



The History and Management of DKA

Prof Ketan Dhatariya MBBS MSc MD MS FRCP PhD

Consultant in Diabetes and Endocrinology
Norfolk and Norwich University Hospitals



Before 1922

- Type 1 was universally fatal despite all efforts



1857

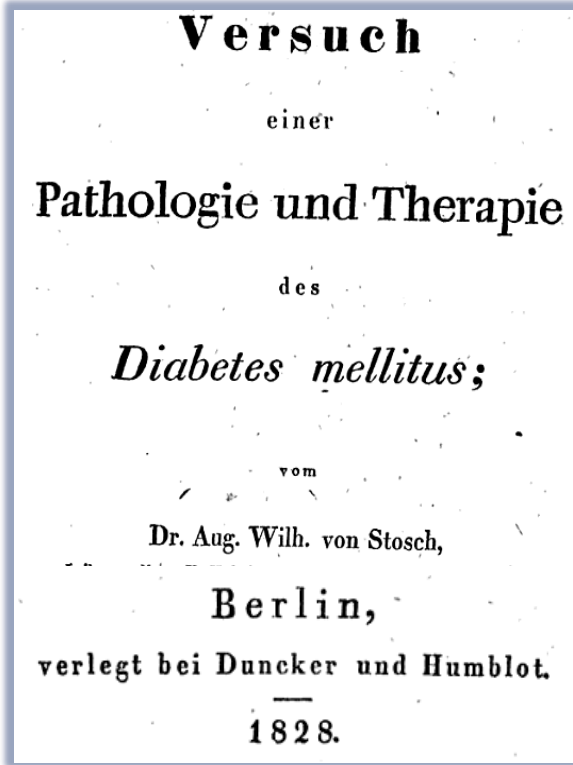


1857



Type 1
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Differentiation

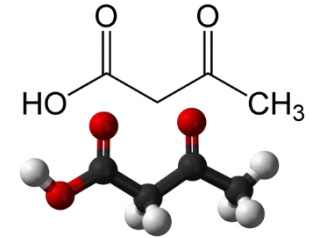


- The first mention of “Diabetic Coma”
– but it was in a German textbook

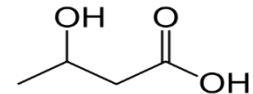
The Discovery of Urinary Ketones

- In 1857, Petters was the first to show that acetone was present in the urine of people with diabetes
- Confirmed 20 years later in the UK
- And in the 1880's, β OHB was also identified in the urine

Aceto Acetic Acid



Beta-Hydroxybutyric Acid



Petters W Untersuchungen über die Honigharnruhr. Vrtljschr Prakt Heilk 1857;3:81–94

Foster B BMJ 1878;1:78–81

Stadelmann E Arch Exp Pathol und Pharmakol 1883;17:419–444

Minkowski O Arch Exp Pathol und Pharmakol 1884;18:35–48

Adolf Kußmaul in 1874



- Described patients in a diabetic coma with ‘peculiar breathing and dyspnoea’
- He described 2 types of diabetic coma – those with and without Kussmaul breathing

IX.—ON A PECULIAR MODE OF DEATH IN DIABETES; ON ACETON-
ÆMIA; ON THE TREATMENT OF DIABETES BY GLYCERINE,
AND INJECTION OF DIASTASE INTO THE BLOOD.

By Professor KUSSMAUL, of Freiburg. Translated by DAVID FOULIS,
M.B., and SAMSON GEMMELL, M.B.

WITHIN the last year I have seen three cases of diabetes die with remarkably similar symptoms, in which a peculiar dyspnoea, preceding and accompanying a comatose state, played the chief part. I hold myself therefore justified in

Identification
of acetone in
the urine



1857 1870-1880



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1857

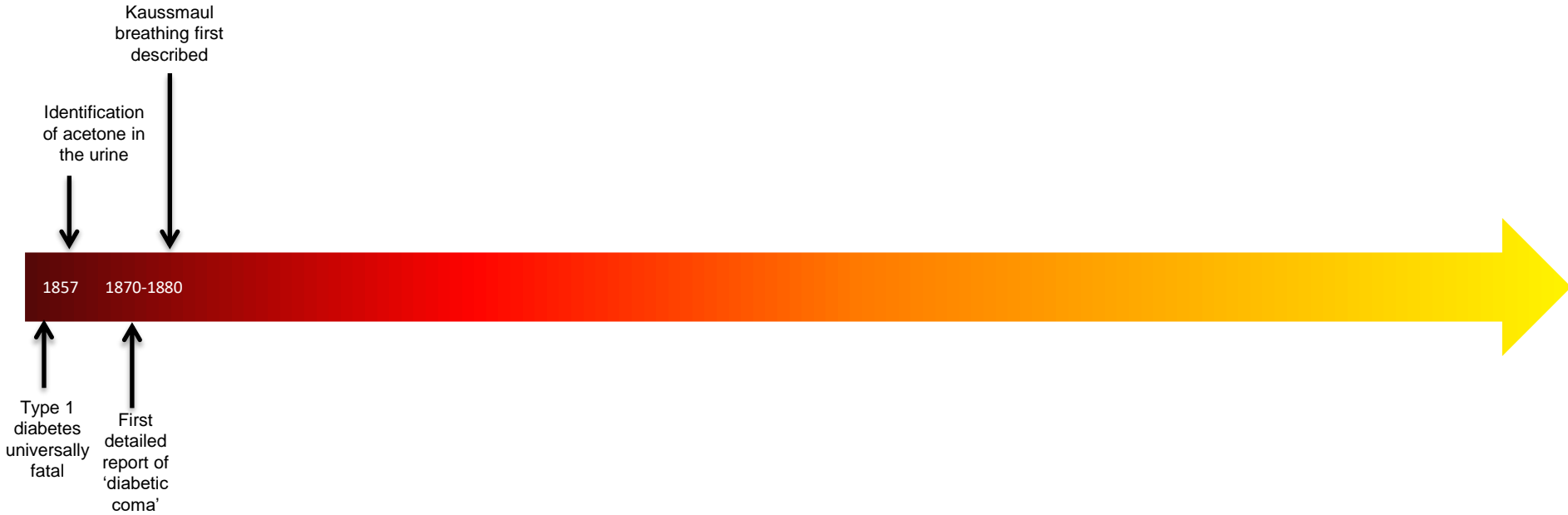
1870-1880

Type 1
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First
detailed
report of
'diabetic
coma'





The Aftermath of the Paris Siege of 1870

MONOGRAPH No. 11

TOTAL DIETARY REGULATION
IN THE TREATMENT
OF DIABETES.

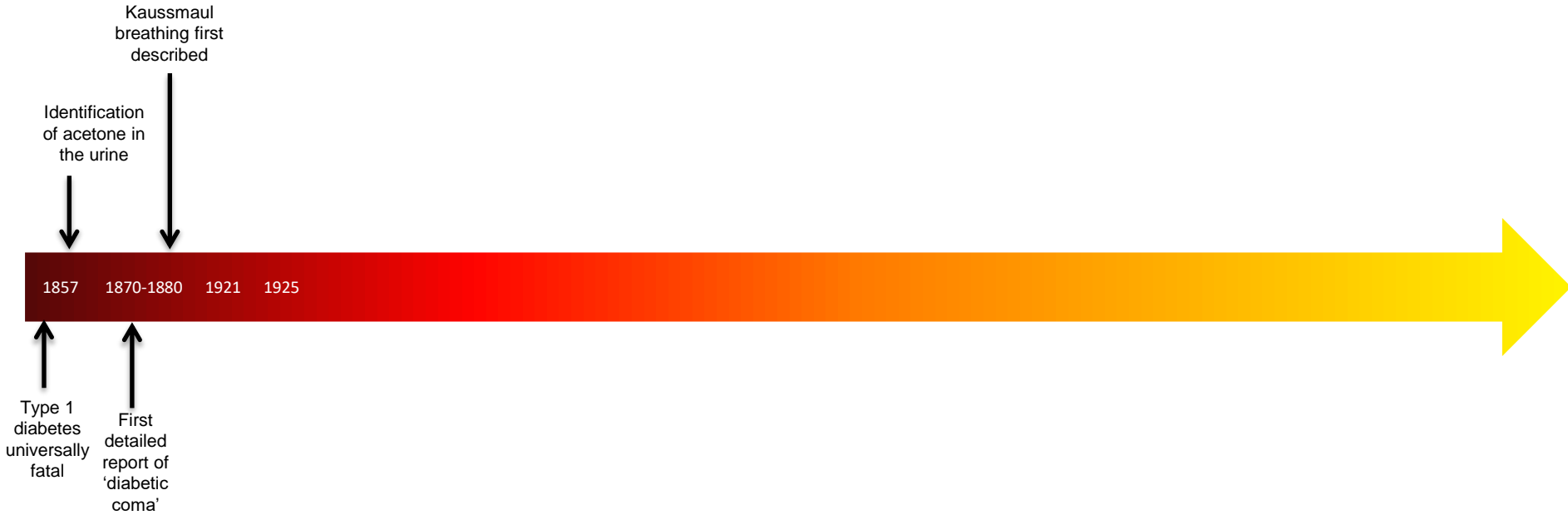
BY

FREDERICK M. ALLEN, M.D., EDGAR STILLMAN, M.D., AND
REGINALD FITZ, M.D.

