Management of Diabetic Ketoacidosis

Rationale for the NYP Algorithm

This presentation discusses the rationale behind the NYP DKA algorithm and recommendations.

Diabetic Ketoacidosis Diagnostic Criteria

- Hyperglycemia (glucose >200)
- Venous pH <7.3 OR bicarb <15mmol/L
- Ketonemia and/or ketonuria

Clinical manifestations

- Polyuria, polydipsia, weight loss
- Dehydration
- Hyperpnea, tachypnea, Kussmaul (deep, sighing) respirations
- Nausea, vomiting, abdominal pain that may mimic an acute abdominal condition
- Confusion, drowsiness, progressive obtundation, loss of consciousness

Diabetic ketoacidosis (DKA) is a condition seen in Type 1 Diabetics where the lack of insulin results in hyperglycemia through several mechanisms (accelerated gluconeogenesis, glycogenolysis, and decreased glucose utilization). Without insulin, glucose uptake into the cells is impaired, and cells are forced to use fat as an energy source as lipolysis increases. Ketones, a byproduct of free fatty acid metabolism, accumulates leading to ketoacidosis. Hyperglycemia also causes an osmotic diuresis and dehydration with loss of both water and electrolytes. Potassium and phosphate are most affected, but sodium and chloride are also lost.

The clinical manifestations of DKA are described on this slide, but the diagnostic criteria include hyperglycemia, acidosis (defined by either a venous pH below 7.3 or a bicarbonate less than 15), and presence of ketonemia and/or ketonuria.

Treating Diabetic Ketoacidosis

Goals of Therapy

1. Correct hyperglycemia
2. Correct ketoacidosis
3. Correct dehydration
4. Correct/avoid electrolyte derangements
5. Avoid cerebral edema

Stages of Therapy

1. **Administer fluid bolus and begin rehydration**
2. **Initiate insulin infusion and follow decrease in blood glucose, continue rehydration**
3. **Maintain blood glucose in the target range until the ketoacidosis resolves**
4. Transition to SC insulin and PO

There are 5 goals that guide the treatment of diabetic ketoacidosis: 1) correct hyperglycemia, 2) correct ketoacidosis, 3) correct dehydration, 4) correct/prevent electrolyte derangements, and 5) avoid cerebral edema.

Because of the different time courses by which these therapeutic goals can be achieved, therapy can be divided into 4 stages: 1) correcting shock if present and initiating rehydration, 2) initiating the insulin infusion, 3) “clamping” the blood glucose in the target range, and 4) transition to PO intake with SC insulin. The blood glucose typically falls significantly after the fluid bolus is administered and will continue to fall as insulin is administered. The ketoacidosis takes longer to correct, and this requires insulin—even after the hyperglycemia is corrected. It will be necessary to administer intravenous glucose in order to prevent further decreases in blood glucose while the insulin continues to treat the ketoacidosis. Typically, when the ketoacidosis is corrected, the patient will be sufficiently rehydrated to be able to complete their rehydration by mouth.

This presentation addresses the first three stages of therapy. Stage 4, the transition to subcutaneous insulin and oral intake can be done once all the other therapeutic goals have been met. The specific plan for Stage 4 is guided by the Endocrinologists/Diabetologists.

Let’s start by discussing the IV fluids – the initial bolus and the initiation of continuous fluids for rehydration

Administer Fluid Bolus
and
Begin Rehydration

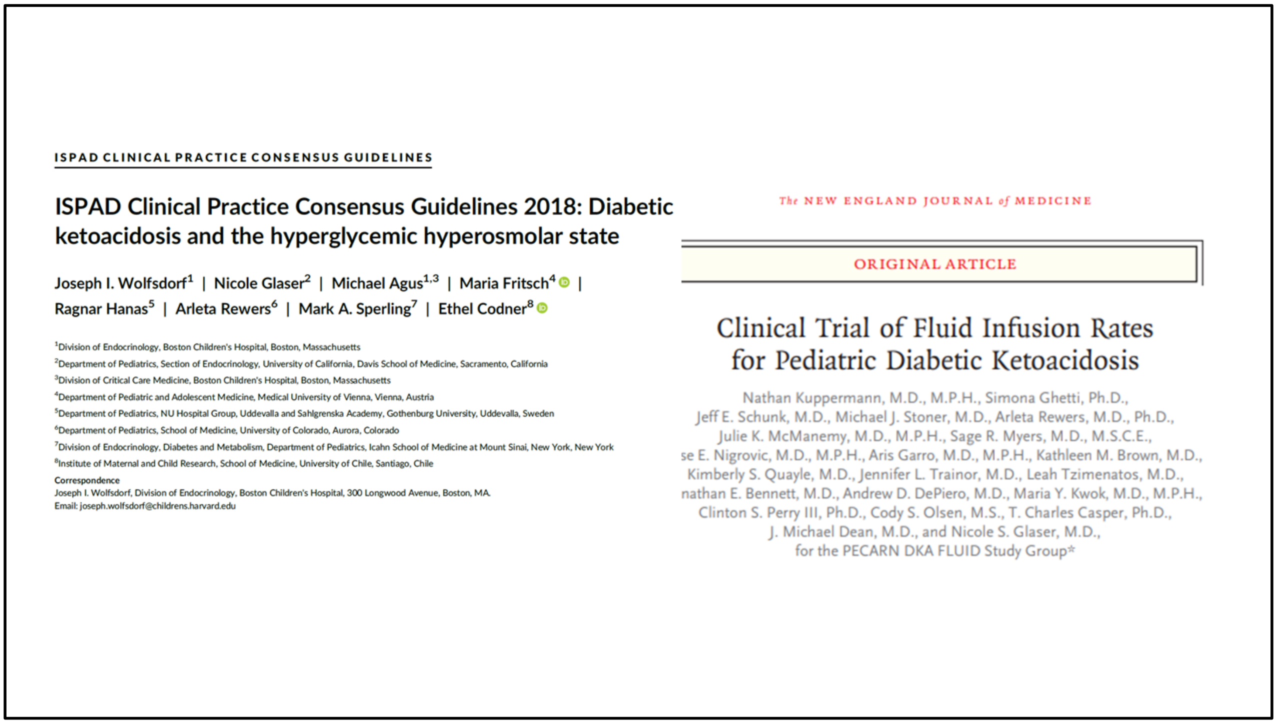
What is the recommended volume of bolus fluids?

How fast should the IV fluids run after the fluid bolus?

Most clinicians do not hesitate to treat severely dehydrated patients with large volumes of intravenous fluids administered rapidly. In DKA, the fear of cerebral edema tempers this approach.

Early theories ascribed cerebral edema to overexuberant fluid resuscitation, but this was likely an oversimplification. More recent evidence points to brain hypoperfusion (from dehydration and hypocapnia) coupled with reperfusion injury during rehydration. While this and neuroinflammation are thought to be more likely mechanisms to cause cerebral edema, many clinicians remain reluctant to administer large volumes of fluid to patients in DKA.

Because of differences in fluid regimens and other aspects of treatment, guidelines were developed to better guide the treatment of DKA.


ISPAD CLINICAL PRACTICE CONSENSUS GUIDELINES

ISPAD Clinical Practice Consensus Guidelines 2018: Diabetic ketoacidosis and the hyperglycemic hyperosmolar state

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ORIGINAL ARTICLE

Clinical Trial of Fluid Infusion Rates for Pediatric Diabetic Ketoacidosis

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The 2018 International Society for Pediatric and Adolescent (ISPAD) Clinical Practice Guidelines for treating DKA provides valuable guidance. Its recommendations for fluid resuscitation are largely based on the 2018 Pediatric Emergency Care Applied Research Network (PECARN) study of fluid management in pediatric DKA with the primary outcome being the incidence of cerebral edema.

