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Consensus document

In-hospital management of hyperglycemia

Tratamiento de la hiperglucemia en el hospital

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Relevance of the hyperglycemia during hospitalization

The individuals with diabetes constitute an out of proportion and increasing percentage of the hospitalized patients, although it is frequently infra-estimated.[1-7] Diabetic patients represent 30-40% of the patients who are seen in the hospital emergency services, 25% of the hospitalized, both in medical areas and surgical, and approximately 30% of the patients undergoing aortocoronary surgery. This is due to the increased prevalence of diabetes mellitus, the associated comorbidity and the indicated diagnostic and therapeutic procedures that need hospitalization. Moreover, diabetic patients remain in the hospital an average of 1-3 days more than the non-diabetic patients, and patients with hyperglycemia at entry will need more probably the use of the intensive care unit (ICU).

The recognition of the hyperglycemia impact in the morbimortality and costs of the hospitalized patients is also increasing.[7-11] At present, experimental data are available about the potential mechanisms and also observational and intervention clinical studies that support the fact that hyperglycemia, besides being a marker of seriousness, entails important adverse effects that have an influence on the prognosis, including the increase in mortality, in infection rates and in hospital stay.[7,12-15] Finally, some studies suggest that a more strict control of the glycemia in critical patients with or without diabetes might improve the prognosis.[16-20]

These results have replaced the concept that proposed to keep the hospitalized patient within "safe-considered" glycemia limits (150-250 mg/dL) for another more active approach whose objective is a more demanding control of the glycemia. Related to this hypothesis, during the last years, management of the hyperglycemia during hospitalization has achieved a special relevance and recommendations have been stated, suggesting that the glycemia target during hospital admission should be close to normoglycemia.[21-25] However, the rule in most of the centers, uses to be the low recognition of hyperglycemia and the poor management of hospitalized patients with diabetes or hyperglycemia.[26-30]

Thus, in 999 hospitalized individuals with diabetes diagnosis from 44 hos-

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pitals in the US, 60% had at least a glycemia of >250 mg/dL and between 18 and 38% showed glycemias of >200 mg/dL during 3 consecutive days.[30] In the study of Knecht et al.[27] most of the patients had hyperglycemias and approximately a third remained with mean glycemias of >200 mg/dL. On the contrary, only 11% showed ≥1 glycemia event <70 mg/dL. However, the most worrying fact is that in this study only in 34% of the patients the treatment was modified.[27] In the study of Wexler et al.[30] 16% of patients with T1D and 35% of patients with T2D previously treated with insulin received only an insulin treatment with corrective algorithms of rapid acting insulin (*sliding scales).*

The causes of deficient control are multiple and include previous bad control, difficulties in the treatment of hyperglycemia during hospitalization and lack of knowledge/familiarization about treatment with insulin and clinical inertia[29,31,32] (table 1). In this sense, it is well known that insulin requirements to keep glycemia within acceptable limits during hospitalization varies remarkably due to modifications of nutrient support (fasting or reduction of meals, intravenous (IV) glucose support, enteral or parenteral nutrition), release of contraregulatory hormones as response to stress, use of drugs with hyperglycemic effect and other factors. Hyperglycemia seems to play an important role as a safety measure in order to avoid hypoglycemias. During hospitalization, besides classic hypoglycemia risk factors, there are additional risk factors such as sudden reduction of corticoid doses, altered capacity of the patients to detect the symptoms, reduction of the oral intake, vomits, reduction or withdrawal of parenteral/enteral nutrition or IV glucose. Altered consciousness by anesthesia can also alter the typical hypoglycemic symptoms. Therefore, hypoglycemia, though infrequent, is an important concern reason in the hospitalized patient with diabetes and it is an important barrier in the optimization of glycemic control during hospitalization.[31,33] Clinical inertia, that leads to the non modification of treatment when the situation requires it, is specially emphasized with the use of rapid insulin algorithms without basal insulin. If prescribed at the patient's admission it is quite probable that it is kept during the whole hospital stay though the control might be deficient.[27,29,30] Finally, under use of the IV insulin infusion and, overall, overuse of rapid insulin algorithms alone are factors that mostly contribute to the deficient control of hyperglycemia during hospitalization.[24,34,35]

Table 1. Main causes of deficient glycemic control in the hospitalization

- Tolerance to hyperglycemia
  - As a safety measure in case of hypoglycemia
  - Clinical inertia
- Ignoring the patient's previous treatment
- The underuse of the intravenous insulin infusion pumps
- The overuse of the *sliding scales* or rapid insulin only guidelines

Hospital management of hyperglycemia

From the treatment point of view of the patients hospitalized with hyperglycemia, it remains useful to determine what should be done on the first day of hospitalization, management during hospitalization and planning of the hospital discharge (figure 1).

On the first day of hospitalization, the evaluation should be directed to detection of hyperglycemia, to establish its origin and the hospital context of the patient. A second fundamental aspect at these moments is to plan the treatment adequately, as it is quite probable that what has been prescribed is kept during the hospital stay, independently from the obtained glycemic control.[27,29,30] Hyperglycemia treatment and the patient's control level previous to the hospitalization are fundamental in order to plan the discharge treatment. All hospitalized diabetic patients should have at least a determination of the glycosylated hemoglobin (HbA_{1c}), if it is not available from the previous 2-3 months. Treatment during hospitalization is based on glucose monitoring. Adjustments or the change of prescribed treatment were made on the basis of glycemic monitoring and patient's clinical situation. It is also necessary in this phase to foresee the patient's educational needs and ensure the survival aspects. Finally, a treatment plan and adequate follow-up should be determined at discharge.

