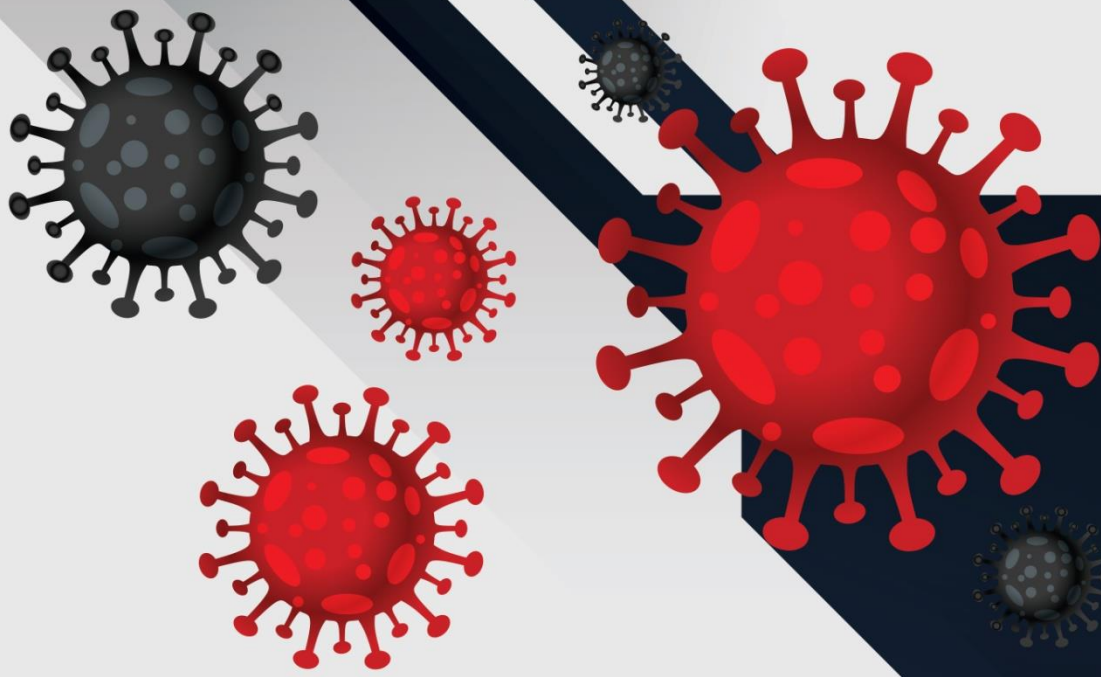
ACEDB CLINICAL PRACTICE GUIDELINE FOR THE TREATMENT OF DIABETES, ENDOCRINE AND METABOLIC DISEASES IN PATIENTS WITH COVID-19

ASSOCIATION OF CLINICAL ENDOCRINEOLOGIST AND DIABETOLOGIST OF BANGLADESH

ACEDB CLINICAL PRACTICE GUIDELINE FOR THE TREATMENT OF DIABETES, ENDOCRINE AND METABOLIC DISEASES IN PATIENTS WITH COVID-19

Publication date : December 2020
Published by : ACEDB

ASSOCIATION OF CLINICAL ENDOCRINEOLOGIST AND DIABETOLOGIST OF BANGLADESH



Dedicated to the sacred memory of doctors who sacrificed their lives during Covid-19 pandemic to serve the Humanity.

ASSOCIATION OF CLINICAL ENDOCRINEOLOGIST AND DIABETOLOGIST OF BANGLADESH

Preface:

The world is now facing an unprecedented catastrophe of coronavirus disease-19(COVID-19) after its first diagnosis in December 2019 in Wuhan, Hubei Province of China as a cluster of pneumonia cases of unknown etiology. After deep sequencing analysis revealed a novel coronavirus as the causative agent, subsequently named as Severe Acute Respiratory Syndrome Coronavirus-2(SARS-CoV-2) and disease it causes called COVID-19. SARS-CoV-2 has shown phylogenetic and clinical similarities with SARS-CoV, but this novel coronavirus appears to have higher transmissibility. Within a short span of time, the disease spreads exponentially almost all parts of the globe with huge number of infected cases and mortality.

On 30 January 2020, the World Health Organization (WHO) declared the COVID-19 outbreak a Public Health Emergency of International Concern, and on March 11, the epidemic was upgraded to pandemic.

As on 19 December, 2020 total number of confirmed cases in Bangladesh are 4,99,560 and death 7242. Total global infected cases are 7,42,99,042 and death 16,69,982 involving 213 Countries & Territories.

Diabetes mellitus is one of the most important co-morbidities linked to the severity of COVID-19. Evidence from epidemiological observations in regions heavily affected by SARS-CoV-2, reports from the Centre for Disease Control and Prevention (CDC), other national health centers and hospitals showed that the risk of a fatal outcome from COVID-19 is up to 50 percent higher in patients with diabetes than those who do not have diabetes. Patients suffering from other endocrine and metabolic diseases like thyroid disorders, adrenal dysfunction, obesity etc. are also adversely affected by COVID-19.

The health care system and facilities of different countries including Bangladesh are facing tremendous burden in managing this outbreak. Association of Clinical Endocrinologist and Diabetologist of Bangladesh(ACEDB) has come forward to develop a clinical guideline with the objective of better management of diabetes, endocrine and metabolic diseases in patients with COVID-19. As a novel viral disease, new information are coming every day. This is a living document, will be updated from time to time with necessary corrections and modifications incorporating newer evidences to full fill the need of the time.

I extend my heartfelt thanks and gratitude to all members of the Committee for their sincere and hard labor to develop this ***rapid advice guideline*** within a short time. I also extend my gratitude to President and Secretary General of ACEDB for their full hearted co-operation.

Prof. Md. Nazrul Islam Siddiqui

Chairman
ACEDB Clinical Practice Guideline Committee

Table of Contents:

Chapter	Title	Page
	Introduction to development of guideline	3
	Executive summary	6
1.	Background	9
2.	Epidemiology, pathophysiology & presentation of COVID-19 in diabetes	14
3.	Glycemic targets & blood glucose monitoring	19
4.	Life style management of diabetes in COVID-19 patients	22
5.	Sick day rules in COVID-19 with diabetes: indication for hospitalization	26
6.	Management of diabetes in patients with COVID-19 at hospital settings	31
7.	Pharmacological management of diabetes mellitus in COVID-19	86
8.	Glycemic management after recovery from COVID-19	91
9.	Management of diabetes in pregnancy during COVID-19 pandemic	92
10.	Management of endocrine & metabolic diseases during COVID-19 pandemic	115
11.	Measures for prevention and control of COVID-19 pandemic	140
	Annex-1 and Annex-2	153

List of Abbreviations

Abbreviation	Elaboration
AACE	American Association of Clinical Endocrinologists
ACE	American College of Endocrinologist, Angiotensin - converting enzyme
ACTH	Adrenocorticotropic hormone
ARB	Angiotensin II receptor blocker
ARDS	Acute respiratory distress syndrome
ASBMR	American Society for Bone and Mineral Research
ATD	Anti thyroid drugs
BADAS	Bangladesh Diabetic Somity
BMD	Bone mineral density
BMI	Body mass index
CBG	Capillary blood glucose
CDC	Centers for Disease Control and Prevention
CGM	Continuous glucose monitoring
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus disease 2019
CPG	Clinical practice guideline
CRRT	Continuous renal replacement therapy
CSII	Continuous subcutaneous insulin infusion
DGHS	Directorate General of Health Services
DKA	Diabetic ketoacidosis
DM	Diabetes mellitus
DPP4	Dipeptidyl peptidase 4
CDC	Centers for Disease Control and Prevention
CGM	Continuous glucose monitoring
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus disease 2019
CRRT	Continuous renal replacement therapy
CSII	Continuous subcutaneous insulin infusion
DGHS	Directorate General of Health Services
DKA	Diabetic ketoacidosis
DM	Diabetes mellitus
DPP4	Dipeptidyl peptidase 4
eGFR	Estimated glomerular filtration rate
ESPEN	European Society of Clinical Nutrition And Metabolism
FPG	Fasting plasma glucose
FRAX	Fracture risk assessment tool
GDM	Gestational diabetes mellitus
GLP1	Glucagon-like peptide 1
HCP	Health care provider
HHS	Hyperosmolar hyperglycemic state
HPA	Hypothalamic–pituitary–adrenal
ICU	Intensive care unit
IDF	International Diabetes Federation
IGF1	Insulin-like growth factor 1

Abbreviation	Elaboration
IUD	Intrauterine death
IV	Intravenous
JAMA	Journal of the American Medical Association
MERS	Middle east respiratory Syndrome
MRI	Magnetic resonance imaging
NGSP	National Glycohemoglobin Standardization Program
NHS	National Health Services
NICE	National Institute for Health and Care Excellence
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NOF	National Osteoporosis Foundation
NPH	Neutral protamine Hagedorn
NSAID	Non-steroidal anti-inflammatory drugs
OAD	Oral antidiabetic drug
OGSB	Obstetrical and Gynaecological Society of Bangladesh
OGTT	Oral glucose tolerance test
OPD	Outpatient department
PHPT	Primary hyperparathyroidism
PP	Post prandial
PPE	Personal protective equipment
PPG	Post prandial glucose
RAAS	Renin angiotensin aldosterone system
RBG	Random blood glucose
RCOG	Royal College of Obstetrics and Gynaecology
RPG	Random Plasma glucose
RSSDI	Research Society for the Study of Diabetes in India
SARS	Severe acute respiratory syndrome
SC	Subcutaneous
SD	Strandard deviation
SE	Standard error
SGLT2	Sodium glucose transporter 2
SMBG	Self-monitoring of blood glucose
TSH	Thyroid stimulating hormone
TV	Testicular volume
UFC	Urinary free cortisol
WHO	World Health Organization

Introduction to development of guideline

Prof. Abdus Saleque Mollah
President, ACEDB

Background:

The novel severe acute respiratory syndrome corona-virus 2 (SARS-CoV-2) is the cause of a rapidly spreading illness, Coronavirus Disease 2019 (COVID-19), affecting thousands of people around the world with significant morbidity and mortality. Diabetes is an established risk factor for severe infection and higher mortality from COVID -19. Better glycemic control can significantly improve the outcome of disease by reducing the progression to severity and mortality.

The World Health Organization (WHO), International diabetes Federation (IDF), United States Center for Disease Control and Prevention (CDC), and many other national and international organizations devoted to diabetes and endocrine disease management have issued preliminary guidance on infection control, screening, diagnosis and treatment of COVID-19. As the new knowledge is emerging every day on SARS-CoV-2, the existing guidelines are continuously updating and there are demands for new guidelines.

According to the IDF 2019 report, 8.4 million people have had diabetes and the same number of people are at risk of developing diabetes in Bangladesh. Like all other countries in the world, Bangladesh is working continuously to control and contain, as well as for better treatment of the disease. At this moment, it is essential for the health care providers of the country to have a general updated guideline for the management of diabetes and other endocrine diseases of the patients suffering from COVID-19. ACEDB, as an authoritative voice in the field of endocrinology and diabetology of the country came forward to help the HCPs concerned and developed this guideline.

Procedure:

The purpose of this guideline is to maximize the benefit and safety of patients who need diabetes and endocrine care during the COVID-19 pandemic, while protecting staff from infection. It will also reduce unnecessary variations in practice and enable diabetes and endocrine HCPs to make the best use of the available resources.

Executive Committee of ACEDB realized the absolute necessity of such a guideline as early as possible to help HCPs who are caring these patients. The EC named the guideline as "ACEDB Clinical Practice Guideline For The Management Of Diabetes, Endocrine And Metabolic Diseases In Patients With COVID-19'' (ACEDB CPG: DM & COVID-19 in abbreviated form). An 11-member guideline development committee (Annex 1) headed by Professor Md. Nazrul Islam Siddiqui and a 7-member guideline review committee (Annex 2) headed by Professor Abdus Saleque Mollah has been formed. Members of both the committees are the imminent endocrinologists and diabetologists of Bangladesh. Members of the guideline development committee were chosen by the chair of the committee based primarily on their interest and willingness to contribute to the writing of the different chapter of this guideline, as well as on their clinical experience and expertise in patient management on diabetes and endocrine diseases. Members of the review committee were chosen by the chair of the committee based on their previous experience in development of guidelines and recommendations, in addition to clinical experience and expertise in patient management on diabetes and endocrine diseases. Regarding the experience of management of COVID-19

pandemic, all the members were novel. The members were included from the medical universities, medical colleges and academic health institutes and hospitals throughout the country. The opinions or views expressed in this professional education guideline are those of the authors and do not necessarily reflect the opinions or recommendations of the ACEDB. All the members of both the committee declared to have no conflict of interest.

