# Government of India Ministry of Health & Family Welfare

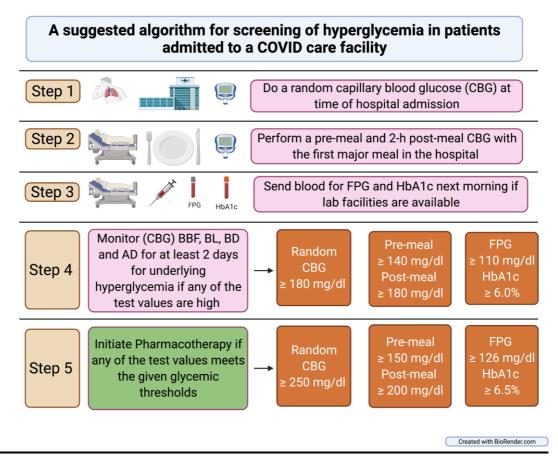
## **Clinical Guidance on Diagnosis and Management of Diabetes at COVID-19**

# Patient Management facility.

Version 2.0.

**Important points:** 

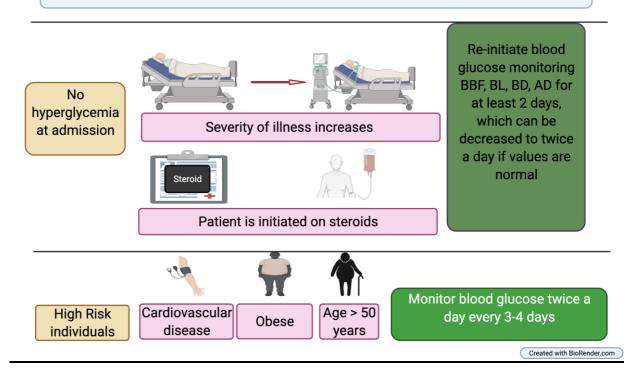
- Screen every patient at admission for hyperglycemia with at least two capillary blood glucose values (1 pre-meal and 1 post-meal value) by a glucometer.
- Every patient with diabetes should be started on a diabetic diet. Kindly ensure that the patient strictly adhere to the timing and quantity advised in the diet chart.



Abbreviations: BBF: Before breakfast, BL: Before lunch, BDN: Before dinner, ADN: After dinner

- We have suggested three steps (Step 3 if lab facilities are available) for screening of undiagnosed hyperglycemia in initial 24 hours of admission.
- If BG level is ≥250 mg/dl, check urine/blood ketone levels →if positive, immediately consult endocrinologist/physician.
- Start "Diabetic Diet" if the values are higher than the cut-offs given in Step 4
- Start "**Pharmacotherapy**" if the values are higher than the cut-offs given in Step 5.
- FPG  $\geq$ 126 mg/dl and/or HbA1c  $\geq$ 6.5% (lab values) are diagnostic of Diabetes Mellitus
- Even if initial blood glucose monitoring was normal, repeat monitoring should be considered if: a) steroids or drugs with a potential to affect glycemic status are initiated, and b) there is an increase in severity of COVID-19 (to account for stress hyperglycemia) [see figure given below]
- High RBG at admission and outcomes in COVID-19: Coppelli et al explored its association with mortality in patients hospitalized for coronavirus disease 2019 (COVID-19). They found that RBG ≥ 140 mg/dl was found in 24.3% of patients. Mortality was greater in patients with RBG ≥ 140 mg/dl (39.4% vs. 16.8%; unadjusted hazard ratio [HR] 2.20, 95% CI 1.27-3.81, P = 0.005) than in patients with RBG < 140 mg/dl (16.8%) and even higher than seen in patients with known diabetes (28.6%; 1.73, 0.92-3.25, P = 0.086). The study was published in Diabetes Care "Hyperglycemia at hospital admission is associated with severity of the prognosis in patients hospitalized for COVID-19: The Pisa COVID-19 Study"</li>

# Blood glucose monitoring strategy for individuals with no evidence of stress hyperglycemia or undiagnosed diabetes at the initial screen



 A patient with normal initial glycemic profile may develop stress hyperglycemia during the course of illness, especially if COVID severity increases. Besides, institution of glucocorticoids for treatment of primary disease may also contribute to hyperglycemia in such an individual. Thus, glycemic assessment should be an ongoing dynamic process and not a one-time event

