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Practice Guidelines

Treatment of hospitalized patient with hyperglycemia: An EFIM critically appraised and adapted guideline

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ABSTRACT

Background: Over the past decade, diabetes mellitus (DM) has emerged as a growing epidemic, with a direct link to an increased risk of hospitalization and a strong effect of glycemic control on clinical outcomes. The aim of this document was to critically appraise and adapt existing clinical practice guidelines (CPGs) to provide specific recommendations for the management of hyperglycemia in hospitalized adults with and without previously known DM, in an attempt to provide a practical tool to reduce the risk of major in-hospital complications.

Methods: The first step of the adaptation process was to identify unsolved clinical questions (PICOs) in hospitalized persons with hyperglycemia. This was followed by a critical appraisal of updated existing CPGs and the selection of recommendations that were most applicable to specific clinical situations.

Results: From the four updated high-quality evidence-based CPGs, 75 recommendations were selected, focusing on five common clinical scenarios in real-world practice: 1) glycemic targets; 2) persons with comorbidities; 3) elderly adults with low consciousness or dementia with irregular feeding or parenteral/enteral nutrition; 4) special hyperglycemic scenarios (stress hyperglycemia, corticosteroid treatment, fasting); and 5) glucose-lowering therapy at discharge. Of the 75 selected recommendations (59 strong and 16 weak), 37 were based on high-quality evidence, 8 on moderate-quality evidence, and 17 on low-quality evidence, while 13 were based on consensus (best practice statements). The recommendations apply to adults who are hospitalized or discharged from the hospital.

Conclusion: Using a systematic methodology, this guideline provides an updated and ease-to-use tool for the management of hospitalized adults with hyperglycemia.

1. Background

Over the past decade, diabetes mellitus (DM) has emerged as a growing epidemic with an estimated global prevalence of 10.5 % (537 million people) in 2021, according to the International Diabetes Federation [1]. It is projected that the prevalence will reach 12.2 % (783 million people) over the next 20 years [1]. Of note, DM seems to be significantly more common in urban than in rural areas, and in high-income than in low-income countries [1]. In addition to the increasing prevalence, another public health concerns that most cases of DM remain undiagnosed until the person develops diabetic complications. In 2021, it was estimated that 44.7 % of adults with DM were unaware of their condition, particularly in Africa, Western Pacific, and Southeast Asia [2]. It has also been estimated that by 2050, almost half of the world's countries and territories (89 of 204, 43.6 %) will have an age-standardized rate of DM greater than 10 % due to an increase in the prevalence of obesity, which is recognized as a driver of DM, particularly type 2 DM (T2DM) [3]. As DM becomes more prevalent, morbidity and mortality rates are expected to increase significantly. DM is estimated to contribute to 11.3 % of all deaths worldwide, half of which occur in adults younger than 60 years [4].

DM is directly and strongly associated with an increased risk of hospitalization, with the level of glycemic control playing a critical role in clinical outcomes. Adults with established DM and glycated hemoglobin A_{1c} (HbA_{1c}) levels of 7.0 % or greater were shown to have a 3.1-fold higher hospitalization rate than those without DM and a 1.5-fold higher hospitalization rate than those with known DM but with adequate glycemic control [5]. In addition, persons with undiagnosed DM have a 1.6-fold higher hospitalization rate compared with adults without DM at baseline [5]. Cardiovascular disease, particularly coronary artery disease and heart failure, is the leading cause of hospitalization in adults with DM [5]. Infections are another significant concern in this population, as they increase the risk of hospitalization. Mortality due to infection may be higher in adults with type 1 DM (T1DM) than in those with T2DM [6]. While DM and related hospitalizations represent a considerable emotional burden for persons with diabetes and their families, they also significantly increase health care costs, which are even higher in the presence of established diabetic complications or comorbidities [7].

The management of hyperglycemia in hospitalized persons with previously known or newly diagnosed DM or with stress hyperglycemia is challenging, with insulin remaining the main treatment option in most

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cases [8]. Despite significant advances in the treatment of DM in recent years, similar progress has not been observed in the hospital setting, where the use of most oral antidiabetic drugs is limited only to specific cases [9]. However, with the development of new classes of antidiabetic drugs and the availability of different combinations that can be tailored to individual person's needs [10], it seems that specific recommendations are necessary for hospitalized adults with DM, including those previously undiagnosed or those who develop stress hyperglycemia.

The Hyperglycemia Task Force (HG-TF) was appointed by the Critical Appraisal of Guidelines in Internal Medicine Working Group of the European Federation of Internal Medicine (EFIM) with the aim to review and critically appraise the most relevant and up-to-date guidelines to provide clear and specific recommendations for the management of hospitalized adults with or without previously known DM. These efforts are aimed to elaborate an ease-to-use tool to reduce the length of hospital stay and minimize the risk of in-hospital death, major complications, and rehospitalization.

2. Methods

We followed the methodology developed by the EFIM Clinical Practice Guidelines Appraisal Working Group (CPG-WG) [11]. The EFIM CPG-WG appointed the chairperson (IML) and 14 members (OAU, IR, JS, SB, JB, RGH, BI, JCG, JW, WL, LMPB, DP, DD, and TD) of the HG-TF according to the previously defined structure.

2.1. Definition of the clinical questions

To identify potential gaps in clinical practice regarding the management of hyperglycemia in the internal medicine department and to select the clinical PICO (Population, Intervention, Comparison and Outcomes) question to be included in the guidelines, a two-step process was used.

First, an open-ended survey was distributed to internists in Spain asking about the most difficult challenges in the in-hospital management of hyperglycemia. Based on responses from 64 physicians, four main areas of challenge were identified:1) hyperglycemia treatment in adults with and without diagnosed DM; 2) management of drug interactions during hyperglycemia treatment; 3) coping with comorbidities in the treatment of hospitalized persons with hyperglycemia; and 4) clinical decisions before discharge. Within these areas, 12 specific questions were formulated to provide a more detailed description.

In the second step, a detailed questionnaire containing the 12 questions within the four main areas was distributed via e-mail to 179 internists around Europe, who ranked the most clinically relevant issues in the questionnaire. **(Document available at request)**.

Finally, five PICOs were selected through an internal consensus process based on the results of the questionnaire and the clinical relevance of potential PICOs to daily practice (see Table 1).