The recommendations are based on queries that have been emphasized to be important by clinicians, questions that have been raised by colleagues and social media, and recommendations guided by using focused-literature review. ACEDB CPG: DM & COVID-19 committee searched the literature for direct and indirect evidence on relevant questions regarding the management of diabetes in patents with COVID-19. The committee also searched the literature for relevant questions regarding the management of endocrine diseases other than diabetes in patents with COVID-19. This guidance is based on the latest scientific evidences available from the literature on management of diabetes, other endocrine diseases and COVID-19. In this guideline we do not rate the recommendations on the basis of the strength (A, B, or C) or the quality (I, II, or III) of the evidence that supports the recommendation. Recommendations in this guideline is based on also the balance between benefit and harm, resource and cost implications, perspective, and feasibility.

After submission by the guideline development committee each chapter of the initial draft of the guideline has been reviewed and suggested for modification as necessary by the review committee. Then in a joint meeting of the guideline development committee and the review committee each chapter was finalized. Any disputed matter was voted on by all the members of joint committee. A majority vote was required for a suggestion or recommendation to be included in the final guideline. Before publication, the ACEDB CPG: DM & COVID-19 was approved by the executive committee of ACEDB. The steps in the process of development of the guideline has been summarized in Figure. Because clinical information about the optimal management of COVID-19 is evolving quickly, this guideline will be updated frequently as published data and other authoritative information becomes available.

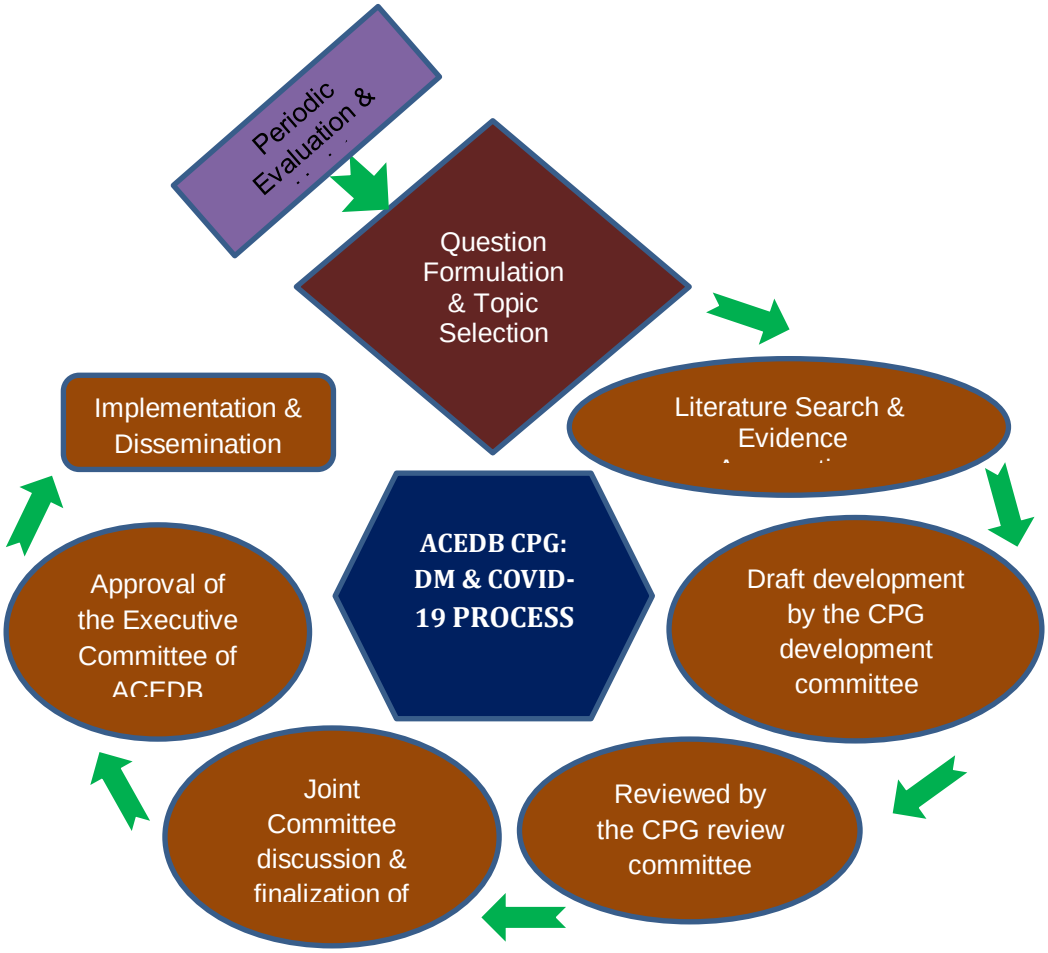


Figure- Steps in the process of the development of ’ACEDB Clinical Practice Guideline For The Management Of Diabetes, Endocrine And Metabolic Diseases In Patients With COVID-19’’ (ACEDB CPG: DM & COVID-19)

This guideline is expected to be very helpful as Bangladesh has a very significantly growing population that is affected by diabetes irrespective of age, sex, socioeconomic strata, and areas of living. At the same time, the number of people with diagnosed or undiagnosed COVID-19 has been increasing rapidly across the country, and there is little chance that the COVID-19 will be irradicated completely from the country in near future.

Executive Summary

Dr. Indrajit Prasad

Introduction and scope

This rapid advice guideline has been prepared by the members of ACEDB to provide guidance on management of diabetes mellitus and other endocrine-metabolic disorders during the COVID-19 pandemic.

The scope of this guideline is to review the available literatures and recommend an appropriate strategy to manage cases in the context of available resources in Bangladesh.

Diabetes has been found to be an independent predictor of admission to ICU, invasive ventilation or death in COVID-19.The risk of a fatal outcome from COVID-19 may be up to 50% higher in patients with diabetes than in Patients without diabetes.

Glycemic targets & blood glucose monitoring

Plasma glucose concentration: 4-8 mmol/L (72-144 mg/dL) for outpatients or 4-10 mmol/L (72-180 mg/dL) for inpatients/intensive care, with possible upward adjustment of the lower value for frail patients to 5 mmol/L (90 mg/dL).

Self-monitoring of blood glucose (SMBG) of capillary blood is an acceptable alternative to plasma glucose estimation in present scenario. For patients on insulin with poor glycemic control or recurrent hypoglycemia, SMBG is advised at least 4 times/day, i.e., at fasting, before lunch, before dinner and at bedtime. For patients on oral hypoglycemic agents with acceptable control, measuring fasting and post-prandial capillary blood glucose once or twice a week is acceptable.

Life style management: dietary advice & home based physical activity

Life style management is an integral part of diabetic management. Patient should continue to take a previously planned balanced diet as he was taking previously. Eat green, leafy vegetables. Eat fruits in two or three servings. Frequent drinking of plain water or sugar free drink to maintain hydration. Critical patients who cannot take orally, should receive NG feeding or parenteral nutrition, psychological intervention should be carried out for patients in need.Emphasis should be given on home based exercise, however Symptomatic COVID-19 patient should avoid exercise.

COVID-19 with diabetes - Indication for hospitalization

In non-severe cases virtual consultation is encouraged.

Indication for Hospitalization:

a) Clinical feature of moderate, severe and critical Covid-19 cases b) Blood glucose > 15 mmol/l on repeated measurements) ketones in urine, d) excessive thirst, e) Vomiting or diarrhea persist for more than 6 hours, f) Unable to take food and drinks for 6 hours, g)Weight loss of ≥2.5 kg during the illness, h)Rapid breathing, i)Abdominal pain, j) Reduced level of consciousness (drowsiness), k) Co-existing serious morbidities.

Diabetes management at hospital settings in patients with COVID-19

Subcutaneous insulin is reasonable for most general surgical and medical patients outside the ICU. Insulin analogues usually produce a lower incidence of hypoglycemia.

Basal insulin or a basal plus bolus correction insulin regimen is the preferred treatment for noncritical ill hospitalized patients with poor oral intake or those who are taking nothing by mouth. An insulin regimen with basal, prandial, and correction components is the preferred treatment for noncritical ill hospitalized patients with good nutritional intake and also for patients requiring glucocorticoid. Use of only a sliding scale insulin regimen in the inpatient hospital setting is strongly discouraged.
Calculate total daily insulin dose using 0.5 units/kg and give half the total dose as basal/background insulin and half as bolus/mealtime rapid acting insulin.

- DKA (defined as glucose >11mmol/L or history of diabetes, blood ketones ≥ 3mmol/L or urine ketones ≥ +2 and pH <7.3 or bicarbonate <15). Note: glucose can be normal in SGLT-2 inhibitor associated DKA & pregnancy associated DKA
- HHS (defined as glucose ≥ 30mmol/L, Serum Osmolality ([(2 x Na) + glucose + urea] > 320mOsm/kg and pH > 7.3)
- Treatment of DKA & HHS should be as per protocol.

Pharmacological management of diabetes mellitus in COVID-19

a) Mild cases : There is no need to adjust the original regime too much. Both OAD ,insulin or combination treatment can be maintained
b) Moderate cases : Original treatment regime is to be maintained if patient's cognitive condition, appetite and glucose control are within normal range. In patients with obvious COVID-19 symptoms who cannot eat regularly, OAD is to be switched to insulin
c) Severe and critical cases : Intravenous insulin injection should be the first-line treatment
d) Metformin & SGLT2 inhibitors should be avoided in severe or critically ill patient

Glycemic management after recovery from COVID 19

- During diabetes management in hospital with COVID 19 insulin is the preferred treatment.
- Insulin should be continued for at least six weeks after discharge, because patient cannot take oral food adequately .
- They should do SMBG; BBF, 2hrs after breakfast, 2hrs after lunch, and before dinner per day initially.
- Maintain contact with endocrinologist to modify insulin dose and schedule at least initial few days.
- Patients who were on OAD prior to hospital stay; they can be shifted to OAD after six weeks.
- As physical wellbeing resume, they can start physical exercise .

Hyperglycemia in pregnancy, delivery & lactation with COVID-19

Diabetes in pregnancy may be either pre-existing diabetes or gestational diabetes mellitus (GDM).

Glycemic Target:

- Fasting glucose < 95 mg/dL (5.3 mmol/L) and either
- One-hour postprandial glucose <140 mg/dL (7.8 mmol/L) or
- Two-hour postprandial glucose <120 mg/dL (6.7 mmol/L)[7]

Virtual consultation for diabetes management is encouraged to avoid COVID-19 transmission during the pandemic.
If lifestyle management fails to control blood glucose, insulin should be started & closely monitored.

Breast feeding: There is currently insufficient evidence regarding the safety of breastfeeding and the need for mother/baby separation. Except in the sickest women with COVID-19

infections (i.e., those requiring respiratory support or intensive care admission), the benefits of breast feeding outweigh any potential transmission risks

Mood of delivery : COVID- 19 is not an indication for cesarean section, unless the woman's respiratory condition demands urgent delivery, or pregnant women have other indications.

Management of endocrine and metabolic disorders during COVID -19 pandemic

Thyroid disorders: there are reports of subacute thyroiditis due to COVID-19, so we need to carefully evaluate the patient with thyrotoxicosis. TSH receptor antibody (TRAb) can help to differentiate from nondestructive causes instead of radioiodine uptake which is time consuming thus lead to disease transmission. Thyroid nodule evaluation may be deferred if there no feature suspicious of malignancy.

Acute adrenal insufficiency: May be due to a thrombotic event at the adrenal level in COVID-19 patients. This could cause an acute adrenal insufficiency with consequent shock and worsening to severe respiratory distress.

Patients with active Cushing's syndrome are immunocompromised and are at a high risk of viral and other infections. So rapid normalization of cortisol secretion and active management of diabetes and hypertension are needed to minimize the risk of infection.

COVID-19 and Obesity

- Obesity is one of the most important conditions that increases exponentially the mortality risk of the SARS-CoV-2 patients. It is recommended to Lose weight through healthy eating, being more physically active and making other lifestyle changes. Anti-obesity drugs should be used if criteria is fulfilled.

General Preventive Measures:

Currently vaccines are not available. So, it is better to avoid the virus with some preventive measures. General preventive measures are same as general population without co-morbidity, but people with diabetes must follow preventive measures strictly for example hand washing, wearing mask, social distancing & so on.

Measures for health care professionals with diabetes

Health care professionals are the frontline warriors and are playing critical role. Till date up to 21% of them infected with Covid-19 and many of them sacrifice their lives.

