Management bei Diabetesmanifestation und metabolischen Entgleisungen

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Kompetenznetz Diabetes mellitus

kidsap

Typ 1 Diabetes Epidemiologie in Europa

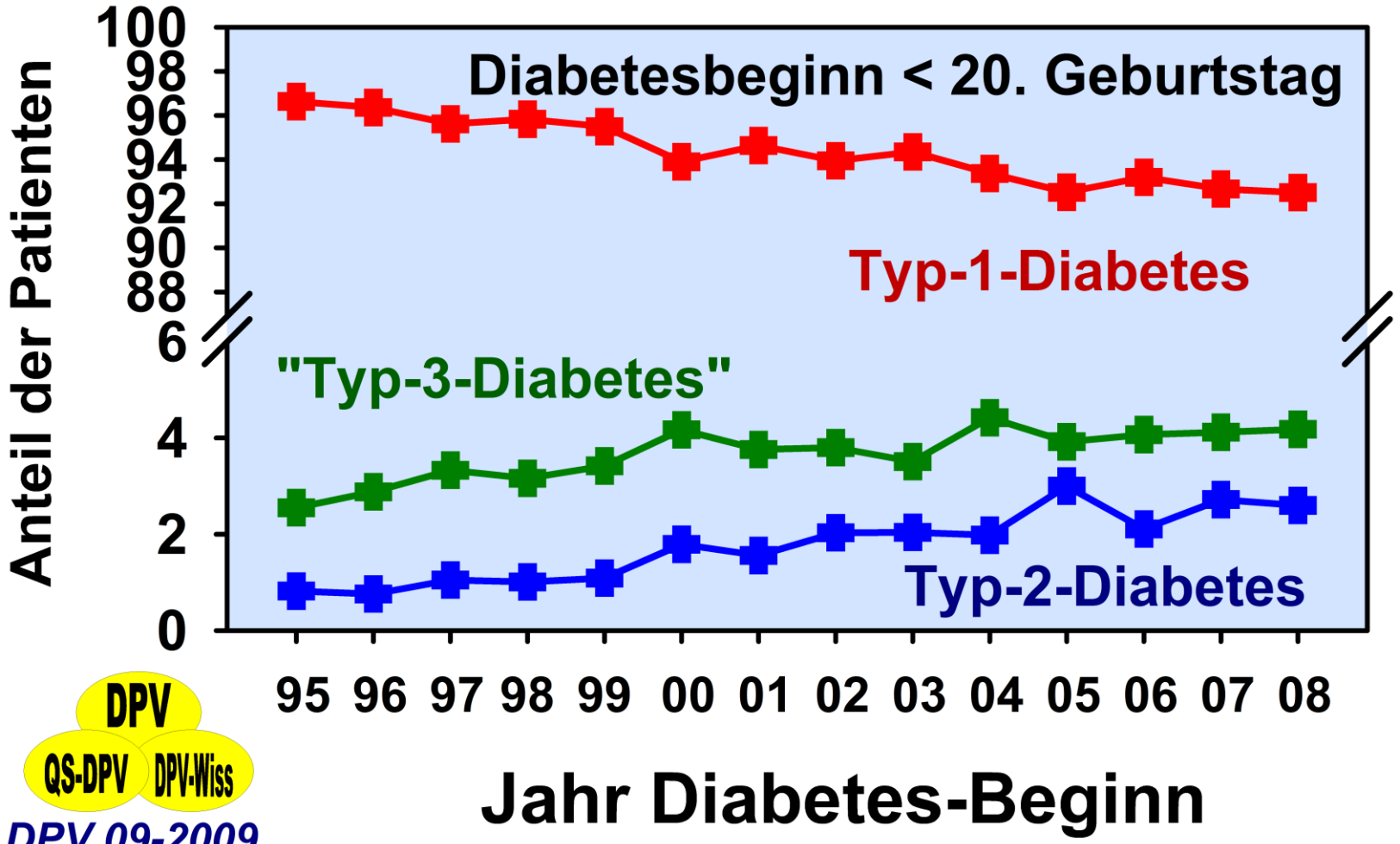
Der jährliche Inzidenzanstieg beträgt in europäischen Kinder- Diabetesregistern 3,9%.

0-4 Jahre:	5,4%
5-9 Jahre:	4,3%
10-15 Jahre:	2,9%

Neue Fälle 2005:	15.000/Jahr
Voraussage 2020:	24.400/Jahr

D.h. die Prävalenz von Kindern und Jugendlichen mit Typ 1 Diabetes steigt in 2020 um 70% auf etwa 160.000 in Europa

Diabetes-Typ nach Manifestationsjahr



DPV
QS-DPV DPV-Wiss

DPV 09-2009

Diabetestypen DPV

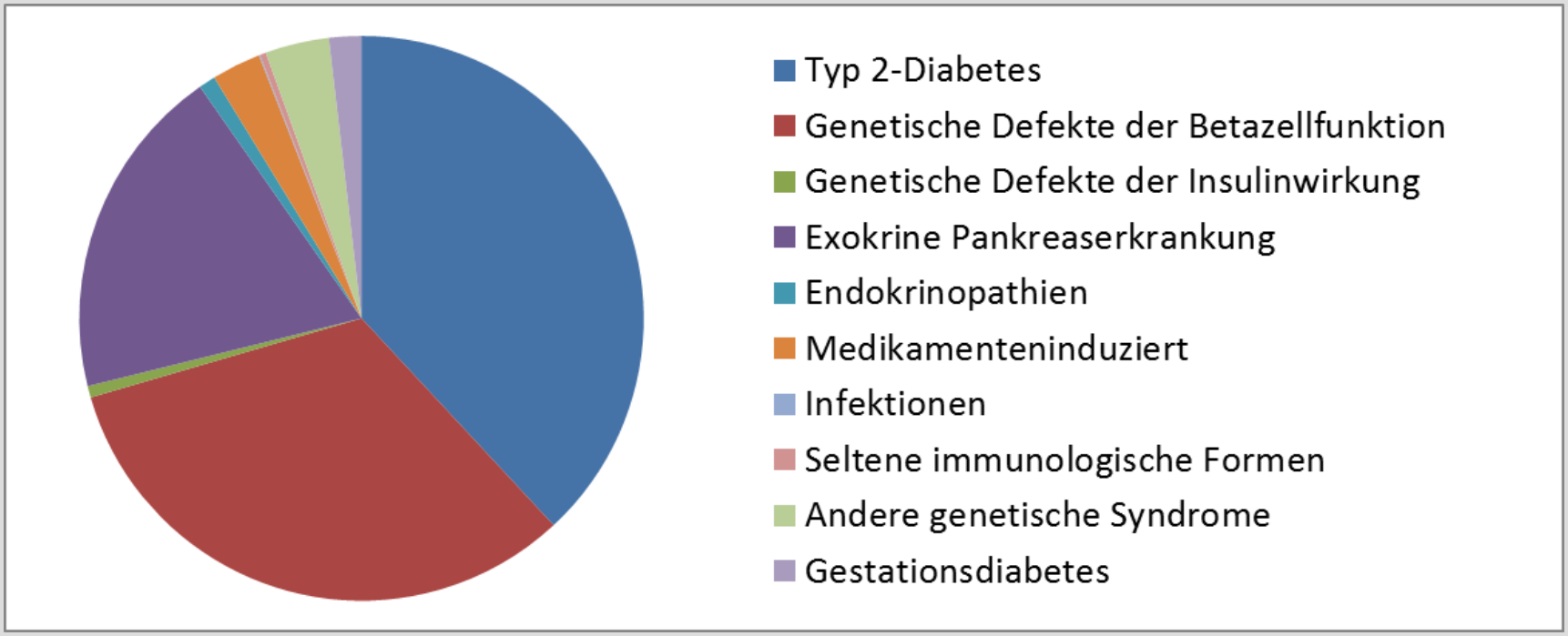


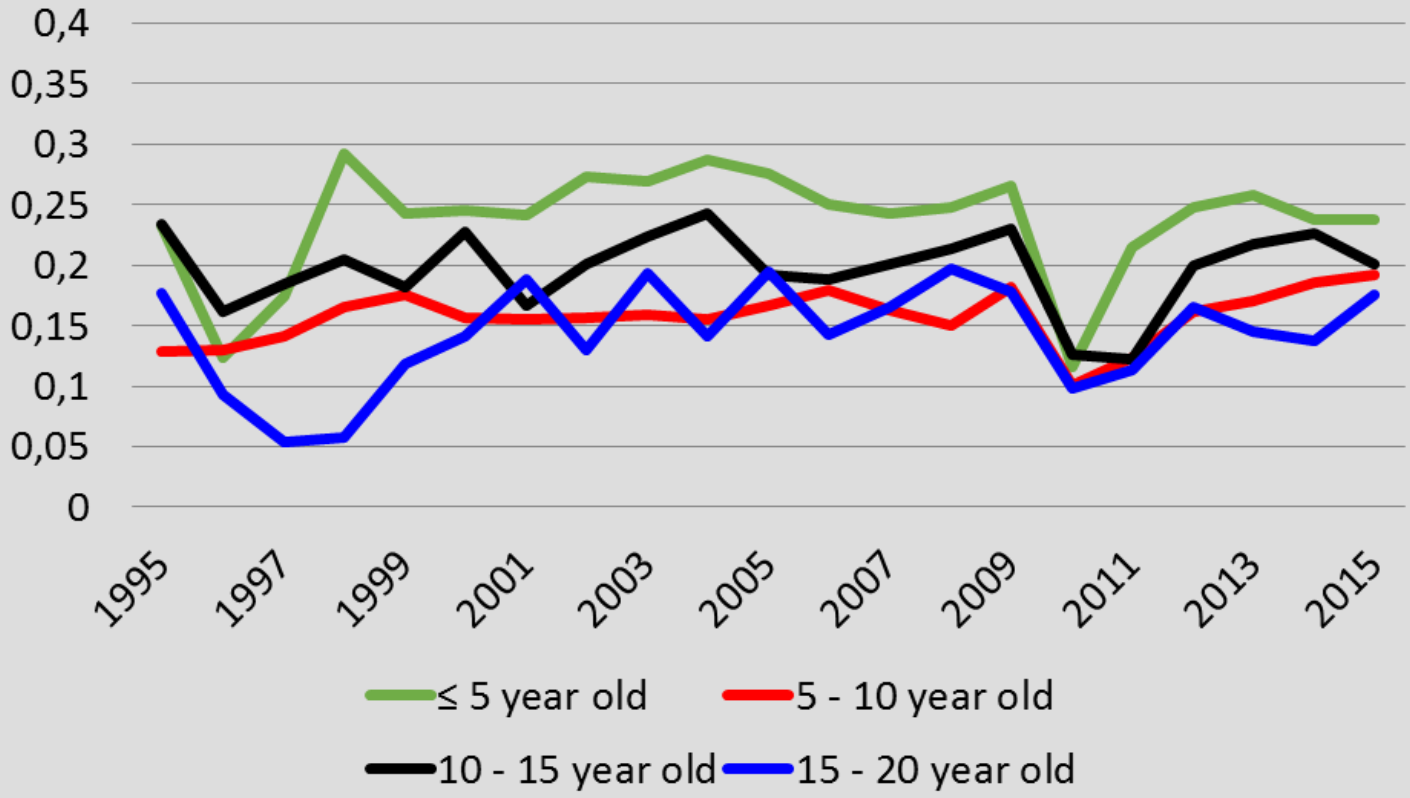
Abb. 1B: Diabetesformen ohne Typ 1 Diabetes in der DPV-Kohorte (n=1663)

Meissner et al Med. Welt 2012

Epidemiologie: DKA bei Manifestation

DKA(%)	Land	Quelle
29,8	Deutschland	**Kapellen Monatsschr.Kinderheilk 2001:679-682**
22%	DPV/Deutschland	**Kintzel Diabetes und Stoffw 2003:8-12**
69%	Russland	**Betts Diabet Med 1999:772-778**
50%	Kuwait	**Al Kawahri Diabetes Res Clin Pract 1997:123-128**
21,1%	DPV 1995-2007	**Neu et al. Diabetes Care 2009**

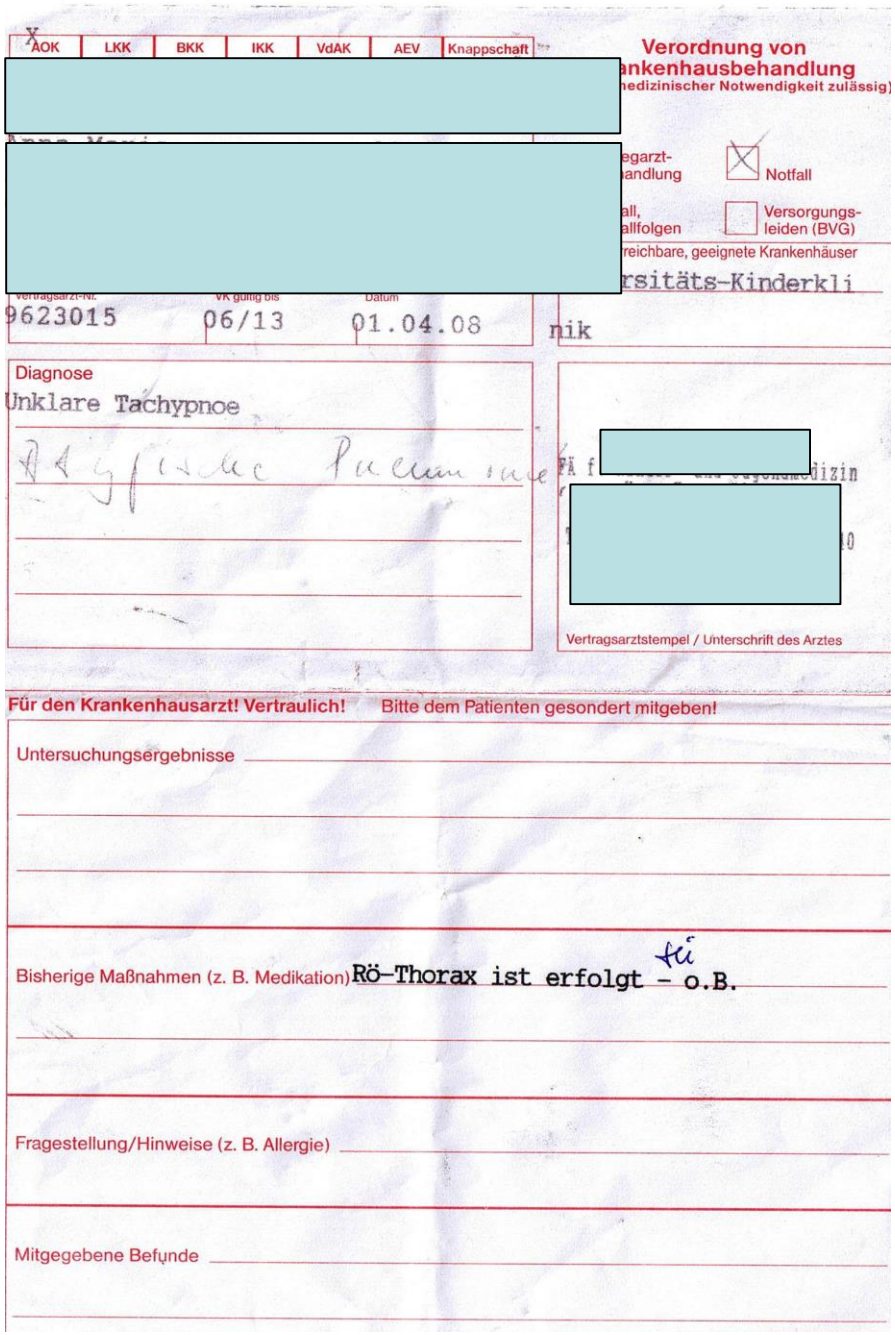
Percentage of DKA (pH < 7.3) at T1D onset, grouped by Age



Nagl, Neu, Kapellen et al. Poster ISPAD 201

Clinical manifestation and misdiagnoses at manifestation

Symptoms	Misdiagnoses
Polyuria Secundary enuresis Polydipsia	Urinary tract infection Diabetes insipidus Psychogenic Polydipsia
Exsikkosis Vomiting Abdominal pain Paleness	Constipation, angina tonsillaris Gastroenteritis Appendicitis Anemia
Heavy breathing	Pneumonia Psychogenic hyperventilation
Unconsciousness	Meningoencephalitis
Muscle weakness	Myopathy Anorexia



Diagnosis of diabetic ketoacidosis missed !

Pneumonia

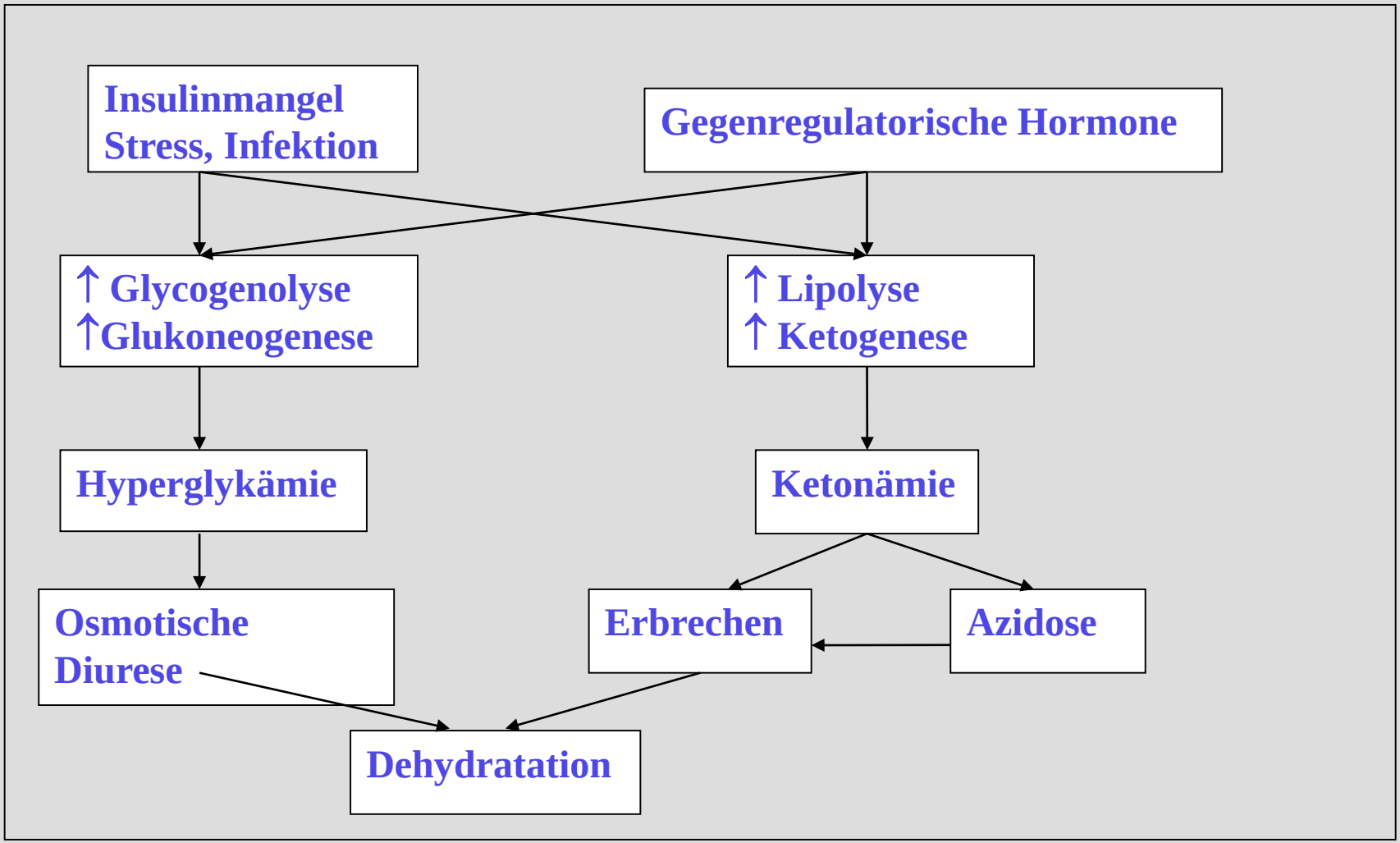
X-ray performed

Metaanalysis of risk factors for DKA at diabetes manifestation

DKA at manifestation	
Risk factors	**Protective factors**
Young age (<2 years; <5 years)	First degree relative with diabetes
Misdiagnosis at manifestation	High incidence/prevalence of diabetes in country/region
Infection	
Ethnic minority	
Low income/no insurance	

Usher-Smith J et al BMJ 2011

Pathogenese der DKA



Behandlungsziele DKA

- Kreislaufstabilisierung (initialer Volumenbolus)
- Langsamer bilanzierter Flüssigkeits- und Elektrolytausgleich
- Ausgleich der Azidose und Ketose
- Langsame Blutzuckernormalisierung
- Vermeidung von Komplikationen (Hirnödem, Hypokaliämie, Hypoglykämie)
- Ggf. Ursachenforschung für Ketoazidoseentstehung

Initiale Kreislaufstabilisierung/ Flüssigkeitssubstitution

NaCL 0.9% 10-20ml/kg i.v. sofort über 1-2h

Danach Ausgleich des Flüssigkeitsdefizits über 36-48h

In den ersten 4-6h plasmaisotone Vollelektrolytlösung (NaCl 0.9%/ Ringerlaktat; zu Ringeracetat liegen keine Daten vor)

Maximale Tagesdosis <1.5-2 fache Erhaltungsdosis für Alter und Gewicht.

5% Glukose/0.45% NaCl Beginn bei BZ <15mmol/l/270mg/dl
oder bei BZ Abfall >5mmol/l/h (90mg/dl/h)

AGPD Leitlinie Diabetologie und Stoffwechsel 2016

Insulintherapie

- Beginn erst nach 1-2h nach Volumengabe
- Normalinsulin
- 0.1 IE / kg KG / h Insulin
- **bei Kindern (AGPD : jüngere Kinder)< 5 Jahren 0.05 IE/kg KG/h**
- gewünschter BZ-Abfall: 2-5mmol/l/h
- Bei BZ unter 15mmol oder zu schnellem BZ Abfall Zugabe von 5% Glukoselösung (Leipzig 10%)
- Keine Unterbrechung der Insulinsubstitution bis pH 7,3
- Steuerung der Insulintherapie in schriftlichem Behandlungsplan

AGPD Leitlinie Diabetologie und Stoffwechsel 2016

Kaliumsubstitution

- **Hyperkaliämie**: erst nach Einsetzen der Diurese und nach Beginn der Insulintherapie
- **Normokaliämie**: mit Beginn der Insulintherapie
- **Hypokaliämie**: sofort
- 40mmol/l Volumen
- 5mmol/kg/d
- Nicht mehr als 0.5mmol/kg/h
- zu erwartender Kaliumbedarf in 24 h: 3-6 mmol/kg

AGPD Leitlinie Diabetologie und Stoffwechsel 2016

Azidosekorrektur:

- Bikarbonatgabe nicht grundsätzlich empfohlen, da RF für die Entwicklung eines Hirnödems

- Vorsichtige Gabe:

1.) bei lebensbedrohlicher Hyperkaliämie

2.) anhaltende nicht beeinflussbare Azidose

3.) drohende oder Kreislaufdekompensation

- dann Substitution mit:

1-2 mmol/kg NaBi 8,4% über 1 Stunde

AGPD Leitlinie Diabetologie und Stoffwechsel 2016

Monitoring

- Stündlich Puls, Atemfequenz, RR, EKG Monitoring
- 2-4 stündlich Temperaturmessung
- Stündlich Ein-Ausfuhr, Bilanz alle 2h, ggf Blasenkatheter
- Stündliche Blutzuckermessungen, zunächst stdl. BGA Ketonbestimmung bis negativ
- Hirnödemmonitoring (s.u.)

AGPD Leitlinie Diabetologie und Stoffwechsel 2016

Hirnödem – Klinik

- Zeitpunkt der ersten Symptome: meist nach 4-12h
- Krankenbeobachtung:
  - Kopfschmerzen, Erbrechen, ansteigender RR, Unruhe, Apathie o. Irritabilität, Inkontinenz, zunehmende Eintrübung, dann RR Abfall und Bradykardie, Hirnnervenausfälle
- Monitoring:
  - bei Kindern < 5 Jahre mit pH < 7,0 : arterielle RR-Messung
  - bei älteren Kindern individuelle Entscheidung je nach Gesamterscheinung
- Pupillenreaktion:
  - in ersten 3 Stunden: 1-stündlich
  - ab 4. Stunde: ½ -stündlich

Hirnödembehandlung

	ISPAD	DDG
Hirnödemmonitoring	+ Spezieller Score	+ ISPAD Score
Flüssigkeitmanagement	Reduktion der Infusionsmenge um 1/3	Reduktion der Infusionsmenge um 1/3
Lagerung	Kopf hoch	Kopf hoch
Mannitol	0.5-1 g/kg IV über 20` Wdh. möglich	0.5-1 g/kg IV über 10-15` Wdh. möglich
3% NaCl	5 ml/kg über 30 Minuten	2.5-10 ml/kg über 10-15` alternat. oder bei mangelndem Erfolg
Beatmung	Ja, keine Hyperventilation	Ja, wenn nötig
Bildgebung	CT nach Therapiebeginn	MRT (CT) nach Ther.beg.

