

*Insulinsteuerung –
geht es auch automatisch ?*

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Intensive Insulin Therapy for Critically Ill Patients

- **Van den Berghe et al.** – surgical patients
N Engl J Med 2001;345:1359-67
- **Finney et al.** - surgical patients
JAMA 2003;290:2041-47
- **Furnary et al.** - cardiac surgery patients
J Thorac Cardiovasc Surg 2003;125:1007-21
- **Krinsley** - medical / surgical
Mayo Clin Proc 2004;79:992-1000
- **Van den Berghe et al.** – medical patients
N Engl J Med 2006;354:449-61

Intensivierte Insulintherapie bei kritisch kranken Patienten

ICU
Patient

1. Glucose Messung

Kapillarblut
Venöses Blut
Arteriell Blut

Bettseitige Messung
Standard Labor Analyse



Arzt

Schwester

2. Algorithmus

Sliding Scale
Dynamic Scale
Intuition

...

3. Insulin Applikation



Intravenös
IV Insulin Infusion/Bolus

Reguläres Human Insulin

Accuracy and feasibility of point-of-care and continuous blood glucose analysis in critically ill ICU patients

Anouk M Corstjens¹, Jack JM Ligtenberg², Iwan CC van der Horst³, Rob Spanjersberg², Joline SW Lind², Jaap E Tulleken², John HJM Meertens² and Jan G Zijlstra²

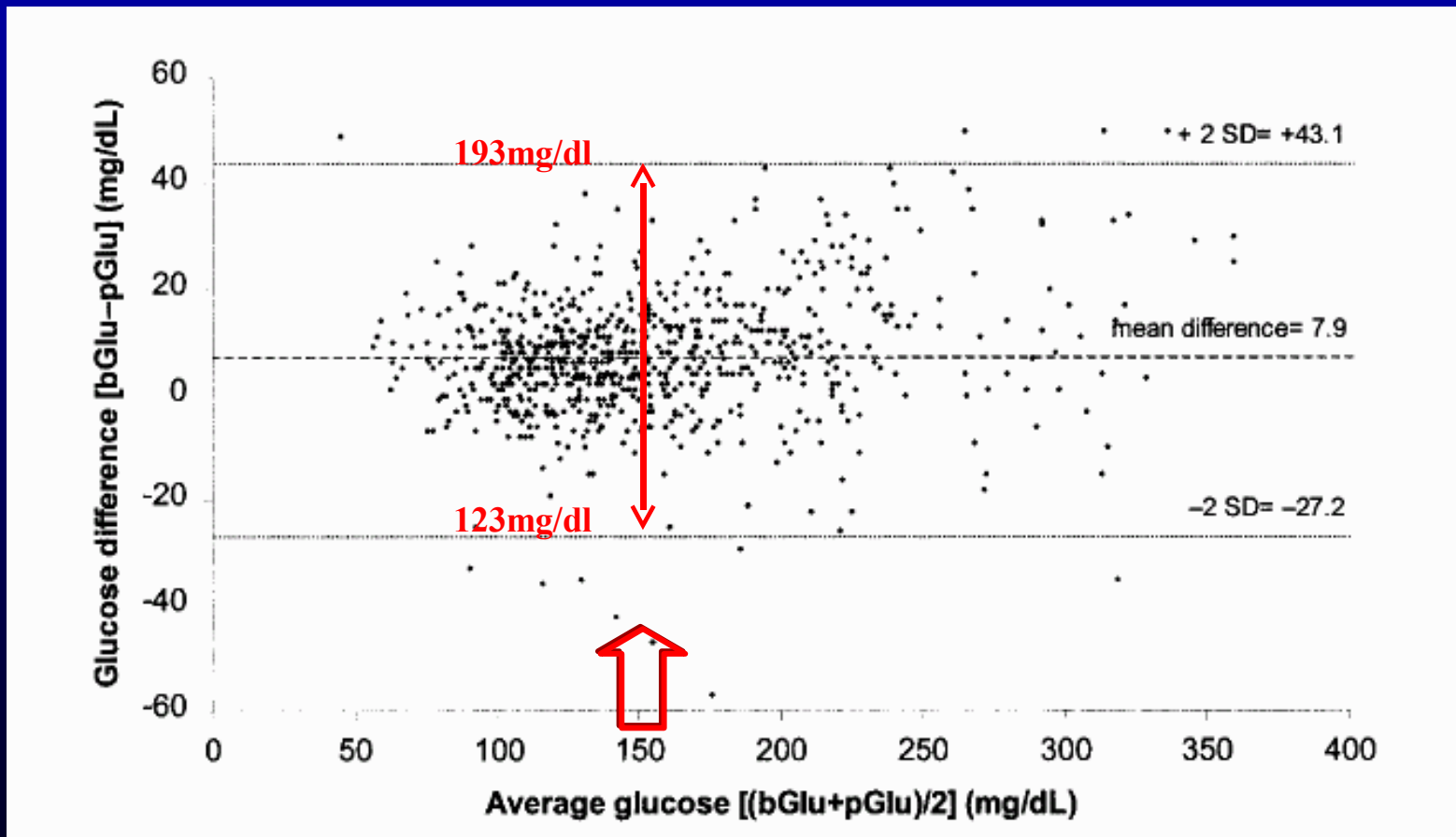
Critical Care R135; 2006

Key messages

- ***The turnaround*** time for glucose determinations by the central ***hospital laboratory is too long*** for fast adjustment of the insulin infusion dose as required in a glucose regulation protocol.
- The ICU-based blood gas/blood glucose analyser ***ABL715 is a rapid and accurate alternative for laboratory glucose*** determination and can serve as a standard for ICU blood glucose measurements.
- When implementing a glucose-insulin algorithm, one should realise that ***the absolute glucose level may differ systematically among various measuring methods***, influencing targeted glucose level

Agreement Between Bedside Blood and Plasma Glucose Measurement in the ICU Setting

Javier Daniel Finkelman CHEST 127; 2005



Conclusions: On average, bGlu provides a reasonable estimate for pGlu. However, for the individual patient, bGlu gives an unreliable estimate for pGlu

Blutzuckereinstellung basierend auf derzeit publizierten Infusionsprotokollen

- An 30 kardiochirurgischen Patienten wurden bis zu 48h post. Op an 3 Zentren mittels unterschiedlicher Insulininfusionsprotokolle die Blutzuckerwerte auf einen Zielwert von 80-110mg/dl titriert.
- Die Blutzuckermessung erfolgte *stündlich* aus arteriellem Blut

Protokolle



Simple sliding scale (SSS)



Complex sliding scale (CSS)



Dynamic scale (DS)

Einfaches Insulininfusionsprotokoll

1. Application of insulin
 - a. Insulin infusion for all insulin dependent diabetic patients and TX-patients
 - b. Insulin bolus for all other patients
2. Preparation of insulin infusion
 - a. Standard concentration is 100 IU in 50 ml Voluven
 - b. Solution is stable for at the most 24 h
3. Frequency of measurement:
 - i. First measurement at admission
 - ii. At least six measurements per physician
 - iii. 60 minutes after each intervention
 - iv. 60 minutes after stop of glucose
4. Glucose target value
 - a. ICU: 4.4 – 6.1 mmol/l (below 6.6 mmol/l)
 - b. General ward: <11 mmol/l

FIXE DOSIS

5. Insulin Dosing Scheme
 - a. Insulin Infusion
 - i. $BG > 12,2$ mmol/l ($BG > 220$ mg/dl) 8 IU/h
 - ii. $8,3$ mmol/l $< BG < 12,2$ mmol/l (150 mg/dl $< BG < 220$ mg/dl) 6 IU/h
 - iii. $6,7$ mmol/l $< BG < 8,3$ mmol/l (120 mg/dl $< BG < 150$ mg/dl) 4 IU/h
 - iv. $3,3$ mmol/l $< BG < 4,4$ mmol/l (60 mg/dl $< BG < 80$ mg/dl) Insulin Stop
 - v. $3,3$ mmol/l $< BG$ (60 mg/dl $< BG$) Insulin Stop + 10 g Glucose (20%) IV
 - b. Insulin Bolus
 - i. $BG > 12,2$ mmol/l ($BG > 220$ mg/dl) 8 IU
 - ii. $8,3$ mmol/l $< BG < 12,2$ mmol/l (150 mg/dl $< BG < 220$ mg/dl) 6 IU
 - iii. $6,7$ mmol/l $< BG < 8,3$ mmol/l (120 mg/dl $< BG < 150$ mg/dl) 4 IU

Komplexeres Insulininfusionsprotokoll

BASIC STARTING DOSAGE:

Blood glucose	Bolus iv. insulin (IU)	Starting insulin infusion rate (ml/h)
6.5 – 7.9	0	1
8 – 9.9	5	1
10 – 12.9	7	2
13 – 15.9	10	3
16 – 19.9	13	4
20 or more	15	5