Health care facility should maintain a protocol to prevent their HCP with diabetes:

A) All interventions that have the potential to aerosolized aerodigestive secretions should be avoided or used when only mandatory

B) HCP with pregnancy, aged over 55 to 65 years should avoid clinical attention of a potentially infected patient and if possible should be exempted.

C) Institutional training must be arranged regarding indications and proper use with disposal of PPE along regular surveillance

D) For mental health strengthening appropriate training should also be included

E) Immediate isolation facilities for HCP who have

a) Unprotected close contact with Covid-19 patient having pneumonia
b) Onset of cough, fever, shortness of breath or other symptoms suggesting Covid-19

F) If they are affected, treatment must be initiated as priority basis.

Chapter 1

Background

Dr. Md. Abu Jar Gaffar

In December 2019, a new coronavirus causing severe acute respiratory syndrome (SARS-CoV-2) emerged in Wuhan, China. The virus spread rapidly globally to more than 150 countries and, by the March 19th 2020, it affected>230,000 individuals causing almost 10,000 deaths [1].

The World Health Organization (WHO) on March 11, 2020, has declared the novel coronavirus (COVID-19) outbreak a global pandemic [2,3].

By the time we are preparing this guidelines (August 15th 2020), total 13,568,578 cases with 583,620 confirmed deaths of COVID-19 reported worldwide [4]. USA remaining top of the list considering total cases and deaths followed by Brazil, India and Russia [5].

In Bangladesh, COVID-19 infections are being reported from Directorate General of Health Service on daily basis. Since 1st case detection on March 08 2020, So far, total 193,500 Confirmed cases and 2,457 deaths are reported (Dated 15 July 2020). Incidence is highest in Dhaka division followed by Chittagong [6].

The estimated incubation period for COVID-19 is up to 14 days from the time of exposure, with a median incubation period of 4 to 5 days [7,8,9]. The spectrum of illness can range from asymptomatic infection to severe pneumonia with acute respiratory distress syndrome (ARDS) and death. In a summary of 72,314 persons with COVID-19 in China, 81% of cases were reported to be mild, 14% were severe, and 5% were critical [10]. In a report of 1,482 hospitalized patients with confirmed COVID-19 in the United States, the most common presenting symptoms were cough (86%), fever or chills (85%), and shortness of breath (80%), diarrhea (27%), and nausea (24%) [11]. Other reported symptoms have included, but are not limited to, sputum production, headache, dizziness, rhinorrhea, anosmia, dysgeusia, sore throat, abdominal pain, anorexia, and vomiting.

Individuals of all ages are at risk for infection and severe disease. However, the probability of fatal disease is highest in people aged ≥65 years and those living in a nursing home or long-term care facility. Others at highest risk for COVID-19 are people of any age with certain underlying conditions, especially when not well-controlled, including hypertension, cardiovascular disease, diabetes, chronic respiratory disease, cancer, renal disease, and obesity [12-16].

Epidemiological data available so far on COVID-19 do not support the hypothesis that diabetic patients are at increased risk than the general population for SARS-CoV-2 [17], but it seems clear that diabetes, particularly when not well controlled, exposes people to be more complicated and prone to die [18,19].

Data suggest that diabetes has been found to be an independent predictor of admission to ICU, invasive ventilation or death in COVID-19. There is no clear distinction between Type 1 and Type 2 DM, both are considered as poor prognostic factor in COVID-19 [20,21].

Management of diabetes in covid-19 patient today has been addressed as an exciting confusion [22]. Considering the fast spread of the ‘‘Corona Virus Disease 2019 (COVID-19)” due to the ‘‘Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)”,there is currently a considerable debate on several important topics related to the most appropriate way to manage people with diabetes during this pandemic, including the susceptibility to this new infection, the severity of the complications, as well as the role of the drugs to use for the glycemic control [23].
Our knowledge on the new SARS-CoV-2 is increasing day by day, and the lessons learnt from this pandemic in different countries are very precious to establish the best approach to manage the disease in people with diabetes [24,25].

Along with diabetes other endocrine diseases such as obesity, malnutrition and adrenal insufficiency may also be strongly impacted by COVID-19 [27,28,29]. Higher susceptibility and worse outcome have been observed when various endocrine organs were affected by COVID-19 (Fig. 1.1) [26].

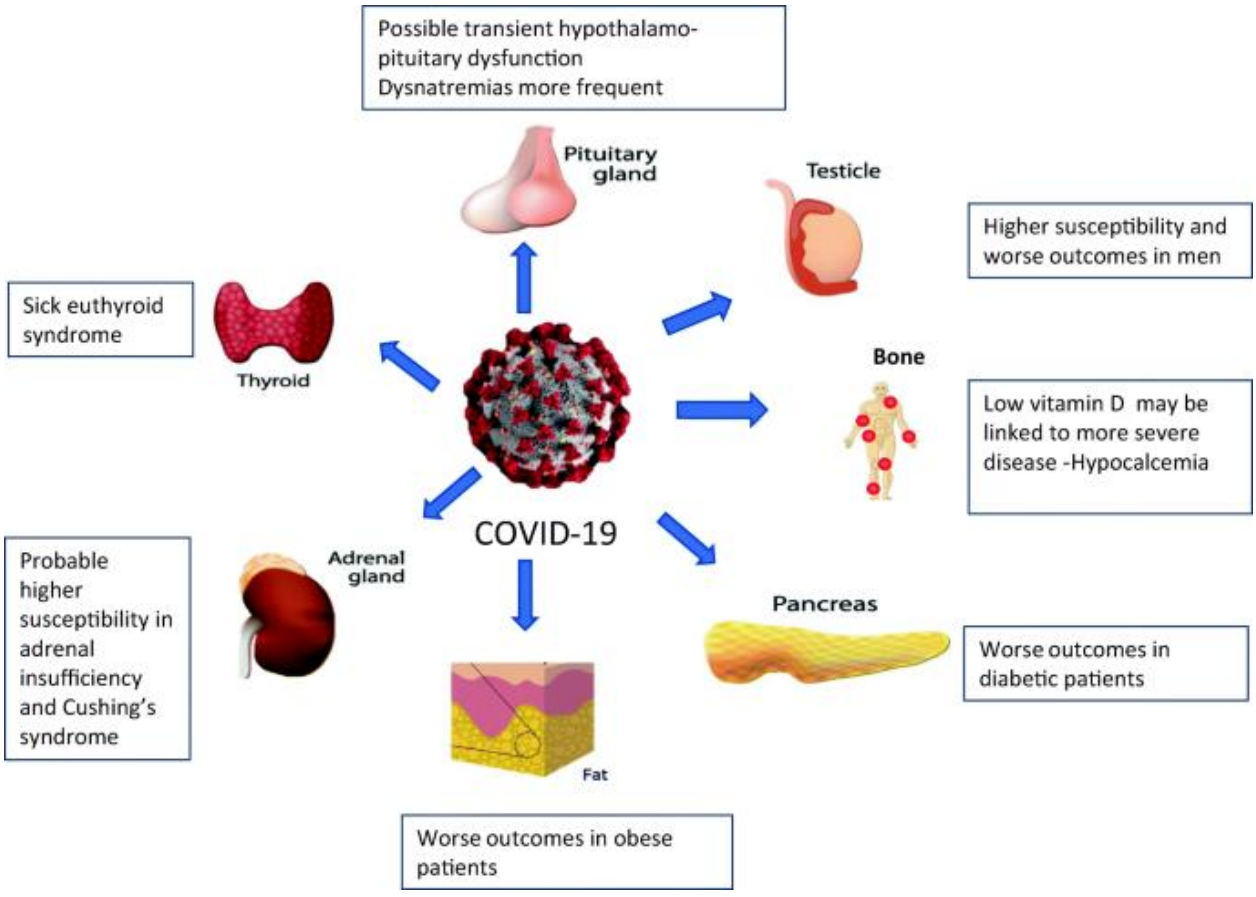


Fig.1.1. Different endocrine glands/organs that can be affected by COVID-19: 1) Pituitary: possible hypothalamic-pituitary disfunction and alterations in antidiuretic hormone metabolism. 2) Thyroid: sick euthyroid syndrome; 3) Adrenal: probable higher susceptibility to COVID-19 in adrenal insufficiency and Cushing’s syndrome; 4) Bone: Low vitamin D may be linked to more severe disease, Increased risk of hypocalcemia. 5) Testicle: Higher susceptibility and worse outcomes have been reported in men; 6) Diabetes. Worse outcomes

in diabetic patients; 7) Obesity. Worse prognosis in obese patients. [Adapted from Marazuela M et al. Ref. 26].

People with endocrine and metabolic diseases particularly with diabetes are exposed to a worse prognosis if infected with covid-19. Therefore, it is a scientific and clinical need to provide a precise and practical clinical guideline to the HCPs for the treatment of diabetes and other endocrine and metabolic diseases to ensure better outcome of the covid-19 infection.

References:

1. John Hopkins University of Medicine: Coronavirus Resource Center. Available from: https://coronavirus.jhu.edu/map.html. [Accessed 15 Aug 2020].

2. WHO Director-General's opening remarks at the media briefing on COVID19 -11 March 2020. Available from: https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020. [Accessed 15 Aug 2020].

3. Cucinotta D, Vanelli M. WHO Declares COVID-19 a Pandemic. Acta Bio Med [Internet]. 2020Mar.19 [cited 2020Aug.14];91(1):157-60. Available from: https://www.mattioli1885journals.com/index.php/actabiomedica/article/view/9397. [Accessed 15 Aug 2020].

4. World Health Organization. Coronavirus disease (COVID-19) outbreak situation. Available at: https://www.who.int/ emergencies/diseases/novel-coronavirus-2019. Accessed on 15 July 2020.

5. World Health Organization. WHO Coronavirus Disease (COVID-19) Dashboard. Available at: https://covid19.who.int/. Accessed on 15 July 2020. Accessed on 15 July 2020. Accessed on 15 July 2020.

6. Coronavirus disease 2019 information Bangladesh. Available at: https://corona.gov.bd/ graph. Accessed on 15 July 2020.

7. Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32109013.

8. Li Q, Guan X, Wu P, et al. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. N Engl J Med. 2020;382(13):1199-1207. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31995857.

9. Lauer SA, Grantz KH, Bi Q, et al. The incubation period of coronavirus disease 2019 (COVID-19) from publicly reported confirmed cases: estimation and application. Ann Intern Med. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32150748.

10. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72,314 cases From the Chinese Center for Disease Control and Prevention. JAMA. 2020. Available at:

https://www.ncbi.nlm.nih.gov/pubmed/32091533.

11. Garg S, Kim L, Whitaker M, et al. Hospitalization rates and characteristics of patients hospitalized with laboratory-confirmed coronavirus disease 2019 - COVID-NET, 14 states, March 1-30, 2020. MMWR Morb Mortal Wkly Rep. 2020;69(15):458-464. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32298251.

12. Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32167524.

13. Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32109013.

14. Cai Q, Chen F, Luo F, et al. Obesity and COVID-19 severity in a designated hospital in Shenzhen, China. Preprints with the Lancet. 2020;[Preprint]. Available at: https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3556658.

15. Centers for Disease Control and Prevention. Coronavirus disease 2019 (COVID-19): People who are at higher risk for severe illness. 2020. Available at: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-at-higher-risk.html. Accessed April 8, 2020.

16. Garg S, Kim L, Whitaker M, et al. Hospitalization rates and characteristics of patients hospitalized with laboratory-confirmed coronavirus disease 2019 - COVID-NET, 14 states, March 1-30, 2020. MMWR Morb Mortal Wkly Rep. 2020;69(15):458-464. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32298251.

17. Fadini GP, Morieri ML, Longato E, Avogaro A. Prevalence and impact of diabetes among people infected with SARS-CoV-2. J Endocrinol Investig 2020. https://doi.org/10.1007/s40618-020- 01236-2.

18. Yang J, Zheng Y, Gou X, Pu K, Chen Z, Guo Q, et al. Prevalence of comorbidities in the novel Wuhan coronavirus (COVID-19) infection: a systematic review and meta-analysis. Int J Infect Dis 2020. https://doi.org/10.1016/j.ijid.2020.03.017.

19. Grasselli G, Zangrillo A, Zanella A, Antonelli M, Cabrini L, Castelli A, Cereda D, Coluccello A, Foti G, Fumagalli R, Iotti G, Latronico N, Lorini L, Merler S, Natalini G, Piatti A, Ranieri MV, Scandroglio AM, Storti E, Cecconi M, Pesenti A, COVID-19 Lombardy ICU Network. Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy Region, Italy. JAMA 2020: e205394. https://doi.org/10.1001/jama.2020.5394.

