

# L'Ipoglicemia del Neonato: un approccio pratico per evitare rischi

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## Adattamento Metabolico

1. Adattamento ad una nuova forma di Nutrizione
2. [Glucosio] adeguata

↑ **Glucagone**

↑ **Catecolamine**

↑ **GH**

↑ **Cortisolo**

↓ **Insulina**

↑ **Glicogenolisi**

↑ **Gluconeogenesi**

↑ **Lipolisi**

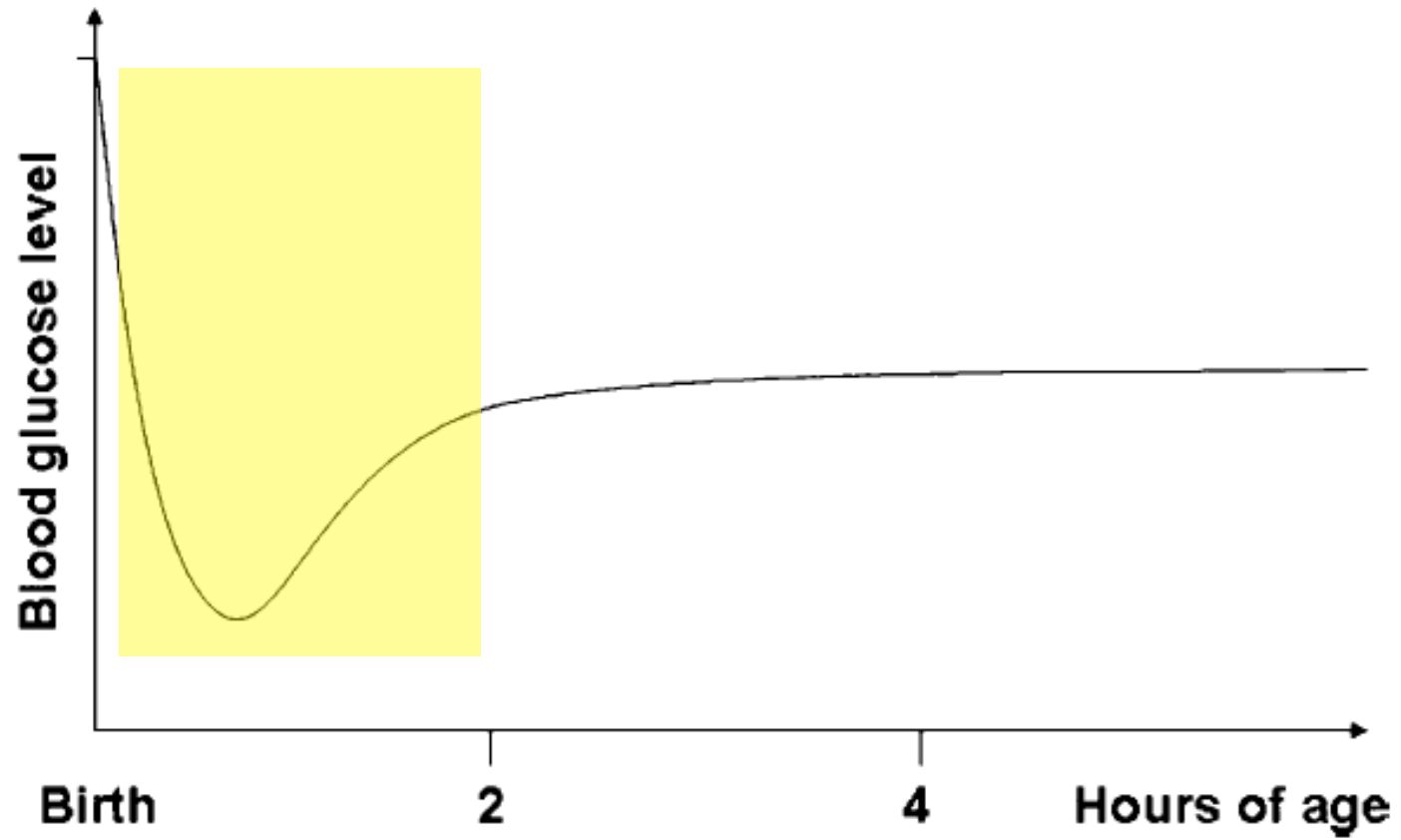
↑ **B Ossidazione**

↑ **Glicemia**

↑ **C.Chetonici**

↑ **Lattato**

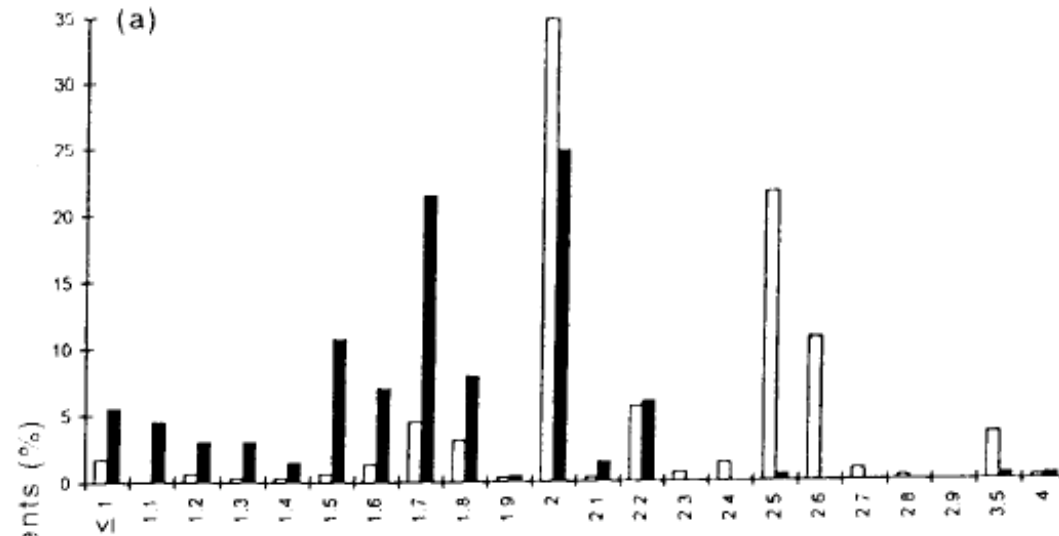
↑ **AA**



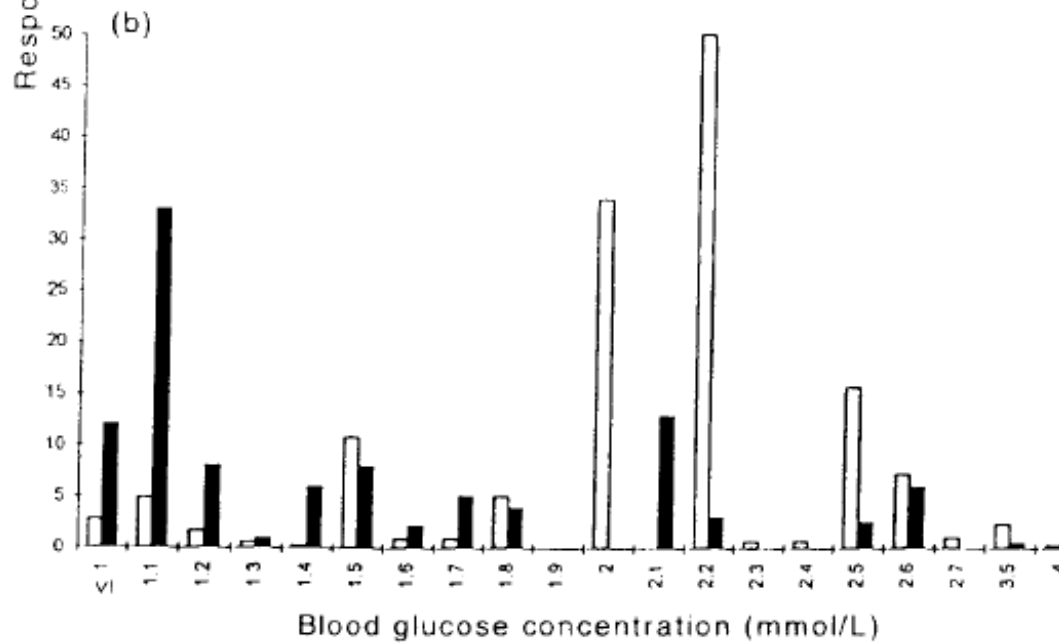
Martin Ward Platt, Sanjeev Deshpande. Metabolic adaptation at birth. *Semin Fet Neo Med* 2005; 10,341-350

