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## Editorial

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**Budi Suprapti[1,2] / Fairuza Syarfina[3] / Chrismawan Ardianto[3] / Cahyo Wibisono[4,5]**

# Intravenous insulin therapy in diabetes mellitus with hyperglycemic crisis and intercurrent illness

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**Abstract:**
**Background:** Hyperglycemic crisis is one of the complications of diabetes mellitus, which is common in hospitalized diabetic patient with intercurrent illness, requiring immediate action to control blood glucose. As an effort to attain rapid, gradually and more definite blood glucose, insulin is given intravenously. This study aimed to explore the patterns of blood glucose in hyperglycemic crisis and intercurrent illness, precipitating conditions, insulin regimen and blood glucose (BG) level results.
**Methods:** It was a cross-sectional study conducted on type 2 diabetic patients. The inclusion criteria were as follows: hospitalized in the general/internal medicine ward with or without any complication or comorbidity receiving intravenous insulin therapy; have pre- and post-BG data after insulin intervention.
**Results:** In 3 months of the study period, 22 patients fulfilled the inclusion criteria with 28 cases of intravenous insulin therapy, and 1 patient could get more than one intervention. The major condition toward a hyperglycemic crisis condition was infection. The patient's BG before interventions was 243 mg/dL to more than 600 mg/dL. The dosage of insulin varied from 4 to 10 units per hour, intravenously with a frequency of 1–4 times. The dosage consideration was not only based on BG levels but also on the patient's condition. The reduction in BG level varied greatly between 0.2 and 28.1 mg/dL per unit of insulin. The BG level of three patients did not decrease. On the other hand, one patient experienced mild hypoglycemia.
**Conclusions:** Infection conditions were the most common factor for the hyperglycemia crisis. Moreover, intravenous insulin dosing was done individually, and there was a large variation in the results of the decrease in BG levels.

**Keywords:** diabetes mellitus, hyperglycemic crisis, intravenous insulin
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## Introduction

Type 2 diabetes mellitus (T2DM) is characterized by the defect of insulin action and secretion. T2DM begins with insulin resistance that first occurs during the pre-diabetes state. Because of their function failure, pancreatic cells are unable to overcome insulin resistance, causing increased blood glucose (BG) levels [1]. Patients with a history of T2DM have a three times greater chance of being hospitalized than those without a history of T2DM [2]. Hospitalized patients with intercurrent illness often experience uncontrolled blood sugar conditions that may even bring patients to hyperglycemia crisis conditions, that is, hyperosmolar hyperglycemia and diabetic ketoacidosis (DKA) [1]. Uncontrolled BG levels increase the risk of infection in patients with DM. Patients with DM are susceptible to infections such as pneumonia, urinary tract infections (UTIs) and infections of the skin. Furthermore, sepsis due to hyperglycemia would increase the virulence of the pathogen; decrease chemotaxis and phagocytosis of immune cells; decrease cytokines release, immobilization of T cells and polymorphonuclear neutrophil; and decrease gastrointestinal and urinary tract motility [3], [4]. The susceptible infection state brings the patient to an emergency condition. A hyperglycemic crisis in DKA and hyperosmolar hyperglycemic state is associated with uncontrolled T2DM. It is reported that measurements of blood sugar levels of more than 250 mg/dL twice or the presence of vomiting is a sign of ketoacidosis. Mortality increases

**Budi Suprapti** is the corresponding author.

in many hyperglycemia conditions in hospitalized patients. Other intercurrent medical illnesses in hospitalized patients produce uncontrolled BG and lead to hyperglycemia crisis including acute myocardial infarction, trauma, acute kidney injury, stroke, pancreatitis and steroids. This condition needs efforts to inhibit the development of hyperglycemic crisis and attain a rapid, gradual and more definite BG decrease. In such cases, insulin is given intravenously [1], [4]. Thus, the aim of this study was to examine and analyze the patterns of BG in hyperglycemic crisis and intercurrent illness, the precipitating conditions, insulin regimen and BG level results.

## Subjects and methods

The study was conducted on patients with T2DM who were hospitalized at Universitas Airlangga Hospital on March to May 2017. The inclusion criteria were DM patients with or without any complication or comorbidity receiving intravenous (IV) insulin therapy, who had the data of BG levels before and after IV insulin therapy. The hyperglycemic crisis was confirmed by the physician through BG level and other manifestations, for example, air hunger, nausea, vomiting, abdominal pain and Kussmaul respiration. The BG data were collected from the patient's medical record. The methodology of this study was approved by the ethics committee of Universitas Airlangga Hospital.

