

End-Stage Renal Disease Increases Rates of Adverse Glucose Events When Treating Diabetic Ketoacidosis or Hyperosmolar Hyperglycemic State

Caitlin M. Schaapveld-Davis,¹ Ana L. Negrete,^{1,2} Joanna Q. Hudson,¹⁻³ Jagannath Saikumar,³ Christopher K. Finch,^{1,2} Mehmet Kocak,⁴ Pan Hu,⁴ and Megan A. Van Berkel^{1,2}

■ IN BRIEF Treatment guidelines for diabetic emergencies are well described in patients with normal to moderately impaired kidney function. However, management of patients with end-stage renal disease (ESRD) is an ongoing challenge. This article describes a retrospective study comparing the rates of adverse glucose events (defined as hypoglycemia or a decrease in glucose >200 mg/dL/h) between patients with ESRD and those with normal kidney function who were admitted with diabetic ketoacidosis (DKA) or hyperosmolar hyperglycemic state (HHS). These results indicate that current treatment approaches to DKA or HHS in patients with ESRD are suboptimal and require further evaluation.

Management strategies for diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS) are well established in patients with normal kidney function. Therapy typically includes aggressive fluid resuscitation, electrolyte replacement, insulin administration, and treatment of the precipitating cause (if identified). However, treatment strategies for these key principles may differ for patients with DKA or HHS and severe kidney dysfunction (1–3). For example, aggressive fluid resuscitation in a patient with end-stage renal disease (ESRD) is complicated by the risk of developing or furthering significant pulmonary edema and uncontrolled hypertension (4). In addition to intravascular fluid depletion, patients with normal kidney function who suffer from DKA or HHS frequently have reduced total-body potassium, despite normal or elevated serum measurements. This metabolic derangement often stems from the combination of the hemocentrating effect of osmotic diuresis and an inherent mechanism of reducing the patient's acidotic bur-

den, characterized by an exchange of the intracellular potassium ion pool for the newly increased extracellular hydrogen ion concentration (1–3). In contrast, patients with ESRD and DKA or HHS are routinely observed to have hyperkalemia resulting from a combination of transcellular shifts and a lack of renal clearance, thus eliminating the need for electrolyte replacement (4).

In patients with ESRD and DKA or HHS, adjustments in insulin administration may be warranted. Normally, insulin is primarily metabolized into useful amino acids by the kidneys' proximal tubular cells. Insulin gains access to these cells through two mechanisms: 1) glomerular filtration followed by luminal reabsorption and 2) diffusion through peritubular capillary membranes and ensuing binding to basolateral membranes of tubular cells (5,6). Therefore, in patients with impaired kidney function, delayed insulin clearance can complicate titration of the continuous insulin infusion and increase the risk of rapid decreases in blood glucose and consequent

¹Methodist University Hospital, Memphis, TN

²University of Tennessee Health and Science Center College of Pharmacy, Memphis, TN

³University of Tennessee Health and Science Center College of Medicine, Memphis, TN

⁴University of Tennessee Department of Preventative Medicine, Memphis, TN

Corresponding author: Megan A. Van Berkel, megan.vanberkel@mlh.org

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hypoglycemic events (7,8). Rapid reductions in blood glucose alter serum tonicity and osmolality, which can place patients at an increased risk of neurological sequelae such as seizures or cerebral edema (3,4,9). In patients with normal kidney function, low-dose insulin drips are expected to decrease serum glucose by approximately 50–70 mg/dL/h, but no study has demonstrated an analogous correlation in the decline of glucose in patients with severely impaired kidney function (1,2).

These variations in insulin kinetics in patients with ESRD present clinicians with an additional challenge when determining an insulin dosing regimen to achieve target glucose levels. Despite these added complications of DKA or HHS management in patients with ESRD, only case reports are available to describe treatment approaches (4,10). This retrospective study was designed to compare the DKA and HHS treatment practices and safety outcomes of patients with ESRD to those of patients without significant kidney impairment.