**Definizione**

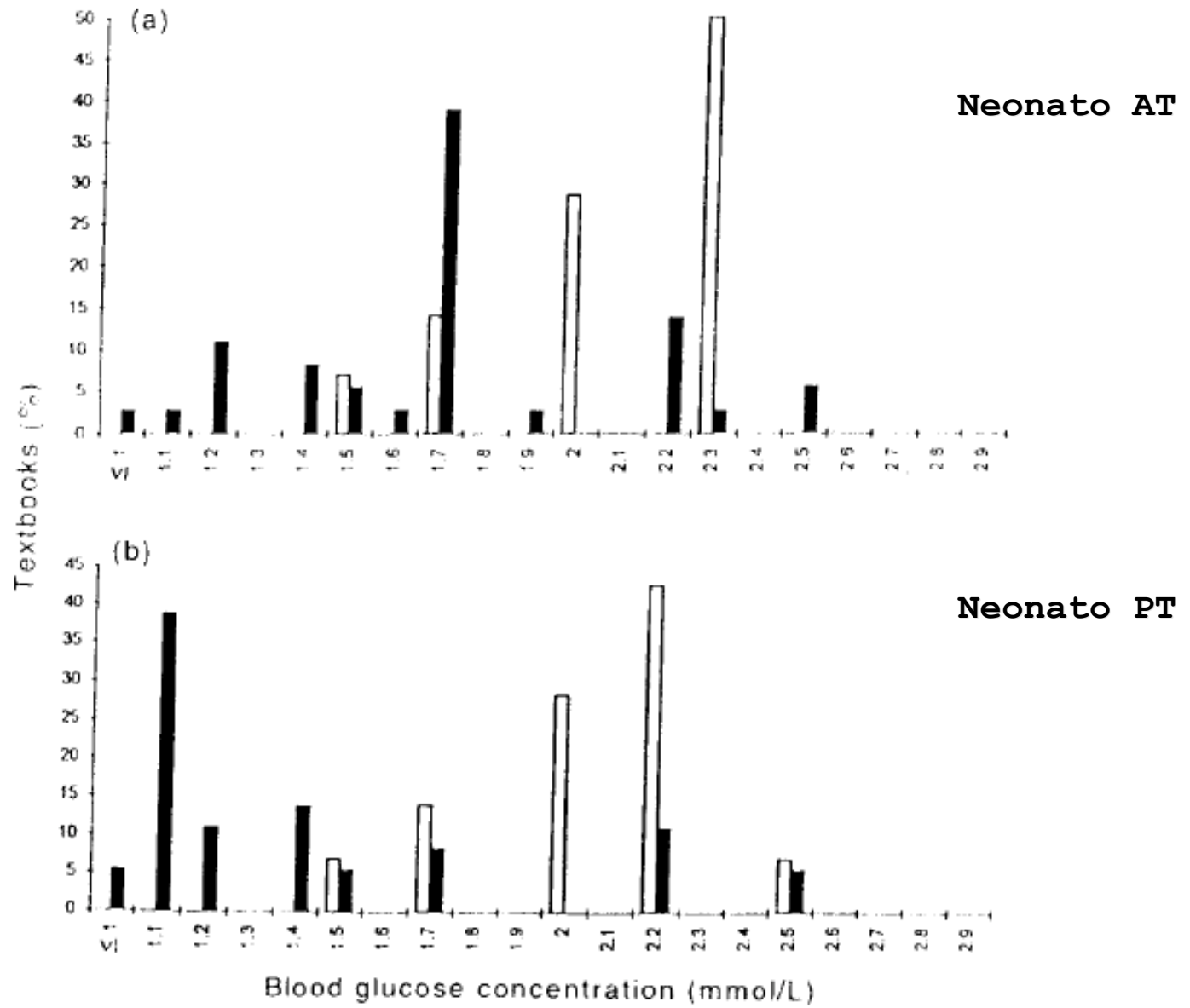
**420  
Neonatologi**



**Neonato AT**



**Neonato PT**

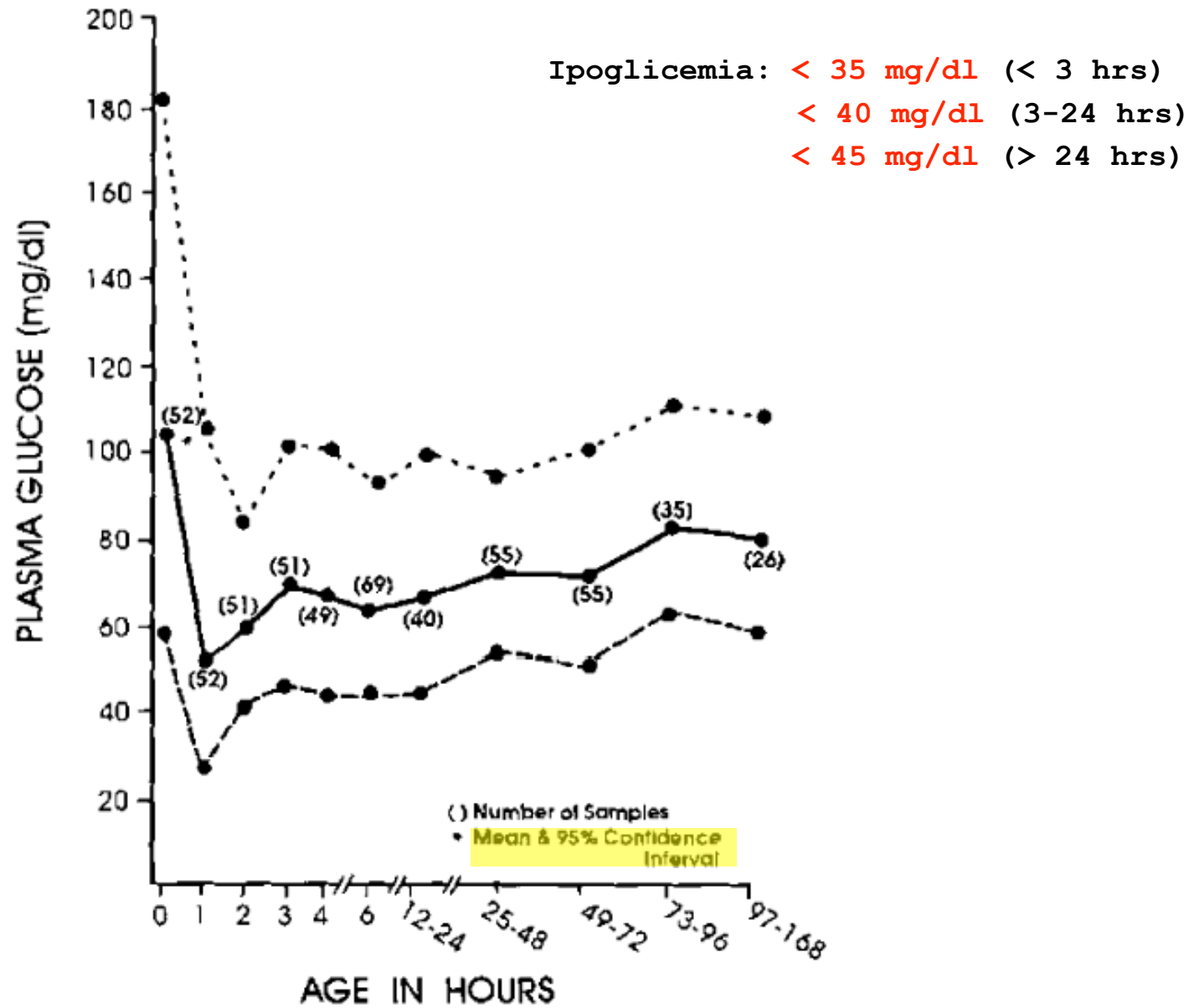


Koh THHG, Vong SK. Definition of hypoglycaemia: is there a change? *J Paed Child Health* 1996;32:302-5.