#### Section 2: Oral antihyperglycemic drugs (OAD)

#### 2A: Treatment of patients with known diabetes who are on OAD at admission

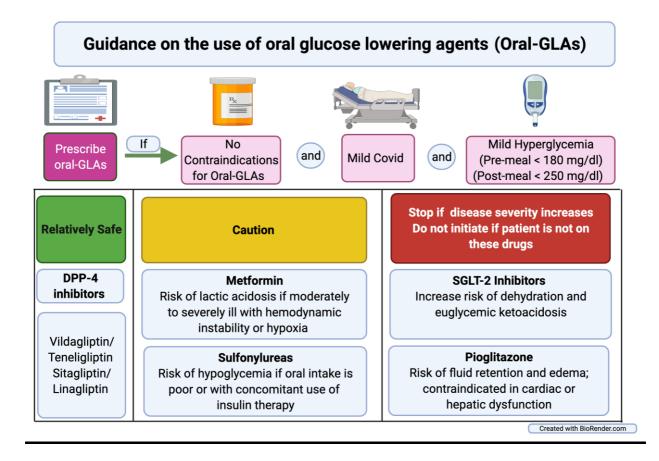
- A. To continue existing OAD if all of the below mentioned criteria are fulfilled:
- i. BG levels are controlled (Pre-meal <140 mg/dl and post-meal <180 mg/dl)
- ii. Patient is conscious, oriented and has good oral acceptance
- iii. COVID symptoms are mild
- iv. KFT and LFT are normal
  - B. If patient *does not fulfil all of the above criteria*, consult endocrinologist/physician [to start on basal-bolus insulin regimen (also called as multiple subcutaneous insulin injections or MSII regimen) or intravenous (IV) insulin infusion, depending on BG levels [section 3B]

#### 2B: To initiate OAD in patients newly detected to have diabetes at admission

(At admission: pre-meal BG: 150 to 180 mg/dl and/or post-meal BG 200 to 250 mg/dl)

- A. Consult Endocrinologist/physician at earliest to initiate or optimize OAD
- B. If there is an anticipated delay in consulting endocrinologist/physician, initiate on Tab Metformin (either immediate or sustained release) 500 mg BD and a Gliptin (Tab Vildagliptin 50 mg BD or Tab Sitagliptin 100 mg OD or Tab Linagliptin 5 mg OD or Tab Teneligliptin 20 mg OD), provided patient meets all the following criteria:
- Pre-meal blood glucose is between 150 and 180 mg/dl <u>and/or</u> post-meal blood glucose is between 200 and 250 mg/dl.
- ii. Other criteria as mentioned in Section 2A are fulfilled.
  - C. If BG levels at admission are above the range mentioned (pre-meal ≥180 mg/dl or post-meal blood glucose ≥250 mg/dl) → start on insulin (Preferably consult endocrinologist or physician/ refer section 3A)
  - D. Do not initiate drugs like pioglitazone and SGLT2 inhibitors in patients with COVID.
  - E. In moderate to severe COVID, stop pioglitazone and SGLT2 inhibitors if patient is already taking them. (See figure given below)

# \*Capillary BG monitoring in both section 2A and 2B: BBF, ABF, BL, AL, BDN and ADN (refer to table 1)



#### Section 3: Basal-bolus insulin regimen

#### 3A: To initiate insulin for patients newly detected with diabetes

Indication: At admission: pre-meal BG: ≥180 mg/dl or post-meal BG ≥250 mg/dl

- A. Total daily dose (TDD) = 0.4 units/kg/day (age > 65 yr, nephropathy or liver disease, use 0.2 units/kg/day)
- B. Total daily dose is divided equally into 4 doses (25% each): 3 doses are for bolus insulin (Regular insulin 30 min before breakfast, before lunch and before dinner) and 1 dose for basal insulin (Inj. NPH insulin at bed time/ 2 hours after dinner)

Example: 58 yr old male with body weight of 60 kg presented with pre-meal BG of 184 mg/dl and post-meal BG of 302 mg/dl

Total daily dose = 0.4 units/kg/day =  $0.4 \ge 60 = 24$  units per day Initial insulin regimen to be prescribed for him:

- Inj. Regular insulin 6 units SC 30 min before breakfast, 6 units SC 30min before lunch and 6 units SC 30 min before dinner
- Inj. NPH insulin 6 units SC at bed time/ 2 hours after dinner

## 3B: If patient is on OAD and blood glucose levels are uncontrolled (Pre-meal BG ≥140 mg/dl or postmeal BG ≥180 mg/dl)

- A. If pre-meal BG value is 140 to 180 mg/dl and/or post-meal BG value is 180 to 250 mg/dl → consult endocrinologist/physician for OAD optimization
- B. If pre-meal BG value ≥180 mg/dl and/or post-meal BG value ≥250 mg/dl despite being on OAD → start basalbolus insulin regimen using calculation mentioned in section 3A (Kindly note that in this particular scenario, OADs apart from Metformin and Gliptins need to be stopped). Consult endocrinologist/physician for optimization.

Caveat: Bolus insulin (Inj. Regular insulin) may not always be needed for all the three meals and can only be added to individual meals requiring prandial coverage (i.e., for meals with pre-meal to post-meal BG increment of >40 mg/dl on a given day, regular insulin should be added before these meals on the next day). For example, on a given day BG levels increased from 112 mg/dl (BL) to 204 mg/dl (2h AL). Since increment is >40 mg/dl (92 mg/dl), Inj. Regular insulin should added before lunch on the next day.

C. If FPG is ≥140mg/dl and post-meal increment in BG level is normal (<40 mg/dl), then one can just add basal insulin (Inj. NPH insulin bedtime/ 2 hours after dinner)</p>

#### 3C: Patient is already on basal-bolus insulin regimen at admission

Continue existing regimen. Monitor blood glucose levels and review with BG log to an endocrinologist/ physician.

#### 3D: To switch to basal-bolus insulin regimen from insulin infusion

- A. Consult endocrinologist/ physician to switch to basal-bolus insulin regimen
- B. If there is an anticipated delay in consulting the endocrinologist/physician, follow the steps mentioned below to switch to basal bolus regimen:
- Calculate the total daily dose (TDD) based on insulin infusion requirements for the last 24 hours: TDD = 80% of the total daily insulin requirement on IV infusion in the last 24 hours.
- ii. Once you have the TDD, calculate the doses of bolus insulin (Inj. Regular insulin) and basal insulin (Inj. NPH insulin) as described in section 3A (refer step B and example)
- iii. Important pointers:
  - a. Do not switch from insulin infusion to basal bolus regimen until BG levels are controlled on insulin infusion, patient is orally accepting or on RT feeds and is hemodynamically stable
  - b. Insulin infusion has to be overlapped with basal-bolus insulin regimen for 60-120 minutes before stopping.
    Do not stop insulin infusion abruptly.

Example: A 54-year-old male patient is on IV insulin infusion and his BG levels are adequately controlled for the last 24 hours. His oral acceptance is good and vitals are stable. At **11 am his BG level is 132 mg/dl and we decide to switch to basal-bolus insulin regimen**. We calculate the dose and plan to start Inj. Regular insulin 6 units SC BBF, 6 units SC BL and 6 units SC BDN and Inj. NPH insulin 6 units SC at bed time/ 2 hours after dinner. We should not stop insulin infusion at **11 am, rather continue it till lunch. At 12.30 pm we give Inj. Regular insulin 6U SC (as calculated), patient takes lunch at 1:00 pm, insulin infusion is continued as per scale and finally stopped 1 hour later at <b>1.30 pm (after the overlap).** 

#### 3E: Patient is on Ryles Tube (RT) feeds

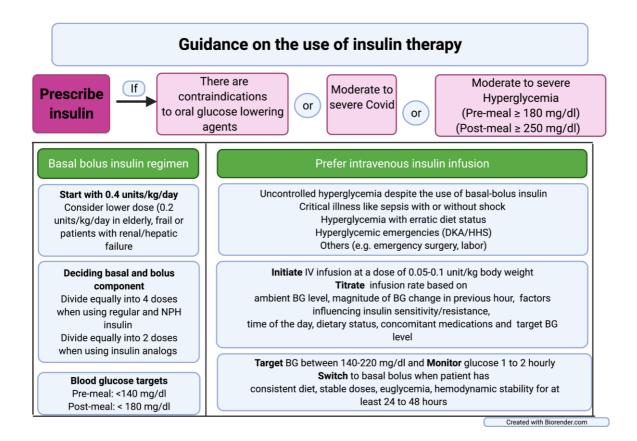
A. Like standard meals, RT feeds should be divided into 3 major and 3 minor feeds. Major and minor feeds are defined by calories/quantity of feeds. (Example: major feed: 300ml each and minor feed: 150 ml each)

Timings of major feed: 9 am, 1.30 pm, 7 pm.