20. Bornstein SR, Rubino F, Khunti K et al. Practical recommendations for the management of diabetes in patients with COVID-19. www.thelancet.com/diabetes-endocrinology Published online April 23, 2020.

21. Remuzzi A, Remuzzi G. COVID-19 and Italy: what next ? Lancet 2020;

395:1225–28.

22. Ceriello A. Management of diabetes today: An exciting confusion. Diabetes Res Clin Pract 2020;162:108129. https:// doi.org/10.1016/j.diabres.2020.108129.

23. Bhadada SK. Should anti-diabetic medications be reconsidered amid COVID-19 pandemic?. Diabetes Res Clin Pract 2020. https://doi.org/10.1016/j.diabres.2020.108146.

24. Gentile S, Strollo F, Ceriello A. COVID-19 Infection in italian people with diabetes: lessons learned for our future (an experience to be used). Diabetes Res Clin Pract 2020. https:// doi.org/10.1016/j.diabres.2020.108137.

25. Hussain A, Bhowmik B, Cristina do Vale Moreira N. COVID-19 and diabetes: knowledge in progress. Diabetes Res Clin Pract 2020. https://doi.org/10.1016/j.diabres.

26. Marazuela M, Giustina A, Domingo MP. Endocrine and metabolic aspects of the COVID-19 pandemic. Reviews in Endocrine and Metabolic Disorders https://doi.org/10.1007/s11154-020-09569-2.

27. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. JAMA. 2020;323:1239. CAS Google Scholar

28. Deng S-Q, Peng H-J. Characteristics of and public health responses to the coronavirus disease 2019 outbreak in China. J Clin Med. 2020;9:575. PubMed Central Google Scholar

Chapter 2

Epidemiology, pathophysiology & presentation of COVID -19 in diabetes

Dr. Md. Anowar Hossain

General characteristics of COVID-19

2.1: Incubation period

The incubation period is described as the time from infection to illness onset. In a study of 1099 patients from China with laboratory-confirmed symptomatic COVID-19, the median incubation period was four days (interquartile range, 2–7)[1]. Another study including 181 confirmed cases reported a median incubation period of approximately 5 days, and that symptoms would develop in 97.5% of infected individuals within 12 days[2]. Based on the incubation period of SARSCoV and MERS-CoV, as well as observational data, the United States CDC has estimated that symptoms of COVID-19 will usually develop within 2–14 days after exposure. Therefore, fourteen days has been the time applied internationally for monitoring and restricting the movement of healthy individuals (quarantine period)[3].

2.2: Modes of transmission

The virus can be mainly transmitted through droplets, direct contact and aerosols. Droplets transmission may occur when respiratory droplets, produced when an
infected person coughs or sneezes, are ingested or inhaled by individuals nearby (within about 6 feet). A subject can also get infected by touching a surface or object contaminated with the virus and subsequently touching his/her mouth,
nose, or eyes[4]. Additionally, it has been shown experimentally that the virus can remain viable in aerosols for at least 3 h[5], and can be transmitted in closed environments if inhaled into the lungs[4].

2.3: Period of infectivity

It is uncertain how long an individual with COVID-19 remains infectious. The period of infectivity is often assessed indirectly by detection of viral RNA from respiratory specimens. However, viral RNA does not necessarily confirm the presence of infectious virus. Higher viral loads have been detected soon after symptom onset, suggesting that transmission may be more likely to occur in the earlier stages of infection[6].The viral shedding duration seems to vary according to the disease severity. It has been found that around 90% of patients with milder symptoms had a negative viral RNA test on nasopharyngeal swabs by day 10 post-onset, while the test remained positive for a longer time in all severe cases[7]. On the other hand, it has been reported that the viral load detected in asymptomatic patients was similar to that in symptomatic subjects[6]. Indeed, transmission from asymptomatic carriers or individuals within the incubation period has been described[8]. Nevertheless, the extent to which this occurs remains to be determined.

2.4: Demography

Even though all age groups have been affected by COVID-19, the median age appears to be around 47–59 years, and usually higher among severe cases and non-survivors. No specific gender bias seems to exist for the contamination with the virus, but men tend to have a higher propensity of the cases[9]. Fewer cases have been identified among children and infants. In a large Chinese report including 72,314 patients, only 2% of those infected were younger than 20 years old[10].

2.5: Presentation

The clinical spectrum of COVID-19 can be very heterogeneous. Most adults and children present mild flu-like symptoms, but some may rapidly develop acute respiratory distress syndrome (ARDS), respiratory failure, arrhythmias, acute cardiac injury, shock, multiple organ failure and death. The most commonly reported symptoms are fever, cough, fatigue, sputum production and shortness of breath. However, headache, upper respiratory symptoms (e.g., sore throat and rhinorrhea) and gastrointestinal symptoms (e.g., nausea and diarrhea) occur less often[11]. Although not described in the initial Chinese studies, smell and taste disorders (e.g., anosmia and dysgeusia) have also been found frequently in patients with COVID-19 in Italy[12].

2.6: COVID-19 and comorbidities

Although the pathophysiological mechanisms are still not understood, it has been observed that most severe and fatal cases with COVID-19 have occurred in the elderly or in patients with underlying comorbidities, particularly CVDs, diabetes mellitus, chronic lung and renal disease, hypertension, and cancer[13]. One Chinese meta-analysis including 1527 patients showed that the most prevalent cardiovascular metabolic comorbidities with COVID-19 were hypertension (17.1%, 95% CI 9.9–24.4%) and cardio-cerebrovascular disease (16.4%, 95% CI 6.6–26.1%), followed by diabetes (9.7%, 95% CI 6.9–12.5%). In this report, patients with diabetes or hypertension had a 2-fold increase in risk of severe disease or requiring intensive care unit (ICU) admission, while those with cardio-cerebrovascular disease had a 3-fold increase[14]. In a subset of 355 patients with COVID-19 in Italy who died, the mean number of pre-existing underlying conditions was 2.7, and only 3 subjects did not have any comorbidity[15]. It has been consistently reported that, in addition to pneumonia, SARS-CoV-2 may cause damage to other organs including the heart, liver and kidneys[11]. Therefore, full attention should be paid to the treatment of the original co morbidities, especially in older patients with already severe underlying conditions.

2.7: Association between COVID-19 and diabetes

General considerations and potential mechanisms Diabetes is one of the leading causes of morbidity and mortality throughout the world. The condition is associated with several macrovascular and microvascular complications, that ultimately impact the overall patient's survival[16]. A relationship between diabetes and infection has long been clinically recognized. Diabetes and uncontrolled glycaemia were reported as significant predictors of severity and deaths in patients infected with different viruses, including the 2009 pandemic influenza A (H1N1), SARS-CoV and MERS-CoV[17]. Reports from China[10] and Italy[15] showed that older patients with chronic diseases, including diabetes, were at higher risk for severe COVID-19 and mortality. Scarce data exist regarding glucose metabolism and development of acute complications of diabetes (e.g., ketoacidosis) in patients with COVID-19. Infection of SARS-CoV-2 in those with diabetes possibly triggers higher stress conditions, with greater release of hyperglycemic hormones, e.g., glucocorticoids and catecholamines, leading to increased blood glucose levels and abnormal glucose variability. Poorly controlled diabetes has been linked to inhibited lymphocyte proliferative response to different kinds of stimuli[18], as well as impaired monocyte/macrophage and neutrophil functions. Abnormal delayed type hypersensitivity reaction and complement activation dysfunction[19] have also been described

in patients with diabetes. In vitro studies have shown that pulmonary epithelial cells exposure to high glucose concentrations significantly increases influenza virus infection and replication, indicating that hyperglycemia may enhance viral replication in vivo[20].

Aspects of SARS-CoV-2 pathogenesis and potential implications for clinical management of patients with COVID- 19 and diabetes

Patients with COVID-19 commonly show on admission lymphocytopenia, and to a lesser extent thrombocytopenia and leukopenia, which are more prominent among those with severe disease. Further, elevated levels of proinflammatory cytokines, including interleukin-6 (IL-6) and C-reactive protein, as well as increased coagulation activity, marked by higher d-dimer concentrations, were also associated with severity[21]. In T2DM, besides the marked inflammatory process previously discussed, an imbalance between coagulation and fibrinolysis takes place, with increased levels of clotting factors and relative inhibition of the fibrinolytic system. Both insulin resistance and T2DM are associated with endothelial dysfunction, and enhanced platelet aggregation and activation. These abnormalities favor the development of a hypercoagulable pro-thrombotic state[22]. Upon exposure of the host to the virus, all CoVs, through a Spike protein, bind to cells that express specific receptors. After binding to the target cells, the hostcell protease cleaves the spike, which allows the virus to enter and replicate[23]. The angiotensin-converting enzyme 2 (ACE2) has been identified as one of the main receptors for both SARS-CoV and SARS-CoV-2[24]. ACE2 is widely expressed on the respiratory tract, heart, kidneys, intestines, cerebral neurons, endothelium of arteries and veins, immune cells and pancreas. A Chinese study compared 39 SARSCoV patients without previous diabetes, who did not receive steroid treatment, with 39 matched healthy siblings and showed that 20 of the 39 SARS-CoV patients developed diabetes during hospitalization. Since immunostaining for ACE2 was strong in the pancreatic islets, it was suggested that SARS-CoV might have damaged islets and caused acute insulin dependent diabetes mellitus[25]. Therefore, although further evidence is needed, pancreatic damage may also be present in COVID-19 patients, possibly contributing to worse
outcomes in subjects with diabetes.

References:

1. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020:1–13. https://doi.org/10.1056/NEJMoa2002032. PubMed PMID: 32109013. Epub 2020/02/29. PubMed PMID: 32109013.
2. Lauer SA, Grantz KH, Bi Q, Jones FK, Zheng Q, Meredith HR, et al. The incubation period of coronavirus disease 2019 (COVID-19) from publicly reported confirmed cases: estimation and application. Ann Intern Med 2020. https://doi. org/10.7326/M20-0504. Epub 2020/03/10. PubMed PMID: 32150748; PubMed Central PMCID: PMCPMC7081172.
3. Centers for Diasease Control and Prevention. Symptoms of Coronavirus 2020 [cited 31/03/2020]. Available from: https:// www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/ symptoms.html.
4. Adhikari SP, Meng S, Wu YJ, Mao YP, Ye RX, Wang QZ, et al. Epidemiology, causes, clinical manifestation and diagnosis, prevention and control of coronavirus disease (COVID-19) during the early outbreak period: a scoping review. Infect Dis Poverty 2020;9(1):29. https://doi.org/10.1186/s40249-020- 00646-x. Epub 2020/03/19. PubMed PMID: 32183901; PubMed Central PMCID: PMCPMC7079521.

5. van Doremalen N, Bushmaker T, Morris DH, Holbrook MG, Gamble A, Williamson BN, et al. Aerosol and surface stability of SARS-CoV-2 as compared with SARS-CoV-1. N Engl J Med 2020. https://doi.org/10.1056/NEJMc2004973. Epub 2020/03/18 PubMed PMID: 32182409. .
6. Zou L, Ruan F, Huang M, Liang L, Huang H, Hong Z, et al. SARS-CoV-2 viral load in upper respiratory specimens of infected patients. N Engl J Med 2020;382(12):1177–9. https:// doi.org/10.1056/NEJMc2001737. Epub 2020/02/20. PubMed PMID: 32074444.
7. Liu Y, Yan LM, Wan L, Xiang TX, Le A, Liu JM, et al. Viral dynamics in mild and severe cases of COVID-19. Lancet Infect Dis 2020. https://doi.org/10.1016/S1473-3099(20)30232-2. Epub 2020/03/23 PubMed PMID: 32199493.
8. Rothe C, Schunk M, Sothmann P, Bretzel G, Froeschl G, Wallrauch C, et al. Transmission of 2019-nCoV infection from an asymptomatic contact in Germany. N Engl J Med 2020;382 (10):970–1. https://doi.org/10.1056/NEJMc2001468. Epub 2020/ 02/01. PubMed PMID: 32003551.
9. Zhang JJ, Dong X, Cao YY, Yuan YD, Yang YB, Yan YQ, et al. Clinical characteristics of 140 patients infected with SARSCoV-2 in Wuhan, China. Allergy 2020. https://doi.org/10.1111/ all.14238. Epub 2020/02/23 PubMed PMID: 32077115.
10. Wu Zunyou, McGoogan Jennifer M. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. JAMA 2020;323(13):1239. https://doi.org/ 10.1001/jama.2020.2648.
11. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAbMA 2020. https://doi.org/10.1001/jama.2020.1585. Epub 2020/02/ 08. PubMed PMID: 32031570; PubMed Central PMCID: PMCPMC7042881.
12. Giacomelli A, Pezzati L, Conti F, Bernacchia D, Siano M, Oreni L, et al. Self-reported olfactory and taste disorders in SARSCoV-2 patients: a cross-sectional study. Clin Infect Dis 2020. https://doi.org/10.1093/cid/ciaa330. Epub 2020/03/28 PubMed PMID: 32215618.
13. Yang J, Zheng Y, Gou X, Pu K, Chen Z, Guo Q, et al. Prevalence of comorbidities in the novel Wuhan coronavirus (COVID-19) infection: a systematic review and meta-analysis. Int J Infect Dis 2020. https://doi.org/10.1016/j.ijid.2020.03.017. Epub 2020/ 03/17 PubMed PMID: 32173574.
14. Li B, Yang J, Zhao F, Zhi L, Wang X, Liu L, et al. Prevalence and impact of cardiovascular metabolic diseases on COVID-19 in China. Clin Res Cardiol 2020. https://doi.org/10.1007/s00392- 020-01626-9. Epub 2020/03/13 PubMed PMID: 32161990.
15. Onder G, Rezza G, Brusaferro S. Case-fatality rate and characteristics of patients dying in relation to COVID-19 in diabetes research and clinical practice 162 (2020) 108142 7 Italy. JAMA 2020. https://doi.org/10.1001/jama.2020.4683. Epub 2020/03/24 PubMed PMID: 32203977.
16. Williams R, Karuranga S, Malanda B, Saeedi P, Basit A, Besanc¸on S, et al. Global and regional estimates and projections of diabetes-related health expenditure: results from the International Diabetes Federation Diabetes Atlas. Diabetes Res Clin Pract 2020;162:108072. https://doi.org/ 10.1016/j.diabres.2020.108072.