Hirnödemprävention

- DKA Prävention
- Insulin nicht sofort, kein Insulinbolus (verhindert Na/H Aktivierung)
- Vermeidung freien Wassers (Art der Infusionslösung, genaue Anamnese)
- Flüssigkeitsbilanzierung, nicht zu viel Infusion
- kein Bikarbonat
- Verhinderung des Abfalls der Plasmaosmolarität
- d.h. auch adäquater Na-K Ersatz und geringer Glukoseabfall
- Monitoring

Populationsbasierte Studien zur Inzidenz von Hirnödem bei DKA

Publikation	Glaser	Edge	Lawrence	Ragnas
Land	USA	UK	Canada	Schweden
Datenerhebung	1982-1997	1995-1998	1999-2001	2000-2004
Publiziert	2001	2001	2005	2007
Alter	< 19 Jahre	< 16 Jahre	< 16Jahre	< 20 Jahre
DKA-Episoden	6997	2940	1960	296
DKA onset		1095	?	265
Hirnödem	61 (0.9%)	20/34 (0.68%)	13 (0.51%)	2 (0.68%)
Hirnödem onset	66% 13/1000	13 (65%) 10/1000	76% 6.7/1000	100% 6.8/1000
Bei Aufnahme	5%	? 2 Todes-fälle vor Aufn.	19%	?
Tod	13 (21%)	8 (24%)	3 (23%)	0
Neurologische Schäden	13 (21%)	9 (35%)	2 (15%)	0

Prevention of cerebral edema

- DKA prevention
- Insulin not immediately given, no insulin bolus (prevents Na/H activation)
- Avoid free water (type of infusion/solutions, exact history)
- Fluid ballance, not too much
- No bicarbonate
- Avoid decrease of plasma osmolarity
- adequate Na-K substitution and slow decrease of blood glucose concentrations
- Monitoring

Ceberal edema criteria according to ISPAD

- **Diagnostic criteria:**
  - abnormal motoric or verbal reaction to pain
  - Rigidity of extremities, decortikation/decerebration
  - Central nerve paresis (III, IV, VI)
  - abnormal breathing

- **Major criteria:**
  - Disturbed consciousness
  - Pulse deceleration (decrease of at least 20/min, unrelated to wakefulness or volume administration)
  - Incontinentia

Ceberal edema criteria according to ISPAD

- **Minor criteria:**
  - Vomiting
  - Headache
  - Lethargy, sleepiness
  - RR diastolic >90mmHg
  - age < 5 years

→ 1 diagnostic criterium <u>or</u>
→ 2 major criteria <u>or</u>
→ 1 major - and 2 minor criteria

→→ Sensitivity of 92%

Treatment of cerebral edema

	ISPAD	DDG
Cerebral edema monitoring	+ Score	+ ISPAD Score
Fluid/volume management	Reduction of volume by 1/3	Reduction of volume by 1/3
Position	Head up	Head up
Mannitol	0.5-1 g/kg IV over 20` Repeat if necessary	0.5-1 g/kg IV over 10-15` Repeat if necessary
3% NaCl	5 ml/kg over 30 minutes	2.5-10 ml/kg over 10-15` if not succesful
Ventilation	Yes, no hyperventilation	Yes
Imaging	CT after initiation of therapy	MRT (CT) after initiation of therapy

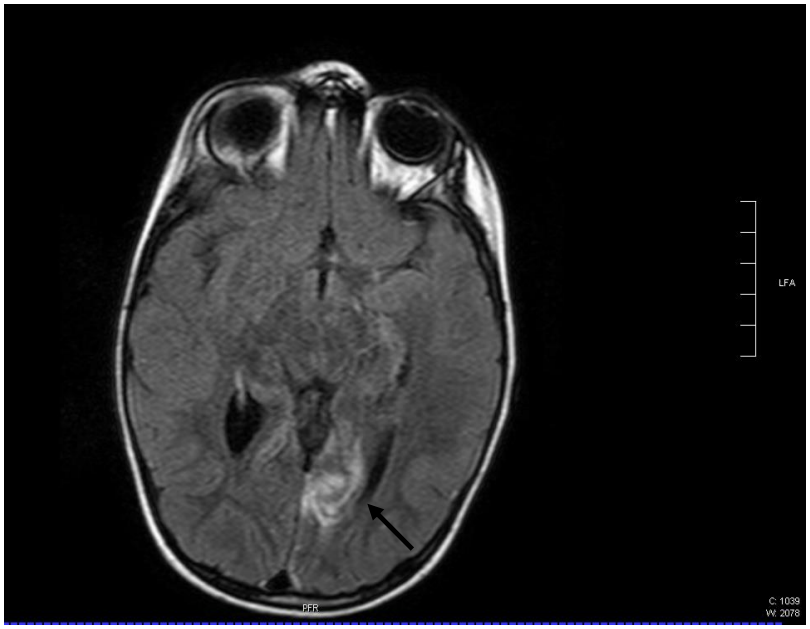
Initial treatment concept (Leipzig)

- Immediately if cerebral edema is suspected
- Reduction of infusion volume by 1/3
- Positioning head up
- 1. initial furosemide bolus 0.5mg/kg
- 2. Mannitol 20% 1g/kg = 5 ml/kg over 20 minuntes
- 3. thereafter second furosemide bolus von 0.5mg/kg

Cerebral infarction during brain edema during DKA

figure 1:

a



b

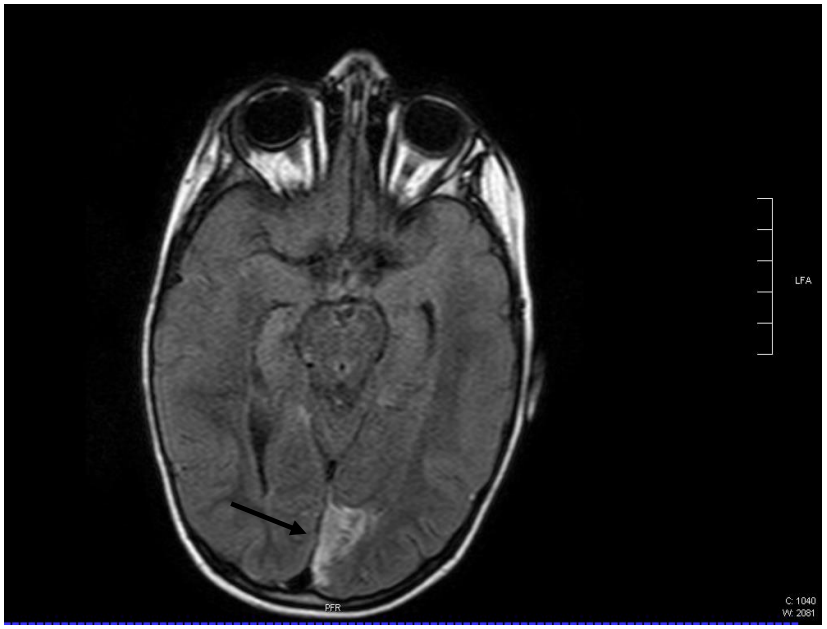


Figure 1) Cranial magnetic resonance imaging (16 days after therapy start) showing hyperdense areas in the occipital area (a/b; solid arrow) consistent with infarction in the distribution of the left posterior cerebral artery in a 2-year-old child with new onset of type 1 diabetes.

Extrapontine myelinolysis after DKA/cerebral edema

figure 2:

a **b**

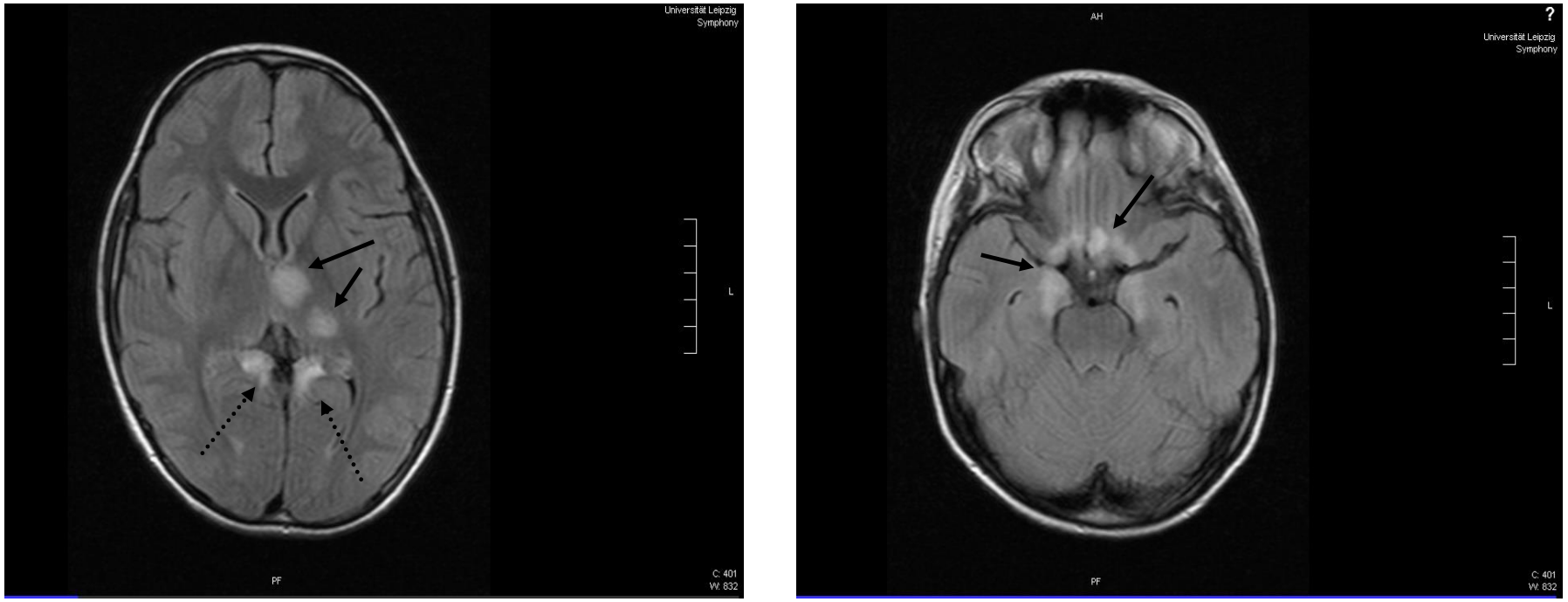


Figure 2) Cranial magnetic resonance imaging of a 14-year-old child with new onset of type 1 diabetes (three days after therapy start) showing multifocal hyperdense lesions in the left thalamus (a; solid arrows) and temporomesial in both sides of the thalamus with affections of the paraterminal gyrus of the frontal lobe (b; solid arrows), also bilateral in the praecuneus (a; discontinued arrows) without contrast medium enhancement – compatible with extrapontine myelinolysis

How many hospitals keep written SOPs/guidelines for DKA ?

- **Survey in the USA**
- **269 hospitals**
- **49-77% (depends upon hospital type) provide a DKA protocol**
- **Only 15-39% provide quality-management protocol with interventions for critically ill patients with diabetes**

Cook CB et al. Endocrine pract 2010:219

Original Investigation

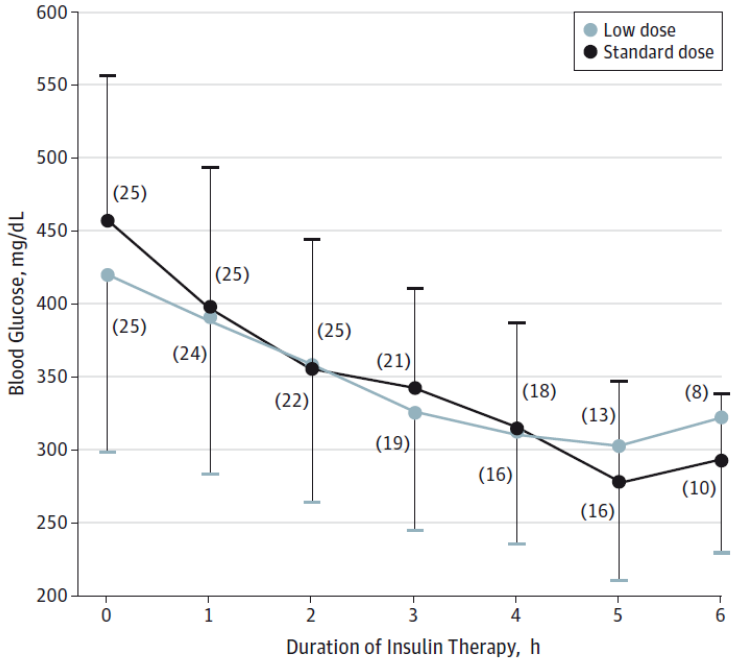
Low-Dose vs Standard-Dose Insulin in Pediatric Diabetic Ketoacidosis
A Randomized Clinical Trial

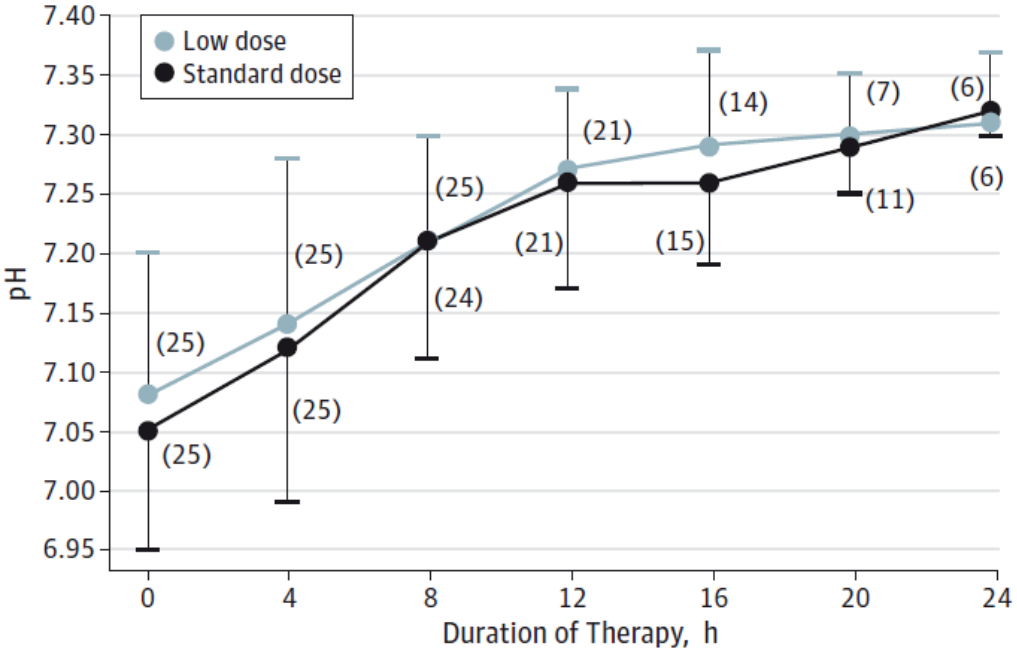
= 0.05 vs 0.1 IE/kgh

JAMA Pediatr. 2014;168(11):999-1005.

Karthi Nallasamy, MD, DM; Muralidharan Jayashree, MD; Sunit Singhi, MD; Arun Bansal, MD

Figure 2. Mean Blood Glucose Decrease With Insulin Therapy





Original Investigation

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	0.05 IE/kgh (n=25)	0.1/kg/h (n=25)	p
Mittlerer BZ Abfall bis 250mg/dl, mg/dl h	45.1 (±17.6)	52.2 (±23.4)	
Zeit bis pH≥ 7.3 (h)	16.5 (±7.2)	17.2(±7.7)	0.73
Hypokaliämie	**5 (20%)**	**12 (48%)**	**0.07**
Hypoglykämie	1 (4%)	5 (20%)	0.17
Notwendigkeit von 10% Glukose	2 (8%)	7 (28%)	0.14
Hirnödem	0	1	
Therapieversager	2 (8%)	1 (4%)	

Pediatric Diabetes

ISPAD International Society for Pediatric and Adolescent Diabetes

Pediatric Diabetes 2013: 14: 435–446
doi: 10.1111/pedi.12027

Pediatric Diabetes

Table 1. Treatment protocol overview

	Protocol A1	Protocol A2	Protocol B1	Protocol B2
Standard initial fluid bolus*	10 cc/kg bolus of 0.9% saline	10 cc/kg bolus of 0.9% saline	10 cc/kg bolus of 0.9% saline	10 cc/kg bolus of 0.9% saline
Additional intravenous fluid bolus	Additional 10 cc/kg of 0.9% saline	Additional 10 cc/kg of 0.9% saline	No additional bolus	No additional bolus
Assumed fluid deficit	10% of body weight	10% of body weight	5% of body weight	5% of body weight
Replacement of deficit	Replace half of fluid deficit + maintenance fluids over initial 12 h, remaining deficit + maintenance fluids over subsequent 24 h	Replace half of fluid deficit + maintenance fluids over initial 12 h, remaining deficit + maintenance fluids over subsequent 24 h	Replace deficit + maintenance fluids evenly over 48 h	Replace deficit + maintenance fluids evenly over 48 h
Fluid used for deficit replacement	0.45% Saline	0.9% Saline	0.45% Saline	0.9% Saline

*This is standard treatment at all participating centers and is not part of the study protocol. Consent will occur during this initial fluid bolus after which the study treatment will be randomized.

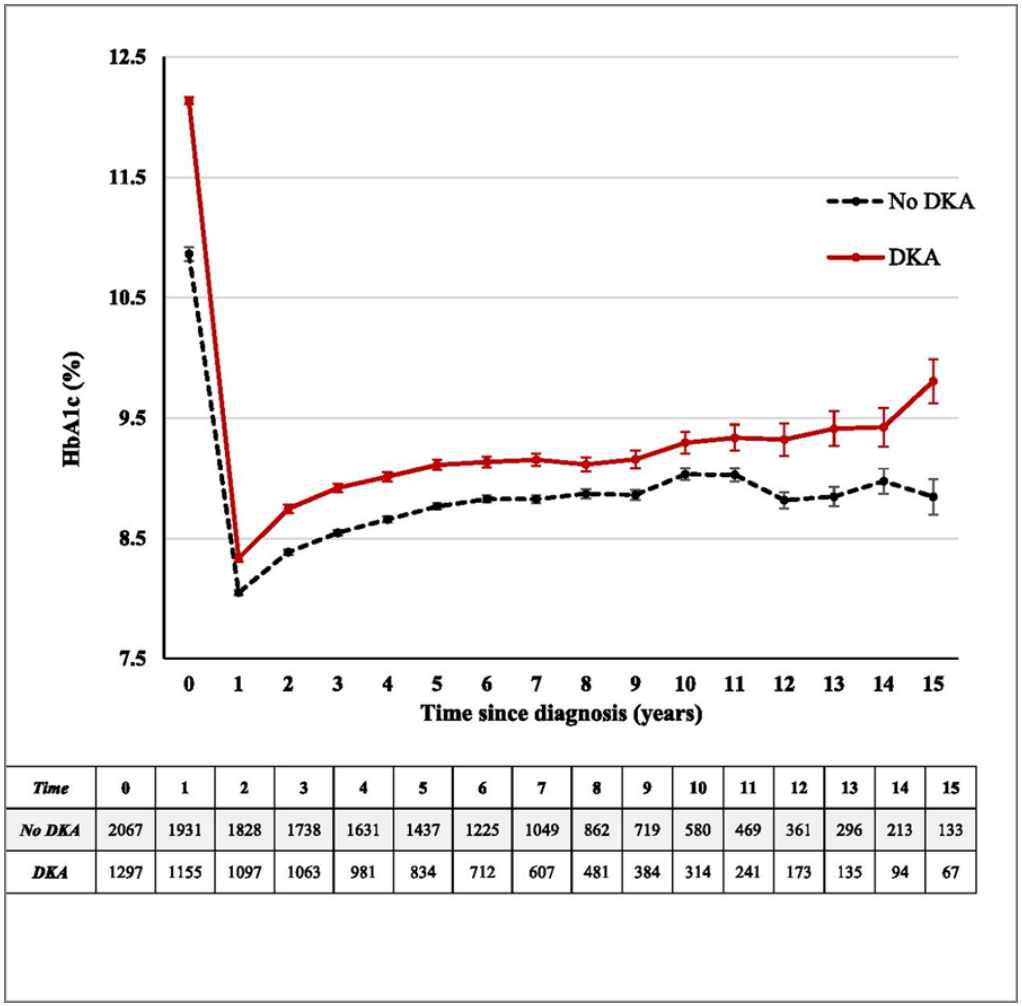
Diabetic ketoacidosis 2019

- **Prevention of DKA – why?**
- **Prevention of DKA at manifestation**
- **Prevention of DKA after manifestation**
- **Prevention/treatment of complications of DKA**

Diabetic Ketoacidosis at Diagnosis of Type 1 Diabetes Predicts Poor Long-term Glycemic Control.

Duca LM, Wang B, Rewers M, Rewers A.

Diabetes Care. 2017 Sep;40(9):1249-1255. doi: 10.2337/dc17-0558. Epub 2017 Jun 30.

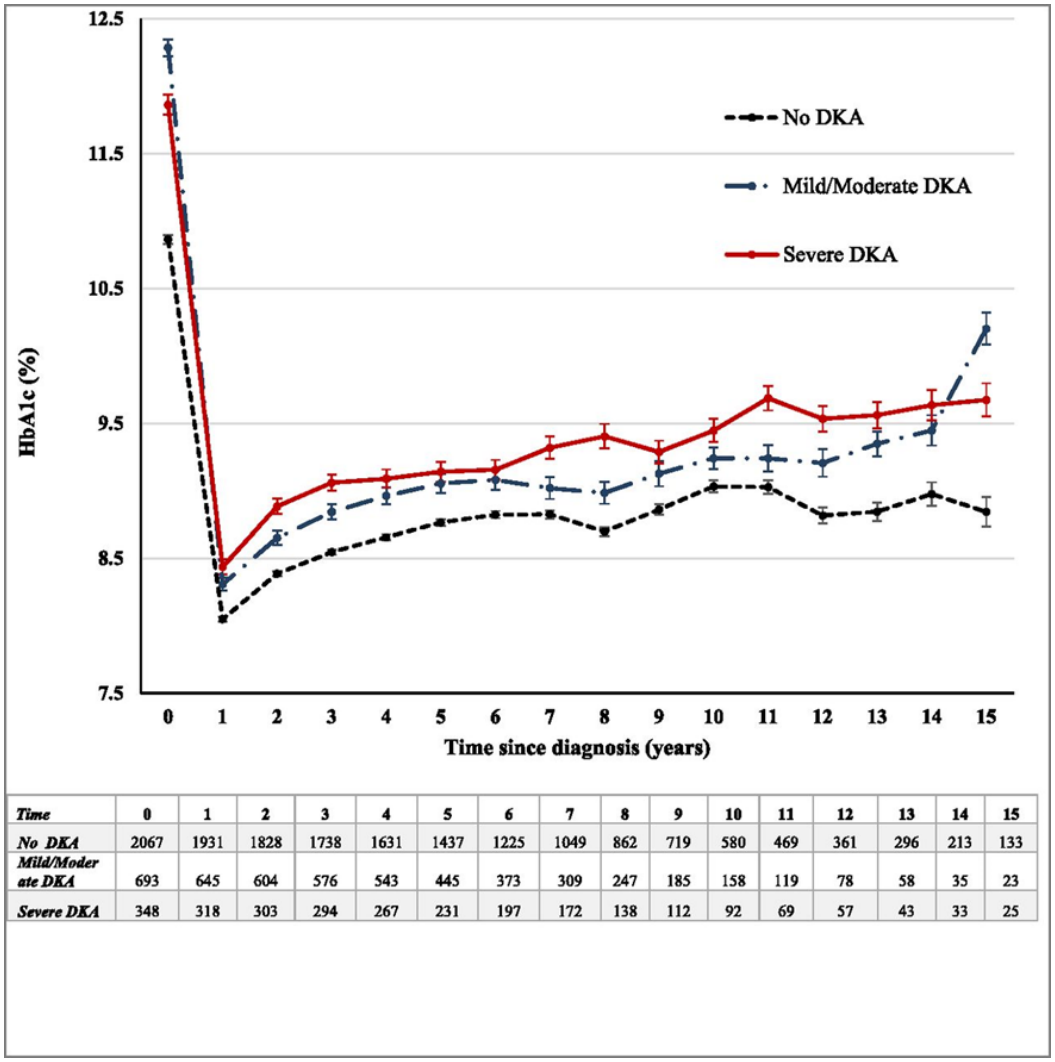


Time	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
No DKA	2067	1931	1828	1738	1631	1437	1225	1049	862	719	580	469	361	296	213	133
DKA	1297	1155	1097	1063	981	834	712	607	481	384	314	241	173	135	94	67

DKA at diagnosis of type 1 diabetes predicts poor long-term glycemic control, independent of demographic or socioeconomic factors.

Figure 1. DKA at diagnosis of children with type 1 diabetes and long-term glycemic control. The numbers reported below the figure represent the number of participants contributing the overall HbA_{1c} level during that point in time. Data presented are mean ± SE from unadjusted linear mixed model.

(Diabetic Ketoacidosis at Diagnosis of Type 1 Diabetes Predicts Poor Long-term Glycemic Control. Duca LM, et al. Diabetes Care. 2017 Sep;40(9):1249-1255. doi: 10.2337/dc17-0558. Epub 2017 Jun 30.)