2.2. Searching and screening for eligible guidelines to be used for adaptation

To identify relevant clinical practice guidelines (CPGs) related to the topic, various sources were searched, including databases and websites such as PubMed, SCOPUS, Epistemonikos, Trip medical database, NICE, SIGN, GUIASALUD.ES, AHRQ, Danish Health Authority, Magicapp, CMAJ, ADA, AACE, and GIN. The following keywords were used: inpatient, hyperglycemia, management, treatment, diabetes, and internal medicine. In addition, filters were applied such as the last 5 years, English language, and CPG. The final date of the search was February 5, 2023.

After reviewing the titles and abstracts, the full texts were selected for assessment (see Fig. 1). Subsequently, the quality of CPGs included after full-text assessment was critically appraised.

2.3. CPGs: quality assessment and selection for adaptation

The eight eligible guidelines were assessed according to the EFIM methodology [11]. The quality of the included CPGs was assessed independently by three members of the HG-TF (IML, JW, WL), using the AGREE-II scores for Domain 1 (Scope and Purpose) and Domain 3 (Rigor of Development) [12]. A CPG was included if: a) the mean score for each item was t least 3 (i.e., at least 9 in Domain 1 and at least 24 in Domain 3); b) at least 50 % of the maximum possible score for each of these two domains was reached. Following this assessment, the better CPGs were chosen to address the selected PICOs. For the CPGs selection assessment score data, **see Supplementary File** #1.

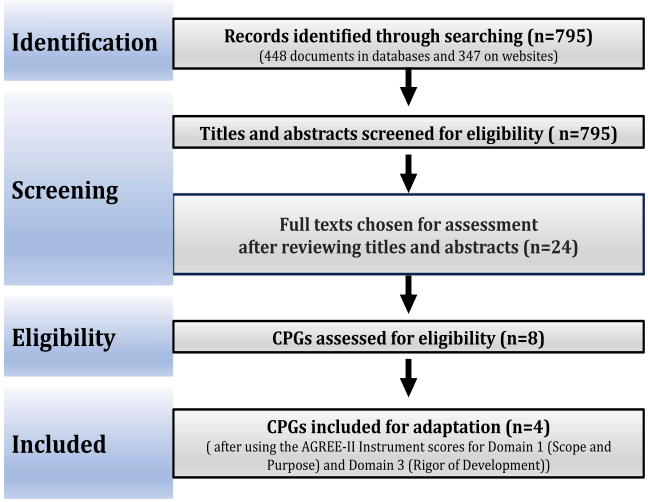

Fig. 1. Flow chart of the clinical practice guidelines (CPGs) selection process, following the PRISMA statement.

Table 1
Clinical questions selected for review.

PICO #1: What are the targets for glucose control for hospitalized persons with T2DM?
PICO #2: In which adults with DM (including those with comorbidities such as heart failure, chronic kidney disease, frailty) should non-insulin agents (GLP-1RA, SGLT2i, DPP4i, metformin) not be used in the hospital?
PICO #3: How to treat hyperglycemia in persons with low consciousness or dementia with irregular feeding or parenteral/enteral nutrition?
PICO #4: How to manage special hyperglycemic scenarios:
a) Stress hyperglycemia;
b) Hyperglycemia related to glucocorticosteroid treatment;
c) Fasting before surgery or diagnostic testing?
PICO #5: Hypoglycemic therapy to prepare for discharge:
a) Medications (oral vs parenteral treatments; insulin vs non-insulin);
b) Insulin dose titration at discharge;
c) Hypoglycemic treatment options for person with T2DM who received insulin during hospitalization.

PICO: Population, Intervention, Comparison and Outcomes; T2DM: type 2 diabetes mellitus; DM: diabetes mellitus; GLP-1 RA: glucagon-like peptide-1 receptor agonists; SGLT2i: sodium-glucose co-transporter-2 inhibitors; DPP4i: dipeptidyl peptidase-4 inhibitors.

2.4. Selection of recommendations from the existing original CPGs

Within the HG-TF, five different PICO teams of two to three panelists were formed (one for each PICO). Recommendations were selected and developed in a three-step process, as previously described [13–15]. First, each panelist independently identified the recommendations addressing the PICOs in the critically assessed included CPGs and adapted these recommendations by: a) using the GRADE format for the quality of the evidence (QoE) (high: H, moderate: M, low: L, very low: VL) and the strength of the recommendation (SoR)(strong: S, weak: W) if available in the original guideline; b) adapting the level of the evidence provided to the four levels as proposed by GRADE [16];c) integrating the information from the different CPGs that addressed the clinical question; and d) labeling the QoE as "consensus" if the recommendations in the original guidelines were supported by best practice knowledge without relevant evidence. In the next step, the panelists from each PICO team resolved discrepancies in their opinions. Finally, during a face-to-face meeting, all HG-TF members resolved discrepancies and approved the final recommendations by consensus. Best practice statements and comments on the recommendations were added when the included CPGs did not provide clear recommendations or when clarification was needed.

2.5. Dissemination phase

In the dissemination phase, the draft document developed and approved by the HG-TF was reviewed by three experts in guideline methodology and hyperglycemia management, and sent to the EFIM Executive Committee for publication and dissemination.

3. Results

The literature search identified 448 documents in databases and 347 documents on websites (see Fig. 1). After applying filters, removing duplicates, and screening titles and abstracts to exclude irrelevant articles, a total of 24 records were retained. After full-text screening, eight CPGs were selected for quality assessment using the AGREE-II instrument, and four were finally included to address the five PICOs of this guideline [17–20].

Based on this process, five teams extracted and adapted recommendations **(RECs)** from the selected CPGs as described below.

3.1. PICO#1: what are the targets for glucose control for hospitalized persons with T2DM?

We identified recommendations in three of the four critically appraised CPGs [17–19]. However, the target glucose range differed between these documents. Therefore, we selected the recommendations for baseline targets from the most widely used guideline and provided some comments on the differences.