17. Schoen Karla, Horvat Natally, Guerreiro Nicolau FC, de Castro Isac, de Giassi Karina S. Spectrum of clinical and radiographic findings in patients with diagnosis of H1N1 and correlation with clinical severity. BMC Infect Dis 2019;19(1). https://doi.org/10.1186/s12879-019-4592-0.
18. Moutschen MP, Scheen AJ, Lefebvre PJ. Impaired immune responses in diabetes mellitus: analysis of the factors and mechanisms involved. Relevance to the increased susceptibility of diabetic patients to specific infections. Diabete Metab 1992;18(3):187–201. Epub 1992/05/01. PubMed PMID: 1397473.
19. Ilyas R, Wallis R, Soilleux EJ, Townsend P, Zehnder D, Tan BK, et al. High glucose disrupts oligosaccharide recognition function via competitive inhibition: a potential mechanism for immune dysregulation in diabetes mellitus. Immunobiology 2011;216(1–2):126–31. https://doi.org/10.1016/ j.imbio.2010.06.002. Epub 2010/08/03. PubMed PMID: 20674073; PubMed Central PMCID: PMCPMC3088832.
20. Kohio Hinissan P, Adamson Amy L. Glycolytic control of vacuolar-type ATPase activity: a mechanism to regulate influenza viral infection. Virology 2013;444(1-2):301–9. https://doi.org/10.1016/j.virol.2013.06.026.
21. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID19 in Wuhan, China: a retrospective cohort study. Lancet 2020. https://doi.org/10.1016/S0140-6736(20)30566-3. Epub 2020/03/15. PubMed PMID: 32171076.
22. Dunn EJ, Grant PJ. Type 2 diabetes: an atherothrombotic syndrome. Curr Mol Med 2005;5(3):323–32. https://doi.org/ 10.2174/1566524053766059. Epub 2005/05/17. PubMed PMID: 15892651.
23. Letko Michael, Marzi Andrea, Munster Vincent. Functional assessment of cell entry and receptor usage for SARS-CoV-2 and other lineage B betacoronaviruses. Nat Microbiol 2020;5 (4):562–9. https://doi.org/10.1038/s41564-020-0688-y.
24. Li W, Moore MJ, Vasilieva N, Sui J, Wong SK, Berne MA, et al. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. Nature 2003;426(6965):450–4. https:// doi.org/10.1038/nature02145. Epub 2003/12/04. PubMed PMID: 14647384.
25. Yang Jin-Kui, Lin Shan-Shan, Ji Xiu-Juan, Guo Li-Min. Binding of SARS coronavirus to its receptor damages islets and causes acute diabetes. Acta Diabetol 2010;47(3):193–9. https://doi. org/10.1007/s00592-009-0109-4.

Chapter 3

Glycemic targets & blood glucose monitoring

Dr.Mirza Sharifuzzaman

Patients with diabetes had a threefold higher mortality rate compared with the mortality rate in COVID-19 patients overall[1]. Poor glycaemic control impairs several aspects of the innate and adaptive immune response to viral infections and to the potential secondary bacterial infection in the lungs[2, 3]. Again hypoglycaemia which could occur during treatment of diabetes may additionally worsen the clinical outcomes[4].Therefore a good glycaemic control is essential.

3.1: Glycemic targets

3.1.1: HBA1C targets for diabetic patients[5]

- For most patients with DM, the goal of therapy is a level below 7.0%.
- A goal of less than 6.5% may be appropriate for some patients who can achieve this without significant episodes of hypoglycemia (eg, persons newly diagnosed with diabetes, individuals with diabetes who are managed with diet and exercise alone)
- For elderly patients, patients with a short life expectancy, and patients with frequent/severe episodes of hypoglycemia, a less strict goal of below 8% may be more appropriate and must be determined on an individualized basis.

3.1.2: Therapeutic aims for blood sugar in non COVID-19 patients

- For non covid-19, non pregnant patient recommended blood sugar level is as follows

Recommending body	Fasting blood sugar	Post parandial blood sugar
AACE	<6.1 mmol/L	<7.8 mmol/L
ADA	4.4-7.2 mmol/L	< 10 mmol/L

Table 1: Target blood sugar level in non COVID-19 patients.

3.1.3: Therapeutic aims for blood sugar in COVID-19 patients[6, 7]

- Plasma glucose concentration: 4-8 mmol/L (72-144 mg/dL) for outpatients or 4-10 mmol/L (72-180 mg/dL) for inpatients/intensive care, with possible upward adjustment of the lower value for frail patients to 5 mmol/L (90 mg/dL).

- Continuous glucose monitoring/flash glucose monitoring targets:

  Time-in-range (3.9-10 mmol/L) > 70% of time (or > 50% in frail and older people).

  Hypoglycemia< 3.9 mmol/L (< 70 mg/dL): < 4% (< 1% in frail and older people).

Target blood sugar		
	OPD Setting	Inpatient setting
Routine blood sugar monitoring	4-8 mmol/L	4-10 mmol/L
Continuous blood glucose monitoring	----------	3.9- 10 mmol/L. TIR >70% time (>50% in frail patient) Hypoglycaemia < 4% time (<1% in frail)

Table 2: Target blood sugar in COVID- 19 patient. TIR= Time in range.

3.2: BLOOD GLUCOSE MONITORING:

frequent monitoring of capillary glucose is important. Considering increased risk of exposure of health care provider frequent Self-monitoring of blood glucose (SMBG) or CGM may be performed.

For patients with type 1 diabetes, monitoring of ketone levels (particularly for people who are persistently hyperglycaemic) and vigilance for the development of symptoms of DKA are important[8].

3.2.1: Self-monitoring of blood glucose (SMBG)[8, 9]:

- SMBG of capillary blood is an acceptable alternative to plasma glucose estimation in present scenario[8].
- For patients on insulin with poor glycemic control or recurrent hypoglycemia, SMBG is advised at least 4 times/day, i.e., at fasting, before lunch, before dinner and at bedtime.
- Each value is to be recorded over a span of at least 3 days to avoid multiple pricks a day. In addition, capillary glucose should be checked at any clinical suspicion of hypoglycemia.
- For patients on oral hypoglycemic agents with acceptable control, measuring fasting and post-prandial capillary blood glucose once or twice a week is acceptable.

- Capillary glucose should be checked at any clinical suspicion of hypoglycemia.
- Frequent monitoring of blood glucose (every hour or every 2 h) in patients with very poor oral intake or those in ICU or Non-ICU who are on mechanical ventilation who would require intravenous insulin infusion.

3.2.2: Continuous glucose monitoring (CGM)[8]:

1. Continuous glucose monitoring (CGM) and flash glucose monitoring systems are useful and allow remote monitoring by healthcare providers.
2. Patients receiving multiple dose insulin injections, continuous subcutaneous insulin infusion (CSII) or insulin pump or intravenous insulin syringe pump might be benefited by CGM.
3. Paracetamol or NSAIDs may interfere with CGM monitoring.

References:

1. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72314 cases from the Chinese Center for Disease Control and Prevention. JAMA. 323(13):1239.
2. Carey IM, Critchley JA, DeWilde S, Harris T, Hosking FJ, Cook DG. Glycemic control and risk of infections among people with type 1 or type 2 diabetes in a large primary care cohort study. Diabetes Care 2018;41:513–21.
3. Ferlita S, Yegiazaryan A, Noori N, Lal G, Nguyen T, To K, et al. Type 2 diabetes mellitus and altered immune system leading tosusceptibility to pathogens, especially mycobacterium tuberculosis. J Clin Med. 2019;8:2219. Available at https://doi.org/10.3390/jcm8122219. Accessed on 08.07.20.
4. Ritesh Gupta, Akhtar Hussain, Anoop Misra. Diabetes and COVID-19: evidence, current status and unanswered research questions. European Journal of Clinical Nutrition (2020) 74:864–870. Available at https://doi.org/10.1038/s41430-020-0652-1. Accessed on 09.07.20.
5. American Diabetes Association. 6. Glycemic Targets: *Standards of Medical Care in Diabetes-2018*. *Diabetes Care*. 2018 Jan. 41 (Suppl 1):S55-S64.
6. *Stefan R Bornstein, Francesco Rubino, Kamlesh Khunti, Geltrude Mingrone, David Hopkins, et al*. **Practical recommendations for the management of diabetes in patients with COVID-19**. ***Lancet Diabetes Endocrinol* 2020;8:546–50.**
7. Miriam E. Tucker. More Guidance on 'Vulnerable Subgroup' With Diabetes and COVID-19 - *Medscape* - Apr 28, 2020.
8. Prasad Katulanda, Harsha A. Dissanayake, Ishara Ranathunga, Vithiya Ratnasamy, Piyumi S. A. Wijewickrama et al. Prevention and management of COVID-19 among patients with diabetes: an appraisal of the literature. Diabetologia 2020. Avaiable at https://doi.org/10.1007/s00125-020-05164-x. Accessed on 09.07.20.
9. Banerjee M, Chakraborty S, Pal R. Diabetes self-management amid COVID-19 pandemic. Diabetes Metab Syndr. 2020 Apr 13;14(4):351-354.

Chapter 4

Life style management of diabetes in COVID-19 patients

Dr.Mirza Sharifuzzaman

Life style management is an integral part of diabetic management. It encompasses all activity including management of diet, behavior & physical activities that helps to maintain good health.

4.1: How covid-19 pandemic affects life style?

Covid- 19 pandemic affects life style in several ways:

- Patients may find it difficult to procure healthy foods, medicines, insulin, needles and glucose strips etc. Dietary irregularity could occur because of staying at home. [1]
- Diet supplied to all admitted covid-19 patient including diabetic & nondiabetic patients are uniform. So diabetic patient may not get appropriate diet.[2]
- There are limited opportunities for exercise as regular walks and visits to gyms or swimming pools are not possible[1]. Quarantined inpatients are unable to exercise due to limited indoor space.
- There is considerable mental stress[3].

4.2. Medical nutrition therapy in covid-19 patients at home and hospital

4.2.1: Macronutrients[4,5,6,7, 8]:

- Patient should continue to take a previously planned diet as he was taking previously.
- Maintain adequate carbohydrate intake as previous. Avoid fasting.
- Priority should be given to foods with a low glycaemic index (e.g. vegetables, whole wheat pasta/noodles).
- Patient should keep glucose drink or lozenge or tablet with you in isolation room or ward
- Avoid or limit consumption of junk food.
- Ensure adequate protein intake (1gm/kg/day or more in polymorbid conditions). Choose lean proteins (eg. fish, meat, eggs, milk, beans after fully cooked).
- Fat and carbohydrate needs are adapted to the energy needs while considering an energy ratio from fat and carbohydrates be-tween 30:70 (subjects with no respiratory deficiency) to 50:50(ventilated patients) percent[7].
- Eat green, leafy vegetables.
- Eat fruits in two or three servings
- Frequent drinking of plain water or sugar free drink to maintain hydration.
- Critical patients who cannot take orally, should receive NG feeding or parenteral nutrition.