Time	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
No DKA	2067	1931	1828	1738	1631	1437	1225	1049	862	719	580	469	361	296	213	133
Mild/Moderate DKA	693	645	604	576	543	445	373	309	247	185	158	119	78	58	35	23
Severe DKA	348	318	303	294	267	231	197	172	138	112	92	69	57	43	33	25

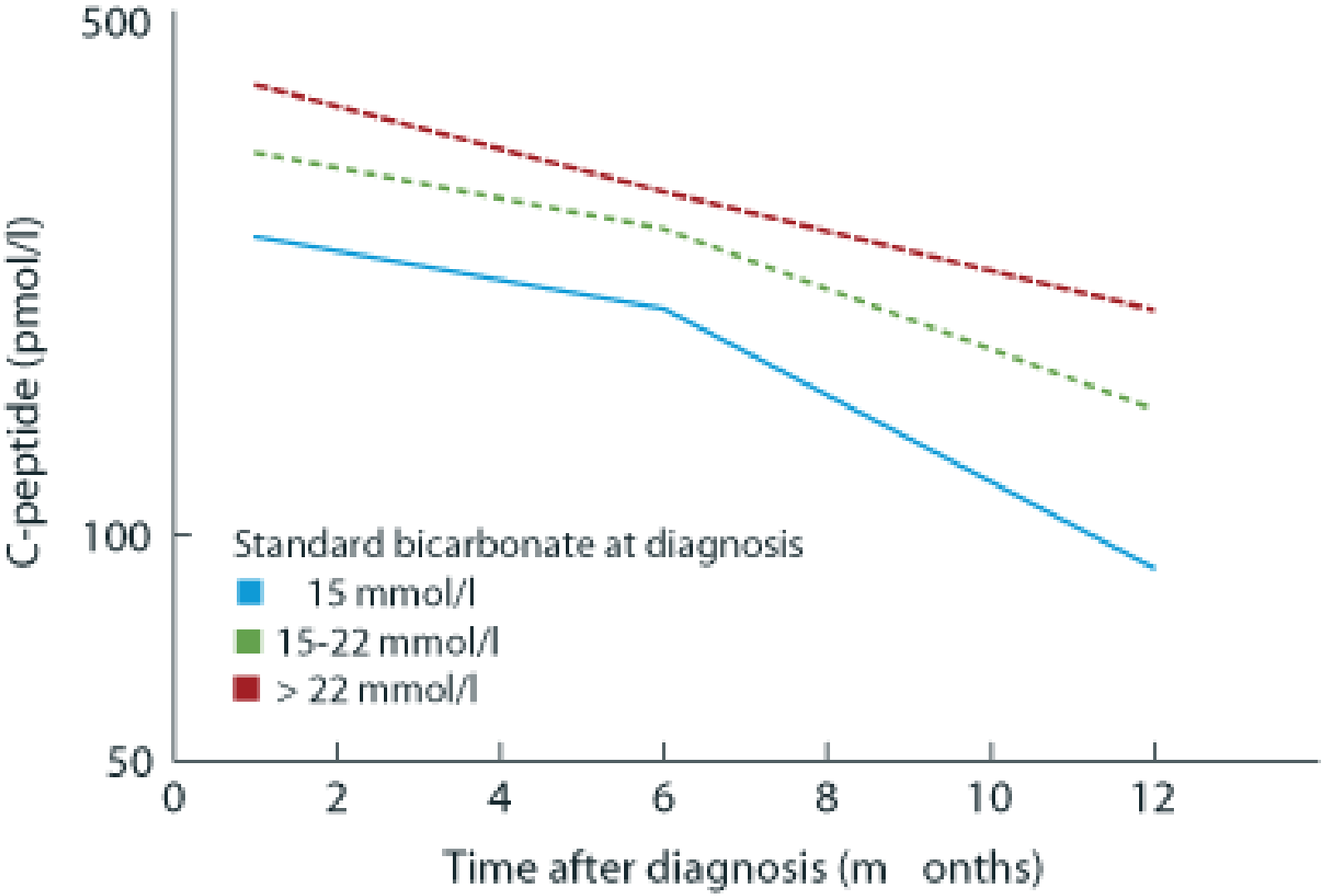
´Dose effect´

Severe DKA at diagnosis of type 1 diabetes predicts poor long-term glycemic control more than mild/moderate DKA

Figure 2. DKA severity at diagnosis of children with type 1 diabetes and long-term glycemic control. The numbers reported below the figure represent the number of participants contributing the overall HbA_{1c} level during that point in time. Data presented are mean ± SE from unadjusted linear mixed model.

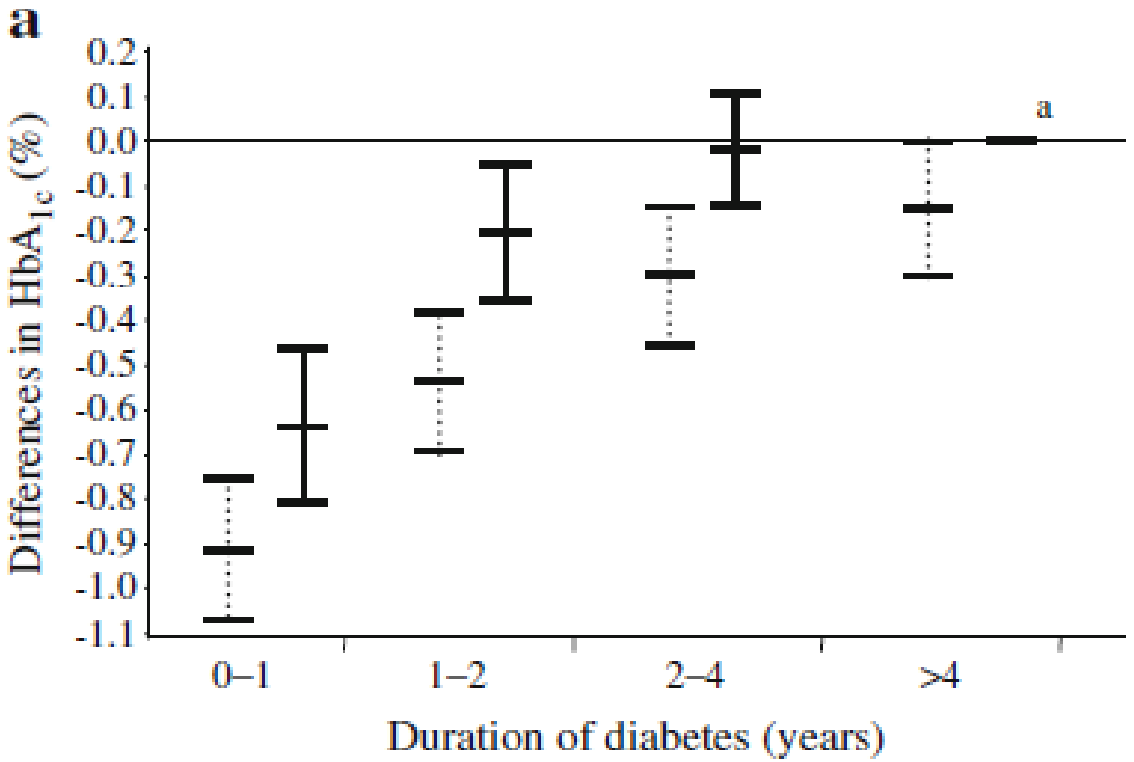
(Diabetic Ketoacidosis at Diagnosis of Type 1 Diabetes Predicts Poor Long-term Glycemic Control. Duca LM, et al. Diabetes Care. 2017 Sep;40(9):1249-1255. doi: 10.2337/dc17-0558. Epub 2017 Jun 30.)

Residual insulin secretion and DKA



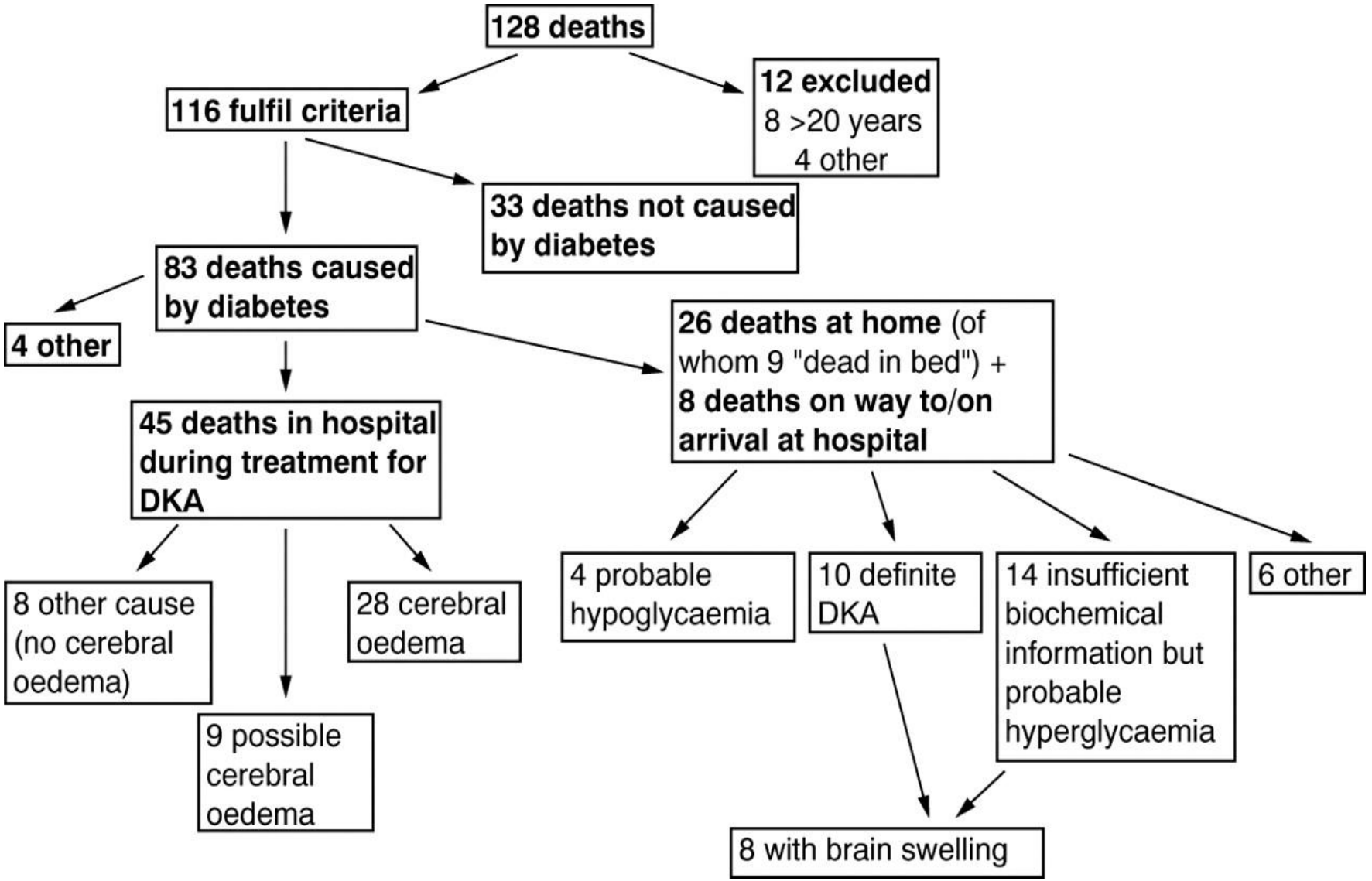
Mortensen et al. Pediatr Diabetes 2010:218-26

DKA and HbA1c in the longterm



Black Lines: medium/severe DKA
Dotted lines: no/mild DKA
Data from the Danish childhood diabetes registry

Fredheim Diabetologia 2013



7 hypoglycemia, 69 DKA

Edge, J. A et al. Arch. Dis. Child. 1999;81:318-323

DKA after manifestation

Table 1—Descriptive data by registry

	Overall *N* = 49,859	DPV *n* = 22,397	NPDA *n* = 16,314	T1DX *n* = 11,148	*P* value
Male	52.2	52.2	53.0	51.1	0.013
Age, years	13.3 (10.3, 15.7)	13.8 (10.5, 16.3)	13.2 (10.4, 15.3)	12.7 (9.8, 15.2)	<0.001
Age at diagnosis, years	6.9 (3.9, 10.0)	7.1 (4.0, 10.4)	7.1 (3.9, 10.2)	6.0 (3.0, 9.0)	<0.001
Type 1 diabetes duration, years	4.9 (2.7, 7.8)	5.0 (2.9, 8.1)	4.7 (2.6, 7.5)	4.0 (2.0, 7.0)	<0.001
BMI *z* score, WHO	0.72 (0.08, 1.40)	0.65 (0.02, 1.30)	0.81 (0.13, 1.52)	0.79 (0.16, 1.48)	<0.001
Pump use	36.1	44.2	11.5	56.1	<0.001
Ethnic minority	18.0	20.4	10.4	22.6	<0.001
Mean HbA_{1c}					
%	8.4 ± 1.5	7.9 ± 1.4	9.0 ± 1.6	8.5 ± 1.4	<0.001
mmol/mol	68 ± 16	63 ± 15	75 ± 17	69 ± 15	
HbA_{1c}					
<58 mmol/L (7.5%)	28.3	42.9	12.0	20.9	<0.001
≥75 mmol/mol (9%)	27.2	16.9	42.0	28.0	<0.001
With ≥1 DKA event	6.0	5.0	6.4	7.1	<0.001

Data shown are unadjusted percentages, mean ± SD, or median and quartiles.

Maahs et al Diabetes Care 2015

Risik factors for DKA after manifestation

- Bad metabolic control
- Previous episodes of DKA
- Puberty/adolescent girls
- Eating disorders
- Low socioeconomic status
- Migrant background (DPV)
- Weight manipulation with insulin
- No insurance (USA)
- Infections (infants/toddlers)

Risk factor unexperienced therapist

Evaluation of the outside therapy of DKA in pediatric patients (Bradley et al Am J Ther 2008)

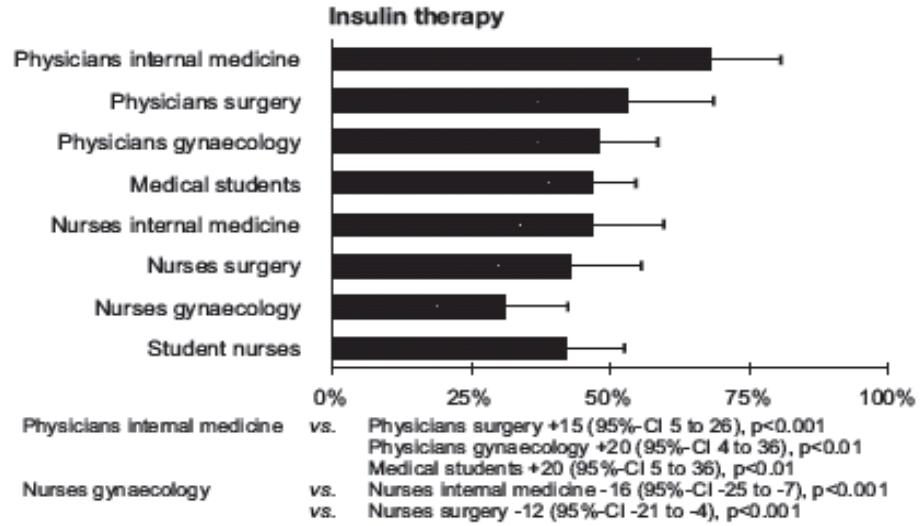
Laboratory: only 58% with blood gas data

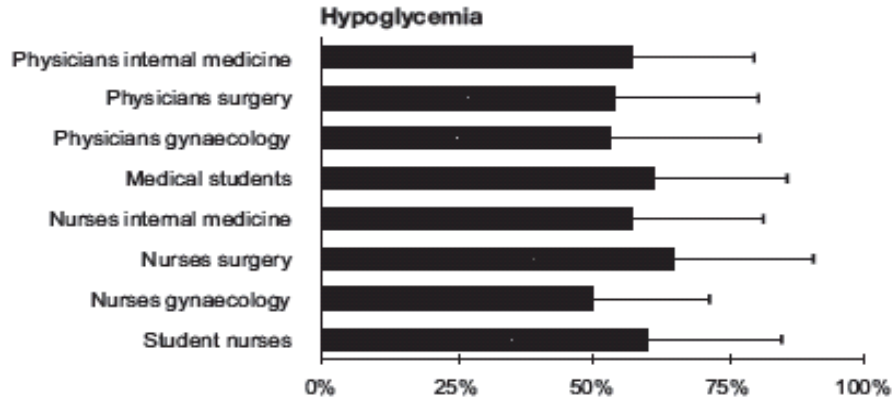
Insulin: bolus in 64% (s.c., i.v.)

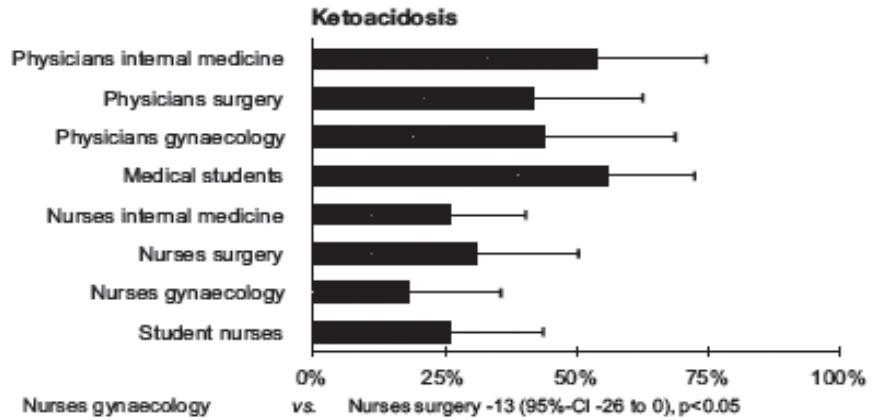
Fluid volume: from 0 to 60ml/kg/h

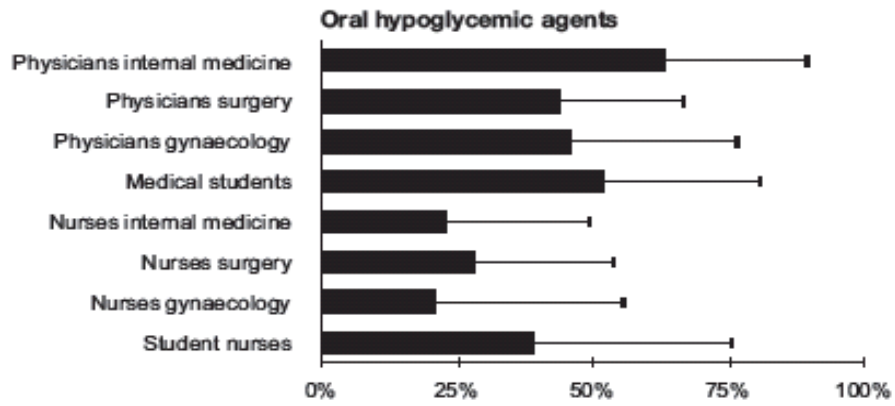
$\Rightarrow$ Lack of guideline-based treatment before hospital admission

Diabetes knowledge in medical professions



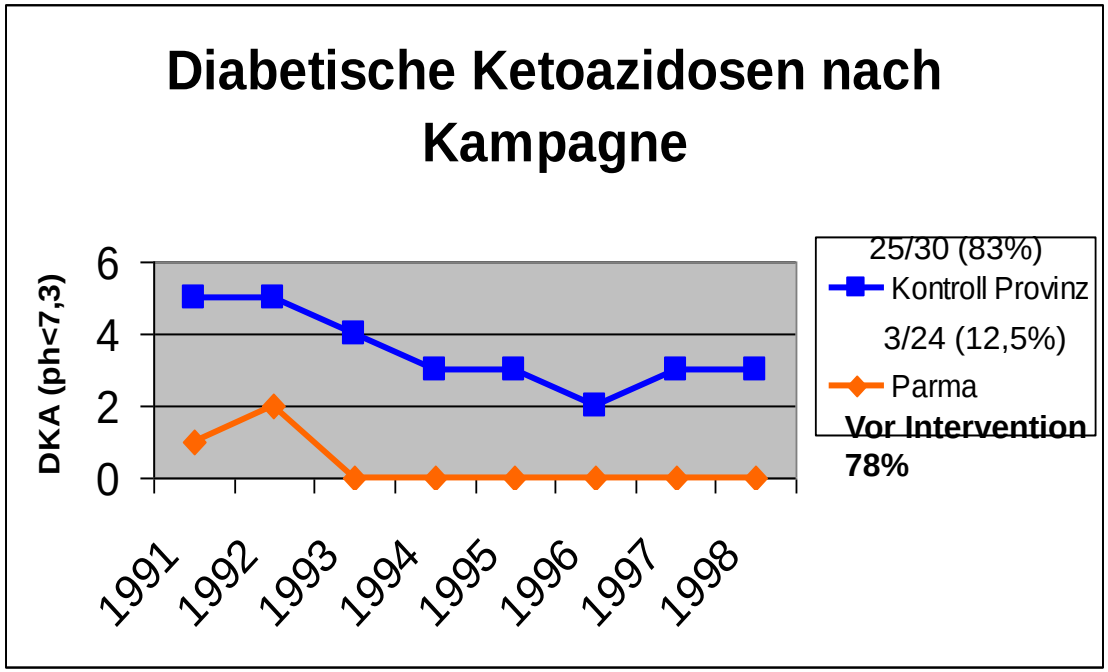




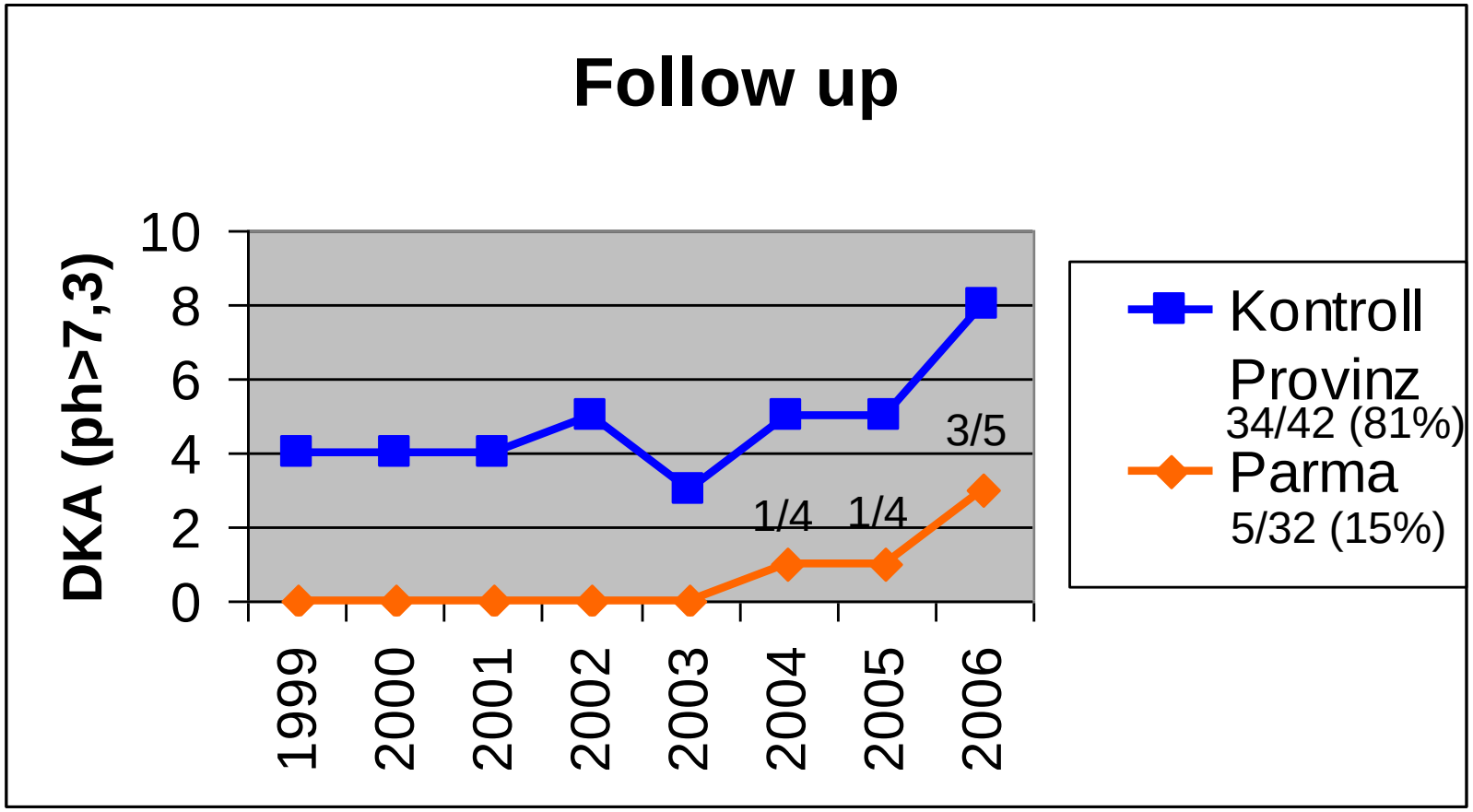


Trepp R et al. Swiss Med wkly 2010:370

Prevention of DKA: Parma campaign



Vanelli et al. Diabetes Care 1999:7-9



Vanelli et al Acta Biomed 2008

world diabetes day
14 November

International Diabetes Federation

www.worlddiabetesday.org/dka

ISPAD
International Society for Pediatric and Adolescent Diabetes

Austrian DKA prevention campaigne

No reduction of DKA incidence

Despite large effort:
Poster for pediatricians, school doctors/nurses,
TV film (once)
and via ÖGD homepage