# Definizione CLINICA

1. Irritabilità
2. Letargia
3. Ipotonia
4. Scarsa reattività
5. Tremori
6. Convulsioni
7. Apnea
8. Tachipnea
9. Crisi di Cianosi
10. Difficoltà alimentari
11. Ipotermia

Definizione  
**EPIDEMIOLOGICA**



Ipoglicemia: < 30 mg/dl ( $\leq$  24 hrs)  
 < 40 mg/dl ( $>$  24 hrs)

Percentile	Maternal	Cord	1 Hr	2 Hr	5-6 Hr	10-14 Hr	20-28 Hr	44-52 H
5th	73	63	36	39	34	33	46	48
50th	104	90	56	58	56	56	60	65
95th	188	158	99	89	77	74	81	79
n	97	110	113	107	105	102	101	92
Mean	112	97	60	61	56	56	61	64
SD	37	29	18	15	11	12	10	10

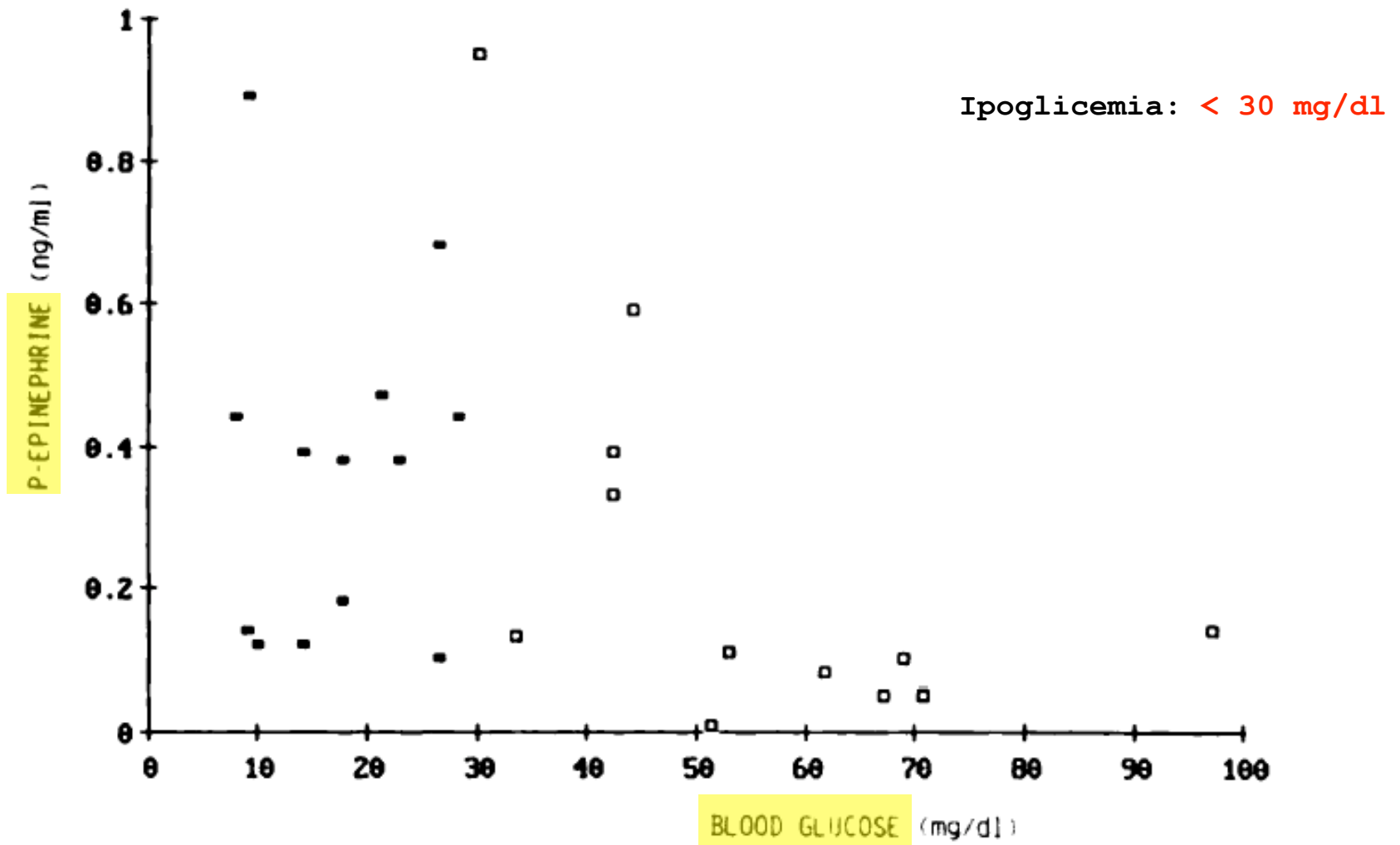
Heck LJ, Erenburg A. Serum glucose levels in term neonates during the first 48 hours of life. *J Pediatrics* 1987;110:119-122.

## Limiti

1. Glicemia valore singolo vs continuum
2. Fattori predisponenti (SGA, FMD, Asfissia)
3. Inizio Alimentazione enterale
4. Tipo Alimentazione
5. Metodologia statistica (IC, ds, percentili)
6. Statistica vs Biologia

Definizione  
**METABOLICA**

25 < 34 sett EG - 2h

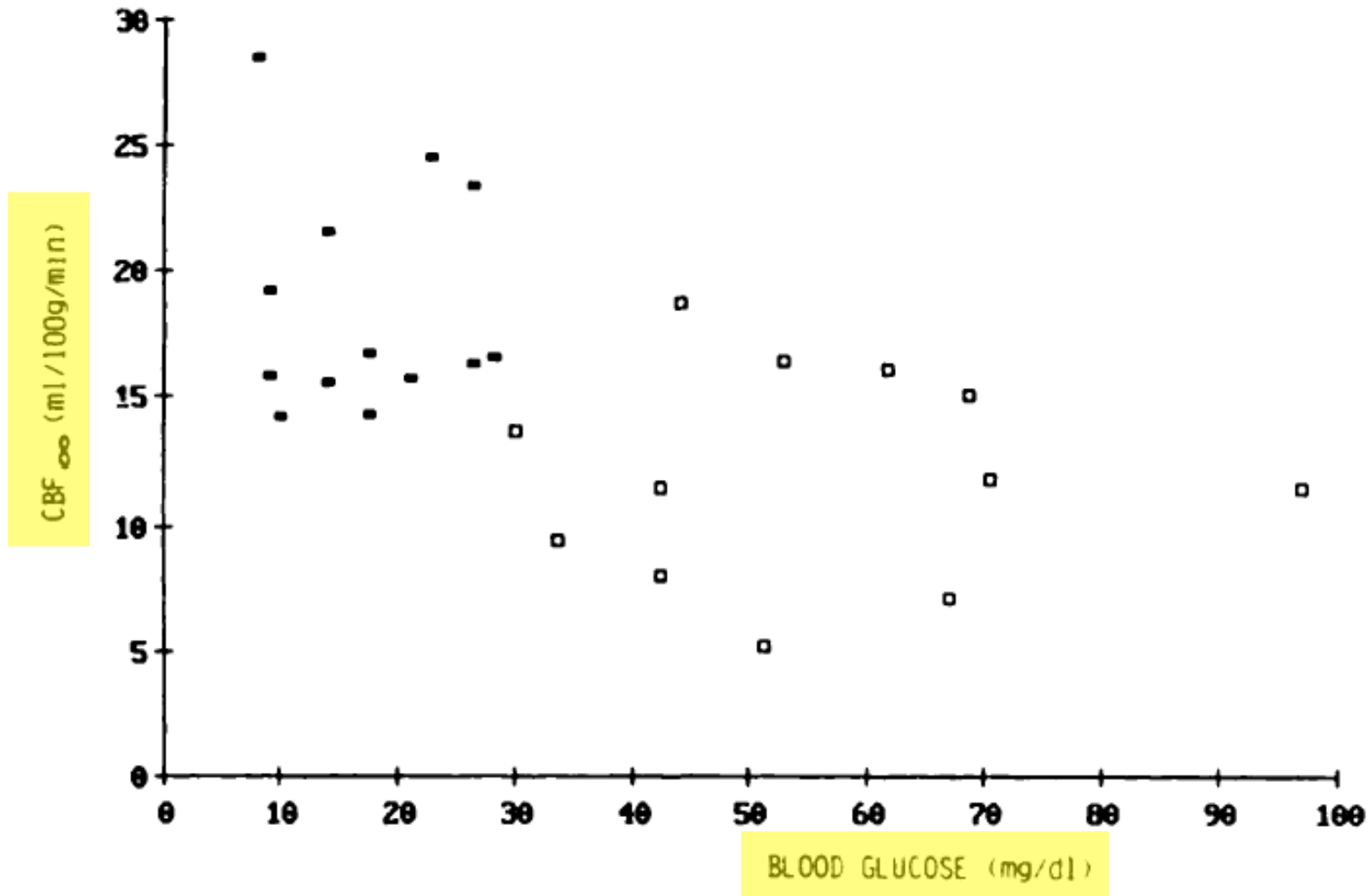


Pryds O, Christensen NJ, Friis-Hansen B. Increased cerebral blood flow and plasma epinephrine in hypoglycaemic preterm neonates. *Pediatrics* 1990;85:172-6.