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Wolfsdorf JI, Glaser N, Agus M, Fritsch M, Hanas R, Rewers A, Sperling MA, Codner E. ISPAD Clinical Practice Consensus Guidelines 2018: Diabetic ketoacidosis and the hyperglycemic hyperosmolar state. Pediatr Diabetes. 2018 Oct;19 Suppl 27:155-177. doi: 10.1111/pedi.12701. PMID: 29900641.

Kuppermann N, Ghetti S, Schunk JE, Stoner MJ, Rewers A, McManemy JK, Myers SR, Nigrovic LE, Garro A, Brown KM, Quayle KS, Trainor JL, Tzimenatos L, Bennett JE, DePiero AD, Kwok MY, Perry CS 3rd, Olsen CS, Casper TC, Dean JM, Glaser NS; PECARN DKA FLUID Study Group. Clinical Trial of Fluid Infusion Rates for Pediatric Diabetic Ketoacidosis. N Engl J Med. 2018 Jun 14;378(24):2275-2287. doi: 10.1056/NEJMoa1716816. PMID: 29897851; PMCID: PMC6051773.

Clinical Trial of Fluid Infusion Rates for Pediatric Diabetic Ketoacidosis

Table 1. Treatment Regimens.

Variable	Fast Administration of 0.45% Sodium Chloride Solution	Fast Administration of 0.9% Sodium Chloride Solution	Slow Administration of 0.45% Sodium Chloride Solution	Slow Administration of 0.9% Sodium Chloride Solution
Standard initial fluid bolus*	10 ml per kilogram bolus of 0.9% sodium chloride solution	10 ml per kilogram bolus of 0.9% sodium chloride solution	10 ml per kilogram bolus of 0.9% sodium chloride solution	10 ml per kilogram bolus of 0.9% sodium chloride solution
Additional intravenous fluid bolus	10 ml per kilogram of 0.9% sodium chloride solution	10 ml per kilogram of 0.9% sodium chloride solution	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
Process for replacement of deficit	During the initial 12 hours, replace half the fluid deficit, plus maintenance fluids. Then replace remaining deficit, plus maintenance fluids, during the subsequent 24 hours.	During the initial 12 hours, replace half the fluid deficit, plus maintenance fluids. Then replace remaining deficit, plus maintenance fluids, during the subsequent 24 hours.	Replace deficit, plus maintenance fluids, evenly during a period of 48 hours.	Replace deficit, plus maintenance fluids, evenly during a period of 48 hours.
Fluid used for replacement of deficit†	0.45% sodium chloride solution	0.9% sodium chloride solution	0.45% sodium chloride solution	0.9% sodium chloride solution

* Initial fluid bolus volumes were subtracted from the fluid deficit that was used to calculate the rate of fluid replacement. Fluid boluses could be repeated at the discretion of the treating physician to restore peripheral perfusion and hemodynamic stability. Insulin treatment was initiated after the initial intravenous fluid boluses as a continuous intravenous infusion at a rate of 0.1 U per kilogram of body weight per hour. Dextrose was added to the intravenous fluids when the serum glucose level declined to below 200 to 300 mg per deciliter (11.1 to 16.7 mmol per liter) to maintain the serum glucose level between 100 and 200 mg per deciliter (5.6 to 11.1 mmol per liter).

† Replacement of potassium was provided with the use of an equal mixture of potassium chloride and potassium phosphate or an equal mixture of potassium acetate and potassium phosphate. Potassium salts used for replacement were identical among the groups at each site but varied among the trial sites.

The PECARN FLUID study subjects were randomized to one of 4 groups in a 2-by-2 factorial design of fast versus slow fluid administration rates and isotonic versus hypotonic fluid. The outcome measure was a decreased GCS score below 14 as an indicator of cerebral edema. The bottom line was that there were no differences among any of the groups.*

The fluid bolus is typically administered over 30-60 minutes but can be given more rapidly (over 15 minutes as given in shock) and repeated at if necessary to restore peripheral perfusion and hemodynamic stability.

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Glaser NS, Ghetti S, Casper TC, Dean JM, Kuppermann N; Pediatric Emergency Care Applied Research Network (PECARN) DKA FLUID Study Group. Pediatric diabetic ketoacidosis, fluid therapy, and cerebral injury: the design of a factorial randomized controlled trial. Pediatr Diabetes. 2013 Sep;14(6):435-46. doi: 10.1111/pedi.12027. Epub 2013 Mar 13. PMID: 23490311; PMCID: PMC3687019.

Caveat: The sample-size calculation for the PECARN FLUID study used a 15% incidence of GCS <14 in patients treated for DKA. The group with the highest rate of abnormal GCS was assumed to be 20%. They sought to detect an absolute beneficial treatment effect of 7.5 with 90% power and a two-sided type I error rate of 0.025. The total sample size was calculated to be 1200. Accounting for a 5% non-adherence rate, the target sample size was set to 1330. The incidence of altered GCS in the actual study was <5% in all groups. There was no difference among the groups; and given the factorial design, there was no evidence of any interaction between the two parameters: administration rate and fluid tonicity.

Rehydration

How fast should the IV fluids run after the fluid bolus?

"It seems that maintenance x2 is too fast."

The conclusions of the PECARN FLUID study were that neither "fast administration" of fluids nor the fluid tonicity contributed to the development of cerebral edema. This Fast Administration regimen consists of a bolus of 10 mL/kg of NS x2 followed by correction of 10% dehydration with half of the deficit replaced over the first 12 hours and the remaining half replaced over the subsequent 24 hours. The volume of the fluid bolus was subtracted from the deficit fluid volume.

But some people are still concerned that 2x maintenance is just too fast.

Let's do the math.

Correcting Dehydration

20 kg Patient

- Maintenance: 62.5 mL/hr
- Maintenance x2: 125 mL/hr
- PECARN first 12h: 129 mL/hr followed by 24h @ 96 mL/hr
  - Maintenance: 1500 mL/24hr
  - Deficit - bolus:1600 mL/12hr
  - 0-12hr: (750+800)/12
  - 12-36hr: (1500+800)/24

50 kg Patient

- Maintenance fluids: 87.5 mL/hr
- Maintenance x2: 175 mL/hr
- PECARN first 12h 254 mL/hr followed by 24h @ 171 mL/hr
  - Maintenance: 2100 mL/24hr
  - Deficit - bolus: 4000 mL/12hr
  - 0-12hr: (1050+2000)/12
  - 12-36hr: (2100+2000)/24

These are the calculations for two patients, a 20 kg patient and a 50 kg patient (in columns). Twice maintenance fluids are compared with the infusion rates to correct 10% dehydration using the Fast Administration regimen in the PECARN FLUID paper.

The first row has the calculated maintenance fluids.
The second row lists twice maintenance fluids.
For the 20 kg patient, twice maintenance is 125 mL/hr.

For the PECARN FLUID calculation, first determine the remaining deficit to be replaced. The 10% deficit is 2 kg or 2000 mL. From this a fluid bolus of 20 mL/kg (400 mL) is subtracted, leaving 1600 mL. The first half of this (800 mL) is to be replaced over 12 hours. Add that to the maintenance fluids over those 12 hours (750 mL). Thus 800 + 750 = 1600 mL. Divide that by 12 hours yields 129 mL/hr. For the subsequent 24 hours, add the 800 mL remaining deficit to the maintenance fluids over 24 hours (1500 mL) to get 2300 mL, and divide this by 24 hours for an hourly rate of 96 mL/hr. This rate should run between hours 12 and 36 of the IV fluid infusion.

For the 50 kg patient, twice maintenance is 175 mL/hr.

For the PECARN FLUID calculation, first determine the remaining deficit to be replaced. The

10% deficit is 5 kg or 5000 mL. From this a fluid bolus of 20 mL/kg (500 mL) is subtracted, leaving 4000 mL. The first half of this (2000 mL) is to be replaced over 12 hours. Add that to the maintenance fluids over those 12 hours (1050 mL). Thus 2000 + 1050 = 3050 mL. Divide that by 12 hours yields 254 mL/hr. For the subsequent 24 hours, add the 2000 mL remaining deficit to the maintenance fluids over 24 hours (2100 mL) to get 4100 mL, and divide this by 24 hours for an hourly rate of 171 mL/hr. This rate should run between hours 12 and 36 of the IV fluid infusion.

