

MANAGEMENT PERSPECTIVE

A dose-defining insulin algorithm for attainment and maintenance of glycemic targets during therapy of hyperglycemic crises

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Practice Points

- Successful treatment of hyperglycemic crises requires attention to all components of care, including patient monitoring; fluid, potassium and other electrolyte management; timely provision of intravenous dextrose; evaluation for precipitating cause; and treatment of comorbidities.
- Rehydration contributes to the rate of fall of blood glucose.
- Lowering of blood glucose in diabetic ketoacidosis and correction of acidosis and ketosis do not require high dose insulin therapy.
- Regardless of severity of the initial presentation, nonresponsiveness to low dose intravenous insulin infusion is rare.
- During low-dose insulin infusion for diabetic ketoacidosis, lack of insulin dose effect has been reported, such that a steady rate of decline of blood glucose is generally observed during the early hours of treatment.
- Lower compared with higher insulin doses in the first 2 h of treatment, or omission of insulin for the first 1 h of treatment, may be associated with a lesser risk of cerebral edema in children.
- Hypokalemia and hypoglycemia may have been more common under higher insulin dose regimens than under current low-dose insulin regimens.
- Hypokalemia and hypoglycemia continue to occur under current low-dose regimens.
- Failure to reduce insulin infusion rate as the blood glucose approaches its target may be associated with hypoglycemia.
- The effects of a revision of intravenous insulin infusion rate will not be expressed until a lag time has elapsed.

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SUMMARY According to current standards of care, insulin therapy of the hyperglycemic crises diabetic ketoacidosis and hyperglycemic hyperosmolar state may be ordered using a combination of weight-based and qualitative rules for the initiation and adjustment of the rate of intravenous insulin infusion. The early hours of treatment are often managed with a fixed-dose insulin regimen, such as 0.1–0.14 units/kg/h of insulin. Higher-dose insulin protocols, once used routinely, were replaced safely and effectively in the 1970s by low-dose regimens, possibly with a reduction in late hypoglycemia and hypokalemia. In a pediatric study comparing 43 cases of cerebral edema to 169 matched control subjects, the dose of insulin in the first 2 h was significantly associated with the risk of cerebral edema ($p < 0.02$ for trend over categories of insulin dose). Even with the use of low-dose insulin therapy, hypokalemia and hypoglycemia continue to occur. In one series, 13% (18 out of 144) of diabetic ketoacidosis patients had blood glucose <60 mg/dl at some time during insulin infusion. In hyperinsulinemic-euglycemic clamp studies of nondiabetic subjects, after interruption of infusion of intravenous regular insulin infusions, the time required for deactivation from maximum to half maximum effect upon the glucose disposal rate was 63 ± 5 min. Insulin action, although declining in effect, may persist for at least 90 min after interruption of insulin infusion. We hypothesize that late glycemic excursions and possibly hypokalemia after the first 4 h of treatment might be reduced by replacing a fixed-dose rule with a standardized, but dynamic, insulin titration protocol in the early hours of treatment, to be used in conjunction with attention to other aspects of care.

Hyperglycemic crises may be classified as diabetic ketoacidosis (DKA) or hyperglycemic hyperosmolar state (HHS) [1–45]. In 2005, DKA was responsible for approximately 120,000 hospital discharges in the USA, amounting to 7.4 discharges per 1000 diabetes patient population, with the highest rate of discharges occurring in the group of diabetes patients under 45 years of age. In the years 1987 and 2005, the annual rates of discharges for DKA per 1000 diabetes patient population under 45 years of age were 55.4 and 31.6, respectively [101]. The incidence of DKA exceeds that of HHS, but reports of the relative frequency of the two conditions have differed widely, perhaps reflecting differences in patient characteristics and demographics [4,32,40].

In a large academic center it was shown that hospital charges, length of stay and readmission rate were lower when care was delivered by an endocrinologist, but in reality DKA and HHS more often were treated under the supervision of general providers [35]. Treatment delays upon admission and omissions of subcutaneous insulin prior to interruption of intravenous insulin infusion have pointed to the opportunity for improvement through more active involvement of nursing staff [41]. Development of standardized protocols for low-dose intravenous insulin infusion and adherence to use of protocols have reduced the rate of metabolic complications [23,33,42]. Reviews published recently have provided comprehensive advice on the general management of hyperglycemic crisis in adult and pediatric age groups [38,39,42,45]. The target ranges

for blood glucose (BG) during treatment, after initial correction of admission hyperglycemia, are stated to be 150–199 mg/dl for DKA and 200–299 mg/dl for HHS [45].

Treatment of hyperglycemic crisis does not invariably result in timely attainment or uneventful maintenance of glycemic targets. After initial attainment of target range control, recovery may be complicated by BG falling below target levels, overt hypoglycemia, hypokalemia, recurrent hyperglycemia or recurrent ketoacidosis. Determinants of deviation from target range control may include the state of hydration, utilization of intravenous dextrose, patient comorbidities and concomitant medications, timeliness of implementation of orders, and other factors, as well as intravenous insulin infusion rate. The intent of establishing strategies and targets during recovery from hyperglycemic emergency is to promote safe recovery, to minimize the risk of disequilibrium states and to reduce the likelihood of complications, including disability or fatality. One reason given for the avoidance of overly aggressive insulin and fluid therapy is the possibility that such avoidance would reduce the risk for the complication of symptomatic or fatal cerebral edema. The recommendation against overly aggressive insulin and fluid therapy is widely accepted despite uncertainty on the pathogenesis of cerebral edema and the strong likelihood of a multifactorial pathogenesis of this complication [46–56]. Algorithms for intravenous insulin infusion might incorporate an understanding of endogenous insulin secretion, insulin disappearance, pharmacodynamic

delay of action of intravenous insulin, insulin sensitivity, intravenous carbohydrate exposure, assimilation of enteral carbohydrate and other considerations that define the insulin–glucose relationship. Among critically ill patients, algorithms expressing physiologic behavior or pharmacodynamic effects have achieved differences of glycemic control compared with algorithms that were not similarly engineered [57–60]. These algorithms were not specifically designed for, or evaluated during, treatment of DKA or HHS. The use of low-dose insulin therapy for hyperglycemic crisis has been based on our understanding of the physiology of endogenous insulin action and the pharmacodynamics of insulin administration in normal physiology and in hyperglycemic crises [61–71].