Definizione  
**NEUROFISIOLOGICA**

25 < 34 sett EG - 2h

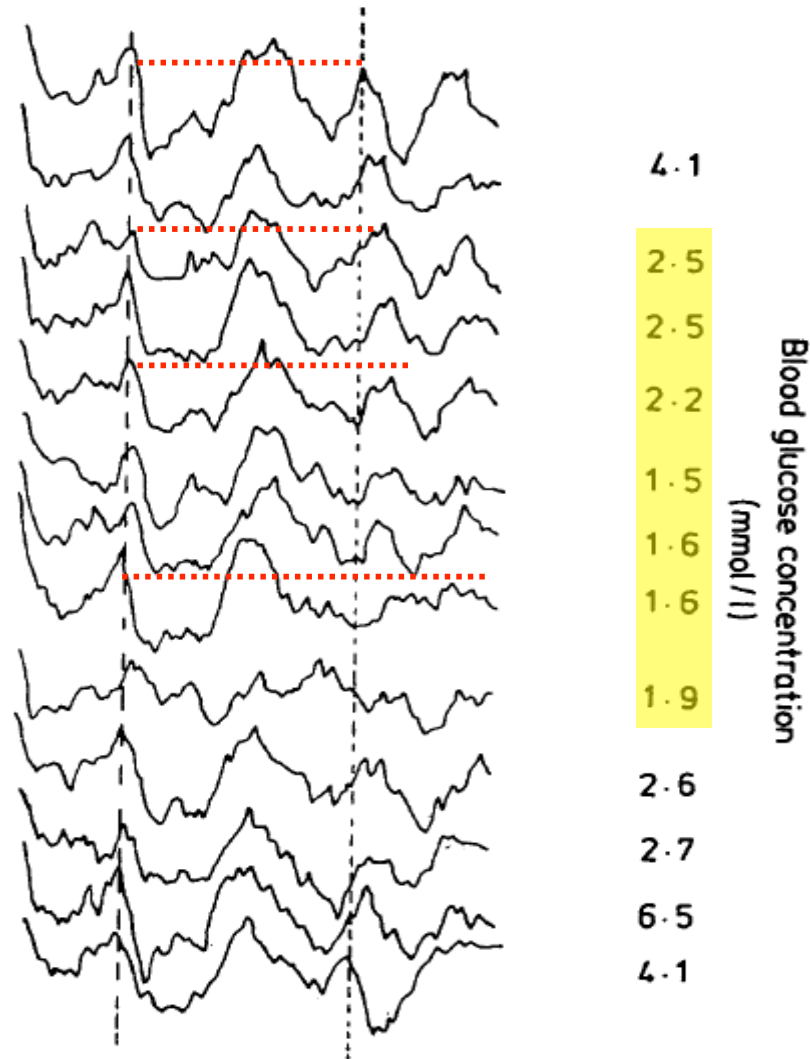
Ipoglicemia: < 30 mg/dl



Pryds O, Christensen NJ, Friis-Hansen B. Increased cerebral blood flow and plasma epinephrine in hypoglycaemic preterm neonates. *Pediatrics* 1990;85:172-6.

Ipoglicemia: < 47 mg/dl

### Serial brainstem evoked potentials



N 17
✓ IpoG Asintomatica
✓ Correzione lenta
✓ Età 1g-16 aa( 5N AT)
✓ No Ketogenesi

Koh THHG, Aynsley-Green A, Tarbit M, Eyre JA. Neural dysfunction during hypoglycaemia. Arch Dis Child 1988; 63:1353-8.

27 AGA AT

23 AGA PT (> 1500 PN)

	Wave I-V interpeak latency		Wave V latency	
	F	p	F	p
Independent variables	13.752	<0.0001	5.366	<0.0001
Gestational age		0.0002		0.0027
Blood glucose concentration		0.5408		0.3107

Cowett RM, Howard GM, Johnson J, Vohr B. Brain stem auditory-evoked response in relation to neonatal glucose metabolism. *Biol Neonate* 1997;71:31-6.

Definizione basata  
sull'ESITO  
NEUROLOGICO

## Criteri di Inclusione

- ✓ Età < 1 settimana
- ✓ Dati prospettici
- ✓ G. Controllo
- ✓ Fattori confondenti
- ✓ Outcome NM  $\geq$  1 anno

## Criteri di Validità

### ■ Definizione

- ✓ Popolazione
- ✓ Ipoglicemia
- ✓ Trattamento

### ■ Follow up > 80%

### ■ Esito

- ✓ Oggettivo
- ✓ Valutazione in cieco

### ■ Correzione per le variabili confondenti

- ✓ AMV
- ✓ Matching
- ✓ Esclusione

Autore	Anno	Gruppo	N	mg%
Brand	2004	AT LGA	75	39,6 45
Gentz	1969	AT AGA SGA	18	19,8
Kinnala	1999	AT AGA SGA	19	45
Lucas	1988	PT	661	10,8 28,8 46,8
Creery	1966	AT PT	22	19,8
Haworth	1967	AT PT	46	19,8
Griffiths	1971	AT PT	41	19,8
Kumart	1971	AT PT	19	19,8 30,6
Koivisto	1972	AT PT	151	30,6
Pildes	1974	AT PT	39	30,6
Fluge	1975	AT PT	67	ND
Abel	1987	AT PT	58	ND
Singh	1991	AT PT	72	30,6
Yamaguchi	1997	AT PT	135	25,2 34,2
Haworth	1967	FMD	25	19,8 30,6
Persson	1984	FMD	94	30,6
Cresto	1998	Iperinsul	26	ND
Dacou	1998	Iperinsul	15	ND

661 PT - PN < 1850 g

FU 18 mesi

**Ipoglicemia: < 47 mg/dl**

	Eu Gly	Hypo Gly > 5 d	Adj	CI 95%
Mental Dev Index	96,2 ± 1,3	84,4 ± 3,2	+ 14,0	6, 22
Motor Dev Index	102 ± 1,5	85,6 ± 3,7	+ 13,0	5, 20
CP o Score < 70		3.5 (3.1, 9.4)		

Lucas A, Morley R, Cole TJ. Adverse neurodevelopmental outcome of moderate neonatal hypoglycaemia. **BMJ 1988;297:1304-1308**

Numeri

IpoG Asintomatica

Non Ruolo EG

Studio “Satellite”

Associazione vs Causa

FU 7.5 - 8 aa

Hypoglycemia: < 40 mg/dl ( $\leq$  1 h)  
< 46 mg/dl ( $>$  1 h)

Test or subscale	Normoglycaemic children	Hypoglycaemic children	95% CI for difference
DDS total score (% definitively normal)	100%	93%	-14 to 16%
DDS social behaviour (% definitively normal)	100%	93%	-14 to 16%
DDS adaptive behaviour (% definitively normal)	100%	93%	-14 to 16%
DDS language behaviour (% definitively normal)	100%	97%	-17 to 11%
DDS motor behaviour (% definitively normal)	67%	68%	-28 to 20%
CBCL withdrawal (% normal)	100%	95%	-16 to 14%
CBCL physical complaints (% normal)	100%	95%	-16 to 14%
CBCL anxiety/depression (% normal)	100%	97%	-17 to 11%
CBCL social problems (% normal)	100%	98%	-19 to 9%
CBCL thinking problems (% normal)	93%	93%	-24 to 11%
CBCL attention problems (% normal)	93%	97%	-27 to 7%
CBCL delinquent behaviour (% normal)	87%	98%	-36 to 1%
CBCL aggressive behaviour (% normal)	87%	90%	-29 to 11%
CBCL internalising T score, mean (SD)	48.4 (10.6)	50.4 (10.7)	-8.1 to 4.2
CBCL externalising T score, mean (SD)	54.7 (12.4)	51.4 (10.7)	-3.1 to 9.6
CBCL total T score, mean (SD)	52.9 (10.8)	51.3 (11.7)	-5.0 to 8.2
SON spatial orientation IQ, mean (SD)	108.9 (12.8)	108.2 (16.3)	-8.3 to 9.7
SON reasoning IQ, mean (SD)	116.8 (16.1)	107.6 (13.2)	1.3 to 17.2
SON total IQ, mean (SD)	114.3 (14.5)	108.9 (14.1)	-2.8 to 13.5

P L P Brand, N L D Molenaar, C Kaaijk, W S Wierenga. Neurodevelopmental outcome of hypoglycaemia in healthy, large for gestational age, term newborns. Arch Dis Child 2005;90:78-81.