Compare the red boxes. Note that twice maintenance fluids is less than than the PECARN FLUID study replacement rate.

Bottom line:

Twice Maintenance Fluids*

is more conservative than
the PECARN study protocol

(for the first 12 hours for all patients
and for 36 hours for bigger patients)

Fluid calculations should be based on an approximation of ideal body weight for height.

The bottom line is that twice maintenance fluids is more conservative than the fastest PECARN FLUID rate in the first 12 hours is higher than for both patients—the rate that has been shown to safely avoid cerebral edema.

PECARN Rehydration Formulae

A. Fluid bolus (10-20 mL/kg)
B. 10% deficit (Wt * 100 mL/kg)
C. Remaining Deficit (**B** – **A**)
D. Half of Remaining Deficit (**C** ÷ 2)
E. Maintenance fluids (Holliday-Segar Formula for 24 hours)
F. Maintenance_{12} (**E** ÷ 2)
G. Maintenance_{12} + Half of Remaining Deficit (**F** + **D**)/12 hrs
H. Maintenance_{24} + Half of Remaining Deficit (**E** + **D**)/24 hrs

Administer **G** for the first 12 hrs. Administer **H** for the subsequent 24 hrs

This is the step-by-step calculation for the PECARN FLUID Fast Administration regimen.

Needless to say, it's easier to use twice maintenance fluids as the rehydration rate.

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WILEY ISPAD

ISPAD CLINICAL PRACTICE CONSENSUS GUIDELINES

ISPAD Clinical Practice Consensus Guidelines 2018: Diabetic ketoacidosis and the hyperglycemic hyperosmolar state

Joseph I. Wolfsdorf[1] | Nicole Glaser[2] | Michael Agus[1,3] | Maria Fritsch[4] | Ragnar Hanas[5] | Arleta Rewers[6] | Mark A. Sperling[7] | Ethel Codner[8]

"Calculate the … rate of fluid administration, including the provision of maintenance fluid requirements, aiming to replace the estimated fluid deficit over 24 to 48 hours."

"The risk of cerebral injury does not appear to be associated with differences in fluid protocols within these ranges. Therefore, clinicians should not unnecessarily restrict fluid administration if clinical signs suggest the need for circulatory volume expansion."

The 2018 International Society for Pediatric and Adolescent Diabetes guidelines for diabetic ketoacidosis cites the PECARN FLUID study, stating that "the risk of cerebral injury does not appear to be associated with differences in fluid protocols within these ranges. Therefore, clinicians should not unnecessarily restrict fluid administration if clinical signs suggest the need for circulatory volume expansion."

It provides additional guidance for fluid administration that allows some latitude. It recommends that the clinician "calculate the … rate of fluid administration, including the provision of maintenance fluid requirements, aiming to replace the estimated fluid deficit over 24 to 48 hours." It also provides a table with specific recommendations based on patient weight, apparently correcting 10% dehydration evenly over 48 hours without requiring any calculation, but "for body weights >32 kg, the volumes have been adjusted so as not to exceed twice the maintenance rate of fluid administration"* —in which case, using twice maintenance would just be easier.

It also recommends that fluid calculations be based on an approximation of ideal body weight for height to avoid excessive fluid administration in obese patients.

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Wolfsdorf JI, Glaser N, Agus M, Fritsch M, Hanas R, Rewers A, Sperling MA, Codner E. ISPAD Clinical Practice Consensus Guidelines 2018: Diabetic ketoacidosis and the hyperglycemic

hyperosmolar state. Pediatr Diabetes. 2018 Oct;19 Suppl 27:155-177. doi: 10.1111/pedi.12701. PMID: 29900641.

Correcting Dehydration

20 kg Patient

- Maintenance: 62.5 mL/hr
- Maintenance x2: 125 mL/hr
- PECARN first 12h: 129 mL/hr followed by 24h @ 96 mL/hr
- ISPAD over 48h: 93 mL/hr
  - Maintenance: 3000 mL/48hr
  - Deficit: 2000 mL/48hr

50 kg Patient

- Maintenance fluids: 87.5 mL/hr
- Maintenance x2: 175 mL/hr
- PECARN first 12h 254 mL/hr followed by 24h @ 171 mL/hr
- ISPAD over 48h: 175 mL/hr
  - Maintenance: 4200 mL/48hr
  - Deficit: 5000 mL/48hr
  - But not to exceed maintenance x2

This slide again shows the maintenance and PECARN FLUID calculations for our two patients. The ISPAD recommended fluid administration rates are added at the bottom for comparison.

As in our earlier slide, the first row has the calculated maintenance fluids based on the Holliday-Segar Formula.
The second row lists twice maintenance fluids.
The PECARN protocol calls for the administration of 129 mL/hr for the first 12 hours and 96 mL over the subsequent 24 hours.

The ISPAD number comes from the table that will be shown on the next slide, but the recommendation is for the 10% deficit to be replaced over 48 hours. Here, because we calculate this over 48 hours, we double the daily maintenance fluids and add that to the 10% deficit. In this case, the initial fluid bolus was subtracted from the deficit. The sum is then divided by 48 hours to give us 100 mL/hr for the 20 kg patient. This number does not match the number from the ISPAD table because its fluids are based on Darrow* rather than the Holliday-Segar Formula.

For the 50 kg patient, twice maintenance plus the deficit, all divided by 48 hours would give us an hourly rate of 181 mL/hr; however, this guideline limits the total fluid rate to 2x maintenance. I the case of this 50 kg patient, the limit would be 175 mL/hr.

This slide highlights the differences among the ways to determine the rehydration rate. Note which is the highest—the one that was shown to safely avoid cerebral edema.

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* Darrow DC. The physiologic basis for estimating requirements for parenteral fluids. Pediatr Clin N Am. 1959;6(1):29-41.

TABLE 2 Fluid maintenance and replacement volumes based on body weight and an assumption of 10% dehydration

Body weight (kg)	Maintenance (mL/24 h)	DKA: give maintenance +5% of body weight/24 h	
		mL/24 h	mL/h
4	325	530	22
5	405	650	27
6	485	790	33
7	570	920	38
8	640	1040	43
9	710	1160	48
10	780	1280	53
11	840	1390	58
12	890	1490	62
13	940	1590	66
14	990	1690	70
15	1030	1780	74
16	1070	1870	78
17	1120	1970	82
18	1150	2050	85
19	1190	2140	89
20	1230	2230	93
22	1300	2400	100
24	1360	2560	107
26	1430	2730	114
28	1490	2890	120
30	1560	3060	128
32	1620	3220	134
34	1680	3360	140
36	1730	3460	144
38	1790	3580	149
40	1850	3700	154
45	1980	3960	165
50	2100	4200	175
55	2210	4420	184
60	2320	4640	193
65	2410	4820	201
70	2500	5000	208
75	2590	5180	216
80	2690	5380	224

Fluid volumes are calculated based on data from Darrow DC. The physiologic basis for estimating requirements for parenteral fluids. *Pediatr Clin N Am*. 1959;6(1):29-41.

This is the ISPAD table for fluid administration. For our purposes, you can safely ignore it.

However, if you want to use it, look up the body weight in the first column. Daily maintenance fluids (based on Darrow* rather than Holliday-Segar) are presented in the second column. Half of the 10% fluid deficit (5%) is added to the maintenance fluids, and the sum listed in the third column. (It's half because the deficit will be replaced over 48 hours.) The number in the third column is divided by 24 hours for the infusion rate per hour in the last column. Any oral intake by the patient can be subtracted from the total in column 3 and the rate recalculated.