4.2.2: Micronutrients:

- In general, low levels or intakes of micronutrients such as vitamins A, E, B6 and B12, Zn and Se have been associated with adverse clinical outcomes during viral infections[8].
- Though the role of empirical use of supraphysiological doses of micronutrient in the prevention or favorable outcome of COVID-19 is not established, regular intake of in malnourished person is recommended[7].

4.3: Psychological care of COVID- 19 patients with DM.

- The anxiety levels of inpatients should be evaluated[2].
- Psychological intervention should be carried out for patients in need[2].
- Regular sleep routines are important. Relaxation techniques such as meditation can help people with stress and anxiety[9].
- Maintaining contact with relatives, friends and neighbours via telephone conversations or using online communication platforms can help to reduce the effects of social isolation[10].

4.4: Smoking & alcohol[9].

a. Avoid smoking.
b. Avoid or minimize alcohol consumption.

4.5: Physical activity in healthy and sick

Increasing physical activity is a formidable public health challenge that we must address in this guideline. The task is hard, but the potential rewards are momentous: preventing premature death, unnecessary illness, and disability; controlling health care costs; and maintaining a high quality of life.

4.5.1: General consideration:

- In general, moderate intensity physical activity (such as brisk walking) to at least 150 min/week is recommended for all patient with diabetes & prediabetes[11].
- Symptomatic COVID-19 patient should avoid exercise[12]. Otherwise, under particular precautions, even outdoor activities can be considered. such as garden work (if a own garden is present), garden exercise (i.e. badminton), or walking/running in the forest (alone or in small family groups while maintaining a distance of 2 m minimum to others)[7].
- Reducing infectious risk is achieved best by quarantine at home, which is heavily recommended presently for all people at risk of COVID-19 and also for those infected with a rather moderate disease course[7].

4.5.2: Home based physical exercise:

In the covid- 19 era, since there is limited provision for outdoor exercise, Emphasis should be given on home based exercice[5].

- **Treadmill**: one-hour brisk walking (no need to run), which can also be split into three 20-minute sessions. If possible, the slope should be adapted to individual fitness levels, to simulate an uphill walk.
- **Stationary bicycle** (either reclined or classic): two 15-minute sessions at variable intensity (if the equipment allows it). The sessions can be longer on a reclined bicycle since the effort is reduced by the backrest.
- **Bodyweight exercises** such as push-ups, squats, deep stationary lunges, sit-ups or crunches (to strengthen the abdomen) and forward flexes (to strengthen the lower-back muscles). These help maintain muscle tone and, when performed correctly, can have excellent results.
- **Joint mobility and stretching exercises** that can be sourced from common workout, yoga and pilates' routines.

- **Several other way that may fulfill the daily exercise requirements[5]:**
    - Walk up and down 8 sets of stairs, for at least 6 floors. This is not recommended for people with type 2 diabetes who do not exercise regularly.
    - Jump rope.
    - Use small weights and home fitness accessories such as rubber bands, kettlebells, wrist weights, ankle weights and pockets filled with heavy objects. Makeshift objects can also be used, such as buckets, cases, bottles filled with water or even small backpacks filled with objects of different weight.
    - Two series of 20 Jumping Jacks (on-site jumps with synchronized leg and arm spreading and closing)
    - Two series of 15 crunches (abdomen strengthening).
    - Two series of 15 forward flexes (lower back muscle strengthening)
    - Two series of 10 rowing exercises using dumbbells and slight forward flexion (back muscle strengthening)
    - Two series of 8 push-ups (pectoral muscle strengthening – knees to floor for beginners).
    - Two series of 8 sitting/standing hand-weight lifts (shoulder muscle strengthening).
    - Five minutes of treadmill training or stationary/reclined bicycle.
    - Three series x 15 squats (lower limb strengthening).
    - Final stretching and relaxation.
    - Make sure to avoid overload and adapt exercise intensity to individual ability and fitness level.

References:

1. Ritesh Gupta, Akhtar Hussain, Anoop Misra. Diabetes and COVID-19: evidence, current status and unanswered research questions. European Journal of Clinical Nutrition (2020) 74:864–870. Available at: https://doi.org/10.1038/s41430-020-0652-1. Accessed on:11.07.20.
2. Jun Zhou, Jie Tan. Diabetes patients with COVID-19 need better blood glucose management in Wuhan, China. Metabolism Clinical and Experimental. 107 (2020) 154216. Available at: https://doi.org/10.1016/j.metabol.2020.154216. Accessed on:11.07.20.
3. Zhang SX, Wang Y, Rauch A, Wei F. Unprecedented disruption of lives and work: health, distress and life satisfaction of working adults in China one monthinto the COVID-19 outbreak. Psychiatry Res. 2020;288:112958. Available at: https://doi.org/10.1016/j.psychres. 2020.112958. Accessed on:11.07.20.
4. NHS. Sick day rules: how to manage Type 2 diabetes if you become unwell with coronavirus and what to do with your medication, NHS, London Available at: https://www.england.nhs.uk/london/wp-content/uploads/sites/8/2020/04/3.-Covid-19-Type-2-Sick-Day-Rules-Crib-Sheet-06042020.pdf. Accessed on 10.07.20.
5. **COVID-19 and diabetes. IDF. Available at https://www.idf.org/aboutdiabetes/what-is-diabetes/covid-19-and-diabetes/1-covid-19-and-diabetes.html. Accessed on 11.07.20.**
6. Brugliera, L., Spina, A., Castellazzi, P. *et al.* Nutritional management of COVID-19 patients in a rehabilitation unit. *Eur J Clin Nutr* **74,** 860–863 (2020). Available at: https://doi.org/10.1038/s41430-020-0664-x. Accessed on 10.07.20.
7. Barazzoni R, Bischoff SC, Krznaric Z, Pirlich M, Singer P. Espen expert statements and practical guidance for nutritional management of individuals with sars-cov-2 infection. Clin. Nutr. ESPEN. Available From: https://doi.org/10.1016/j.clnu.2020.03.022. Accessed on 08.07.20.
8. Semba RD, Tang AM. Micronutrients and the pathogenesis of human immunodeficiency virus infection. Br J Nutr 1999;81:181-9.
9. Prasad Katulanda, Harsha A. Dissanayake, Ishara Ranathunga, Vithiya Ratnasamy, Piyumi S. A. Wijewickrama et al. Prevention and management of COVID-19 among patients with diabetes: an appraisal of the literature. Diabetologia 2020. Available at https://doi.org/10.1007/s00125-020-05164-x. Accessed on 11.07.20.
10. World Health Organization (2020) Mental health and psychosocial considerations during COVID-19 outbreak: document number: WHO/2019-nCoV/MentalHealth/2020.1. Available from https:// www.who.int/docs/default-source/coronaviruse/mental-healthconsiderations.pdf. Accessed 8th July 2020.
11. . Diabetes Prevention Program (DPP) Research Group. The Diabetes Prevention Program (DPP): description of lifestyle intervention. Diabetes Care 2002;25:2165–2171.
12. COVID 19 & Diabetes *BADAS Guide for Healthcare Professionals*. Available at http://www.nhn-dab.org.bd/WebSite/nboard/8. Accessed on 09.07.2020.

Chapter 5

Sick day rules in COVID-19 with diabetes and Indication for hospitalization

Dr. Md. Qamrul Hassan

A diabetic patient may become ill. He/ She may suffer from any illness as a non-diabetic people. Covid-19 can cause a serious acute illness in patients with diabetes by increasing the risk of a rapid worsening of diabetes control which can lead to life-threatening conditions called diabetic ketoacidosis (DKA) and hyperosmolar hyperglycaemic state (HHS), increasing susceptibility to other infections including pneumonia, chest and foot infections, and sepsis, worsening symptoms and signs in those with frailty, kidney disease and/or cardiovascular (heart) disease. **1**
When people living with diabetes are ill, their bodies react by releasing hormones to fight the illness. The hormones released during an illness raise blood sugar levels and at the same time make it more difficult for insulin to lower them.

Illnesses most likely to have an effect on blood glucose levels: 2

-Common cold or flu, including COVID-19
-Sore throat
-Urinary tract infections
-Bronchitis or chest infections, Stomach upsets and diarrhea
-Skin infections such as abscesses (especially if these conditions are followed by a fever or high temperature)
-Starting a course of cortisol, or increasing the amount of cortisol taken, also has a significant impact on blood sugar levels.

Signs of diabetic ketoacidosis: 3

- Excessive thirst, Polyuria, Dehydration
- Shortness of breath and labored breathing
- Abdominal pain, Leg cramps
- Nausea and vomiting
- Mental confusion and drowsiness
- Ketones can be detected on the person's breath (pear-drop smell) or in the blood or urine

Ketoacidosis patient requires to urgent hospitalization

Signs of hyperosmolar hyperglycaemic state: 3

- Typically seen after several days with glucose levels consistently above 30 mmol/L
- Disorientation or confusion
- Polyuria
- Thirst and dry mouth l Nausea l In the later stages, the person becomes drowsy and gradually loses consciousness

HHS is potentially life-threatening and requires urgent admission to hospital

Need to Hospitalization: 2,3

Diabetic patients with moderate to severe symptoms of COVID 19

- If they are not sure what to do

- If they vomit repeatedly (not able to hold down any food or drink for more than six hours), as they can quickly become very dehydrated

- Rapid breathing with fruity-smelling breath

- Abdominal pain

- Reduced level of consciousness (drowsiness)

- If their blood glucose stays high for more than 24 hours

- If they develop symptoms which could be indicative of their developing diabetic ketoacidosis

General guidelines to manage diabetes during an illness: 2,3

If a person with diabetes becomes ill, the following steps should be followed, even if the blood sugar levels are within the target range:

-Take diabetes medication as usual. Insulin treatment should never be stopped

-Test blood glucose every four hours, and keep track of the results

-Drink extra (calorie-free) fluid*, and try to eat as normal

-Weigh yourself every day. Losing weight while eating normally is a sign of high blood glucose

-Check temperature every morning and evening.

-A fever may be a sign of infection

There are several classes of drugs that should be temporarily stopped in conditions that could lead to complications: 3

Table -1

SGLT2 inhibitors	If taken during an acute illness that can lead to dehydration, there is an increased risk of developing euglycaemic DKA
ACE inhibitors	If taken during an acute illness that can lead to dehydration, there is an increased risk of developing AKI due to reduced renal efferent vasoconstriction
Diuretics	If taken during an acute illness that can lead to dehydration, there is an increased risk of developing AKI
Metformin	If taken during an acute illness that can lead to dehydration, there is an increased risk of developing lactic acidosis
ARB	If taken during an acute illness that can lead to dehydration, there is an increased risk of developing AKI
NSAIDs	If taken during an acute illness that can lead to dehydration, there is an increased risk of developing AKI due to reduced renal afferent vasodilation

Once the person is feeling better and able to eat and drink for 24–48 hours, these medications should be restarted.

****Drink plenty of fluids*** – 120 to 180 ml every half an hour to prevent dehydration. It might also be necessary to drink sugary beverages if it is not possible to take in 50 grams of carbohydrates through food. The amount of sugary beverages should nevertheless be carefully controlled to prevent blood sugar levels from rising too much.

Guidelines for People with Type 1 Diabetes: 2

During a period of illness:
-Insulin treatment should never be stopped
-The insulin dose may need to be increased and it might be necessary to take additional doses of Fast-acting insulin to bring down the blood sugar levels
-Blood glucose levels should be checked at least every four hours
-Plenty of non-sweet fluids should be drunk to avoid dehydration
-Ideal blood sugar levels should be between 6-10mmol/l (110-180 mg/dl)
If the blood sugar levels are in the following ranges at any time:

Table-2

Blood Sugar Levels	Insulin Intake	Monitoring
>10-15 mmol/l (180-270 mg/dl)	increase insulin dose; table-3	Monitor blood glucose every 2-4 hours
>15 mmol/l [270 mg/dl] Ketones in urine	increase insulin dose; table-3	Monitor every 2 hours

Table-3

Blood sugar tests (mmol/l [mg/dl])	Blood ketone tests (mmol/l)	ACTION NEEDED * Able to take fluids
Blood sugar <3.9 [70]	-	No extra Insulin. Decrease dose of pre-meal insulin as directed. Contact your healthcare team if vomiting!
Blood sugar 4.0-16.0 [72-288]	Blood ketones <0.6	Use usual insulin dose (and scale) as for normal (nonillness) days.
Blood sugar 4.0-16.0 [72-288]	Blood ketones ≥0.6	Take a 10% supplement of rapid or fast-acting insulin, in addition to usual baseline insulin doses
Blood sugar >16 [288]	Blood ketones <0.6	Take a 10% supplement of rapid or fast-acting insulin, in addition to usual baseline insulin doses.
Blood sugar >16 [288]	Blood ketones ≥0.7 – 1.4	Take a 15% supplement of rapid or fast-acting insulin, in addition to usual baseline insulin doses.
Blood sugar >16 [288]	Blood ketones ≥1.5 – 3.0	Take a 20% supplement of rapid or fast-acting insulin, in addition to usual baseline insulin doses. Contact your healthcare team as soon as possible.