## Results

During the study, 21 patients met the inclusion criteria that were in the hyperglycemic crisis state or defined and receiving IV insulin therapy. From the samples, 28 cases of IV insulin therapy were found. Of the 21 patients, 67% were female and 33% were male. The highest distribution of patient age was 50–59 years (Figure 1).

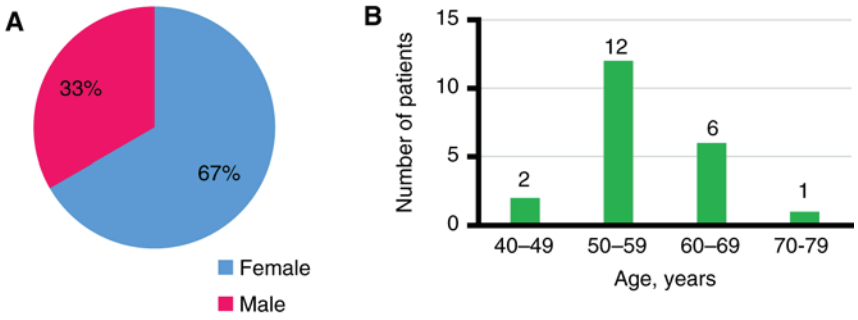


**Figure 1:** The profile of patients with type 2 diabetes mellitus based on gender (A) and age (B; n = 21).

The present study showed that subjects experienced acute DM complications such as hypoglycemia and hyperosmolar hyperglycemia, chronic microvascular complications, that is, nephropathy, and macrovascular complications, that is, hypertension, heart disease and stroke (Table 1). Further, it was found that sepsis, UTIs and other infectious diseases including gangrene-ulcus-abscess pedis were evidenced in the subjects (Table 1).

**Table 1:** Complications and comorbidity of patients with hyperglycemic crisis (n = 21).

| Diabetes complication | Frequencies, % | Comorbid | Frequencies, % |
|---|---|---|---|
| Post hypoglycemia | 14.3 | Sepsis | 42.9 |
| Hyperglycemia | 4.8 | Urinary tract infection | 9.5 |
| Hyperosmolar | 14.3 | Acute gastroenteritis | 9.5 |
| Hypertension | 9.5 | Pneumonia | 9.5 |
| CAD | 4.8 | Acute pharyngitis | 4.8 |
| Cardiac decompensation | 4.8 | Typhoid fever | 4.8 |
| Stroke | 9.5 | Cholelithiasis | 4.8 |
| Heart failure | 9.5 | Cholecystitis | 4.8 |
| Gangrene pedis | 14.3 | Ca mammae | 4.8 |
| Ulcus pedis | 14.3 | Febris obs. | 4.8 |
| Abscess pedis | 19.0 | | |
| Diabetic nephropathy | 4.8 | | |

| | |
|---|---|
| Acute kidney injury | 4.8 |
| Diabetic gastropathy | 4.8 |

One patient could have more than one complication or comorbid.

Pre-interventional BG data of 28 cases showed that the patient's pre-interventional BG levels were above 243 mg/dL. Moreover, one patient was found with pre-interventional BG levels above 600 mg/dL. The insulin regiment was listed based on the glucose level and the condition of the patients. Patients with the glucose level of 243 to <300 mg/dL received 4–6 units of IV insulin with 1–4 times daily regiments. Patients with the glucose level of 300 to <400 mg/dL received 4–10 units of IV insulin with 1–3 times daily regiments. However, patients with a glucose level of 400 to <500 mg/dL received only 4–8 units of IV insulin with 3 times daily regiments. Furthermore, patients with the glucose level of >500 mg/dL received only 6–8 units of IV insulin with 2–3 times daily regiments (Table 2).

**Table 2:** Blood glucose level range and insulin regiments for patients with hyperglycemic crisis.

| Blood glucose, mg/dL | IV insulin dosage (times daily× units) | Number of patients |
|---|---|---|
| 243 to <300 | 1 × 4 | 2 |
| | 3 × 4 | 1 |
| | 4 × 4 | 1 |
| | 2 × 6 | 1 |
| 300 to <400 | 2 × 4 | 4 |
| | 3 × 4 | 3 |
| | 1 × 6 | 1 |
| | 2 × 6 | 1 |
| | 1 × 8 | 2 |
| | 1 × 10 | 1 |
| | 2 × 10 | 2 |
| | 3 × 10 | 1 |
| 400 to <500 | 3 × 4 | 3 |
| | 3 × 6 | 2 |
| | 3 × 8 | 1 |
| 500 to <600 | 3 × 8 | 1 |
| >600 | 2 × 6 | 1 |

The present study showed the profile of the correction of the patient's BG after the intervention. The present result showed that there were 18 cases in which BG levels did not reach the target of BG level, remaining at the level of more than 180 mg/dL. Three patients were reported experiencing unchanged BG levels after intervention as compared to the levels before. Furthermore, one patient was reported as having a BG level of about 67 mg/dL after intervention (Figure 2).