For a 20 kg patient, the fluid administration rate is listed as 93 mL.

For patients greater than 32 kg, the fluid administration is capped at twice maintenance fluids. For those patients, the total fluids in the third column are back calculated from the number equal to twice maintenance fluids.

To reiterate, the rates in the PECARN FLUIDS study are higher than any other rehydration rate, and the best evidence shows that this fluid regimen is safe. Anything less should be just as effective in avoiding cerebral edema.

Let's move on.

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* Darrow DC. The physiologic basis for estimating requirements for parenteral fluids. Pediatr Clin N Am. 1959;6(1):29-41.

Stage 3: Maintain blood glucose in the target range until the ketoacidosis resolves

"Why can't I just give dextrose at some concentration and adjust it as needed?"

After the initial bolus, typically given over 30-60 minutes, both the rehydration fluids and the insulin infusion are started. The insulin infusion is given at rate of 0.1 units/kg/hr and should not be changed.

On insulin, the patient's blood glucose will decrease over time. Once the blood glucose falls into the target range of 200-300 mg/dL, the next goal of therapy is to keep it in that range. This is done by starting a glucose (dextrose) infusion. More precisely, glucose is added to the resuscitation fluid.

How much dextrose should be added? An older protocol called for starting an arbitrary amount of glucose and adjusting that rate based on the blood glucose checks. The problem with this approach is that the dextrose concentration required varies with each patient, and it may take several adjustments to arrive at the needed dextrose concentration.

But there's a way to start with a good estimate of an appropriate dextrose concentration.

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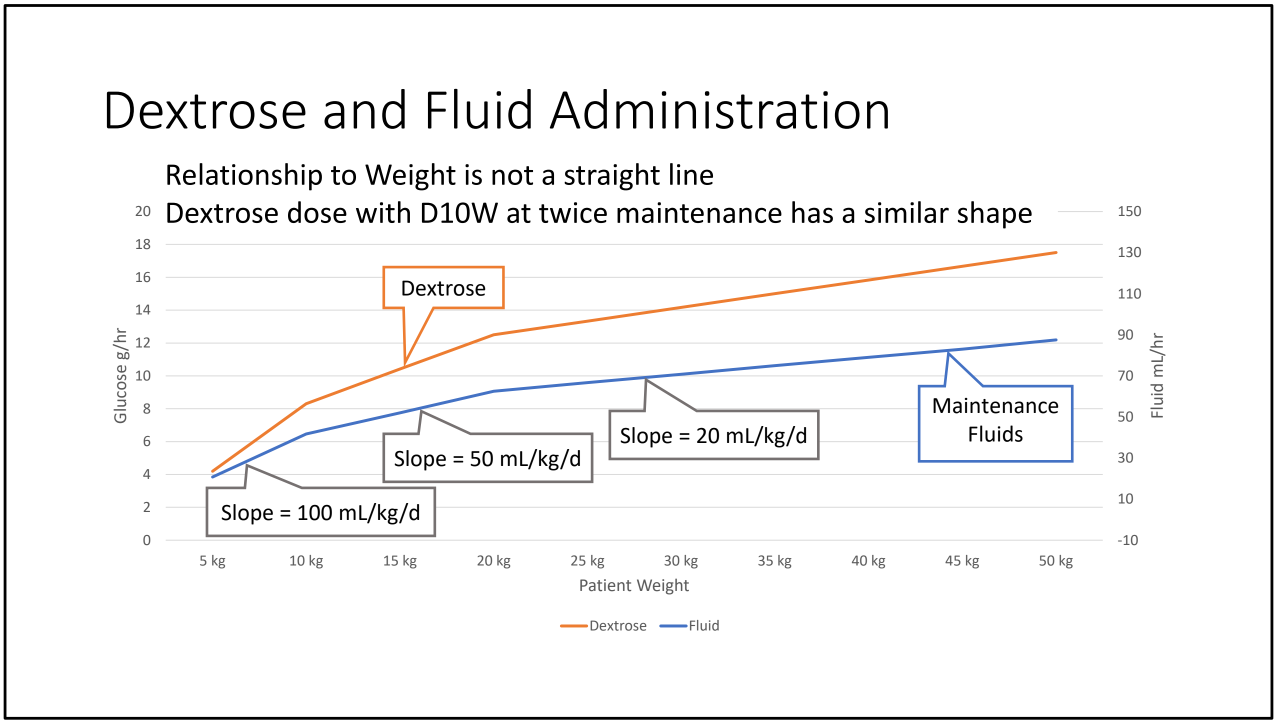
Felner EI, White PC.
Improving management of diabetic ketoacidosis in children.
Pediatrics. 2001 Sep;108(3):735-40.
doi: 10.1542/peds.108.3.735. PMID: 11533344.

"[T]o provide a 4:1 glucose (in grams) to insulin (in units) ratio …
10 g/dL of glucose (D10) was added to a separate solution that was otherwise identical to the initial fluid. The rate of infusion of each of the 2 solutions was varied as necessary to control the level and rate of decrease of serum glucose, with both the insulin and total fluid delivery remaining constant. Therefore, 3 separate IV solutions including the insulin solution (3-bag protocol) were needed

The method of "clamping blood glucose" we've adopted was described in 2001 by Felner and White from the University of Texas Southwestern Medical Center, Dallas, Texas. Central to this method is the fact that each unit of insulin will help metabolize a certain amount of glucose. The more insulin you give, the more dextrose you'll need to keep the blood glucose stable. If you dose the insulin by weight, you should also dose the dextrose by weight.

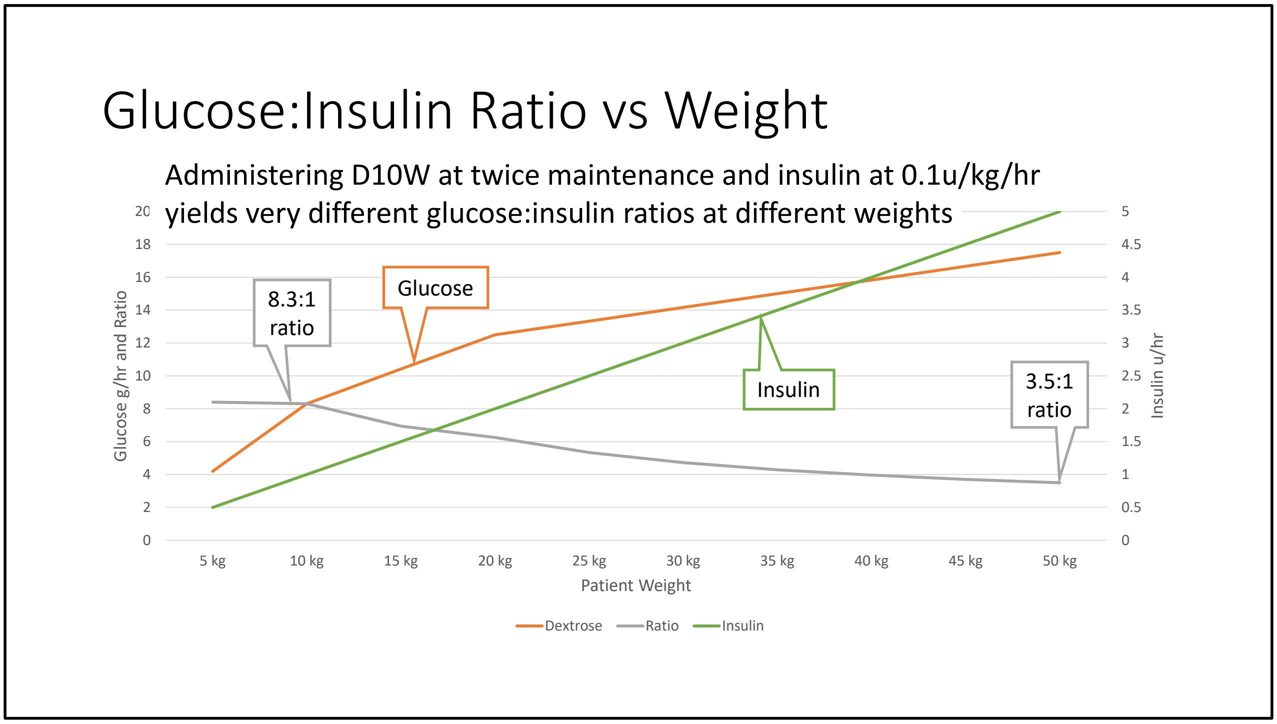
Let's do the math.