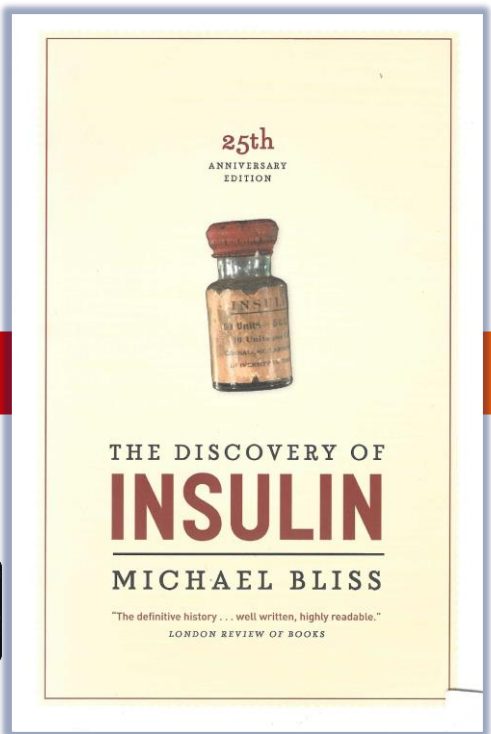
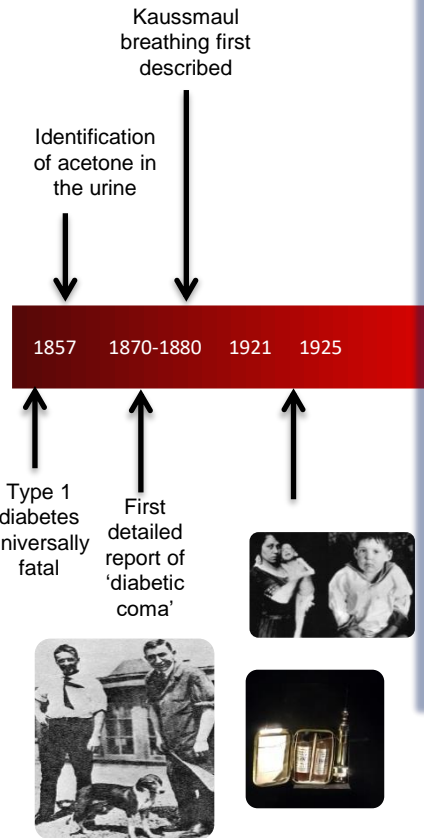


NEW YORK
THE ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH
1919

- After the siege of Paris in 1870, it was realised that strict diets could prolong life for a year or two
- But it was a life of misery – alleviated temporarily by opium (if you could afford it)







Elliott Joslin in 1925

CONTRIBUTION BY DRS. ELLIOTT P. JOSLIN,
HOWARD F. ROOT, AND PRISCILLA WHITE

FROM THE NEW ENGLAND DEACONESS HOSPITAL

DIABETIC COMA AND ITS TREATMENT

Recoveries from coma are so frequent today that it is easy for the impression to spread that coma need not be regarded seriously. Such a view is false. Coma patients recover as the result of hard work by day and by night of doctors, usually young, who intelligently apply the most modern methods of medical practice.

33 Cases Treated with Insulin

THIRTY-THREE CONSECUTIVE CASES OF COMA OR IMPENDING COMA TREATED WITHOUT ALKALI BUT WITH INSULIN

Case No.	Age at coma, yrs.	Duration of D. M., yrs.	Date.	Clinical data.		Blood.									Urine.		Insulin.			
				Respiration.	Mental condition.	Sugar, per cent.			Plasma CO ₂ combining power volumes, per cent.			Non-protein nitrogen mgm. per 100 c.c.			At entrance.		Sugar free after entrance, hours.	Units.		
						Day.			Day.			Day.			Diabetic acid.	Sugar, per cent.		Day.		
						1	2	3	1	2	3	1	2	3				1	2	3
1923																				
1609	17.1	6.4	Dec. 7	Kussmaul.	Drowsy.	0.33	0.26	—	24	—	—	26	—	—	+++	3.0	—	60	30	40
2448	19.3	1.3	Apr. 24	Kussmaul.	Drowsy.	0.33	0.21	—	21	37	—	—	—	—	+++	5.4	192	60	30	30
2448	19.6	1.7	Aug. 11	Kussmaul.	Drowsy.	0.27 ¹	0.25	—	31 ¹	43	—	—	—	—	+++	3.2	34	130	50	55
2687	25.4	1.7	Aug. 28	Kussmaul.	Drowsy.	0.23	0.21	—	26	55	—	—	—	—	+++	3.8	—	75	60	60
2801	15.9	1.1	June 10	Kussmaul.	Drowsy.	0.33 ²	0.28	—	36, 22 ²	43	17	29	—	—	+++	3.5	24	260	30	115
3021 ¹⁹	22.5	1.2	Oct. 21	Kussmaul.	Unresponsive.	0.72	—	—	12	—	—	47	—	—	+++	2.8	—	80	—	—
3040	11.3	1.0	Oct. 3	Kussmaul.	Drowsy.	0.34	0.24	0.29	12	31	—	25	31	—	+++	4.0	7.5	55	30	40
3129	24.4	3.7	Dec. 30	Kussmaul.	Drowsy.	0.37	0.28	—	22	36	—	27	—	—	+++	3.8	72	90	55	55
3137	45.2	2.3	May 13	Kussmaul.	Drowsy.	0.37	—	0.16	20	—	65	32	—	—	+++	5.0	144	70	40	30
3240 ¹	16.0	0.7	July 20	Kussmaul.	Stuporous.	0.49	—	—	13	—	—	—	—	—	+++	4.0	60	60	—	—
3382	28.4	3.4	Sept. 15	Kussmaul.	Unresponsive.	0.55	0.17	0.30	11	71	20	66	36	—	+++	1.8	19	160	90	80
1924																				
2988	56.3	4.0	Apr. 21	Kussmaul.	Stuporous.	0.48	0.29	—	14	49	—	49	61	—	+++	3.0	17	170	100	80
3129	25.3	4.5	Oct. 27	Kussmaul.	Stuporous.	0.46	0.27	0.36	8	19	20	37	26	—	+++	3.5	105	120	35	30
3143	17.5	1.1	Mar. 29	Kussmaul.	Stuporous.	0.50	0.26	0.24	20	29	34	50	39	—	+++	1.2	27	170	210	100
3502	14.0	1.3	Dec. 5	Kussmaul.	Drowsy.	0.40	0.09	—	16	39	—	29	—	—	+++	2.6	14	165	25	20
3666	29.0	0.8	May 11	Kussmaul.	Drowsy.	0.43 ³	0.36	—	19 ³	37	—	—	30	—	+++	3.0	20	150	110	112
3859	29.0	0.1	Mar. 26	Kussmaul.	Drowsy.	0.37	0.31	—	31	25	32	30	—	—	+++	4.0	34	100	200	175
3877	15.3	0.7	Dec. 16	Kussmaul.	Drowsy.	0.37	—	0.17	22	20	—	—	31	—	+++	3.3	8	30	20	30
4033	46.1	0.1	July 24	Kussmaul.	Stuporous.	0.60 ⁴	0.29	0.36	21 ⁴	50	—	85	61	56	+++	4.0	168	210	110	80
4109	38.8	2.6	Sept. 2	Kussmaul.	Stuporous.	0.40 ⁵	0.05	0.18	14	32	45	—	23	—	+++	3.5	54	240	40	30
4110	12.0	1.7	Sept. 1	Kussmaul.	Stuporous.	0.16 ⁶	0.19	0.31	13 ⁶	22	30	27	37	—	+++	1.4	5	110	20	25
4115	51.8	0.5	Aug. 21	Kussmaul.	Stuporous.	0.30	0.03	0.29	20	45	—	—	27	—	+++	3.6	22	195	30	38
4157	54.9	9.8	Oct. 1	Kussmaul.	Unresponsive.	0.63	0.06	0.43	13	24	19	61	30, 3	—	+++	3.0	36	250	15	60
4171	67.0	0.9	Sept. 23	Kussmaul.	Unresponsive.	0.66	0.44	0.17	14	20	25	58	63	—	+++	3.6	30	120	110	35
4194	61.3	9.6	Oct. 31	Kussmaul.	Drowsy.	0.30	0.17	—	18	33	—	36	—	—	+++	3.0	—	65	65	—
4232	16.9	1.6	Aug. 18	Kussmaul.	Unresponsive.	0.49 ⁶	0.16	0.36	11 ⁵	22	20	53	69.1	139	+++	2.0	20	300	70	50
4271	30.3	0.4	Dec. 3	Kussmaul.	Drowsy.	—	0.13	—	16	35	—	—	22	—	+++	4.0	12	25	10	25
4279	61.2	2.3	Oct. 28	Kussmaul.	Drowsy.	0.36	0.44	0.18	24	33	48	39	—	—	+++	2.8	22	20	100	45
4289	29.4	0.1	Dec. 6	Kussmaul.	Drowsy.	0.54	0.62	0.33	11	18	32	—	—	—	+++	2.2	8	145	95	45
1925																				
2024	15.3	4.3	Feb. 24	Kussmaul.	Emotional.	0.46	—	—	16	—	—	—	—	—	+++	3.0	—	65	—	—
2786	44.5	2.7	Mar. 8	Kussmaul.	Unresponsive.	0.59 ⁷	0.36	0.29	10 ⁷	21	24	43	—	—	+++	4.0	12	270	80	50
3391	37.3	2.4	Jan. 9	Kussmaul.	Stuporous.	0.55	0.21	0.25	15	39	37	74	69	—	+++	5.0	13	170	50	55
3877	15.4	0.8	Mar. 22	Kussmaul.	Stuporous.	0.77 ⁸	0.15	—	16 ⁸	46	—	61	38	—	+++	6.5	10	270	55	40

¹ Insulin 40 units during five hours preceding blood-sugar.
² Insulin 240 units during twelve hours preceding blood-sugar.
³ Insulin 50 units during five hours preceding blood-sugar.
⁴ Insulin 35 units during five hours preceding blood-sugar.
⁵ Insulin 60 units during eight hours preceding blood-sugar.
⁶ Insulin 30 units during two hours preceding blood-sugar.