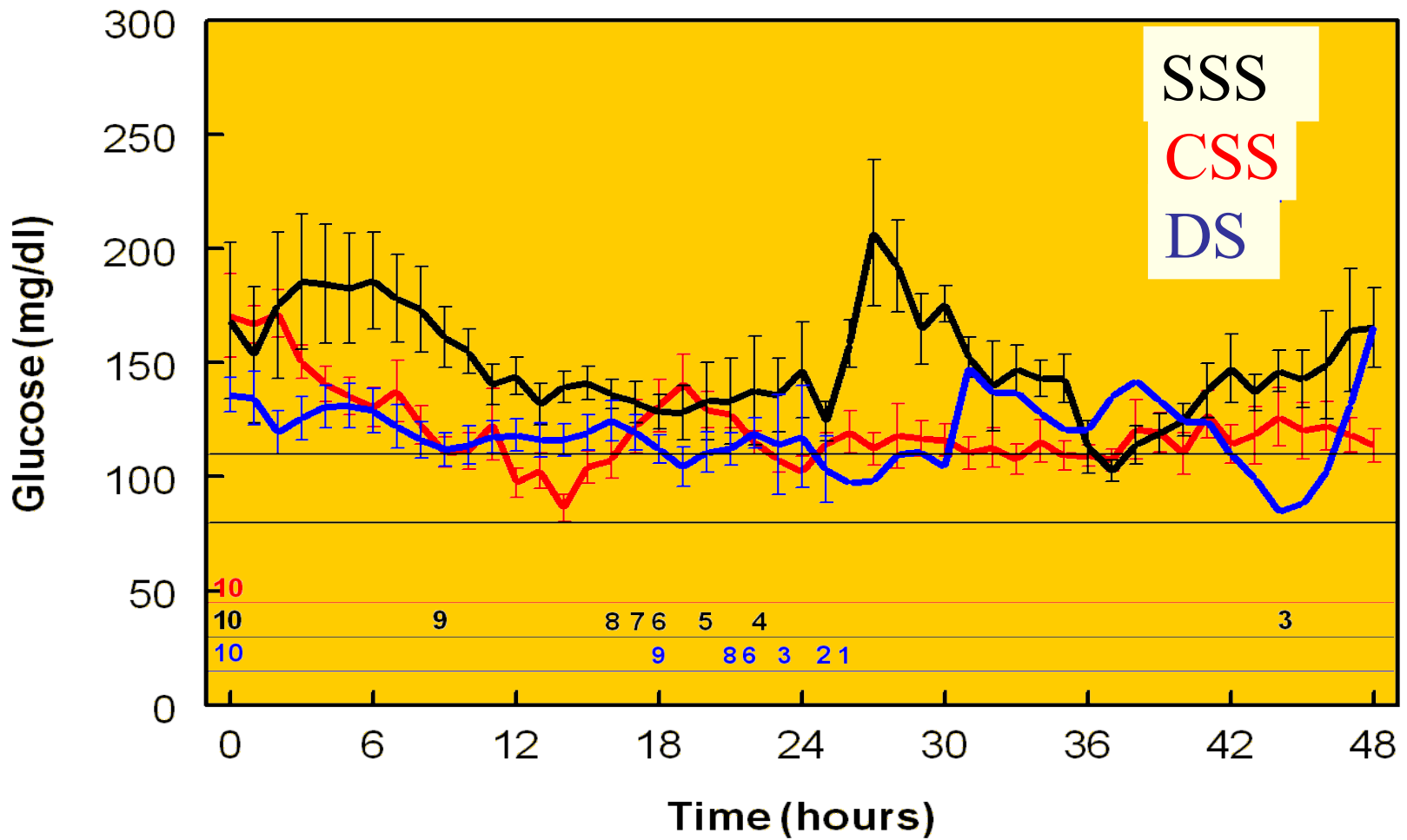
In 2 hours after start of insulin infusion check glycemia, if:

	Check
--	-------

Bolus & Infusion

5.1 – 5.9	Keep the same rate, if glycemia is stable in 2 following measurements, next level could be checked in 4 hours	2 hour
6.0 – 6.9	Increase by 0,5 ml/h	2 hour
7.0 – 7.9	Increase rate by 1 ml/h	2 hour
8.0 – 9.9	Increase rate by 2 ml/h	2 hour
10.0 – 12.9	Bolus 5 IU, increase rate by 3 ml/h	1 hour
13.0 – 15.9	Bolus 5 IU, increase rate by 4 ml/h	1 hour
16.0 – 19.9	Bolus 10 IU, increase rate by 5 ml/h	1 hour
>20.0	Bolus 15 IU, increase rate by 5 ml/h	1 hour

If blood glucose drops by more than 8 mmol/l between 2 following measurements decrease rate to half and call for ICU doctor

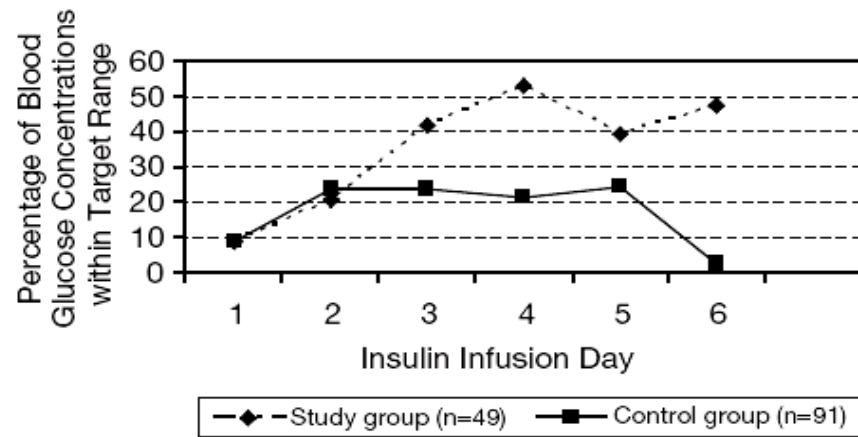
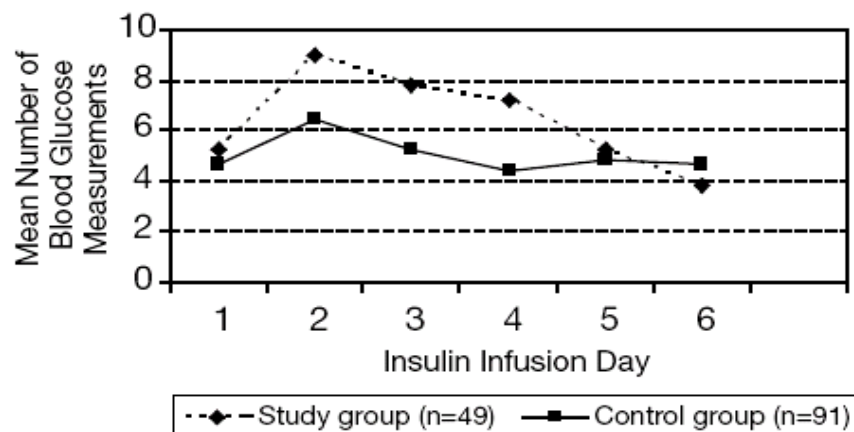


A Practical Approach to Hyperglycemia Management in the Intensive Care Unit: Evaluation of an Intensive Insulin Infusion Protocol

J.A. Qinn Pharmacotherapy 26; 2006

Protokoll wurde 2002 implementiert

4 Pilotstudien über ein Jahr vor Beginn der Studie !!



The median amount of *insulin infused on each day was 84 U in the protocol group (range 4–255.4 U) and 91 U in the control group (range 10.5–728 U).*

A Practical Approach to Hyperglycemia Management in the Intensive Care Unit: Evaluation of an Intensive Insulin Infusion Protocol

J.A. Quinn Pharmacotherapy 26;

Table 2. Safety and Effectiveness: Blood Glucose Data for Patients in the Control and Protocol Groups

Blood Glucose Parameter	Control Group (n=143)	Protocol Group (n=70)	p Value
Concentration at start of insulin infusion (mg/dl)			
Mean ± SD	348 ± 118	294 ± 86	0.001
Median (range)	356 (112–596)	286 (130–540)	—
Concentration while receiving insulin infusion (mg/dl)			
Mean ± SD	193 ± 46	170 ± 40	<0.001
Median (range)	184 (128–376)	161 (87–284)	—
Mean no. of hypoglycemic episodes/patient ^a	2.12	2.13	—
Concentrations relative to target range, no. (%) ^b			
Below	395 (7)	316 (8)	—
Within	1265 (23)	1287 (34)	<0.001
Above	3800 (70)	2159 (57)	—
Parameters after target reached			
Patients who reached target concentration, no. (%)	131 (92)	65 (93)	—
Time to reach target concentration (hrs)			
Mean ± SD	26.2 ± 29.2	21 ± 15.3	0.06
Median (range)	17.5 (3–214)	17.25 (2–56.5)	—
Concentrations maintained relative to target range, no. (%)			
Below	358 (9)	267 (9)	—
Within	1225 (29)	1265 (43)	<0.001
Above	2577 (62)	1347 (48)	—
No. of measurements/patient			
Mean ± SD	37 ± 40	54 ± 50	0.01
Median (range)	27 (4–279)	35 (3–291)	0.02

Effect of an Intensive Glucose Management Protocol on the Mortality of Critically Ill Adult Patients

Krinsley JS, Mayo Clin Proc 79; 2004

800 Patienten (medizinisch, chirurgisch, kardial)

Ziel: Blutzucker < 140 mg/dl

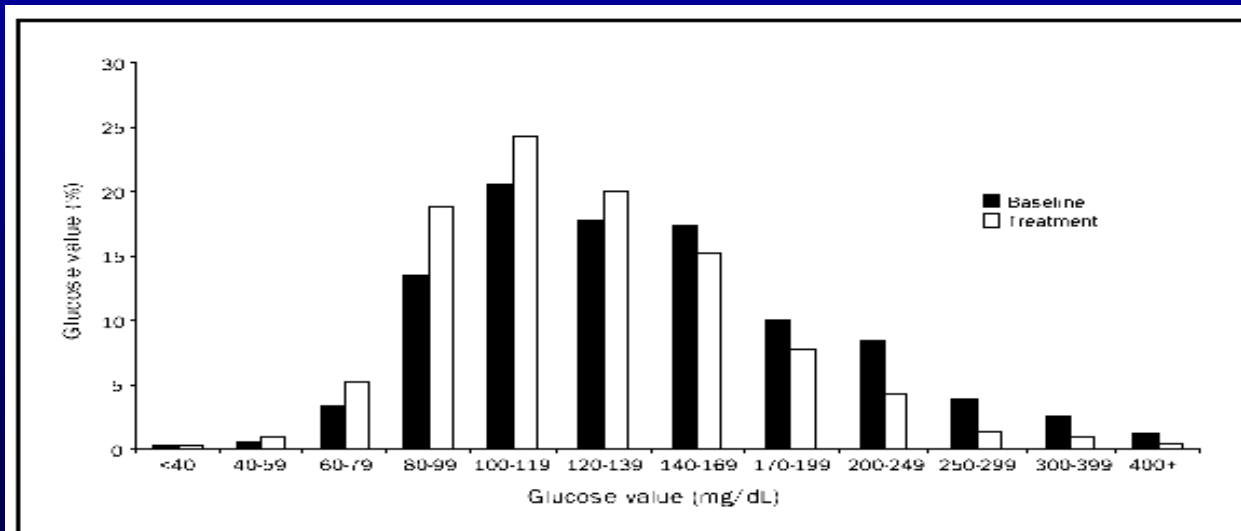


TABLE 6. Temporal Trends in Glucose Control

One-year period beginning	Mean (SD) glucose (mg/dL)	% Glucose values ≥ 200 mg/dL
February 2000	154.7 (85.9)	18.8
February 2001	152.9 (78.8)	19.1
February 2002	152.5 (93.2)	16.4
February 2003	130.7 (55.1)	7.3