Timings of minor feed: 11 am, 4.30 pm, 10 pm.

B. Basal-bolus insulin regimen would be preferred in such patients. Bolus insulin (Inj. Regular insulin) should be given 30 min before each major feed and basal insulin (Inj. NPH insulin) should be given at 10 pm. along with the last minor feed. Capillary blood glucose monitoring should be performed before and 2 h after each major feed.

C. Dose calculation for basal-bolus insulin regimen (section 3A) and indications for insulin infusion (section 4) discussed elsewhere in the document would similarly apply for such patients (See figure given below).



#### 3F. Titration of insulin doses and glycemic targets

A. The most important point to remember while titrating insulin doses is that we titrate proactively and not reactively, i.e., insulin doses are adjusted based on the previous day's BG log (taking into account action of bolus and basal insulin on the previous day) and not the current BG value.

B. The dose of bolus insulin for each major meal (or major feed) is titrated such that pre-meal to postmeal BG increment remains around 30 to 50 mg/dl. If postprandial excursion is above this range, one should check whether the insulin injection technique is correct, there is an adequate time gap between the injection of prandial insulin and the meal (30 minutes for regular insulin) and that the quality and quantity of carbohydrate in the meal is appropriate and relatively fixed. If these factors do not contribute to the postprandial excursion or the excursion persists despite addressing these factors, the dose of prandial insulin (regular insulin) should be increased on a subsequent day.

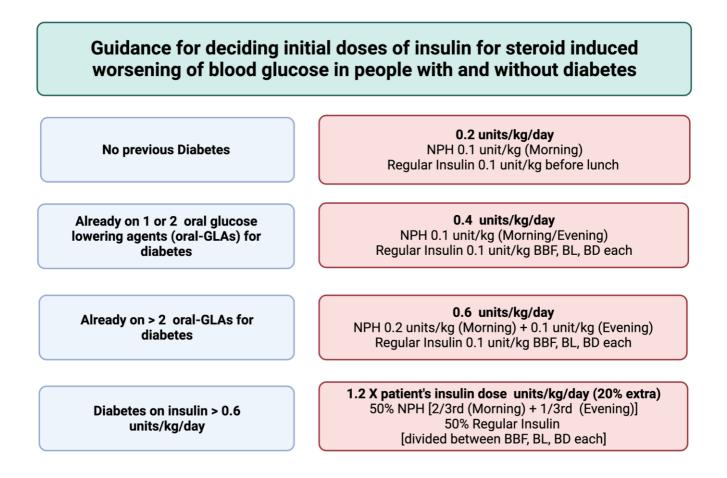
Example: At lunch (or major feed # 2), if at a dose of 6 units (Inj. Regular insulin), pre-meal to post-meal BG increment was 80 mg/dL (refer to table 1, date: 22/6/2020 and 23/6/2020), the insulin dose can be increased to 8 units (Inj. Regular insulin) from the next day provided the insulin injection technique is correct, the time gap between regular insulin and meal was appropriate and quantity and quality of carbohydrate in lunch was appropriate and consistent.

C. Basal dose is adjusted based on FPG. If FPG is  $\geq$ 140 mg/dl, the basal dose (Inj. NPH insulin) administered at bed time should be increased (usually by 2 units, but may be higher) to target the FPG to <140 mg/dl on the next day. (Refer to table 1, date 25/6/2020 and 26/6/2020). Increment in the dose of basal insulin should be done after excluding nocturnal (especially 3 am) hypoglycemia.