Materials and Methods

This was a multicenter, retrospective study that evaluated adult patients who presented with DKA or HHS to the emergency department of one of four hospitals within a single health care system between September 2011 and December 2014. Patients had to receive at least 1 hour of continuous intravenous insulin infusion to be eligible for inclusion. Diagnoses of DKA or HHS were identified by *International Classification of Diseases*, 9th edition, codes and independently verified by the primary investigator using objective diagnostic criteria based on the American Diabetes Association (ADA) 2009 guidelines (1), and analysis of available laboratory measurements (i.e., arterial pH, presence of ketones, anion gap, serum bicarbonate, and serum osmolality). The study was approved by the University of Tennessee Health

Science Center institutional review board.

Patients with ESRD with documentation of chronic hemodialysis (HD) were compared to a control group of patients with normal kidney function. Chronic HD was defined as scheduled HD for at least 3 months before admission. Patients were included in the control group if they presented to the emergency department with DKA or HHS and had a documented estimated glomerular filtration rate (eGFR) ≥ 60 mL/min/1.73 m² (calculated with the Modified Diet of Renal Disease Study equation) within 24 hours of hospital presentation (11). To achieve a homogenous patient population within the cohorts and control for the effects of HD on DKA resolution, patients with stages I–IV of chronic kidney disease and an eGFR < 60 L/min/1.73 m² were not included. Patients were excluded if they received cardiopulmonary resuscitation or had a withdrawal of care within 24 hours of hospital presentation, were transferred from an outside facility, receive peritoneal dialysis, or had incomplete data as determined by the primary investigator (e.g., no weight documented or lack of charting of rate changes for the insulin drip).

The primary objective of this study was to compare the rate of adverse glucose events (AGEs) among patients with ESRD to that of patients with normal kidney function. AGEs were defined as a blood glucose < 70 mg/dL or a decrease of > 200 mg/dL in a 1-hour period. Blood glucose levels were recorded and evaluated for hypoglycemia from hospital admission until 24 hours after admission or until the resolution of DKA or HHS, whichever was longer. A rapid decrease in blood glucose was defined as > 200 mg/dL/hour to assess patients at increased risk for adverse neurological sequelae (3,4,9). Resolution of DKA was defined as blood glucose < 200 mg/dL and two of the following clinical criteria:

serum bicarbonate level ≥ 15 mEq/L, venous pH > 7.3 , or a calculated anion gap ≤ 12 mEq/L. Resolution of HHS was defined as normal osmolality (278–300 mOsm/kg), glucose < 300 mg/dL, and recovery of normal mental status (1,2). Mental status is very subjective and not always consistently charted, so objective data such as serum osmolality had to be used in some cases for clearing of HHS.

Secondary outcomes were to evaluate differences in insulin administration, fluid, and electrolyte replacement for up to 24 hours or until the resolution of DKA or HHS. Additionally, hospital length of stay (LOS), intensive care unit (ICU) LOS, and time to resolution of DKA or HHS were evaluated. Serum tonicity was calculated as shown in Eq. 1.

$$2 \times [(\text{serum sodium concentration}) + (\text{serum glucose concentration})]$$

EQ. 1

Secondary outcomes were also stratified by early and late inpatient HD, compared to patients with normal kidney function. Early inpatient HD was defined as initiation of HD ≤ 12 hours after hospital presentation and late inpatient HD was defined as HD initiation > 12 hours after hospital presentation. The cutoff of 12 hours was chosen to represent the average time to resolution of DKA or HHS in patients with normal kidney function (12).

Statistical Analysis

Descriptive statistics were provided as frequency (percentages) for categorical variables and mean \pm standard deviation (SD) or median (25–75% interquartile range [IQR]), as appropriate, for continuous variables. The association between categorical variables of interest was investigated using a χ^2 test or Fisher's exact test, as appropriate. Distribution of continuous variables was compared via a Wilcoxon-Mann-Whitney test. The primary response variable was