Objectives of the glycemic control in the hospitalized patient

Preliminary studies in critical patients showed that good glycemic control was translated into better results.[16,17,19,20] A study conducted in only one site in postoperative cardiac surgery patients,[18] found that the strict maintenance of the normoglycemia (glycemia between 70 and 110 mg/dL) reduced mortality. However, later studies were not able to reproduce these results and found that intensive treatment with insulin to achieve normoglycemia increases hypoglycemia risk, whose appear-

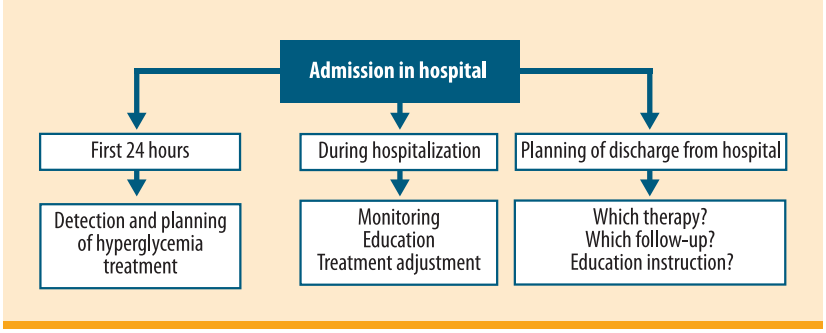

Figure 1. Scheme for the evaluation and management of hyperglycemia during hospitalization

ance constitutes a mortality independent prognosis factor.[37-41] In a clinical trial with a before-after design,[42] it has been found that the application of a protocol in critical patients addressed to keep glycemia below 140 mg/dL was associated to a reduction of mortality, morbidity and stay in the ICU without a relevant increase in hypoglycemia risk. Based on previous studies, new recommendations have been stated for management of in-hospital hyperglycemia, as those of the American College of Endocrinology.[22] These recommendations include objectives for the hyperglycemic patients with or without diabetes, both in critical condition and non-critical and have been incorporated to the Standards of Medical Care in Diabetes of the American Diabetes Association (table 2) [21]:

1. Patients in critical situations: glycemia should be closed to 110 mg/dL and generally <140 mg/dL. These patients will usually require IV insulin.
2. Patients in non-critical situations: should be closed to the following values, taking into account the clinical situation, as preprandial glycemia <130 mg/dL and postprandial glycemia <180-200 mg/dL.

The evidence to determine the objectives for non-critical patients is lower and is based on the results of epidemiological and physiological studies. Waiting for the data of prospective studies, recommendations suggest that glycemic targets during admission in non-critical patients should be similar as those proposed for the outpatients.

Table 2. Objectives for glycemia in hospitalization (Standards of Medical Care, American Diabetes Association 2009)[21]

Critical patient	Non critical patient
• As close as possible to 110 mg/dL and generally or 140mg/dL (A)	• There are no clear evidences (E)
• These patients require an intravenous insulin protocol which has proven to be efficient and safe when reaching the desired glucose range without increasing the risk of severe hypoglycemia (E)	• Basal glycemia or 130mg/D Land postprandial glycemia or 180-200mg/dL • Insulin is the preferred drug for treating hyperglycemia in most cases

A and E: degrees of evidence.

Two recent clinical trials in critical patients were stopped prematurely due to higher hypoglycemic risk with protocols of intensive insulin treatment to keep the normoglycemia.[38,39] However, this higher risk has not been observed in other treatment protocols of critical patients treated with insulin by IV continuous perfusion in which the glycemia values were monitored frequently.[43] Efficiency and safety of these protocols should, however, be proved in new clinical trials. Meanwhile, the prevailing opinion at present is to pursue the most conservative glycemic control targets until the results of these studies are available.[44] Either in critical and non-critical condition, in order to determine the targets, patient's situation and available tools have to be taken into account to select the treatment. In patients with high hypoglycemia risk or elderly people, low vital expectation, and in general when symptomatic relief is the main and only consideration in the hospitalized patient, objectives should be less strict. It is also advisable to start the protocol with less strict glycemic targets and then reduce them until reaching the recommended values.

Therapeutic options in the hospitalized diabetic patient

Treatment with oral agents

The role of the oral agents in the hospitalized diabetic patient is limited due to potential adverse effects, slow starting action and long duration that results in lack of flexibility to adapt to changing requirements during the day. Secretagogues (sulfonylureas, glinides) are a relative contraindication during hospitalization, especially in situations in which feeding cannot be ensured and in which insulin requirements might

vary drastically at different hours of the day, due to the hypoglycemia risk, especially with long-acting sulfonylureas.[45] Metformin has not an immediate effect and should be initiated at low and progressive doses in order to avoid gastrointestinal effects. On the other hand, metformin is frequently not recommended due to the possibility of developing a lactic acidosis. In the hospitalized patient, there are frequent situations that predispose to this complication due to tissular hypoxia (presence or risk of heart failure, chronic lung disease, hypoperfusion) and those that might interfere in the elimination of the lactic acid (presence or risk of renal and hepatic serious failure).[46,47] Glitazones are not useful either in the hospitalization due to the late starting effect (2-4 weeks), which obviously does not allow a short-term adjustment, necessary in the hospitalized patient. Moreover, weight gain, liquid retention and edema usually increase with these agents, and might induce or worsen heart failure. There is no information about the use of DDP-4 inhibitors and the GLP1 analogues during hospitalization, but due to their characteristics the efficacy will be probably limited, especially in patients without oral feeding.

Treatment with insulin

Therefore, oral agents are not useful for most patients. Consequently, the already mentioned glycemic control targets might only be reached with insulin treatment administered through IV route or subcutaneously (SC). At present, insulin is considered the most effective and the preferred option to treat hyperglycemia in hospitalized patients. Selection of the route for insulin administration will depend on the clinical situation of the patient and material availability.