This is a graph of maintenance IV fluids calculated by the Holliday-Segar formula as a function of body weight. The blue line graphs the hourly fluid rate (right vertical scale) against body weight (horizontal axis). Note that the slope of the maintenance fluid line changes as patient weight increases.

The orange line graphs the rate of dextrose administration (left vertical scale) if the IV fluids contain 10% dextrose and is run at twice maintenance. Note that the shape of that line is similar to that of the maintenance fluid line—the slope changes as the weight increases.

(We use glucose and dextrose interchangeably because, as you know, dextrose is a glucose dimer. They are equivalent by weight.)

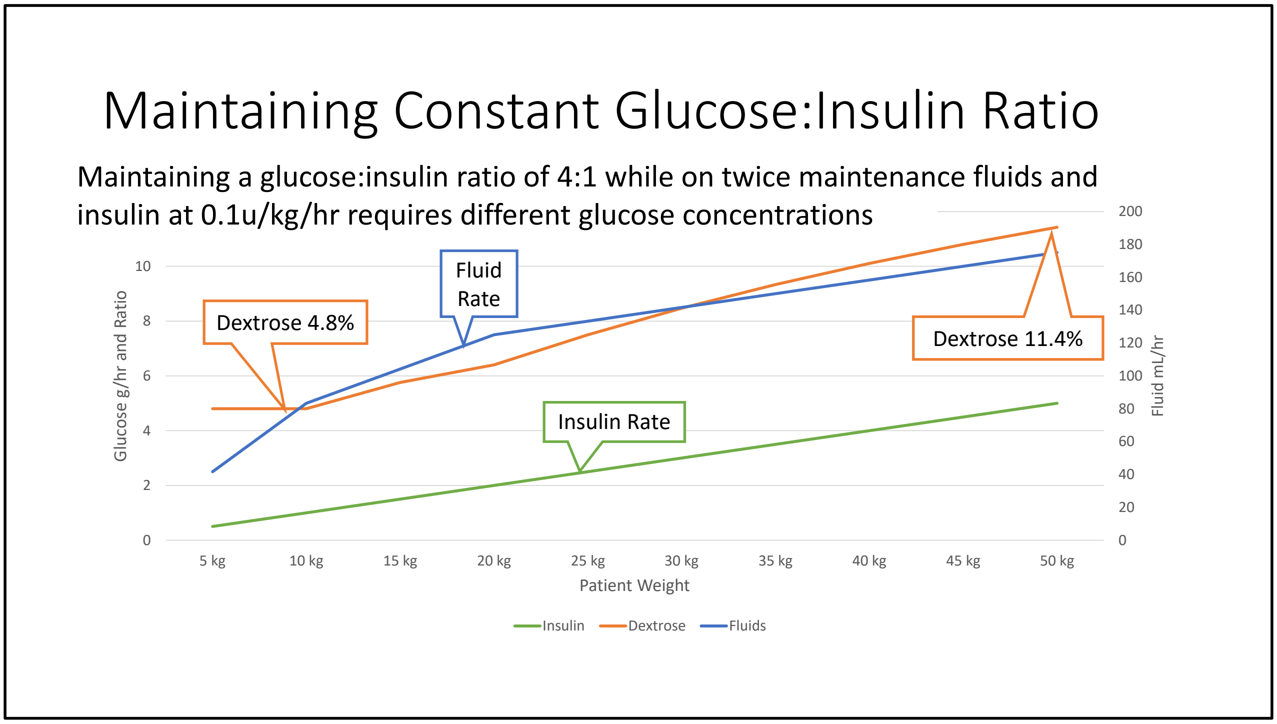


Here again, we have the same orange, glucose-infusion rate (left vertical scale) graphed against body weight (horizontal axis).

The green line is the absolute insulin-infusion rate (right vertical scale) dosed at 0.1 units/kg/hr, as specified by our protocol. Unlike the glucose line, the insulin dose a straight line because it's directly proportional to body weight.

If you divide the amount of glucose by the amount of insulin given, you'll get the glucose-to-insulin ratio, and that is graphed here as the gray line (also using the left vertical scale). Note that the glucose-to-insulin ratio decreases as the body weight increases.

For a patient 10 kg or less, 10% dextrose administered at twice maintenance will deliver 8.3 grams of glucose for every 1 unit of insulin. For a 50-kg patient, giving 10% dextrose at twice maintenance will deliver only 3.5 grams of glucose for every 1 unit of insulin. This explains why we often have a harder time maintaining a stable blood glucose in larger patients. Patients typically require 3 to 4 grams of glucose for every unit of insulin, and we can't deliver enough glucose using D10 running at twice maintenance for the amount of insulin they are getting.



Since most patients require 3 to 4 grams of glucose for every unit of insulin infused, it would make sense to start our dextrose infusion to give that ratio. If the fluid administration rate is fixed at twice maintenance, the only way to do that would be to adjust the concentration of dextrose. The concentration of dextrose needed to keep the glucose-to-insulin ratio constant at 4:1 is graphed in orange. It shows that the concentration of dextrose must increase as patient weight increases. A small patient needs less than 5% dextrose, but a larger patient needs more than 10% dextrose. In fact, patients bigger than 40 kg CANNOT get the required amount of glucose on 10% dextrose at 2x maintenance.

DKA Fluids Calculator

Calculate | Reset | Instructions | Algorithm | Print | Close

Patient Name: Test
Patient Weight: 20 kgs / lbs
Insulin Dose: 0.1 units/kg/h
Rehydration Rate: 126 mL/hr / X maintenance
Maintenance: 63 mL/h

Table 1. Use with D10%

Row	Glucose : Insulin Ratio (g : unit)	Insulin* Rate (mL/h)	Rate of fluid WITHOUT Dextrose (mL/h)	Rate of fluid WITH 10% Dextrose (mL/h)	Total Fluid Rate (mL/h)	Effective Dextrose Concentration (%)
0	0 : 1	2	124	0	126	0
1	1 : 1	2	104	20	126	1.6
2	2 : 1	2	84	40	126	3.2
3	3 : 1	2	64	60	126	4.8
4	4 : 1	2	44	80	126	6.3
5	5 : 1	2	24	100	126	7.9
6	6 : 1	2	4	120	126	9.5

Target **Range**: 200-300 mg/dL blood glucose
Target **Rate of Fall**: 50-100 mg/dL per hour

1. After the initial fluid bolus, start with **Row 0**. (Use first blood glucose AFTER the bolus as baseline.)
2. If the blood glucose **Rate of Fall** is > 100 mg/dL per hour, go to **Row 1**. If the blood glucose Rate of Fall continues >100 mg/dL per hour, go to the next line (below). If the blood glucose Rate of Fall is <50 mg/dL per hour, go to the previous row.
3. When the blood glucose falls below the 300 mg/dL upper **Range** limit, go to **Row 3**. If the blood glucose falls below the 200 mg/dL lower **Range** limit, go to the next row (below). If the blood glucose rises back up over 300 mg/dL, go to the previous line (or sometimes in between). If the blood glucose continues to fall despite being at the highest glucose:insulin ratio (Row 6), change to D12.5 and **use Table 2**.