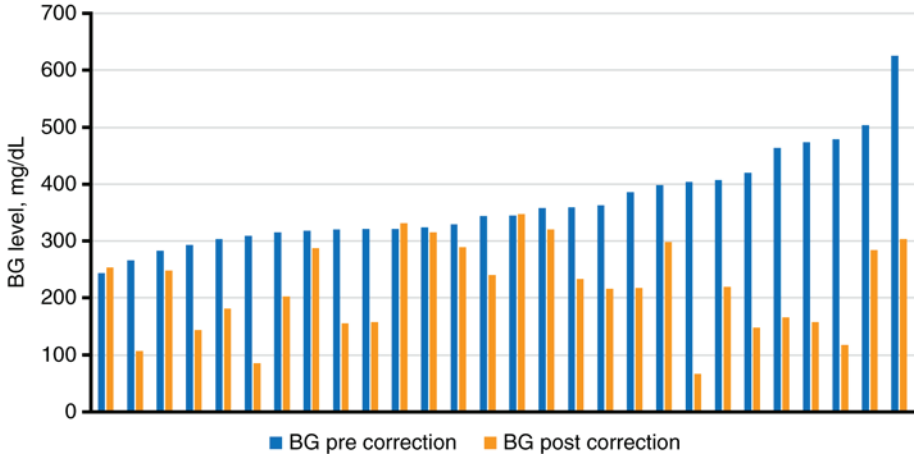


**Figure 2:** Pre- and post-insulin correction BG profile in 28 cases with intravenous insulin intervention.
The blue bar graphs represent the pre-BG levels and the yellow bar graphs represent the post-BG levels.

The present study showed that there is a considerable variation in the decrease of the BG as normalized with the insulin unit administered. This was evidenced not only in the DM patient with a specific additional

condition such as infection or else, but also in patients with no infection. The reduction in BG level ranged between 0.2 and 28.1 mg/dL for 1 unit of insulin. Three patients in infection and infection plus other condition groups did not achieve a decrease in BG. The data showed that 21 of 28 cases were diabetic condition with an infection event (Figure 3).

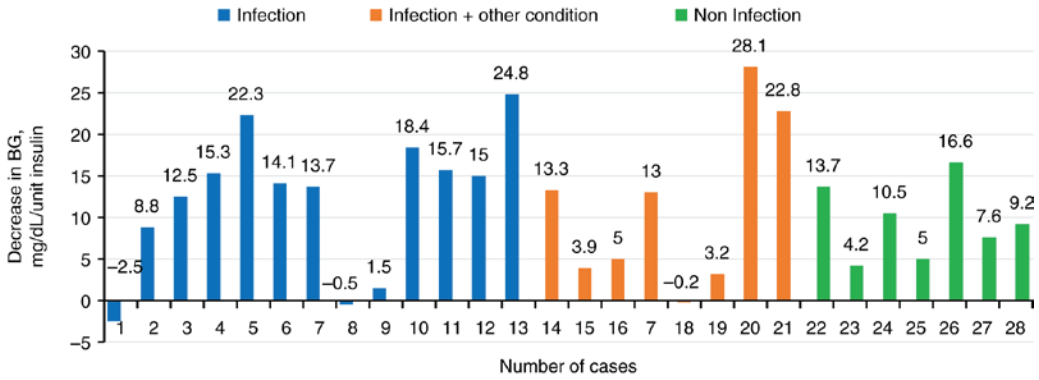


**Figure 3:** Profile of the decrease in blood glucose for 1 unit insulin.
The data are clustered into infection, infection and other condition and non-infection.

## Discussion

During the study period, 21 patients met the inclusion criteria comprising 28 cases of IV insulin therapy, and some of the cases involving more than one intervention with IV insulin. The proportion of the cases based on gender was 67% female and 33% male, with the highest age group 50-59 years (Figure 1). It was previously reported that the increase in the prevalence of T2DM in women is associated with low physical activity and the condition of obesity, which is more common in women [5]. The age distribution of these patients is consistent with the results of previous studies showing that insulin is used for patients at the age of 45–64 years [6]. It is known that T2DM that occurs at a young age is associated with obesity and lack of physical activity, which cause insulin resistance [7].

