بسم الله الرحمن الرحيم

TREATMENT OF DKA

An evidence based approach

By

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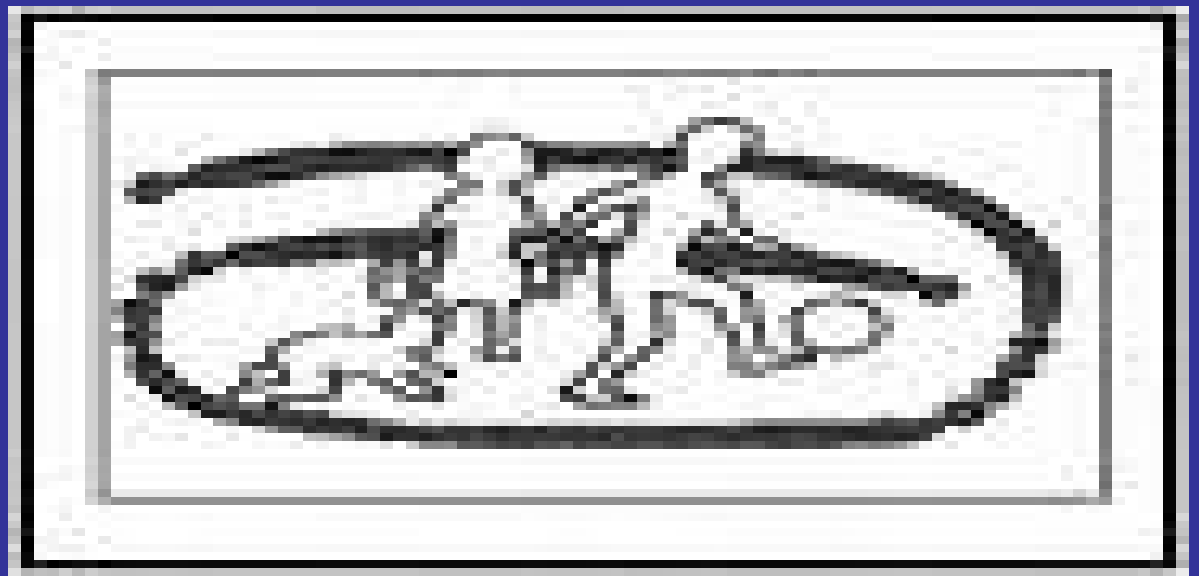