But: parents not addressed/involved

No redundant/repeated campaigne

bm:uk Bundesministerium für Unterricht, Kunst und Kultur

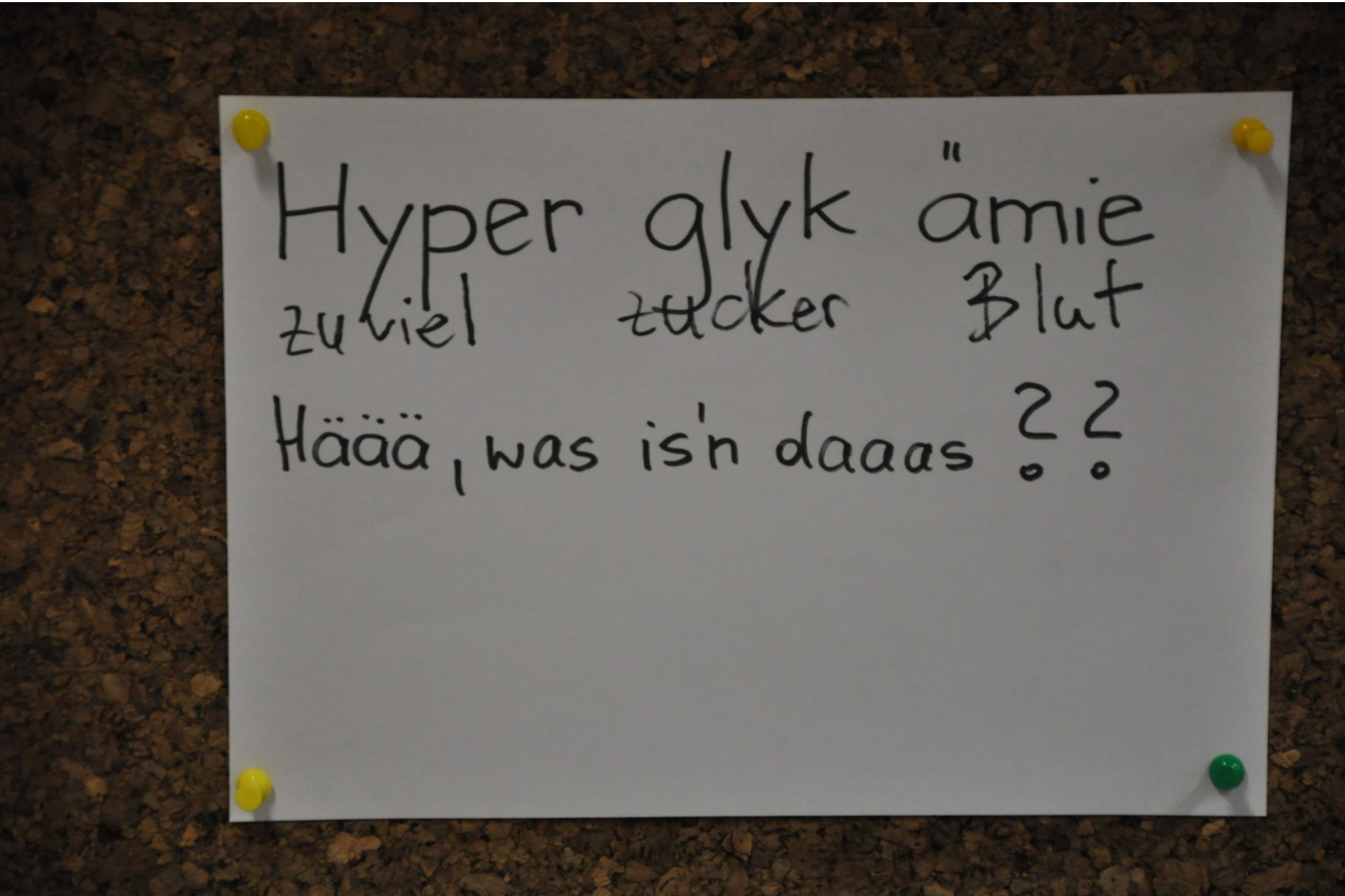
ÖDG Österreichische Diabetes Gesellschaft
helfen, heilen, forschen

Prevention

- **Education**
- **Guidelines/hand outs for patients**
- **Telefon hotline**
- **After repetitive episodes: multidisciplinary management**
- **If necessary home care/social services (child protection laws?)**

Education

- **Ketone and development of DKA is difficulty to comprehend (both to explain and to understand)**
- **Of all diabetes education topics this is to be forgotten earliest/fastest**
- **Need for repetitive educational efforts**


Hyper glyk ämie
zu viel ~~zucker~~ Blut
Häää, was is'n daaas ??

Education

- Follow-up education when pump and/or at manifestation after 3-6 months
- „Just do it“ with practical examples
- Schematics
- Ask when in outpatient clinic and check understanding.


Hyper glyk "amie
zuviel ~~zucker~~ Blut
Haaa, was is'n daaas ??


Urine/Orina
2 min.
neg.
0,1 (5,6)
0,25 (14)
0,5 (28)
1 (56)
2 (111)
3 (167)
5% (278)
(mmol/L)
%=g/dL

Was könnte ich haben?

Antwort: ……..

Ketoazidose-Notfallplan

Blutzucker >240 mg/dl bzw. 15 mmol/l und/ oder Übelkeit, Erbrechen, Bauchschmerzen

Sofort Azeton testen.
(Wichtig: Teststreifen vor Verfall vom Arzt neu verordnen lassen!)

Azeton ++/+++

Azeton negativ

Sofort doppelte Dosisanpassung kurzwirkendes Insulinanalogon mit Spritze/ Pen spritzen.
Viel trinken!

Wie gewohnt den Blutzucker korrigieren (ca. 2 Std. nach kurzwirkendem Insulinanalogon.)

Diabeteszentrum oder Hausarzt informieren, nicht einschlafen

Nach 2 Stunden Blutzucker messen.

Blutzucker < 10 mmol/l
Azeton -/+

Blutzucker < 15 mmol /l
Azeton ++/+++

Blutzucker > 15 mmol/l
Azeton ++/+++

Kein weiteres Insulin spritzen.
2 BE gegen Hypo-Gefahr essen und weiterhin viel trinken.

Sofort normale Dosisanpassung kurzwirkendes Insulinanalogon mit Spritze / Pen spritzen.
Viel Wasser trinken.

Ist der Blutzucker wieder im Zielbereich, suchen Sie nach der Ursache der Blutzuckerentgleisung.

Regeln:

* Keine körperliche Anstrengung und viel Mineralwasser trinken!
* Falls Trinken nicht möglich ist, begeben Sie sich bitte in ein Krankenhaus.
* Korrektur-Insulin muss immer mit Einmalspritze oder Insulinpen zugeführt werden

Mein Insulin-Tagesgesamtbedarf

_____

Notfall-Telefonnummer: 0175/2240459
Diabeteszentrum: 0341/9726115
0341/9726345

Education

Table 2—*Baseline and follow-up data of patients with one or no episodes versus two or more episodes of severe ketoacidosis during the year before the DTTP*

	Diabetic ketoacidosis during the year before the DTTP	
	One or no events · patient^{-1} · year^{-1}	Two or more events · patient^{-1} · year^{-1}
Patients (*n*)	9,488	95
Age at enrollment (years)	38.2 ± 14	31.5 ± 13
Mean duration of diabetes (years)	13.4 ± 10.9	12.3 ± 9.8
GHb at baseline (%)	8 ± 2	9.4 ± 2.8
GHb at follow-up (%)	7.3 ± 1.5	8.7 ± 2.5
Severe ketoacidosis at baseline (events · patient^{-1} · year^{-1})	0.06 ± 0.2	3.25 ± 2.4
Severe ketoacidosis at follow-up (events · patient^{-1} · year^{-1})	0.03 ± 0.2	0.58 ± 1.6
HD at baseline (days · patient^{-1} · year^{-1})	5.6 ± 13.2	19.4 ± 23.1
HD at follow-up (days · patient^{-1} · year^{-1})	3.5 ± 12.9	10.2 ± 22.6

Data are means ± SD. HD, hospital days.

Sämann A et al Diabetes Care 2006

Telefone support

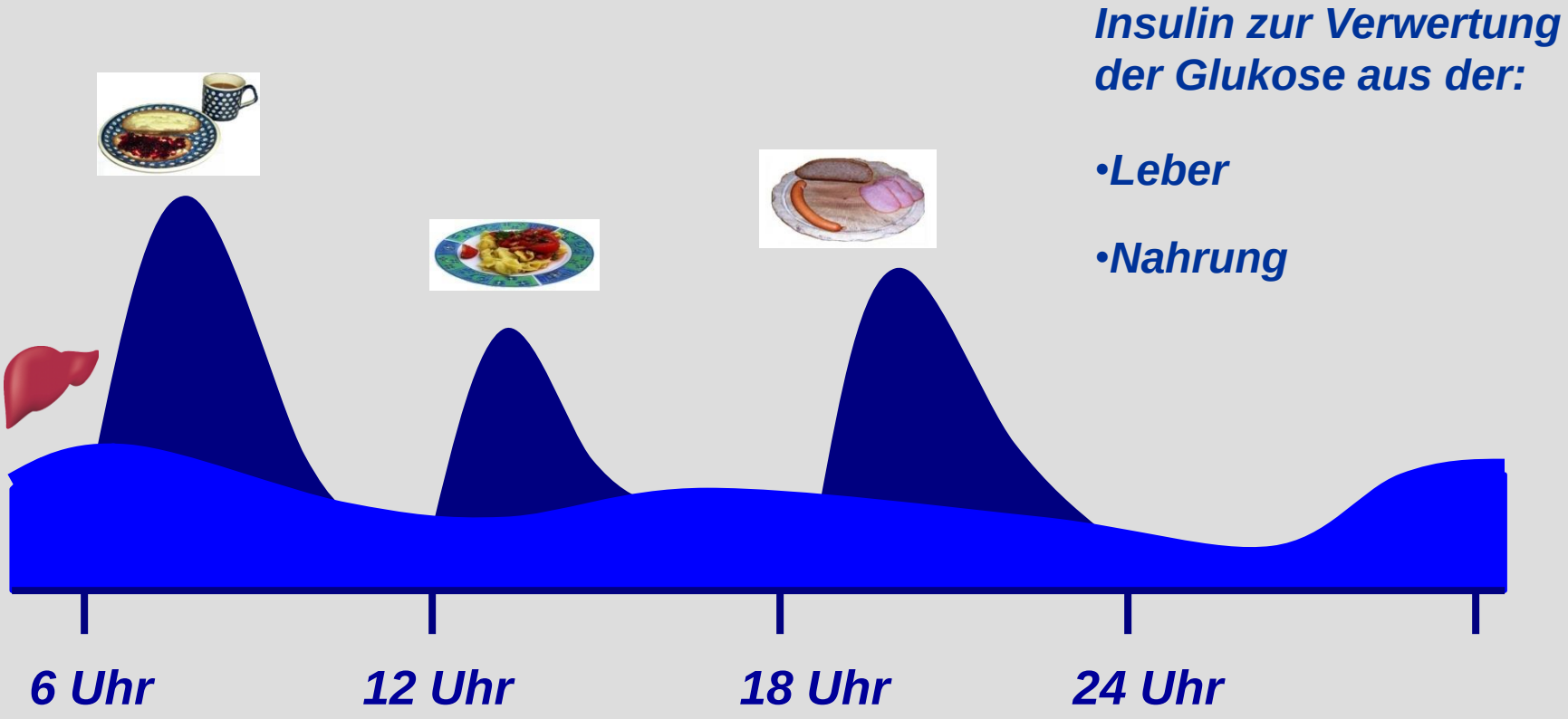
- Two-hourly blood glucose level and ketone testing
- Usual insulin doses are continued
- Supplemental insulin doses are calculated as 1/2 morning quick-acting dose and given 2- to 3-hourly—depending on insulin type (or 1/3 premixed insulin dose given as quick-acting insulin)—and are advised to be administered if ketones are present at the levels detailed above
- Increased fluids advised, sweetened drinks if blood glucose monitor reading < 12 mmol/l
- Symptom relief using readily available remedies for flu, nausea or diarrhoea
- Return 2-hourly phone calls to check progress
- General practitioner presentation encouraged if precipitating illness persists
- Support to maintain regular insulin injections if omitting

Farrell K, et al Diabetic Med 2011

… und nicht vergessen ….

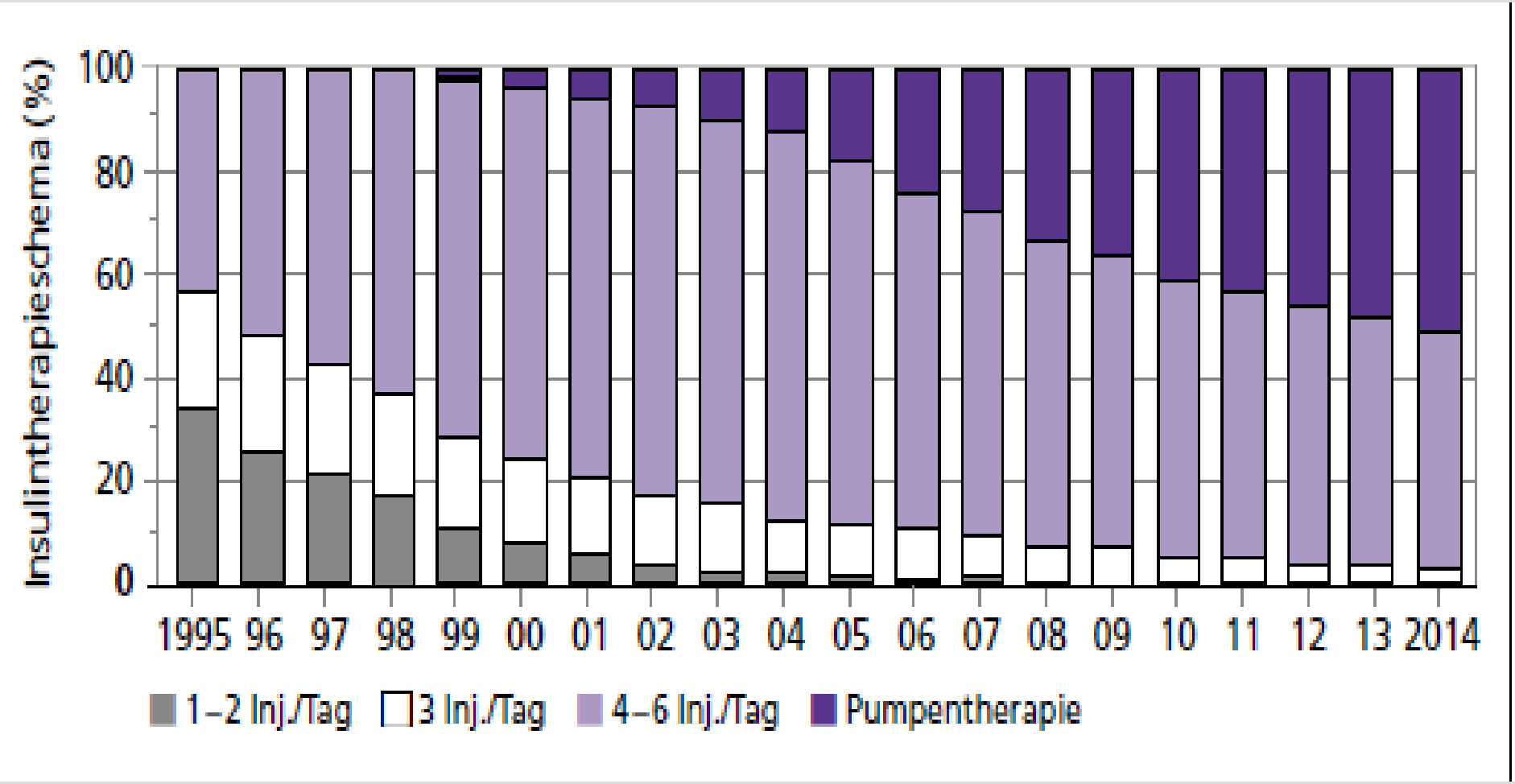
Vielen Dank für Ihre Aufmerksamkeit !

Natürliche Ausschüttung des Insulins bei einem Menschen ohne Diabetes



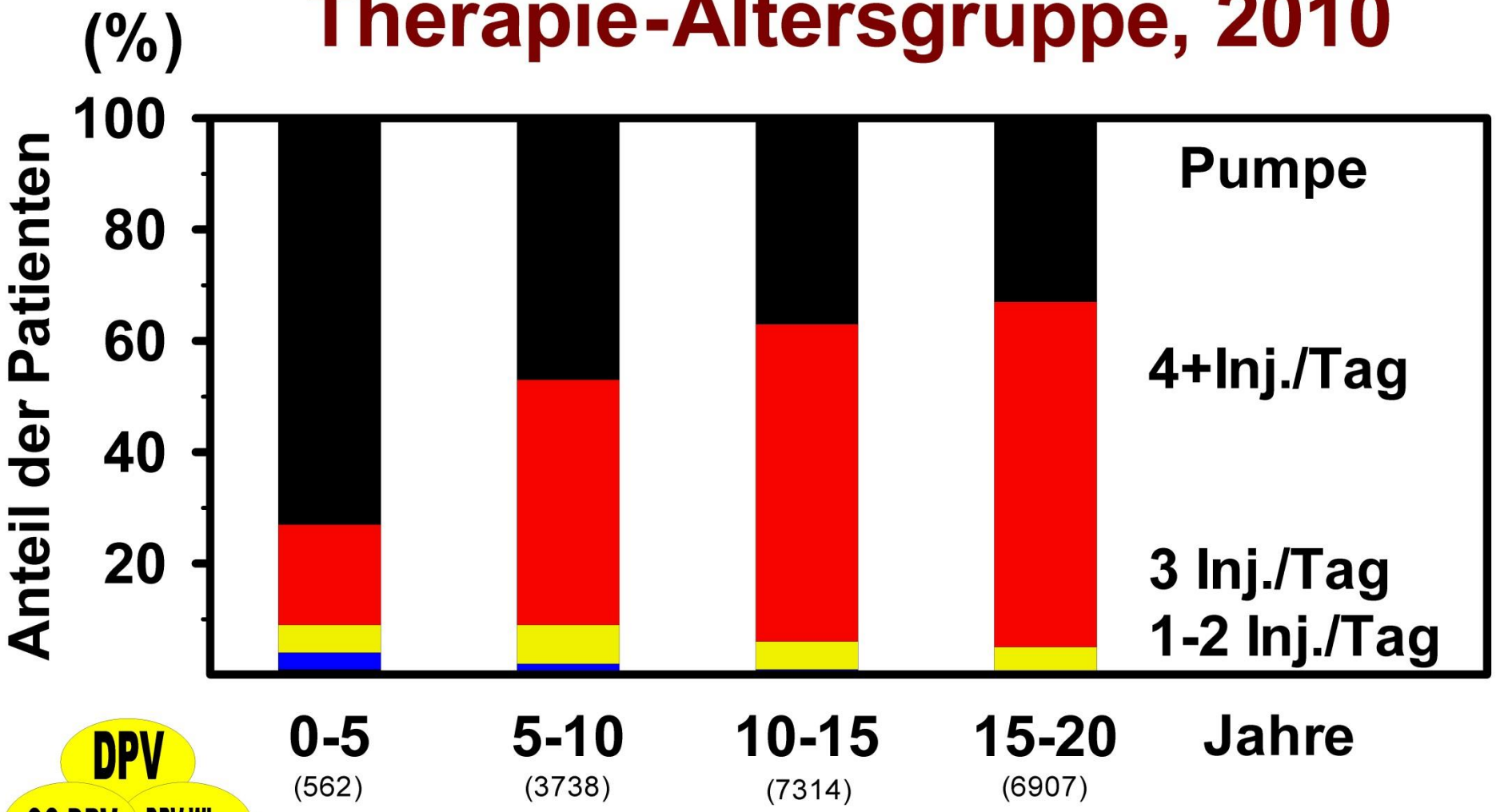
Insulin zur Verwertung der Glukose aus der:

- Leber
- Nahrung



Diabetesgesundheitsbericht 2016

Therapie-Altersgruppe, 2010



DPV
QS-DPV
DPV-Wiss

(Pädiatrie 03/2011)

aktuellste Therapie im Behandlungsjahr
Typ-1-DM, DM-Dauer > 1 Jahr

Insulinbedarf bei Manifestation

Kleinkind < 5 Jahre:	0,8 IE/kgKG
Schulkind 6-12 Jahre:	1,0 IE/kgKG
Jugendlicher:	1,0-1,2IE/kgKG

Abhängig von der Dauer der Symptome,

Dem pH, der Exsikkose, dem Gewichts-verlust

Faustregeln zu Dosis

- 50% des Tagesinsulinbedarfs als Basalinsulin
- 3/5 morgens , 2/5 abends (zunächst 21.00)
- 50% als Mahlzeiteninsulin mit KE-Faktoren

Manifestations-Management

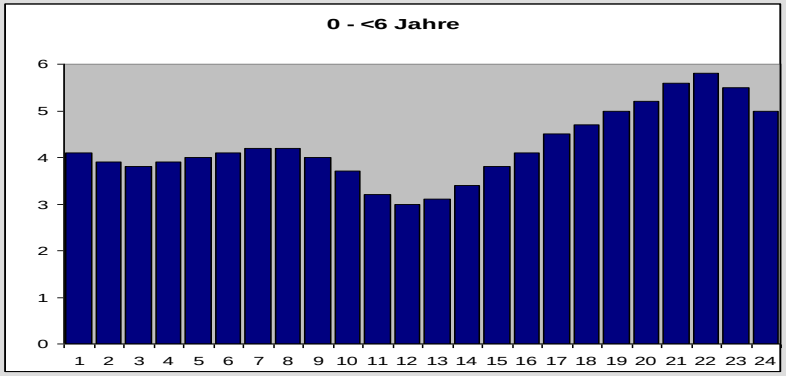
Es werden folgende **KE Faktoren** empfohlen:

	Kleinkind (1-5 Jahre)	Schulkind (6-9 Jahre)	Teen (10-12 Jahre)	Jugendlicher
Früh:	0,75IE/KE	1.0IE/KE	1,5IE/KE	2.0IE/KE
v.m.:	0,5IE/KE	0,75IE/KE	1.0IE/KE	2.0IE/KE
mittags:	0,5IE/KE	0,5IE/KE	1.0IE/KE	1.5IE/KE
n.m.:	0,5IE/KE	0,75IE/KE	1.0IE/KE	1.5IE/KE
abends:	0,75IE/KE	1.0IE/KE	1.5IE/KE	2.0IE/KE
spät:	0,5IE/KE	0,5IE/KE	1.0IE/KE	1.0IE/KE

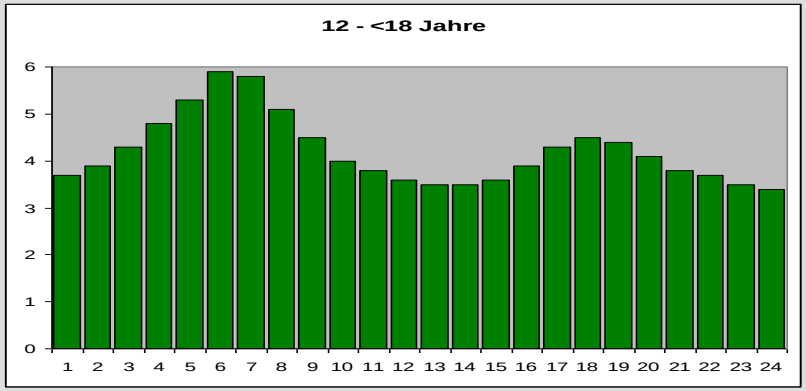
Ausserdem folgende **Korrekturtabellen:**

BZ < 3.0	-0.5 IE	-1.0 IE	-1.0 IE	-2.0 IE
3.1-4.9	-0.12IE	-0.5IE	-0.5IE	-1.0IE
5.0-7.9	± 0IE	± 0IE	± 0IE	± 0IE
8.0-9.9	+0.25IE	+0.5IE	+0.5IE	+1.0IE
10.0-11.9	+0.5IE	+1.0IE	+1.0IE	+2.0IE
12.0-13.9	+0.75IE	+1.5IE	+1.5IE	+3.0IE
>14.0	+1.0IE	+2.0IE	+2.0IE	+4.0IE