# ~~Cut off Ipoglicemia~~

Il danno da Ipoglicemia dipende da

1. **Ipoglicemia**

- a. Durata
- b. Gravità

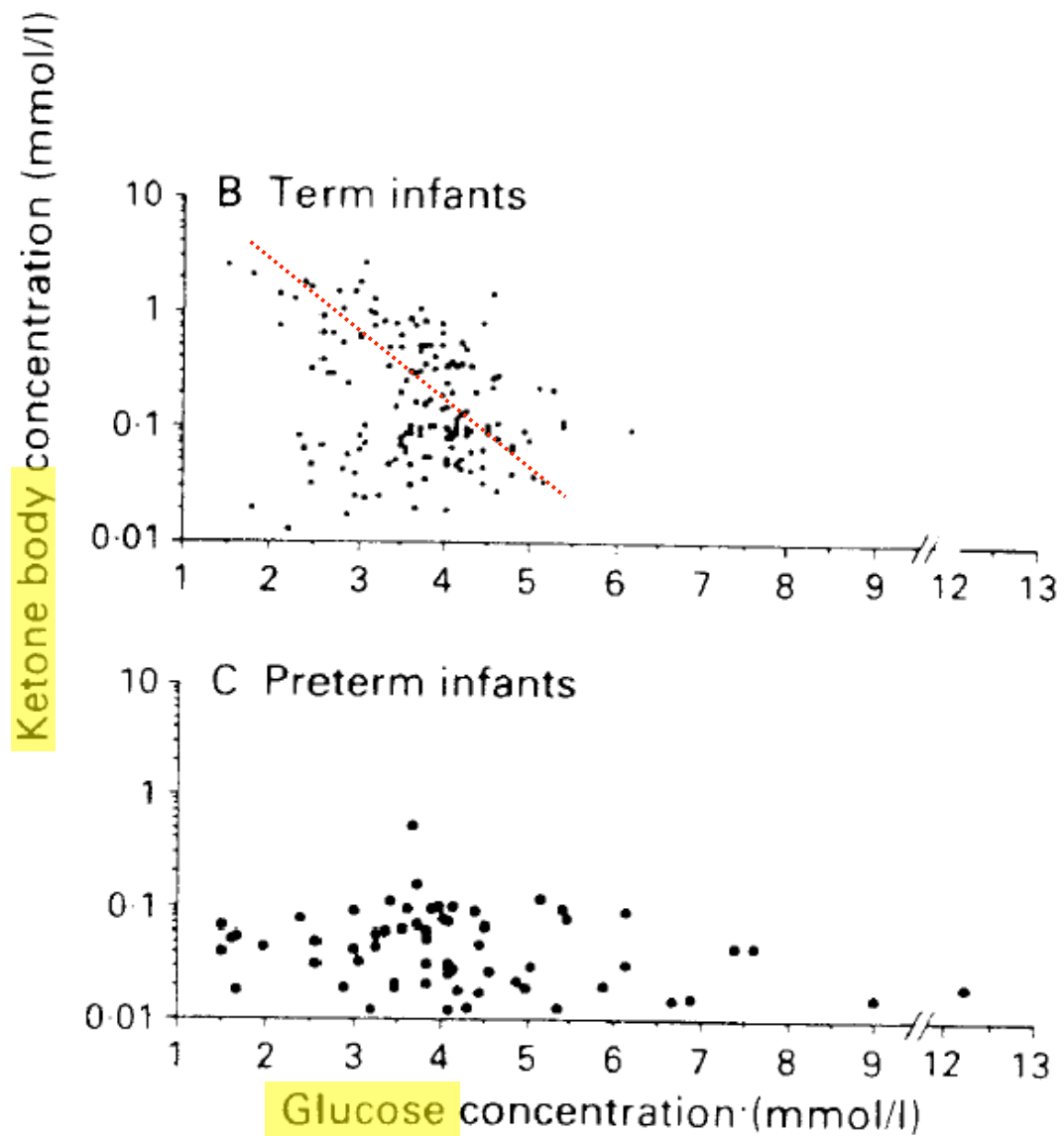
2. **Condizione Cerebrale**

- a. Maturità (EG)
- b. Patologia (IVH - LMPV)
- c. Richieste metaboliche (Convulsioni)

3. **Adattamento del Microcircolo**

4. **Difese Metaboliche**

- a. Glicogeno
- b. Gluconeogenesi
- c. Ketogenesi



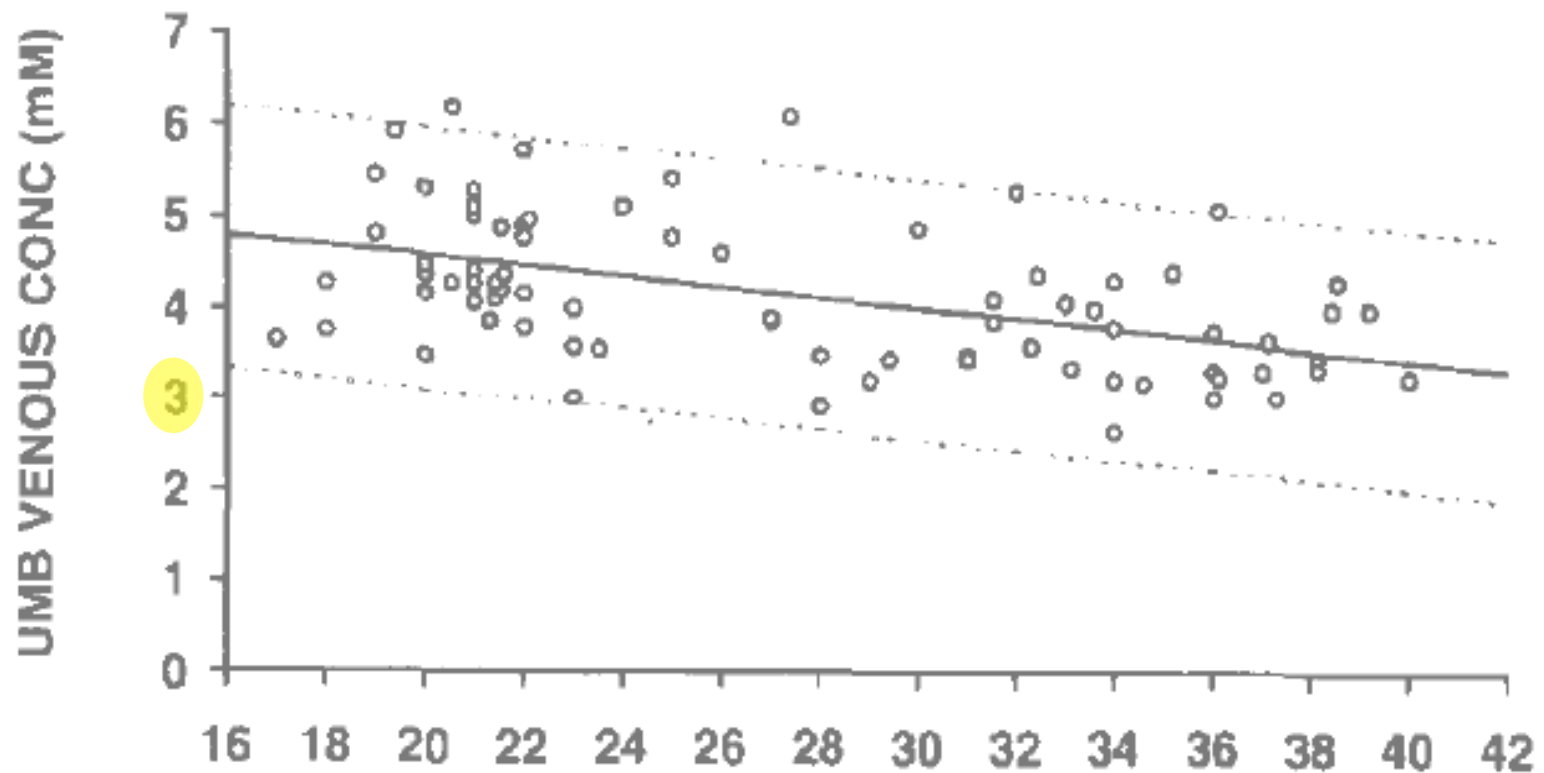
Hawdon J, Ward Platt M, Aynsley-Green A. Patterns of metabolic adaptation for preterm and term infants in the first neonatal week. *Arch Dis Child* 1992;67:357-65.