Insulin therapy for hyperglycemia emergency

The 2009 American Diabetes Association (ADA) consensus statement on hyperglycemic crises provides a pathway for volume resuscitation, potassium therapy and initiation of dextrose, and thoroughly references other components of care [45]. A guideline is given concerning insulin infusion rate, suggesting an initial rate of 0.1–0.14 units/kg/h. It is stated that “Low-dose insulin infusion protocols decrease plasma glucose concentration at a rate of 50–75 mg/dl/h. If plasma glucose does not decrease by 50–75 mg from the initial value in the first hour, the insulin infusion should be increased every hour until a steady glucose decline is achieved” [45]. The 2009 ADA consensus statement here refers to its **Table 1** for elaboration [45]. The consensus statement also specifies: “When the plasma glucose reaches 200 mg/dl in DKA or 300 mg/dl in HHS, it may be possible to decrease the insulin infusion rate to 0.02–0.05 units/kg/h, at which time dextrose may be added to the intravenous fluids.” Additionally, the text reads: “Thereafter, the rate of insulin administration or the concentration of dextrose may need to be adjusted to maintain glucose values between 150 and 200 mg/dl in DKA or 250 and 300 mg/dl in HHS until they are resolved” [45].

Current insulin dosing rules for hyperglycemia emergency

In this article, we discuss the background for current guidelines regarding insulin dosing, describe ambiguities within the ADA statement as it pertains to insulin therapy, and conclude

with a proposal to address those ambiguities with dose-defining rules (**Table 1**).

■ Background of low-dose insulin therapy

High-dose insulin protocols for DKA were once the standard of care, potentially calling for the use of hundreds of units of insulin in the first few hours of treatment, given subcutaneously and as intravenous bolus therapy [1,2]. Current treatment standards have been based on a large body of experience and clinical research, representing a movement away from high-dose insulin therapy, toward lower dose regimens that gained momentum in the 1970s. Historically, there was attention to identifying the optimal route for delivery of insulin, and to deciding whether a loading dose of insulin was necessary to initiate treatment under a low-dose regimen. It was also necessary to determine whether one route of administration by any low-dose regimen was superior to other routes, and to evaluate the effect of insulin dose and timing in the treatment of both DKA and HHS.

■ Mortality

Reduction of mortality for treatment of DKA and HHS during use of higher dose protocols had already occurred during a timeframe when all aspects of care had improved, including fluid and electrolyte management, prevention of hypokalemia, and treatment of precipitating causes and comorbidities, historically prior to the evaluation of low-dose insulin regimens. At the University of Frankfurt (Germany), among 406 patients with DKA and 66 with HHS, when 58 fatalities consequent to comorbidities were discounted, there were 59 additional fatalities that were attributed to the metabolic crisis between 1945 and 1969 (50 with DKA and nine with HHS). The treatment regimens were not reported in detail. However, between 1965 and 1969, the fatality rate due to diabetic crisis, formerly 13–17%, at this center had fallen to 4% [4]. When high-dose regimens were replaced with lower-dose regimens in the early 1970s, investigators had to justify departure from what had generally been thought to be a life-saving necessity for higher doses, by showing that a lower insulin dose protocol was as effective or even superior to the older regimens. It was held that the older high-dose regimens had not been necessary but had simply been tolerated, and that the improvement of mortality over time in the past had been attributable to improved attention to all components of care, not necessarily to the high doses of insulin.

Table 1. Equations of the algorithm.	
Variable, parameter or condition	Definition or consequence
$IR_{@BG70}$	= Insulin infusion rate at BG = 70 mg/dl, 0.1 units/h
MR	= Column-specific maintenance rate, assigned at $BG_{true\ target'}$ in units/h
G-per-DIEM	= Glucose per daily dose of insulin, exogenously mediated = 1800 mg/dl
$ROD_{@BG\ critical\ high}$	= Ideal rate of descent of BG, at critical high BG = 75 in $mg \cdot dl^{-1} \cdot h^{-1}$
$CR_{@BG\ critical\ high}$	= Correction rate at $BG_{critical\ high}$ in units/h = $24\ h \cdot MR \cdot ROD_{@BG\ critical\ high} / G\text{-per-DIEM}$
$ROD_{ideal, next, max}$	= Maximum assignable ideal ROD of BG, for the next iteration = 150 in $mg \cdot dl^{-1} \cdot h^{-1}$
CR_{max}	= Maximum correction rate in units/h = $24\ h \cdot MR \cdot ROD_{ideal, next, max} / G\text{-per-DIEM}$
Diabetic ketoacidosis	
$BG_{critical\ high}$	= 428 mg/dl
$BG_{upper\ target}$	= 200 mg/dl
$BG_{true\ target}$	= 184 mg/dl
$BG_{lower\ target}$	= 150 mg/dl
Hyperglycemic hyperosmolar state	
$BG_{critical\ high}$	= 702 mg/dl
$BG_{upper\ target}$	= 300 mg/dl
$BG_{true\ target}$	= 271 mg/dl
$BG_{lower\ target}$	= 200 mg/dl
FEBG	= Fractional elevation of blood glucose above $BG_{upper\ target'}$ compared to elevation of $BG_{critical\ high}$ above $BG_{upper\ target}$
If $BG \geq BG_{upper\ target'}$	then $FEBG = (BG - BG_{upper\ target'}) / (BG_{critical\ high} - BG_{upper\ target})$
If $BG < BG_{upper\ target'}$	then $FEBG = 0$
FCABG	= Fractional completeness of ascent of blood glucose from 70 mg/dl to $BG_{true\ target}$
If $BG > BG_{true\ target'}$	then $FCABG = 1$
If $BG \leq BG_{true\ target'}$	then $FCABG = (BG - 70) / (BG_{true\ target} - 70\ mg/dl)$
CR	= Correction rate of insulin infusion, in units/h = $CR_{max} \cdot (1 - [(CR_{max} - CR_{@BG\ critical\ high}) / CR_{max}]^{FEBG})$
IR_{next}	= Insulin infusion rate for the next iteration of the algorithm, in units/h = $IR_{@BG70} \cdot [MR / IR_{@BG70}]^{(FCABG)} + CR$
BG: Blood glucose; CR: Correction rate; FCABG: Fractional completeness of ascent of blood glucose; FEBG: Fractional elevation of blood glucose; G-per-DIEM: Glucose per daily dose of insulin, exogenously mediated; IR: Insulin infusion rate; MR: Maintenance rate; ROD: Rate of descent.	

The historical movement away from high-dose regimens together with comparative mortality data has been reviewed by Kitabchi *et al.* [22]. Subsequent to the introduction of low-dose insulin regimens in the early 1970s, the percentage mortality from hyperglycemic crisis, which had already improved in later compared with earlier series [1,2], remained relatively low, but in some series the mortality did not improve to zero. The fatalities that continued

to occur were partly due to underlying comorbidities, and were only infrequently due to metabolic causes or cerebral edema (discussed later), with generally higher mortality in older patients and in those with HHS compared with in younger patients [27–29,32,33,36]. In a series of DKA patients described by Malone and colleagues, for 27 patients aged ≥ 65 years and 193 patients aged < 65 years the mortality rates were 22 versus 2%, respectively ($p = 0.001$) [27].

