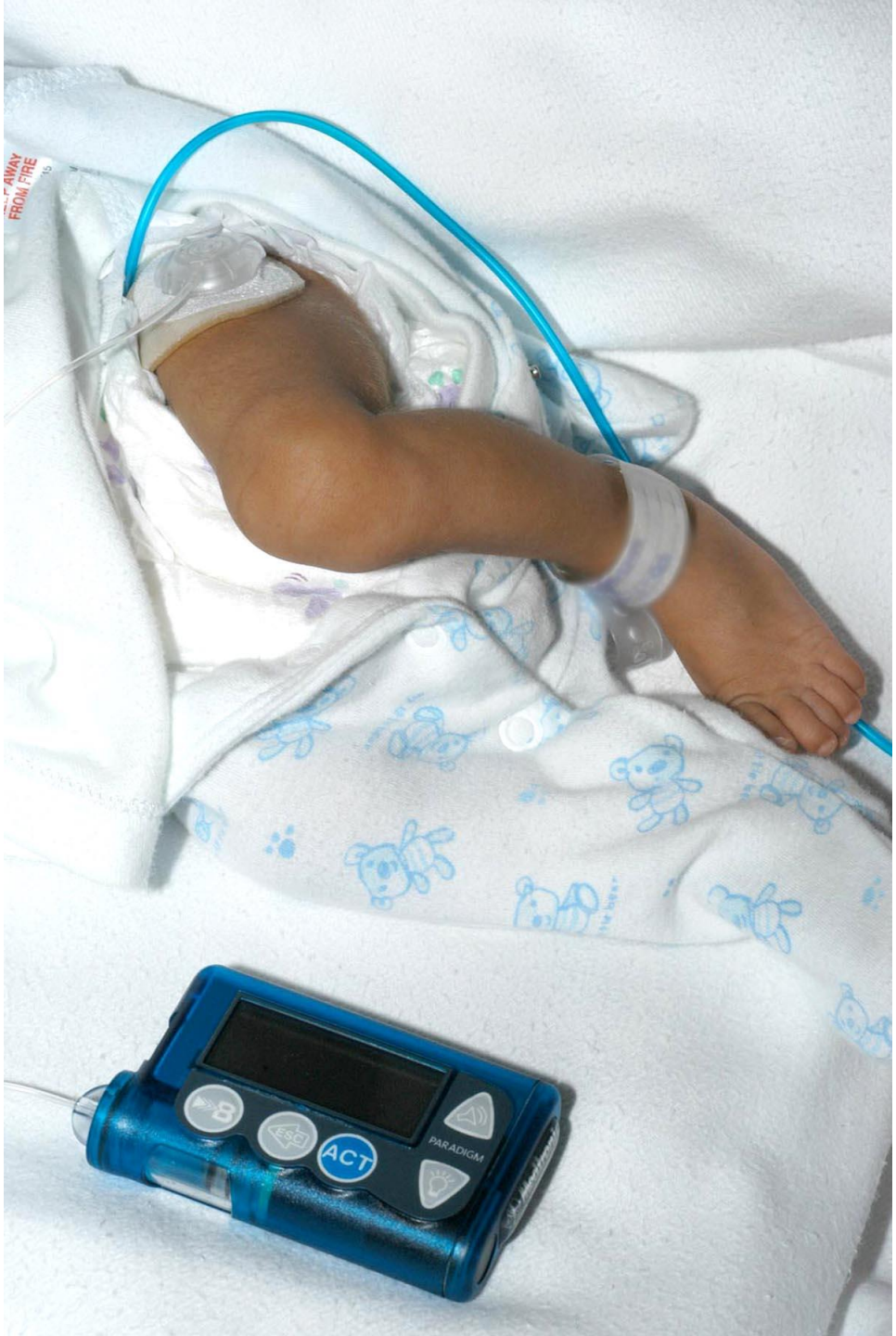
Time of Day

- Signs very subtle – crying, irritable “ratty”, loss of consciousness, hypoglycaemic fit
- Treatment:- 30mls of lucozade via the gastrostomy
- No long acting CHO required
- Hypostop not appropriate due to oral hypersensitivity
- Glucagon less likely to be effective


ACT


ACT
PARADIGM

Type II Diabetes in Children

- Achieve glycaemic control to target HbA1c<7% without hypoglycaemia
- Reduce BMI to <95th centile for age and sex
- Exercise for 60mins each day
- Look for and treat associated co-morbidities of hypertension,hyperlipidaemia and microalbuminuria
- Oral therapy with one agent
  - Metformin- licensed and used for over 60 yrs
  - Early use of Insulin


D-TRON plus
excelle

Adolescence

- Physiological changes of puberty
- Associated diseases
- Psychological issues
- Insulin omission
- Insulin, weight and eating
- Emotional/ behavioural problems
- Social support networks
- Clinic non- attendance
- Transition

Transition of care from Paediatrics to Adult Services

- NICE recommendations 2004
- Personalised care package from a multidisciplinary team experienced in the issues of teenagers
- Age banded clinics
- Adolescent/young adult service run jointly with adult colleagues
- In UK 2005
  - 7% of hospitals had age stratification
  - 63% had adolescent clinics
  - 48% had joint service with adults

With Thanks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