Infonet > Departments > Pediatrics > Calculators > Diabetic Ketoacidosis Fluids Calculator

Ordering custom fluids with specific concentrations of dextrose is untenable for numerous reasons. The system described by Felner achieves the same result simply and with the flexibility to accommodate the needs of different patients. This system calls for setting up three fluids, each on a different IV pump, and all Y-ed together to one intravenous catheter. The fluids are 1) the insulin infusion, 2) one fluid without dextrose and 3) one fluid with dextrose. We call this the “3-bag method."

Calculating the proper rates for the three fluids can be challenging. An on-line calculator was created to eliminate calculation errors and to simplify care.
Access it on **Infonet** > **Departments** > **Pediatrics** > **Calculators** > **Diabetic Ketoacidosis Fluids Calculator**.
It should also be available through a direct link from the DKA order set.

Enter the patient weight in kg and the insulin dose in units/kg/hr. For obese patients, enter the ideal body weight. Enter the name if you want a printout, but it isn’t mandatory.
There are three options for entering the Rehydration Rate:

1. Leave the box blank if you want the default rate of 2-times-maintenance. The program will fill in the number;
2. Enter a specific rehydration rate in mL/hr; or
3. Enter a multiple of maintenance fluids such as 2.5 (must be < 4) and select the “x

maintenance” button.

Click on the “Calculate” button and the table will populate. Click on “Instructions” for help using the calculator. Click on “Algorithm” to get the most recent treatment flow chart. Hover your cursor over the blue text to get the “tool tips” on that item.

After the initial fluid bolus, set the pumps according to numbers in Row 0 (highlighted by the red box on this slide). In the example here, this 20-kg patient will be rehydrated with twice-maintenance fluids calculated to be 126 mL/hr. The insulin pump is set at 2 mL/hr, the fluid **without** dextrose at 124 mL/hr, and the fluid **with** dextrose at 0 mL/hr. The total fluid rate and the effective dextrose concentration of the combined fluids are displayed for informational purposes in the last two columns.

If the blood glucose falls too quickly, meaning more than 100 mg/dL per hour, set the pumps according to Row 1.

When the blood glucose falls into the target range, 200-300 mg/dL, go to Row 3. For this patient, the fluid without dextrose should run at 64 mL/hr and fluid with 10% dextrose at 60 mL/hr. This would give a total fluid rate of 126 mL/hr with an average dextrose concentration of 4.8%. (For your information, the target range in the ISPAD guidelines is 100-200 mg/dL. We think this puts patients at an unnecessary higher risk of hypoglycemia.)

Go to the next or previous row based on either the rate of change or the blood glucose measurement relative to the target range. It may sometimes be necessary to go “in between” the rows if, for example, a ratio of 4:1 is too much but 3:1 is not enough.

DKA Fluids Calculator

Calculate | Reset | Instructions | Algorithm | Print | Close

Patient Name: Test
Patient Weight: 50 (kgs) lbs
Insulin Dose: 0.1 units/kg/h
Rehydration Rate: 176 (mL/hr) X maintenance
Maintenance: 88 mL/h

Table 1. Use with D10%

Row	Glucose : Insulin Ratio (g : unit)	Insulin* Rate (mL/h)	Rate of fluid WITHOUT Dextrose (mL/h)	Rate of fluid WITH 10% Dextrose (mL/h)	Total Fluid Rate (mL/h)	Effective Dextrose Concentration (%)
0	0 : 1	5	171	0	176	0
1	1 : 1	5	121	50	176	2.8
2	2 : 1	5	71	100	176	5.7
3	3 : 1	5	21	150	176	8.5
4	3.4 : 1	5	0	171	176	9.7
5	3.4 : 1	5	0	171	176	9.7
6	3.4 : 1	5	0	171	176	9.7

Table 2. Use with D12.5%

Row	Glucose : Insulin Ratio (g : unit)	Insulin* Rate (mL/h)	Rate of fluid WITHOUT Dextrose (mL/h)	Rate of fluid WITH 12.5% Dextrose (mL/h)	Total Fluid Rate (mL/h)	Effective Dextrose Concentration (%)
0	0 : 1	5	171	0	176	0
1	1 : 1	5	131	40	176	2.8
2	2 : 1	5	91	80	176	5.7
3	3 : 1	5	51	120	176	8.5
4	4 : 1	5	11	160	176	11.4
5	4.3 : 1	5	0	171	176	12.1
6	4.3 : 1	5	0	171	176	12.1

For larger patients, it may be impossible to administer the concentration of dextrose required to achieve the required glucose:insulin ratio with 10% dextrose. In this case, the table will display in the left column the highest ratio that can be achieved.

In this example of a 50-kg patient being rehydrated at 2x maintenance, the highest ratio that can be achieved is 3.4:1 (highlighted by the first red box). If the patient requires more glucose, it may be necessary to change the glucose-containing fluid from 10% to 12.5% dextrose. Table 2 shows the calculated values based on glucose-containing IV fluid with 12.5% dextrose. If this 50-kg required more than a 3.4:1 ratio, the user would change the IV fluid to 12.5% dextrose with electrolytes (Second red box) and set the pumps based on the numbers in Row 4 (indicated by the red arrow): insulin at 5 mL/hr, the fluid without dextrose at 11 mL/hr, and the 12.5% dextrose fluid at 160 mL/hr. This would deliver total fluids of 176 mL/hr with an average dextrose concentration of 11.4%.

To administer more glucose, the alternative to increasing the dextrose CONCENTRATION is to increase the fluid administration RATE. Specifically, in this case, the user could choose to increase the rehydration rate from 2x to 2.5x maintenance or just enter a specific rehydration rate, e.g., 200 mL/hr.

As an absolutely last resort, the insulin dose can be reduced if the blood glucose cannot be maintained in a safe range. To do so, generate a new table using the desired insulin dose. Keep in mind that this may prolong the ketoacidosis.

Fluid and Electrolytes

TABLE 1 Losses of fluid and electrolytes in diabetic ketoacidosis and maintenance requirements in normal children

	Average (range) losses per kg	24-hour maintenance requirements	
Water	70 mL (30-100)	*≤10 kg	100 mL/kg/24 h
		11-20 kg	1000 mL + 50 mL/kg/24 h for each kg from 11 to 20
		>20 kg	1500 mL + 20 mL/kg/24 h for each kg >20
Sodium	6 mmol (5-13)	2-4 mmol†	Maintenance electrolyte requirements in children are per 100 mL of maintenance IV fluid.
Potassium	5 mmol (3-6)	2-3 mmol	
Chloride	4 mmol (3-9)	2-3 mmol	
Phosphate	0.5-2.5 mmol	1-2 mmol	

In addition to loss of fluid, patients in DKA lose significant amounts of electrolytes. The potassium and phosphate deficits, because they are primarily intracellular, are often not initially apparent but become more evident as the DKA is treated.

The most important takeaway from this slide is that any fluid administered to a patient with DKA MUST contain electrolytes—at least 0.45% NS, though our algorithm calls for isotonic fluids—LR or NS.

Pediatric DKA Fluids Order Panel: IVF

- ◯ LR and D10NS, each with 40 mEq/L potassium acetate
- ◯ LR and D10NS, each with 40 meEq/L potassium chloride
- ◯ LR and D12.5NS, each with 40 mEq/L potassium acetate
- ◯ LR and D12.5NS, each with 40 mEq/L potassium chloride
- ◯ LR and D10NS
- ◯ NS and D10NS
- ◯ NS and D10NS, each with 40 mEq /L potassium acetate
- ◯ NS and D10NS, each with 40 mEq/L potassium chloride
- ◯ NS and D10NS, each with 20 mEq/L potassium chloride and 15mmol/L KPhos
- ◯ NS and D12.5NS, each with 40 mEq/L potassium acetate
- ◯ NS and D12.5NS, each with 40 mEq/L potassium chloride
- ◯ NS and D12.5NS, each with 20 mEq/L potassium chloride and 15mmol/L KPhos
- ◯ Pediatric Fluid Builders (Please ensure both fluids contain sodium chloride in the base diluent. Do NOT order dextrose alone.)