The standard definitions of glucose abnormalities compiled from the guidelines are as follows:

- Hyperglycemia in hospitalized persons is defined as blood glucose (BG) levels >140 mg/dL (7.8 mmol/L).
- Hypoglycemia in hospitalized persons is categorized by BG levels and clinical correlates[20]:
  - Level 1 hypoglycemia is a BG level of 54–70 mg/dL (3.0–3.9 mmol/L);
  - Level 2 hypoglycemia is a BG level <54 mg/dL (3.0 mmol/L), which is typically the threshold for neuroglycopenic symptoms;
  - Level 3 hypoglycemia is a clinical event characterized by altered mental and/or physical functioning that requires assistance from another person for recovery.

Levels 2 and 3 hypoglycemia require immediate correction of low BG levels. The target ranges for BG levels in various clinical scenarios are presented in Table 2.

Recommendations for BG targets in the following different clinical scenarios were presented A1) Common considerations in the hospitalized adults management of hyperglycemia on admission; A2) Hyperglycemia in persons with known DM; A3) Hyperglycemia in persons without previous diagnosis of DM; A4) Perioperative glucose targets; A5) Targets in critically ill adults; A6) Targets in persons on insulin; and A7) Targets in elderly or frail adults at risk of hypoglycemia.

3.1.1. Common considerations in the hospitalized adults management of hyperglycemia on admission

REC 1: All persons should have a BG test on admission to the hospital. If BG levels are elevated, HbA_{1c} levels should be tested if not done in the previous 3 months to differentiate between stress hyperglycemia (BG >140 [7.8 mmol/L] and HbA_{1c}<6.5 % [48 mmol/mol]) or newly undiagnosed diabetes (HbA_{1c}>6.5 % [48 mmol/mol]).

(QoE:H; SoR: S)

Best Practice Comments: Initial orders for BG testing should include the type of diabetes (i.e., T1DM, T2DM, gestational DM, other types of diabetes) if known. Initial orders should also include BG testing in persons on tube feeding or total parenteral nutrition, before meals and at bedtime, or every 6 hours if the person is *nihil per os* (NPO). Treatment and discharge planning are more effective if based on preadmission glycemia.

REC 2: All persons with T1DM, T2DM, those on high-dose steroids, or those with stress hyperglycemia should have their BG levels monitored with point-of-care (POC) checks testing at least 4 times a day (before meals and at bedtime), or every 6 hours if receiving parenteral or enteral nutrition. (QoE: **Consensus;** SoR: **S**)

Best Practice Comments: For hospitalized persons with DM who are not eating, glucose monitoring every 4–6 hours is recommended. More frequent bedside BG testing, ranging from every 30 minutes to every 2 hours, is the standard for safe use of intravenous insulin [17].

REC 3: In conditions associated with an altered relationship between HbA_{1c} and glycemia (hemoglobinopathies, pregnancy, recent blood loss, transfusion, or erythropoietin therapy), only plasma BG criteria should be used to diagnose DM. (QoE: **M**; SoR: **S**)

Best Practice Comments: In certain conditions associated with an altered relationship between HbA_{1c} and glycemia, estimated HbA_{1c} ratios based on BG levels can be used [18] (see Table 3).

3.1.2. Hyperglycemia in persons with known DM

REC 4: If capillary blood glucose (CBG) levels are measured, the hyperglycemic threshold for hospitalized persons with T1DM should be 200 mg/dL (11.1 mmol/L). (QoE: **Consensus;** SoR: **S**)

Best Practice Comments: Ketone levels should be checked when CBG levels are ≥11.1 mmol/L (200 mg/dL) in the setting of acute illness (See Table 4). If capillary ketone levels are ≥1.5 mmol/L, diabetic ketoacidosis (DKA) must be excluded. If the person fulfills the diagnostic

Table 2
Target ranges for blood glucose levels according to clinical scenarios (adapted from ADA CPG-2023 [18]).

In Hospital Clinical scenarios	Blood glucose mg/dL (mmol/L)	HbA_{1c} (%) [mmol/mol}
Hyperglycemia threshold	>140 (7.8)	6.5 (42–47)
Hypoglycemia threshold	< 70 (3.9)	
Level 1	54–70 (3–3.9)	NA
Level 2	< 54 (3)	NA
Perioperative period (see REC 7)	80–180 (4.4–10.0)	4.2–8 (31–64)
Critically ill adults (see REC 8)	140–180 (7.8–10)	6.5–8 (42–64)
Person on insulin	140–180 (7.8–10)	6.5–8 (42–64)
Older adult (>65 years) with intact cognitive function/ functional status	155–169 (8.6–9.4)	< 7.0–7.5 (53–58)
Older adult (>65 years) with cognitive impairment/dependence	180–250 (10–13.9)	>8 (>64)

HbA_{1c}: glycated hemoglobin A_{1c}; NA: not applicable.

Table 3
Correlation of HbA1c with blood glucose levels (adapted from Nathan et al. [21]).

HbA_{1c}(%)	HbA_{1c}(mmol/mol)	Glucose (mg/dL)	Glucose (mmol/L)
5	31	97 (76–120)	5.4 (4,2–6.7)
6	42	126 (100–152)	7.0 (5.5–8.5)
7	53	154 (123–185)	8.6 (6.8–10.3)
8	64	183 (147–217)	10.2 (8.1–12.1)
9	75	212 (170–249)	11.9 (9.4–13.9)
10	86	> 240 (193–282)	13.4 (10.7–15.7)

Table 4
Diagnostic criteria of Diabetic ketoacidosis and Hyperglycemic hyperosmolar state*.

CRITERIA	Diabetic ketoacidosis (DKA)	Hyperglycemic hyperosmolar state (HHS)
Hyperglycemia	Glucose ≥ 11.1 mmol/l (200 mg/dl) OR prior DM	Glucose ≥ 33.3 mmol/l (600 mg/dl)
Ketosis	B-hydroxybutyrate ≥ 3.0 mmol/l OR urine ketone strip 2+ or greater	B-hydroxybutyrate < 3.0 mmol/l OR urine ketone strip less than 2+
Metabolic Acidosis	pH < 7.3 and/or bicarbonate < 18 mmol/l	pH ≥ 7.3 and bicarbonate ≥ 15 mmol/l
Hyperosmolarity	Absense	Calculated serum osmolality >300 mOsm/kg (calculated as [2xNa mmol/*l* + glucose (mmol/l)]), OR total serum osmolality >320 mOsm/kg (2xNa+glucose (mmol/*l* + urea (mmol/l)
Mild DKA	Glucose ≥ 11.1 mmol/l (200 mg/dl)	
Level of care: Regular-Observation Unit	+ *B*-hydroxybutyrate 3.0 - 6.0 mmol/l + pH >7.25 to <7.30 or bicarbonate 15–18 mmol/l + mental status alert	
Moderate DKA	Glucose ≥ 11.1 mmol/l (200 mg/dl)	
Level of care: Intermediate Unit	+ *B*-hydroxybutyrate 3.0 - 6.0 mmol/l + pH 7.0 to 7.25 or bicarbonate 10 to <15 mmol/l + mental status drowsy	
Severe DKA	Glucose ≥ 11.1 mmol/l (200 mg/dl)	
Level of care: Intensive Care Unit	+ *B*-hydroxybutyrate > 6.0 mmol/l + pH < 7.0 or bicarbonate < 10 to mmol/l + mental status stupor/coma	