Guidelines for people living with Type 2 Diabetes: 2

People with Type 2 Diabetes should check whether they develop the following symptoms which may be indicative of high blood sugar levels:

- Thirst/dry mouth
- Passing large amounts or urine (this can lead to dehydration)
- Tiredness
- Weight Loss

Guidelines for people with Type 2 Diabetes on tablets:2

The aim to keep blood glucose levels between 6 and 10 mmol/l (110 and 180 mg/dl).

If a person with T2D takes metformin tablets, it may be necessary to temporarily stop these tablets. This is usually advised if the person has a severe infection or becomes dehydrated.

If it is necessary to stop taking metformin, then an alternative treatment needs to be put in place until the metformin treatment can be resumed (this may include other anti-diabetic pills or even insulin sometimes, depending on the individual levels of blood sugar rise).

People on other oral diabetes treatment may have been provided with blood glucose testing equipment to ensure that their blood glucose levels do not fall too low (hypoglycaemia) and to routinely monitor their diabetes.

Guidelines for people with Type 2 Diabetes on insulin: 2

The aim should be to keep blood glucose levels between 6 and 10 mmol/l [110 and 180 mg/dl].

If the blood glucose levels stay above 10 mmol/l (180 mg/dl), they should increase their insulin dose.

Extra blood glucose testing will often be necessary.

Testing should be done every four hours, especially if the blood glucose levels are high (over 15 mmol/l [270 mg/dl]).

Ketones: If the blood glucose levels get too high (over 15 mmol/l [270 mg/dl]), then they may need to perform a urine test for ketones. If it is positive, they should contact their health-care provider for advice

References :

1. Professor Alan Sinclair (Co-Chair), Professor Ketan Dhatariya (Co-Chair), Olivia Burr, Dr Dinesh Nagi, Professor Partha Kar, David Jones, Dr Philip Newland-Jones, Dr Kath Higgins, Dr Mayank Patel, Dr Ahmed Abdelhafiz, Dr David Hopkins, Dan Howarth, Simon O'Neill, Catherine Gooday Covid-19 and Diabetes: Interim Care Home Guidance 12th May 2020.
2. International diabetic federation(Europe)-How to manage diabetes during an illness? "sick dayrules".www.idf-europe.org
3. Down S (2020) How to advise on sick day rules. Diabetes & Primary Care 22: 47–8

Chapter 6

Management of diabetes in patients with COVID-19 at hospital settings

Professor Abdus Saleque Mollah

A strategic plan and a framework should be developed for the management of patients with diabetes and COVID-19 at the Outpatient and Inpatient department of every hospital of the country. An Expert Committee will be formed including relevant experts from the field of Diabetes and Endocrine Diseases, Cardiology, Nephrology, Hematology, Neurology, Gastroenterology, Public Health, Infectious Diseases, ICU Care, Anesthesiology, Internal Medicine, Obstetrics and Gynecology, Nursing, Pediatric and Geriatric Medicine according to the availability. Recommendations for treatment will be based on type and severity of diabetes, severity of COVID-19 infection, age and other comorbidities of patients. Special considerations should be given for subgroup population of diabetes and COVID-19 like elder patients, pregnancy, breast feeding, renal and hepatic impairment.A protocol with predefined criteria for discharge and follow up of patients also to be developed.

6.1. Severity of illness and categories of COVID-19

Patients with COVID-19 infection can experience a range of clinical manifestations, from no symptoms to critical illness [1]. In a summary of 72,314 persons with COVID-19 in China, 81% of cases were reported to be mild, 14% were severe, and 5% were critical [2]. In general, adults with COVID-19 can be grouped into the following severity of illness categories as shown in **Table 6.1**, although the criteria in each category may overlap or vary across guidelines and clinical trials [1].

Table 6.1 Categories of COVID-19 according to the severity of illness

Illness category	Criteria of diagnosis
Asymptomatic or Pre-symptomatic Infection	Individuals who test positive for SARS-CoV-2 by virologic but have no symptoms.
Mild Illness	Individuals who have any of the various signs and symptoms of COVID 19 (e.g., fever, cough, sore throat, malaise, headache, muscle pain) without shortness of breath, dyspnea, or abnormal chest imaging.
Moderate Illness	Individuals who have evidence of lower respiratory disease by clinical assessment or imaging and a saturation of oxygen (SpO2) ≥94% on room air at sea level.
Severe Illness	Individuals who have respiratory frequency >30 breaths per minute, SpO2 <94% on room air at sea level, ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO2 /FiO2) <300 mmHg, or lung infiltrates >50%.
Critical Illness	Individuals who have respiratory failure, septic shock, and/or multiple organ dysfunction.

6.2. Diabetes, other comorbidities and their impact on COVI-19

COVID-19 is a new disease. Currently there are limited data and information about the impact of underlying medical conditions and whether they increase the risk for severe illness from COVID-19. Based on what we know at this time, people with age more than 60 years (increasing with age), underlying noncommunicable diseases (NCDs), immunosuppression state, pregnancy and smoking are at an increased risk for severe illness from COVID-19 and have been associated with higher mortality (**Box 6.1**) [3-7]. In COVID-19 patients with diabetes and pre-existing ischaemic heart disease, limited cardiac reserve may increase morbidity and mortality risk [8].

Box 6.1. Risk factors for severe disease and higher mortality
Age more than 60 years (increasing with age) **Noncommunicable diseases (NCDs):** Diabetes, hypertension, cardiac disease, chronic lung disease, cerebrovascular disease, chronic kidney disease, cancer and obesity. **Immunocompromised state (weakened immune system):** Organ transplantation, immune deficiency, HIV, use of steroid, or use of other immune weakening medicines. **Pregnancy** **Smoking**

Diabetes is one of the most important comorbidities of COVID-19 infection. 20–50% of patients in the coronavirus disease 2019 (COVID-19) pandemic had diabetes [9]. Evidence from epidemiological observations in regions heavily affected by SARS-CoV-2 and reports from the Centers for Disease Control and Prevention (CDC) and other national health centres and hospitals showed that the risk of a fatal outcome from COVID-19 is up to 50% higher in patients with diabetes than in those who do not have diabetes [10]. Diabetes is associated with increased morbidity and mortality risk from pneumonia; hyperglycaemia (>11 mmol/l) on admission for pneumonia predicts poor outcome [11]. Diabetes was an independent predictor of increased mortality risk (OR 3.0; 95% CI 1.4, 6.3; p = 0.005) during the SARS epidemic in 2002/2003 [12] and during the Middle East respiratory syndrome-coronavirus (MERSCoV) epidemic in 2012 (adjusted HR 3.74; 95% CI 2.57, 5.67) [13]. Similarly, among young patients with novel influenza A (H1N1) in 2009, diabetes increased the risk of intensive care unit (ICU) admissions (adjusted OR 4.72; 95% CI 1.81, 12.3) [14]. A study by Yang X, et al. [15] described that diabetes was the most distinctive comorbid condition of non-survivors. These findings are in line with published data in those with respiratory infection [16-19].

People with diabetes develop similar symptoms as in non-diabetic. However, the initial manifestation could be milder, fever may be less common (59.5% vs 83.2%; p = 0.02), and deterioration could occur rapidly in later stages [20]. Deteriorating glycemic control and hyperglycemic emergencies may be a presenting feature, and those with type 1 diabetes may present with diabetic ketoacidosis (DKA) [21]. Data on acute complications during pandemic-related healthcare crises (e.g. diabetic ketoacidosis, hypoglycemia) almost do not exist, but will hopefully be generated in the aftermath of SARS-CoV-2, as this may allow planning in comparable future events. In a case series 10.3% (3/29) of the patients suffered at least one episode of hypoglycemia (<70mg/dl, i.e. <3.9mmol/l) [22]. Among 174 COVID-19 patients in Wuhan, China, people with diabetes had a greater inflammatory response (higher

CRP, ESR and IL-6, and relative neutrophilia and lymphopaenia), higher incidence of coagulopathy (higher Ddimer levels), metabolic derangements (hyperglycaemia, transaminitis), severe pneumonia (higher radiological scores) and higher mortality rate, compared with those without [20].

6.3. The potential links between diabetes and COVID-19 infection

It is well-recognized that illness by itself, particularly when severe, leads to "stress hyperglycemia" through the activation of counter-regulatory hormones, primarily cortisol and epinephrine, which increase endogenous glucose production and decrease glucose uptake into peripheral tissues, while also elevating circulating levels of free fatty acids through the stimulation of lipolysis **(Figure 6.1)**. Conversely, increased glucose and fatty acids may secondarily exacerbate illness through altered tissue metabolism, oxidative stress, hypercoagulability, and suppressed immunity and wound healing [23].

There is an established relationship between glucose levels and adverse clinical outcomes in the critically ill. In 2003, Krinsley et al [24] reported that in a mixed medical-surgical intensive care unit (ICU), mortality increased progressively as mean blood glucose concentrations increased. For example, mortality was 9.6% in patients whose mean ICU glucose concentration fell between 80 and 99 mg/dL but was more than 4-fold higher (42.5%) in those whose mean glucose exceeded 300 mg/dL.

Coexistence of diabetes and COVID-19 is an unholy situation wherein one tends to compliment the other. Possible interactions between the two raging pandemics have been summarized below.

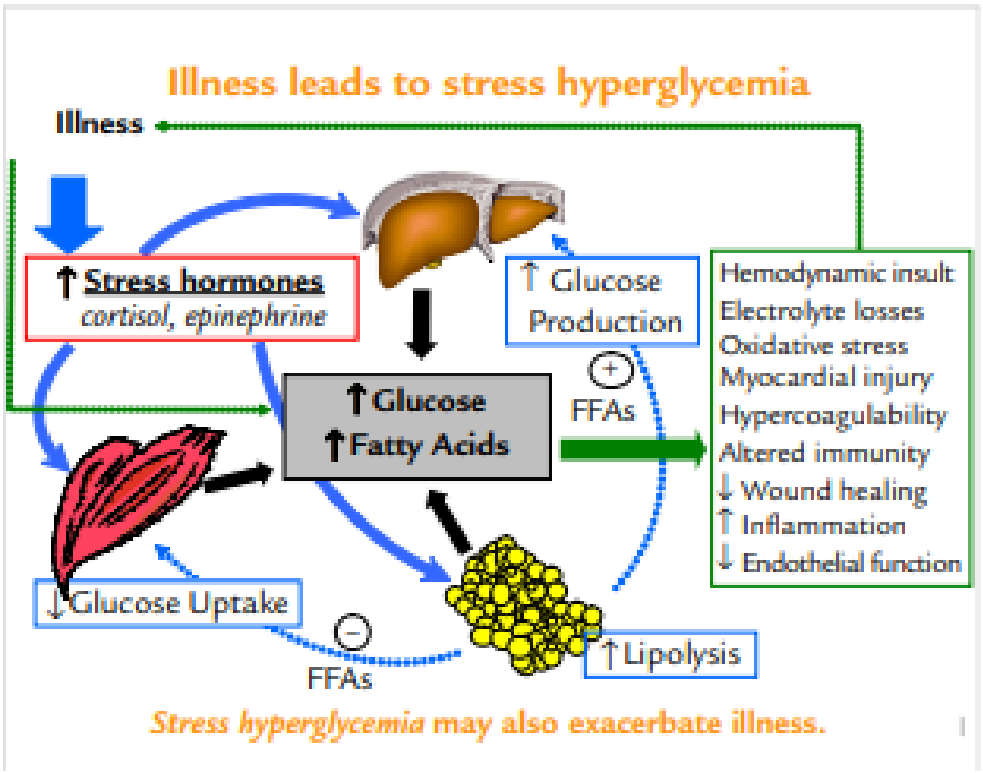


Figure. 6.1. Schematic overview of the relationship between stress hyperglycemia and illness. Through counter-regulatory hormones, illness promotes increased circulating glucose and free fatty acid concentrations. These, in turn, theoretically, could exacerbate illness through the intermediary effects listed. Adapted from **Bogun et al. [23].**

6.3.1. How does diabetes mellitus affect COVID-19?

Multiple pathophysiological explanations can be put forward supporting the association between diabetes and COVID-19 severity. Innate immune system, the first line of defense against SARS-CoV2, is compromised in patients with uncontrolled diabetes [25]. Moreover, diabetes is a pro-inflammatory state characterized by inappropriate and exaggerated cytokine response; this has been depicted in COVID-19 patients wherein serum levels of interleukin-6 (IL-6), C-reactive protein and ferritin were significantly higher in patients with diabetes than those without diabetes [26]. In addition, the aforementioned study also showed that COVID-19 patients with diabetes had higher D-dimer levels than those without diabetes [26]; perhaps signifying over-activation of the hemostatic system. Amid an already underlying pro-thrombotic hypercoagulable state predisposed by the mere presence of diabetes [27], over-activation of the coagulation cascade in COVID-19 can lead to fatal thromboembolic complications and eventual mortality [28]. Low ACE2 expression in diabetes might explain the increased incidence of severe lung injury and ARDS with COVID-19 [29].