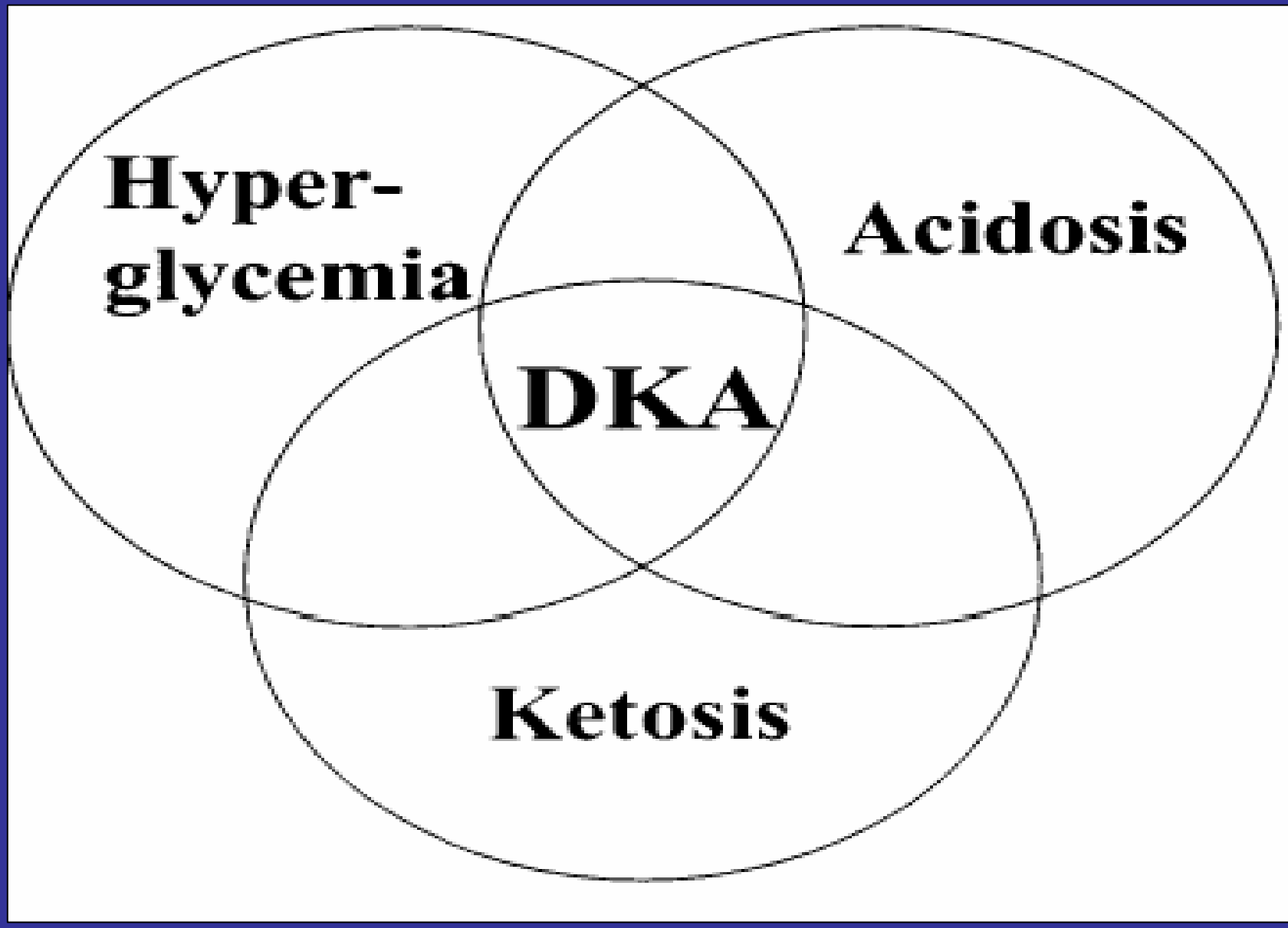
Hyper-
glycemia
Acidosis
DKA
Ketosis

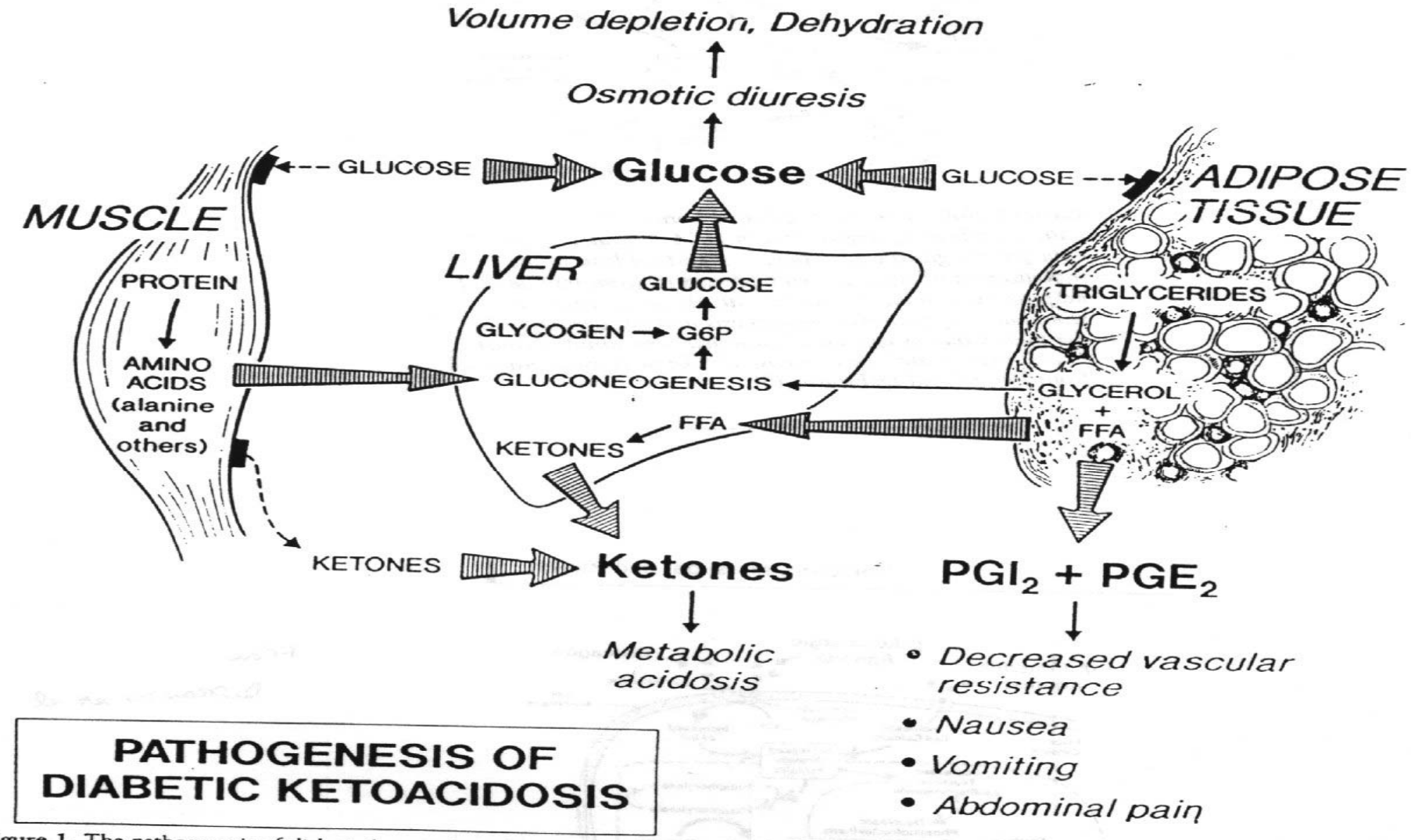

Figure 1. The pathogenesis of diabetic ketoacidosis. Severe insulin deficiency causes hyperglycemia, ketosis, and increased production of PGI_2 and PGE_2. Hyperglycemia is due to increased gluconeogenesis from amino acids, glycerol, and lactate and to decreased peripheral utilization of glucose. Ketosis is due to increased triglyceride lipolysis and increased FFA release from adipose tissue, to preferential utilization of FFAs for ketogenesis in the liver, and to deceased peripheral utilization of ketones. Increased PGI_2 and PGE_2 production by adipose tissue is due to accelerated triglyceride lipolysis and enhanced production of PGI_2 and PGE_2 in adipose tissue. Hyperglycemia causes an osmotic diuresis, volume depletion, hypotension, and dehydration. Ketosis causes an anion gap metabolic acidosis due to the dissociation of the ketoacids in the circulation and/or a hyperchloremic metabolic acidosis due to the loss of potential bicarbonate in the urine in the form of ketone bodies and the retention of chloride. Increased production of PGI_2 and PGE_2 causes decreased peripheral vascular resistance, hypotension, tachycardia, nausea, vomiting, and abdominal pain. Black rectangles denote impaired peripheral utilization of glucose and ketones, as indicated.

PRECIPITATING FACTORS:

- Infection
- Cerebrovascular accidents
- Myocardial infarction
- Pancreatitis
- Trauma
- Drugs :corticosteroids
- sympathomimetics
- thiazides
- Psychological and eating disorders esp in young patients

Guidelines for diagnosis of DKA

- Subjective findings:
- The clinical presentation is usually subacute,with patients presenting with 12-36 hours of:
  * Weakness
  * Report of changes in input and output i.e. polyuria ,polydepsia

*As DKA progresses ,the following symptoms may be present :•