Implementierung von Insulininfusionsprotokollen bei kritisch kranken Patienten

Resümee aus vorliegenden Studien

✓ **Zielwert der Blutglukose (80-130-144mg/dl) in \leq 50% aller Glukosekonzentrationen**

Kanji Intensive Care Med 2004

Chant Pharmacotherapy 2005

Krinsley Mayo Clin Proc 2004

Goldberg Diabetes Care 2004

Gonzales Critical Care Congress Phoenix 2005

✓ **Ausführliche Schulungen des Pflegepersonals in der Handhabung der Protokolle notwendig**

✓ **Unterschiedliche Triggerwerte als Start einer Insulintherapie**

✓ **Unterschiedliche Zielwerte**

Schlußfolgerung aus bisherigen Studien

*Blutzuckereinstellung trotz hohem Arbeitsaufwand
des Pflegepersonals ungenügend*

Gründe:

- ☹ Angst vor Hypoglykämien
- ☹ Hohe Variabilität der Insulinsensitivität
- ☹ Änderungen der Ernährungstherapie
- ☹ Intuitive Entscheidungen und Verantwortung erforderlich
- ☹ Ergebnisse im entscheidenden Maße abhängig vom Pflegepersonal
- ☹ Protokolle nicht konsequent befolgt

Efficacy and Safety of an Insulin Infusion Protocol in a Surgical ICU

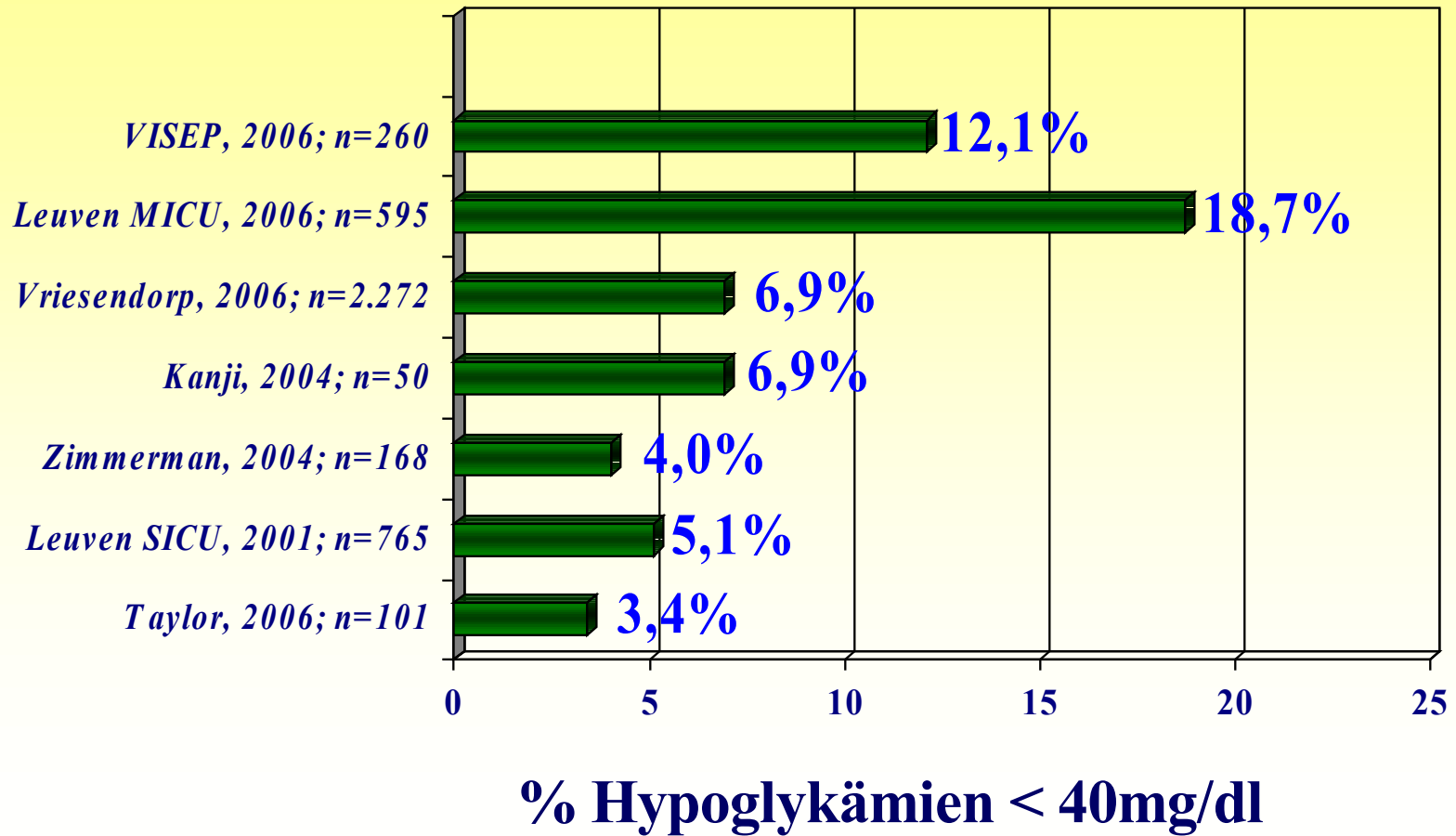
B. E Taylor J Am Coll Surg 2002; 2006

Table 1. Definition of Minor and Major Protocol Deviations

Minor deviations	Major deviations
BG check missed $\times 1$	BG check missed 2 or more consecutive times
Failure to give IVP	Insulin titration missed or done incorrectly 2 or more consecutive times
Incorrect IVP amount given	Insulin infusion not turned off to protocol
Insulin titration missed or done incorrectly $\times 1$	Insulin infusion restarted > 2 hours late
Insulin infusion restarted ≤ 2 hours late	Titration of insulin infusion not adjusted to q 3 hours for creatinine ≥ 1.5 mg/dL
Insulin infusion off for OR	No D5, TF, or TPN running
BG in "call House Officer" range and no intervention done or documented	Insulin infusion off for unknown reason

BG, blood glucose; IVP, intravenous push; OR, operating room; TF, tube feeding; TPN, total parenteral nutrition.

Hypoglykämierate aus verschiedenen Studien



Ursachen und Risiken für das Auftreten einer Hypoglykämie

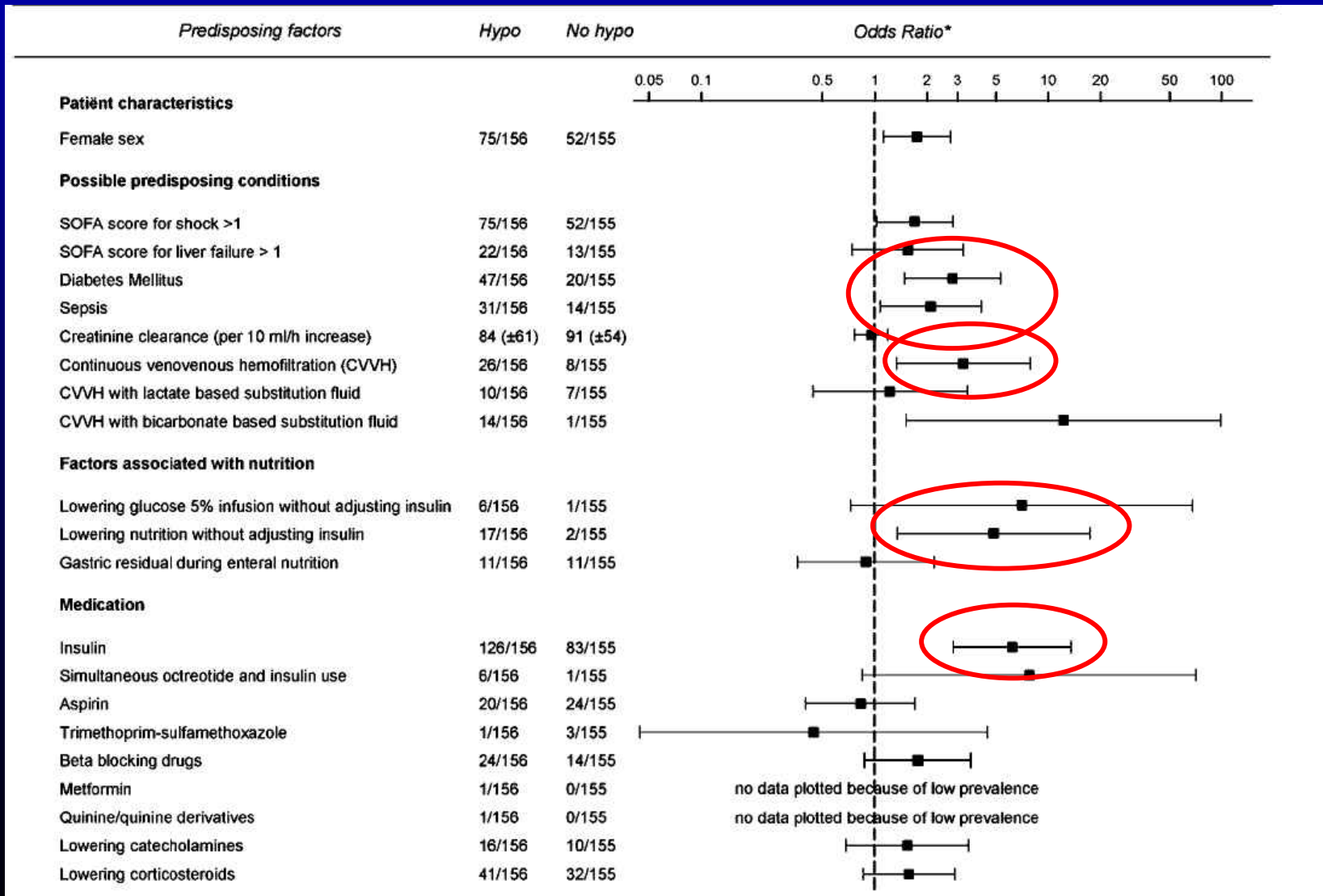
- 👉 Plötzliche Nahrungskarenz oder Reduzierung der Nährstoffzufuhr
- 👉 Absetzen der enteralen Ernährung
- 👉 Absetzen der parenteralen Ernährung oder Glukoseinfusionen
- 👉 Applikation von Insulin ohne nachfolgende Nahrungsaufnahme
- 👉 Transfer von der Intensivstation nach kurzzeitigem Absetzen der Insulininfusion oder eines zuvor applizierten kurzwirksamen Insulin
- 👉 Reduzierung einer Kortisontherapie