Treatment with intravenous insulin

The situations in which treatment with IV insulin is indicated are diabetic ketoacidosis and hyperosmolar nonketotic syndrome, critical patients and other diseases or processes in which glycemic control is considered important for their evolution, perioperative period in major surgery, especially in heart surgery and organ transplant, and hyperglycemia exacerbated by treatment with high doses of glycocorticoids or parenteral nutrition. These situations have in common metabolic instability, independently if the patient is or not in an area of critical patients. Moreover, in most patients there is a tendency to sudden and important changes as regards to insulin requirements, which, together with the risk of developing tissular hypoperfusion, limits SC insulin treatment. Regular insulin by IV route, due to its rapid action and mean short-life (4-5 minutes), as well as the predictability of the hypoglycemiant effect, is the most recommendable route of insulin administration in these situations.

Although combination of glucose-insulin-potassium (GIK) is still being used, insulin infusion by means of an IV infusion pump is the most recommended system because is the most efficient, safe and easy to use for glycemic control. Rapid-acting insulin should be administered usually at a concentration of 1 U/1 mL of saline solution at 0.9%. Protocols are multiple and there are no head-to-head studies that compare them, but those who use dynamic scales for insulin administration according to the glycemic level are those that usually offer better results in terms of glycemic control and low frequency of hypoglycemias.[5,48-51] The principal factor that contributes to protocol safety is the frequency of glucose monitoring, but there are also other important factors as the use of relative low infusion rates in glycemic levels close to the euglycemia, to establish less strict objectives, at least initially, and to foresee situations of hypoglycemia or in which the physician should be informed. Other important aspects in order to establish a protocol in a certain center is to consider the characteristics of each hospital to adapt it, indicating the starting moment, as well as the amount of glucose and the initial insulin dose or algorithm, to allow adaptation to requirements of each patient according to patient's sensibility to insulin, including mechanisms to change the infusion rate in case of important glycemic changes.

Annex 1 depicts the protocol that was designed and established in the Hospital de Sant Pau of Barcelona, which is based on the Markovitz protocol and its modifications and later adpatations.[49] In order to assess efficacy and safety of the protocol, we have compared the results observed in the first 6 months with those obtained in a retrospective cohort 6 months before implementation of the protocol.[52,53] Mean glycemia during ICU stay (includes treatment period with IV and SC insulin), was clearly lower after the implementation of the protocol (mean [standard deviation] of 118 [16] mg/dL versus 143 [32] mg/dL) and the relative reduction of the glycemias >200 mg/dL was of 62.7% without a significative increase of the hypoglycemias (3.8 versus 7.3%). The protocol consists of 6 al-

gorithms or scales that consider the patient's sensibility level to the insulin and each algorithm is made up of a decision table that indicates insulin infusion speed according to the glycemic value. For safety, it is recommended to start by the algorithm 1 in most patients or by the algorithm 2 in patients in which high requirements are expected.

Insulin infusion discontinuation and transfer to a SC insulin treatment are as important as infusion starting. Mean half-life of IV insulin is 4-5 minutes, biological action is 20 minutes and after 30-60 minutes insulin levels are undetectable. Therefore, to keep adequate insulin values in plasma and avoid a possible hyperglycemic decompensation, it is essential to keep IV infusion at least up to 2 hours after having administered rapid-acting SC insulin (regular rapid-acting or insulin analogues) or up to 2-4 hours after the NPH, NPL, glargine or determir insulin.

Estimation of the initial dose of SC insulin is carried out based on the infusion rate of the last 4-8 hours. Although there are no conclusive data, it is usually recommended to start with 50-100% of the estimated dose, usually 75-80%.[23,43,54-56] In the estimation it should be taken into account that requirements may be modified in the following hours due to the likely evolution of underlying factors, both to reduce them as consequence of optimization of the glycemic control, improvement of disease or complication or reduction-discontinuation of catecholamines or steroids treatment, and to increase them in the event of infection or fever, catecholamines or steroids treatment, or enteral and parenteral nutrition.

Treatment with subcutaneous insulin during hospitalization

In most hospitalized patients who do not receive a treatment with IV insulin, treatment with SC insulin is the best therapeutic option in case a pharmacology treatment of hyperglycemia is required. This treatment allows achieving a good glycemic control in most hospitalized diabetic patients. This is possible if insulin physiological secretion is taken into account, as well as the pharmacokinetic characteristics of exogenous insulin and the clinical condition of the patient in order to design an insulin algorithm. However, what is not clear enough is when to start treatment with insulin in patients who have not been treated previously with insulin and which is the insulin administration algorithm to be used.

In order to start insulin treatment, we should take mainly into account the level of glycemia, type of diabetes and its previous treatment.[34,43,50,55-57]

In patients treated previous only with a diet, if glycemias are <150 mg/dL, it can only be implemented the corrective algorithms. Later, if corrective doses are frequent or glycemias are >150 mg/dL a scheduled insulin algorithms should be established. If the glycemia at admission is between 150-200 mg/dL, start insulin therapy with 0.3 U/kg/day and if it is >200 mg/dL with 0.4 U/kg/day. In patients treated previously with diet and oral agents, if glycemias are <150 mg/dL we can only implement the corrective algorithms (patients treated with only one oral agent and low stress condition) or scheduled insulin algorithms (patients treated with two or more oral agents and an important stress condition or extended admission). If the glycemias at admission are >150 mg/dL, start insulin therapy with 0.4 U/kg/day if the glycemia at admission is between 150-200 mg/dL, or with 0.5 U/kg/day if the glycemia at admission is >200 mg/dL. In the patients treated with night insulin monodoses with or without oral agents, suppression of the oral agents suggest a suppression of an important proportion of insulin requirements, which we have to take into account for the estimation of the total daily dose. The initial dose will be 0.4 U/kg/day if the glycemia at admission is <150 mg/dL, 0.5 U/kg/dL if the glycemia at admission is between 150-200 mg/dL and 0.6 U/kg/day if the glycemia at admission is >200 mg/dL. Patients treated previously with complete insulinization programs (2 doses or multiple doses) require insulin since admission and for the estimation of insulin doses the patients' previous insulin requirements should be taken into account and consider the clinical conditions that might modify them during hospitalization. Finally, in patients treated previously with IV insulin infusion, the best option is to estimate insulin doses on the basis of the requirements with infusion during the last 4-8 hours.