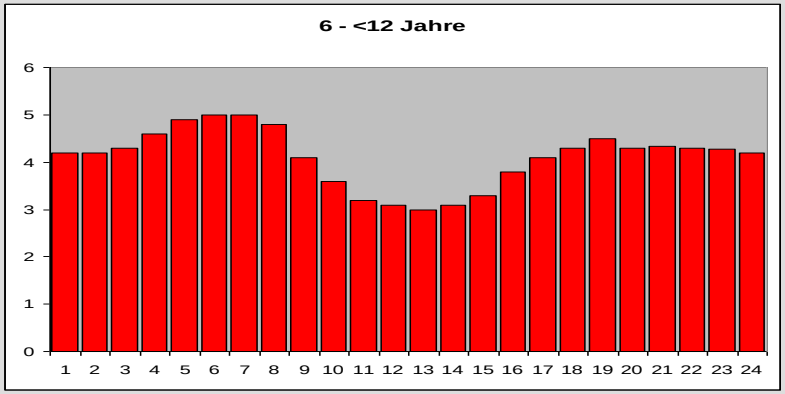
Altersabhängige Basalratenprofile



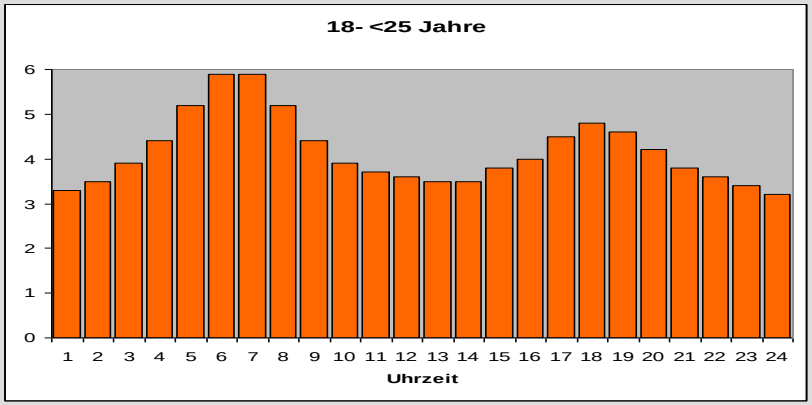
40.5% = 0.25IE/kg/d



41.2% = 0.45IE/kg/d



40.1% = 0.33IE/kg/d



48.0% = 0.35IE/kg/d

DPV QS-DPV DPV-Wiss

N= 5911, Data 1995-2008

Bachran et al. Pediatric Diabetes 2012

Diabetic ketoacidosis: clinic, treatment and prevention

Professor Wieland Kiess

Hospital for Children and Adolescents

Center for Pediatric Research

University of Leipzig, Germany

Universitäts-Kinderklinik -Leipzig-

Kinder-Diabetes-Register - Sachsen -

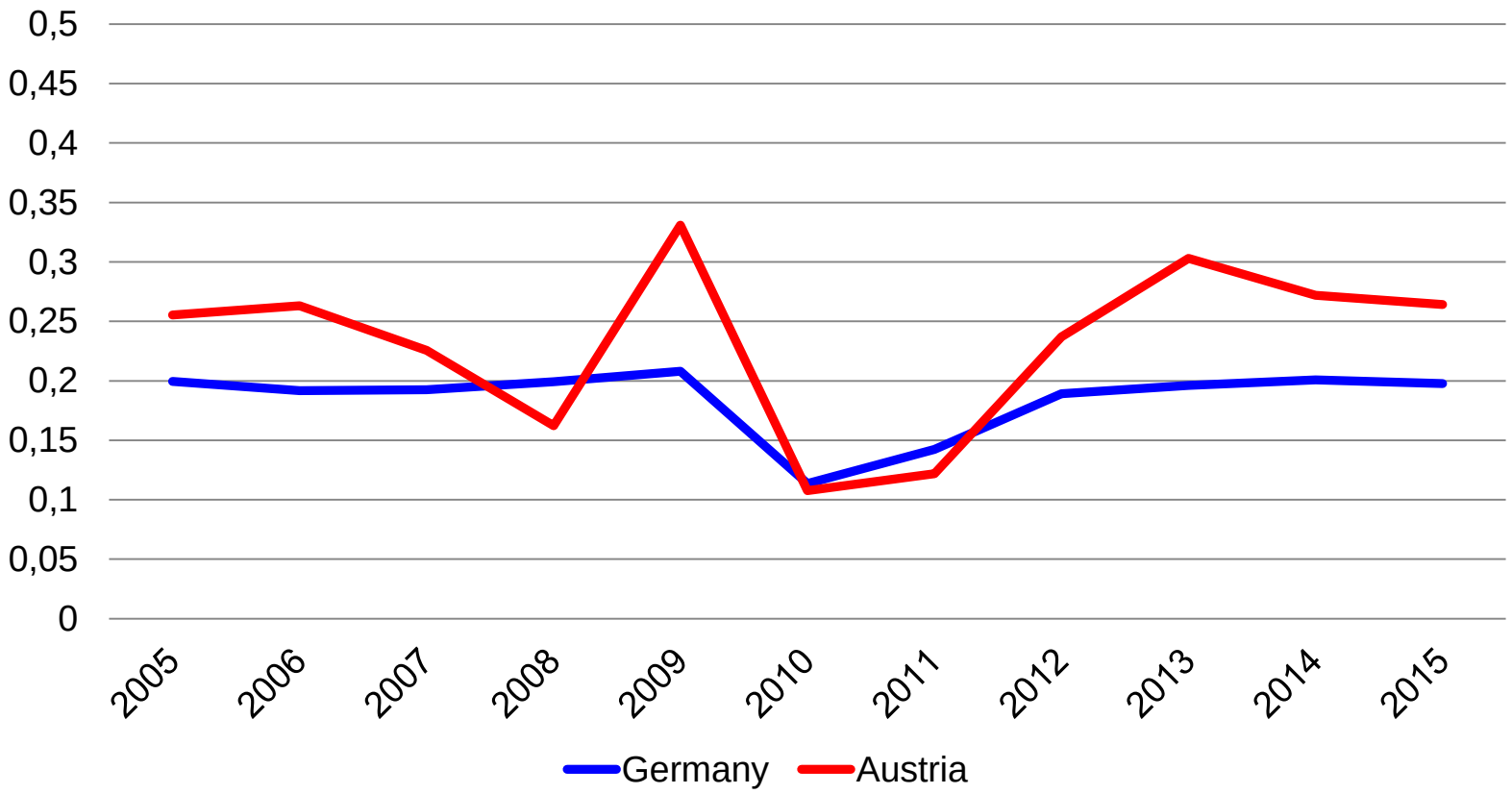
Kompetenznetz Diabetes mellitus

Definition

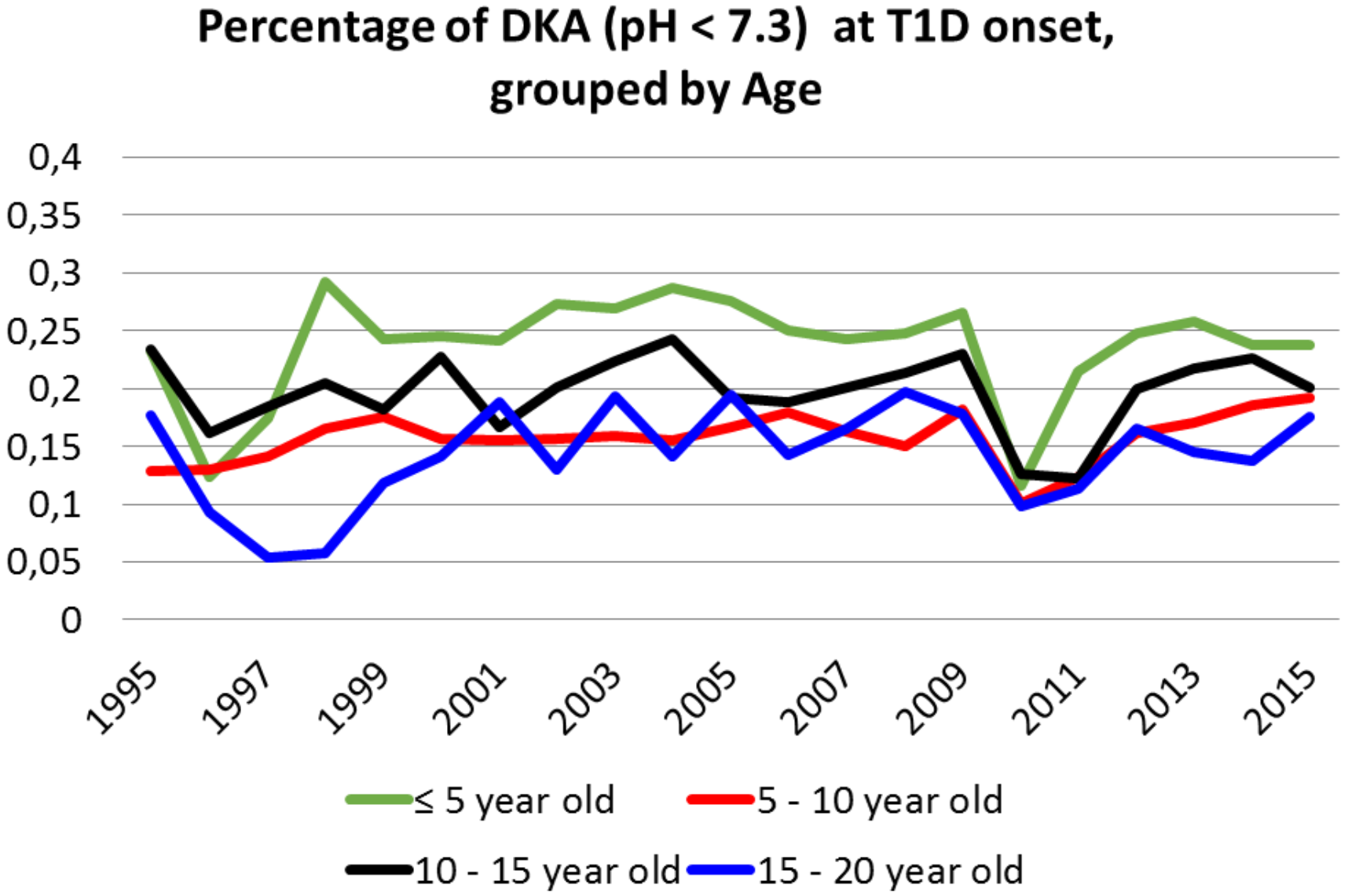
- Hyperglycemia (blood glucose >200mg/dl (11mmol/l))
- pH<7.3
  or standard bicarbonate <15mmol/l
- and ketonuria/ketonemia

AGPD-Leitlinie/ISPAD guideline

Percentage (10-35%) of DKA (pH < 7.3) at T1D onset Comparison between Austria and Germany

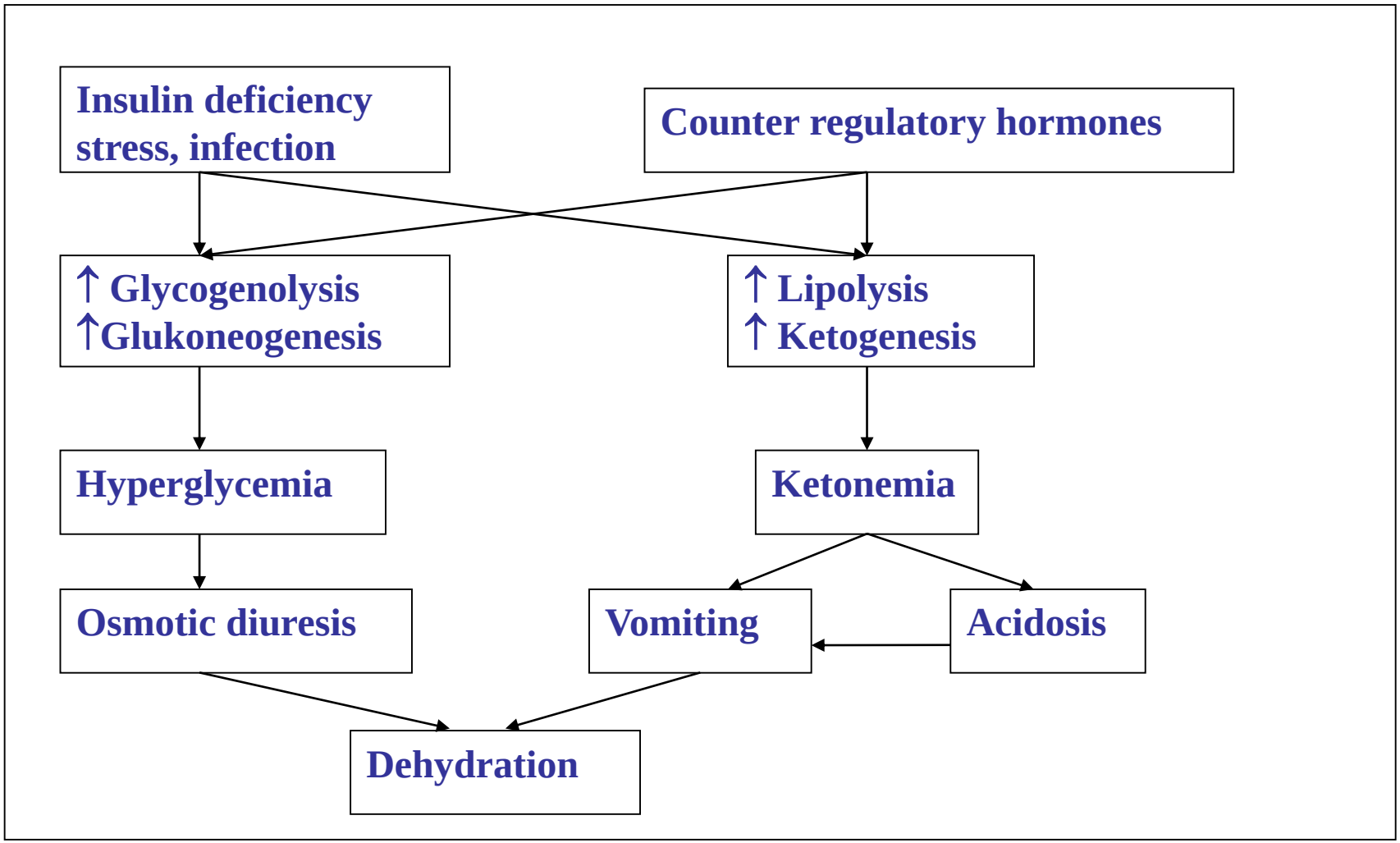


Nagl, Neu, Kapellen et al. Poster ISPAD 2016



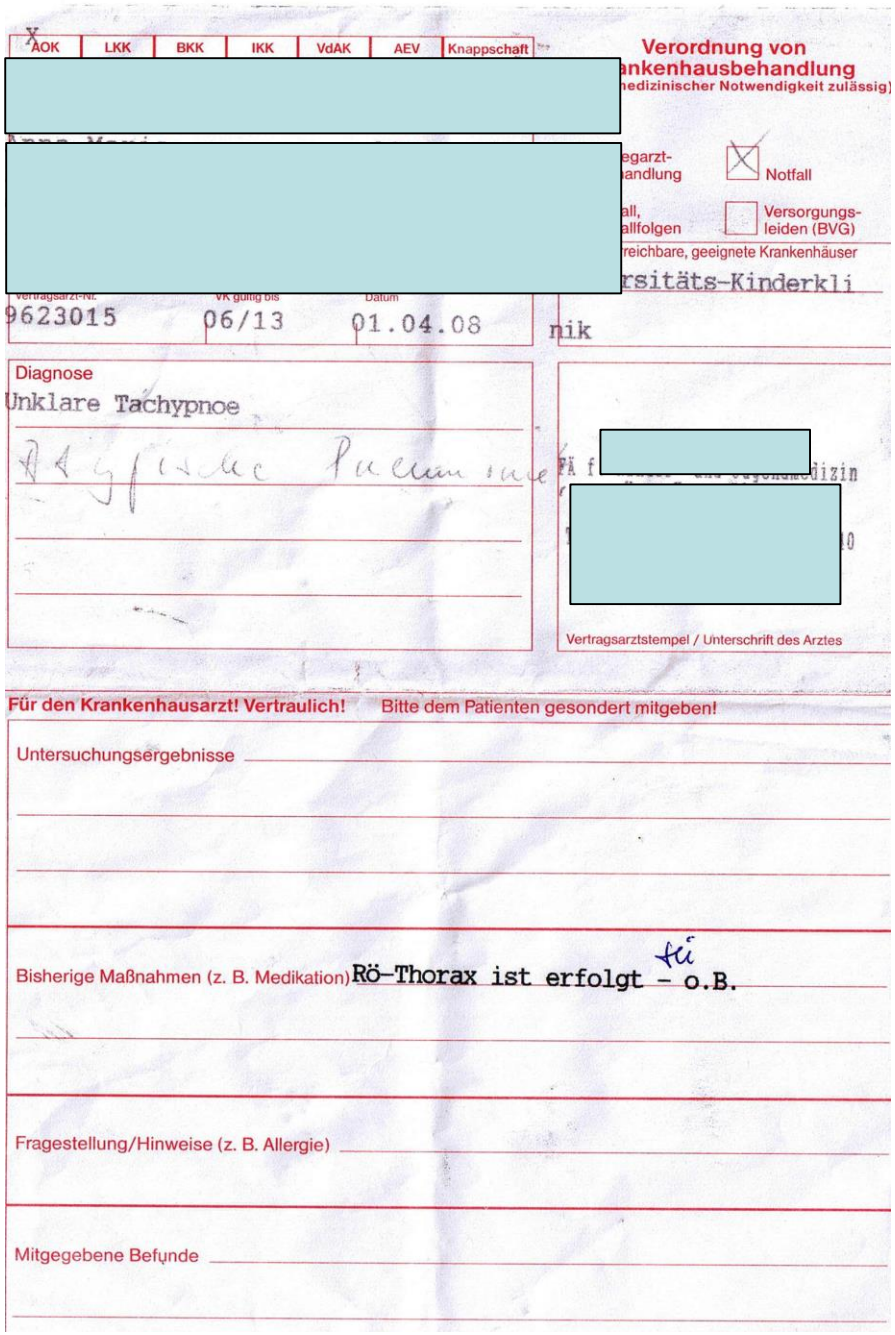
Nagl, Neu, Kapellen et al. Poster ISPAD 2016

Pathogenesis of DKA



Clinical manifestation and misdiagnoses at manifestation

Symptoms	Misdiagnoses
Polyuria Secundary enuresis Polydipsia	Urinary tract infection Diabetes insipidus Psychogenic Polydipsia
Exsikkosis Vomiting Abdominal pain Paleness	Constipation, angina tonsillaris Gastroenteritis Appendicitis Anemia
Heavy breathing	Pneumonia Psychogenic hyperventilation
Unconsciousness	Meningoencephalitis
Muscle weakness	Myopathy Anorexia



Diagnosis of diabetic ketoacidosis missed !

Pneumonia

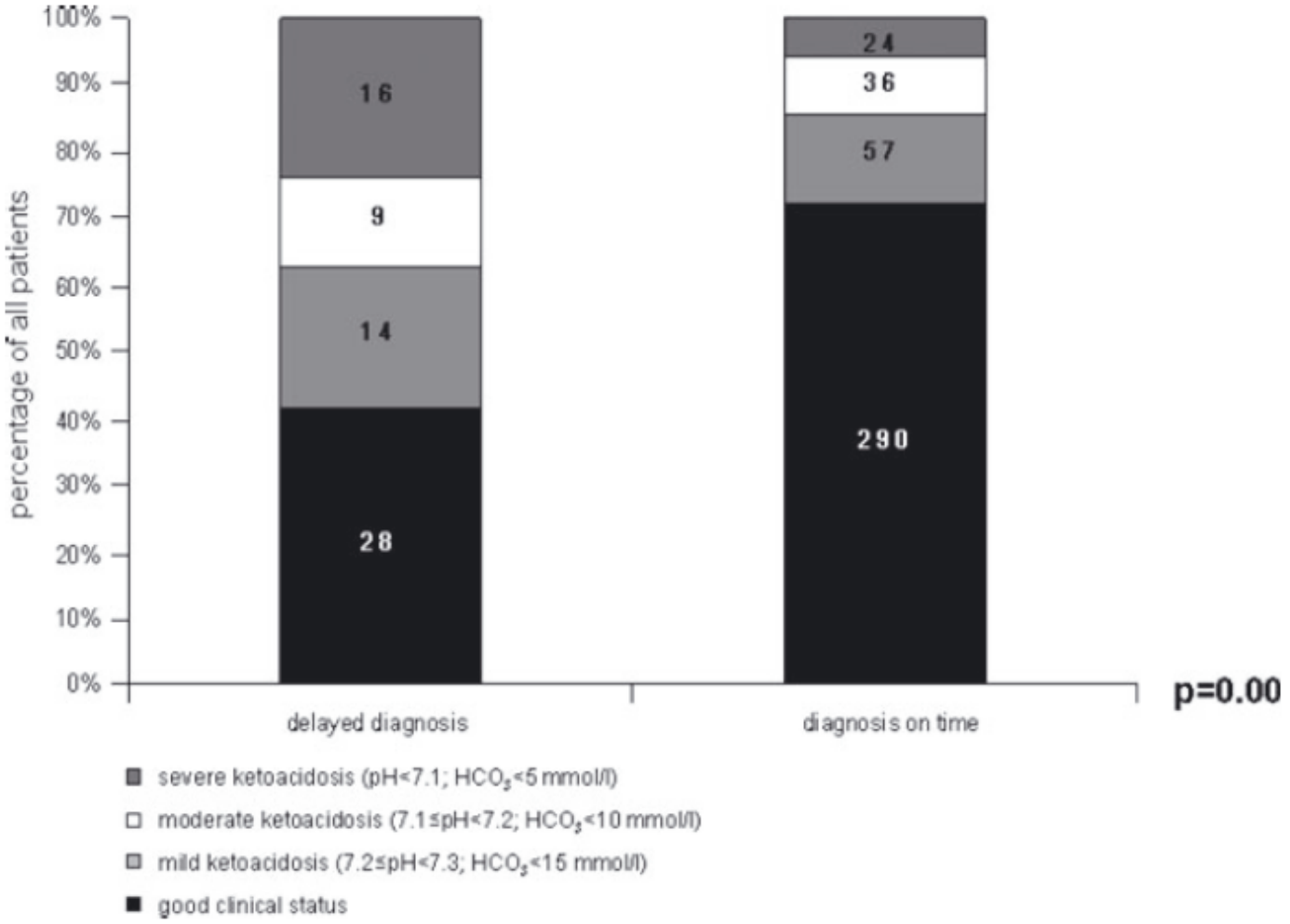
X-ray performed

Metaanalysis of risk factors for DKA at diabetes manifestation

DKA at manifestation	
Risk factors	**Protective factors**
Young age (<2 years; <5 years)	First degree relative with diabetes
Misdiagnosis at manifestation	High incidence/prevalence of diabetes in country/region
Infection	
Ethnic minority	
Low income/no insurance	

Usher-Smith J et al BMJ 2011

Late diagnosis of DKA



Pawlowicz M et al Pediatric Diabetes2009

Treatment goals in DKA

- Cardiovascular stabilisation (initial volume bolus)
- Slow, ballanced fluid and electrolyte rescue
- Correction of acidosis and ketosis
- Slow normalisation of blood glucose
- Avoid complications (cerebral edema, hypokalemia, hypoglycemia)
- Investigate cause of ketoacidosis (underlying condition?)

ITS-Leitlinien Diabetische Ketoazidose

! Info Hintergrund bei pH < 7,2 !

1. Diagnostik :

initiale BE:

- Astrup, Harnstoff, Osmolarität i.S., BB, CrP, Ketonkörper im Serum, Urinstatus, Ketonkörper i. Urin
- 1 gr. EDTA + 1 großes Serum-Röhrchen für das Forschungslabor

Folgeabnahme:

- HbA1C, TSH, Anti-TPO-AK, Cholesterol, TG, LDH, HDL,

regelmäßige Kontrollen:

- Astrup + BZ ½ stündlich
- ab pH >7,15: Astrup stdl., BZ ½ -stdl. bis stabil
- je Urinportion Ketonkörper und Glucose i. Urin

2. Infusionstherapie:

Art der Infusionslösung:

initial:

- bei pH > 7,0: NaCl0,9%
- bei pH < 7,0: Ringer-Lactat

später:

- wenn ab Beginn der Insulintherapie BZ von ≤ 17 mmol/l oder BZ-Abfall von > 5mmol/l/h: vollisotone Glucose 5% bzw.10% (70ml NaCl 1000 a 500ml G5% o. G10%)

- ab Stunde 6 je nach Natrium halbisotone Infusionslösung mgl.

Infusionsgeschwindigkeit:

Kinder unter 5 Jahren:
1. Stunde: 20 ml/kg/h (aber nicht mehr als 500ml/h)
2. Stunde: 10 ml/kg/h (aber nicht mehr als 500ml/h)
3. Stunde: 6 ml/kg/h
4. Stunde: 4 ml/kg/h
ab Stunde 5: 2 - 4 ml/kg/h

Kinder über 5 Jahren:
1. Stunde: 20ml/kg/h (aber nicht mehr als 500ml/h)
2. - 4. Stunde: 10ml/kg/h (aber nicht mehr als 500ml/h)
ab Stunde 5: 2 - 4 ml/kg/h

Systematic monitoring of conditions, treatments, clinical statu

Stunde	BZ	pH	Na	K	Urin-menge/ Keton-körper)	Insulin IE/kgKG/h	K-Substitution (mmol/kg/h)	NaCl 0,9% bzw. Ringer-Laktat	TJHG5	G5%	G 10 %	Trink-menge
0												
0,5												
1,0												
1,5												
2,0												
2,5												
3,0												
3,5												
4,0												
4,5												
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10,5												
11,0												
11,5												
12,0												
12,5												
13,0												

Systematic and controlled insulin treatment

Normalinsulin im Bypass

0,5 IE / kg KG in 50 ml NaCl 0,9%

BZ (mmol/l)	Insulindosis (IE / kg / h)	Infusionsgeschwindigkeit (ml/h)
> 10	0,1	10
9,9 - 8	0,075	7,5
7,9 - 5	0,05	5
4,9 - 3	0,025	2,5
< 3	kein Insulin	0

Initial cardiovascular stabilisation/ fluid/volume substitution

NaCl 0.9% 10-20ml/kg i.v. for 1-2h

Thereafter correction of fluid deficit over 36-48 hours

During first 4-6h plasma isotonic electrolyte solution (NaCl 0.9%/ Ringer lactate; no data re Ringer acetate)

Maximal daily dose <1.5-2 fold fluid dose for age and weight.