Weitere Faktoren, die eine Hypoglykämie begünstigen

- ☹️ Herzversagen
- ☹️ Nieren- und Leberversagen
- ☹️ Maligne Erkrankungen
- ☹️ Infektion
- ☹️ Sepsis

Predisposing factors for hypoglycemia in the intensive care unit

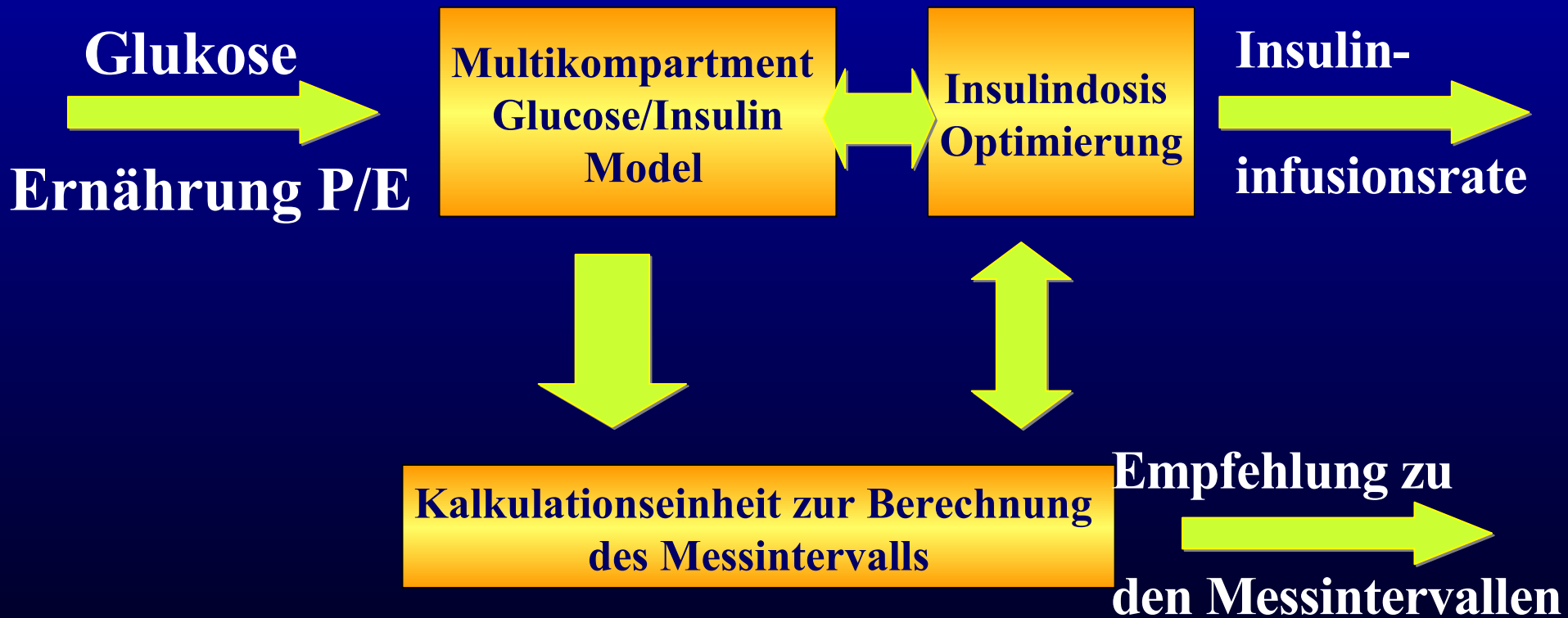
T. M. Vriesendorp CCM 34; 2006



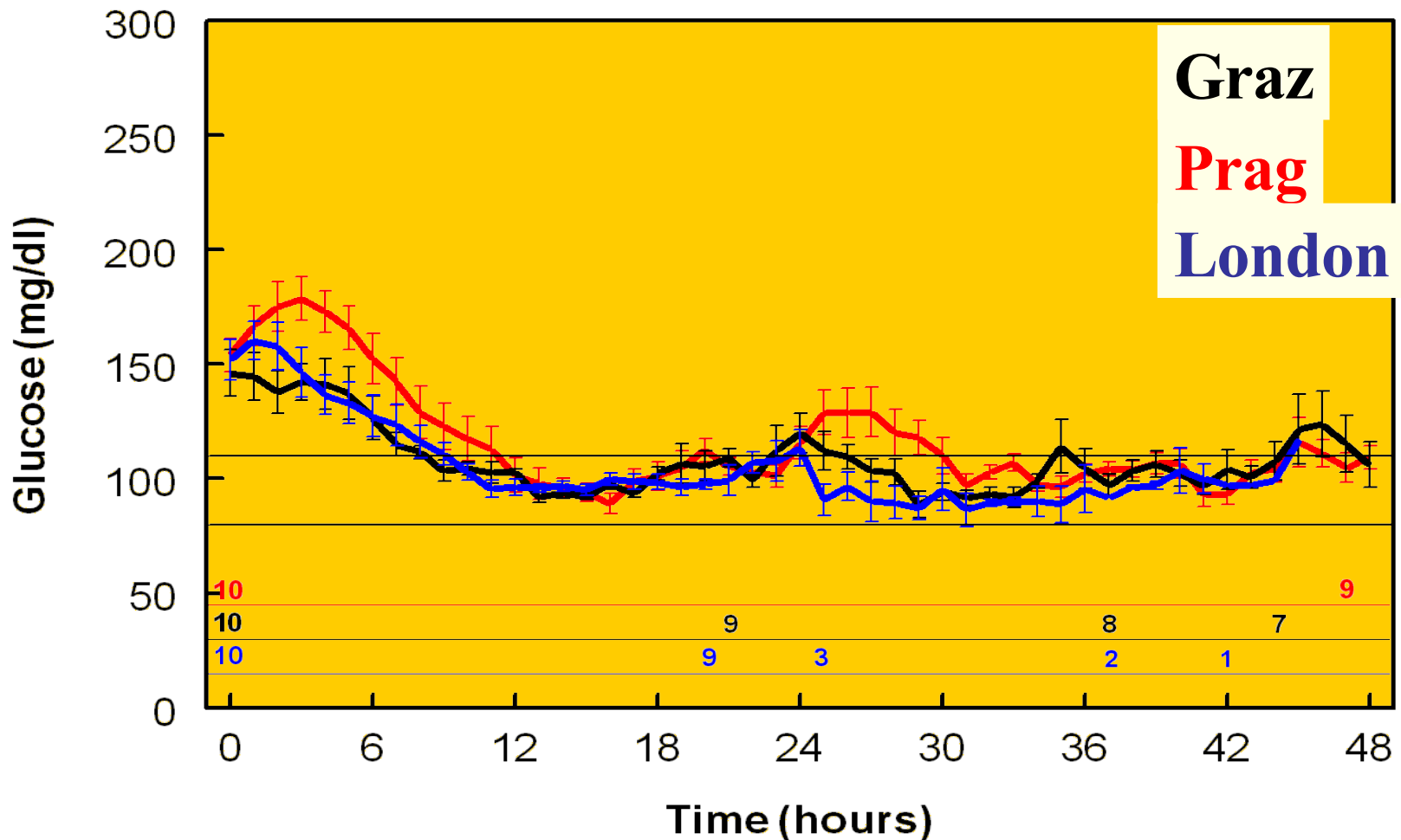
Blutzuckereinstellung basierend auf einem multimodalen Computerprogramm

- An 30 kardiochirurgischen Patienten wurden bis zu 48h post. Op an 3 Zentren basierend auf einem computergestützten Algorithmus die Blutzuckereinstellungen (MPC) durchgeführt.
- Die Blutzuckermessung erfolgte *stündlich* aus dem arteriellen Blut
- Frage:
Ist die Blutzuckereinstellung mittels MPC Algorithmus ohne intuitive Entscheidungen möglich

- **Model Predictive Control (MPC)**

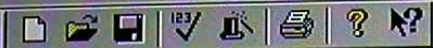


Blutzuckereinstellung basierend auf einem multimodalen Computerprogramm



Ergebniss:

- ☺ **Sicher – keine Hypos**
- ☺ **Effektiv – 52% lagen innerhalb des Zielwertes (80-110 mg/dl)**
- ☺ **Automatisch – keine intuitive Entscheidung erforderlich**
- ☺ **Leicht zu implementieren – minimale Einschulung notwendig**
- ☺ **Keine Interferenz mit dem enteralen /parenteralen Ernährungsprotokoll**
- ☹ **Stündliche Messung**



DW 234 75 kg ID



Blood glucose (mg/dl)

09/09/2006 07:46	139
09/09/2006 08:46	138
09/09/2006 09:47	113
09/09/2006 10:54	110
09/09/2006 13:20	149
09/09/2006 15:38	132
09/09/2006 17:39	127
09/09/2006 21:47	91
10/09/2006 01:56	111

Parenteral glucose infusion (g/h)

09/09/2006 11:33	6,6
09/09/2006 13:20	6,6
09/09/2006 15:38	6,6
09/09/2006 17:39	6,6
09/09/2006 19:14	6,6
09/09/2006 21:47	6,6
09/09/2006 21:50	6,6
10/09/2006 01:03	6,6
10/09/2006 01:56	6,6

Enteral glucose infusion (g/h)

09/09/2006 19:14	0,8
09/09/2006 21:47	0,8
09/09/2006 21:50	0,8
10/09/2006 01:03	0,8
10/09/2006 01:56	0,8
10/09/2006 04:53	0,8
10/09/2006 06:05	0,0
10/09/2006 10:22	0,8
10/09/2006 11:03	0,8

Insulin infusion (U/h)

10/09/2006 01:56	6,7
10/09/2006 04:54	6,7
10/09/2006 06:06	6,7
10/09/2006 08:58	7,9
10/09/2006 10:22	7,3
10/09/2006 11:03	7,8
10/09/2006 12:55	7,8
10/09/2006 17:02	7,8
10/09/2006 21:36	8,7

Suggested measurement in

230

Parenteral glucose bolus (g)

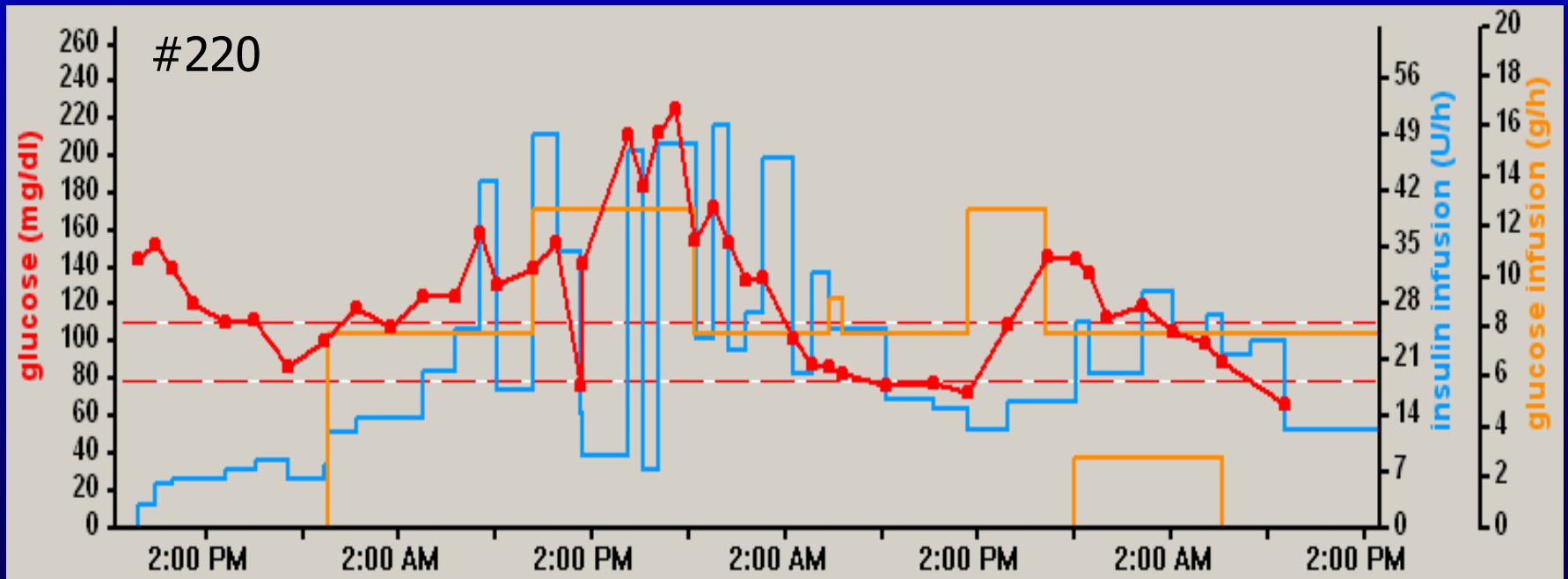
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Enteral glucose bolus (g)

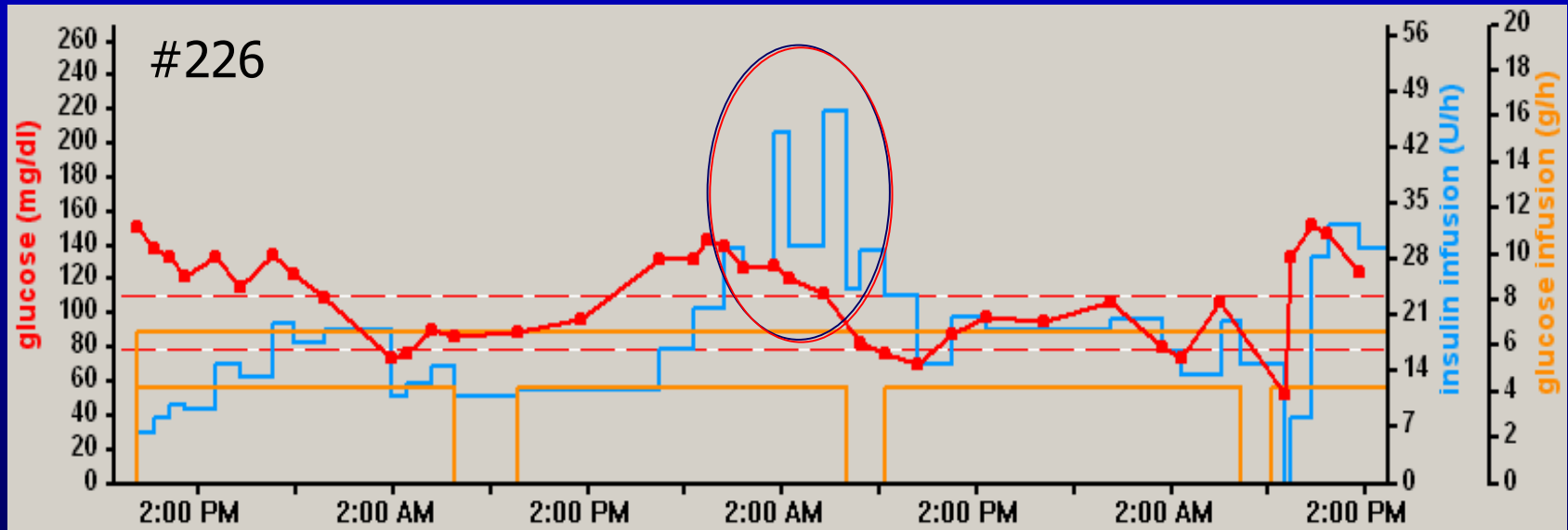
Add

Insulin bolus (U)