⁷ Insulin 40 units during three hours preceding blood-sugar.
⁸ Insulin 60 units during three hours preceding blood-sugar.
⁹ Patient given soda bicarbonate before entrance.
¹⁰ Insulin 60 units during three hours preceding blood-sugar.
¹¹ Death three and a half hours after admission.
¹² Death six hours after admission.

Insulin Doses

Treatment.—*Insulin Dosage.*—The size of the first dose of insulin in coma depends upon the doctor's estimate of the probable number of hours the patient can live without insulin. If the expectation of life is twenty-four hours, one would inject 20 units and repeat every hour until clinical improvement is evident or sugar in the urine or blood is clearly diminishing; if the expectation is twelve hours one would inject 40 units and repeat the dose in the same manner, changing the quantity to 20 units as the state of the patient warrants; but if the expectancy is only six hours one would inject 40 units every thirty minutes until improvement is manifest. Finally, in a case like our Case No. 3021, who died three and a half hours after entrance, today we would give 40 units of insulin every fifteen minutes. We never

Fluids

Introduction of Liquids Into the Body.—A coma patient is dry. When the coma is severe even the eyeballs are as soft as a jelly-fish. Obviously liquids must be supplied. It is liquid, not food, which the patient needs. Hot drinks are the best tolerated.

Whatever the liquid one uses, one should always treat the patient as if he had just had a laparotomy, so gently, so carefully, should one administer it. To spare the stomach one gives salt solution or tap-water by the rectum.



Identification of acetone in the urine

Kaussmaul breathing first described

Type 1 diabetes universally fatal

First detailed report of 'diabetic coma'



First reports of successful DKA treatment – Joslin reports that 31 out of 33 patients with DKA survive – with gentle fluid replacement



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RD Lawrence at King's

**THE TREATMENT OF DESPERATE CASES
OF DIABETIC COMA.**

BY

R. D. LAWRENCE, M.D., M.R.C.P.,*
CHEMICAL PATHOLOGIST, KING'S COLLEGE HOSPITAL.

Fluids

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The fluid has been given at the rate of a litre in half to three-quarters of an hour, never faster.

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The fluid has been given at the rate of a litre in half to three-quarters of an hour, never faster.

Enough intra-venous saline should be given as soon as possible to fill visibly the shrunken tissues and re-establish the fullness and strength of the pulse. This may require 3 to 5 or more pints of fluid, and I consider it wise to finish the infusion with a pint of gum acacia, a fluid which remains in the circulation, while much of the saline rapidly leaves the blood and enters the tissues.

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The Next Few Years

J. THE PROGNOSIS IN DIABETIC COMA.

In the year between February 5, 1934, and February 5, 1935, there were no deaths from diabetic coma in patients under our care at the Deaconess Hospital.

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2. **Insulin.**—On admission, after the diagnosis has been verified by history, physical examination and examination of the urine, a preliminary subcutaneous dose of insulin usually of 20 to 100 units is given. This dose must be varied to suit the age of the patient, the degree of acidosis, and previous insulin administration. Pro-

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The average amount of insulin used in our cases (see Table 63) in the first twenty-four hours varied from 154 units for Series I, in the early days of insulin experience to 252 units in Series IV, from February, 1929, to September, 1931.

Fluids

Treatment must have, then, as one of the primary aims, the restoration of fluid and electrolytes to the body. This is best done by the subcutaneous administration (by gravity) of 1000 to 1500 cc. of normal salt solution within the first hour. If required, an infusion of 500 to 750 cc. of salt solution may be given intravenously later and indeed, a second or third subcutaneous infusion of 1000 to 1500 cc. may also be necessary within the first few hours. We

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The beneficial effect of an *adequate* dose of insulin is clinically manifest as a rule in less than 15 minutes ; if a single dose of insulin fails to produce an obvious improvement within about 15 minutes it may be inferred that the dose was grossly inadequate.

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start with 100 units, and if there is no obvious improvement in half an hour give 100 units every half-hour until an improvement is obvious.

If the patient is inaccessible (“unconscious”) start with 500 units, and be prepared to give more if no improvement is seen at the end of half an hour.

Insulin Doses

OUTLINE OF TREATMENT

(1) As soon as the diagnosis is established, an initial dose of soluble insulin 200–400 units is given intravenously. The exact dosage depends on a clinical assessment of the severity of the case. Broadly speaking, we administer 200 units to cases in stage 1, 300 units to those in stage 2, and 400 units to those in stage 3

TABLE I—USUAL DOSAGE OF INSULIN AND DURATION OF KETOSIS

	Stage 1	Stage 2	Stage 3
No. of cases	8	12	4
Ave. dose of insulin required to abolish ketosis (units)	265	726	870
Range of insulin dosage (units) ..	140–500	250–1400	500–1400
Ave. duration of ketosis (hours) ..	15.4	11.4	17.6
Range of duration of ketosis (hours)	7–23	4–27	14–27

TABLE II—DOSAGE OF INSULIN AND DURATION OF KETOSIS IN DIFFERENT METHODS OF GIVING INSULIN

Method of insulin administration	Hypo-dermic	Intra-muscular	Intra-venous
Ave. dose of insulin required to abolish ketosis (units)	250	480	656
Range of insulin dosage (units) ..	140–530	430–530	350–1400
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Mortality

TABLE III—MORTALITY IN 170 CASES OF DIABETIC KETOSIS

	Group 1 *	Group 2 †	Group 2a ‡
No. of cases	80	90	30
Over-all mortality	23 = 28.7 %	9 = 10.0 %	2 = 6.6 %
Average insulin dosage in first 3 hr. after admission	107.5	220	316
Deaths from uncontrolled ketosis	12 = 15.0 %	6 = 6.6 %	1 = 3.3 %
Deaths from causes other than uncontrolled ketosis	11 = 12.2 %	3 = 3.3 %	1 = 3.3 %

* Period January, 1943, to February, 1946.

† Period February, 1946, to June, 1948.

‡ Period August, 1947, to June, 1948, being the last 30 consecutive cases of group 2.

TABLE 1.—Decline in Mortality in Diabetic Coma

	478 Cases January 1923 to August 1940	123 Cases August 1940 to May 1, 1944	
Number of deaths.....	58	2	
Percentage of deaths.....	12	1.6	
Age, average.....	29 years	29 years	
Duration of diabetes.....	4.3 years	6.3 years	
Blood sugar.....	490 mg.	500 mg.	
Blood carbon dioxide, average *.....	12 vols. %	13 vols. %	
Nonprotein nitrogen, average.....	45 mg.	51 mg.	
Insulin (first 24 hours).....	237 units	287 units	
	1923-1927	1932-1934	1942-1943
Insulin in first 3 hours of treatment...	83	136	216

* Only cases showing blood carbon dioxide values of 20 volumes per cent (8.8 millimols) or less are included with the exception of case 52.

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1857 1870-1880 1921 1925 1940-1950

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High dose insulin used - reports reduction in mortality from 12% to 1.6% between 1940 and 1944 using between 500 and 2000 units depending on severity of coma

Low Dose Hourly IM Insulin

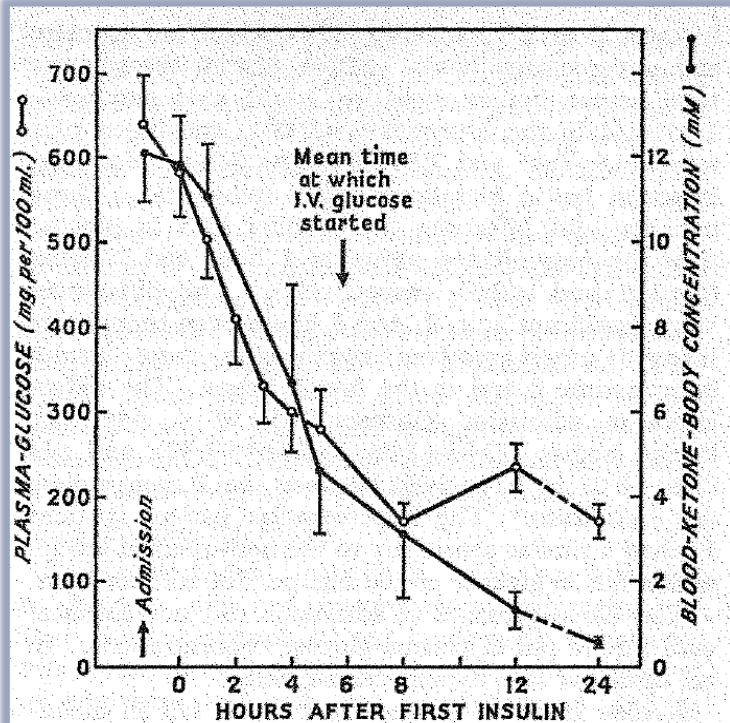


Fig. 2—Mean plasma-glucose and blood-ketone-body concentrations in 14 ketoacidotic patients after treatment with low doses of I.M. insulin.