# Definizione OPERATIVA

	Glicemia
	mg/dl
Neonato a Rischio	< 36
Neonato Sintomatico	< 45
Neonato in NP	< 45
Neonato Prematuro	< 47
Iperinsulinismo	< 60

Marvin Cornblath, Jane M. Hawdon, Anthony F. Williams, Albert Aynsley-Green, Martin P. Ward-Platt, Robert Schwartz, and Satish C. Kalhan. Controversies Regarding Definition of Neonatal Hypoglycemia: Suggested Operational Thresholds. **Pediatrics** 2000;105:1141- 1145

Ipoglicemia: < 54 mg/dl



Marconi AM, Paolini C, Buscaglia M, Zerbe G, Battaglia FC, Pardi G. The impact of gestational age and fetal growth on the maternal-fetal glucose concentration difference. *Obstet Gynecol* 1996;87:937-42.

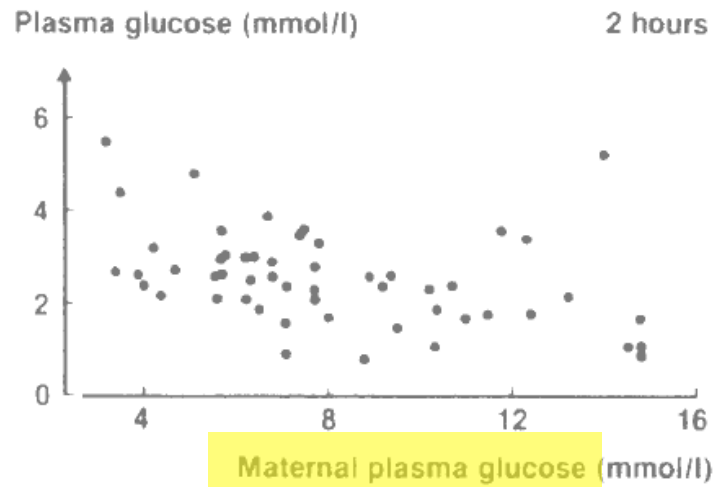
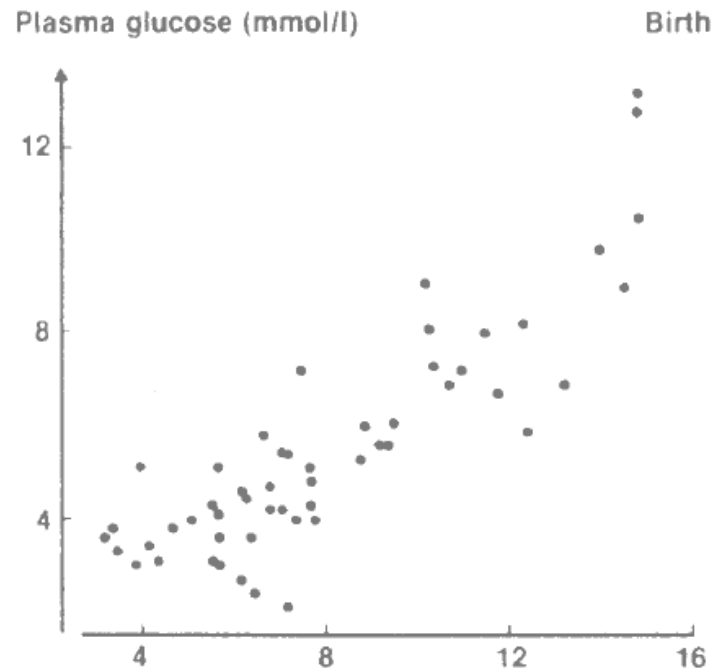
**Screening**

**Chi?**

## **N a Rischio**

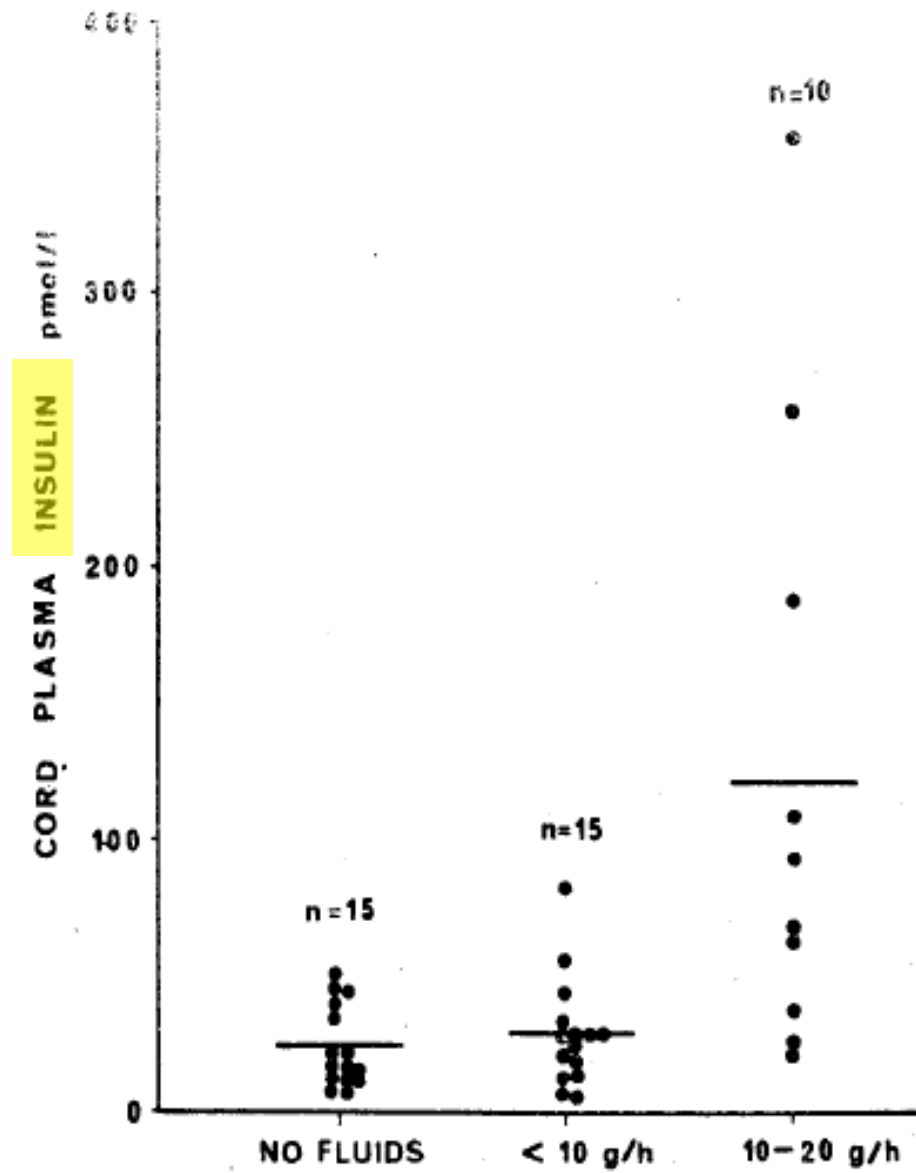
1. Prematurità
2. IUGR
3. SGA
4. LGA
5. Asfissia
6. Infezione
7. Ipotermia
8. Policitemia
9. Isoimmunizzazione
10. Cp Congenita
11. Patologia

**N a Rischio**



Andersen O, Hertel J, Schmilker L, Kuhl C. Influence of maternal plasma glucose on the risk of hypoglycaemia in infants of insulin dependent diabetic mothers. *Acta Paediatr Scand* 1985;74:268-73.