For the selection of the insulin algorithm, similar to what happens for the diabetic outpatient treatment; we should consider the 3 components of the insulin physiological secretion. The physiological insulin production by the pancreas includes a basal and a prandial component. Basal insulin is necessary in the fasting situation and prandial insulin is needed after meals (figure 2). The basal component suggests a more or less constant

secretion that is necessary to suppress glucose production from different energetic substrates during the periods without nutrients support. That represents the 50% of the requirements approximately. The prandial component is necessary to favour utilization of nutrients after intake, avoiding postprandial hyperglycemia. It is frequent that one or more conditions are superimposed on this scenario during the hospitalization (disease, treatment with corticoids, etc.) that might increase insulin requirements (correction component).[5,43]

Combinations of different available preparations of insulin (table 3 and figure 3) allow designing multiple options for its administration during hospitalization, which enable us, in a greater or lesser extent, to adjust ourselves the basal, prandial and corrective requirements.

Only SC rapid insulin **(sliding scales)**. They include only administration of rapid-acting insulin before the meals or each 4-6 hours (sliding scales). These are the administration algorithms still more often used, although its inefficiency is widely proven.[24,34-36,58,59] In many centers they constitute the standard algorithm for management of T2D during hospitalization and are used up to 75% of patients. To this fact has contributed the transmission of this algorithm among generations as an easy, safe and frequently effective, and the more complex and non-standardized guidelines used by endocrinologists, which have elicited low acceptance by the rest of the physicians and absence of clear evidenced-based recommendations that can be used even by health personnel non expert in diabetes.

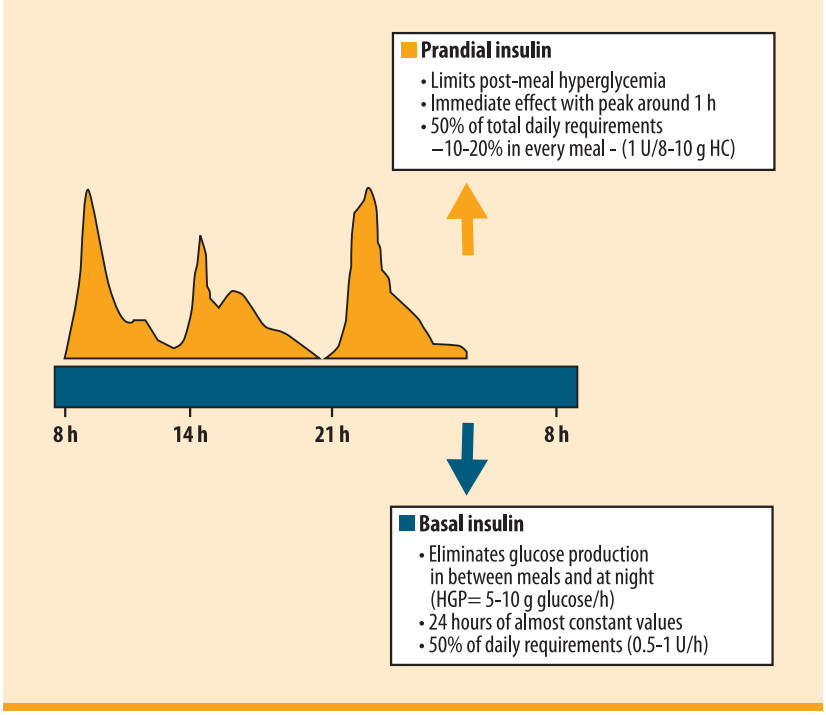

Figure 2. Physiological secretion of insulin HGP: hepatic glucose production; HC: carbohydrates

The inefficiency of these algorithms is related with its "reactive" approach, as it treats the existing hyperglycemia but it does not prevent it and does not consider the different components of physiological secretion of insulin and, therefore, the physiological replacement. These algorithms usually do not administer insulin to the patient below a specific glycemic value, above which increasing doses of rapid-acting insulin are recommended. They do not cover basal insulin needs. Then, especially in the insulinopenic patients they facilitate the development of hypo and hyperglycemia events. These algorithms might be only considered in some cases in which the diabetes control is achieved with nutritional recommendations, as an intermittent correction for hyperglycemia.

Two doses of NPH/NPL insulin or premixed NPH/NPL insulin with rapid-acting insulin analogues (figure 4).

These strategies are the most used in outpatients with T2D and permit an acceptable control in many patients, when a certain endogenous insulin production is still present, but not when insulin endogenous production is minimum or inexistent, regardless of the presence of insulin resistance. The advantages of these algorithms vs. basal-bolus therapy are based in the lower number of injections and required capillary glycemic measurements and a lower need to self-adjustment by patient. Therefore, they are more acceptable for patients and health professionals.

However, considering the action profile of NPH and NPL insulins, these algorithms are associated with low

Table 3. Characteristics of the main types of insulin

Insulin blends	Action start (h)	Peak (h)	Duration of the action (h)
Human insulin			
Regular (Actrapids®, Humulinas®)	0,5-1	2-4	6-8
NPH (Insulatard NPH Plexpens®, Humulina NPH®)	1-3	4-12	10-20
Analogs			
Glulisine (Apidra®)	10-15 min	1	4-5
Lispro (Humalog pen®)	10-15 min	1	4-5
Aspart (Novorapid®)	10-15 min	1	4-5
NPL (Humalog NPL®)	1-3	4-12	10-16
Glargine (Lantus®)	1-2	No peak	≤24
Detemir (Levemir®)	1-2	No peak	12-18
Fixed blends			
50% NPL/50% lispro (Humalog Mix50®)	5-15 min	Dual	10-16
75% NPL/25% lispro (Humalog Mix25®)	5-15 min	Dual	10-16
70% NPH/30% aspart (Novomix30®)	5-15 min	Dual	10-16
70% NPH/30% regular (Mix tard 30®)	30-60 min	Dual	10-16

The action time of any insulin may vary in different people or different times and doses in the same person. For this reason, these periods can only be deemed as general recommendations.