This is the carefully curated fluid choice list in the Pediatric DKA Fluids order panel (in the PICU DKA Admission and the Pediatric ED DKA order sets). The choices are limited to minimize the risk of error. Please refrain from using the Pediatric Fluid Builder to create a custom fluid. If this is unavoidable, use extreme care.

Each entry contains a fluid pair, one with dextrose and the other without. The three parameters to consider when ordering are:

1. the concentration of dextrose, either 10% or 12.5%
2. the kind of added potassium salt, if any, and
3. the base fluids, either LR or NS

Always start with a fluid pair that contains 10% dextrose because Pharmacy can make it faster. The calculator will help you determine when to order a 12.5% dextrose solution.

Adding potassium 40 mmol/L to the IV fluid is appropriate once the patient has been shown to be neither hyperkalemic nor anuric. The potassium salt should typically be potassium acetate (ordered as 40 mEq/L of potassium acetate).

Potassium phosphate can comprise up to half of the potassium added to the IV fluids. (Note that there are 4.4 mEq of potassium for every 3 mmol of phosphate, because phosphate has a valence of 3 and the solution contains a mixture of KH_2PO_4 and K_2HPO_4. Phosphate is ordered here as 15 mmol/L of potassium phosphate.)

LR is generally preferred because it's a buffered solution. It helps mitigate the hyperchloremic metabolic acidosis that will occur if excess chloride is administered. This is the same reason that potassium chloride is the least favored potassium salt to give these patients. Acetate has the added advantage of essentially creating bicarbonate when it's metabolized (by consuming two H+ ions in the Krebs cycle). Please note that "bicarbonate administration is not recommended except for treatment of life-threatening hyperkalemia or unusually severe acidosis (venous pH <6.9) with evidence of compromised cardiac contractility." (ISPAD Guidelines)

There are other considerations that limit the fluid choices available. D10LR is not available because the dextrose added to a bag of D5LR would dilute the electrolytes to an unacceptable degree. (On the other hand, D10NS is made by adding hypertonic saline to a bag of D10W.) Phosphate should not be added to LR because LR contains calcium. While the PECARN FLUIDS study showed that 0.45% saline can be used, we opted to simplify this order panel and include only LR or NS.

Takeaways

- Bolus 10-20 mL/kg of LR or NS over 30-60 minutes.
  Initiate rehydration at 2x maintenance fluids with LR or NS.
- Once the blood glucose falls below 300 mg/dL, replace a portion of the IV fluid with one that contains dextrose to achieve the required glucose:insulin ratio.
- Electrolytes in the IV fluids will correct or prevent derangements. Use the fluid pairs in the order sets. Refrain from creating custom fluids.
- Correcting the ketoacidosis typically takes the longest of the goals of therapy. When corrected, transition to SC insulin and PO intake.
- Monitor for evidence of cerebral edema.

These are the key points of this presentation.

- We recommend an initial bolus of up to 20 mL/kg and rehydration rate of twice maintenance. Within certain parameters, the rate of rehydration is not associated with the incidence of cerebral edema. While there are many ways to calculate the rate of rehydration, there is general agreement that 2x maintenance is safe.
- Insulin is dosed as a direct proportion of patient weight (0.1 unit/kg/h) BUT fluid and dextrose are NOT related to weight in quite the same way. Delivering a specific glucose:insulin ratio accounts for the complex relationships among the important parameters.
- Electrolytes must be added to all fluids. Buffers help to minimize the hyperchloremic metabolic acidosis that often replaces the ketoacidosis. Use the fluids in the order sets and refrain from creating custom fluids.
- When all therapeutic goals have been achieved, including the ketoacidosis, transition to subcutaneous insulin and oral intake with the guidance of Endocrinology/Diabetology. To avoid delays, it’s best to have this transition plan in place well before the patient meets criteria.
- Throughout treatment, monitor for evidence of cerebral edema.

Cerebral Edema

"What am I looking for?"

Avoiding cerebral edema is one of the "goals" of therapy for DKA.
Early recognition and treatment are key to avoiding death or disability.

Table 1—*Bedside evaluation of neurological state of children with DKA*

Diagnostic criteria
Abnormal motor or verbal response to pain
Decorticate or decerebrate posture
Cranial nerve palsy (especially III, IV, and VI)
Abnormal neurogenic respiratory pattern (e.g., grunting, tachypnea, Cheyne-Stokes respiration, apneusis)
Major criteria
Altered mentation/fluctuating level of consciousness
Sustained heart rate deceleration (decline more than 20 bpm) not attributable to improved intravascular volume or sleep state
Age-inappropriate incontinence
Minor criteria
Vomiting
Headache
Lethargy or being not easily aroused from sleep
Diastolic blood pressure >90 mmHg
Age <5 years

Signs that occur before treatment should not be considered in the diagnosis of cerebral edema.

Early recognition of cerebral edema is key to survival. This method of clinical diagnosis is cited in the ISPAD Guidelines.

Treatment for increased intracranial pressure is warranted if a patient has
- Any one of the diagnostic criteria
- Any two major criteria
- One major and two minor criteria

This has a sensitivity of 92% and a false-positive rate of 4%.

Diagnostic criteria – need no other evidence to warrant treatment of increased ICP
- Abnormal motor or verbal response to pain
- Decorticate or decerebrate posture
- Cranial nerve palsy (especially III, IV, and VI)
- Abnormal neurogenic respiratory pattern (e.g., grunting, tachypnea, Cheyne-Stokes
- respiration, apneusis)

Major criteria – seen frequently in cases of cerebral edema
- Altered mentation/fluctuating level of consciousness
- Sustained heart rate deceleration (decline more than 20 bpm) not attributable to improved
- intravascular volume or sleep state

- Age-inappropriate incontinence

Minor criteria – less specific indicators of neurological disease

- Vomiting
- Headache
- Lethargy or being not easily aroused from sleep
- Diastolic blood pressure >90 mmHg
- Age <5 years

Following the Glasgow Coma Score is an additional way to monitor patients. A score less than 14 is associated with cerebral edema, though it doesn't necessarily mean the patient warrants treatment.

Cerebral edema usually develops within the first 12 hours after initiation of treatment but can occur as late as 24 – 48 hours.

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Muir AB, Quisling RG, Yang MC, Rosenbloom AL. Cerebral edema in childhood diabetic ketoacidosis: natural history, radiographic findings, and early identification. Diabetes Care. 2004 Jul;27(7):1541-6. doi: 10.2337/diacare.27.7.1541. PMID: 15220225.

Associations and Risk Factors

- Younger age
- New onset diabetes
- Longer duration of symptoms
- Greater hypocapnia at presentation after adjusting for degree of acidosis
- Increased serum urea nitrogen at presentation
- More severe acidosis at presentation
- Bicarbonate treatment for correction of acidosis
- A marked early decrease in serum effective osmolality
- An attenuated rise in serum sodium concentration or an early fall in glucose-corrected sodium during therapy
- Greater volumes of fluid given in the first 4 hours
- Administration of insulin in the first hour of fluid treatment

Why is age < 5 years a minor criterion? It's because cerebral edema is more common in young patients and those with new onset diabetes.

Other associations and risk factors for cerebral edema are listed here. Most of these risk factors relate to severe ketoacidosis and dehydration.

Treatment of Cerebral Edema

- Notify the PICU fellow and attending
- Elevate head of the bed to 30° and head midline
- Adjust IV fluids to avoid excessive fluid administration but more importantly, avoid hypotension
- Consider 3% hypertonic saline 2.5 – 5 mL/kg
- Consider intubation with ICP precautions to control oxygenation and ventilation
- Consider cranial imaging
- Consider Neurosurgical consultation

While the treatment of cerebral edema is outside the scope of this protocol, these are the initial steps.