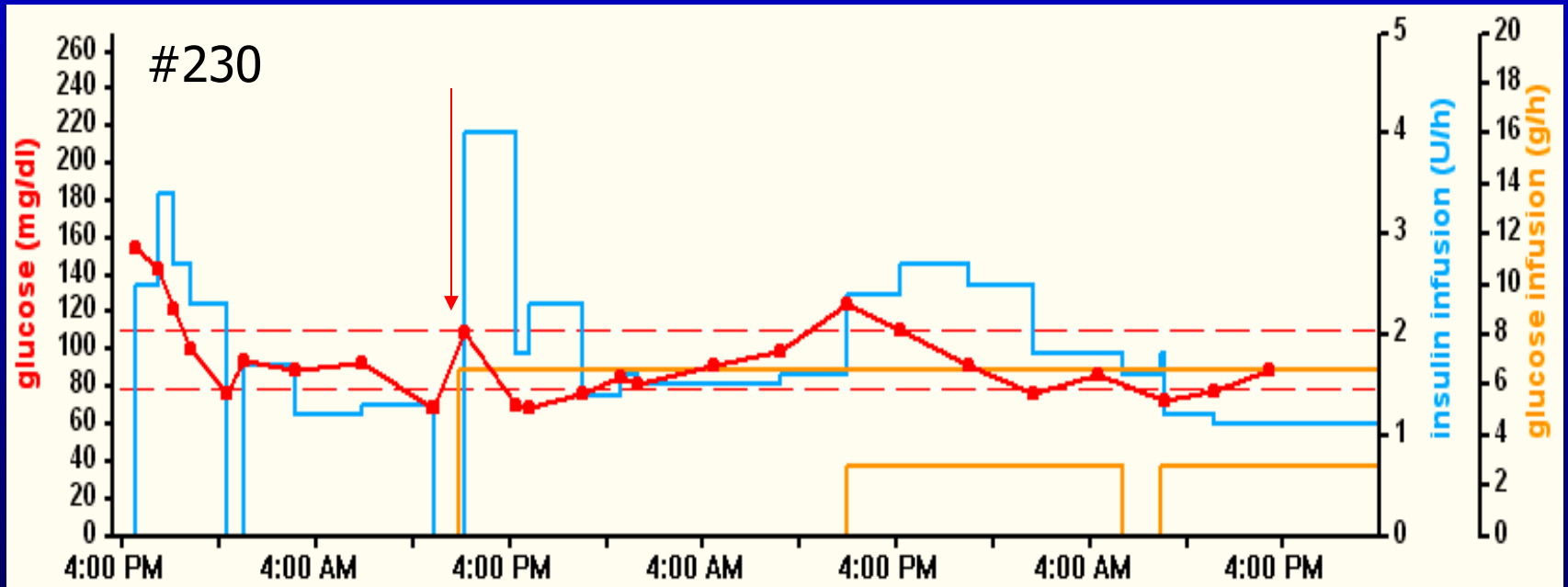
Add



- Pat. 78a, männlich
- Massive PAE, sek. Pneumonie, beatmet



- Männlich, 53 Jahre
- intrazerebral Hämatom
- Apache Score: 25



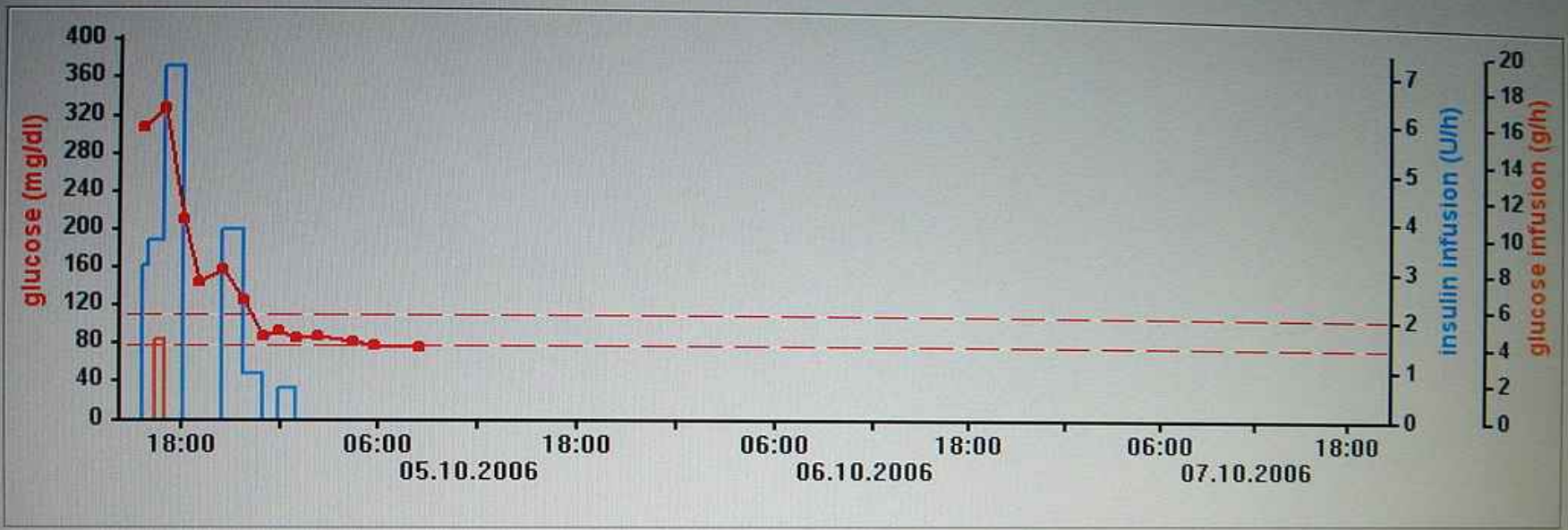
- Weiblich, 68 Jahre
- Grand-mal Anfall, sek. Asystolie
- Apache Score: 23



241 BA

85 kg

ID



Blood glucose (mg/dl)

04/10/2006	15:40	307
04/10/2006	16:57	328
04/10/2006	18:08	211
04/10/2006	19:07	145
04/10/2006	20:32	158
04/10/2006	21:49	126
04/10/2006	22:59	89
04/10/2006	23:54	94
05/10/2006	00:57	86

Parenteral glucose infusion (g/h)

Add

Enteral glucose infusion (g/h)

04/10/2006	16:23	4.2
04/10/2006	16:57	0.0

Add

Insulin infusion (U/h)

04/10/2006	18:08	0.0
04/10/2006	19:08	0.0
04/10/2006	20:32	3.7
04/10/2006	21:49	0.9
04/10/2006	22:59	0.0
04/10/2006	23:55	0.6
05/10/2006	00:57	0.0
05/10/2006	02:15	0.0
05/10/2006	04:27	0.0

Suggested measurement in

0.36

Parenteral glucose bolus (g)

Add

Enteral glucose bolus (g)

Add

Insulin bolus (U)

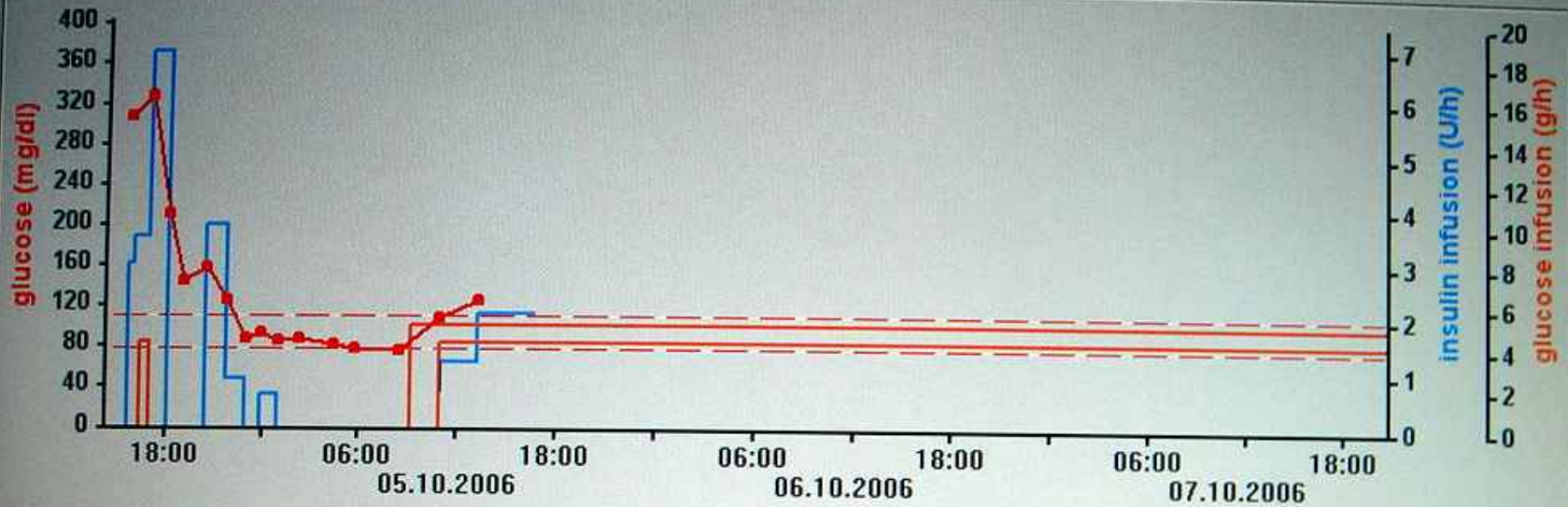
Add



241 BA

85 kg

ID



Blood glucose (mg/dl)

04/10/2006 15:40	307
04/10/2006 16:57	328
04/10/2006 18:08	211
04/10/2006 19:07	145
04/10/2006 20:32	158
04/10/2006 21:49	126
04/10/2006 22:59	89
04/10/2006 23:54	94
05/10/2006 00:57	86

Parenteral glucose infusion (g/h)

05/10/2006 09:10	5.0
05/10/2006 13:14	5.0
Add	

Enteral glucose infusion (g/h)

04/10/2006 16:23	4.2
04/10/2006 16:57	0.0
05/10/2006 10:56	4.2
05/10/2006 13:14	4.2
Add	

Insulin infusion (U/h)

04/10/2006 15:40	3.0
04/10/2006 16:02	3.5
04/10/2006 16:57	6.9
04/10/2006 18:08	0.0
04/10/2006 19:08	0.0
04/10/2006 20:32	3.7
04/10/2006 21:49	0.9
04/10/2006 22:59	0.0
04/10/2006 23:55	0.6

Suggested measurement in

120

Parenteral glucose bolus (g)

Add

Enteral glucose bolus (g)

Add

Insulin bolus (U)