D. Titration of insulin doses in patients prescribed glucocorticoids: Glucocorticoids are known to worsen hyperglycemia and may necessitate adjustment in insulin doses. The adjustment will depend upon the type of glucocorticoid used: short acting (hydrocortisone, duration of action: 8-12 hours), intermediate acting (prednisolone, duration of action: 12-36 hours) and long acting (dexamethasone, duration of action: 36 hours) and frequency of its administration. Methylprednisolone and dexamethasone are the commonly used glucocorticoids in patients with COVID-19. If patient receives a long acting glucocorticoid (say 8 mg dexamethasone) as a single daily dose or twice daily methylprednisolone, the hyperglycemic effect is likely to persist throughout the day and so the titration of insulin doses would be same as mentioned above (point A to C) with the exception that higher insulin doses/increments would be required in case of steroids.

If patient is on high-dose intermediate acting steroid (say prednisolone or methylprednisolone 60 mg) administered as a single dose at 9 am, the peak hyperglycemic effect is expected in the afternoon and evening hours (between 12pm to 8pm). Accordingly, the patient would require a higher dose before lunch. Alternatively, Inj. NPH insulin may be useful since pharmacokinetics of NPH closely mimics the effect of steroid (prednisone/methylprednisolone) on blood glucose level; NPH insulin can be administered at before breakfast or at 9 am in such a scenario.

Guidance on approximate doses required in different scenarios when steroids are used is provided in the figure given below. The doses of insulin will vary depending upon steroid type, dose and frequency of administration.



E. Glycemic targets: For most patients on basal-bolus insulin regimen (or for in-patient hyperglycemia management, in general), pre-meal BG level of <140 mg/dl and post-meal BG level of <180 mg/dl can be targeted. In selected individuals, target levels of <120 mg/dl (pre-meal) and <160 mg/dl (post-meal) can be considered, provided these can be achieved without causing undue hypoglycemia.

\*Capillary BG monitoring in section 3A to D: BBF, ABF, BL, AL, BDN and ADN (refer to table 1)

#### Table 1: Blood glucose log

### Blood glucose Log

Date		BBF	ABF	BL	AL	BD	AD	3am
	Glucose							
	Insulin							
	Steroid				I			<u> </u>
	Glucose							
	Insulin							
	Steroid		1	1	1			<u> </u>
	Glucose							
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	Steroid							•
	Glucose							
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	Glucose							
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	Steroid							
	Glucose							
	Insulin							
	Steroid							

Abbreviations: BBF: Before breakfast, ABF: After breakfast, BL: Before lunch, AL: After lunch, BDN: Before dinner, ADN: After dinner, R: Regular insulin, N: NPH insulin

# Monitor 3 am blood glucose when fasting blood glucose is persistently out of target

#### Section 4: Intravenous insulin infusion

#### A. Indications for the use of intravenous insulin infusion

Advised when blood glucose is persistently above 180 mg/dl (two or more values) under following situations:

- 1. Patients with nothing by mouth (NPO) status or those having erratic diet pattern (in time and content)
- 2. Diabetic Ketoacidosis (DKA)
- 3. Uncontrolled hyperglycemia despite MSII use
- 4. Severe hyperglycemia at onset (Pre-meal BG level ≥300 mg/dl and post-meal BG level ≥400 mg/dl)- despite use of subcutaneous insulin. Ketone status should be checked before starting infusion
- 5. Critically ill like in sepsis and septic shock

#### **B.** Initiation of insulin infusion:

Insulin can be initiated at dose of 0.05-0.1 units/kg body weight/hour.

- **C. Infusion preparation:** 50 units of regular insulin in 50 ml NS (1unit/ml). A full label should be placed on the 50 ml syringe barrel which should not obscure the numerical scale. Priming should be done before starting the infusion by flushing 20 ml of prepared solution through intravenous tubing. Any unused insulin solution should be discarded after 24 hours. If syringe pumps are not available, gravity-assisted pediatric infusion sets could be used for IV insulin delivery.
- **D. Frequency of blood glucose monitoring:** 2 hourly. Can be extended to 4 hourly, where requirement is low, glucose values are stable and in target.
- **E. Glycemic targets**: To achieve and maintain blood glucose of 140 to 180 mg/dl for most individuals. BG target can be tightened to 110-180 mg/dl in a scenario where this target can be achieved without causing significant hypoglycemia and relaxed to 200-220 mg/dl where even a target of 140-180 mg/dl is unsafe and associated with increased risk of hypoglycemia.
- **F.** Further titration of insulin infusion rate: Further titration of insulin infusion rates should be done based upon ambient blood glucose level, target blood glucose level and magnitude of blood glucose change in the previous hour. Other factors that should be accounted for are timing and content of meals, insulin sensitivity, and previous day's glycemic response.