We prefer hypertonic saline to mannitol because an osmotic diuresis is more likely with mannitol, and this may compromise the hemodynamics.

Hyperglycemic Hyperosmolar State

Recognition & Treatment

A different animal that is dangerous, especially if not treated appropriately

If your patient clearly has DKA, you can skip this section.

The hyperglycemic hyperosmolar state may be confused with DKA. While it isn't often seen in pediatrics, its incidence may be increasing. This critical condition can result in significant injury or death and merits discussion here if only to raise awareness.

Hyperglycemic Hyperosmolar State
Diagnostic Criteria

- Plasma glucose concentration >33.3 mmol/L (600 mg/dL)
- Effective serum osmolality >320 mOsm/kg
- Venous pH >7.25; arterial pH >7.30
- Serum bicarbonate >15 mmol/L
- Small ketonuria, absent to mild ketonemia
- Altered consciousness (e.g., obtundation, combativeness) or seizures (in approximately 50%)

The diagnostic criteria for HHS is similar to DKA but are different in certain key aspects.

The diagnosis of HHS is based on the extreme hyperglycemia and hyperosmolarity. The absence of a ketoacidosis and alteration of consciousness help to make the diagnosis. Note that the altered consciousness is NOT secondary to cerebral edema, and it should not dissuade anyone from giving the fluid these patients need—which is substantial.

The onset of HHS may go unrecognized as the polyuria and polydipsia are more gradual, resulting in profound dehydration and electrolyte losses. Fluid losses can be twice those of DKA. Despite severe volume depletion and electrolyte losses, hypertonicity preserves intravascular volume and signs of dehydration may be less evident, partly because many of these patients are obese.

The treatment plan must account for the decreased intravascular volume. Even as volume is administered, a decreasing serum osmolarity promotes movement of water out of the intravascular space across the osmotic gradient into the tissues. An osmotic diuresis may also result in considerable urinary fluid losses. Because intravascular volume can decrease rapidly during treatment, aggressive replacement of intravascular volume is required to avoid vascular collapse—in sharp contradistinction to the treatment of children with DKA.

Goals & Treatment of HHS

- Restore circulating volume
  - Bolus 20 mL/kg of NS until perfusion is restored
- Rehydration
  - Replace 12 - 15% fluid deficit over 24 - 48 hours
  - Use 0.45% - 0.9% saline or LR
  - Consider replacing urinary losses with 0.45% - 0.9% saline
- Correct hyperglycemia
  - Use fluids initially to decrease blood glucose by 50 – 100 mg/dL per hour
  - When blood glucose falls < 50 mg/dL per hour, add insulin 0.025 – 0.05 units/kg/hr

The goals and treatments of HHS are similar to but not the same as those in DKA.

Bolus rapidly with 20 mL/kg of NS and repeat as necessary to restore peripheral perfusion.

Calculate replacement for a fluid deficit of 12% to 15% and replace over 24 to 48 hours using 0.45% to 0.9% saline. Use 0.9% saline if there is any hemodynamic instability to keep more fluid in the intravascular space. Consider replacing hourly urine output if it's excessive using 0.45% to 0.9% saline. (We suggest using 2-3 mL/kg/hr as the criterion for "excessive.")

The rate of decline in serum glucose concentration is typically higher during the first several hours of treatment when an expanded vascular volume leads to improved renal perfusion. If serum glucose continues to fall rapidly (more than 100 mg/dL/h) after the first few hours, consider adding 5% dextrose as D5-1/2NS as a portion (not all) of the total IV fluids.

With adequate rehydration and without insulin, serum glucose concentrations should decrease by 75-100 mg/dL per hour. If the serum glucose falls < 50 mg/dL per hour, initiate an insulin infusion of 0.025 – 0.05 units/kg/h. Failure of the expected decrease of plasma glucose concentration should prompt reassessment and evaluation of renal function.

There should be a gradual decline in corrected serum sodium concentration and serum osmolality. Serum sodium concentrations should be measured frequently and the sodium concentration in fluids adjusted to promote a gradual decline in corrected serum sodium concentration (~0.5 mmol/L/h). Mortality has been associated with failure of the corrected serum sodium concentration to decline with treatment, which may be an indication for hemodialysis. (Serum sodium concentration is "corrected" for hyperglycemia by adding to the measured sodium 1.6 mEq/L for every 100 mg/dL of blood glucose.)

Complications of HHS

- Venous thrombosis with central venous catheters
- Rhabdomyolysis leading to
  - Acute renal failure
  - Severe hyperkalemia
  - Hypocalcemia
  - Compartment syndromes
- Malignant hyperthermia
- Altered mental status (but not from cerebral edema)
- Mixed HHS and DKA

ISPAD Clinical Practice Consensus Guidelines 2018: Diabetic ketoacidosis and the hyperglycemic hyperosmolar state

HHS patients are known to be prone to several serious, life-threatening complications.

Venous thrombosis associated with central venous catheters occurs commonly, but there are no data yet to support the use of prophylactic anticoagulation. Clinicians should just be aware that it happens so alternatives can be considered.

Rhabdomyolysis may occur. It may result in acute kidney failure, severe hyperkalemia, hypocalcemia, and muscle swelling with compartment syndrome. Monitor creatine kinase concentrations (every 2 to 3 hours), and for myalgia, weakness, and dark urine. Hypophosphatemia may be associated with rhabdomyolysis. Adding phosphate to the IV fluids may be helpful.

Rarely, clinical manifestations consistent with malignant hyperthermia have been observed in patients with HHS. Fever associated with a rise in creatine kinase may be treated with dantrolene, but its effectiveness is unclear. (Follow the NYP policy for malignant hyperthermia.)

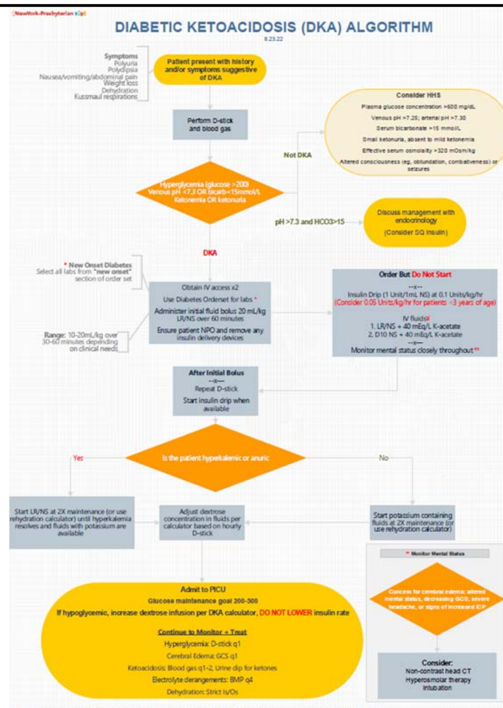
Altered mental status is common in adults whose serum osmolality exceeds 330 mOsm/kg; however, cerebral edema is rare.

Rarely, patients present with a mixture of HHS and DKA. Treatment must take into account sometimes competing priorities and the potential complications of each.

Refer to the ISPAD Clinical Practice Consensus Guidelines 2018: Diabetic ketoacidosis and the hyperglycemic hyperosmolar state for more information on the mixed HHS and DKA presentation and other aspects of care in both DKA and HHS.

The NYP Pediatric DKA Algorithm

August 23, 2022



Infonet >
Departments >
Pediatrics >
Resources >
Calculators >
Diabetic Ketoacidosis Fluids Calculator

The NYP Pediatric DKA Algorithm is available on the Infonet.
It can also be accessed via the "Algorithm" button on the DKA Fluids Calculator.

The ISPAD Clinical Practice Consensus Guidelines 2018 is available in PDF format on a link at the bottom of the calculator page.

Introduction to The NYP Pediatric DKA Algorithm

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