*Deep and rapid breathing (Kussmaul respirations)•

* Blurring of vision•

* Abdominal pain, nausea ,vomiting •

* Dehydration , dry mouth , dizziness•

* Confusion, usually in those with severe hyperglycemia•

* Infection (Fever may be masked in DKA)•

Objective findings:

- Dehydration
- Acidosis
- Tackycardia
- Orthostatic hypotension
- Dry mucous membranes
- Fever which may be masked despite advanced infection
- Fruity breath odour due to acetone
- Altered mental status, mild confusion or frank lethargy

*Cellulitis and infected lower extremity ulcers

*Abdominal findings may be similar to appendiocitis or cholecystitis (e.g. abdominal tenderness)

*A clinical picture consistent with shock (less common finding)

Differential diagnosis of DKA

- Hypoglycemia
- Hyperglycemia,especially in type II diabetes
- Hyperglycemic hyperosmolar nonketotic coma
- Myocardial infarction
  Abdominal emergencies (e.g. mesenteric ischemia,cholecystitis, appendicitis)
- CNS infections
- Bacteremia from any cause may present primarily as DKA.

LABORATORY DIAGNOSIS:

- Plasma glucose
- Urea and creatinine
- Ketones in serum and urine
- Electrolytes= anion gap
- Osmolality
- Urine analysis
- Initial arterial blood gas
- CBC =
- Xray
- ECG

Diagnostic criteria of diabetic ketoacidosis and hyperosmolar hyperglycemic syndrome

	DKA			
	Mild	Moderate	Severe	HHS
Plasma glucose (mg/dl)	>250	>250	>250	>600
Arterial pH	7.25–7.30	7.00–7.24	<7.00	>7.30
Serum bicarbonate (mEq/l)	15–18	10 to <15	<10	>15
Urine ketones*	Positive	Positive	Positive	Small
Serum ketones*	Positive	Positive	Positive	Small
Effective serum osmolality (mOsm/kg)†	Variable	Variable	Variable	>320
Anion gap‡	>10	>12	>12	Variable
Alteration in sensoria or mental obtundation	Alert	Alert/drowsy	Stupor/coma	Stupor/coma

*Nitroprusside reaction method; †calculation: 2[measured Na (mEq/l)] + glucose (mg/dl)/18; ‡calculation: $(Na^+) - (Cl^- + HCO_3^-)$ (mEq/l). See text for details.