TABLE 1. Baseline Characteristics of Patient Encounters

	ESRD (n = 44)	Control (n = 44)	P
DKA (n [%])	33 (75)	39 (88.6)	0.17
HHS (n [%])	11 (25)	5 (11.4)	0.17
Male sex (n [%])	26 (59.1)	21 (47.7)	0.39
African American (n [%])	39 (88.6)	31 (70.5)	0.063
Age (years)*	42 (35.5–51)	38 (20.5–55.5)	0.17
Weight (kg)*	64.7 (60.7–72.3)	67.9 (59.9–85.8)	0.33
History of diabetes (n [%])†	43 (98)	42 (100)	—
Type 1 diabetes (n [%])	32 (72.7)	24 (57.1)	0.18
Type 2 diabetes (n [%])	11 (25.6)	18 (42.9)	0.11
Insulin-dependent (n [%])‡	42 (95.5)	39 (92.9)	0.43
Initial laboratory parameters			
Serum glucose (mg/dL)*	836 (635–1045)	659 (466–861)	0.011
Calculated anion gap (mEq/L)*§	21 (18–27)	25 (21–30)	0.05
pH*	7.29 (7.17–7.33)	7.15 (7.09–7.29)	0.13
Sodium (mmol/L)*	129 (122.5–133)	132 (127.5–136)	0.0097
Chloride (mmol/L)*	90 (83–94)	97 (91–100.5)	0.0001
Bicarbonate (mmol/L)*	17.5 (12–21)	10.5 (7.5–17)	0.0023
Potassium (mmol/L)*	4.7 (4.1–5.4)	4.9 (4.35–5.8)	0.21
Blood urea nitrogen (mg/dL)*	47.5 (29–66)	22 (16–30)	<0.0001

*Data presented as median (25–75% IQR).

†Data missing for history of diabetes in two patients in the control group.

‡Represents type 1 and type 2 diabetes.

§Anion gap calculation: sodium – (chloride + bicarbonate).

||Data available for 23 patients with ESRD and 25 patients in the control group.

the likelihood of AGEs. Associations with categorical and continuous predictors of interest were explored using univariable logistic regression models, which formed the basis for a final multivariable logistic regression model. Several patients presented on multiple occasions with DKA or HHS over the study period; however, each encounter was evaluated independently. An additional analysis was performed using only the first visit of each patient who was included more than once and found similar results. All analyses were conducted using SAS Version 9.4 (SAS, Cary, N.C.).

Results

A total of 88 patient visits for DKA or HHS were evaluated; 44 for the ESRD group (28 patients total) and 44 for the control group (39 patients

TABLE 2. Frequency of AGEs

	ESRD Group	Control Group	P
Experienced an AGE (n [%]) ^a	33 (75)	16 (36.4)	0.0005
Blood glucose <70 mg/dL (n [%])			
≥4 episodes	5 (11)	0 (0)	0.011
3 episodes	7 (15.9)	1 (2.3)	
2 episodes	4 (9.1)	1 (2.3)	
1 episode	7 (15.9)	7 (15.9)	
>200 mg/dL drop in blood glucose in 1 hour (n [%])			
3 episodes	3 (6.8)	0 (0)	0.009
2 episodes	5 (11.4)	1 (2.3)	
1 episode	13 (29.5)	6 (13.6)	

^aEpisodes represent the number of values either <70 mg/dL or indicating a 1-hour drop of >200 mg/dL.

total). The patient visits in the control and ESRD groups were selected from the same hospital location and month of treatment to minimize any

differences in general treatment practices. The baseline characteristics of sex, race, age, weight, and diagnosis of either DKA or HHS were similar

TABLE 3. Treatments Received for DKA or HHS by Group

	ESRD	Control	P
Insulin bolus received (n [%])	41 (93.2)	36 (81.8)	0.2
Insulin bolus dose (units; mean \pm SD)	14.5 \pm 7	9.7 \pm 1.9	0.0008
Insulin infusion rate (units/kg/h; mean \pm SD)	0.1 \pm 0.04	0.11 \pm 0.04	0.2
Crystalloid bolus received (n [%])	27 (67.4)	40 (90.9)	0.0022
Crystalloid dose (mL; median [25–75% IQR])	1,000 (500–1,000)	2,000 (2,000–3,000)	<0.0001
Time to dextrose (hours; median [25–75% IQR])	12 (9–18)	9 (7–11.5)	0.0069
Potassium received (n [%])	13 (29.5)	12 (27.3)	0.99
Potassium dose (mEq; mean \pm SD)	44 \pm 22	63 \pm 56	0.57
Phosphate received (n [%])	3 (6.8)	8 (18.2)	0.2
Phosphate dose (mmol; median [25–75% IQR])	15 (8–30)	30 (23–68)	0.24
Bicarbonate received (n [%])	5 (11.4)	4 (9.1)	0.99
Bicarbonate dose (mEq; mean \pm SD)	70 \pm 27	52 \pm 38	0.51