- 14 of these 17 had DKA, the others had HHS
- 5 or 10 units hourly IM
- Initial mean insulin dose was 16units
- Average IV fluids given was 6.9L in the first 6 hours to those in DKA
- Once glucose was between 4.4 and 16.7 mmol/l, insulin switched to SC

Low Dose Hourly IM Insulin

- 14 of these 17 had DKA, the others had HHS

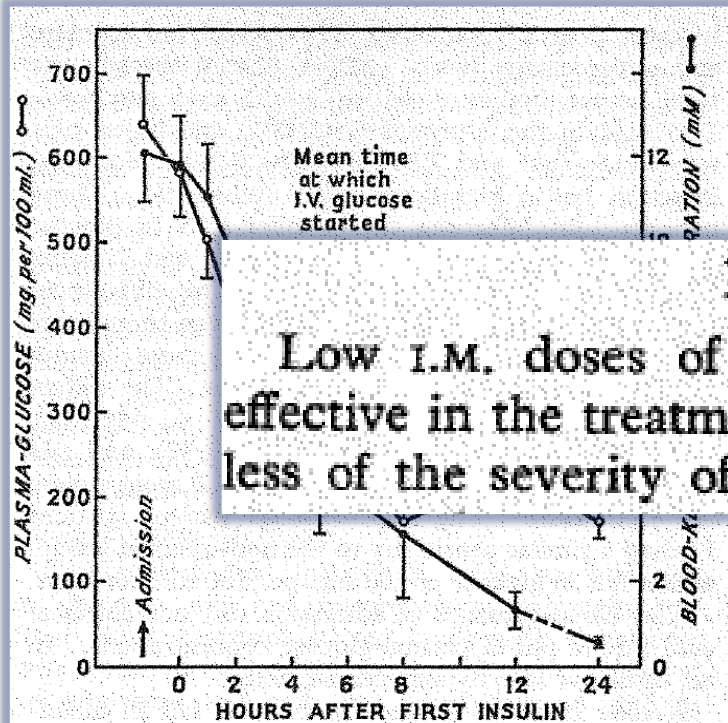


Fig. 2—Mean plasma-glucose and blood-ketone-body concentrations in 14 ketoacidotic patients after treatment with low doses of I.M. insulin.

Discussion

Low I.M. doses of insulin are, in our experience, as 16 units effective in the treatment of diabetic “coma”, regardless of the severity of the metabolic disturbance. In 6.9L in the first 6 hours to those in DKA

- Once glucose was between 4.4 and 16.7 mmol/l, insulin switched to SC

Low Dose IV Insulin Infusions

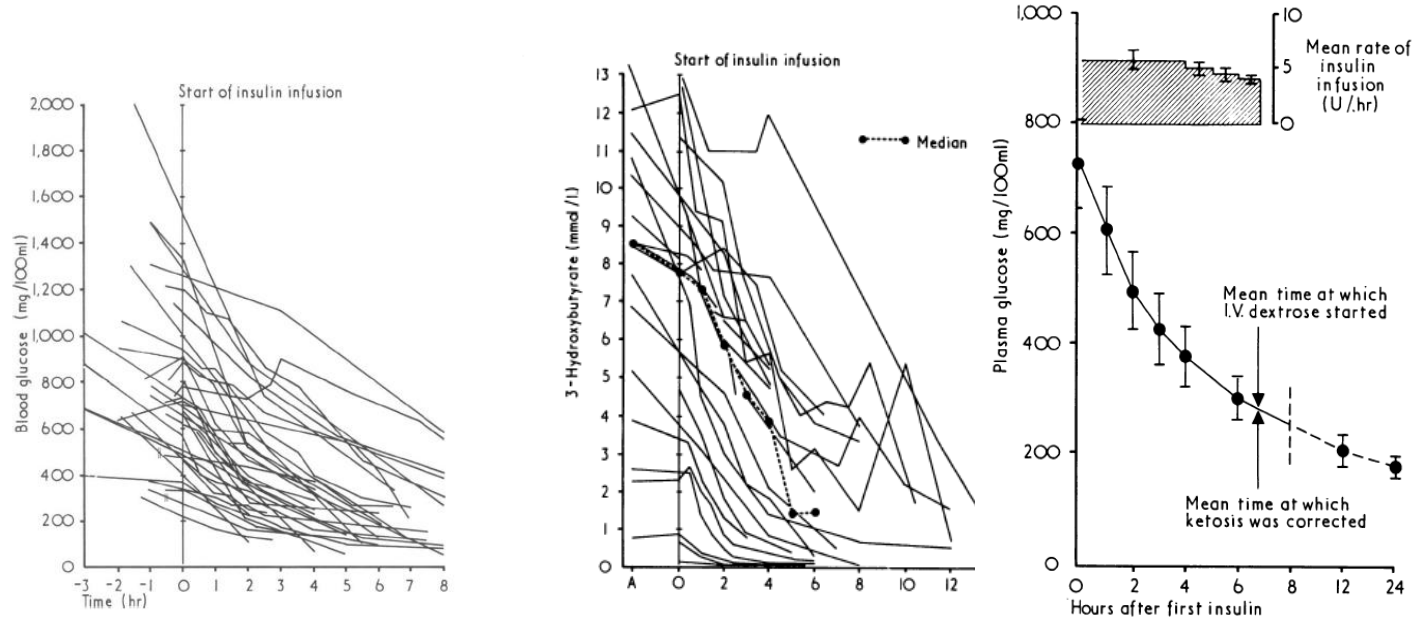


FIG. 1—Individual plasma glucose concentrations during insulin infusion.

Rate of glucose and β -OHB drop with low dose (5-6 units/hr) insulin infusion

Low Dose IM vs SC vs IV Insulin

- 45 people admitted with DKA – diagnosed
 - Blood glucose >16.7 mmol/l
 - Blood acetone positive after 1:2 dilution
 - pH <7.3
 - Serum bicarbonate <15 mmol/l
 - Glucosuria ($\geq 3+$)
 - Ketonuria

Properly Sick

Table 1. Clinical and Biochemical Profile on Admission.*

CHARACTERISTIC	TREATMENT GROUP		
	INTRA-MUSCULAR [15]‡	SUB-CUTANEOUS [15]	INTRA-VEINOUS [15]
Age (yr)†	40.7 (19–64)	44.3 (28–75)	37.2 (21–69)
Mean weight (kg)	65.1±4.1	66.4±4.9	63.4±2.9
Glucose (mg/dl)	523±57	579±62	590±58
Sodium (meq/liter)	134±2	136±2	138±2
Potassium (meq/liter)	5.5±0.4	5.8±0.3	6.0±0.3
Bicarbonate (meq/liter)	4.3±0.7	5.7±0.8	5.5±0.8
Blood urea nitrogen (mg/dl)	33±5	28±4	31±4
pH	7.09±0.02	7.11±0.03	7.10±0.02
Cortisol (µg/dl)	44±7	58±8	68±8
Glucagon (pg/ml)	588±140	543±167	377±74
β-hydroxybutyrate (mM)	9.6±0.6	10.0±1.0	10.0±1.0
Acetoacetate (mM)	2.9±0.3	3.7±0.4	3.0±0.3
Pyruvate (mg/dl)	0.89±0.2	0.66±0.07	0.74±0.09
Lactate (mg/dl)	25.4±5.4	22.2±2.4	20.0±2.5

*All data, except for age, are mean values ±SEM.

†Means and ranges (in parentheses) are shown.