In an observational study of 132 episodes of HHS reported by Piniés and colleagues, the 22 nonsurvivors (16.9%) differed from the 110 survivors with respect to age, hypotension, and biochemical parameters [29]. Although the nonsurvivors received higher doses of insulin in the first 24 h than the 110 survivors (115.2 vs 98 units; $p < 0.01$), neither group was treated on average with extremely high doses of insulin [29]. Zouvanis and colleagues reported a mortality rate of 6.8% among 58 patients with severe DKA and 16.6% among 24 patients with HHS [32]. Among 144 patients with DKA and 23 patients with HHS admitted to a large inner-city hospital in the USA and reported in 1997, there were three deaths associated with DKA and one death with HHS. All deaths were thought to be most likely related to the underlying precipitating illness [33]. With conservative intravenous insulin dosing at 0.5–4.0 units/h and slow fluid resuscitation, designed to achieve a reduction in BG of 50 mg/dl/h, in a series of 114 consecutive patients between 11 and 74 years of age with DKA, one center reported a mortality rate of zero [34].

■ Hypoglycemia & hypokalemia

Owing to the rapidity with which circulating insulin levels can be reduced by treatment withdrawal, it might be speculated that a low-dose regimen for intravenous insulin infusion during hyperglycemic emergency would present the lowest risk for hypoglycemia and hypokalemia. In a randomized trial of low-dose intramuscular insulin compared with high-dose subcutaneous and intravenous bolus insulin therapy in 48 DKA patients, Kitabchi and colleagues showed the patient rate of hypoglycemia in the first 12 h (BG <50 mg/dl) was 25% (6 out of 24 patients) in the high-dose subcutaneous and intravenous insulin group but none in the low-dose intramuscular insulin group of 24 patients [16]. In one case within each group, hypokalemia was observed on admission, but hypokalemia developed during treatment in seven patients in the high-insulin dose group, and was observed in only one patient in the low-dose group [16]. Nevertheless, despite the potential for risk reduction compared with high-dose therapy, during and after low-dose intravenous insulin infusion, hypokalemia and both early and late hypoglycemia continued to be reported, as well as BG readings not quite hypoglycemic but below present day targets [23,26,27,33]. Burghen

and colleagues found among children that BG <100 mg/dl during the first 12 h of treatment was seen not only in 12 out of 16 patients treated with high-dose insulin therapy, but also in two out of 16 treated with low-dose insulin infusion [23]. Their study showed hypokalemia ($K < 3.4$ meq/l) in ten out of 16 high-dose patients and also in three out of 16 low-dose patients. Umpierrez and colleagues described treatment results in a series of 144 consecutive patients with DKA and 23 patients with HHS admitted between 1993 and 1994 [33]. A low-dose insulin infusion protocol was available, with a loading dose of insulin as a bolus of 0.1 unit/kg, followed by 0.1 unit/kg intravenously until BG was 250 mg/dl. Thereafter, dextrose insulin was started and the insulin infusion rate was reduced by 50%. A scale of adjustments was available for subsequent incremental insulin rate revisions and for treatment of hypoglycemia, based on five levels of BG results. The authors reported that hypoglycemia was the most common complication, occurring in 23% of patients treated without the protocol, and 5% of those treated by adherence to the protocol, such that 13% (18/144) of DKA patients had BG <60 mg/dl at some time during insulin infusion. Only one out of 23 patients with HHS experienced hypoglycemia. The hypoglycemia was most likely to be seen in the second 12 h of treatment. Failure to reduce the insulin infusion rate upon attainment of a BG of 250 mg/dl was identified as a risk factor for hypoglycemia.

■ Cerebral edema

Among children, one of the persisting causes of mortality has been cerebral edema. In a population-based review of pediatric cases, 34 cases of cerebral edema among 2940 episodes of DKA were identified. Cerebral edema was associated with 24% mortality and with significant morbidity among survivors [52]. A review on the pathogenesis of cerebral edema is beyond the scope of this article. The development of cerebral edema is probably multifactorial, related to cerebral ischemia before treatment, and vasogenic edema during treatment, with change of the integrity of the blood–brain barrier [56]. Bicarbonate therapy causes cerebral edema (in dogs) by causing hypoxic ischemic vasoconstriction [48]. Although the mechanisms of cerebral edema remain controversial, it had been argued that a rapid fall in serum osmolality through

aggressive use of insulin and large volumes of hypotonic solutions might increase the risk for treatment-related coma and cerebral edema in treated humans with DKA [34,55]. There is some observational evidence to both contradict and support these beliefs. Glaser *et al.*, in a multicenter study, identified 61 patients with cerebral edema during the treatment of DKA [51]. The investigators reported two control groups who did not have cerebral edema, 181 randomly selected children and 174 children who were matched to the cerebral edema group for variables such as age at presentation, onset of diabetes (established vs newly diagnosed disease), initial serum glucose concentration and initial venous pH. Elevated serum urea nitrogen levels ($p = 0.003$) and low arterial carbon dioxide levels ($p < 0.001$) were found to be risk factors for the development of cerebral edema in children with DKA. The group also found that increases in serum sodium concentration during treatment was associated with increased risk of cerebral edema. However, serum glucose concentration and the rates of fluid and insulin administration in their study were not associated with the development of cerebral edema [51]. On the other hand, the national UK case-control study of cerebral edema conducted by Edge and colleagues, found a higher odds ratio (OR) of insulin administration in the first hour of fluid treatment (OR: 12.7 [1.41–114.5]; $p = 0.02$) and volume of fluid administered over the first 4 h (OR: 6.55 [1.38–30.97]; $p = 0.01$) among 43 cases of cerebral edema, compared with 169 matched control subjects [54]. When categories of insulin doses given over the first 2 h (0 units, 0.2–1.9 units, 2.0–4.2 units or 4.4–11.0 units) were compared, the dose of insulin in the first two was significantly associated with the risk of cerebral edema ($p < 0.02$ for trend).

■ Route of administration of regular insulin & subcutaneous use of insulin analogs

In this section, we will address modalities of low-dose insulin treatment other than intravenous insulin infusion, with recognition that some centers will find intravenous insulin infusion less practicable than intramuscular injections of regular insulin or subcutaneous insulin analog injections, but our subsequent review of previous literature will focus on the method of treatment proposed in this work (i.e., continuous intravenous use of insulin). Comparing small