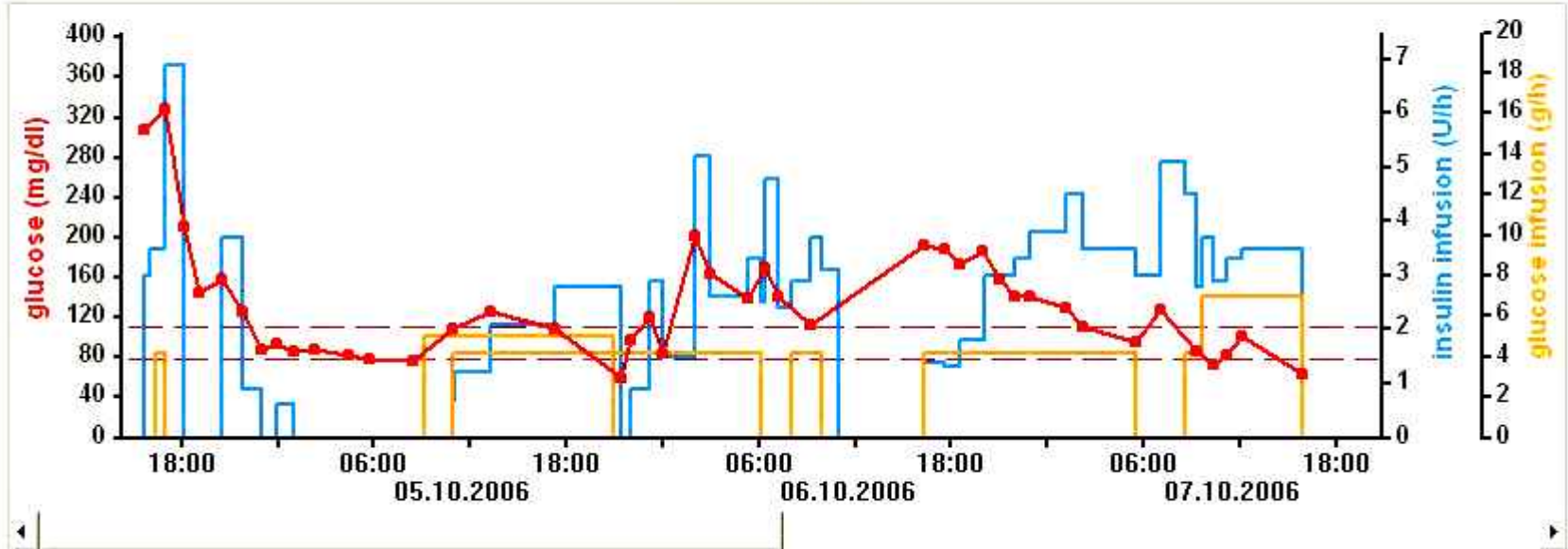
Add



241 BA

85 kg

ID



Blood glucose (mg/dl)

07/10/2006 02:10	110
07/10/2006 05:28	96
07/10/2006 07:06	128
07/10/2006 09:16	87
07/10/2006 10:20	73
07/10/2006 11:14	82
07/10/2006 12:08	101
07/10/2006 15:57	63
Add	

Parenteral glucose infusion (g/h)

05/10/2006 09:10	5.0
05/10/2006 13:14	5.0
05/10/2006 17:15	5.0
05/10/2006 20:53	0.0
Add	

Enteral glucose infusion (g/h)

07/10/2006 08:34	4.2
07/10/2006 09:16	4.2
07/10/2006 09:39	7.0
07/10/2006 10:20	7.0
07/10/2006 11:14	7.0
07/10/2006 12:08	7.0
07/10/2006 15:57	7.0
07/10/2006 15:57	0.0
Add	

Insulin infusion (U/h)

07/10/2006 08:34	4.5
07/10/2006 09:16	2.8
07/10/2006 09:39	3.7
07/10/2006 10:20	2.9
07/10/2006 11:14	3.3
07/10/2006 12:08	3.5
07/10/2006 15:57	1.7
07/10/2006 15:57	0.0
Add	

Suggested measurement in

159

Parenteral glucose bolus (g)

Add

Enteral glucose bolus (g)

Add

Insulin bolus (U)

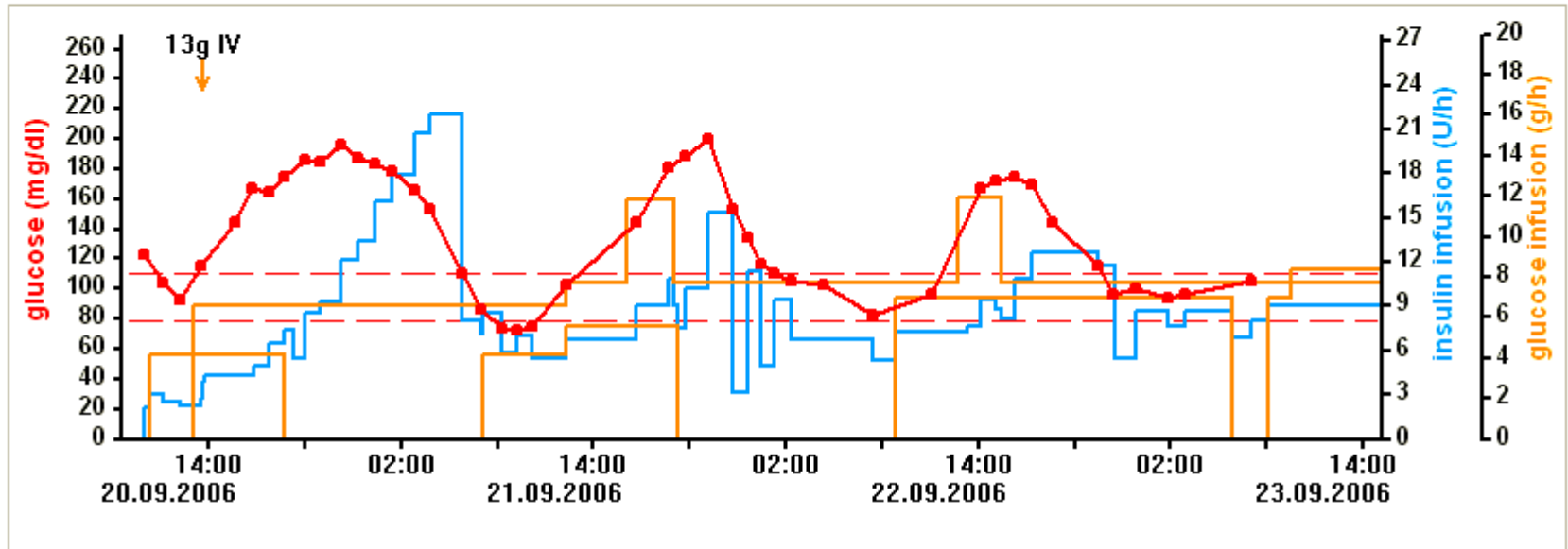
Add



236 SW

82 kg

ID



Blood glucose (mg/dl)

22/09/2006 17:19	170
22/09/2006 18:34	145
22/09/2006 21:28	116
22/09/2006 22:27	97
22/09/2006 23:49	100
23/09/2006 01:51	94
23/09/2006 02:53	97
23/09/2006 06:58	106

Add

Parenteral glucose infusion (g/h)

22/09/2006 21:28	7,7
22/09/2006 22:27	7,7
22/09/2006 23:49	7,7
23/09/2006 01:51	7,7
23/09/2006 02:53	7,7
23/09/2006 05:12	7,7
23/09/2006 05:52	7,7
23/09/2006 06:58	7,7

Add

Enteral glucose infusion (g/h)

22/09/2006 22:27	7,0
22/09/2006 23:49	7,0
23/09/2006 01:51	7,0
23/09/2006 02:53	7,0
23/09/2006 05:12	7,0
23/09/2006 05:52	0,0
23/09/2006 08:08	7,0
23/09/2006 09:32	8,4

Add

Insulin infusion (U/h)

22/09/2006 23:49	8,7
23/09/2006 01:51	7,6
23/09/2006 02:54	8,7
23/09/2006 05:12	8,7
23/09/2006 05:52	6,9
23/09/2006 06:58	8,0
23/09/2006 08:08	9,1
23/09/2006 09:32	9,1

Add

Suggested measurement in

0:00

Parenteral glucose bolus (g)

20/09/2006 13:46	13
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Add

Enteral glucose bolus (g)

Add

Insulin bolus (U)

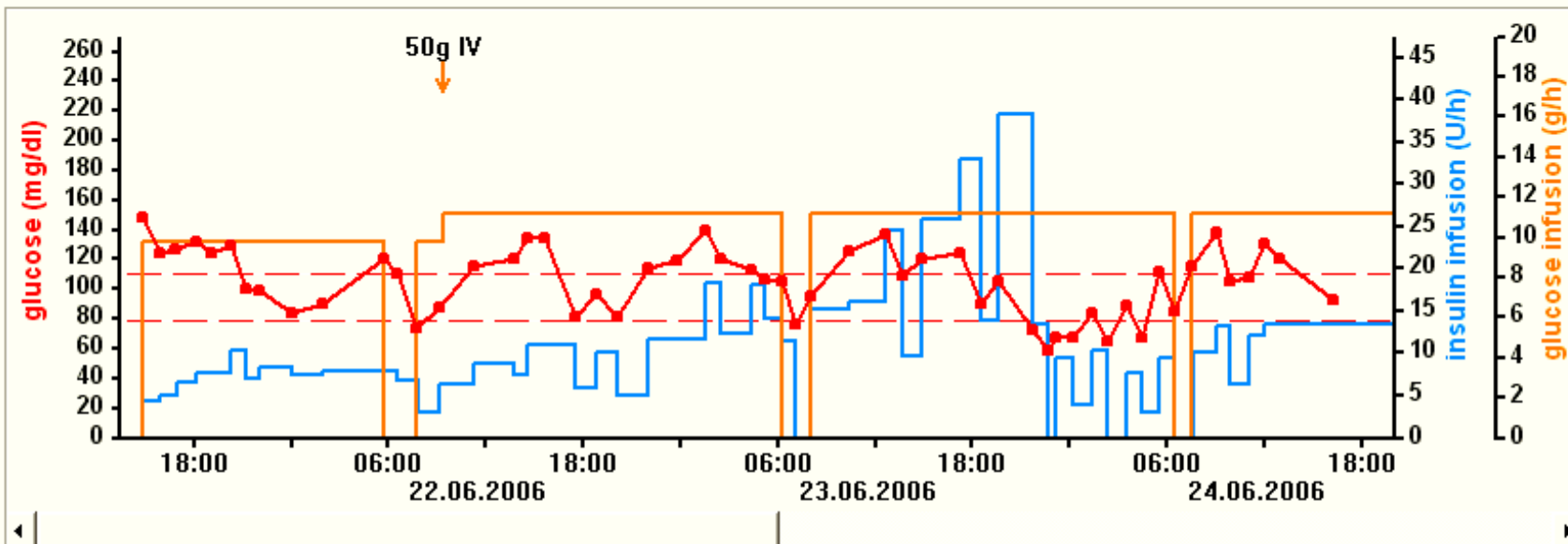
Add



203 FR

110 kg

ID



Blood glucose (mg/dl)