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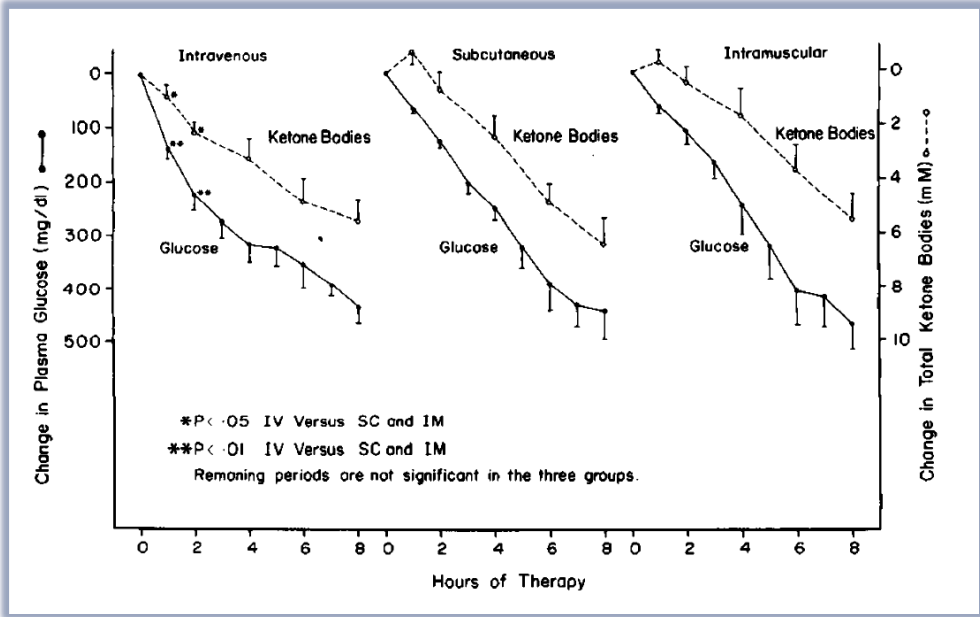
No Differences in Any Outcomes

Table 2. Comparison of Results of Low-Dose Insulin Therapy by Different Routes.*

	ROUTE		
	INTRAMUSCULAR	SUBCUTANEOUS	INTRAVENOUS
Plasma glucose <250 mg/dl	4.9±1.1†	5.6±0.9†	6.0±1.4†
Serum HCO ₃ >15 meq/L	12.2±1.4†	10.8±1.1†	13.0±2.2†
Blood pH >7.3	7.5±1.1†	6.0±0.8†	8.7±1.5†
Serum acetone <1:2	15.2±2.4†	14.0±1.6†	15.6±1.3†
Total fluid (ml):			
1st 8 hr	4,889±274	4,622±334	4,976±351
In 24 hr	7,874±526	7,249±564	8,109±587
Insulin given (U)	57±10	57±7	58±11
to achieve glucose of 250 mg/dl	(0.84±0.2)‡	(0.87±0.1)‡	(0.90±0.2)‡
Amount of insulin (U) for total control	94±15	85±8	100±11
	(1.4±0.2)‡	(1.4±0.18)‡	(1.6±0.2)‡

*No differences statistically significant: all data shown are means ± SEM.

†Hr to achieve designated biochemical value.
 ‡Figures in parentheses express insulin dosage as U/kg.



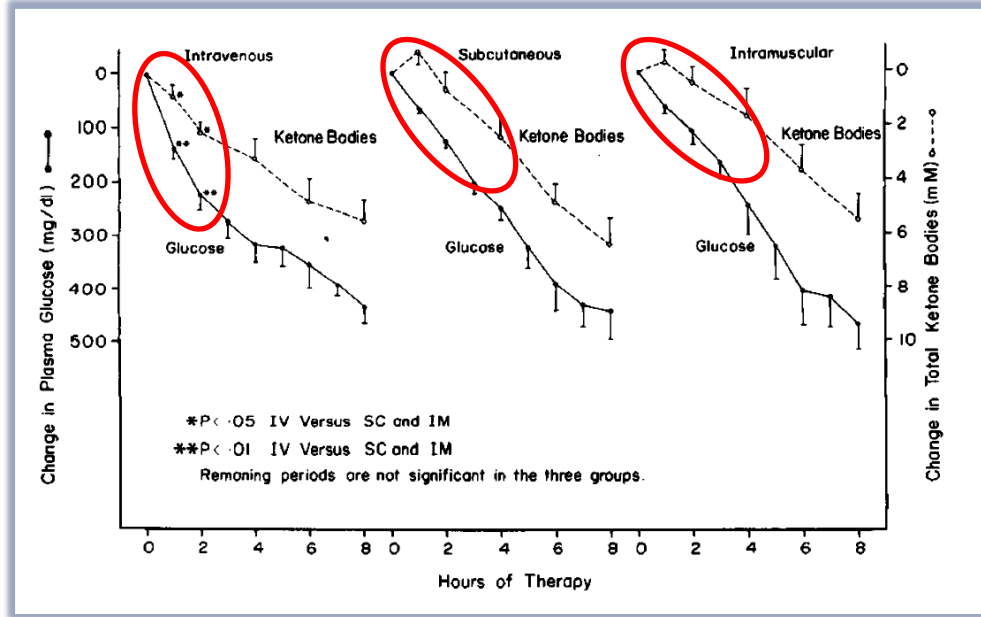
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Their Conclusions

In conclusion, the present investigation has indicated the effectiveness of low-dose insulin therapy in diabetic ketoacidosis whether administered by the intramuscular, subcutaneous, or intravenous routes.

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From results presented (Fig. 1), however, it appears that an initial bolus of insulin given intravenously may more quickly establish therapeutic levels that will produce a more rapid fall in plasma glucose and ketone bodies in the early hours of treatment.

On that basis we recommend that therapy be initiated with an intravenous bolus of insulin followed immediately by hourly intramuscular insulin according to the stated protocol.

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Kausssmaul breathing first described

Identification of acetone in the urine

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Type 1 diabetes universally fatal

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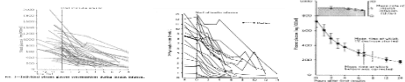


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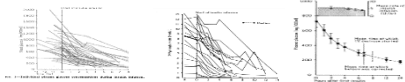


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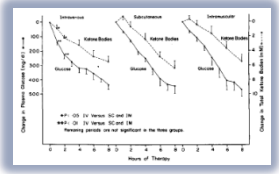
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And then in the NEJM



Cerebral Oedema

**CEREBRAL LESIONS IN UNCOMPLICATED FATAL DIABETIC
ACIDOSIS.***

By EDWARD S. DILLON, M.D.,

CHIEF, METABOLIC DIVISION, PHILADELPHIA GENERAL HOSPITAL; ASSISTANT PROFESSOR
OF DISEASES OF METABOLISM, GRADUATE SCHOOL OF MEDICINE,
UNIVERSITY OF PENNSYLVANIA,

H. E. RIGGS, M.D.,

CHIEF, DIVISION OF NEUROPATHOLOGY, PHILADELPHIA GENERAL HOSPITAL,
AND

W. WALLACE DYER, M.D.,

ASSISTANT CHIEF, METABOLIC DIVISION, PHILADELPHIA GENERAL HOSPITAL,
PHILADELPHIA, PA.

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**CEREBRAL EDEMA WITH IRREVERSIBLE COMA IN SEVERE
DIABETIC KETOACIDOSIS**

EUSEBIO YOUNG, M.D.,* AND ROBERT F. BRADLEY, M.D.†

BOSTON

W. WALLACE DYER, M.D.,

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Cerebral Edema Complicating Therapy for Diabetic Ketoacidosis

*Stephen C. Duck, M.D., Virginia V. Weldon, M.D., Anthony S. Pagliara, M.D., and
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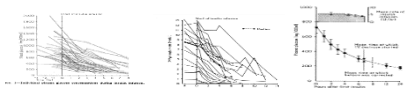
Cerebral edema associated with
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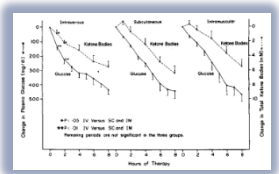
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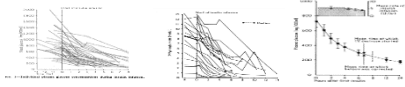


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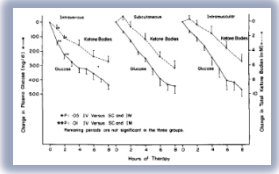
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Phosphate

A Randomized Study of Phosphate Therapy in the Treatment of Diabetic Ketoacidosis*

JOSEPH N. FISHER, AND ABBAS E. KITABCHI

The Departments of Medicine and Biochemistry, and the Clinical Research Center, The University of Tennessee Center for the Health Sciences, Memphis, Tennessee 38163

Bicarbonate

Bicarbonate Therapy in Severe Diabetic Ketoacidosis

LAWRENCE R. MORRIS, M.D.; MARY BETH MURPHY, R.N., M.S.; and ABBAS E. KITABCHI, Ph.D.,
M.D.; Memphis, Tennessee

If patients gave consent, lumbar punctures were done at baseline, at 6 to 8 hours, and at 12 to 24 hours after therapy, and the cerebrospinal fluid was assayed

- If you infuse bicarbonate, the rise in plasma pH induces a hypoventilation in people with an acidosis – this leads to a rise in $p\text{CO}_2$ which readily diffuses across the BBB to cause the CSF pH to drop further

Abbas Kitabchi

Abbas E. Kitabchi, PhD, MD: An Exemplary Mentor and Clinical Researcher

Guillermo E. Umpierrez

Diabetes Care 2016;39:333–336 | DOI: 10.2337/dc15-0552

The word “mentor” was first used in Homer’s epic poem *The Odyssey*. When Odysseus, the king of Ithaca, went to fight the Trojan War, he asked Mentor to serve as a teacher and overseer to his son Telemachus. Mentor failed in his duties, and it was Athena, goddess of war and patroness of the arts and industry, who assumed the form of Mentor and served as Telemachus’ wise and trusted adviser and counselor. The first recorded modern usage of the term can be traced to the 18th century book entitled *Les Aventures de Télémaque*, by the French writer Fénelon. Since then, the word “mentor” has evolved to mean trusted adviser, a wise and responsible tutor who shares knowledge with and inspires, challenges, and serves as a role model to a less experienced person. Dr. Abbas E. Kitabchi exemplifies all the attributes of a great mentor, as can be attested by the large number of health care professionals that have