doses of intramuscular insulin with intravenous insulin infusion or bolus therapy, the retrospective study by Soler found that intramuscular therapy sometimes resulted in delayed correction of hyperglycemia [12]. Soler also reported that low-dose therapy compared with high-dose bolus intravenous insulin therapy resulted in poor potassium retention, evident in the later hours of treatment [12]. Another randomized study of 30 patients treated with low-dose regimens accompanied by an initial loading bolus failed to show these differences between intramuscular and intravenous route [20]. A group reporting from Lagos, Nigeria, found that even though the overall time required to lower plasma glucose level to 250 mg/dl in the treatment of 32 patients having hyperglycemic emergency was shorter during use of intravenous insulin infusion (3.6 ± 0.2 h; $n = 17$) compared with intramuscular insulin therapy (4.2 ± 0.3 h; $n = 15$), the difference was not statistically significant; the investigators judged that in settings such as theirs, in which most hyperglycemic emergency patients are managed outside tertiary health centers, the intramuscular protocols might be the preferred route in the management of hyperglycemic emergencies. The insulin analog glulisine given intravenously yields results comparable to those obtained with intravenous infusion of regular insulin for treatment of DKA [44]. Umpierrez and colleagues randomly assigned adults presenting with DKA to three groups of 15 patients each, to receive the rapid-acting insulin analog, aspart, delivered subcutaneously every 1 h, aspart every 2 h or regular insulin by continuous intravenous infusion. The times to correction of hyperglycemia between the groups and times to resolution of ketoacidosis were similar, and there was one episode of hypoglycemia (BG <60 mg/dl) in each group [37]. In the study of subcutaneous aspart, patients were excluded if persistent hypotension was present after administration of 1 liter of normal saline. Of course, in practice, the exclusion of patients with hypotension would limit the generalizability of use of subcutaneous therapy with a rapid-acting analog. However, the evidence suggests that for hemodynamically stable patients, low-dose intramuscular regular insulin therapy and subcutaneous insulin analog therapy are reasonable alternatives to the more labor intensive and technologically demanding use of low-dose intravenous insulin infusion.

■ Loading dose

Kitabchi *et al.* reported on a randomization study in which 45 patients with DKA were separated into groups of 15 and received either low-dose intramuscular insulin, subcutaneous insulin, or low-dose intravenous infusion [17]. The amount of insulin treatment required to reach a BG level of 250 mg/dl was 57 ± 10 , 57 ± 7 and 58 ± 11 units, respectively. In each group, a loading bolus was given intravenously (0.33 units/kg), and repeated after 1 h if the BG had not fallen by 10%. The need to repeat the loading dose occurred in two, three, and five patients in each group, respectively. The fall in BG ($p < 0.01$) and ketone bodies ($p < 0.05$) was greater in the first 2 h in the intravenous insulin group compared with the other two groups. In a follow-up randomized study of 30 patients, the same group concluded that with routine use of a loading dose of insulin of 0.44 units/kg, the time for metabolic control of DKA was similar using either intramuscular or continuous intravenous therapy [20]. In order to evaluate the necessity for a loading dose when using intravenous insulin infusion, Kitabchi and colleagues randomized patients (aged 17–66 years) to three groups, each receiving intravenous insulin infusion according to the following rules [43]:

- 0.07 units/kg/h with an initial single intravenous loading bolus of 0.07 units/kg ($n = 12$, the ‘load’ group);
- 0.07 units/kg/h without a loading bolus ($n = 12$, the ‘no load’ group);
- 0.14 units/kg/h ($n = 13$, the ‘twice no load’ group).

Although the ‘load’ group experienced a higher peak of insulin (~ 460 $\mu\text{U/ml}$ at 5 min), the insulin level reached a plateau of ~ 86 $\mu\text{U/ml}$ by 30 min. By 60 and 120 min, there was not a significant difference of insulin levels for the ‘load’ and ‘no load’ groups, but the ‘twice no load’ group maintained higher levels of insulin than the other two groups during 30–120 min of infusion. Five of the patients in the ‘no load’ group received additional insulin to decrease initial glucose levels by 10%. The time to recovery was similar between groups. Hypokalemia was not observed. The investigators concluded that attainment of the desired rate of fall in BG in the ‘no load’ group might require an initial loading dose. It is noted that a pediatric consensus statement, with reference to risk of cerebral edema, recommends against use of a loading dose [39].

■ Insulin levels necessary & sufficient for response

Some of the early literature presented a rationale for low-dose therapy based on saturation behavior of the insulin receptor as shown, for example, in isolated adipocyte studies [61], and based on studies of the pharmacodynamics of low-dose insulin administration by different routes [66]. The half-life of a bolus of regular insulin measurable in the blood is not more than 5 min [63]. Pharmacologic doses of insulin achieving insulin blood levels of >1000 $\mu\text{U/ml}$ were shown to augment the hypoglycemic response of dexamethasone treated diabetic subjects [67]. However, for a near-maximal biologic response, sufficient insulin levels are considered to be 20–200 $\mu\text{U/ml}$ [61,62,64]. Whereas plasma levels in excess of 540 $\mu\text{U/ml}$ were reported with higher dose regimens used for treatment of DKA [8], lower infusion rates used experimentally to achieve insulin levels between 20–100 $\mu\text{U/ml}$ were known to result in steady decline of BG [64]. Semple and colleagues reported that at an insulin infusion rate of 4 U/h for treatment of DKA, the mean plasma insulin was 75.6 ± 8 $\mu\text{U/ml}$ [9]. Kidson and colleagues reported that in some hyperglycemic patients, insulin infusion rates as low as 1.2 or 2.4 units/h achieved a decline of BG at measured insulin levels in the physiologic range of 38–83 $\mu\text{U/ml}$ [11]. The four-center series of treatment courses using low-dose insulin infusion reported by Page achieved insulin levels of 20–200 $\mu\text{U/ml}$ [10]. In the randomized trial of 48 patients conducted by Kitabchi and colleagues, the high-dose group received an average of 232.9 ± 59.6 U of insulin in the first 6 h, achieving plasma insulin levels of 442 ± 168 $\mu\text{U/ml}$ by the sixth hour, whereas the low dose group (in the first 7 h) received 55.8 ± 6 U intramuscular insulin, achieving plasma insulin levels of 82.5 ± 13.2 $\mu\text{U/ml}$ at the third hour and 89.3 ± 26.2 $\mu\text{U/ml}$ at the seventh hour [16]. Luzi and colleagues, using insulin clamp techniques to study five patients with DKA, showed that during insulin infusion at a rate of 1 mU/kg/min, a decline in BG of 60 ± 5 mg/dl/h resulted mainly from suppression of hepatic glucose production [70].