Patients with T2DM are usually hospitalized due to complications and/or comorbidities that may trigger hyperglycemic conditions [1], [8]. The results of the present study showed that patients experienced acute DM complications, chronic microvascular complications and macrovascular complications (Table 1). Another study shows that hypertension, coronary heart disease and stroke are the most common diseases experienced by patients with T2DM who are hospitalized in northern China [9]. Stroke and cardiovascular disease contribute to the development of stress hyperglycemia through a highly complex interplay of counter-regulatory hormones such as catecholamine, growth hormone, cortisol and cytokines. A complex feedforward and feedback mechanisms between hormones and cytokines leads to excessive hepatic glucose production and insulin resistance. High hepatic output of glucose, primarily through gluconeogenesis, seems to be the most important contributor to stress hyperglycemia [10]. The most comorbidities that existed in these patients were sepsis, UTIs, and other infectious diseases, in addition to infections associated with DM complications, that is, gangrene-ulcus-abscess pedis (Table 1). It is known that infections are related to an increase in counter-regulatory hormones, that is, glucagon, cortisol, catecholamine and growth hormones that work to counteract the action of insulin, which triggers insulin resistance and hyperglycemia [11].

It has been known that infection conditions are susceptible to lead patients with DM to an emergency condition, that is, hyperglycemia hyperosmolar and ketoacidosis, that requires rapid, gradual BG control, for which insulin is given intravenously [1], [4]. Pre-interventional BG data of 28 cases presented in Figure 2 showed that the patient's pre-BG levels were above 243 mg/dL. In this case, metabolic stress and infection conditions in the patient need to be handled aggressively, and BG control is carried out intensively to prevent patients from entering the hyperglycemia crisis. Insulin is given intravenously.

The present data showed that insulin dosage does not always increase with increasing BG levels (Table 2). There are several considerations in insulin dosing, including the degree of infection of the patient, insulin response from the previous intervention and patient intake. Administration of insulin is given intravenously with hourly intervals in a dose of 4–10 units. In the hyperglycemic crisis, generally, insulin is given 5–10 units/hour. This gradual method of administration is intended to obtain a gradual decrease in BG and to avoid the occurrence of shock hypoglycemic reactions. Rapid correction of BG reflected in a reduction greater than 75–100 mg/dL is not recommended, as it can result in cerebral edema [1].

The present data demonstrated that there was a considerable variation in the patient's BG decrease response. In patients with critical conditions, BG targets are less than 180 mg/dL [1]. In this study, 60% of patients had BG more than 180 mg/dL after intervention. There were 10% of the cases showing the failure of the intervention in reducing BG. It is reported in another study that the difficulty in BG control may occur because of the low achievement of the BG target in hospitalized patients [12]. On the other hand, in the present study, there was one patient who experienced hypoglycemia. Given that IV bolus insulin administration may have a rapid effect on the decrease of BG, and that there was great variability in the individual response to insulin, thus severe hypoglycemic events should be anticipated. The method of insulin administration in the present study was IV bolus injection. Since the method of administration may contribute to the outcome and the adverse event of the IV insulin injection, further study is needed to profile and examine the effect of the method of administration on the therapeutic efficacy.

It is known that a unit of insulin theoretically decreases 30–50 mg/dL BG [12]. Figure 3 shows that there was a great variation in insulin response in reducing inpatient BG. The reduction in the BG level varies between 0.2 and 28.1 mg/dL for a unit of insulin. Three patients did not show a decrease in BG. Figure 3 also shows the response variation in decreasing BG not only in infection conditions but also in non-infection states. In some cases, such as coronary artery disease, cardiac decompensation, stroke or heart failure, there is a metabolic stress condition. This condition is related to increased BG due to increasing counter-regulatory hormones and cytokine, which eventually speed up gluconeogenesis [10].

The hyperglycemic crisis is one of the acute complications of T2DM. It is a critical condition that needs gradual IV insulin therapy to reach the target and to avoid the risk of hypoglycemia [1]. The results of the present therapeutic data suggest that the insulin response in individuals considerably varies, and may even bring the patients to a hypoglycemic condition. Rigorous monitoring of insulin administration responses is needed, involving all health care team practices. The success of the contributions of various good health teams, doctors, nurses, pharmacists and others in ensuring successful outcomes for patients with T2DM have been reported [13], [14].

## Conclusions

From the present study, it can be concluded that the most important factor that elicits the hyperglycemia crisis is infection. It is suggested that there is a large variation in blood glucose control using IV insulin during a hyperglycemic crisis. Since the infection and other coexisting conditions may interact with each other and strongly modulate the outcome of IV insulin regimens, further research is still needed to optimize the IV insulin regimen in the hyperglycemic crisis with certain comorbid.