A simple and popular formula: Infusion rate (units/hr) = BG level (mg/dl)/100 is good to calculate initial infusion rate. However, it should not be relied upon for titration because it does not account rate of BG change in the preceding hours.

#### **Examples**:

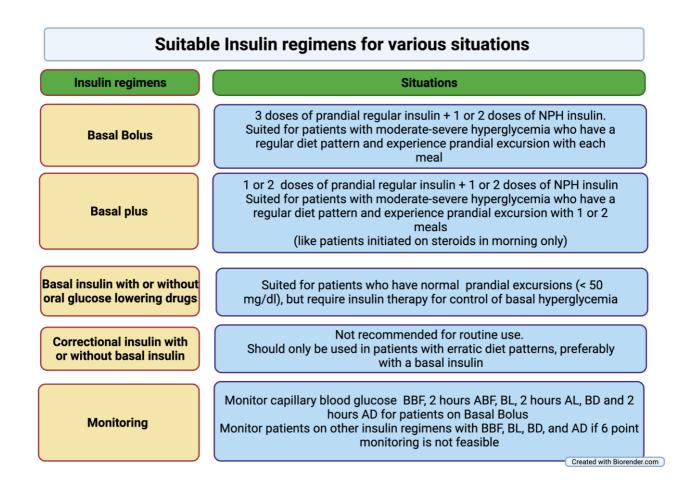
- At an ongoing rate of 3 units/hr, BG decreased from 280 mg/dl 2-hour before to a current level of 250 mg/dl (drop of 15 mg/dl/hour). We expect the level to be 220 mg/dl (above target) after 2 hours at the current rate. So, the infusion rate should be increased.
- At an ongoing rate of 1.8 units/hr, BG decreased from 185 mg/dl 2-hour before to a current level of 170 mg/dl (drop of 7.5 mg/dl/hour) and we expect the level to be 155 mg/dl (in target) after 2 hours at the current rate. So, we can continue the same infusion rate.
- 3. At an ongoing rate of 1.2 units/hr, blood glucose decreased from 144 mg/dl 2-hour before to a current level of 100 mg/dl (drop of 22 mg/dl/hour), and we expect the level to be 56 mg/dl after 2 hours at the current rate. So, the infusion rate should be decreased (say by 50% to 0.6 units/hr).
- 4. At an ongoing rate of 1.2 units/hr, BG decreased in the middle of night from 108 mg/dl 2-hour before to a current level of 60 mg/dl. In such a scenario, infusion should be discontinued, correction should be provided (50 ml of 50% dextrose in a sedated/unconscious patient, and 15-20 grams of oral glucose solution in a conscious patient) and blood glucose checked every 15-20 minutes till 2 or more values are >100 mg/dl, when the infusion can be restarted at 0.6 units/hr with close monitoring every 30-60 minutes for next 2 hours.
- G. Target rate of BG change: Initially, it should be between 50-100 mg/dl/hour (50-75 mg/dl/hour may also be appropriate), target BG levels are reached and steady state is maintained. If the rate of blood glucose change is <50 mg/dl or >100 mg/dl, consider increasing and decreasing the infusion rates, respectively.
- **H.** Coverage for meals: For prandial coverage, increase the infusion rate by 2-4 units/hour over and above the basal rate just before taking the major meal and continue the increased rate for next 2 hours. It is important to remember that IV insulin infusion has two components: a) basal coverage provided by the maintenance rate of IV insulin, and b) prandial coverage provided by an increment in the maintenance rate for 2 hours around a meal.

Example: A 54-year-old male patient is on IV insulin for hyperglycemia management. He has good oral acceptance and is planning to take lunch at 1 pm. At 1 pm, his BG level is 202 mg/dl and according to scale, infusion rate is 2 U/hr, but we increase the infusion rate to 5 U/hr (2+3 U/hr) from 1pm to 3pm to provide prandial coverage. From 3pm onwards, the basal infusion rate (or maintainence rate) is continued till the time of next meal. Increment in rate for meal coverage is subjected to change on the next day based on pre-meal to post-meal change in BG level on the previous day.