■ Lack of insulin dose effect during early hours of treatment

In response to low-dose insulin therapy, observational data suggest that patient differences in

the rate of fall of BG in general are not determined by differences in the amount of insulin given. For regimens utilizing intravenous insulin infusion, a weight-based dose or absolute rate of insulin infusion was used during initiation of treatment. It was observed that without titration of the infusion, even at low insulin rates, each patient exhibited a characteristic rate of change of BG. The report by Alberti and colleagues showed that once insulin was started, and after initial rehydration, any given patient exhibited an even and predictable rate of change of BG [8]. When six patients receiving 8–12 units of insulin per h were compared with seven patients receiving 2–4 units/h, the rates of decline of BG observed by Semple and colleagues were not statistically different, 114 ± 7 and 88.8 ± 21 mg/dl/h respectively [9]. After initiation of insulin by continuous intravenous infusion, Kidson and colleagues also observed a roughly linear rate of decline of BG at a mean rate of 75 mg/dl/h. In two patients whose rate of fall of BG slowed after 3–4 h, the authors found that an increase of infusion rate of insulin did not accelerate the decline of BG. In eight of their series of 11 patients having measured insulin levels, they commented that the rate of decline of BG showed no correlation with serum insulin concentration ($p > 0.05$) [11]. Insulin resistance, not insulin unresponsiveness, may characterize DKA [68]. Under low-dose regimens, true treatment failures, requiring upward revision of the infusion rate for correction, have been reported but are uncommon, and are sometimes possibly related to immunogenicity of older bovine insulin preparations [14,15]. A graphical representation of the rate of fall of BG in the initial hours of treatment, among patients not previously receiving insulin, showed a similar glucose response when high- and low-dose regimens were compared in the randomized studies conducted by Kitabchi and colleagues, despite marked differences in the insulin levels, which were 400–1200 μ U/ml in high dose regimens, or 60–100 μ U/ml in low dose regimens [16,17,22]. In a study by Umpierrez and colleagues reporting 144 patients with DKA and 23 patients with HHS, no patient failed to respond to an intravenous infusion rate of 0.1 units insulin/kg/h [33]. One interpretation of the lack of dose effect might be that after receptor near-saturation has occurred, the biologic effect of incrementally higher insulin levels is negligible.

■ Impact of dehydration & infection upon rate of decline of BG

In response to low-dose insulin therapy, observational data suggest that as long as a minimally sufficient insulin regimen is maintained, the rate of fall of BG may differ depending upon factors such as the state of hydration and the presence or absence of infection. During intramuscular low-dose therapy of DKA, Alberti and colleagues showed an average rate of decline of BG during the first hour of treatment to be 131 ± 19 mg/dl/h for seven noninfected patients but 55 ± 10 mg/dl/h for seven infected patients ($p < 0.05$) [8]. In a series of 38 patients reported by Page and colleagues, having DKA ($n = 31$), HHS ($n = 5$), or hyperglycemia ($n = 2$), the magnitude of fall of BG by 4 h during low-dose insulin infusion was 33% in the presence of bacterial infection, compared with 60% without infection ($0.1 > p > 0.05$) [10]. Once insulin was started, any given patient exhibited an even and predictable rate of change of BG, such that the patients as a group had a linear fall of BG for the next 4 h, averaging 92 mg/dl/h [8]. For nine patients in the series of Alberti and colleagues, the initial hydration prior to administration of insulin accounted for a drop of BG of 53 ± 16 mg/dl [8]. In case of poor glycemic response, caregivers were exhorted to evaluate for insufficiency of hydration as well as the possibility of insufficiency of initial insulin dosing [8]. A report by Semple and colleagues described a mean rate of fall of BG of 101 ± 11 mg/dl/h until intravenous dextrose was begun, but a relatively faster rate of fall of BG in the first hour of intravenous insulin infusion for DKA, speculatively attributable to hemodilution [9]. A report by Kidson and colleagues also showed that initial rehydration, before initiation of insulin therapy, reduced the BG in seven patients with DKA or hyperglycemia by 51–157 mg/dl [11]. In the study of low-dose insulin infusion used for treatment of 38 patients with DKA ($n = 31$), HHS ($n = 5$), or hyperglycemia ($n = 2$) at four sites, Page and colleagues reported that at a mean insulin infusion rate of 7.2 IU/h, the rate of fall of BG was rapid and steady in all but one case, and that a decline of BG occurred with saline alone prior to starting insulin in 12 out of 18 patients with available measurements [10]. Waldhausl *et al.* treated eight ketoacidotic and two hyperosmolar patients with hydration using hypo-osmolar fluids (4364 ± 690 ml) prior to using insulin, and started insulin only when BG ceased to

decline. Rehydration time lasted from 4 to 20 h (10.9 ± 1.6 h, mean $\pm$ SEM). The investigators showed that all but one patient responded with a decline of hyperglycemia, by amounts ranging from 6.1 to 22.6 mmol/l (11.7 ± 2.1 mmol/l, mean $\pm$ SEM) [21]. Kitabchi and colleagues reported that the initial mean plasma glucose concentration may have fallen by approximately 18% after a mean of 1.5 l of fluid was given over several hours prior to insulin injection [22]. The importance of hydration to the correction of hyperglycemia is especially pronounced in HHS, a condition in which successful treatment without insulin has been reported [5]. In severely shocked patients, especially in HHS, a strong safety argument can be made to restore hydration before starting insulin; the use of insulin alone may be followed by further reduction of blood volume and blood pressure and possibly fatal outcome [3,6].

■ Continuation of insulin at a reduced rate after initial correction of hyperglycemia

It has been shown experimentally, during corticosteroid administration to insulin-dependent volunteers, that lipolysis and ketogenesis are suppressed at physiologic insulin levels lower than those pharmacologic levels that maximize the rate of decline of glucose [67]. It is also clear that, during treatment of DKA, the duration of insulin therapy necessary for resolution of ketonemia and acidosis is longer than the duration necessary for initial correction of hyperglycemia. An early report by Soler and colleagues showed that when intravenous insulin infusion was used for low-dose therapy, excluding cases in which bicarbonate was used, the time to correction of hyperglycemia (BG <250 mg/dl) was 5.8 ± 2.8 h, but the time to correct acidosis ($\text{HCO}_3^- >20$ mmol/l) was 14.8 ± 8.3 h [12]. Once target-range glycemic control has been achieved, and when intravenous dextrose infusion commences, some authors describe a lower dose insulin infusion regimen or conversion to subcutaneous insulin to prevent relapsing ketogenesis and promote continued recovery from ketosis and acidosis. For example, from a typical starting infusion rate of 2–12 units/h, once ketosis was corrected and BG was below 300 mg/dl, Semple *et al.* reduced the insulin infusion rate to 0.5–2 units/h for a further 6–12 h, or gave subcutaneous insulin on a sliding scale [9]. From a typical starting infusion rate of 4–5 units/h, Alberti and colleagues

suggested reducing the insulin infusion rate to two units/h once the BG concentration has fallen to less than 250 mg/dl [18]. Umpierrez and colleagues specifically linked late hypoglycemia to a failure to make such an appropriately timed reduction of insulin infusion rate [33]. In summary, in order to prevent relapsing acidosis during treatment with intravenous insulin infusion, the infusion should usually be continued beyond the time that glycemic control is achieved but a reduction of insulin infusion rate should generally be made.