TABLE 4. Treatment Outcomes by Group

	ESRD	Control	P
Time to first AGE (hours; median [25–75% IQR])	11 (6–14)	8.5 (4.5–11)	0.35
Time to resolve DKA or HHS (hours; median [25–75% IQR])	19 (11–29)	14.5 (10–20)	0.10
Time to long-acting insulin (hours; median [25–75% IQR])	16 (12–25)	21 (15–29)	0.13
Hospital LOS (days; median [25–75% IQR])	5.5 (4–8)	4 (3.5–5.5)	0.029
ICU LOS (days; median [25–75% IQR])	2 (2–4)	2 (2–3)	0.068
Resolution serum glucose (mg/dL; mean \pm SD)	127.4 \pm 63.8	158.4 \pm 40.3	0.0031
Tonicity at diagnosis (mean \pm SD)	1,673 \pm 621	1,353 \pm 554.7	0.011
Tonicity at resolution (mean \pm SD)	244 (165–341)	320 (283–384)	0.010

between groups as determined by a between-group analysis (Table 1).

The rate of AGEs was significantly higher in the ESRD group compared to the control group (75% [33/44] vs. 36% [16/44], respectively, $P < 0.0001$). Both hypoglycemia ($P = 0.0005$) and 1-hour decreases in blood glucose > 200 mg/dL ($P = 0.0093$) occurred more frequently in the ESRD group (Table 2). However, no difference in the time to first AGE was observed ($P = 0.35$). Additionally, there was no difference in the percentage of patients in each group who received an insulin bolus (93.2% ESRD vs. 81.8% control, $P = 0.2$); however, patients with ESRD received a higher cumulative insulin bolus dose (14.5 \pm 7.0 vs. 9.7 \pm 1.9 units, $P = 0.0008$) (Table 3).

There was no difference in time to resolution of DKA or HHS, time

to administration of a long-acting insulin, or ICU LOS (Table 4). Additionally, there were no differences in rates of AGEs or time to first AGE when stratified by early HD versus late HD. There was a median of 15.5 hours (IQR 7–25) from admission to when ESRD patients had HD. Patients with ESRD had a longer hospital LOS (mean of 5.5 days [IQR 4–8]) compared to the control group (4 days [IQR 3.5–5.5]) ($P = 0.029$) (Table 4).

With regard to fluid resuscitation, significantly fewer patients with ESRD received a crystalloid bolus compared to the control group (Table 3). There was no difference between the groups in terms of the number of patients requiring electrolyte replacement or the dose of electrolytes received (Table 3).

Multivariable logistic regression models were constructed in which

an AGE was considered to be the response variable; this led to an identification of the following factors as significant predictors of AGEs: ESRD, sex, receipt of an insulin bolus before the insulin infusion, and potassium level at baseline. ESRD status was found to be a significant predictor with an odds ratio (OR) of 8.27 (95% CI 2.6–26.4, $P = 0.0004$). Other predictive variables increasing the likelihood of AGEs included male sex (OR 4.18, 95% CI 1.38–12.61, $P = 0.012$), receiving an insulin bolus (OR 9.66, 95% CI 1.17–79.9, $P = 0.035$), and higher initial serum potassium level, with a 2.43 higher odds of having an AGE for every 1 mmol/L increase in the potassium level (95% CI 1.31–4.51, $P = 0.005$). Initial blood glucose was significant in the univariate analysis, but this did

not achieve significance in the multivariate logistic regression.