24/06/2006 06:28	85	▲
24/06/2006 07:34	115	
24/06/2006 09:02	138	
24/06/2006 09:55	106	
24/06/2006 11:01	108	
24/06/2006 12:00	131	
24/06/2006 12:56	120	
24/06/2006 16:13	93	▼
Add		▼

Parenteral glucose infusion (g/h)

Add

Enteral glucose infusion (g/h)

24/06/2006 06:28	0,0	▲
24/06/2006 07:34	11,2	
24/06/2006 09:02	11,2	
24/06/2006 09:55	11,2	
24/06/2006 11:01	11,2	
24/06/2006 12:00	11,2	
24/06/2006 12:56	11,2	
24/06/2006 16:13	11,2	▼
Add		▼

Insulin infusion (U/h)

24/06/2006 06:55	0,0	▲
24/06/2006 07:36	10,0	
24/06/2006 09:02	13,1	
24/06/2006 09:55	6,4	
24/06/2006 11:02	12,1	
24/06/2006 12:01	13,5	
24/06/2006 12:57	13,5	
24/06/2006 16:13	13,5	▼
Add		▼

Suggested measurement in

9.59

Parenteral glucose bolus (g)

22/06/2006 09:30	50
Add	

Enteral glucose bolus (g)

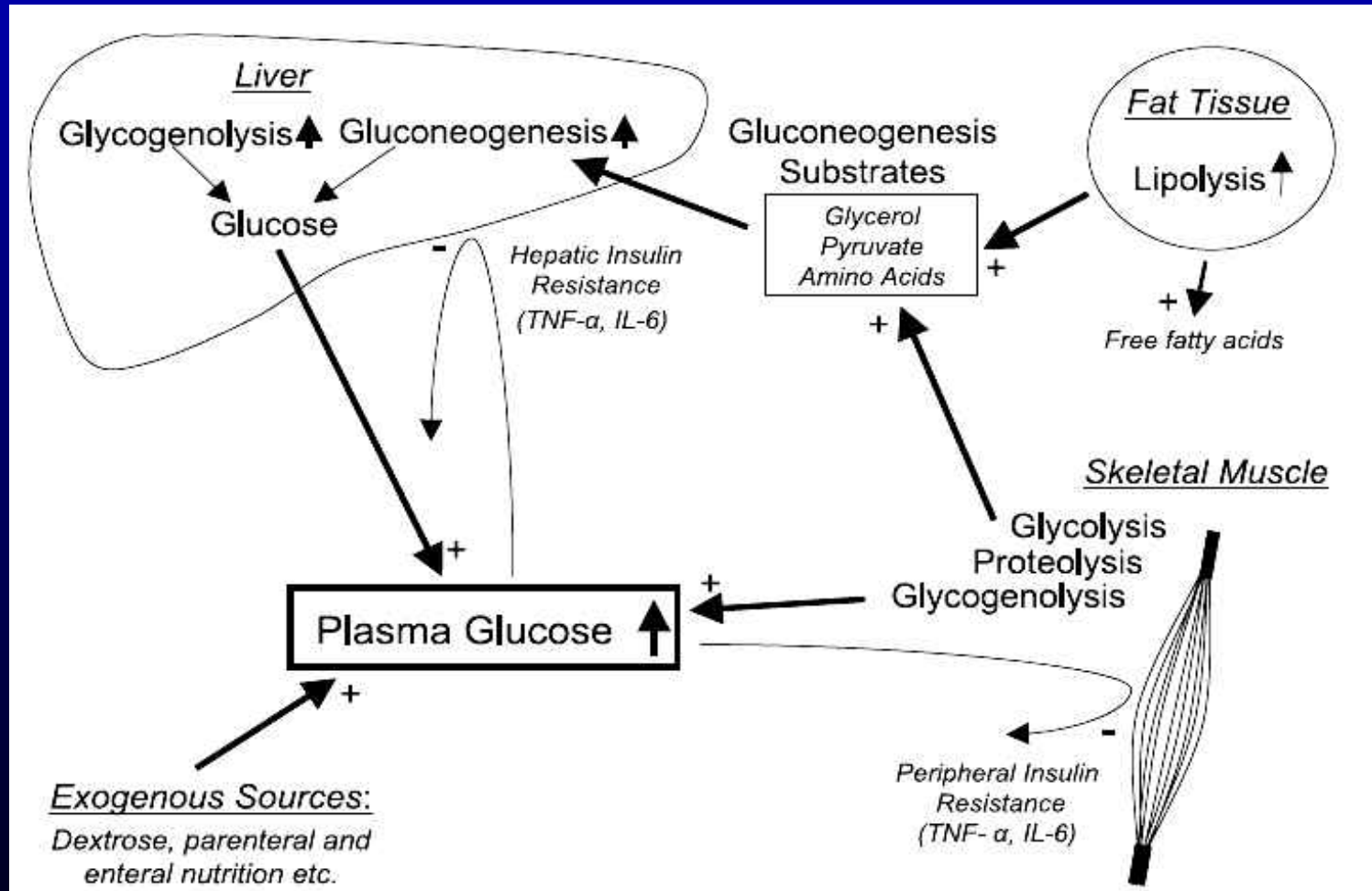
Add

Insulin bolus (U)

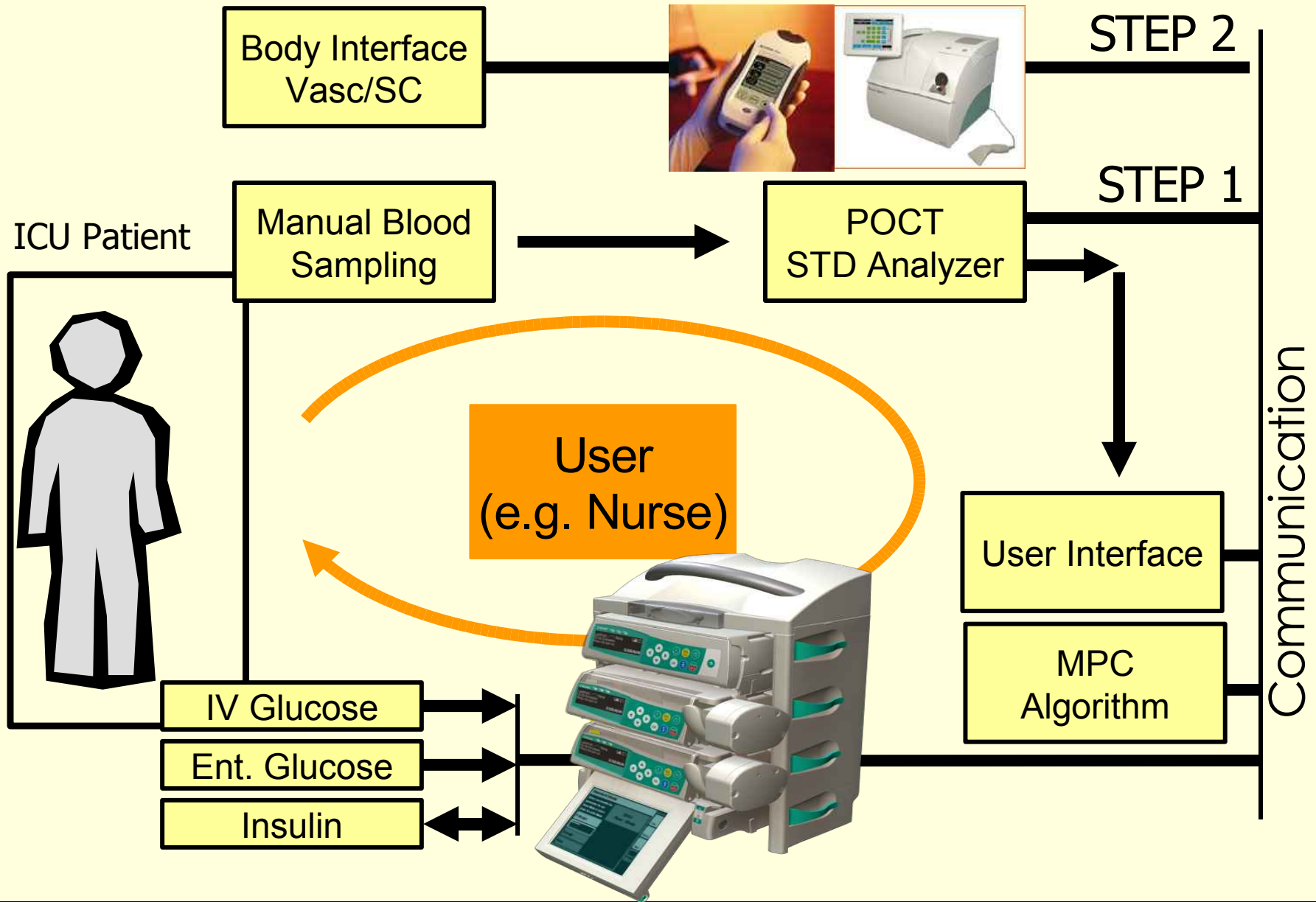
Add

Diabetes and Hyperglycemia: Strict glycemc control

M. Turina CCM 34; 2006



CLINICIP Approach



Fragen, die zur Diskussion stehen

- ☹️ Welche Blutzucker(BZ)-messung sollte als Standard gelten?
- ☹️ Welcher Aufwand an BZ-Messungen ist dem Pflegepersonal zumutbar?
- ☹️ Ist nur um Hypoglykämien zu vermeiden eine weniger stringente BZ-Einstellung gerechtfertigt?
- ☹️ Sind möglicherweise die statischen und dynamischen Insulininfusionsprotokolle hinsichtlich einer Vermeidung von Hypoglykämien zu überdenken?
- ☹️ Wie häufig tritt unter einer strikten BZ-Einstellung eine Hypokaliämie, -magnesiämie, -phosphatämie auf?