■ Potential for delay of insulin action

It is an oversimplification to suppose that measurable levels of circulating insulin under various treatment regimens translate directly to define the rate of change of BG concentration. The effectiveness of repeated five-unit intravenous insulin boluses for treatment of diabetic coma, or persistence of effect of boluses of insulin delivered experimentally, showed that insulin action persists long after the 4–5-min half-life of plasma insulin has elapsed [13,63]. Following initiation or interruption of intravenous insulin infusion, equilibration of the effect upon BG occurs only gradually. When intravenous insulin infusion is initiated at a given rate, equilibration of measurable plasma insulin levels occur after approximately 20–60 min [67]. When glucose disposal rate and suppression of hepatic glucose output have been examined in persons having endogenous insulin secretion, after interruption of intravenous insulin infusion the apparent deactivation time appears to be both dose-dependent and protracted [69,71]. In hyperinsulinemic-euglycemic clamp studies of nondiabetic subjects, after interruption of infusion of regular intravenous insulin infusions, the time required for deactivation from maximum to half-maximum effect upon the glucose disposal rate was 63 ± 5 min [71]. Glycemic effects of the previous infusion may continue to occur for 90 min or more.

In large part, the delay in equilibration of the effect of intravenous insulin administration upon BG or rate of change of BG results from retention of insulin at interstitial sites and time to completion of downstream postreceptor cellular effects. In 1974 a computer-derived analysis of experimental studies using porcine insulin suggested that distribution of infused insulin might be thought of as being distributed to three compartments, in total equal to

approximately 15.7% of the body weight. The plasma space was only 4.5%. According to the model, the other two compartments were extravascular. The largest compartment, constituting 9.5%, equilibrated slowly with plasma insulin during insulin infusion but in clamp studies correlated closely with requirement for glucose administration. The authors concluded that “glucose utilization directly reflected the buildup and decay of insulin in a large, slowly equilibrating compartment, a compartment that appears to represent the interstitial fluid of muscle and adipose tissue” [65]. Therefore, in studies of healthy volunteers, it appears true that insulin, once in the intravascular compartment, must then pass through a depot of interstitial fluid before the final steps of cellular receptor activation and postreceptor insulin tissue effects occur. Comparable studies in DKA are of course not available. In commentary applicable to the treatment of DKA, Kreisberg cited the slowly equilibrating pool of interstitial insulin to argue that supraphysiologic amounts of insulin used therapeutically might predispose to subsequent hypoglycemia [19].

The design of algorithms for the treatment of DKA and HHS should reasonably assume that after insulin is given subcutaneously, intramuscularly, or intravenously, the effects of a given insulin blood level will not be seen immediately. Insulin action, though declining in effect, may persist for at least 90 min after interruption of insulin infusion. In comparison to other critically ill patients, on average in DKA and HHS patients, the volume of distribution of insulin and the dynamics of insulin action are likely to differ. Still qualitatively the principal holds that the full effect of a revision of intravenous infusion rate will not be expressed until a lag time has elapsed. The use of unnecessarily high doses of insulin early in the treatment course creates the possibility of ‘tanking up’ interstitial reservoirs. As target range control is approached, the purpose of insulin dosing revision would be to control future downward glycemic excursions.

Future perspective

Within the 2009 review from the ADA on hyperglycemic crises, the components of fluid and electrolyte management and general medical management are described, and a combination of weight-based and qualitative rules for initiating and adjusting the rate of intravenous

insulin infusion is given [45]. At our hospital a nurse-driven tabular algorithm had been previously adopted for intravenous insulin infusion for hyperglycemic critically ill patients not having hyperglycemic emergency. That insulin protocol did not aim at targets for BG appropriate to DKA or HHS and did not provide a guideline on concomitant care relevant to hyperglycemic emergency [72]. During multidisciplinary rounding in the intensive care unit, a request arose for the development of a similar tabular algorithm that might be modeled after our existing nurse-implemented protocol, which would assign the rate of intravenous insulin infusion appropriate for hyperglycemic crises according to rules that would be implemented by nursing staff, and that would include guidelines for house staff and generalists addressing other components of care. The request led to implementation of the protocol for hyperglycemic emergencies for nonpregnant adults that will be presented here. Our perception of need arose from observation that once target range control has been achieved under conventional low-dose insulin management, glycemic excursions below and above target continued to occur and were handled arbitrarily. We hypothesized that late glycemic excursions and possibly hypokalemia after the first 4 h of treatment might be reduced by use of a standardized insulin titration protocol, to be used before and during the later hours of treatment. The ideal insulin rule for hyperglycemic crisis would correct initial hyperglycemia at the desired rate and maintain glycemic control in the target range once upper target BG had been achieved. The duration of insulin infusion would often be determined by the length of treatment necessary to close the anion gap, usually longer than the time necessary to control BG. A safety precaution of course would be to begin infusion of dextrose once target range glycemic control has occurred. The insulin infusion rate necessary to maintain target range control would have to be adjusted with changes of insulin resistance or dextrose infusion. Excursions outside the target range, once target had been achieved, would have to be met with temporary adjustments of insulin infusion rate commensurate with the distance from target. Hypoglycemia would have to be strictly avoided. To achieve these goals, a dynamic algorithm intended for programming had already been described [73]. Here we report the creation of a new paper

rendition of that algorithm, formatted by a multidisciplinary team to resemble the algorithm we use for other critically ill hyperglycemic patients [72], and we describe the characteristics of the new algorithm.

■ Description of insulin dosing rules

A tabular protocol for insulin dosing for non-pregnant adults having hyperglycemic crisis, adapted from the algorithm being piloted at our hospital, is shown in **Tables 2 & 3**, together with the accompanying set of instructions to nursing staff, shown in **Box 1**. The provider guideline on the reverse side of the order form at our institution references the consensus statement of the ADA [45]; refers to potassium and dextrose therapy; briefly mentions other elements of general care; describes criteria for transitioning to subcutaneous insulin therapy and the need for overlap with intravenous insulin therapy; and concludes as follows: “This order set is not necessarily applicable to lactic acidosis, alcoholic ketoacidosis, ketoalkalosis, or mixed acid base disorders and is not sufficient to define care plans for DKA or HHS complicated by chronic or acute renal failure, dialysis requirement, congestive heart failure, shock, or other comorbidities that modify the evaluation of the patient or conduct of treatment.” When administered by the intravenous route, rapidly acting insulin analogs offer no pharmacodynamic advantage over regular insulin and incur

greater cost. Therefore, the protocol provides for continuous intravenous infusion of regular crystalline insulin.

■ Construction of table of insulin rates

The table was constructed on the assumption that each column corresponds to a maintenance requirement for insulin infusion at a particular time in the treatment course that would maintain target range control for an individual patient. The determinants of the maintenance rate include insulin sensitivity and carbohydrate exposure. Each cell of the table shows an insulin infusion rate. For DKA, the maintenance rate (MR) of insulin infusion associated with each column is shown in a row of cells corresponding to BG 180–199 mg/dl. When the BG lies above or below the range of 180–199 mg/dl, the increments or decrements of insulin infusion rate within each column are commensurate to the MR. For HHS, the MR of insulin infusion associated with each column is shown in a row of cells corresponding to BG 260–299 mg/dl. When the BG lies above or below the range of 260–299 mg/dl, the increments or decrements of insulin infusion rate within each column again are commensurate to the MR.