5% glucose/0.45% NaCl when blood sugar <15mmol/l/ 270mg/dl or blood sugar decrease >5mmol/l/h (90mg/dl/h)

AGPD Leitlinie Diabetologie und Stoffwechsel 2016

Infusion velocity (Leipzig)

- **Children below 5 years:**
  - **1. hour: 20 ml/kg/h (not more than 500ml/h)**
  - **2. hour: 10 ml/kg/h (not more than 500ml/h)**
  - **3. hour: 6 ml/kg/h**
  - **4. hour: 4 ml/kg/h**
  - **from 5. hour: 2 - 4 ml/kg/h**

- **Children above 5 years:**
  - **1. hour: 20ml/kg/h (not more than 500ml/h)**
  - **2. - 4. hour: 10ml/kg/h (not more than 500ml/h)**
  - **fom 5. hour: 2 - 4 ml/kg/h**

Infusion volume (Leipzig)

- Within first four hours do not give more than 40 - 50ml/kg
- Consider and recalculate drinks and fluid therapy before arrival in hospital (for example given in ambulance/by emergency physician etc.)
- Urinary output is not compensated/calculated (when diuresis is high **do not** increase volume/velocity)

Insulin therapy

- **Initiate after 1-2h of start of volume substitution (???)**
- **Normal/regular insulin**
- **0.1 IE / kg body weight / h insulin**
- **Children (AGPD : young children) < 5 years 0.05 IE/kg b.w./h**
- **Glucose decrease: 2-5mmol/l/h**
- **With blood glucose below 15mmol or too rapid decline add 5% Glucose (Leipzig 10%)**
- **Do not interrupt insulin substitution until pH 7.3 is reached**
- **Monitoring of insulin therapy in written treatment plan**

AGPD Leitlinie Diabetologie und Stoffwechsel

Potassium substitution

- **Hyperkalemia**: add potassium only after onset of diuresis and start of insulin treatment
- **Normokalemia**: with start of insulin therapy
- **Hypokalemia**: immediate replacement
- 40mmol/l volume
- 5mmol/kg/d
- Not more than 0.5mmol/kg/h
- Expected potassium requirement in 24 h: 3-6 mmol/kg

AGPD Leitlinie Diabetologie und Stoffwechsel 2016

Correction of acidosis

- **Bikarbonate may not be recommended, due to potentially increased risk for brain edema**

- **Yet, consider if:**

1.) life threatening hyperkalemia
2.) long standing, uncorrectable acidosis
3.) imminent or manifest cardiovascular decompensation

- **substitution with:**

1-2 mmol/kg NaBi 8,4% in one hour

AGPD Leitlinie Diabetologie und Stoffwechsel 2016

Monitoring

- **Hourly pulse, ventilation (frequency), blood pressure, ECG monitoring**
- **2-4 hourly body temperature**
- **Hourly input/output, volume ballance every 2h, urinary catheter**
- **Hourly blood sugar, hourly blood gas analysis, ketones until negative**
- **Brain edema monitoring (Glasgow Coma scale)**

AGPD Leitlinie Diabetologie und Stoffwechsel 2016

Brain edema – clinical signs

- **First symptoms: most likely at 4-12 hours**
- **Clinical signs:**
  - **Headache, vomiting, increase of blood pressure, unrest, apathy or irritability, incontinence, unresponsiveness, blood pressure decrease and bradykardia, loss of cerebral nerve functions**
- **Monitoring:**
  - **Children < 5 Jahre with pH < 7,0 : arterial RR-monitoring**
  - **Older children: individual decision according to clinical picture**
- **Pupillar reaction:**
  - **within first three hours: hourly**
  - **from 4. hour: ½ -hourly**

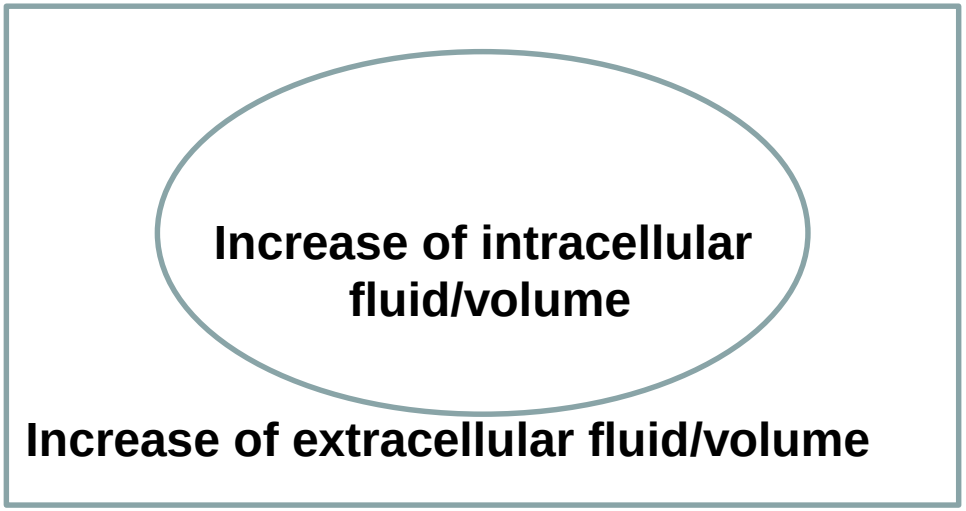
Risk factors for the development of cerebral edema (after Glaser, Mahony, Marcin, Lawrence)

- **Low pCO2 (relative risk 3.4 fold for each 7.8mmHg)**
- **High initial serum urea (relative risk 1.7 fold for each 3.2mmol/l)**
- **Treatment with bicarbonate**
- **Forced ventilation with hyperventilation**
- **DKA at manifestation**
- **Low increase of Na-concentration during rehydration (contradicted by Lawrence)**
- **Fluid volume of more than 50ml/kg within first four hours (controversial; variable)**

DKA and cerebral edema in children

- DKA (with cerebral edema) most common cause of death in children/youths with diabetes
- Clinical brain edema in 0.5-0.9% DKA
- At manifestation (0.7-1.3%) mostly within 4-6 hours after admission
- Neurological sequelae of cerebral edema in 15-35% of cases
- In 21-24% of ceberal edema cases still lethal.
- Subclinical manifestations ? Unclear ?
- **Epidemiology not clear**

Development of cerebral edema



Influenced by: Osmotic pressure intra/extracellular,
Plasma osmolarity,
Blood/brain barrier
Capillary leak
Activation of Na/H-chanel via insulin
Administration of free water !!

Prevention of cerebral edema

- DKA prevention
- Insulin not immediately given, no insulin bolus (prevents Na/H activation)
- Avoid free water (type of infusion/solutions, exact history)
- Fluid ballance, not too much
- No bicarbonate
- Avoid decrease of plasma osmolarity
- adequate Na-K substitution and slow decrease of blood glucose concentrations
- Monitoring

Ceberal edema criteria according to ISPAD

- **Diagnostic criteria:**
  - abnormal motoric or verbal reaction to pain
  - Rigidity of extremities, decortikation/decerebration
  - Central nerve paresis (III, IV, VI)
  - abnormal breathing

- **Major criteria:**
  - Disturbed consciousness
  - Pulse deceleration (decrease of at least 20/min, unrelated to wakefulness or volume administration)
  - Incontinentia

Ceberal edema criteria according to ISPAD

- **Minor criteria:**
  - Vomiting
  - Headache
  - Lethargy, sleepiness
  - RR diastolic >90mmHg
  - age < 5 years

→ 1 diagnostic criterium <u>or</u>
→ 2 major criteria <u>or</u>
→ 1 major - and 2 minor criteria

→→ Sensitivity of 92%

Treatment of cerebral edema

	ISPAD	DDG
Cerebral edema monitoring	+ Score	+ ISPAD Score
Fluid/volume management	Reduction of volume by 1/3	Reduction of volume by 1/3
Position	Head up	Head up
Mannitol	0.5-1 g/kg IV over 20` Repeat if necessary	0.5-1 g/kg IV over 10-15` Repeat if necessary
3% NaCl	5 ml/kg over 30 minutes	2.5-10 ml/kg over 10-15` if not succesful
Ventilation	Yes, no hyperventilation	Yes
Imaging	CT after initiation of therapy	MRT (CT) after initiation of therapy

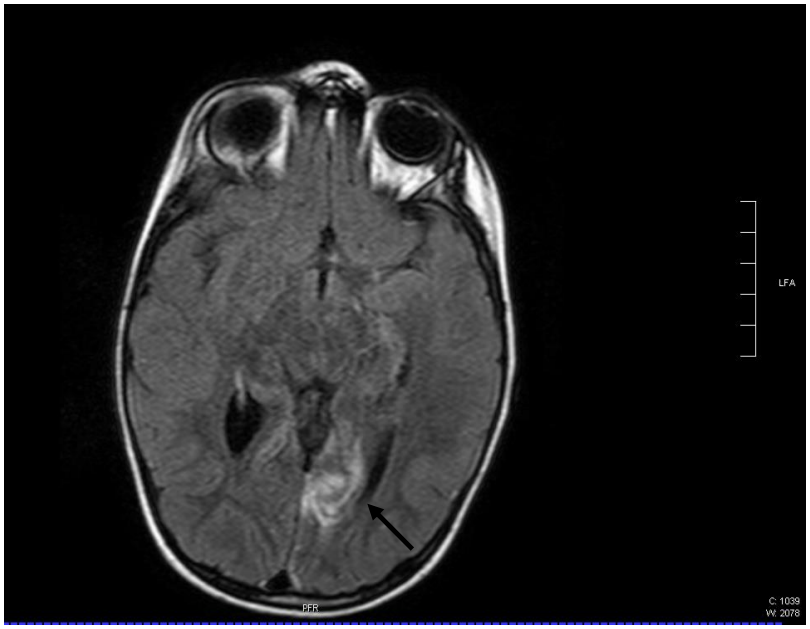
Initial treatment concept (Leipzig)

- Immediately if cerebral edema is suspected
- Reduction of infusion volume by 1/3
- Positioning head up
- 1. initial furosemide bolus 0.5mg/kg
- 2. Mannitol 20% 1g/kg = 5 ml/kg over 20 minuntes
- 3. thereafter second furosemide bolus von 0.5mg/kg

Cerebral infarction during brain edema during DKA

figure 1:

a



b

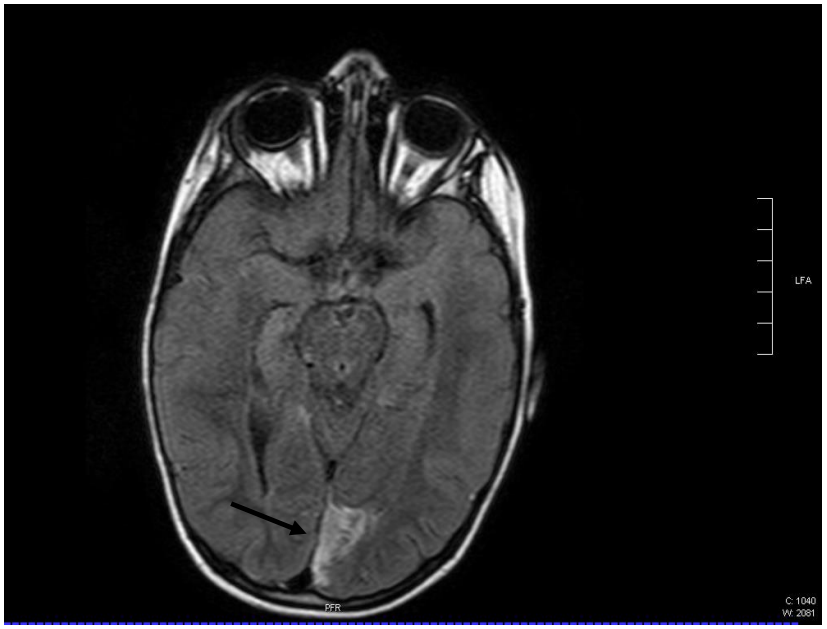


Figure 1) Cranial magnetic resonance imaging (16 days after therapy start) showing hyperdense areas in the occipital area (a/b; solid arrow) consistent with infarction in the distribution of the left posterior cerebral artery in a 2-year-old child with new onset of type 1 diabetes.

Extrapontine myelinolysis after DKA/cerebral edema

figure 2:

a **b**

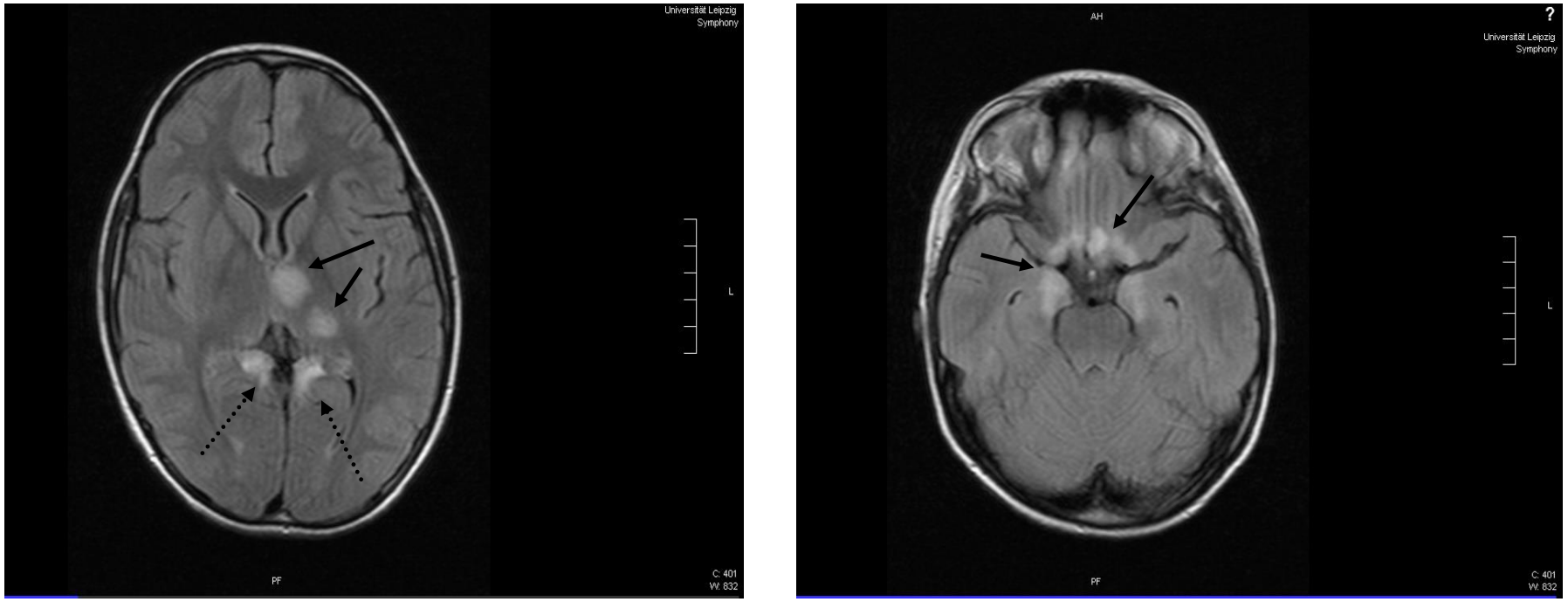


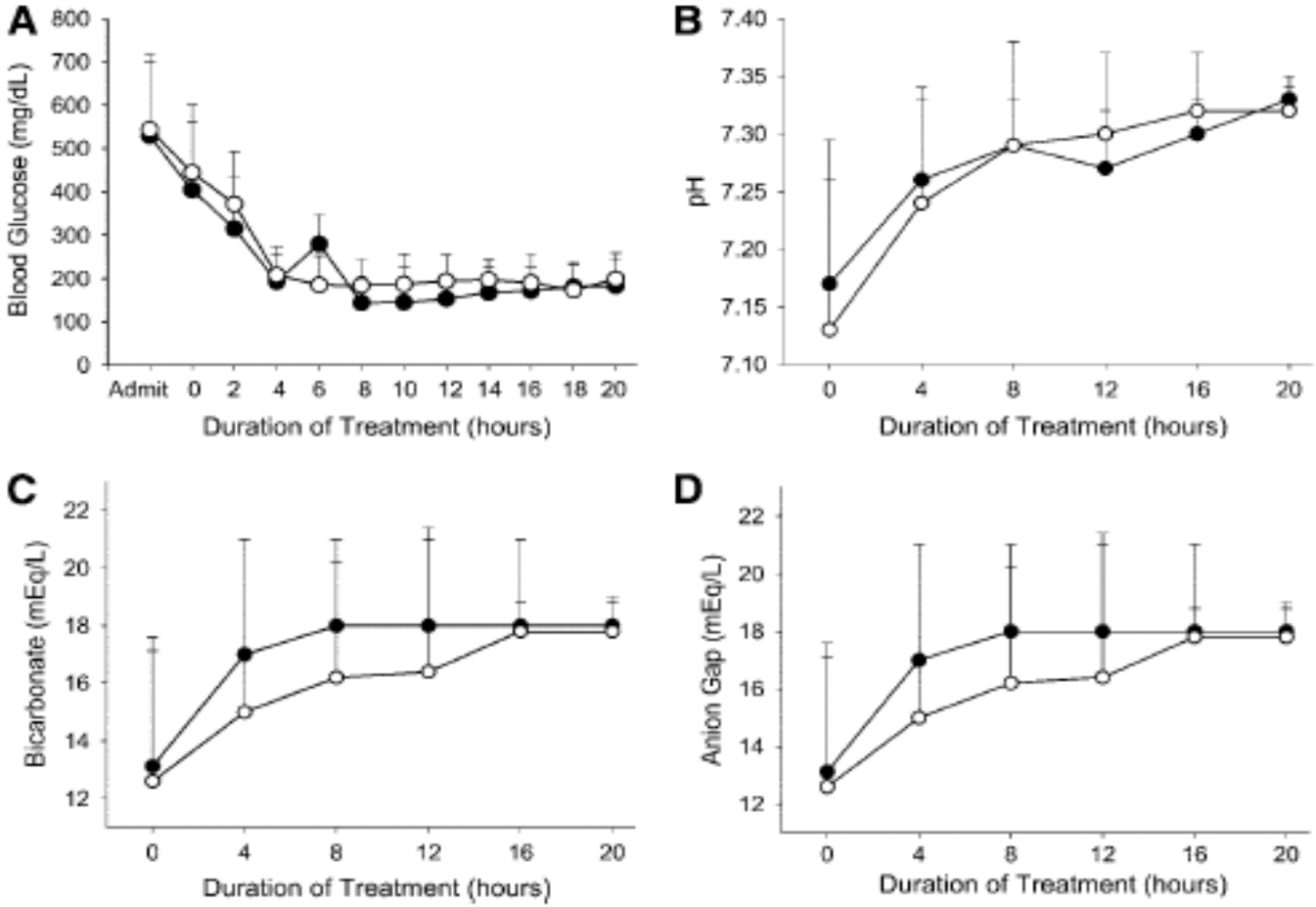
Figure 2) Cranial magnetic resonance imaging of a 14-year-old child with new onset of type 1 diabetes (three days after therapy start) showing multifocal hyperdense lesions in the left thalamus (a; solid arrows) and temporomesial in both sides of the thalamus with affections of the paraterminal gyrus of the frontal lobe (b; solid arrows), also bilateral in the praecuneus (a; discontinued arrows) without contrast medium enhancement – compatible with extrapontine myelinolysis

How many hospitals keep written SOPs/guidelines for DKA ?

- **Survey in the USA**
- **269 hospitals**
- **49-77% (depends upon hospital type) provide a DKA protocol**
- **Only 15-39% provide quality-management protocol with interventions for critically ill patients with diabetes**

Cook CB et al. Endocrine pract 2010:219

Regular/normal or analogue?



Umpierrez et al Diabetes Care 2009:1164

0.025-0.05-0.1IE/Kg?

Treatment of Diabetic Ketoacidosis (DKA) with 2 Different Regimens Regarding Fluid Substitution and Insulin Dosage (0.025 vs. 0.1 units/kg/h)

Authors: T. Kapellen[1], C. Vogel[2], D. Telleis[1], M. Siekmeyer[1], W. Kiess[1]

Affiliations: [1] Hospital for Children and Adolescents, Department for Women and Child Health, University of Leipzig, Germany
[2] Hospital for Children and Adolescents, Klinikum Chemnitz, Germany

	Center A	Center B	p-value
fluid 1st h ml/kgbw	4.27 (0.99–11.8)	9.8 (2.0–52)	<0.0001
fluid 2nd–4th h	3.73 (1.58–17.7)	7.4 (2.2–23.0)	<0.0001
insulin 1st h (IE/kg)	0.027	0.102	<0.0001
bicarbonate (substituted in n cases)	16 (70%)	8 (17%)	0.003

0.1 IE: Acidosekorrektur in 6,5h
0.025IE: Acidosekorrektur in 8h
0.1IE: BZ normal in 10.5h
0.025IE: BZ normal in 18 h ($p<0.005$

Original Investigation

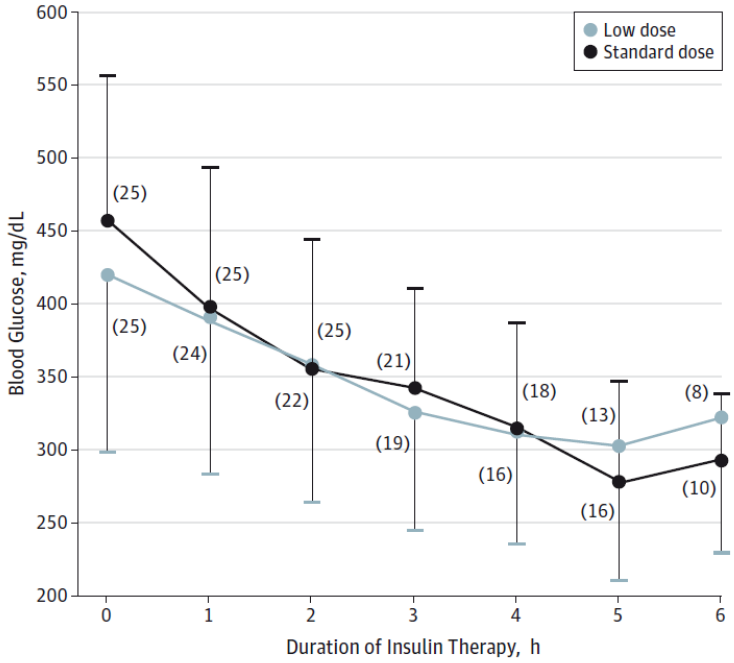
Low-Dose vs Standard-Dose Insulin in Pediatric Diabetic Ketoacidosis
A Randomized Clinical Trial

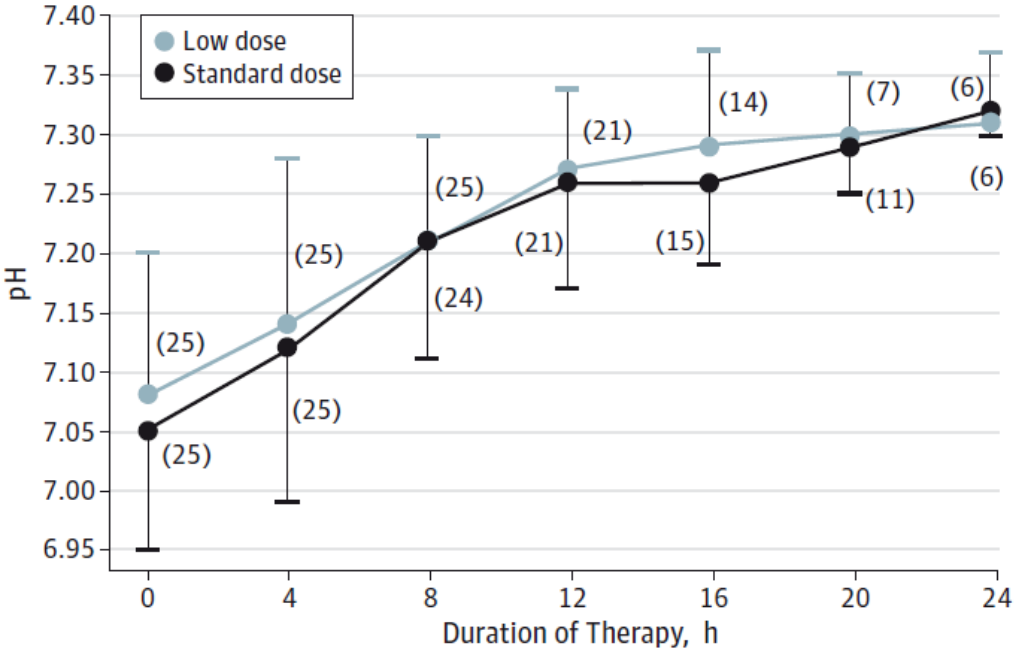
= 0.05 vs 0.1 IE/kgh

JAMA Pediatr. 2014;168(11):999-1005.

Karthi Nallasamy, MD, DM; Muralidharan Jayashree, MD; Sunit Singhi, MD; Arun Bansal, MD

Figure 2. Mean Blood Glucose Decrease With Insulin Therapy





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JAMA Pediatr. 2014;168(11):999-1005.