* Adapted from Umpierrez et al. [24], with permits use by Creative Commons; http://creativecommons.org/licenses/by/4.0/).

criteria for DKA (CBG >11.1 mmol/L, plasma ketones ≥3 mmol/L, pH <7.3 or bicarbonate <18 mmol/L), local DKA management protocols should be followed urgently [22]. We suggest to follow the updated consensus on the management of hyperglycemic crises that provides detailed recommendations [23].

REC 5: While glucose readings of 110–180 mg/dL (6–10 mmol/L) are acceptable for most hospitalized persons, an individualized approach is recommended because some persons (eg, frail or elderly adults, those at risk for falls, or those at the end of life) may not require such tight control as part of individualized care. However, hyperglycemia leading to symptoms or risk of acute hyperglycemic complications should be avoided in all persons. (QoE: **Consensus**; SoR: **S**)

Best Practice Comments: It is important to exclude DKA and HHS (total serum osmolality ≥320 mOsm/kg, BG levels typically ≥30 mmol/L [600mg/dl]) (See Table 4). Outside of hyperglycemic emergencies, persons with T2DM with CBG levels between 200 and 400 mg/dL (11.1–22 mmol/L) require the administration of rapid-acting insulin and CBG monitoring every 2 hours after the correction dose [22].

3.1.3. Hyperglycemia in persons without previous diagnosis of DM

REC 6: If BG levels are>140 mg/dL (7.8 mmol/L) in a person without DM, stress hyperglycemia is considered, and POC glucose testing should be performed before meals and at bedtime. (QoE: **L**; SoR: **S**)

3.1.4. Perioperative glucose targets

REC 7: The recommended target range for BG levels in the perioperative period is 80–180 mg/dL (4.4–10.0 mmol/L). (QoE: **Consensus**; SoR: **S**) (see Table 2)

Best Practice Comments: A comprehensive review concluded that perioperative glycemic control tighter than 80–180 mg/dL (4.4–10.0 mmol/L) did not improve outcomes and was associated with more hypoglycemic episodes; therefore, tighter glycemic targets are generally *not* recommended [24].

3.1.5. Targets in critically ill adults

REC 8: The recommended target range for BG levels in critically ill adults is 140–180 mg/dL (7.8–10.0 mmol/L) in most cases. (QoE: **H**; SoR: **S**)

Best Practice Comments: In a landmark clinical trial, van den Berghe et al. [25]. demonstrated that intensive intravenous insulin therapy to achieve a target glycemic range of 80–110 mg/dL (4.4–6.1 mmol/L) reduced mortality by 40 %, as compared with a standard approach targeting BG levels of 180–215 mg/dL (10–12 mmol/L) in critically ill persons after recent surgery. However, NICE-SUGAR [26] and numerous randomized controlled trials led to a reconsideration of the optimal target range for glucose lowering in critically ill persons. In recent trials [27,28], critically ill persons randomized to intensive glycemic control (80–110 mg/dL) derived no significant treatment benefit compared with a group with more moderate glycemic targets (140–180 mg/dL [7.8–10.0 mmol/L]). In addition, the intensively treated group had 10- to 15-fold higher rates of hypoglycemia and a slightly but significantly higher mortality (27.5 % vs. 25 %).

3.1.6. Targets in persons on insulin therapy

REC 9: Once insulin therapy is started, a target glucose range of 140–180 mg/dL (7.8–10.0 mmol/L) is recommended for most critically ill and non-critically ill persons. (QoE: **H**; SoR: **S**)

REC 10: More stringent targets, such as 110–140 mg/dL (6.1–7.8 mmol/L), may be appropriate for selected persons, provided that these targets can be achieved without significant hypoglycemia. (QoE: **L**; SoR: **W**)

Best Practice Comments: Glucose levels >250 mg/dL (13.9 mmol/L) may be acceptable in terminally ill adults with a short life expectancy. In these persons, less aggressive insulin regimens are often more appropriate to minimize glycosuria, dehydration, and electrolyte disturbances [29].

3.1.7. Targets in elderly or frail adults at risk of hypoglycemia

REC 11: Older adults who are otherwise healthy with few comorbidities and intact cognitive function and functional status, should have lower glycemic targets (such as HbA_{1c} <7.0–7.5 % [53–58 mmol/mol]). On the other hand, older adults with multimorbidity, cognitive impairment, or functional dependence should have less stringent glycemic targets of 180–250 mg/dL (10–13.9 mmol/L) (HbA_{1c}>8.0 % [64 mmol/mol]) as part of individualized care, but hyperglycemia leading to symptoms or risk of acute hyperglycemic complications should be avoided in all persons. (QoE: **L**; SoR: **S**)

REC 12: In older adults with T1DM, continuous glucose monitoring at routine visits should be considered to reduce the risk of hypoglycemia. (QoE: **H**; SoR: **S**)

REC 13: In individual persons, treatment regimens should be reviewed and modified as needed to prevent further hypoglycemia when a BG level of <70 mg/dL (3.9 mmol/L) is documented. (QoE: **L**; SoR: **S**)

REC 14: A plan for the prevention and management of hypoglycemia

should be established for each person. Episodes of hypoglycemia in the hospital should be documented in the medical record and monitored for quality improvement/quality assessment. (QoE: **L**; SoR: **S**)

Best Practice Comments: It seems reasonable to individualize the management of hospitalized persons by considering medical, psychological, and functional (self-management skills) aspects in older adults to provide a framework for determining therapeutic targets and approaches in DM.