Table 7—*Laboratory evaluation of metabolic causes of acidosis and coma*

	Starvation or high fat intake	DKA	Lactic acidosis	Uremic acidosis	Alcoholic ketosis (starvation)	Salicylate intoxication	Methanol or ethylene glycol intoxication	Hyperosmolar coma	Hypoglycemic coma	Rhabdomyolysis
pH	Normal	↓	↓	Mild ↓	↓↑	↓↑*	↓	Normal	Normal	Mild ↓ may be ↓↓
Plasma glucose	Normal	↑	Normal	Normal	↓ or normal	Normal or ↓	Normal	↑↑ >500 mg/dl	↓↓ <30 mg/dl	Normal
Glycosuria	Negative	++	Negative	Negative	Negative	Negative†	Negative	++	Negative	Negative
Total plasma ketones‡	Slight ↑	↑↑	Normal	Normal	Slight to moderate ↑	Normal	Normal	Normal or slight	Normal or slight ↑	Normal
Anion gap	Slight ↑	↑	↑	Slight ↑	↑	↑	↑	Normal	Normal or slight ↑	↑↑
Osmolality	Normal	↑	Normal	↑	Normal	Normal	↑↑	↑↑ >330 mOsm/kg	Normal	Normal or slight ↑
Uric acid	Mild (starvation)	↑	Normal	Normal ↑	↑	Normal	Normal	Normal	Normal	↑
Miscellaneous		May give false-positive for ethylene glycol§	Serum lactate >7 mmol/l	BUN >200 mg/dl		Serum salicylate positive	Serum levels positive			Myoglobinuria, hemoglobinuria

Some pitfalls in diagnosis

- Plasma glucose is usually high but not always
- Increased WBC count may occur without infection
- Infection can occur in absence of fever
- Some assays for creatinine may cross react with ketone bodies
- Hyponatremia is common ,but there is pseudohyponatremia due to hyperglycemia
- Ketonuria doesnot mean ketoacidosis
- Amylase may increase together with non specific abdominal pain -→ ----- panreatitis
- MI may be a precipitating factor , but may be silent
- ECG should be done

WHAT IS EVIDENCE BASED MEDICINE?

- Evidence based medicine (EBM) is the integration of best research evidence with clinical expertise and patient values
- Best research evidence means clinically relevant research ,patient centered
- Clinical expertise means the ability to use clinical skills and past experience to rapidly identify each patients unique health state and diagnosis, their individual risks, and benefits of potential interventions and their personal values and expectations.
- The patient values mean the unique preferences, concerns, expectations, each patient has which must be integrated into clinical decisions if they r to serve the patient.

WHAT IS AN EVIDENCE BASED APPROACH? How to practice EBM?

- ASK an answerable clinical question
- ACQUIRE the best evidence to answer
- APPRAISE that evidence for validity, impact , and applicability
- APPLY that evidence through integrating the critical appraisal with our clinical expertise and patients values and preferences
- ASSESS the effectiveness of the previous steps

GUIDELINES

What are the components of a guideline?

The evidence component

Here is the typical effect of this diagnostic ,therapeutic or preventive intervention on the typical patient

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Requires validity, importance, up to date

The site of generation is national or international

The form of output: levels of evidence

The detailed instructional component

Here is exactly what to do with this patient

Requires local relevance

The site of generation is local

Grades of recommendations, flow charts, protocols.

LEVELS OF EVIDENCE AND GRADES OF RECOMMENDATIONS

Grade A	1a= Systematic review of RCTs (with homogeneity) 1b= individual RCT (with narrow CI) 1c= All or none
Grade B	2a= Systematic review of cohort studies 2b= individual cohort study 3a= SR of case control studies 3b= individual case control study
Grade C	4= case series, poor quality cohort and case control study
Grade D	5= expert opinion without explicit critical appraisal, or based on physiology research

WHAT ARE THE GOALS OF TREATMENT OF DKA?

- IV volume expansion
- Correction of deficits in fluids , electrolytes, and acid base status.
- Initiation of insulin therapy to correct hyperglycemia, catabolism and acidosis.
- Identification and treatment of underlying cause.

WHAT ARE THE LINES OF THERAPY ?