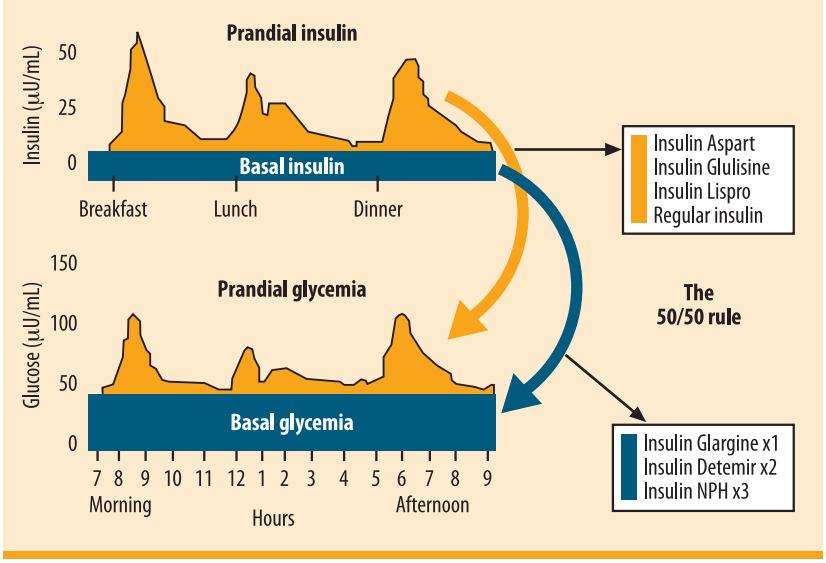

Figure 3. Selection of insulin preparations in the basal-bolus guidelines to cover the insulin requirements in a fast state (basal) and in a prandial state (bolus)

insulin levels before breakfast and dinner, and hyperinsulinemia before lunch and during dawn, which entails an increased hypoglycemia risk at dawn and before lunch and basal hyperglycemia before dinner. Likewise, it does not allow dose preprandial adjustment according to glycemia and quantity of carbohydrates to be ingested, as the NPH and NPL insulins cover basal requirements and, at least in part, prandial needs. A fixed distribution of carbohydrates according to the insulinemia profile is required (in general, 5 intakes with snacks in the morning and before going to bed), including also a fixed amount of carbohydrates to avoid either hypoglycemia or hyperglycemia. If we take into account that prandial requirements in hospitalized patients are frequently unforeseeable and changing, management with two doses of NPH/NPL insulin or fixed mixtures of rapid-acting NPH/NPL or analogues may be more problematic. Moreover, in situations when fasting is required it is necessary to administer IV glucose and insulin algorithms for dose adjustments are more complex. Possibly, all these factors have contributed to the historical failure of standardization of these algorithms for hyperglycemia management during hospitalization and to replace more common used sliding scale algorithms.

The options for the patients treated before hospitalization with guidelines based in the administration of 2 doses of NPH/NPL is to continue with such as guideline, adjusting the doses or using a basal-bolus guideline. It is believed that this option is the most adequate one in many patients due to the above-mentioned reasons. One of the barriers for the use of the basal-bolus guidelines in

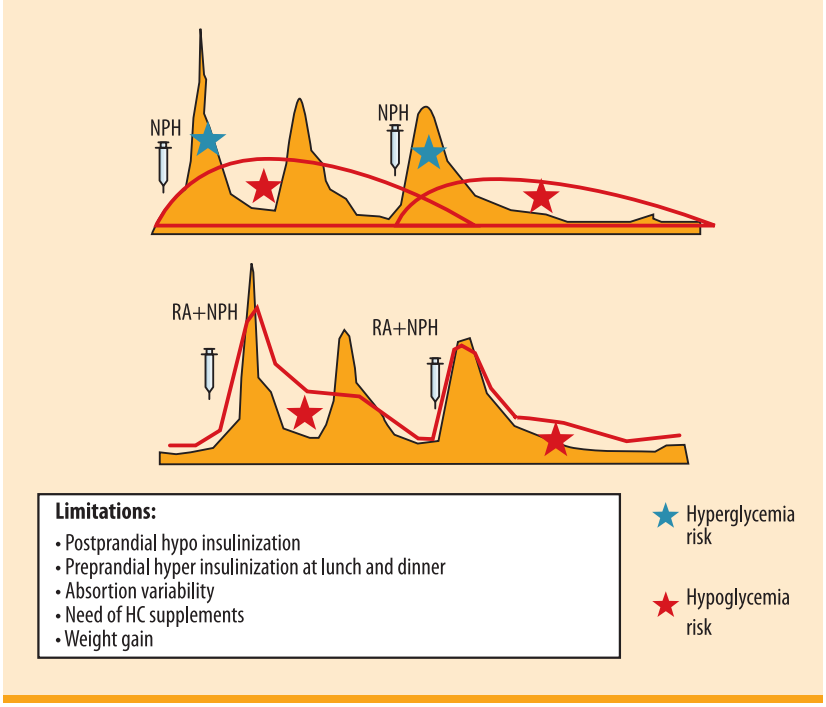

Figure 4. Guidelines with 2 doses of insulin NPH/NPL or fixed mixtures of NPH/NPL with rapid-acting insulin or analogues of rapid-acting (RA). Insulinemia profiles (red), compared to the physiological (grey), limitations and risks. HC: carbohydrates

these patients is the transfer to this discharge guideline. However, the difficulty is more theoretical as they are patients who manage the insulin and, knowing the guideline and the control level (HbA_{1c}) previous to the hospitalization and the requirements during hospitalization, the adjustments of the usual guideline of the patient at discharge can be performed without relevant problems.