Abbas E. Kitabchi at the Clinical Research Unit, UTHSC, Memphis, TN

The First ADA Consensus Document

Reviews/Commentaries/Position Statements

TECHNICAL REVIEW

Management of Hyperglycemic Crises in Patients With Diabetes

ABBAS E. KITABCHI, PHD, MD
GUILLERMO E. UMPIERREZ, MD
MARY BETH MURPHY, RN, MS, CDE, MBA
EUGENE J. BARRETT, MD, PHD

ROBERT A. KREISBERG, MD
JOHN I. MALONE, MD
BARRY M. WALL, MD

DEFINITION OF TERMS, CLASSIFICATION, AND CRITERIA FOR DIAGNOSIS —

DKA consists of the biochemical triad of hyperglycemia, ketonemia, and acidemia (Fig. 1). As indicated, each of these features by itself can be caused by other metabolic

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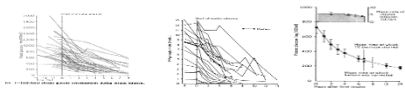


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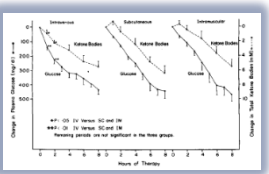


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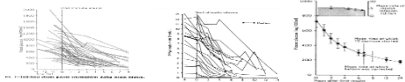
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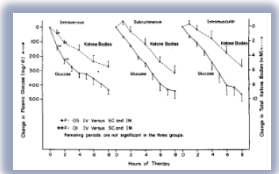
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In the UK – What Should Have been Happening

- ABC
- Lots of normal saline
- Stat intravenous insulin followed by constant or variable rate intravenous insulin infusion
- A few other things (potassium, \pm phosphate, \pm bicarbonate, etc.)

What Was *Actually* Happening

- Hopefully make the right diagnosis
- Give a bit of, or too much insulin
- Give a bit of, or too much fluid
- Criminally assault PWD with arterial blood gas assessment, despite O₂ saturation being 100%
- Put patient in a corner or on a non-medical ward...dependent on what bed manager says

What Was *Actually* Happening

- Forget to repeat bloods, or forget to call lab for result
- Forget to review patient
- Correct potassium 4 hours after it falls
- Stop long-acting subcutaneous insulin to ensure delayed recovery

Launched at DUK in Liverpool 2010

Launched at DUK in Liverpool 2010

Joint British Diabetes Societies
Inpatient Care Group

The Management of Diabetic
Ketoacidosis in Adults

“A Consensus of Worthy Opinion”

Writing Group

Mark W Savage (Chair of Sub Group)

Maggie Sinclair-Hammersley (Chair of JBDS IP Care Group)

Gerry Rayman

Hamish Courtney

Ketan Dhatariya

Philip Dyer

Julie Edge

Philip Evans

Michelle Greenwood

Girly Hallahan

Louise Hilton

Anne Kilvert

Alan Rees

and many others

Overall Quality of JBDS Guidelines



Overall Quality of JBDS Guidelines



Over 90% of respondents
rated the guidelines as
'Excellent' or 'Good'

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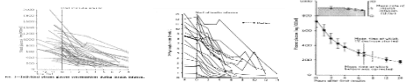


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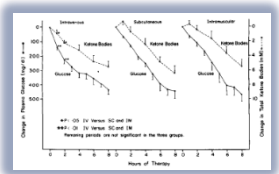
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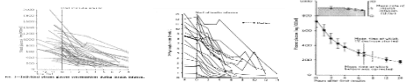
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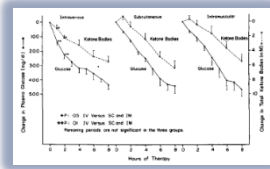


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The first UK national guideline for managing DKA published



Things That Are Now Standard of Care

- Fixed diagnostic criteria
- Using VBG
- Using bedside ketone monitors
- 'FRIII' and 'VRIII' (and avoidance of the term 'sliding scale')
- Continuing long acting insulin alongside the IV insulin

Euglycaemic DKA

Euglycaemic Diabetic Ketoacidosis

J. F. MUNRO, I. W. CAMPBELL, A. C. McCUISH, L. J. P. DUNCAN

British Medical Journal, 1973, 2, 578-580

blood glucose exceeded 650 r

Munro JF et al BMJ 1973;ii(5866):578-580

Jenkins D et al Acta Diabetologica 1993;30(4):251-253

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D. Jenkins, C. F. Close, A. J. Krentz, M. Nattrass, and A. D. Wright

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Incidence of Euglycemic Diabetic Ketoacidosis in Adults With Type 1 Diabetes in the United Kingdom Before the Widespread Use of Sodium Glucose Cotransporter 2 Inhibitors

TABLE. Prevalence of Euglycemic Diabetic Ketoacidosis in People With Type 1 Diabetes in the United Kingdom^a

	Number	Admission glucose <11.0 mmol/L (200 mg/dL) ¹	Admission glucose <13.9 mmol/L (250mg/dL) ²	Admission glucose <16.7 mmol/L (300 mg/dL) ³
National survey (2014) ⁴	277	6	14	23
Local audit (2015) ⁵	57	4	4	6
	334	10	18	29
		3.0%	5.4%	8.7%

^aData from a national survey⁴ and local audit.⁵ Data are divided into different thresholds of "euglycemia"

Munro JF et al BMJ 1973;ii(5866):578-580

Jenkins D et al Acta Diabetologica 1993;30(4):251-253

Macfarlane J et al Mayo Clinic Proceedings 2019;94(9):1909-1910

SGLT inhibitors

Euglycemic Diabetic Ketoacidosis: A Potential Complication of Treatment With Sodium–Glucose Cotransporter 2 Inhibition

Diabetes Care 2015;38:1687–1693 | DOI: 10.2337/dc15-0843

Anne L. Peters,¹ Elizabeth O. Buschur,²
John B. Buse,³ Pejman Cohan,⁴
Jamie C. Diner,³ and Irl B. Hirsch⁵



Press Release

Source: Sanofi (EURONEXT: SAN) (NASDAQ: SNY)

FDA issues Complete Response Letter for Zynquista™ (sotagliflozin)

PARIS and THE WOODLANDS, TX – March 22, 2019 - The U.S. Food and Drug Administration (FDA) issued a Complete Response Letter (CRL) regarding the New Drug Application for investigational Zynquista™ (sotagliflozin)*, a dual SGLT1 and SGLT2 inhibitor for the treatment of adults with type 1 diabetes in combination with insulin.



Date 02/11/2021

AstraZeneca UK Limited
Horizon Place, 600 Capability Green
Luton, LU1 3LU, Bedfordshire
T: +44 01582 836000
www.astrazeneca.co.uk

Forxiga (dapagliflozin) 5mg should no longer be used for the treatment of Type 1 Diabetes Mellitus

Dear Healthcare Professional,

Peters A et al *Diabetes Care* 2015;38(9):1687-1693

<https://www.sanofi.com/-/media/Project/One-Sanofi-Web/Websites/Global/Sanofi-COM/Home/media-room/press-releases/2019/2019-03-22-19-15-00-1759502-en.pdf>

<https://assets.publishing.service.gov.uk/media/619374948fa8f5037ffaa083/20211102-uk-dhpc-forxiga-T1D-withdrawal.pdf>

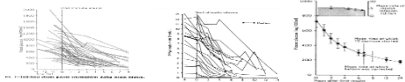
Management of Hyperglycemic Crises in Patients With Diabetes

First reports of successful DKA treatment – Joslin reports that 31 out of 33 patients with DKA survive – with gentle fluid replacement



3 consecutive papers in the BMJ showed that low-dose insulin infusions (5–6 units/h) work just as well as high-dose in lowering glucose and ketones

1st ADA consensus on the management of DKA



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Identification of acetone in the urine



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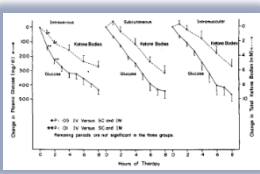


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And then in the NEJM

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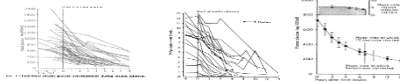
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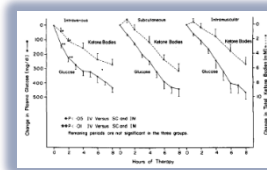


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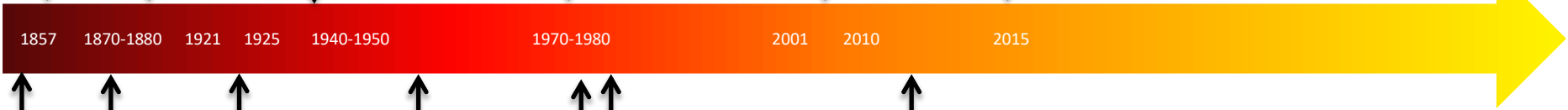