- FLUID THERAPY
  (amount, rate, type of fluids)
- INSULIN THERAPY
  (timing, dosage, route and rate of administration)
- POTASSIUM
  (timing, rate and dosage)
- ?? BICARBNATE
  (needed or not?)
- ? PHOSPHATE
  (needed or not)

PROTOCOL FOR MANAGEMENT OF ADULT PATIENTS WITH DKA

(ADA position statement 2004,National Guideline Clearinghouse 2005)

- Initial evaluation to establish diagnosis:
- DKA DIAGNOSTIC CRITERIA:
- Blood glucose >250 mg/dl
- Arterial pH <7.3
- Bicarbonate <15 mEq/l
- Moderate ketonuria or ketonemia
- Transfer to ICU in case of severe acidosis, respiratory decompensation and hypotension unresponsive to fluids

FLUID THERAPY

= for expansion of extra and intravascular volume and restoration of renal perfusion. (Fluid deficit usually 4-6 l)

= Isotonic saline is the initial hydrating fluid in absence of cardiac compromise.

= Plasma expander may be given in case of shock

= 0.9% saline infusion rate 15-20ml/kg/hour in the first hour (around 1-1.5 l in average adult).

= Subsequent infusion depends on the state of hydration, serum electrolytes and urine output.

FLUID THERAPY

- Pseudohyponatremia is often present. So expect that sodium level will rise during treatment. If not , true hyponatremia may be present (possibly increasing the risk of cerebral oedema)

- if corrected sodium is normal or elevated ,0.45% saline is infused at a rate of 4-14 ml/kg/hour (300-500 ml/hr)

  (corrected sodium measurment = add 1.6 mEq to serum sodium for each 100mg/dl glucose above 100mg/dl)

If corrected sodium is low ,0.9 % saline is appropriate

SO,0.45% saline used in elderly,history of CHF or possibly hypernatremia

0.09 saline in young or hypotensive patients.

FLUID THERAPY

- Once the renal function is assured, the infusion should include 20-30mEq /l potassium(2/3 kcl and 1/3 kPO4) until the patient is stable and can tolerate oral supplementation.

- Progress of fluid replacement by
  hemodynamic monitoring (improvement of BP)
  measurment of fluid input/output
  clinical examination

Fluid deficit should be corrected within 24 hours

When blood glucose <250-300 , glucose D5W infused to prevent hypoglycemia

The change in osmolality should not exceed 3 mOsm/kg/ hour

FLUID THERAPY

- Monitoring is imp in patients with renal or cardiac compromise to avoid iatrogenic fluid overload
- Use data flow sheet to closely monitor the patient at 0,1,2,4,6,8,10,12,16,20.24 hours
- Monitor glucose ,k,pH, or HCO3, insulin infusion,urine output , IV fluids , mental status, pulse,respiration,blood pressure.
- Failure of restoration of hydration is the most serious therapeutic pitfall
- Also overhydration (> 5 l/ 8 hours) --→ ARDS, brain oedema

Suggested Flow sheet For DKA

SUGGESTED

DKA/HHS FLOWSHEET

DATE: HOUR:	ER												
Weight (daily)													
Mental Status*													
Temperature													
Pulse													
Respiration/Depth**													
Blood Pressure													
Serum Glucose (mg/dl)													
Serum Ketones													
Urine Ketones													
ELECTROLYTES													
Serum Na+ (mEq/L)													
Serum K+ (mEq/L)													
Serum CL (mEq/L)													
Serum HCO_3 - (mEq/L)													
Serum BUN (mg/dl)													
Effective Osmolality 2[measured Na(mEq/L)] +Glucose (mg/dl)/18													
Anion Gap													
A.B.G.													
pH Venous(V) Arterial(A)													
pO_2													
pCO_2													
O_2 SAT													
INSULIN													
Units Past Hour													
Route													
INTAKE FLUID/METABOLITES													
0.45% NaCl(ml) Past Hour													
0.9% NaCl(ml) Past Hour													
5% Dextrose(ml) Past Hour													
KCL (mEq) Past Hour													
PO_4 (mMOLES) Past Hour													
Other (e.g., HCO_3^-)													
OUTPUT													
Urine (ml)													
Other													

* A-ALERT D-DROWSY S-STUPOROUS C-COMATOSE

** D-DEEP S-SHALLOW N-NORMAL

INSULIN THERAPY

- Continuous IV infusion of regular insulin is the treatment of choice , sc insulin may be used in mild case.

- Once hypokalemia(k <3.3) is excluded, Start IV regular insulin bolus 0.15 units/kg, followed by continuous infusion at a dose of 0.1 unit/kg/hour (5-7 units /h in adults).