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**Author contributions:** All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

**Competing interests:** Authors state no conflict of interest.

**Informed consent:** Informed consent was obtained from all individuals included in this study.

**Ethical approval:** Research involving human subjects complied with all relevant national regulations, institutional policies and is in accordance with the tenets of the Helsinki Declaration (as revised in 2013), and has been approved by the authors' institutional review board (079/KEH/2017).

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The present data demonstrated that there was a considerable variation in the patient's BG decrease response. In patients with critical conditions, BG targets are less than 180 mg/dL [1]. In this study, 60% of patients had BG more than 180 mg/dL after intervention. There were 10% of the cases showing the failure of the intervention in reducing BG. It is reported in another study that the difficulty in BG control may occur because of the low achievement of the BG target in hospitalized patients [12]. On the other hand, in the present study, there was one patient who experienced hypoglycemia. Given that IV bolus insulin administration may have a rapid effect on the decrease of BG, and that there was great variability in the individual response to insulin, thus severe hypoglycemic events should be anticipated. The method of insulin administration in the present study was IV bolus injection. Since the method of administration may contribute to the outcome and the adverse event of the IV insulin injection, further study is needed to profile and examine the effect of the method of administration on the therapeutic efficacy.

It is known that a unit of insulin theoretically decreases 30–50 mg/dL BG [12]. Figure 3 shows that there was a great variation in insulin response in reducing inpatient BG. The reduction in the BG level varies between 0.2 and 28.1 mg/dL for a unit of insulin. Three patients did not show a decrease in BG. Figure 3 also shows the response variation in decreasing BG not only in infection conditions but also in non-infection states. In some cases, such as coronary artery disease, cardiac decompensation, stroke or heart failure, there is a metabolic stress condition. This condition is related to increased BG due to increasing counter-regulatory hormones and cytokine, which eventually speed up gluconeogenesis [10].

The hyperglycemic crisis is one of the acute complications of T2DM. It is a critical condition that needs gradual IV insulin therapy to reach the target and to avoid the risk of hypoglycemia [1]. The results of the present therapeutic data suggest that the insulin response in individuals considerably varies, and may even bring the patients to a hypoglycemic condition. Rigorous monitoring of insulin administration responses is needed, involving all health care team practices. The success of the contributions of various good health teams, doctors, nurses, pharmacists and others in ensuring successful outcomes for patients with T2DM have been reported [13], [14].

## Conclusions

From the present study, it can be concluded that the most important factor that elicits the hyperglycemia crisis is infection. It is suggested that there is a large variation in blood glucose control using IV insulin during a hyperglycemic crisis. Since the infection and other coexisting conditions may interact with each other and strongly modulate the outcome of IV insulin regimens, further research is still needed to optimize the IV insulin regimen in the hyperglycemic crisis with certain comorbid.

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**Competing interests:** Authors state no conflict of interest.

**Informed consent:** Informed consent was obtained from all individuals included in this study.

**Ethical approval:** Research involving human subjects complied with all relevant national regulations, institutional policies and is in accordance with the tenets of the Helsinki Declaration (as revised in 2013), and has been approved by the authors' institutional review board (079/KEH/2017).

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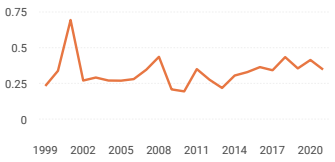


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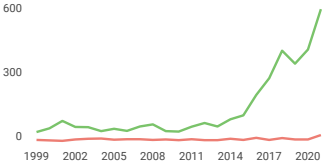


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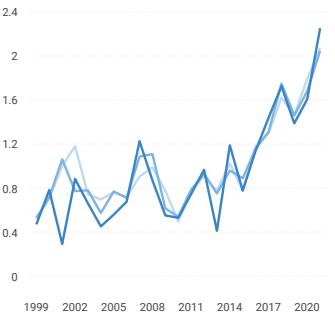


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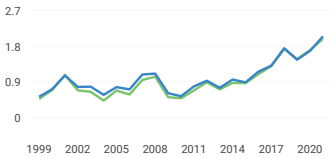


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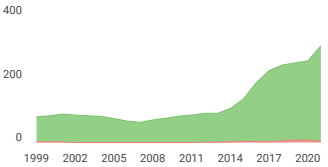


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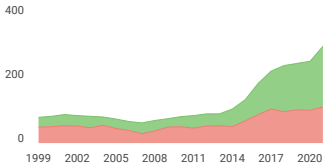



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