3.2. PICO #2: in which adults with DM (including those with comorbidities such as heart failure, chronic kidney disease, frailty) should non-insulin agents (GLP-1RA, SGLT2i, DPP4i, metformin) not be used in the hospital?

The recommendations were selected from all included CPGs [17–20].

REC 15: Oral hypoglycemic agents (OHAs) may be an appropriate choice in hospitalized persons with stable, non-critical disease and mild hyperglycemic excursions who are expected to have regular meals. (QoE: **M**; SoR: **W**)

REC 16.1: Metformin should be continued in hospitalized persons with stable, non-critical disease and mild hyperglycemic excursions who are expected to have regular meals. (QoE: **H**; SoR: **S**)

REC 16.2: Metformin should be discontinued on admission in persons who are acutely ill, are susceptible to hypoxia, or have acute kidney injury (or estimated glomerular filtration rate <45 ml/min/1.73 m^2), and if surgery or the use of contrast media in diagnostic imaging is anticipated. (QoE: **H**; SoR: **S**)

REC 17: Sulfonylureas should be discontinued because of the risk of hypoglycemia due to unpredictable nutritional intake. This applies particularly to glyburide (glibenclamide), which can cause prolonged hypoglycemia. (QoE: **M**; SoR: **S**)

REC 18: Thiazolidinediones should be discontinued because they are very slow acting and can cause fluid retention, decompensation of heart failure, and liver toxicity. (QoE: **H**; SoR: **S**)

REC 19: Sitagliptin and linagliptin can be used as safe and effective therapy for the in-hospital management of medical and surgical persons with T2DM. (QoE: **H**; SoR: **S**)

- Sitagliptin dosing needs to be adjusted according to the person's estimated glomerular filtration rate.
- Linagliptin has the advantage of not requiring adjustment for renal failure.

Best Practice Comments: Of all the dipeptidyl peptidase-4 inhibitors (DPP-4is) approved for out of the hospital treatment of hyperglycemia alone or in combination with insulin or other oral agents, only sitagliptin and linagliptin have been evaluated in randomized controlled trials for hospital use and found to be safe and effective [30].

REC 20: Sodium-glucose co-transporter-2 inhibitors (SGLT2is) are *not* recommended for routine in-hospital use in the management of persons with DM, although they may be considered for the treatment of persons with T2DM with heart failure or at risk for heart failure. However, caution is advised due to the risk of euglycemic ketoacidosis. (QoE: **H**; SoR: **S**)

REC 21: The use of glucagon-like peptide-1 receptor agonists (GLP-1-Ras) carries the risk of gastrointestinal adverse effects (nausea and reduced gastric emptying), particularly during the initiation phase. This limits their widespread use in acutely ill, hospitalized persons with steroid-induced hyperglycemia (SIHG). (QoE: **H**; SoR: **S**)

Best Practice Comments: Potential effectiveness of GLP-1-RA in specific groups of hospitalized persons has been demonstrated in some randomized controlled trials:

- Exenatide alone or in combination with basal insulin is safe and effective for the management of hospitalized medical and surgical persons with T2DM [31].
- Dulaglutide combined with conventional insulin therapy is beneficial for glycemic control in non-critically ill hospitalized persons with T2DM [32].

3.3. PICO #3: how to treat hyperglycemia in adults with low consciousness or dementia with irregular feeding or parenteral/enteral nutrition?

Although consensus guidelines for the management of DM in these current circumstances are lacking, we selected three critically assessed CPGs that address this topic with a high degree of agreement [17–19]. In general, the CPGs distinguish between tube feeding (which can be continuous, nocturnal, or bolus) and total parenteral nutrition. Irregular oral feeding is not specifically addressed, except for the perioperative period. Standard formulas seem to be acceptable for persons with DM.

REC 22: Once alternative or irregular feeding is initiated, CBG monitoring every 4–6 hours and involvement of a specialist diabetes care team is recommended. CBG target is between 140–180 mg/dL (7.8–10.0 mmol/L), and higher targets should be considered in some persons with dose titration by 10 %–20 % every 48–72 hours. (QoE: **Consensus**; SoR: **S**)

REC 23: Standard enteral formulas are acceptable for persons with DM. There is no evidence that enteral formulas for persons with DM have a significant impact on clinical outcomes. (QoE: **L**; SoR: **W**)

3.3.1. Treatment with oral hypoglycemic agents (OHA)

***REC* 24:** OHAs should generally *not* be used in hospitalized persons with T2DM and irregular feeding. Instead, simple insulin regimens should be used, such as intermediate-acting (NPH) insulin twice daily. In individual cases, oral therapy may still be considered. (QoE: **Consensus**; SoR: **S**)

REC 25: Persons with T2DM can receive only metformin in liquid or powder form via a nasogastric tube if not contraindicated, as absorption of other OHAs is unreliable. (QoE: **L**; SoR: **S**)

REC 26: Metformin therapy in liquid or powder form via a nasogastric tube should be closely monitored (signs of infection, renal function, etc.). If suboptimal glycemic control persists, short-acting, rapid-acting, mixed, intermediate-acting, or long-acting insulin preparations can be used, depending on the duration and type of feeding. (QoE: **H**; SoR: **S**)

3.3.2. Insulin treatment

REC 27: Persons with T1DM should continue the use of long-acting insulin with additional doses of rapid-acting insulin depending on the duration and type of tube feeding (continuous, bolus, or nocturnal). When feeding is discontinued, variable rate insulin infusion with dextrose should be started. (QoE: **H**; SoR: **S**)

REC 28: For persons on parenteral/enteral nutrition who require insulin, the regimen should include coverage of basal, prandial, and correctional needs. (QoE: **H**; SoR: **S**)

REC 29: Basal insulin or a basal plus bolus correction insulin regimen is the preferred treatment for non-critically ill hospitalized persons with poor oral intake, dementia, or those who take nothing by mouth. (QoE: **H**; SoR: **S**)

REC 30: It is particularly important that persons with T1DM continue to receive basal insulin even if feeding is discontinued. (QoE: **H**; SoR: **S**)

REC 31: Most persons receiving basal insulin should continue on their preadmission basal dose. Long-acting basal insulin should be 20 %–40 % of the total daily dose. (QoE: **L**; SoR: **S**)