- Plasma glucose is usually lowered by a rate of 50-75 mg/dl/h
- If glucose not decreased by 50 mg in first hour , check hydration status ,if acceptable, insulin infusion may be doubled until a steady decline of glucose bet 50-75 mg/dl occur.
- When plasma glucose reaches 250 mg/dl ,it is possible to decrease the insulin infusion rate to 0.05-0.1 u/kg/h(3-6 u) and glucose 5% may be added

INSULIN THERAPY

Insulin infusion is maintained until resolution of acidosis (insulin should not be stopped if ongoing acidosis present , venous pH =0.03 units lower than arterial pH measurments could be used for follow up and the anion gap)

Anion gap= (Na + K)-(cl+HCO3)

Ketonemia usually takes longer than hyperglycemia (direct measurment of B-OHB in the blood is the preferred method for monitoring DKA , the ordinary method only measures acetoacetic and acetone although beta hydroxy butyric acid is the most prevalent)

During therapy, B-OHB is converted to acetoacetic acid, w may lead the clinician to think that ketosis is worsened.

So , assessment of urine ketones by the conventional method should not be used as an indicator for response to therapy.

In patients with mild DKA regular insulin may be administered sc or IM every hour
An initial bolus of regular insulin0.4-0.6 units/kg (half as IV)
Thereafter 0.1unit/kg/hr sc or IM is administered

Criteria for resolution of DKA
Glucose <200mg/dl
HCO_3 > 18 mEq/l
Venous pH >7.3

After resolution SC regular insulin given every 4 hours as needed (5 units for every 50 mg /dl increase in blood glucose above 150 mg/dl for up to 20 units for blood glucose >300)

When the patient can eat combination of rapid and intermediate acting insulin is needed to control glucose,
, avoid abrupt cessation of iv insulin
, some over lap is preferred

Insulin lispro subcutaneously hourly may be safe alternative to regular insulin IV in adult patients with DKA (Level of evidence 2)

Am J Med 2004, Am Family Physician 2005

COMPLICATIONS

HYPOGLYCEMIA is common

HYPOKALEMIA (due to insulin administration and bicarb treatment)

HYPERGLYCEMIA(due to interruption of insulin infusion without subsequent coverage with sc insulin)

Chloride retention and transient non anion gap acidosis

HYPOXEMIA AND NON CARDIOGENIC PULMONARY OEDEMA rare

CEREBRAL OEDEMA= rare but fatal complication
more in children and youg adults
due to osmotic movement of fluid into CNS when plasma osmolality declines too rapidly
clinically ,deterioration of the level of consciousness , lethargy,decrease arousal , and headache . Neurologic deterioration may be rapid with siezures, incontinence, pupillary changes , bradycardia and resp arrest. ttt = mannitol and hyperventillation

POTASSIUM

There is usually total potassium depletion

However , hyperkalemia may occur

Insulin therapy, correction of acidosis (with entry of k to cells)and volume expansion decrease serum k conc.

To prevent hypokalemia k replacement started once serum k<5.5mE/l, when adequte urine output is ensured

20-30 mEq potassium /l fluid infusion is sufficient, a suggested regimen : according to initial k level add k to hydrating fluid as follows:

5-5.3--------10 mEq/l

4.5-5--------20 mEq/l

4- 4.5-------30 mEq/l

3.5-4-------- 40 mEq/l

<3.5--------- 40 mEq/l

Rarely,DKA may present with significant hypokalemia, in this case k replacement starts with fluid replacement and insulin is delayed until k>3.3 mEq/l to avoid arrythmias or cardiac arrest and respiratory muscle weakness

Monitor hourly for first 2 hours then every 2-4 hours

Monitor urine output

K2PO4 preferred initially due to phosphate deficiency

BICARBONATE

- Usually not administered especially if pH 7 or more
- (establishing insulin activity blocks lipolysis and resolves ketoacidosis without added bicarb) Also ,correction of hyperglycemia usually restores normal pH.
- RCTs failed to show benefit or harm inpatients with pH bet 6.9-7.1), No RCTs in patients with pH<6.9 has been reported.

- In severe (pH <6.9, bicarb <5) acidosis causing crdiorespiratory compromise,
- bicarb may be administered (100 ml bicarb added to 400 ml sterile water ,given in a rate 200ml/hr) or in 0.45 % saline.

Insulin and bicarb -→ hypokalemia, so k suuplementation must be assured

Venous pH assessed every 2 hour

Sudden rise in pH may reduce oxygen delivery to tissues and predispose to lactic acidosis.

PHOSPHATE

- Whole body phosphate deficits
- Normal or increased serum level at presentation.
- Its conc decreases with insulin therapy
- Trials showed no benefit
- Overtreatment can cause hypocalcemia
- To avoid muscle weekness and respiratory depression, careful phosphate replacement in case of very low levels (<1 mg/dl)
- Given a potassium phosphate when needed.