Basal-bolus guideline (figure 5)
These are the SC administration guidelines of insulin that produce the physiological secretion of the insulin more precisely, as they allow differentiating the basal and prandial requirements clearly.

In these guidelines, the basal insulin constitutes the secretion of insulin in fasting conditions and the nutritional insulin would be the insulin that is necessary to cover any nutrient that the patient is receiving as IV glucose, IV or enteral feeding, or the consumed food during the meals. If the patient is eating and is not receiving any other nutrient, the nutritional insulin will be the same as the prandial insulin. Besides the basal and nutritional requirements of insulin, the patients often require complementary insulin doses or corrective doses in order to treat the unexpected hyperglycemias. Therefore, the SC insulin can be administered as scheduled doses (basal insulin plus nutritional insulin) and corrective complementary doses in order to cover any hyperglycemia over the control objectives (table 4). This correction algorithm should not be mixed up with the sliding scale guideline of regular insulin doses.

For the distribution of the scheduled doses, though it will be influenced by other factors (stress level, medications, characteristics of the patient, etc.); the main factor that has to be considered is diet. If the patient is fasting with glucose serum, enteral or parenteral nutrition, the necessary basal insulin supposes to be 100% of the scheduled dose, while if the patient is eating, the basal insulin dose will be of 50% of the scheduled dose and the other 50% as prandial insulin. The additional correction doses will be administered as rapid-acting insulin (regular or rapid-acting analogues) in addition to the scheduled guideline to correct the preprandial hyperglycemia, in the case of the patients with oral diet, or each 4-6 hours in the case of patients with glucose serum or artificial nutrition. The correction doses are determined according to the glycemia and the individual sensitivity to the insulin of each patient assessed by the daily insulin requirements or the body weight (table 4).

The replacement of the insulin basal requirements (figure 3) can be performed through slow-acting insulin analogues (insulin glargine once daily, insulin detemir in 2 doses) or NPH or NPL insulin in order to mitigate the peaks. In order to cover the prandial requirements (figure 3), we have rapid-acting insulin and ultrarapid action analogues (insulin aspart, glulisine and lispro), which have a quicker action profile and less duration, which fits better to the prandial period.

In the outpatients, the basal-bolus insulin guidelines are more efficient and constitute the option guideline for patients with T1D.[21] During hospitalization, the scant available data to present goes in this way.[34,60]

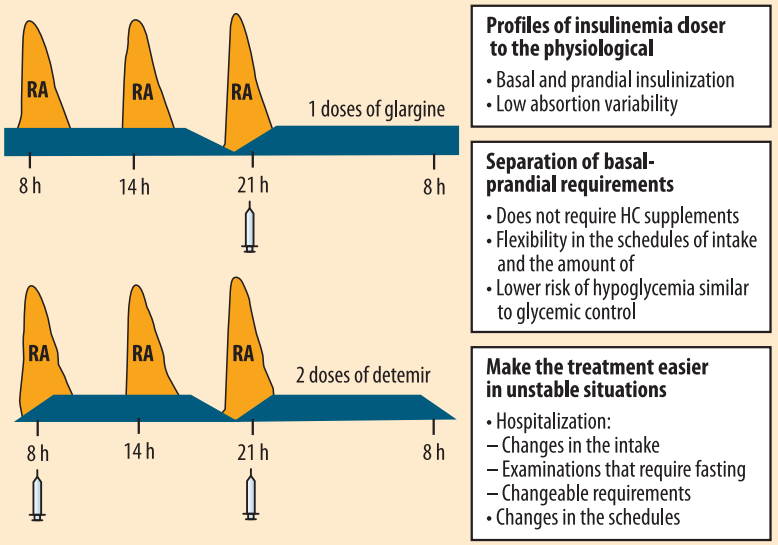

Figure 5. Characteristics and advantages of the guidelines of insulin that distinguish the basal and prandial (basal-bolus guidelines)

Table 4. Supplementary insulin dose (rapid-acting regular or analogical) in order to correct the hyperglycemia, according to the sensitivity expected from the insulin requirements or the body weight

Glycemia pre-intake (mg/dL)	Additional insulin doses (U)			
	<40 U/day or <60 kg	40-80 U/day or <60-90 kg	>80 U/day or >90 kg	Individualized
<80	–1	–1	–2	
<80-129	0	0	0	
130-149	0	1	1	
150-199	1	1	2	
200-249	2	3	4	
250-299	3	5	7	
300-349	4	7	10	
>349	5	8	12	

In the RABBIT 2 study, the use of a basal-bolus guideline achieved a better glycemic control than the sliding scale or guidelines of rapid insulin/6 hours in patients without previous insulin treatment.[36] In this study, the mean glycemia during hospitalization was lower (media [DE] of 166 [32] versus 193 [54] mg/dL) and the percentage of patients who reached the glycemia target <140 mg/dL was higher (66 versus 38%) with the bolus-basal guideline, without increasing the incidence of hypoglycemia. Moreover, during hospitalization these guidelines offer additional advantages such as: a) not to take carbohydrates supplements between the principal meals in order to avoid the hypoglycemia; b) the adjustment algorithms of the doses are simpler than for the guidelines with two doses of intermediate insulin, facilitating the standardization, and c) overall, the flexibility to get adapted to the changing situation of the hospitalized patients as the changes of the intake hour, the reduction of the intake due to loss of appetite and fasting due to explorations or minor surgery, through the adaptation of the prandial insulin administration hour, its reduction or omission, respectively, without the modification of the basal insulin or the IV glucose support.

Annex 2, sums up the adjustments of the basal-bolus insulin guideline in minor surgery/situations that require a brief fast and in the secondary hyperglycemia to glucocorticoids. The flexibility for the adaptation of the patients who require one or more components of the guideline (table 5), the frequently changing situation of the hospitalized patients and the easy standardization of the diet in 3 intakes and the doses adjustments (table 6) should facilitate the development of standardized protocols that might allow improving hyperglycemia control during hospitalization.