The equations and parameters shown in **Table 1** were designed to produce the desired output for insulin infusion rate as shown in **Tables 2 & 3**. The initially assigned insulin infusion rates for the adult algorithm are not

Table 2. Intravenous insulin infusion protocol for diabetic ketoacidosis.

Blood glucose (mg/dl)	Column 1 Insulin (units/h)	Column 2 Insulin (units/h)	Column 3 [†] Insulin (units/h)	Column 4 Insulin (units/h)	Column 5 Insulin (units/h)
<90	0.1	0.1	0.1	0.1	←
90–129	0.2	0.3	0.3	0.4	←
130–149	0.4	0.6	0.8	1.0	←
150–169	0.6	1.1	1.5	1.8	2.5
170–179	0.8	1.6	2.3	3.0	4.3
180–199	1.0	2.0	3.0	4.0	6.0
200–229	1.1	2.2	3.3	4.4	6.5
230–259	1.3	2.5	3.8	5.0	7.5
260–289	1.4	2.8	4.2	5.6	8.4
290–319	1.5	3.1	4.6	6.2	9.3
320–359	1.7	3.4	5.1	6.8	10.2
360–399	1.8	3.7	5.5	7.4	11.1
≥400	2.0	4.0	6.0	8.0	12.0

Excerpts from the tabular dosing algorithm similar to the pilot protocol for diabetic ketoacidosis (DKA) at Saint Francis Hospital, to be used together with nursing order in **Box 1**. DKA target point-of-care blood glucose 150–199 mg/dl until recovery (in bold). Classification as DKA is suggested by plasma glucose >250 mg/dl, arterial pH <7.3, bicarbonate <15, anion gap >12 meq/l, and moderate ketonuria or ketonemia

[†]Default column.

Table 3. Intravenous insulin infusion protocol for hyperglycemic hyperosmolar state.

Blood glucose (mg/dl)	Column 1 Insulin (units/h)	Column 2 Insulin (units/h)	Column 3 [†] Insulin (units/h)	Column 4 Insulin (units/h)	Column 5 Insulin (units/h)
<100	0.1	0.1	0.1	0.1	←
100–149	0.2	0.2	0.3	0.3	←
150–199	0.3	0.5	0.6	0.7	←
200–219	0.5	0.8	1.1	1.3	1.7
220–239	0.6	1.1	1.5	1.9	2.6
240–259	0.8	1.5	2.1	2.7	3.9
260–299	1.0	2.0	3.0	4.0	6.0
300–329	1.1	2.1	3.2	4.2	6.3
330–359	1.1	2.3	3.4	4.6	6.9
360–399	1.3	2.5	3.8	5.0	7.5
400–449	1.4	2.8	4.2	5.6	8.3
450–599	1.6	3.3	4.9	6.6	9.9
≥600	2.0	4.0	6.0	8.0	12.0

Excerpts from the tabular dosing algorithm similar to the pilot protocol for hyperglycemic hyperosmolar state (HHS) at Saint Francis Hospital, to be used together with nursing order in **Box 1**. HHS target point-of-care blood glucose 200–299 mg/dl until recovery (in bold). Classification as HHS is suggested by plasma glucose >600 mg/dl, serum osmolality >320 mOsm/l, arterial pH >7.3, bicarbonate >15 meq/l, and minimal ketonuria and ketonemia.

[†]Default column.

dependent upon patient body weight. However, a comparable algorithm for children would be weight based, giving insulin infusion rates expressed in units/kg/h [73]. The parameters, including the default value for the initial MR (the initial column assignment), were chosen to yield output of the equations giving insulin infusion rates that would fall in the ranges created for patients of average body weight under low-dose insulin infusion protocols currently in use. After the first 4 h of treatment, during which rehydration may be responsible for much of the decline of BG, with the use of the column-change rules the algorithm dynamically rediscovers the maintenance rate, as indicated by patient response to therapy.

The rows of the table were constructed using conventional units of measure for BG (Tables 2 & 3). Each row represents a range of BG values. Use of round numbers for the lower BG value was intended to facilitate implementation by nursing staff. Entries to each cell were computed by using equations and parameters shown in Table 1. A single mid-range BG value was selected to substitute for any BG within the range of BG values represented by each row. For DKA there is one row each for BG <90 or ≥400 mg/dl, and for HHS there is one row each for BG <100 or ≥600; computations for these rows were performed by substituting BG = 70, 430, 70 and 700 mg/dl in the equations of the algorithm to represent any BG in each the

respective four rows. Otherwise a mid-range BG for each row was used in the equations to substitute for any BG value within the range represented by the row. Thus the BG values used to construct each row for the table for DKA were 70, 110, 140, 160, 175, 190, 215, 245, 275, 305, 340, 380 and 430; and for HHS they were 70, 125, 175, 210, 230, 250, 280, 315, 345, 380, 425, 525 and 700 mg/dl.

To facilitate use, it is recommended that conversion to SI units be accomplished not by direct conversion of each BG value, but rather by re-definition of each row, using round numbers to represent the lower BG of each row in SI units, with use of new midrange BG values in SI units. The midrange BG will yield the insulin infusion rate for each cell when used as the independent variable in the equations. Unless direct conversion to SI units is performed, the algorithm will deliver slightly different instructions for insulin infusion rate at given BG, depending upon whether it is expressed in conventional or SI units, but the differences will be negligible. Our future performance evaluation will be based upon the algorithm as shown using conventional units for BG.

■ Use of the protocol

The algorithm is intended for treatment of non-pregnant adults. The algorithm is ordered as a nursing protocol with a single signature by the provider. The algorithm presently has completed

piloting at our institution and has been introduced as an approved hospital protocol, implemented by nursing staff, and overseen by the multidisciplinary staff of the intensive care unit. An essential component of the guideline is a set of instructions to nursing staff governing use of the algorithm. These instructions define column assignment, the use of the table to assign insulin infusion rate, and the frequency of monitoring of BG, initially every 1 h, and later, if appropriate conditions are met, every 2 h (Box 1). The initial column assignment will be selected by the provider, or may be column 3 by default if the prescriber has made no selection. After the first 4 h of treatment, if the BG remains above 200 mg/dl for DKA, or above 300 mg/dl for HHS, the protocol provides that the nurse may make algorithm-driven upward changes of column assignment. Upward column reassignments, after the initial 4 h of rehydration, might be required for maintenance of control once dextrose infusion has been started. For DKA, if BG ≥ 200 mg/dl $\times$ three successive hourly tests or for 2 h and not falling, the nurse is instructed by the protocol to go to next higher column. For HHS, if BG ≥ 300 mg/dl $\times$ three successive hourly tests or for 2 h and not falling, the nurse is instructed by the protocol to go to next higher column. Based upon patient response, there are also rules for nurse-implemented column down-titration after the fourth hour of treatment or for

BG < 80 mg/dl at any time. For DKA, after the 4th hour if BG < 180 mg/dl on three successive tests or for 2 h during infusion of fluids containing 5% dextrose, or if any BG < 150 mg/dl, the nurse is instructed by the protocol to go to next lower column. For HHS, after the 4th hour if BG < 280 mg/dl on three successive tests or for 2 h during infusion of fluids containing 5% dextrose, or if any BG < 200 mg/dl, the nurse is instructed to go to next lower column. Revision of column assignment prior to completion of 4 h of treatment requires the provider's order. The protocol specifies that any upward column assignment during the first 4 h of treatment is to be made by the physician, who may need to judge whether a problem of insufficient response is due to insufficiency of hydration or insufficiency of insulin. The protocol does not provide for a loading bolus of insulin. A decision to administer a bolus of insulin is at the discretion of the physician.