Management of the Adult Patient With DKA or HHS
Consider Early Referral to Internal Medicine

IV FLUIDS

Start IV Fluids
1.0L/hr of 0.9% NaCl initially. May need more aggressive fluid resuscitation depending on hydration & Hemodynamic status

Patients with history of renal failure may not have a fluid deficit as large as patients with normal renal function. Watch vital signs and urine output to monitor response

When patient Euvolemic (Vital signs stabilizing & Urine output adequate), may switch Fluid to 0.45% NaCl (4-14ml/kg/hr). Corrected serum Na should be High or Normal

When serum glucose reaches 13.5mmol/L, change fluid to D5W 0.45% NaCl and decrease insulin drip to 0.05-0.1U/kg/hr to maintain serum glucose between 10-15mmol/L

INSULIN

Hold insulin until serum K+ available. If serum K <3.3MEq/L, HOLD INSULIN
If serum K >3.3MEq/L, run insulin infusion

Insulin Infusion: Add 75U of regular insulin to 500 mls of NS Run 100mls of solution through the tubing, then connect directly to the patient. start insulin drip at 40ml/hr (0.1units/hr)

Check glucose hourly. If glucose not falling by 2-4mmol/L/hr, double your insulin drip until glucose falls at a steady rate of 2-4mmol/L/hr

When glucose reaches <15mmol/L, switch to D5W 0.45% NS. Adjust insulin to lower glucose no faster than 1mmol/L/hr. Need to continue insulin to clear Ketones for approx. 24 hrs.

POTASSIUM

If RENAL FAILURE, use Potassium infusion cautiously

If serum K+ >5.5mEq/L, HOLD POTASSIUM
Consider DIALYSIS if Renal Failure
Check K+ every 2 hours

If serum K+ >3.3mEq/L give 10-30mEq/L of KCl in each litre of fluid.
Goal is to maintain serum K+ 4-5mEq/L

If serum K+ <3.3mEq/L, HOLD INSULIN
Give 40mEq/L of KCl until serum K+ >3.3mEq/L
Goal is to maintain serum serum between K+ 4-5mEq/L

BICARBONATE

Emerging trend is to use NO BICARBONATE regardless of the patient's pH on presentation. The pH and HCO3 will correct with fluids and insulin.

Maintain Serum glucose 10-15mmol/l. Start SC insulin when patient drinking well and abdominal pain, if present, has resolved. Overlap IV and SC insulin by 60 min.

If possible, start patient on SC insulin regimen in morning. Resume previous SC insulin schedule or consider mixture of intermediate and short acting insulin. Talk with Intensivist on call for dosing