Karthi Nallasamy, MD, DM; Muralidharan Jayashree, MD; Sunit Singhi, MD; Arun Bansal, MD

	0.05 IE/kgh (n=25)	0.1/kg/h (n=25)	p
Mittlerer BZ Abfall bis 250mg/dl, mg/dl h	45.1 (±17.6)	52.2 (±23.4)	
Zeit bis pH≥ 7.3 (h)	16.5 (±7.2)	17.2(±7.7)	0.73
Hypokaliämie	**5 (20%)**	**12 (48%)**	**0.07**
Hypoglykämie	1 (4%)	5 (20%)	0.17
Notwendigkeit von 10% Glukose	2 (8%)	7 (28%)	0.14
Hirnödem	0	1	
Therapieversager	2 (8%)	1 (4%)	

Pediatric Diabetes

ISPAD International Society for Pediatric and Adolescent Diabetes

Pediatric Diabetes 2013: 14: 435–446
doi: 10.1111/pedi.12027

Pediatric Diabetes

Table 1. Treatment protocol overview

	Protocol A1	Protocol A2	Protocol B1	Protocol B2
Standard initial fluid bolus*	10 cc/kg bolus of 0.9% saline	10 cc/kg bolus of 0.9% saline	10 cc/kg bolus of 0.9% saline	10 cc/kg bolus of 0.9% saline
Additional intravenous fluid bolus	Additional 10 cc/kg of 0.9% saline	Additional 10 cc/kg of 0.9% saline	No additional bolus	No additional bolus
Assumed fluid deficit	10% of body weight	10% of body weight	5% of body weight	5% of body weight
Replacement of deficit	Replace half of fluid deficit + maintenance fluids over initial 12 h, remaining deficit + maintenance fluids over subsequent 24 h	Replace half of fluid deficit + maintenance fluids over initial 12 h, remaining deficit + maintenance fluids over subsequent 24 h	Replace deficit + maintenance fluids evenly over 48 h	Replace deficit + maintenance fluids evenly over 48 h
Fluid used for deficit replacement	0.45% Saline	0.9% Saline	0.45% Saline	0.9% Saline

*This is standard treatment at all participating centers and is not part of the study protocol. Consent will occur during this initial fluid bolus after which the study treatment will be randomized.

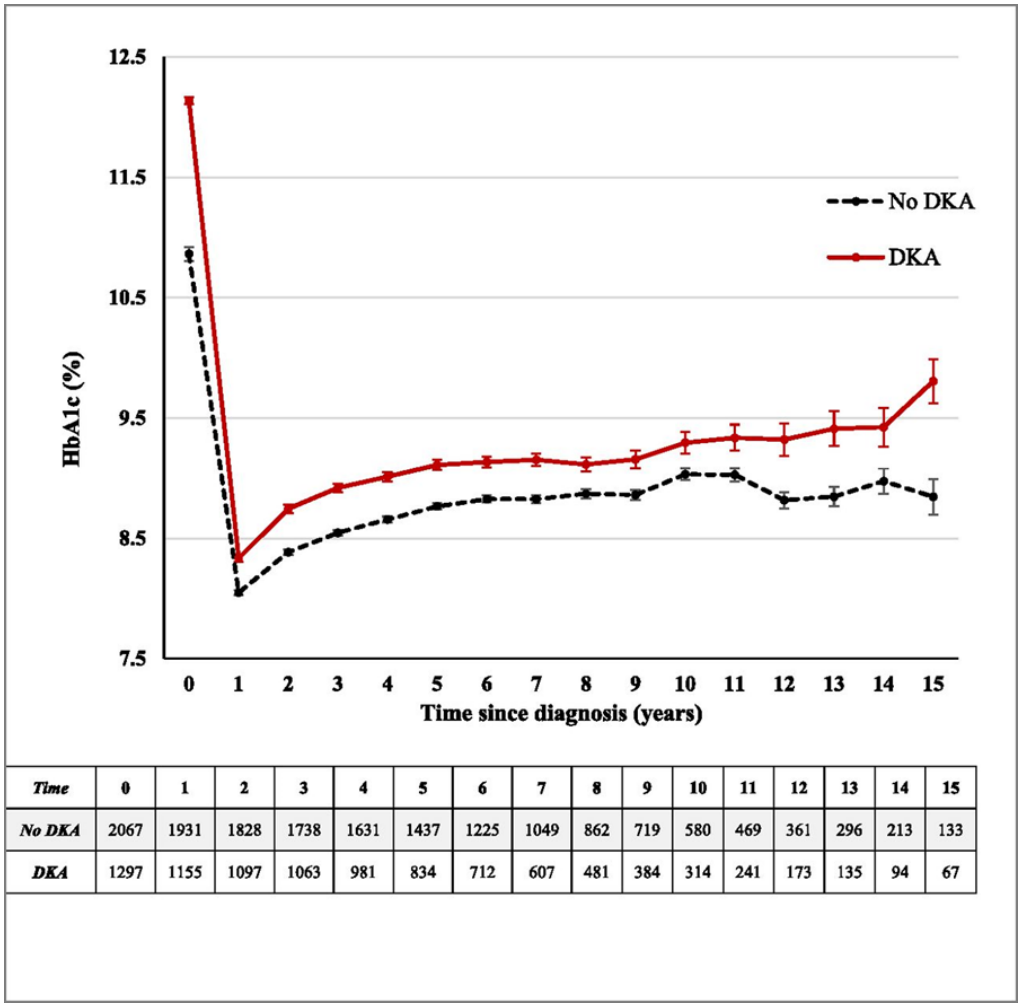
Diabetic ketoacidosis 2019

- **Prevention of DKA – why?**
- **Prevention of DKA at manifestation**
- **Prevention of DKA after manifestation**
- **Prevention/treatment of complications of DKA**

Diabetic Ketoacidosis at Diagnosis of Type 1 Diabetes Predicts Poor Long-term Glycemic Control.

Duca LM, Wang B, Rewers M, Rewers A.

Diabetes Care. 2017 Sep;40(9):1249-1255. doi: 10.2337/dc17-0558. Epub 2017 Jun 30.

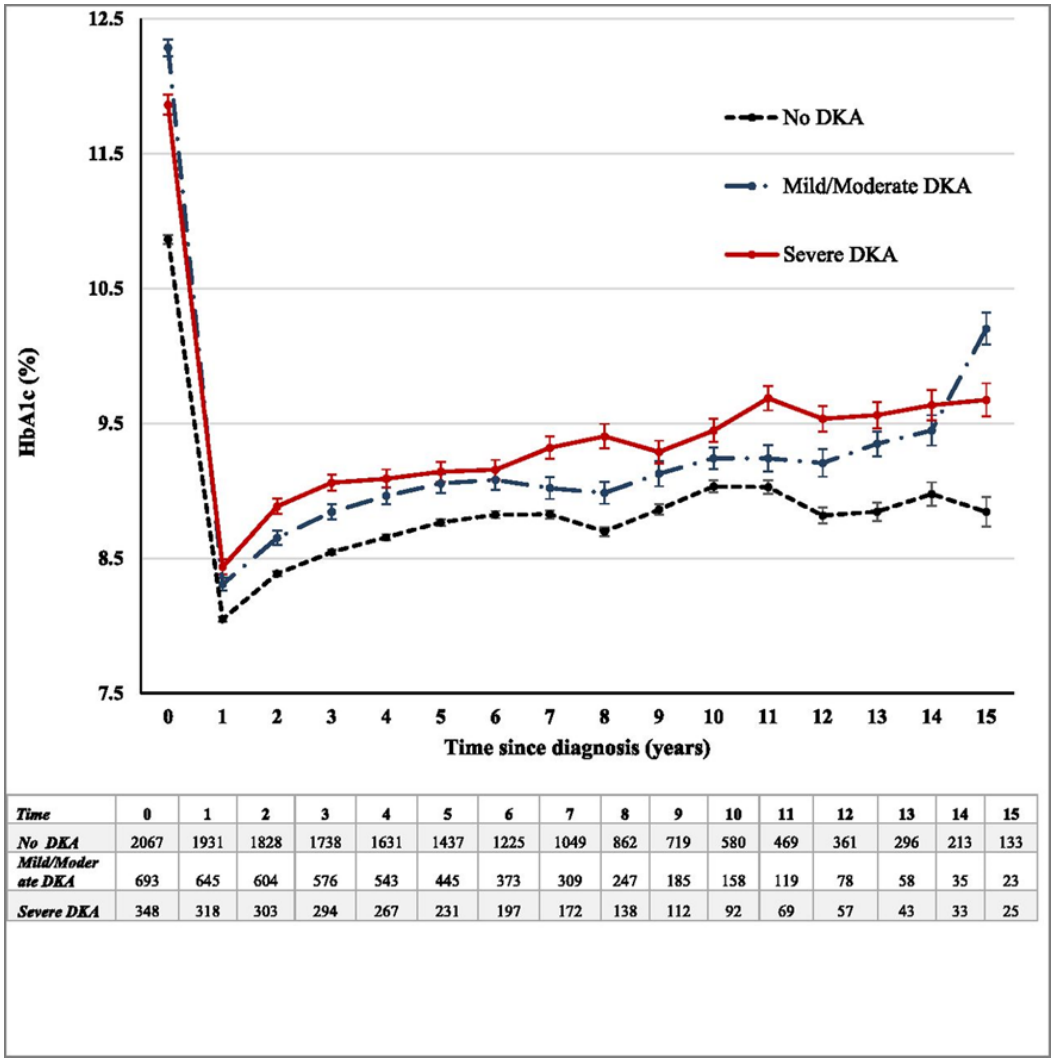


Time	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
No DKA	2067	1931	1828	1738	1631	1437	1225	1049	862	719	580	469	361	296	213	133
DKA	1297	1155	1097	1063	981	834	712	607	481	384	314	241	173	135	94	67

DKA at diagnosis of type 1 diabetes predicts poor long-term glycemic control, independent of demographic or socioeconomic factors.

Figure 1. DKA at diagnosis of children with type 1 diabetes and long-term glycemic control. The numbers reported below the figure represent the number of participants contributing the overall HbA_{1c} level during that point in time. Data presented are mean ± SE from unadjusted linear mixed model.

(Diabetic Ketoacidosis at Diagnosis of Type 1 Diabetes Predicts Poor Long-term Glycemic Control. Duca LM, et al. Diabetes Care. 2017 Sep;40(9):1249-1255. doi: 10.2337/dc17-0558. Epub 2017 Jun 30.)



Time	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
No DKA	2067	1931	1828	1738	1631	1437	1225	1049	862	719	580	469	361	296	213	133
Mild/Moderate DKA	693	645	604	576	543	445	373	309	247	185	158	119	78	58	35	23
Severe DKA	348	318	303	294	267	231	197	172	138	112	92	69	57	43	33	25

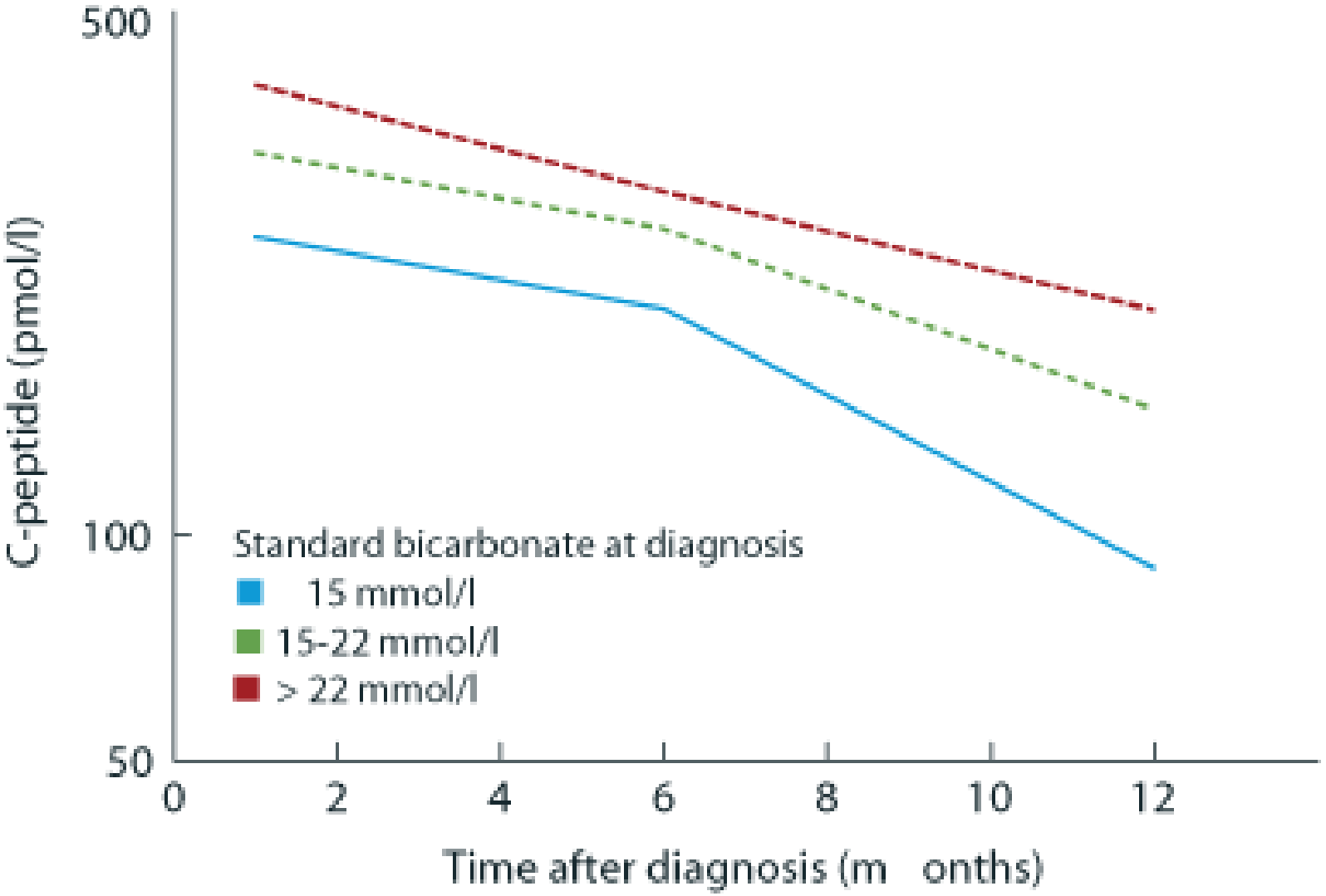
´Dose effect´

Severe DKA at diagnosis of type 1 diabetes predicts poor long-term glycemic control more than mild/moderate DKA

Figure 2. DKA severity at diagnosis of children with type 1 diabetes and long-term glycemic control. The numbers reported below the figure represent the number of participants contributing the overall HbA_{1c} level during that point in time. Data presented are mean ± SE from unadjusted linear mixed model.

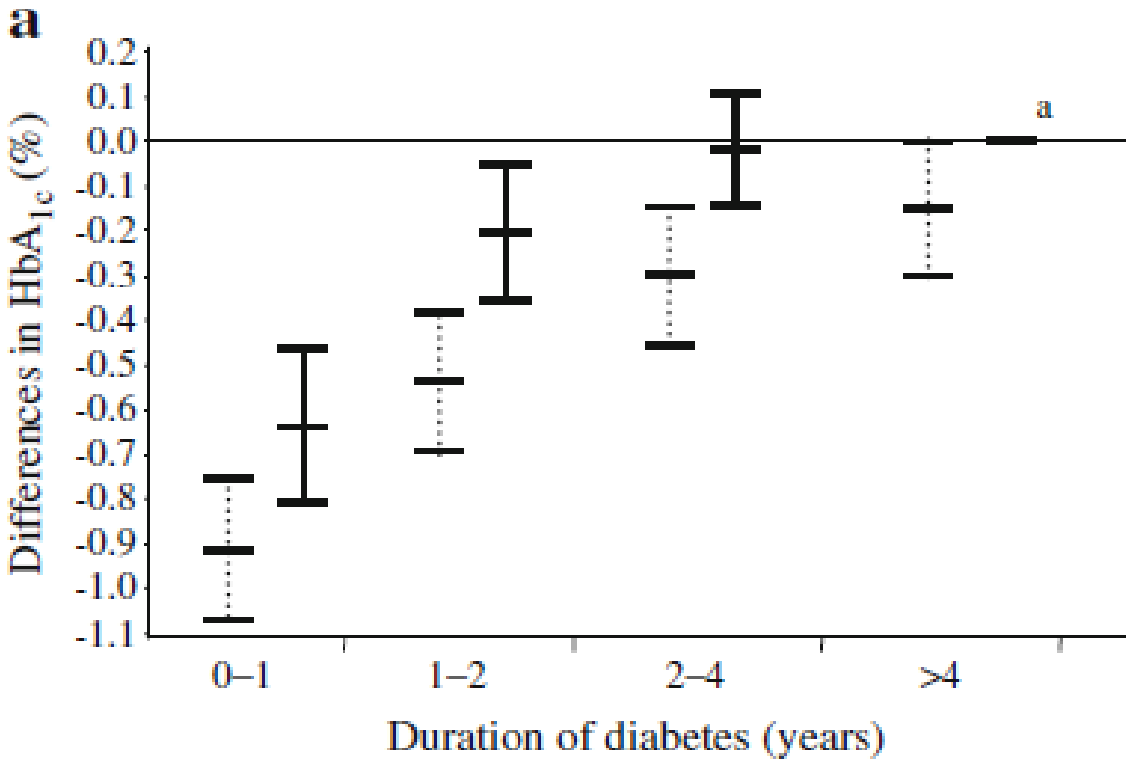
(Diabetic Ketoacidosis at Diagnosis of Type 1 Diabetes Predicts Poor Long-term Glycemic Control. Duca LM, et al. Diabetes Care. 2017 Sep;40(9):1249-1255. doi: 10.2337/dc17-0558. Epub 2017 Jun 30.)

Residual insulin secretion and DKA



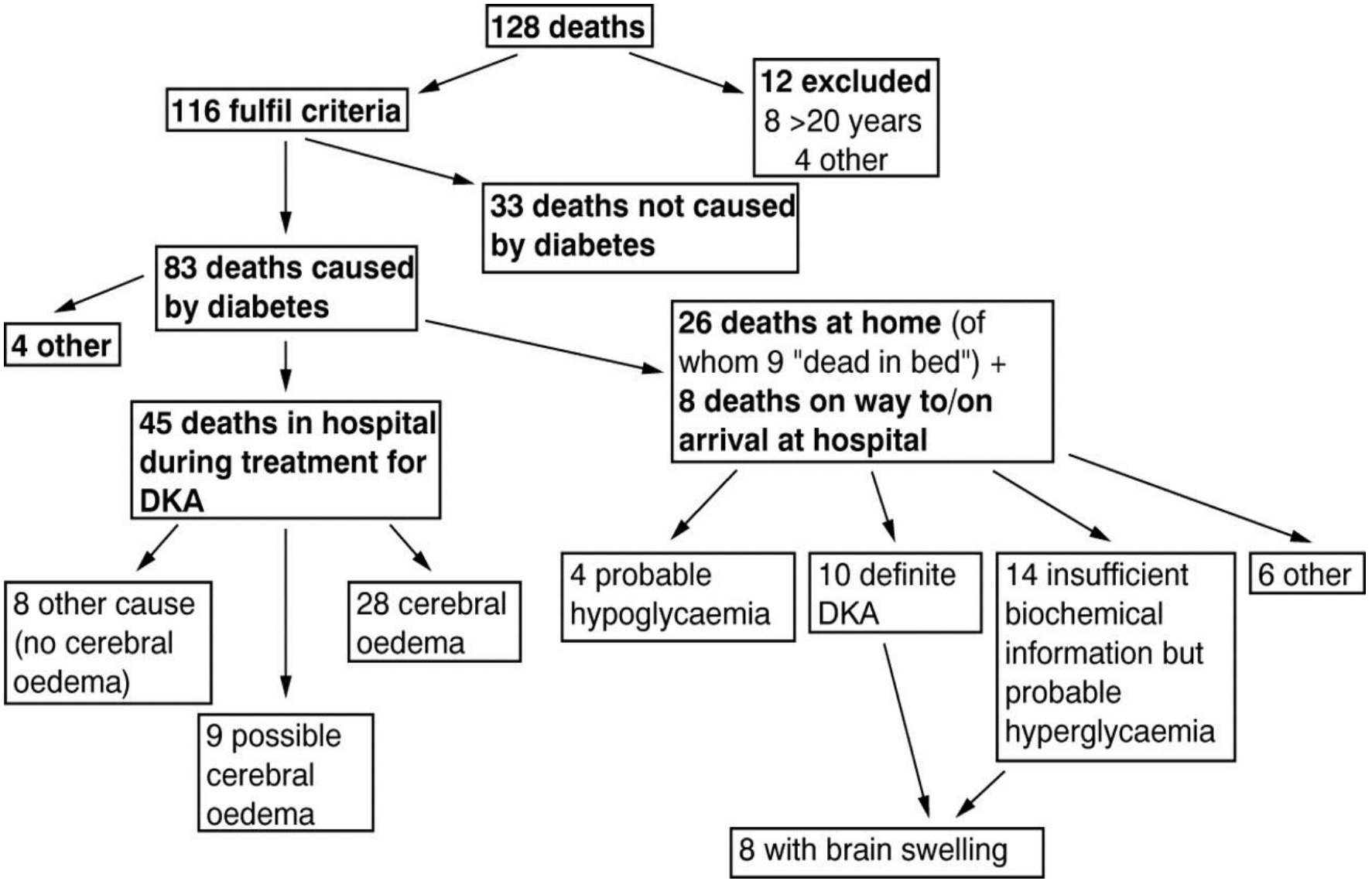
Mortensen et al. Pediatr Diabetes 2010:218-26

DKA and HbA1c in the longterm



Black Lines: medium/severe DKA
Dotted lines: no/mild DKA
Data from the Danish childhood diabetes registry

Fredheim Diabetologia 2013



7 hypoglycemia, 69 DKA

Edge, J. A et al. Arch. Dis. Child. 1999;81:318-323

DKA after manifestation

Table 1—Descriptive data by registry

	Overall *N* = 49,859	DPV *n* = 22,397	NPDA *n* = 16,314	T1DX *n* = 11,148	*P* value
Male	52.2	52.2	53.0	51.1	0.013
Age, years	13.3 (10.3, 15.7)	13.8 (10.5, 16.3)	13.2 (10.4, 15.3)	12.7 (9.8, 15.2)	<0.001
Age at diagnosis, years	6.9 (3.9, 10.0)	7.1 (4.0, 10.4)	7.1 (3.9, 10.2)	6.0 (3.0, 9.0)	<0.001
Type 1 diabetes duration, years	4.9 (2.7, 7.8)	5.0 (2.9, 8.1)	4.7 (2.6, 7.5)	4.0 (2.0, 7.0)	<0.001
BMI *z* score, WHO	0.72 (0.08, 1.40)	0.65 (0.02, 1.30)	0.81 (0.13, 1.52)	0.79 (0.16, 1.48)	<0.001
Pump use	36.1	44.2	11.5	56.1	<0.001
Ethnic minority	18.0	20.4	10.4	22.6	<0.001
Mean HbA_{1c}					
%	8.4 ± 1.5	7.9 ± 1.4	9.0 ± 1.6	8.5 ± 1.4	<0.001
mmol/mol	68 ± 16	63 ± 15	75 ± 17	69 ± 15	
HbA_{1c}					
<58 mmol/L (7.5%)	28.3	42.9	12.0	20.9	<0.001
≥75 mmol/mol (9%)	27.2	16.9	42.0	28.0	<0.001
With ≥1 DKA event	6.0	5.0	6.4	7.1	<0.001

Data shown are unadjusted percentages, mean ± SD, or median and quartiles.

Maahs et al Diabetes Care 2015

Risik factors for DKA after manifestation

- Bad metabolic control
- Previous episodes of DKA
- Puberty/adolescent girls
- Eating disorders
- Low socioeconomic status
- Migrant background (DPV)
- Weight manipulation with insulin
- No insurance (USA)
- Infections (infants/toddlers)

Risk factor unexperienced therapist

Evaluation of the outside therapy of DKA in pediatric patients (Bradley et al Am J Ther 2008)

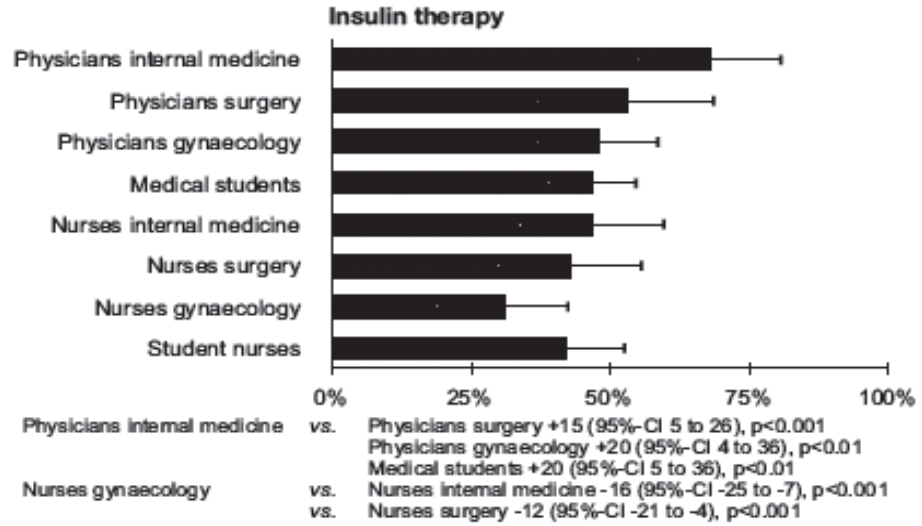
Laboratory: only 58% with blood gas data

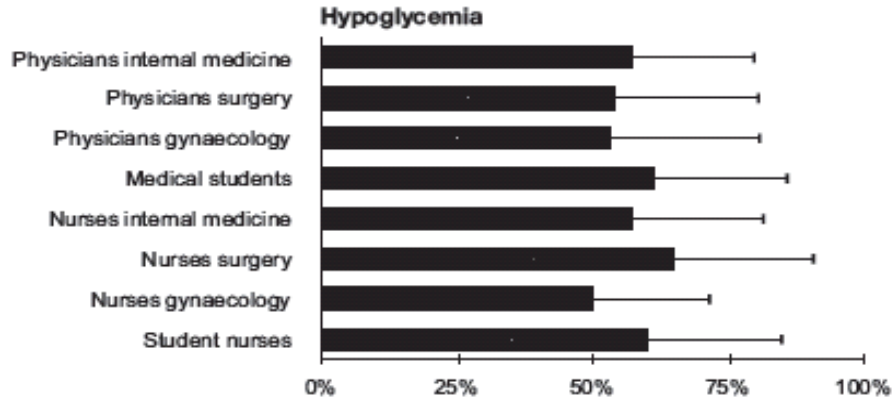
Insulin: bolus in 64% (s.c., i.v.)