■ Rationale for insulin rules of the protocol

The tabular protocol described here gives an initial hourly insulin dose comparable to that described by the literature on low-dose intravenous insulin infusion but provides a set of dose-defining insulin titration rules aiming to prevent late complications. As the BG first approaches goal during the first 4 h of treatment, the assigned insulin infusion rate declines

Box 1. Physician orders for nursing staff for intravenous insulin infusion for diabetic ketoacidosis and hyperglycemic hyperosmolar state.

Initiation of insulin drip, monitoring of BG and termination of insulin drip

- Initiate intravenous insulin infusion using selected or default column assignment. Reassignment to a higher column before the fourth hour of treatment requires MD order. Between hours 1 and 4, if BG fails to fall each hour, then notify MD.
- Adjust column assignment for DKA or HHS as shown below. Adjust drip rate according to Table 2 for DKA or Table 3 for HHS, respectively.
- BG (fingerprick blood sugar or capillary BG) initially every 1 h.
- If BG within target range for 4 h, then $\rightarrow$ BG every 2 h. If column reassignment occurs, then $\rightarrow$ BG every 1 h.
- Record BG results, insulin drip rate changes, and column reassignments on intensive care unit flow sheet.
- Get order for subcutaneous insulin, to be administered 1–2 h before discontinuing insulin drip therapy.

Algorithm for order to treat patient if BG < 80 mg/dl

- If BG < 80 mg/dl, administer 25 ml of 50% dextrose iv. Notify MD.
- Go to next lower column, and use pretreatment BG to assign row.
- Re-check BG in 5 min. If BG is still below 80 mg/dl, repeat administration of 25 ml 50% dextrose iv.

Column change rules after fourth hour of treatment of DKA

- If BG ≥ 200 mg/dl $\times$ three successive hourly tests on the same column (or for 2 h) and not falling, $\rightarrow$ go to next higher column.
- If BG < 180 mg/dl $\times$ three (or for 2 h) during infusion of fluids containing D5%, or if any BG < 150 , $\rightarrow$ go to next lower column.

Column change rules after fourth hour of treatment of HHS

- If BG ≥ 300 mg/dl $\times$ three successive hourly tests on the same column (or for 2 h) and not falling, $\rightarrow$ go to next higher column.
- If BG < 280 mg/dl $\times$ three (or for 2 h) during infusion of fluids containing D5%, or if any BG < 200 , $\rightarrow$ go to next lower column.

BG: Point-of-care blood glucose; D5%: 5% dextrose in water; DKA: Diabetic ketoacidosis; HHS: Hyperglycemic hyperosmolar state; iv: Intravenous; MD: Medical doctor.

to approach the initially assigned value of the maintenance rate MR. During the first 4 h, rehydration may account for decline of BG. After the first 4 h, any needed revisions to the MR are discovered by patient response to therapy, (i.e., by the rate of change of BG at given insulin infusion rate). At each BG outside of the target range, the algorithm uses a simple single exponential equation to assign insulin infusion rate as a function of MR and distance of BG levels from target. For BG levels above target, the algorithm assigns the recommended insulin infusion rate, according to a bounded decaying exponential rule dependent upon BG distance from target, to be a value higher than MR. For BG levels below target, the algorithm reduces the insulin infusion rate exponentially, according to distance from target, to be a value less than the MR. The insulin infusion rate may be revised with each iteration of the algorithm.

The specific dosing ranges of our algorithm most closely resemble the 'no load' group studied by Kitabchi and colleagues [43]. The findings of that group suggested that unless a loading dose is given, under an algorithm using an infusion rate of 0.1 unit/kg the initial decline of BG might be delayed. Using our algorithm, caregivers might reactively order reassignment to a higher column than column 3 early in the treatment course, if there is initial delay of decline of BG. Therefore, the alternative of using a loading dose of insulin might be recommended upon initiation of our protocol. However, because those higher insulin doses ultimately may not be necessary or might promote late hypoglycemia, another reasonable alternative could be expectant waiting during use of the protocol, with attention to fluid resuscitation, without use of a loading dose of insulin, and without upward adjustment of the column assignment during the initial 4 h of treatment.

The insulin rules are issued together with a physician guideline concerning not only insulin but also other aspects of therapy. The guideline states the classification of hyperglycemic crises and gives advice on monitoring the patient, fluid and electrolyte management, and the use of intravenous dextrose, but it is not a completely automated algorithm; rather, clinical judgment is required. The consideration of withholding insulin despite severe hyperglycemia should apply in patients with arterial hypotension, and in patients with significant hypokalemia; these conditions emergently require volume

expansion and initiation of potassium replacement respectively, before starting insulin [31]. Limitations of applicability of the algorithm are stated in the physician guideline. It cannot be overemphasized that successful treatment demands strict attention to all aspects of care; the user is referred to the ADA consensus statement for additional components of care [45]. In fact, by individualizing the insulin therapy using a standardized but dynamic protocol, it is hoped that caregivers can devote more attention to the necessary individualization of fluid and electrolyte therapy and treatment of other comorbidities of the patient.

From the description it can be seen that the traditional use of a fixed insulin infusion rate during the early hours of treatment is replaced by the dynamic insulin dosing rule, reactive to patient response and to the eventual administration of dextrose-containing fluids. The specific hope is that episodes of late hypoglycemia and hypokalemia might be reduced as well as excursions below target range control.

This algorithm presently has just completed the pilot phase and has been introduced as a standard hospital protocol.

Conclusion

The purpose of the protocol presented here is to address one limitation of existing guidelines, namely the qualitative language or appeal to intuition that is recommended for adjusting the insulin infusion during the treatment course of DKA or HHS. We believe that the algorithm rendered in tabular form as a nurse-implemented dose-defining rule may attain target range control safely and effectively, without requiring hourly decisions by providers on how best to interpret a more qualitative rule. We expect that rules for temperate titration of insulin prior to and after attainment of target-range BG will reduce the risk for delayed glycemic excursions and possibly hypokalemia.

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