**N a Rischio**



Lucas A, Adrian TE, Aynsley-Green A, Bloom SR. Iatrogenic hyperinsulinism at birth. *Lancet* 1980;i:144-5.

## N a Rischio

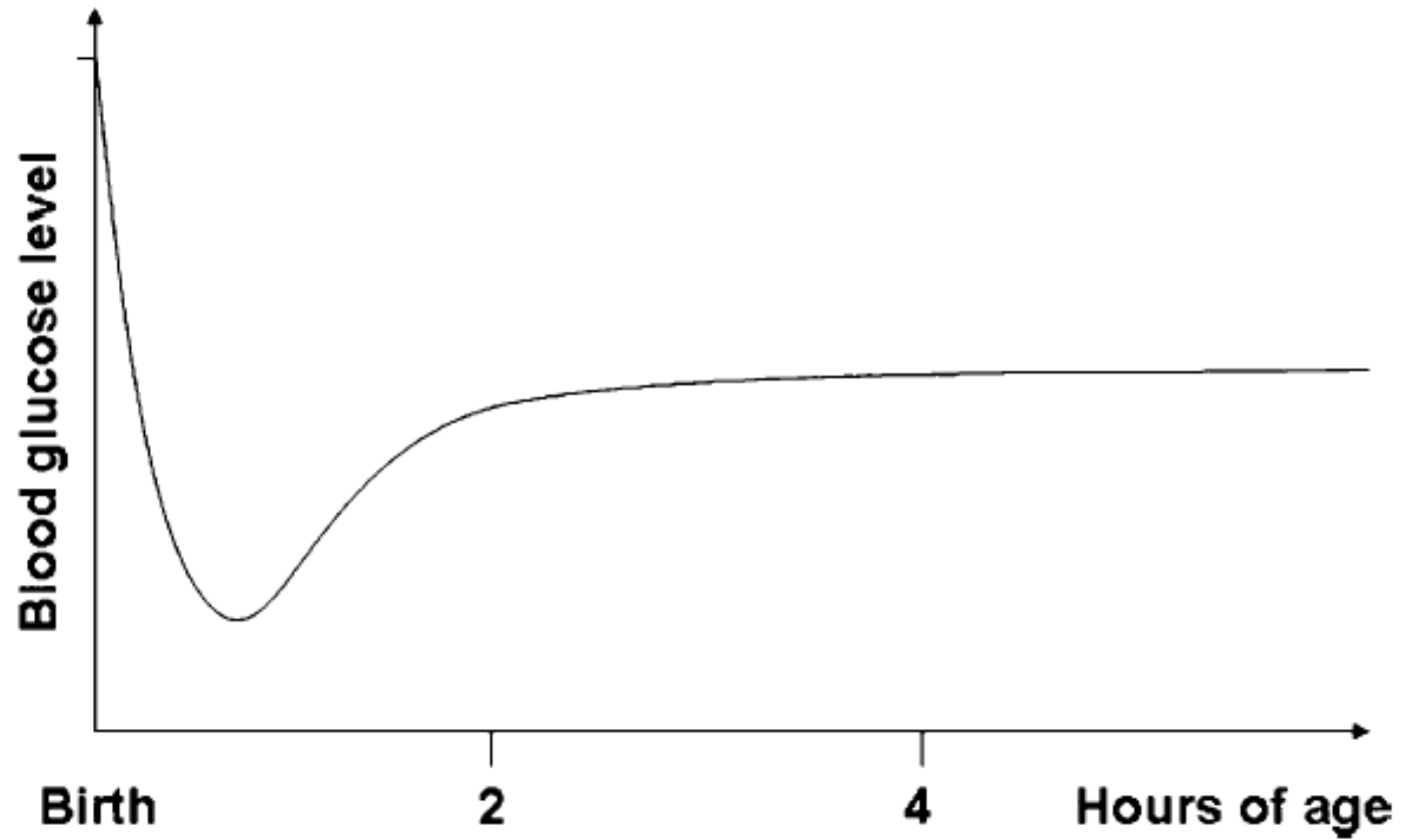
	<i>Treated group</i>	<i>Control group</i>
n	18	21
Gestational age (wk)	33.3 ± 2.4	34.0 ± 1.6
Range	29-37	32-37
Birth weight (gm)	1,822.2 ± 660.7	2,081.0 ± 496.9
Range	730-2,550	1,300-2,800
Growth retarded infants	2(11.1%)	5(23.8%)
<b>Insulin</b> concentration (μU/ml)	28.7 ± 26.4	14.4 ± 14.2*
Range	2-112	1-35

Procianoy RS, Pinheiro CEA. Neonatal hyperinsulinaemia after short-term maternal beta-sympathomimetic therapy. *J of Pediatrics* 1982; 101: 612-614.

**Screening**

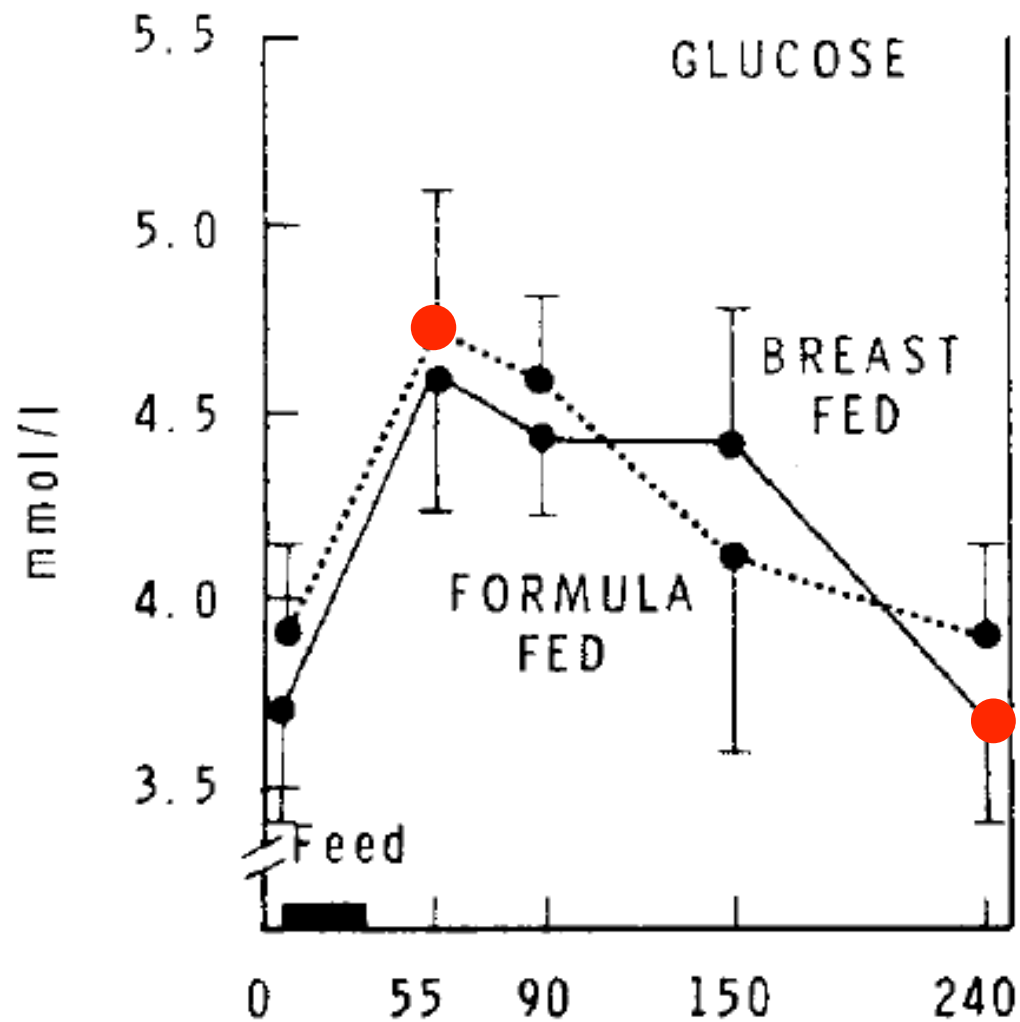
**Quando?**

Dopo le prime due ore di vita



Martin Ward Platt, Sanjeev Deshpande. Metabolic adaptation at birth. *Semin Fet Neo Med* 2005; 10,341-350

Prima del pasto



Lucas A, Boyes S, Bloom SR, Aynsley-Green A. Metabolic and endocrine responses to a milk feed in six-day-old term infants: differences between breast and cow's milk formula feeding. *Acta Paed* 1981, 70: 195-200

**Screening**

**Come?**

# Screening ideale per l'Ipoglicemia

1. Piccole quantità di sangue
2. Rapido
3. Uso in situ
4. Sangue intero
5. Basso costo
6. Preciso
  - a. Controllo di Qualità
  - b. Riproducibilità
  - c. Elevata Sensibilità (↑ Diagnosi)
  - d. Elevato VP Negativo (↓ Interventi inutili)

	Se (%)	Sp (%)	VP Pos (%)	VP Neg (%)
BM Reflolux	83,0	69,0	33	98
Glucotrend	83,3	92,0	92.6	82.1
Advantage	46,7	79,2	73.7	54.1
Elite XL	65,5	69,2	82.6	47.4
Precision	96,4	60,0	81.8	90.0

Ho HT, Yeung WKY, Young BWY. Evaluation of 'point of care' devices in the measurement of low blood glucose in neonatal practice. Arch Dis Child Fetal Neonatal Ed 2004;89:F356-9.