REC 32: The remaining insulin requirement in persons on tube feeding should be managed with appropriate short-acting or rapid-acting insulin. (QoE: **L**; SoR: **S**)

REC 32.1: For continuous tube feeding, regular insulin administration every 6 hours is appropriate. (QoE: **Consensus**; SoR: **W**)

REC 32.2: Persons receiving nocturnal or continuous tube feeding should receive approximately 1 unit of intermediate-acting insulin subcutaneously every 6 hours for every 10–15 g of carbohydrate in the formula. (QoE: **Consensus**; SoR: **S**)

REC 32.3: For bolus tube feeding, administration of rapid-acting insulin before every bolus is appropriate. (QoE: **Consensus**; SoR: **S**)

REC 32.4: Persons on bolus tube feedings should receive approximately 1 unit of rapid-acting insulin subcutaneously for every 10–15 g of carbohydrate in the formula before every bolus. Correction insulin coverage should be added as needed before each bolus feeding. (QoE: **Consensus**; SoR: **S**)

R**EC 32.5:** The sole use of a sliding-scale insulin regimen in the hospital setting is strongly discouraged in persons with feeding difficulties. (QoE: **H**; SoR: **S**)

REC 33*:* For persons receiving peripheral or central parenteral nutrition, 1 unit of regular or short-acting insulin for every 10 g of dextrose in the solution may be added directly to the solution with correction insulin administered subcutaneously. (QoE: **Consensus**; SoR: **W**)

Best Practice Comments: Adding insulin to the parenteral nutrition bag is the safest way to prevent hypoglycemia if parenteral nutrition is stopped or interrupted [19]. Long-acting insulin can be added as 20 %–40 % of the total daily dose in persons with uncontrolled hyperglycemia. However, the risk of hypoglycemia is higher if feeding is discontinued or interrupted [18].

3.4. PICO #4: how to manage special hyperglycemic scenarios?

Recommendations for glucose targets in three different clinical scenarios, including stress hyperglycemia, glucocorticosteroid treatment, and fasting persons before surgery or diagnostic testing, are shown below. Recommendation to these defined scenarios can be found in three of the four selected CPGs [18–20].

3.4.1. Stress hyperglycemia

REC 34.1: The management of stress hyperglycemia in hospitalized persons with a low to moderate bolus correction scale can be initiated immediately if two BG values are >140 mg/dL (>7.8 mmol/L) or one BG value is >180 mg/dL (>10 mmol/L) within 24 hours. (QoE: **L**; SoR: **W**) **(see REC 1 for definitions)**

REC 34.2: For the management of stress hyperglycemia in hospitalized persons without diabetes, a basal or basal-bolus insulin regimen can be initiated if two BG values are >180 mg/dL (>10 mmol/L) within 24 hours. (QoE: **L**; SoR: **W**)

REC 34.3: If BG values are <140 mg/dL (<7.8 mmol/L) for 24 hours with no or minimal insulin correction, BG testing can be discontinued. (QoE: **L**; SoR: **W**)

3.4.2. Hyperglycemia related to steroid (SIHG) treatment

REC 35.1: The type, dose, and duration of action of glucocorticoids must be considered when determining treatment regimens with OHAs or insulin, depending on the degree of hyperglycemia. (QoE:**H**; SoR: **S**)

REC35.2: When starting glucocorticoid therapy (≥7.5 mg prednisone per day), perform POC BG monitoring in all persons (with or without diabetes). (QoE: **H**; SoR: **S**)

Best Practice Comments: Persons with and without DM who start glucocorticosteroid treatment are at high risk for hyperglycemia and require continued monitoring even if they are euglycemic on admission. Glucocorticosteroids increase meal time insulin requirements to a greater extent than fasting (basal) insulin requirements [20].

- If BG levels are <180 mg/dL (<10 mmol/L), POC testing can be discontinued;
- If BG levels are <250 mg/dL (<13.8 mmol/L), increase the sliding scale from moderate to high;
- If BG levels are >250 mg/dL (>13.8 mmol/L), administer insulin plus correction doses based on BG control and duration of glucocorticosteroid action (once or twice daily).

3.4.2.1. OHAs in the treatment of hospitalized persons SIHG. **REC 36.1:** In acutely ill hospitalized persons, the use of insulin sensitizers such as metformin and pioglitazone may be limited by susceptibility to hypoxia, acute kidney injury, and fluid retention, and by the prolonged onset of action of pioglitazone. (QoE: **H**; SoR: **S**) **(see REC 16)**

REC 36.2: Insulin secretagogues stimulate endogenous insulin production and may be suitable for mild SIHG, in non-severely ill hospitalized persons who receive short-acting glucocorticosteroids in the morning. However, insulin secretagogues should be used with caution due to an increased risk of hypoglycemia, particularly when steroid doses are tapered or meals are skipped. (QoE: **H**; SoR: **S**)

REC 36.3: In persons managed with diet or OHAs, a course of short-acting sulfonylureas such as gliclazide may be prescribed in addition to prednisone to manage day time hyperglycemia. (QoE: **H**; SoR: **W**)

REC36.4: DPP4is can be used in hospitalized persons with SIHG mostly as an adjunct to insulin therapy, as their acute glucose-lowering effect is moderate. (QoE: **H**; SoR: **S**)

REC 36.5: The use of the SGLT2i dapagliflozin in hospitalized persons with chronic obstructive pulmonary disease who developed SIHG was shown to be safe, but did not improve glycemic control or clinical outcomes. (QoE: **H**; SoR: **S**)

3.4.2.2. Insulin regimens in the treatment of hospitalized persons SIHG. **REC 37:** Prednisone once daily in the morning results in a peak BG level between lunch and dinner. In persons on glucocorticosteroids once or twice daily, administration of NPH insulin is a standard approach. (QoE: **H**; SoR: **S**)

REC 37.1: NPH insulin is usually administered in addition to daily basal-bolus insulin or in addition to OHAs. (QoE: **H**; SoR: **S**)

REC 37.2: Due to the peak effect of NPH insulin occurring 4–6 hours after administration, it is recommended to administer it concomitantly with glucocorticosteroids. (QoE: **H**; SoR: **S**)

Best Practice Comments: a) If the person is taking a once-daily oral glucocorticosteroid, add once-daily NPH insulin with prednisone. Give NPH insulin at the same time as prednisone and titrate up based on glucose measurements.