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ADA Consensus Document

Reviews/Commentaries/Position Statements

TECHNICAL REVIEW

Management of Hyperglycemic Crises in Patients With Diabetes

ABBAS E. KITABCHI, PHD, MD
GUILLERMO E. UMPIERREZ, MD
MARY BETH MURPHY, RN, MS, CDE, MBA
EUGENE J. BARRETT, MD, PHD

ROBERT A. KREISBERG, MD
JOHN I. MALONE, MD
BARRY M. WALL, MD

DEFINITION OF TERMS, CLASSIFICATION, AND CRITERIA FOR DIAGNOSIS —

DKA consists of the biochemical triad of hyperglycemia, ketonemia, and acidemia (Fig. 1). As indicated, each of these features by itself can be caused by other metabolic

ADA Consensus Document

Reviews/Commentaries/ADA Statements

CONSENSUS STATEMENT

Hyperglycemic Crises in Adult Patients With Diabetes

ABBAS E. KITABCHI, PHD, MD¹
GUILLERMO E. UMPIERREZ, MD²

JOHN M. MILES, MD³
JOSEPH N. FISHER, MD¹

Diabetic ketoacidosis (DKA) and the hyperosmolar hyperglycemic state (HHS) are the two most serious acute metabolic complications of diabetes. DKA is responsible for more than 500,000 hospital

rapid than the overall increase in the diagnosis of diabetes (1). Most patients with DKA were between the ages of 18 and 44 years (56%) and 45 and 65 years (24%), with only 18% of patients <20 years of

glucose utilization by peripheral tissues (12–17). This is magnified by transient insulin resistance due to the hormone imbalance itself as well as the elevated free fatty acid concentrations (4,18). The combination of insulin deficiency and increased counterregulatory hormones in DKA also leads to the release of free fatty acids into the circulation from adipose tissue (lipolysis) and to acute metabolic

ADA Consensus

- No insistence on the 'D', the 'K', and the 'A' to diagnose DKA
- No clear acknowledgement of euglycaemic DKA
- No recommendation to use bedside ketone measurements to monitor and guide treatment
- No recommendation to continue long acting subcutaneous insulin

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**Guidelines for management of diabetic ketoacidosis:
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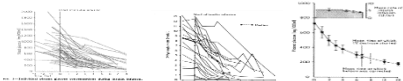
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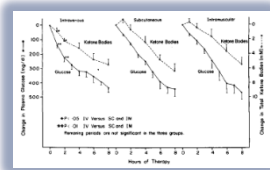
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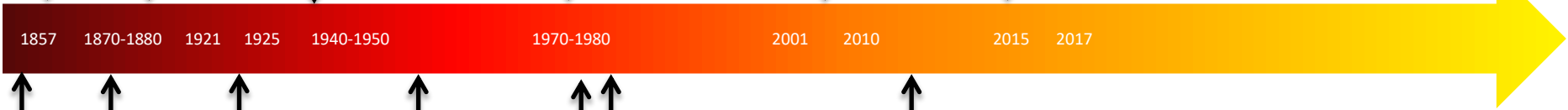


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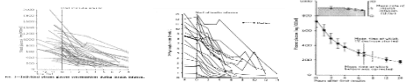


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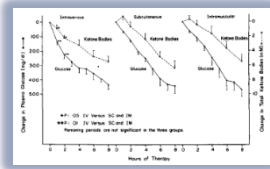
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Back to Cerebral Oedema

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Clinical Trial of Fluid Infusion Rates for Pediatric Diabetic Ketoacidosis

Nathan Kuppermann, M.D., M.P.H., Simona Ghetti, Ph.D.,
Jeff E. Schunk, M.D., Michael J. Stoner, M.D., Arleta Rewers, M.D., Ph.D.,
Julie K. McManemy, M.D., M.P.H., Sage R. Myers, M.D., M.S.C.E.,
Lise E. Nigrovic, M.D., M.P.H., Aris Garro, M.D., M.P.H., Kathleen M. Brown, M.D.,
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J. Michael Dean, M.D., and Nicole S. Glaser, M.D.,
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ORIGINAL ARTICLE

CONCLUSIONS

Neither the rate of administration nor the sodium chloride content of intravenous fluids significantly influenced neurologic outcomes in children with diabetic ketoacidosis.

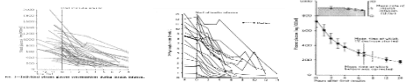
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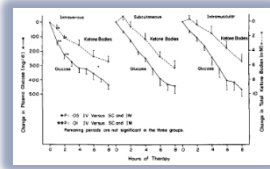
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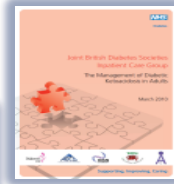
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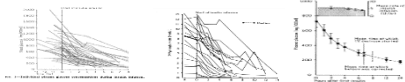


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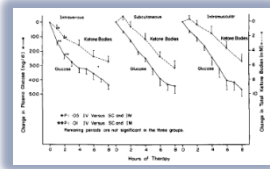
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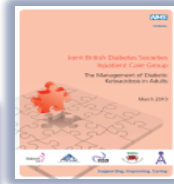


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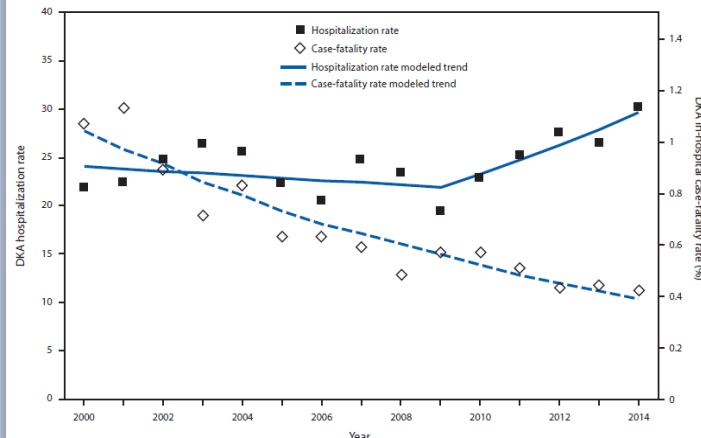
Continued Year-on-Year Improvements - USA

Morbidity and Mortality Weekly Report

Trends in Diabetic Ketoacidosis Hospitalizations and In-Hospital Mortality — United States, 2000–2014

Stephen R. Benoit, MD¹; Yan Zhang, MSPH¹; Linda S. Geiss, MS¹; Edward W. Gregg, PhD¹; Ann Albright, PhD¹

FIGURE. Age-adjusted diabetic ketoacidosis hospitalization rate per 1,000 persons with diabetes and in-hospital case-fatality rate — United States, 2000–2014*



- Despite an increase in hospitalisations, case fatality dropped by 64% from 1.1% in 2000 to 0.4% in 2014

And UK

Diabetologia (2016) 59:2082–2087
DOI 10.1007/s00125-016-4034-0



ARTICLE

Risk of death following admission to a UK hospital with diabetic ketoacidosis

Fraser W. Gibb¹ · Wei Leng Teoh¹ · Joanne Graham² · K. Ann Lockman²

National survey of the management of Diabetic Ketoacidosis (DKA) in the UK in 2014

K. K. Dhatariya¹, I. Nunney², K. Higgins³, M. J. Sampson¹ and G. Iceton⁴

¹Elsie Bertram Diabetes Centre, Norfolk and Norwich University Hospitals NHS Foundation Trust, Norwich, ²Norwich Medical School, University of East Anglia, Norwich, ³University Hospitals of Leicester NHS Trust, Leicester and ⁴Clinical Audit and Improvement Department, Norfolk and Norwich University Hospitals NHS Foundation Trust, Norwich, UK

Accepted 28 July 2015

- No deaths over 6 years in Glasgow, and no deaths in the national survey in 2014

But Mortality Remains High in LDCs

- Rates of >30% mortality in India, parts of Africa and the Caribbean

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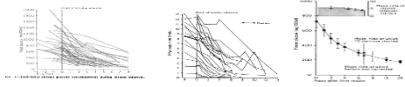
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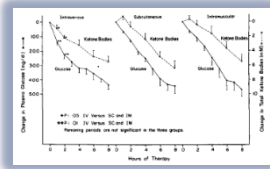
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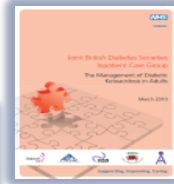
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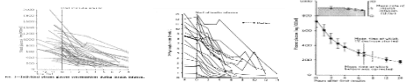


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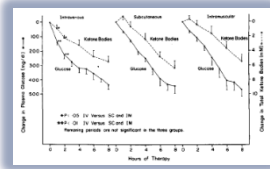
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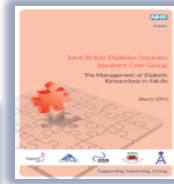


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DKA mortality in adults and children reported at <1% in the USA and other developed nations – although remains up to 30% elsewhere

Trends in Diabetic Ketoacidosis Hospitalizations and In-Hospital Mortality – United States, 2000–2014

Changes needed

National survey of the management of Diabetic Ketoacidosis (DKA) in the UK in 2014