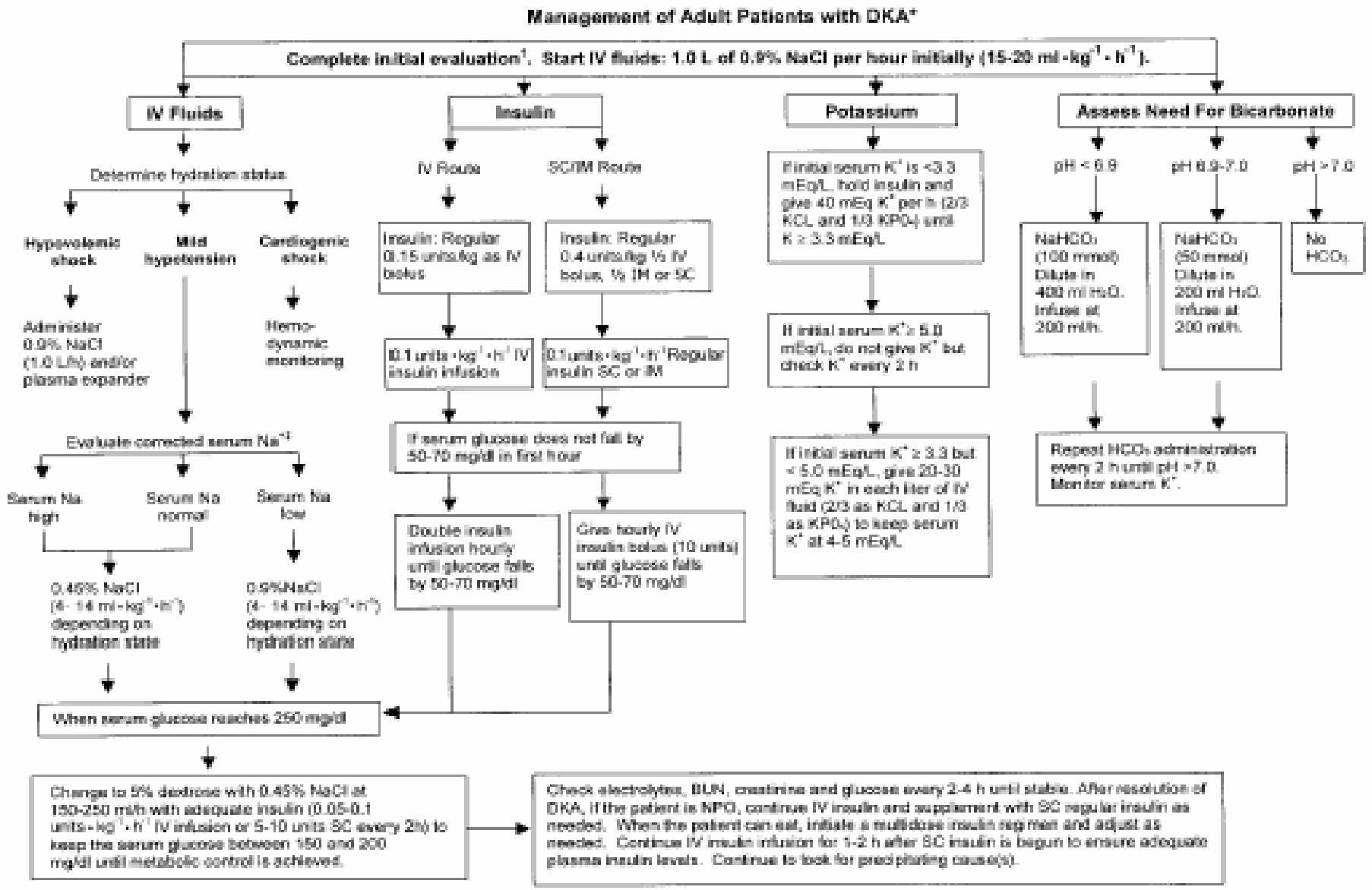

Figure 1—*Protocol for the management of adult patients with DKA. *DKA diagnostic criteria: blood glucose >250 mg/dl, arterial pH <7.3, bicarbonate <15 mEq/l, and moderate ketonuria or ketonemia. Normal ranges vary by lab; check local lab normal ranges for all electrolytes. †After history and physical examination, obtain arterial blood gases, complete blood count with differential, urinalysis, blood glucose, blood urea nitrogen (BUN), electrolytes, chemistry profile, and creatinine levels STAT as well as an electrocardiogram. Obtain chest X-ray and cultures as needed. ‡Serum Na should be corrected for hyperglycemia (for each 100 mg/dl glucose >100 mg/dl, add 1.6 mEq to sodium value for corrected serum sodium value). IM, intramuscular; IV, intravenous; SC subcutaneous.*

Summary of major recommendations of ADA

Recommendations	Grading
● Initiate insulin therapy according to recommendations in position statement.	A
● Unless the episode of DKA is mild, regular insulin by continuous intravenous infusion is preferred.	B
● Assess need for bicarbonate therapy and, if necessary, follow treatment recommendations in position statement: bicarbonate may be beneficial in patients with a pH <6.9; not necessary if pH is >7.0	C
● Studies have failed to show any beneficial effect of phosphate replacement on the clinical outcome in DKA. However, to avoid cardiac and skeletal muscle weakness and respiratory depression due to hypophosphatemia, careful phosphate replacement may sometimes be indicated in patients with cardiac dysfunction, anemia, or respiratory depression and in those with serum phosphate concentration <1.0 mg/dl.	A
● Studies of cerebral edema in DKA are limited in number. Therefore, to avoid the occurrence of cerebral edema, follow the recommendations in the position statement regarding a gradual correction of glucose and osmolality as well as the judicious use of isotonic or hypotonic saline, depending on serum sodium and the hemodynamic status of the patient.	C
● Initiate fluid replacement therapy based on recommendations in position statement.	A

Scientific evidence was ranked based on the American Diabetes Association's grading system. The highest ranking (A) is assigned when there is supportive evidence from well-conducted, generalizable, randomized controlled trials that are adequately powered, including evidence from a meta-analysis that incorporated quality ratings in the analysis. An intermediate ranking (B) is given to supportive evidence from well-conducted cohort studies, registries, or case-control studies. A lower rank (C) is assigned to evidence from uncontrolled or poorly controlled studies or when there is conflicting evidence with the weight of the evidence supporting the recommendation. Expert consensus (E) is indicated, as appropriate. For a more detailed description of this grading system, refer to *Diabetes Care* 24 (Suppl. 1): S1–S2, 2001.

PREVENTION

- Education of patients(sick day management)

THANK YOU