- In persons without known DM, those with newly diagnosed DM, those with DM well controlled on diet, those receiving ≤2 OHAs, or those with end-stage renal disease, starting with 5 units of NPH insulin is appropriate.
- For all other persons with DM, starting from 10 units of NPH insulin is appropriate.
- If the person is not on basal-bolus insulin, use NPH insulin with correction insulin.
- For persons on basal-bolus regimens with insulin analogue, NPH insulin can be added as a third insulin at the same time as prednisone.
- If prednisone is withheld, do *not* give NPH insulin.

b) For persons receiving twice-daily prednisone (or other long-acting steroids) who are already on a basal-bolus regimen, add a high-dose correction scale and increase and titrate the dose per BG reading. Meal time insulin usually needs more adjustment than basal insulin [20].

REC 38: With long-acting glucocorticosteroids such as dexamethasone and/or multidose or continuous glucocorticosteroid use, a long-acting insulin analogue may be required to control fasting BG levels.

(QoE: **L**; SoR: **W**)

Best Practice Comments: Specific recommendations for dexamethasone therapy in hospitalized persons with COVID-19 can be found in the Diabetes UK guidelines [33] and the consensus report about hyperglycaemic crises in adults with diabetes.

REC 39: With higher doses of glucocorticosteroids, increased doses of prandial and correction insulin, sometimes in extraordinary amounts, are often needed in addition to basal insulin with adjustments based on anticipated changes in glucocorticosteroid dosing and POC glucose test results. An insulin drip may be required for uncontrolled hyperglycemia. (QoE: **L**; SoR: **W**)

3.4.3. Fasting persons prior to surgery or diagnostic tests

No specific recommendations for fasting before diagnostic procedures during hospitalization were found in the guidelines reviewed. Many recommendations for perioperative care do not have a robust evidence base. However, the following approach may be considered:

REC 40: Preoperative risk assessment should be performed in persons with DM who are at high risk for ischemic heart disease and those with autonomic neuropathy or renal failure. (QoE: **H**; SoR: **S**) **(see REC 7 and** Table 2)

REC 41: Persons with DM should receive clear instructions on how to adjust their diabetes regimen before surgery. (QoE: **H**; SoR: **S**)

REC 41.1: Insulin doses generally need to be reduced or withheld due to the "nothing by mouth" status. Give half of the NPH insulin dose or 75 %–80 % of the long-acting analogue or pump basal insulin dose. (QoE: **H**; SoR: **S**)

REC 41.2: Non-insulin agents are generally *not* appropriate in the perioperative setting. Withhold OHAs on the morning of surgery or before surgery, except for SGLT2is, which should be withheld at least 2–3 days before surgery, due to the increased risk of euglycemic diabetic ketoacidosis. (QoE: **H**; SoR: **S**)

REC 42: Monitor BG levels at least every 2–4 hours when the person is nil by mouth, and administer with short-acting or rapid-acting insulin as needed. (QoE: **H**; SoR: **S**)

REC 43: When persons arrive in the preoperative area, confirm their most recent doses of insulin and non-insulin agents. For persons using insulin pumps, review current pump settings. (QoE: **M**; SoR: **S**)

REC 44: If preoperative BG levels are>180 mg/dL (>10 mmol/L), or the person has significant insulin resistance, the anesthesia team should *not* administer dexamethasone. (QoE: **L**; SoR: **W**)

REC 45: There are no data on the use of GLP-1 RAs (optimal fasting duration) or ultra-long-acting insulin analogues and their effect on glycemic control in perioperative care. (QoE: **L**; SoR: **W)**

Best Practice Comments: A recent publication from the American Society of Anesthesiologists Task Force on Preoperative Fasting [34] recommends the following approach for persons on GLP-1 RA scheduled for elective procedures:

a) Day(s) before the procedure:

- For persons on daily dosing, consider withholding GLP-1 RAs on the day of the procedure or surgery. For persons on weekly dosing consider withholding GLP-1 RAs a week before the procedure or surgery.
- This recommendation is independent of the indication (T2DM or weight loss), dose, or the type of procedure or surgery.
- If GLP-1 RAs prescribed for DM management are withheld for longer than the dosing schedule, consider consulting an endocrinologist or diabetes specialist to bridge antidiabetic therapy to avoid hyperglycemia.

b) Day of the procedure:

- If gastrointestinal symptoms are present, consider delaying the elective procedure and discuss with the proceduralist or surgeon and the person the "full stomach" concerns regarding the potential risk of regurgitation and pulmonary aspiration.
- If the person has no gastrointestinal symptoms, and GLP-1 RAs have been withheld as advised, proceed as usual.
- If the person has no gastrointestinal symptoms, but GLP-1 RAs have not been withheld as advised, proceed with "full stomach" precautions or consider evaluating gastric volume by ultrasound. If the stomach is empty, proceed as usual. If the stomach is full, or if gastric ultrasound is inconclusive or not feasible, consider delaying the procedure or treating the person as "full stomach".

3.5. PICO #5: hypoglycemic therapy to prepare for discharge

Recommendations for hypoglycemic therapy in three different clinical scenarios, including 1) medications (oral vs parenteral; insulin vs non-insulin), 2) insulin dose titration at discharge, and 3) hypoglycemic treatment options for persons with T2DM receiving insulin during hospitalization, were found in three of the four critically appraised CPGs [18–20].

3.5.1. Medications (oral vs parenteral; insulin vs non-insulin)

REC 46: All persons with T'2DM, especially those on insulin therapy, should receive consolidated in-hospital diabetes education focused on basic survival skills necessary for safe discharge. (QoE: **L**; SoR: **S**).

REC 47*:* There should be a structured discharge plan tailored to the individual person with DM. (QoE: **H**; SoR: **S**)

Best Practice Comments: A discharge plan reduces the readmission rates and increases persons satisfaction. The optimal program should consider the type of DM and its impact on BG levels, as well as person capacities and preferences. A follow-up visit within 1 month after discharge is recommended for all persons who experience hyperglycemia in the hospital or if their diabetes medication is changed. Clear communication with clinical providers can assist them as they assume ongoing care of the persons [19]. See Table 5 for established discharge recommendations.