Discussion

To our knowledge, this is the first report evaluating treatment of DKA or HHS in patients with ESRD compared to patients with preserved kidney function. Our results demonstrate that patients with ESRD being treated for DKA or HHS are at an increased risk of AGEs compared to patients with normal kidney function. Additionally, patients with ESRD had a longer hospital LOS.

The increased rates of AGEs in the ESRD cohort is of concern because hypoglycemia in critically ill patients is associated with increased mortality and hospital LOS (13,14). The mechanism of increased mortality with hypoglycemia is not fully elucidated; however, hypoglycemia appears to affect multiple physiological parameters such as cardiac and brain function (13,14). However, it is important to be vigilant in avoiding hyperglycemic, as well as hypoglycemic, events because they, too, can prolong hospital LOS (15).

According to the Centers for Disease Control and Prevention, the average hospital LOS for DKA in 2009 was 3.4 days (16). In our study, the DKA or HHS patients with normal kidney function had a hospital LOS of 4 days (IQR 3.5–5.5) compared to 5.5 days (IQR 4–8) in patients with ESRD ($P = 0.028$). The absence of a sufficiently standardized protocol for DKA and HHS treatment in our institution may offer a partial explanation for the hospital LOS among the patients in this study being longer than the national average. Use of a DKA and HHS treatment protocol has been shown to reduce LOS by a mean of 0.87 days (12). According to the U.S. Renal Data System annual data report (17), patients on HD spend an average of 11 days in the hospital annually, primarily for cardiovascular events, infections, and vascular access complications. These additional com-

plications seen during hospitalization may have contributed to the prolonged hospital LOS for our ESRD population but were not evaluated.

Our analysis showed that receiving an insulin bolus dose before the insulin infusion was found to be significantly associated with an increased likelihood of AGEs in the multivariable analysis controlling for ESRD status, sex, and potassium level at diagnosis. Patients in the ESRD group had a higher cumulative insulin bolus dose and were frequently given multiple insulin boluses before initiation of an insulin drip. A small prospective trial of adult patients (kidney function not described in the study) concluded that a higher initial insulin drip rate of 0.14 units/kg/h was adequate to treat DKA without an initial bolus dose (18).

When managing chronic diabetes, the American College of Physicians recommends decreasing the recommended insulin dose by 25% when a patient's GFR is 10–50 mL/min and by 50% when the GFR is <10 mL/min because of the increase in the half-life of insulin (7,19). These recommendations stem from pharmacokinetic data showing that insulin sensitivity is decreased in conditions of uremia. After progression to ESRD, uremia is managed with HD and, therefore, a potentially cyclical increase in insulin sensitivity may be observed, depending on the dialysis dose and frequency (7,20). Although there are clinical practice guidelines for insulin management in chronic kidney disease states, there are no corresponding official recommendations for acute hyperglycemic emergencies (21). Our data indicate that receiving a bolus dose of insulin is associated with an increased frequency of complications and perhaps should be avoided in patients with ESRD.

Patients with ESRD were less likely to receive a crystalloid fluid bolus. When evaluating all patients who received a crystalloid bolus, patients with ESRD were given a lower total dose. The ADA guidelines state that

in the “absence of cardiac compromise,” patients should receive isotonic saline at a rate of 15–20 mL/kg/h or 1–1.5 L in the first hour of DKA or HHS treatment (1). Patients with DKA or HHS have a 6 L or 9 L total body water deficit, respectively (22). When replacing the fluid deficit, hypertonic fluids may result in hyperosmolarity via hypernatremia and hyperchloremia. Patients with DKA or HHS and ESRD may already be hyperosmolar; therefore, avoiding hypertonic fluids may be advised (4).

Frequently, patients with ESRD will not have as large of a fluid deficit as patients with normal kidney function (although some are still able to produce a large volume of urine) because of the lack of profound osmotic diuresis (23). Indeed, a corrected sodium concentration within a normal range may indicate that a patient does not require free water replacement (23). If patients with ESRD do have a total body water deficit, they may only require intermittent 250-mL sodium chloride boluses (4). The appropriate doses of fluid resuscitation for these patients warrant further investigation. In the interim, clinical judgment should be used to determine the necessity and volume of crystalloids required for patients with ESRD and DKA or HHS.