Annex 3 depicts a model of standardized sheet for the order of SC insulin, based in the American Association of Clinical Endocrinologists.

Planning of the discharge treatment

The discharge moment is usually one of the most conflictive situations in the hospitalized diabetic patients due to reasons not related to the glycemic control. Common aspects to other patients contribute to this situation,

as the reduction of the hospital stay, the complexity of the patients, the super-specialization and the lack of communication/coordination with the primary care teams,[61] but also more specific elements as the lack of information about the previous management of the diabetes (treatment, self-management capacity and glycemic control level), the lack of prevision of the new needs of the patient in relation to the self-management derived from the treatment that will be implemented and the lack of follow-up planning after discharge.

In order to plan the hyperglycemia treatment after discharge, besides the treatment before hospitalization, it is important to record the previous glycemic control level in the medical history and the HbA_{1c} determination with the pre-surgery or when the patient is admitted, if there is no previous determination available. The HbA_{1c}, besides helping to typify the unknown hyperglycemia,[62] it facilitates the planning of the discharge treatment in patients with previous diabetes.

In patients with an adequate previous control (HbA_{1c} <7%), in the absence of contraindications, the pre-hospitalization treatment should be implemented at discharge, though depending on the patient's clinical condition, it might be necessary to implement a bridge guideline.

In patients with a deficient control (overall if the HbA_{1c} is >8%) with a diet and/or oral agents, and when there is any contraindication to the previous pharmacology treatment, for the treatment selection at discharge, we should follow the recommended scheme for the outpatient follow-up.

Table 5. Selecting and adapting insulin guidelines according to the patient's clinical state

Guidelines	When to use	Example
Only correcting	Intermittent moderate hyperglycemia (150 mg/dL)	Aspart/glulisine/lispro
Basal + correcting	Patients who do not take food orally	Glargine/detemir/ NPH/NPL + aspart/ glulisine/lispro
Basal + prandial + correcting	Stable patients who take food orally	Glargine/detemir/ NPH/NPL + aspart/ glulisine/lispro
Continuous perfusion IV	Critical patient/severe hyperglycemia	Regular insulin IV

IV: intravenously.

Table 6. Making adjustments in basal and prandial insulin doses based on glycemic profiles

Hyperglycemia

- Basal (empty stomach) without nocturnal hypoglycemia:
  – Increase 20% of basal dose
- Preprandial without hypoglycemia since previous meal:
  – Lunch: increase (10-20%) breakfast prandial dose
  – Dinner: increase (10-20%) lunch prandial dose 2 hours after dinner or, before sleeping: increase (10-20%) dinner prandial dose

Hypoglycemia or low blood glucose

- Nocturnal or basal: reduce 20% of basal dose
- During the morning: reduce (10-20%) breakfast prandial dose
- During the afternoon: reduce (10-20%) of lunch prandial dose
- Before dinner or going to bed: reduce (10-20%) of dinner prandial dose

Thus, following the algorithm to select the therapeutical measures proposed by the American Diabetes Association (ADA),[63] and the European Association for the Study for Diabetes (EASD),[64] depending on the previous treatment, we can increase the doses of the drugs that the patient received, add a second oral drug or insulin in night monodoses.

In some patients with contraindication to the oral agents or with a previous deficient control and characteristics that suggest insulinopenia as diabetes of long evolution, slimness and/or spontaneous loss of weight, and predominance of the night hyperglycemia regarding the basal one, the complete insulinization with 2 doses or with multiple doses, depending on the patient's characteristics should be set out.

In patients with new diagnosis, if the characteristics suggest that it is a T1D, the discharge treatment will be insulin in a basal-bolus program of multiple doses with prolonged action and rapid-acting analogues.

The situation is less complex in patients previously treated with insulin, as they are patients who manage the insulin and, knowing the guideline and the control level (HbA_{1c}) previous to hospitalization and the requirements during hospitalization, the adjustments of the previous usual guideline of the patient can be performed without problems. In some patients with T1D or T2D previously treated with 2 doses and with deficient control, this might be the opportunity to transfer them to a basal-bolus guideline, so at discharge it will be necessary only to adjust the doses used during hospitalization.

At discharge, the patient or the family should have received the "survival" information about the medication, the glycemia monitoring and the hypoglycemia management, as well as the follow-up planning after discharge. ■

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Annex 1. The insulin intravenous infusion algorithms designed and evaluated at the Hospital de la Santa Creu i Sant Pau of Barcelona for the critical patient[52,53]

	Algorithm 1	Algorithm 2	Algorithm 3	Algorithm 4	Algorithm 5	Algorithm 6	Algorithm 7
Capillary blood glycemia (mg/dL)	**Rhythm infusion (U/h)**	**Rhythm infusion (U/h)**	**Rhythm infusion (U/h)**	**Rhythm infusion (U/h)**	**Rhythm infusion (U/h)**	**Rhythm infusion (U/h)**	**Rhythm infusion (U/h)**
<60	Hypoglycemia Protocol	Hypoglycemia Protocol	Hypoglycemia Protocol	Hypoglycemia Protocol	Hypoglycemia Protocol	Hypoglycemia Protocol	Hypoglycemia Protocol
61-80	0	0	0.5	0.5	1	1.5	
81-100	0	0.5	1	1.5	2	3	
101-119	0.5	1	2	3	4	5	
120-149	1	1.5	3	4	6	8	
150-179	1.5	2	4	6	9	12	
180-209	2	3	5	8	12	16	
210-239	3	4	6	10	16	22	
240-269	4	5	8	12	20	28	
270-299	5	6	10	16	24	36	
300-349	6	7	12	20	30	44	
350-400	7	9	14	24	36	54	
>401	8	12	16	28	42	64	