REC 48: Any DM medication adjustment must be accompanied by a close follow-up plan and provider contact information for any issues with BG within weeks of discharge. (QoE: **H;** SoR: **S**)

49: It is recommended to reassess HbA_{1c} levels in clinics for early diagnosis, to identify those at risk for DM whose only manifestation may be stress hyperglycemia, and to plan continuity of care. (QoE: **H;** SoR: **S**)

REC 50: In older people with T2DM at increased risk for hypoglycemia, drug classes with a low risk of hypoglycemia are preferred. (QoE: **H**; SoR: **S**)

3.5.2. Insulin dose titration at discharge

REC 51: Deintensification of complex regimens is recommended to reduce the risk of hypoglycemia and polypharmacy, especially in older adults, if this can be achieved without compromising individual HbA_{1c} targets. (QoE: **H**; SoR: **S**) **(see REC 11)**

REC 52: When glucocorticosteroid treatment is maintained at discharge, it is recommended to educate the person on BG self-monitoring and to provide BG targets and a plan for therapy modification in case of changes in BG levels. (QoE: **Consensus**; SoE: **S**)

Best Practice Comments: After discharge, persons often remain in a hyperglycemic state even if glucocorticosteroid treatment has been discontinued. This indicates that these persons are prone to develop T2DM and should be educated on BG self-monitoring and when to seek treatment [34].

REC 53: In general, home OHAs should be resumed before discharge if there are no contraindications (eg, renal failure, intravenous contrast, to reinstitute metformin), and BG control was good when OHAs were used before admission. (QoE: **M**; SoR: **S**)

REC 54*:* Persons with HbA_{1c} levels <7.5 % (58 mmol/mol) before admission, requiring less than three OHAs, with POC BG levels 140–180 mg/dL (7.8–10.0 mmol/L), and no more than one BG value >180 mg/dL

Table 5
Discharge recommendations for persons with diabetes mellitus.

Discharge plan
Medication reconciliation
- Medication must be checked to ensure that chronic medications are not stopped and new drugs are safe.
- Any new medication must be reviewed with the patient and his/her family before discharge.
Structured discharge communication
- Information on medication changes
- Discharge summaries to primary care provider
- Scheduled follow-up appointment
Knowledge review
- Understanding of blood glucose self-monitoring
- Home blood glucose goals
- When to call the provider
- Prevention, recognition, and treatment of hyperglycemia and hypoglycemia
- Healthy meal plan
- Sick-day management
- Proper use of pens, needles, and syringes

can be discharged on OHAs.

Best Practice Comments: Hospital discharge is an opportunity to optimize the antidiabetic therapy keeping in mind two goals: a) adjusting the intensity of hypoglycemic treatment to achieve the individualized glycemic control target, and b) providing adequate cardiorenal protection with SGLT2 inhibitors and/or GLP-1 receptor agonists when are clinically indicated, according to the current guidelines (persons with T2D and high cardiovascular risk, heart failure or chronic kidney disease) [35,36].

REC 55: For persons on non-insulin agents before admission, consider prescribing insulin at discharge if:

a) they require more than 20 UI of insulin per day before discharge (roughly each non-insulin agent is equivalent to 10 UI of insulin), recommend home BG monitoring, and consider either an oral agent or insulin at discharge. (QoE: **M**; SoR: **W**)
b) oral agents become contraindicated during hospitalization (eg, due to changes in renal function). (QoE: **M**; SoR: **S**)

REC 56: Persons with HbA_{1c} levels >8 % (64 mmol/mol) at home may benefit from escalation of their DM regimen at discharge, based on their preadmission home regimen. (QoE: **Consensus**; SoE: **W**)

REC 57: For persons with low acuity who are being transferred to a psychiatric and/or rehabilitation in hospital, or long-term care facility, consider resuming home regimen if there are no contraindications. (QoE:**M**; SoR: **W**)

4. Discussion

Our guideline provides specific recommendations for the most current scenarios in real adult care practice, addressing unknown DM, perioperative or fasting persons, and transition from different levels of care, in a concise and useful tool. The 75 recommendations were selected from four updated high-quality evidence-based CPGs. With this adaptation, we aim to facilitate the decision-making process in the real-world setting and to disseminate the available updated secondary evidence. Of the 75 selected recommendations (59 strong and 16 weak), 37 were based on high-quality evidence, 8 on moderate-quality evidence, and 17 on low-quality evidence, while 13 were based on good practice consensus (best practice statements). This apparent evidence gap highlights the uncertainty regarding persons with DM and multimorbidity [37,38] that needs to be addressed by comprehensive research in the field of internal medicine.

The adaptation process for this guideline was developed according to a clear, previously published methodology, which increases its external validity [11,13–15]. Well-established primary critically appraised guidelines were selected, and in many cases, initial recommendations from the original CPGs were only slightly rephrased and summarized. Of note, the recommendations showed a high degree of agreement and consistency across the original guideline sources. Thus, our guideline, with its narrow scope limited to a few clinical scenarios in the management of in-hospital hyperglycemia, could provide an easy-to-use tool for individualized decision-making in everyday hospital care. As all clinical guidelines cannot be followed blindly by their readers, but require them to adapt the recommendations received to the local reality where they apply, taking into account the social determinants (economic, ethnic, values) prevailing in clinical practice.

Our guideline adaptation has several limitations. First, it is a secondary summary of existing CPGs, and we relied on evidence identified in the primary guidelines. However, this should not be a major concern because there was a high degree of consistency among the original guidelines. Second, since the original CPGs used different methodologies to evaluate recommendations, we developed a non validated compliance system [11] to formulate the SoRs adapted to the GRADE procedure, prioritizing the QoE recorded in the CPGs. Third, there are many recommendations for which evidence is lacking, and these recommendations were therefore based on a consensus agreement in the original guidelines. However, it only reflects the current state of the art and provides an opportunity to stimulate new research and progress. These limitations do not diminish the clinical relevance of this EFIM CPG, which demonstrates the importance of clinical judgment. When caring for persons and making decisions, physicians should not only rely on guideline recommendations, but should also consider different factors such as clinical stability, comorbidities, age, and even the socioeconomic and cultural status of the person.

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