K. K. Dhatariya¹, I. Nunney², K. Higgins³, M. J. Sampson¹ and G. Iceton⁴

¹Elsie Bertram Diabetes Centre, Norfolk and Norwich University Hospitals NHS Foundation Trust, Norwich, ²Norwich Medical School, University of East Anglia, Norwich, ³University Hospitals of Leicester NHS Trust, Leicester and ⁴Clinical Audit and Improvement Department, Norfolk and Norwich University Hospitals NHS Foundation Trust, Norwich, UK

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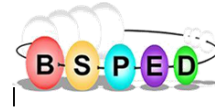
- These data showed that hypokalaemia and hypoglycaemia were common (67% <4.0mmol/l, and 28% <4.0mmol/l respectively)

16 – 18 Year Olds in the UK

**A survey of the management of
16–18-year-olds presenting with diabetic
ketoacidosis in the UK: a need for
standardisation**

KETAN DHATARIYA,^{1,2} PETER WINOCOUR,³ ANDREW RAFFLES⁴

This Led to Immediate Change



BSPED Guideline for the Management of Children and Young People under the age of 18 years with Diabetic Ketoacidosis - 2021

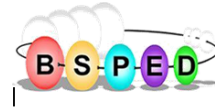
This guideline for the management of DKA replaces the BSPED interim guideline published in 2020 and has been updated in light of the NICE Guidance NG18 which was updated in December 2020 and UK Resuscitation Council recommendations published in May 2021. It has been revised by the BSPED special interest group in diabetic ketoacidosis following a series of meetings. The relatively limited evidence regarding the management of DKA has been reviewed. Where there is appropriate evidence these guidelines have been based on such evidence. For many aspects of the management of DKA the evidence base is limited and where there is limited evidence, consensus recommendations have been consolidated. The guideline is broadly similar to the International Society for Paediatric and Adolescent Diabetes (ISPAD) and takes account of the updated NICE NG18 guidance.

These BSPED guidelines are believed to be as safe as possible in the light of current evidence. However, no guidelines can be considered entirely safe as complications may still arise. In particular the pathophysiology of cerebral oedema is still poorly understood.

The following changes have been made since the last BSPED guideline was published in 2015 and the interim guideline in 2020:

- 1) NICE guidance NG18 applies to all individuals <18 years and does not make explicit recommendation's for the group aged 16-18 years who may be managed by either Adult or Paediatric medical teams. The BSPED special interest group remained of the opinion that where young people aged 16-18 years are managed by adult medical teams because of local arrangements, it is appropriate for them to be managed using local adult guidelines that the teams are familiar with rather than using potentially unfamiliar paediatric guidelines. Where individuals aged 16-18 are managed by Paediatric teams the Paediatric guidelines should be followed.

This Led to Immediate Change



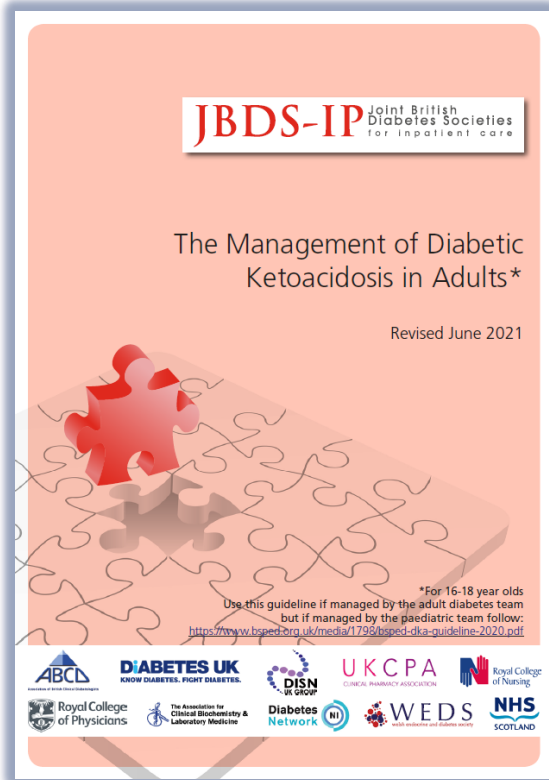
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This is Reflected in the 2021 Adult Guidelines



This is Reflected in the 2021 Adult Guidelines

JBDS-IP Joint British
Diabetes Societies
for inpatient care

*For 16-18 year olds

Use this guideline if managed by the adult diabetes team
but if managed by the paediatric team follow:

<https://www.bsped.org.uk/media/1798/bsped-dka-guideline-2020.pdf>

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JBDS-IP Joint British Diabetes Societies for inpatient care

The Management of Hyperosmolar Hyperglycaemic State (HHS) in Adults*

November 2021

*For 16-18 year olds

Use this guideline if the person aged 16 – 18 is being managed by the adult diabetes team. If they are managed by the paediatric team, they should follow the following guideline: <http://www.a-c-d-c.org/wp-content/uploads/2012/08/Practical-Management-of-Hyperglycaemic-Hyperosmolar-State-HHS-in-children-8.pdf>

This is Reflected in the 2021 Adult Guidelines



JBDS-IP Joint British
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ABCD
DIABETES UK
KNOW DIABETES. PROOF DIABETES.
DiSN
UKCPA
CLINICAL PHARMACY ASSOCIATION
Royal College of Nursing
Royal College of Physicians
The Association for Clinical Biochemistry & Laboratory Medicine
Diabetes Network
WEDS
NHS SCOTLAND

Management of Hyperglycemic Crises in Patients With Diabetes

First reports of successful DKA treatment – Joslin reports that 31 out of 33 patients with DKA survive – with gentle fluid replacement

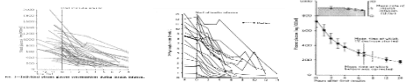


Identification of acetone in the urine

Kaussmaul breathing first described

RD Lawrence advocates very aggressive fluid management

3 consecutive papers in the BMJ showed that low-dose insulin infusions (5–6 units/h) work just as well as high-dose in lowering glucose and ketones



1st ADA consensus on the management of DKA

Euglycemic Diabetic Ketoacidosis: A Potential Complication of Treatment With Sodium–Glucose Cotransporter 2 Inhibition

Reports of SGLT-2i associated DKA

Clinical Trial of Fluid Infusion Rates for Pediatric Diabetic Ketoacidosis

First RCT on fluids in children



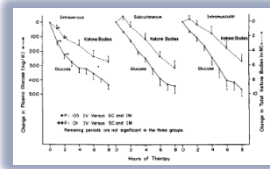
Type 1 diabetes universally fatal

First detailed report of 'diabetic coma'

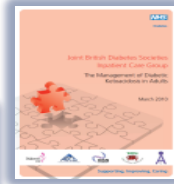


High dose insulin used - reports reduction in mortality from 12% to 1.6% between 1940 and 1944 using between 500 and 2000 units depending on severity of coma

Rate of fluid administration in children questioned – reports of cerebral oedema
And then in the NEJM



The first UK national guideline for managing DKA published



Call for the ADA criteria to be updated

DKA mortality in adults and children reported at <1% in the USA and other developed nations – although remains up to 30% elsewhere

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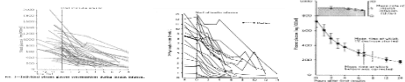


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1857 1870-1880 1921 1925 1940-1950 1970-1980 2001 2010 2015 2017 2018 2021

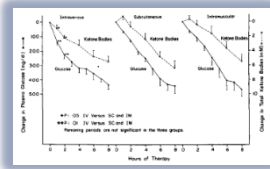
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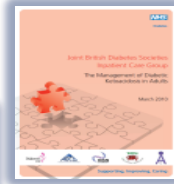


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Revised UK guideline published

A Tribute To Guillermo Umpierrez




If Anyone is Interested

PRIMER



Diabetic ketoacidosis

Ketan K. Dhatariya^{1,2}, Nicole S. Glaser³, Ethel Codner⁴ and Guillermo E. Umpierrez⁵ 

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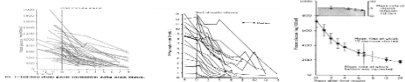


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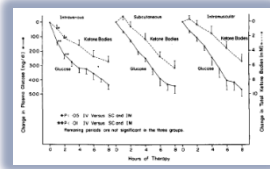
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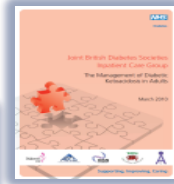


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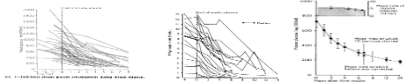


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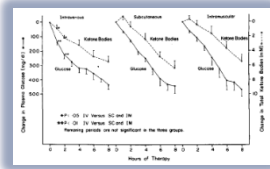
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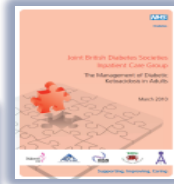


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The Future?

- Things we can't change (quickly)
 - Infections
 - Inequality and deprivation
 - Mental health problems
 - Identification and education of those at risk
- Things that might help
 - Closed loops
 - Longer acting insulins
 -



The History and Management of DKA

www.norfolkdiabetes.com

ketan.dhatariya@nnuh.nhs.uk



[@ketandhatariya](https://twitter.com/ketandhatariya)