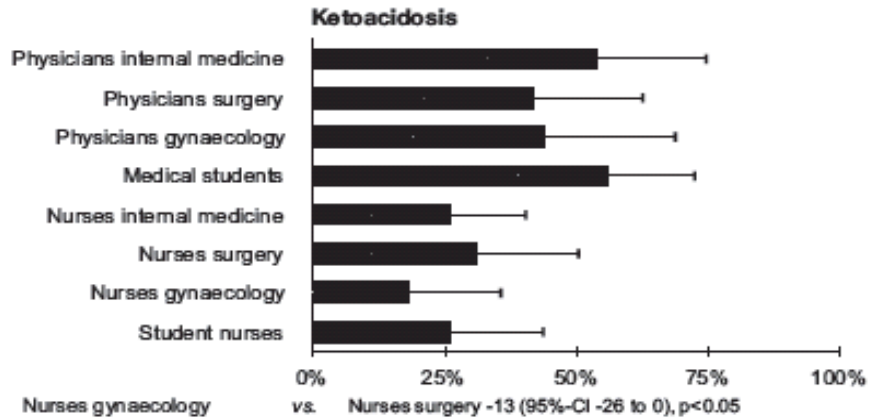
Fluid volume: from 0 to 60ml/kg/h

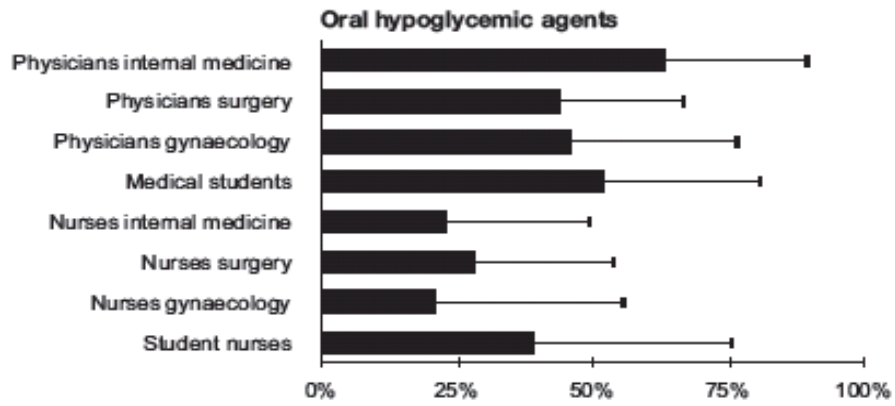
$\Rightarrow$ Lack of guideline-based treatment before hospital admission

Diabetes knowledge in medical professions



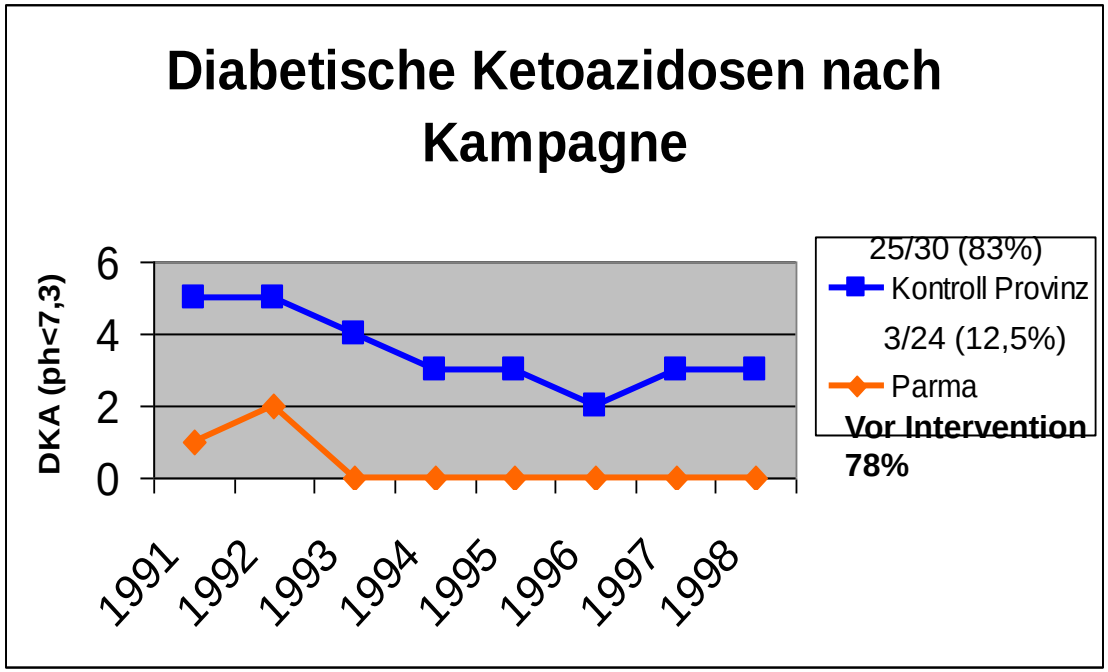




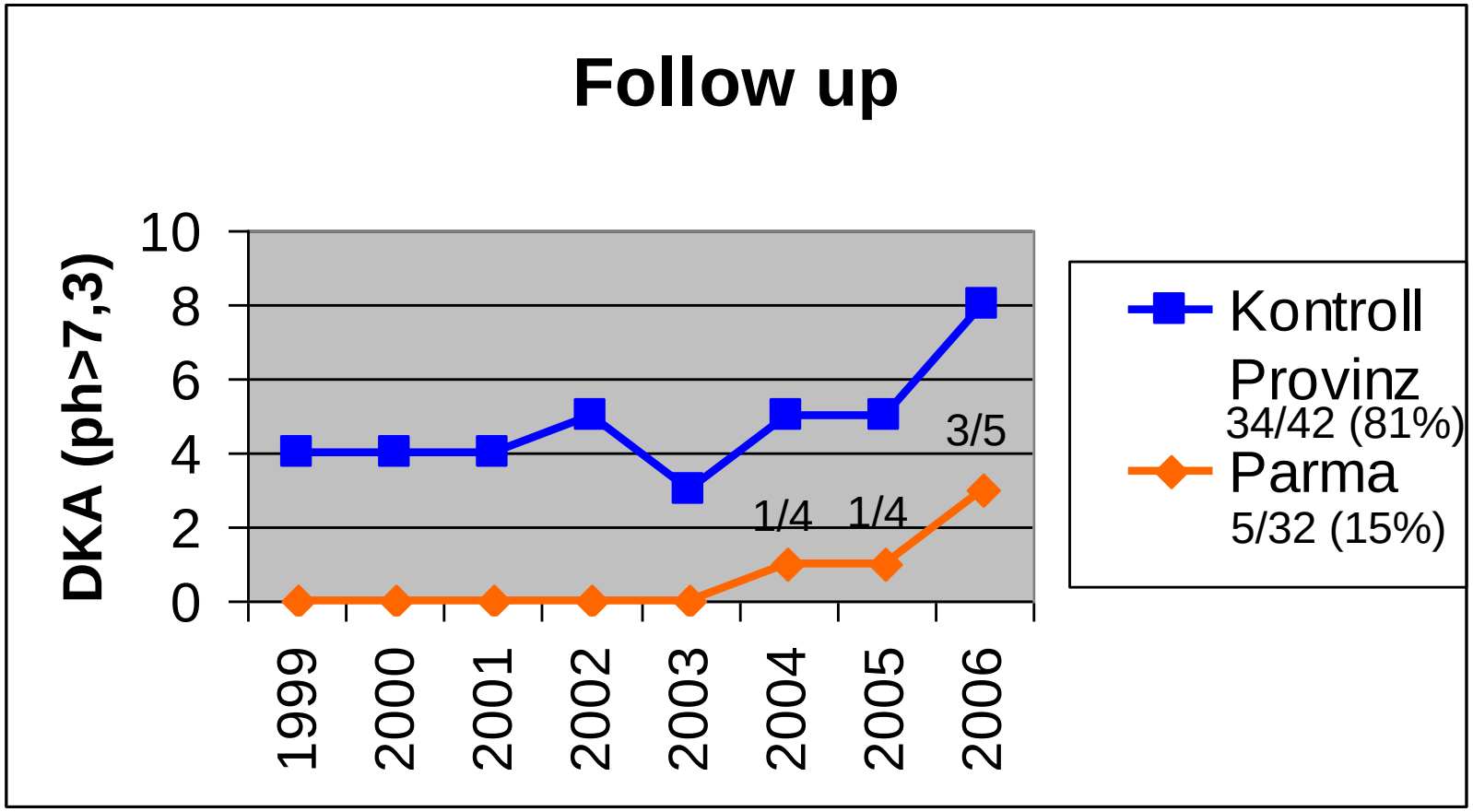


Trepp R et al. Swiss Med wkly 2010:370

Prevention of DKA: Parma campaign



Vanelli et al. Diabetes Care 1999:7-9



Vanelli et al Acta Biomed 2008

world diabetes day
14 November

International Diabetes Federation

www.worlddiabetesday.org/dka

ISPAD
International Society for Pediatric and Adolescent Diabetes

Austrian DKA prevention campaigne

No reduction of DKA incidence

Despite large effort:
Poster for pediatricians, school doctors/nurses,
TV film (once)
and via ÖGD homepage

But: parents not addressed/involved

No redundant/repeated campaigne

bm:uk Bundesministerium für Unterricht, Kunst und Kultur

ÖDG Österreichische Diabetes Gesellschaft
helfen, heilen, forschen

DKA and SMBG

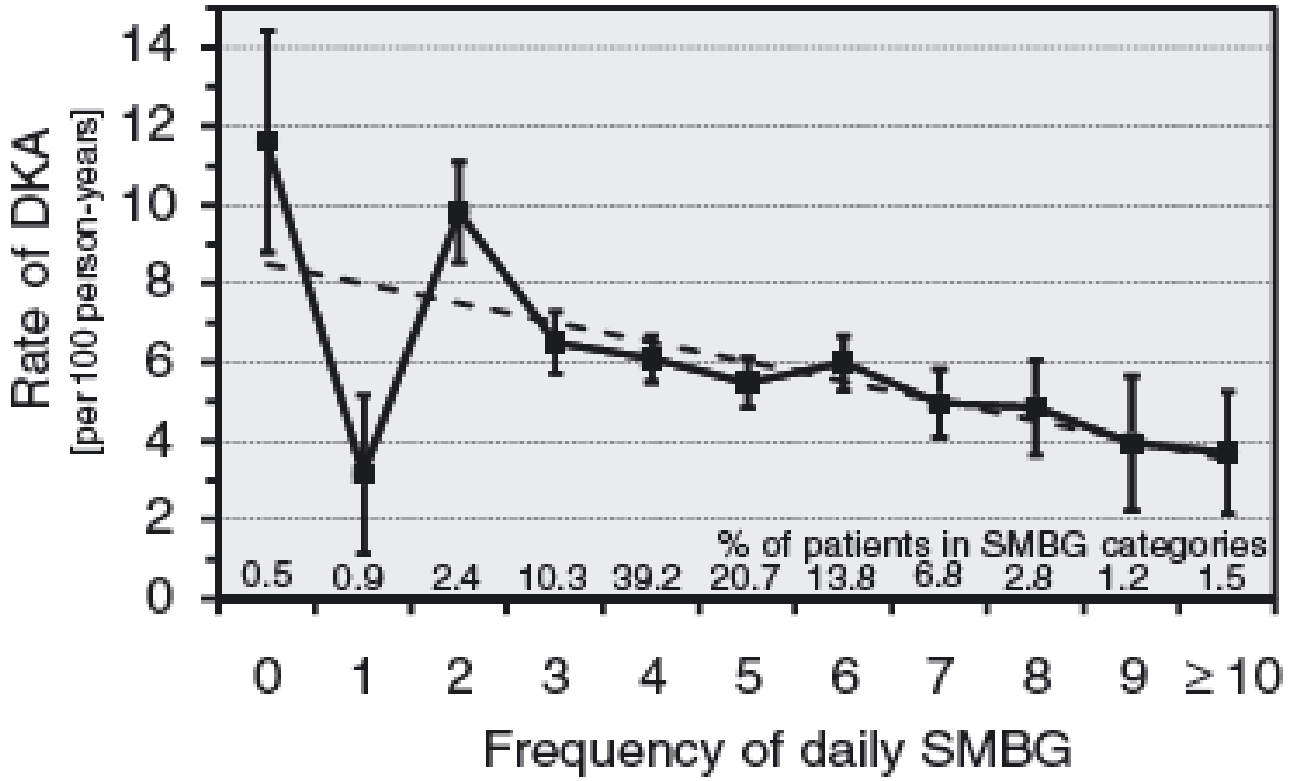


Fig. 6. Rate of diabetic ketoacidosis in relation to frequency of self-monitoring of blood glucose (n = 26 002, vertical bars represent ±SE and dotted line represents linear trend).

Ziegler et al Pediatric Diabetes 2011:11-17

Exposure of insulin/devices to cold and heat

Diabetic ketoacidosis caused by exposure of insulin to low temperature.(Minuto et al Diabet Technol Ther 2010)

Diabetic ketoacidosis caused by exposure of insulin pump to heat and sunlight (Pryce R, BMJ 2009)

Drugs/addiction as risk factor?

Gama *et al. Journal of Medical Case Reports* 2010, **4**:240
http://www.jmedicalcasereports.com/content/4/1/240

CASE REPORT **Open Access**

Diabetic ketoacidosis complicated by the use of ecstasy: a case report

Mirnaluci Paulino Ribeiro Gama[1], Bárbara Vicente de Souza[2*], Ana Carolina Ossowski[3], Rafaela Cristina Perraro[4]

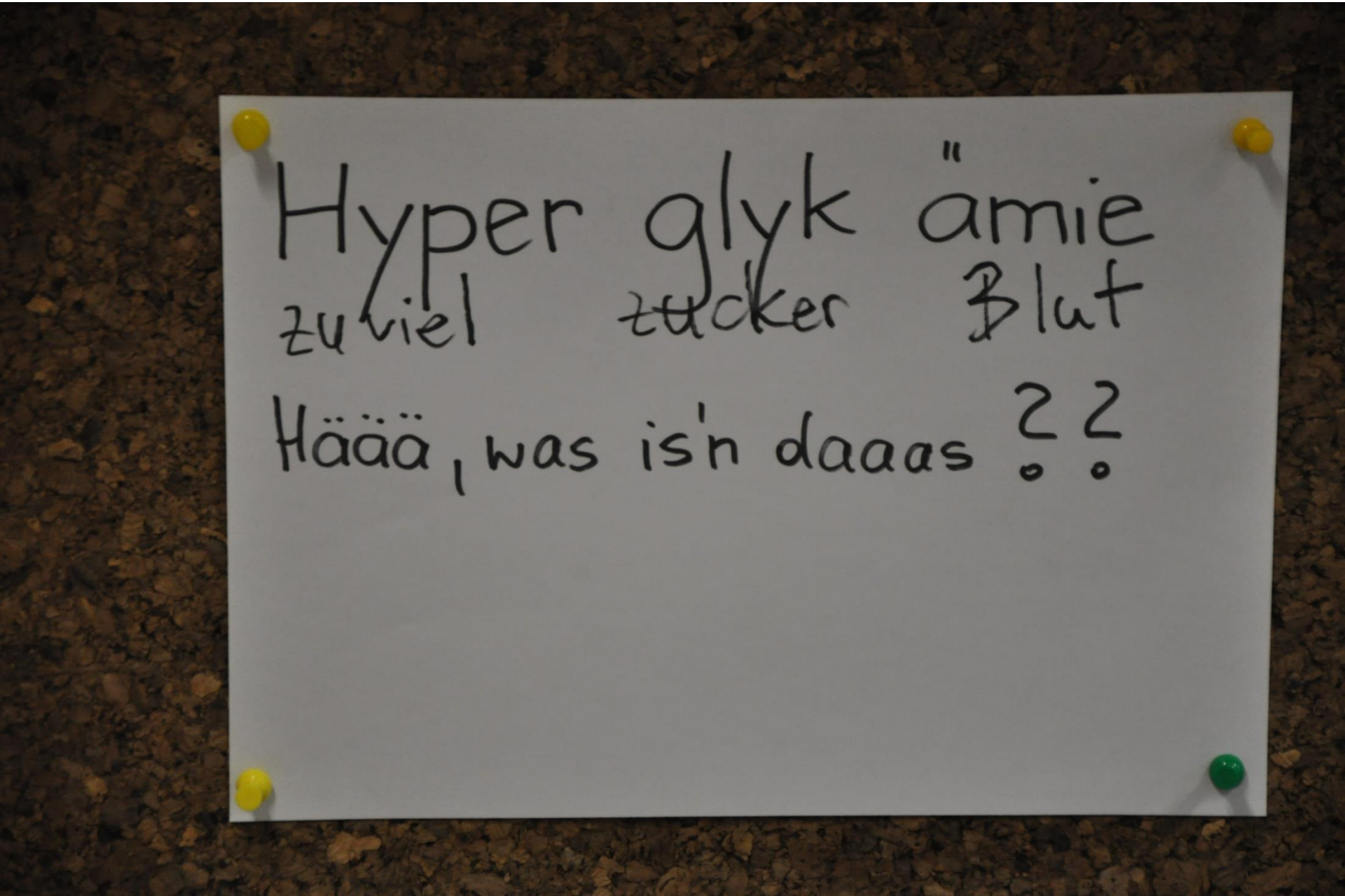
Höherer Grad von Acidose bei Aufnahme von Jugendlichen, die Drogen konsumiert hatten, dafür milde Ketose.
Elektrolytverschiebungen und Dehydratation insbesondere bei Exstasy Bekannt.
Lee et al Diabetes Care 2008

Prevention

- **Education**
- **Guidelines/hand outs for patients**
- **Telefon hotline**
- **After repetitive episodes: multidisciplinary management**
- **If necessary home care/social services (child protection laws?)**

Education

- **Ketone and development of DKA is difficulty to comprehend (both to explain and to understand)**
- **Of all diabetes education topics this is to be forgotten earliest/fastest**
- **Need for repetitive educational efforts**


Hyper glyk ämie
zu viel ~~zucker~~ Blut
Häää, was is'n daaas ??

Education

- Follow-up education when pump and/or at manifestation after 3-6 months
- „Just do it“ with practical examples
- Schematics
- Ask when in outpatient clinic and check understanding.


Hyper glyk "amie
zuviel ~~zucker~~ Blut
Haaa, was is'n daaas ??


Urine/Orina
2 min.
neg.
0,1 (5,6)
0,25 (14)
0,5 (28)
1 (56)
2 (111)
3 (167)
5% (278)
(mmol/L)
%=g/dL

Was könnte ich haben?

Antwort: ……..

Ketoazidose-Notfallplan

Blutzucker >240 mg/dl bzw. 15 mmol/l und/ oder Übelkeit, Erbrechen, Bauchschmerzen

Sofort Azeton testen.
(Wichtig: Teststreifen vor Verfall vom Arzt neu verordnen lassen!)

Azeton ++/+++

Azeton negativ

Sofort doppelte Dosisanpassung kurzwirkendes Insulinanalogon mit Spritze/ Pen spritzen.
Viel trinken!

Wie gewohnt den Blutzucker korrigieren (ca. 2 Std. nach kurzwirkendem Insulinanalogon.)

Diabeteszentrum oder Hausarzt informieren, nicht einschlafen

Nach 2 Stunden Blutzucker messen.

Blutzucker < 10 mmol/l
Azeton -/+

Blutzucker < 15 mmol /l
Azeton ++/+++

Blutzucker > 15 mmol/l
Azeton ++/+++

Kein weiteres Insulin spritzen.
2 BE gegen Hypo-Gefahr essen und weiterhin viel trinken.

Sofort normale Dosisanpassung kurzwirkendes Insulinanalogon mit Spritze / Pen spritzen.
Viel Wasser trinken.

Ist der Blutzucker wieder im Zielbereich, suchen Sie nach der Ursache der Blutzuckerentgleisung.

Regeln:

* Keine körperliche Anstrengung und viel Mineralwasser trinken!
* Falls Trinken nicht möglich ist, begeben Sie sich bitte in ein Krankenhaus.
* Korrektur-Insulin muss immer mit Einmalspritze oder Insulinpen zugeführt werden

Mein Insulin-Tagesgesamtbedarf

_____

Notfall-Telefonnummer: 0175/2240459
Diabeteszentrum: 0341/9726115
0341/9726345

Education

Table 2—*Baseline and follow-up data of patients with one or no episodes versus two or more episodes of severe ketoacidosis during the year before the DTTP*

	Diabetic ketoacidosis during the year before the DTTP	
	One or no events · patient^{-1} · year^{-1}	Two or more events · patient^{-1} · year^{-1}
Patients (*n*)	9,488	95
Age at enrollment (years)	38.2 ± 14	31.5 ± 13
Mean duration of diabetes (years)	13.4 ± 10.9	12.3 ± 9.8
GHb at baseline (%)	8 ± 2	9.4 ± 2.8
GHb at follow-up (%)	7.3 ± 1.5	8.7 ± 2.5
Severe ketoacidosis at baseline (events · patient^{-1} · year^{-1})	0.06 ± 0.2	3.25 ± 2.4
Severe ketoacidosis at follow-up (events · patient^{-1} · year^{-1})	0.03 ± 0.2	0.58 ± 1.6
HD at baseline (days · patient^{-1} · year^{-1})	5.6 ± 13.2	19.4 ± 23.1
HD at follow-up (days · patient^{-1} · year^{-1})	3.5 ± 12.9	10.2 ± 22.6

Data are means ± SD. HD, hospital days.

Sämann A et al Diabetes Care 2006

Telefone support

- Two-hourly blood glucose level and ketone testing
- Usual insulin doses are continued
- Supplemental insulin doses are calculated as 1/2 morning quick-acting dose and given 2- to 3-hourly—depending on insulin type (or 1/3 premixed insulin dose given as quick-acting insulin)—and are advised to be administered if ketones are present at the levels detailed above
- Increased fluids advised, sweetened drinks if blood glucose monitor reading < 12 mmol/l
- Symptom relief using readily available remedies for flu, nausea or diarrhoea
- Return 2-hourly phone calls to check progress
- General practitioner presentation encouraged if precipitating illness persists
- Support to maintain regular insulin injections if omitting

Farrell K, et al Diabetic Med 2011

Telefone support

	Group 1	Group 2	Group 3	Group 4	*P*-value
n	285	31	15	19	
Male/female	140/145	12/19	6/9	6/13	
Age ± SD	22.0 ± 4.9	19.9 ± 2.0	19.9 ± 1.9	22 ± 2.8	NS
Years of diabetes	10.1 ± 5.9	9.8 ± 3.2	6.8 ± 3.1*	NA	0.01*
Age at referral ± SD	18.8 ± 5.4	18.7 ± 1.7	18.5 ± 1.0	NA	
No. on pump (%)	25 (8.6)	5 (16)	0 (0)	0	0.25†
No. of calls phone support	0	83	0	0	NA
Ketoacidosis admissions	0	2	18‡	19	NA
HbA_{1c}	70 mmol/mol	97 mmol/mol	103 mmol/mol	103 mmol/mol	< 0.001
	8.6 ± 2.1%	11.1 ± 2.9%	11.6 ± 2.1%	11.6 ± 2.1%	
Clinic visits/year	2.4 ± 1.3	2.9 ± 1.1	2.1 ± 1.1		0.06

*Clinically significant.
†Similar percentage of pumps in groups 1 and 2.
‡Some patients had more than one admission.
NA, not available; NS, not significant.

Gruppe 2: 83 calls re. ketonuria, 2 admitted, one with no adherence.
Gruppe 3;4: no telefone support

Farrell K, et al Diabetic Med 2011

Acute and chronic complications: telefone hotline

Telefone hotline use (n=120 in 424 days)			
	Anrufer	Gesamtpopulation	Signifikanz
Alter	8,2 Jahre	12,2 Jahre	P<0.001
Diabetesdauer	31 Monate	60 Monate	P>0.05
HbA1c	7.65%	7.48%	n.s.

Causes for calls	
Dosis adjustment	35%
Hypoglycemia	23% 7x schwer
Second illness	10%
Hyperglycemia	10% 1x DKA

Kapellen TM et al. Diabetes Care 1998;21:1365

… und nicht vergessen ….

Thank you for your attention

Danke für Ihre Aufmerksamkeit !