**I. Monitoring of serum potassium:** Intravenous insulin is associated with potassium shifts inside the cell. Therefore, serum potassium should be monitored every 6 hours in patients with NPO status and every 12 hours in those who are accepting orally.

#### **General Comments**

- 1. The discontinuation of insulin infusion (where necessary) should be for a minimum period of time to ensure better glycemic control. For example, if insulin infusion is discontinued for the patient's bath, it should be restarted as soon as patient comes back with total interruption time of less than 10 to 15 minutes.
- 2. The timings and doses of insulin described in this document are with regard to use of Inj. Regular insulin as a bolus (or prandial) insulin and Inj. NPH insulin as a basal insulin. However, in a scenario where insulin analogs are used (rapid-acting analogs such as insulin aspart, insulin lispro, and insulin glulisine, and long-acting basal analogs such as insulin glargine, and insulin degludec) these specifications would change accordingly. For instance, a) the onset of action is faster with rapid-acting insulin analogs and a gap of 5-15 minutes before the meal is adequate, b) long acting basal insulin analogs have a prolonged duration of action lasting 24 hours or more, and can be administered at any relatively fixed time of the day, c) when using insulin analogs for basal-bolus insulin regimen, basal insulin constitutes 50% of TDD, while bolus insulin account for the rest 50% (further divided into three equal portions for each meal)
- 3. A guidance on use of insulin regimens in different scenarios is provided in figure given below.
- 4. Gliptins: Sitagliptin, Teneligliptin, Vildagliptin, Linagliptin
- 5. Abbreviations: ADN: After dinner; BBF: Before breakfast, BDN: Before dinner, BL: Before lunch, BG: Blood glucose; CBG: Capillary blood glucose; COVID-19: Coronavirus disease 2019; DKA: Diabetic ketoacidosis; FPG: Fasting plasma glucose; HbA1c: Hemoglobin A1c; IV: Intravenous; MSII: Multiple subcutaneous insulin injections; N: NPH insulin; NPH: Neutral Protamine Hagedorn; NPO: Nothing by mouth; NS: Normal saline; OAD: Oral antihyperglycemic drug; R: Regular insulin; RT: Ryles tube; TDD: Total daily dose



#### **Suggested Readings**

- 1. Goyal A, Gupta S, Gupta Y, Tandon N. Proposed guidelines for screening of hyperglycemia in patients hospitalized with COVID-19 in low resource settings [published online ahead of print, 2020 May 29]. Diabetes Metab Syndr. 2020;14(5):753-756.
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- 3. Moghissi ES, Korytkowski MT, Dinardo MM et al. American Association of Clinical Endocrinologists and American Diabetes Association consensus statement on inpatient glycemic control. Diabetes Care 2009; 32(6):1119-1131.
- 4. Attri B, Goyal A, Gupta Y, Tandon N. Basal-Bolus Insulin Regimen for Hospitalised Patients with COVID-19 and Diabetes Mellitus: A Practical Approach [published online ahead of print, 2020 Jul 18]. Diabetes Ther. 2020;1-18. doi:10.1007/s13300-020-00873-3.
- 5. Rayman G, Lumb A, Kennon B, et al. Guidance on the management of Diabetic Ketoacidosis in the exceptional circumstances of the COVID-19 pandemic. *Diabet Med.* 2020;37(7):1214-1216. doi:10.1111/dme.14328
- 6. Rayman G, Lumb A, Kennon B, et al. New Guidance on Managing Inpatient Hyperglycaemia during the COVID-19 Pandemic. *Diabet Med.* 2020;37(7):1210-1213. doi:10.1111/dme.14327
- 7. Kelly JL. Continuous Insulin Infusion: When, Where, and How?. Diabetes Spectr. 2014;27(3):218-223.
- 8. Gupta Y, Goyal A, Kubihal S, Golla KK, Tandon N. A guidance on diagnosis and management of hyperglycemia at COVID care facilities in India. Diabetes Metab Syndr. 2021 Jan-Feb;15(1):407-413.

# A guidance on diagnosis and management of hyperglycemia at COVID care facilities in India.