The 2009 ADA guidelines also recommend potassium replacement when serum levels fall to <5.2 mEq/L, with the goal range of 4–5 mEq/L (1). Current evidence suggests that insulin infusions should be held until the serum potassium level is ≥ 3.3 mEq/L (1,2). Because of serum acidosis, a movement of potassium from the intracellular to extracellular spaces occurs in the setting of hypoinsulinemia and hyperglycemia. This frequently results in an initial slight elevation of serum potassium levels but eventual total body depletion due to osmotic diuresis (3). Accordingly, in the setting of DKA or HHS, patients may require potassium supplementation.

Patients with normal kidney function usually do not encounter sequelae from hyperkalemia unless the rise of serum potassium exceeds the rate of clearance. Tzamaloukas et al. (5) suggest that, when treating patients with ESRD and extreme hyperglycemia, the need for electrolyte boluses and large fluid boluses is eliminated. Given the dearth of published literature on this topic, practitioners frequently are hesitant to bolus electrolytes in patients with ESRD. In this analysis, however, we did not observe any differences in the initial serum potassium level, the percentage of patients who received a bolus dose of potassium, or the amount of potassium given.

Whereas fluid resuscitation and electrolyte replacement in patients with ESRD and DKA or HHS have been minimally studied, data on the optimal time to dialyze patients is even scarcer. The time to dialysis did not appear to affect the outcomes in our patients with ESRD and DKA or HHS, nor was there a difference in patients receiving either early or late HD. Glycemic control is further complicated by the fact that plasma insulin and glucose can both be cleared by HD. However, the effect on overall glucose balance needs to be further investigated (24,25). At this time, no clear recommendations can be elucidated from our study regarding the optimal time to dialysis after presentation with DKA or HHS in patients with ESRD.

Our study is not without limitations. Inherent limitations exist based on the retrospective, multi-system study design and small sample size available. In an attempt to minimize misdiagnosis, patients were confirmed to have DKA/HHS using objective data by the primary investigator utilizing the 2009 ADA guidelines; however, some patients had a mixed DKA and HHS presentation and were classified by the investigator as having DKA (1). Treatment guidelines exist for the treatment of DKA and HHS.

However, there was no institutional DKA protocol at the time of this study, so there was some variability in treatment strategies among providers. Treatment was not stratified according to whether patients were previously diagnosed with type 1 or type 2 diabetes because the treatment strategy outlined in the nationally published ADA guidelines does not differ between these patients group. Finally, although this study is limited by its small sample size, this is a select patient population, and we aimed to include a homogenous group of patients by limiting the ESRD group to patients who required chronic HD.

Conclusion

These results suggest that patients with ESRD and DKA or HHS are at an increased risk of hypoglycemic events, indicating that reductions in cumulative insulin doses may be necessary. Although prospective trials are needed to further evaluate the optimal treatment and outcomes of patients with ESRD and DKA or HHS, our study lends evidence to the hypothesis that current practices in the ESRD population are not ideal.

Duality of Interest

No potential conflicts of interest relevant to this article were reported.

References

1. Kitabchi AE, Umpierrez GE, Miles JM, et al. Hyperglycemic crises in adult patients with diabetes. *Diabetes Care* 2009;32:1335–1343
2. Kitabchi AE, Umpierrez GE, Murphy MB, Kreisberg RA. Hyperglycemic crises in adult patients with diabetes: a consensus statement from the American Diabetes Association. *Diabetes Care* 2006;29:2739–2748
3. Nyenwe EA, Kitabchi AE. Evidence-based management of hyperglycemic emergencies in diabetes mellitus. *Diabetes Res Clin Pract* 2011;94:340–351
4. Tzamaloukas AH, Ing TS, Siamopoulos KC, et al. Body fluid abnormalities in severe hyperglycemia in patients on chronic diuresis: theoretical analysis. *J Diabetes Complications* 2008;21:374–380
5. Tzamaloukas AH, Ing TS, Elisaf MS, et al. Abnormalities of serum potassium concentration in dialysis associated hyperglycemia and their correction with insulin: a

unique clinical/physiologic exercise in internal potassium balance. *Int Urol Nephrol* 2010;42:1015–1022