a. General recommendations

- Glycemia targets: 80-120 mg/dL
- Standard solution (50 U regular insulin in 59 cc of physiological serum: 1 U/mL)
- Adequate glucose support: glucose serum at 5% at 100 mL/h speed or equivalent (glucose serum at 10%, enteral nutrition, parenteral nutrition)
- Monitoring; capillary glycemia hour

b. Start

- Any critical patient with known diabetes or hyperglycemia >120 mg/dL
- Start by the algorithm 1 in most of the patients, or algorithm 2 in case of previous insulin requirements >80 U/day, no heart or heart major surgery, organ transplant, treatment with glucocorticoids and parenteral nutrition

c. Algorithm change

- At higher: glycemia >targets during 2 hours and change <50 mg in 1 hour
- At lower: glycemias <80 mg during 2 hours
- The insulin requirements usually reduce, in case of optimization of the glycemic control and improvement of the base process, or increase in case of infection-fever, use of catecholamines or steroids, enteral and parenteral nutrition
- If oral intake: change the higher algorithm during the 4 hours after intake

d. Treatment of the hypoglycemias

- Discontinuation of the insulin infusion
- Administration of intravenous glucose (25-50 mL of glucose serum at 50%) and repeat/10-20 minutes if glycemia <60 mg/dL
- Restore the insulin infusion with the lower algorithm

e. Inform the physician if:

- Change of glycemia >100 mg/dL in 1 hour
- 2 continuous glycemias >350 mg/dL
- Unsolved hypoglycemia in 20 minutes after the administration of intravenous glucose and suppression of the insulin infusion

Annex 2. Adjustments of the basal-bolus insulin guideline in minor surgery and treatment with corticoids.

a. In minor surgery

Surgery during the morning (before 12 am):

- Usual dose of insulin during the previous night
- Night fasting
- After 8-9 hours:
  - Glucose serum at 5% 100 mL/h (optional if glycemia >100 mg/dL)
  - Usual morning dose of basal insulin (glargine or detemir)
  - Do not administer bolus
  - Corrective insulin guideline with IRI or RA/4 h, according to the TDID
- Post surgery:
  - Discontinuation of glucose serum at 5% when the oral route is tolerated
  - Keep the corrective insulin guideline until discharge (outpatient surgery) or restart of the usual guideline (hospitalization)
- At discharge (outpatient surgery) or at the first intake (hospitalization): restart usual treatment

Surgery at last hour of the morning (after 12 am) or at the afternoon:

- Pre and intra-surgery:
  - Usual doses of insulin during the previous night
  - Take breakfast and usual insulin dose (basal and bolus), later fasting
  - Start 1 h or more before the surgery: glucose serum at 5% 100 mL/h
- Corrective insulin guideline with RI/RA/4 h, according to TDID
- Post-surgery:
  - Discontinue glucose serum at 5% when the oral administration is tolerated
  - Keep the corrective insulin guideline until discharge (outpatient surgery) or restart of the usual guideline (hospitalization)
  - At discharge (outpatient surgery) or at the first intake (hospitalization): restart usual treatment

b. During the treatment with corticoids of intermediate action in morning monodoses

Start treatment with corticoids:

- Keep the basal doses
- Increase the pre-intake insulin dose (bolus):
  - Breakfast: +20%
  - Lunch: +30%
  - Dinner: +20%
- Corrective insulin guideline with RI/RA, according to TDID

Reduction of the corticoid doses:

- Reduction of pre-intake insulin dose (bolus):
  - Breakfast: –20%
  - Lunch: –30%
  - Dinner: –20%

Withdrawal of treatment with corticoids:

- Acceptable control: restore the previous guideline
- Bad control: adjust previous guideline

RA: rapid-acting insulin analogue; TDID: total daily insulin dose; RI: regular insulin.

Annex 3. Example of standardized sheet of subcutaneous insulin

Diet ( ): breakfast (HC) _____ lunch (HC): _____ dinner (HC): _____ others: _____

Monitoring glycemia

☐ Before meals and before going to sleep ☐ 2h post ingestion ☐ dawn (4.00 h)

Objectives of the glycemic control

- Basal and preprandial ☐ 90-130 mg/dL ☐ _____
- Postprandial ☐ <180 mg/dL ☐ _____

Insulin	Breakfast (U)	Lunch (U)	Dinner (U)	Bed time (U)
Basal				
Glargine				
Detemir				
NPH				
Prandial				
Aspart				(1)
Glulisine				(1)
Lispro				(1)
Regular				(1)
Correction (2)				
Glulisine				
Lispro				
Aspart				
Regular				

1: if patient has taken HC before sleeping; 2: given to correct preprandial hyperglycemia according to correction algorithms (<40 U/day, 40-80 U/day and >80 U/day).

Hypoglycemia situation (glycemia <60 mg/dL or clinical)

- The patient can ingest: 10-15 g of HC (½-¾ glass with juice, 1 glass with milk, 1 sugar envelope, etc.)
- The patient cannot ingest. 25 mL of glucose serum at 50% through intravenous route (option intravenous route) or subcutaneous glucagon (1 mg) or im (option in absence of intravenous route)
- Glycemia control after 10-15 minutes and repeat while glycemia <80 mg/dL

General recommendations:

- The basal insulin should be administered notwithstanding if the patient eats. The prandial insulin requires support according to the intake (no intake, no prandial insulin, but the correction dose yes)
- In the absence of intake and support of glucose serum or artificial nutrition: all the requirements as basal insulin or intravenous infusion (option especially in T1D and parenteral nutrition)
- The patients with intermediate action glucocorticoids (e.g. prednisone) during the morning have very high insulin requirements in the lunch and dinner

Glycemia pre-intake (mg/dL)	Additional insulin dose to correct hyperglycemia (U)			
	<40 U/day –1	40-80 U/day –1	>80 U/day –2	Individualized
<80	0	0	0	
<80-129	0	1	1	
130-149	1	1	2	
150-199	2	3	4	
200-249	3	5	7	
250-299	4	7	10	
300-349	5	8	12	

HC: carbohydrates.