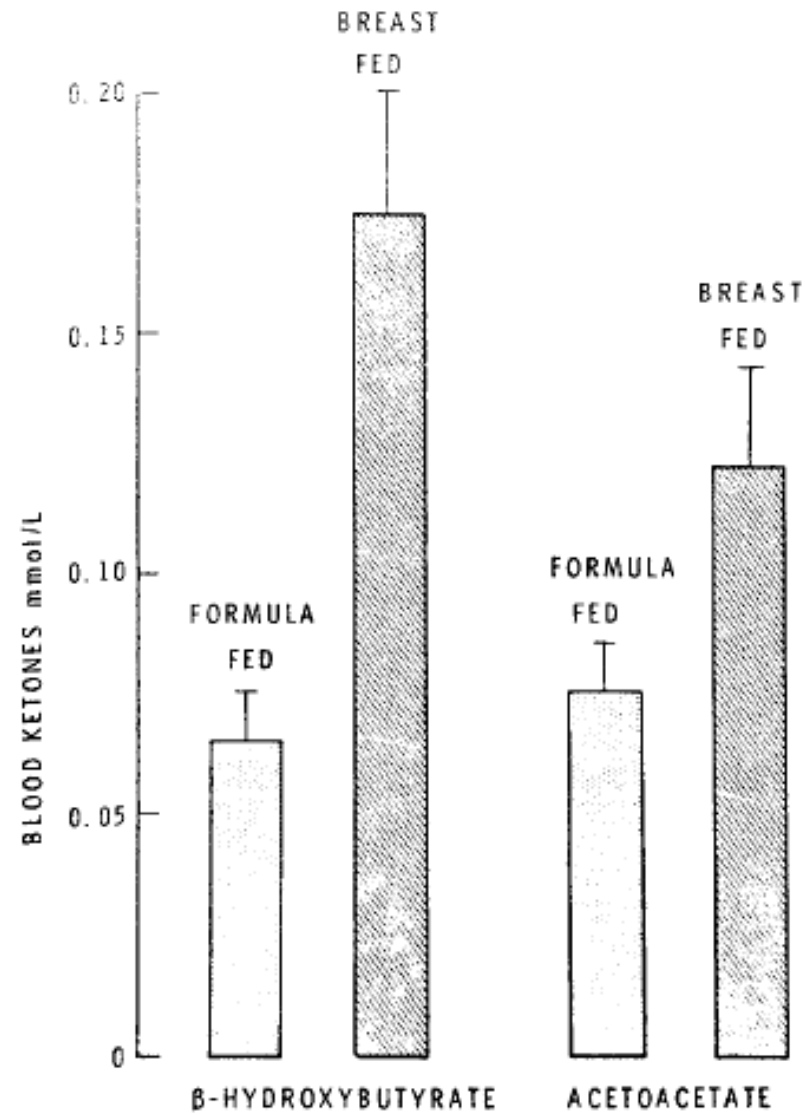
1. G Arteriosa < Capillare < Venosa
2. Plasma > Sangue (18%)
3. Ematocrito (↓)
4. Emolisi (↓)
5. Bilirubina (↓)
6. Tempo Lettura (↓ 7-9 mg% ogni 30')
7. Alcool (↑)

Burrin JM, Alberti KGMM. What is blood glucose: can it be measured? *Diabetic Med* 1990;7:199-206.

Prevenzione

	PO	EV
EG > 36 sett (a rischio)	60 - 120 ml/kg	
EG 33 - 36 sett		
EG $\leq$ 32 sett		70 - 90 ml/kg

## Latte Materno



Lucas A, Boyes S, Bloom SR, Aynsley-Green A. Metabolic and endocrine responses to a milk feed in six-day-old term infants: differences between breast and cow's milk formula feeding. *Acta Paed* 1981, 70: 195-200

Intervento

**N a Rischio - EG > 34 sett.**

■ **Glucostix  $\leq$  40 mg%**

**30-40 mg%**

Pasto supplementare \* e ripetere Gtx dopo 30' dal pasto

- a. Gtx  $\geq$  40 mg%: continuare con i pasti supplementari
- b. Gtx < 40 mg%: Eseguire Glicemia Lab
  - ⊙ G Lab > 36 mg% continuare con i pasti supplementari
  - ⊙ G Lab  $\leq$  36 mg% Infusione ev di SG 10%\*

**20-30 mg%**

Eseguire Glicemia Lab

- ⊙ G Lab > 36 mg% continuare con i pasti supplementari
- ⊙ G Lab  $\leq$  36 mg% Infusione ev di SG 10% \*

**N a Rischio - EG  $\leq$  34 sett.**

■ **Glucostix  $\leq$  50 mg%**

40-50 mg%

Pasto supplementare \* e ripetere Gtx dopo 30' dal pasto

- a. Gtx  $\geq$  50 mg%: continuare con i pasti supplementari
- b. Gtx  $<$  50 mg%: Eseguire Glicemia Lab
  - ⊙ G Lab  $>$  45 mg% continuare con i pasti supplementari
  - ⊙ G Lab  $\leq$  45 mg% Infusione ev di SG 10% \*

30-40 mg%

Eseguire Glicemia Lab

- ⊙ G Lab  $>$  45 mg% continuare con i pasti supplementari
- ⊙ G Lab  $\leq$  45 mg% Infusione ev di SG 10% \*

## Pasto supplementare

- Cosa            Latte (Non SG)
- Quale           Materno > FPT > FAT
- Quanto        10 cc/kg

## Infusione EV

- Cosa: SG 10%
- Quanto:  $\geq 7.0$  g/kg/d
- Aumento: 10-20% ogni 1-2 ore
- Riduzione: 10-20% ogni 6 ore se G > 60 mg/dl e App.Glucosio ev invariato da 12 ore
- Stop: App Glu < 4g/kg/e e G stabile

## FARMACI

**Quando:** Glicemia instabile nonostante l'infusione di Glucosio  $\geq 18$  g/kg/die

### Glucagone

**Meccanismo d'Azione:** Stimolo rapido e transitorio della Glicogenolisi

**Indicazioni:** Soggetti con adeguate riserve di Glicogeno (neonati a termine, AGA)

**Dosaggio:**

⊙ Bolo :

- 30 mcg/kg e fino a 300 mcg/kg in caso di iperinsulinismo
- 100 mcg/kg im come misura temporanea in attesa di via venosa. Può essere ripetuto ogni 2-3h

⊙ Infusione: 20 to 40 mcg/h

**Eff Collaterali:** Segnalazione di Piastrinopenia e Iponatremia (dati non univoci)

### Idrocortisone

**Meccanismo d'Azione:** Riduce l'utilizzazione del Glucosio in periferia

**Dosaggio:** 5 - 15 mg/kg/die ev diviso in due o tre dosi. In presenza di valori stabili di Glicemia ridurre di 5 mg/kg/die e sospendere a 48 h di distanza dall'ultima modifica

**Eff Collaterali:** Ipertensione

**Alternativa:** Prednisone, 2 mg/kg/die

### Altri

■ **Diazoxide:** 5 mg/kg ogni 8 ore - inibisce la secrezione di Insulina

■ **Octreotide:** 5 - 10 mcg/kg ogni 6 - 8 ore - Inibisce la secrezione di Insulina e GH

*Le cose che conosciamo meglio sono  
quelle che non abbiamo mai studiato*

Luc de Clapiers