6. Carone FA, Peterson DR. Hydrolysis and transport of small peptides by the proximal tubule. *Am J Physiol* 1980;238:F151–F158
7. Iglesias P, Diez JJ. Insulin therapy in renal disease. *Diabetes Obes Metab* 2008;10:811–823
8. Dickerson RN, Hamilton LA, Connor KA, et al. Increased hypoglycemia associated with renal failure during continuous intravenous insulin infusion and specialized nutritional support. *Nutrition* 2011;27:766–772
9. Bradley P, Tobias JD. Serum glucose changes during insulin therapy in pediatric patients with diabetic ketoacidosis. *Am J Ther* 2007;14:265–268
10. Tzamaloukas AH, Avasthi PS. Acid-base disorder in hyperglycemia of insulin-dependent diabetic patients on chronic dialysis. *J Diabetes Complications* 1988;2:75–78
11. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009;150:604–612
12. Hara JS, Rahbar AJ, Jeffres MN, Izukora KE. Impact of a hyperglycemic crises protocol. *Endocr Pract* 2013;19:953–962
13. NICE-SUGAR Study Investigators, Finfer S, Chittock DR, Su SY, et al. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med* 2009;360:1283–1297
14. Tan HK, Flanagan D. The impact of hypoglycaemia on patients admitted to hospital with medical emergencies. *Diabet Med* 2013;30:574–580
15. Ables AZ, Bouknight PJ, Bendyk H, Beagle R, Alsip R, Williams J. Blood glucose control in noncritically ill patients associated with a decreased length of stay, readmission rate, and hospital mortality. *J Healthc Qual* 2016;38:e89–e96
16. Centers for Disease Control and Prevention. Average length of stay in days of hospital discharges with diabetic ketoacidosis as first-listed diagnosis, United States, 1988–2009 [Internet]. Available from <http://www.cdc.gov/diabetes/statistics/dkafirst/fig2.htm>. Accessed 4 April 2015
17. National Institutes of health, National Institute of Diabetes and Digestive and Kidney Diseases. *2013 USRDS Annual Data Report, Vol. 2: Atlas of End-Stage Renal Disease in the United States*. Available from http://www.usrds.org/2013/pdf/v2_00_intro_13.pdf. Accessed 8 May 2015
18. Kitabchi AE, Murphy MB, Spencer J, Matteri R, Karas J. Is a priming dose of insulin necessary in a low-dose insulin protocol for the treatment of diabetic ketoacidosis? *Diabetes Care* 2008;31:2081–2085
19. Bennett WM. *Drug Prescribing in Renal Failure: Dosing Guidelines for Adults*

and Children. 5th ed. Philadelphia, Pa., American College of Physicians, 2007

20. Rabkin R, Ryan MP, Duckworth WC. The renal metabolism of insulin. *Diabetologia* 1984;27:351–357

21. National Kidney Foundation. HDOQI clinical practice guidelines and clinical practice recommendations for diabetes and chronic kidney disease. *Am J Kidney Dis* 2007;49(Suppl. 2):S12–S154

22. Van Ness-Otunnu R, Hack JB. Hyperglycemic crisis. *J Emerg Med* 2013;45:797–805

23. Gupta A, Rohrscheib M, Tzamaloukas AH. Extreme hyperglycemia with keto-acidosis and hyperkalemia in a patient on chronic hemodialysis. *Hemodial Int* 2008;12(Suppl. 2):S43–S47

24. Schneditz D, Hafner-Giessauf H, Holzer H, Thomaseth K. Intracorporeal

glucose disposal during hemodialysis after a standardized glucose load. *ASAIO J* 2010;56:204–209

25. Abe M, Okada K, Ikeda K, Matsumoto S, Soma M, Matsumoto K. Characterization of insulin adsorption behavior of dialyzer membranes used in hemodialysis. *Artif Organs* 2011;35:398–403

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