6.3.2. How does COVID-19 affect underlying diabetes mellitus?

Preclinical data and data derived from studies based on the prior SARS outbreak (2003) suggest that COVID-19 can lead to worsening of glycemic control in people with pre-existing diabetes over and above that caused by the stress of a critical illness (i.e., stress

hyperglycemia). Yang et al. had reported that patients with SARS (caused by SARS-CoV, the 'cousin' of SARS-CoV-2) who had never received glucocorticoids had significantly higher fasting plasma glucose levels as compared to patients with non-SARS pneumonia [30]. This was explained on the basis of SARS-CoV mediated damage of the pancreatic b-cells as ACE2 is also expressed on the pancreatic islets [31].

In addition, COVID-19 can lead to worsening of insulin resistance in people with T2 and T1 diabetes (especially those who are obese and have some component of insulin resistance apart from an absolute insulin deficiency). Even mild COVID-19 can induce a pro-inflammatory milieu, as evident by high levels of IL-6, IL-1b, tumor-necrosis factor-a (TNFa), monocyte chemoattractant protein-1 (MCP-1) and inducible protein-10 that can further lead to lowering of insulin sensitivity. Moreover, obesity, commonly associated with T2 diabetes is likely to further aggravate the cytokine response, thereby further worsening insulin resistance [32]. COVID-19 is often associated with hypokalemia; this has been attributed to downregulation of pulmonary ACE2, reduced angiotension-II degradation and subsequent increased aldosterone secretion [29]. Hypokalemia, in turn, can worsen glucose control in patients with T1 and T2 diabetes [33]. Hypovitaminosis D as a result of the prevailing nationwide lockdowns can lead to insulin resistance and worsening of glucose profile in patients subsequently getting infected with COVID-19 [34,35].

The drugs used in the management of COVID-19 such as Corticosteroids, Lopinavir-ritonavir [36], type 1 interferons (interferon-b1) [37] and Azithromycin [38] may contribute to poor glucose profile.

Apart from worsening of hyperglycemia, hypoglycemia, also may contributes to higher number of cardiovascular events in patients with diabetes by undue activation of the sympathetic nervous system and by mobilizing pro-inflammatory mononuclear cells and increasing platelet reactivity [39]. Thus, COVID-19 in patients with underlying diabetes leads to worsening of glycemic profile that further compromises the innate immune response and promotes generation of pro-inflammatory cytokines, thereby setting up a vicious cycle (**Figure 6.2**) [40]

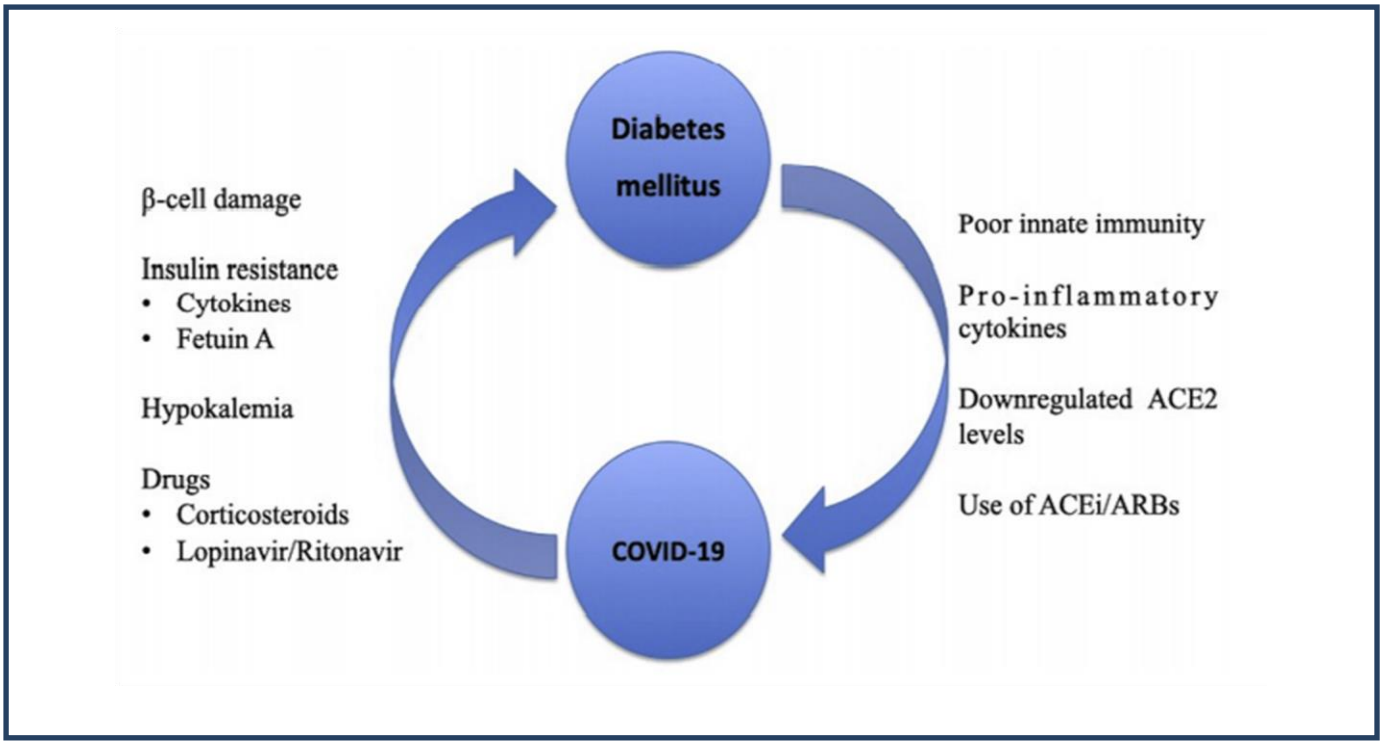


Figure 6.2. Schematic diagram showing the two-way interaction between the novel coronavirus disease (COVID-19) and diabetes mellitus. Diabetes mellitus contributes to increased disease severity of COVID-19 via compromised innate immunity, exaggerated pro-inflammatory cytokine response and low expression of angiotensin-converting enzyme 2 (ACE2). In addition, use of angiotensin-converting enzyme inhibitors (ACEi)/angiotensin-receptor blockers (ARBs) in people with diabetes mellitus have widely been implicated in contributing to disease severity in COVID-19. On the other hand, COVID-19 leads to worsening of glucose control in people with diabetes mellitus perhaps by direct virus-mediated b-cell damage, augmentation of insulin resistance through cytokines and fetuin A and hypokalemia. In addition, drugs being used in the management of COVID-19 like corticosteroids and lopinavir/ritonavir can also contribute to dysglycemia. Adapted from **Pal R, et al. [40].**

6.4. Indication of hospitalization of patients with diabetes and COVID-19

Diabetic patients need special attention and care, since it seems that their disease is associated with increased severity of symptoms and complications with COVID-19 [41]. Patients with a mild clinical presentation (absence of viral pneumonia and hypoxia) may not initially require hospitalization, and many patients will be able to manage their illness at home. [8,42] The decision to monitor a patient in the inpatient or outpatient setting should be made on a case-by-case basis. This decision will depend on the clinical presentation, requirement for supportive care, potential risk factors for severe disease, and the ability of the patient to self-isolate at home [42].

In a multivariable analysis of the full covid-19 positive cohort, the factors most strongly associated with hospital admission were age, including 75 years or older (OR 37.9, 95% CI 26.1 to 56.0) and 65 to 74 years (8.7, 8.7 to 11.2), heart failure (4.4, 2.6 to 8.0), male sex (2.8, 2.4 to 3.2), chronic kidney disease (2.6, 1.9 to 3.6), any increase in BMI (eg, BMI >40: 2.5, 1.8 to 3.4), diabetes (2.24, 1.84 to 2.73) and hypertension (1.78, 1.49 to 2.12) [43]. Because there is a higher risk of adverse outcomes, patients with diabetes should be preferentially managed in hospitals or settings where close monitoring of disease progression is possible [8].

6.5. Metabolic and glycemic control

Among hospitalized patients, both hyperglycemia and hypoglycemia are associated with adverse outcomes, including death [44,45]. Poor glycemic control is powerfully associated with serious infections and should be a high priority [46], while hypoglycemia is associated with increased mortality [47]. Therefore, careful management of diabetes among inpatients has direct and immediate benefits.

Poor glycemic control and chronic hyperglycemic state is an established risk factor for elevated mortality rates in a wide array of acute or chronic diseases, such as cardiovascular diseases, cerebrovascular diseases, cancer and infections [48-51]. In addition, one study showed that fasting hyperglycemia was strongly correlated with mortality in patients with or without diabetes [51]. Evidence indicated that a chronic hyperglycemic state was associated with impaired immunity [50] and hyperglycemia is an independent predictor for lower respiratory tract infection and poor prognosis [50, 52-54]. In particular, a few previous studies have shown that hyperglycemia was a risk factor for high morbidity and mortality from severe acute respiratory syndrome (SARS) [55] and Middle East respiratory syndrome (MERS) [56]. Recently, a descriptive study suggested that diabetes and/or acute uncontrolled hyperglycemia (defined as blood glucose measurements >10 mmol/l twice within any 24 h period) were associated with an increased length of hospital stay and higher mortality due to COVID-19 [57]. In a study of 7,300 cases of COVID-19, among type2 diabetes mortality rate were lower with better control of blood glucose (glycemic variability within 3.9– 10.0 mmol/l) than with poor control of blood glucose (upper limit of glycemic variability exceeding 10.0 mmol/l) [58] as shown in **Figure 6.3**.

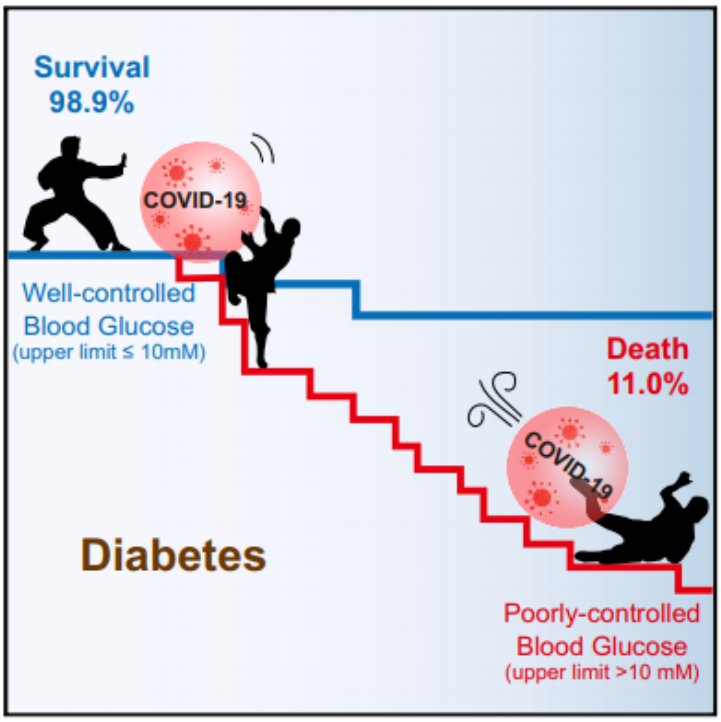


Figure 6.3. Diabetes status increased the mortality risk of patients with COVID-19. Adapted from **Zhu L, et al. [58].**

Glucose level is fluctuating in patients with diabetes and COVID-19 because of irregular diet, reduced exercise, increased glucocorticoids secretion due to stress, the use of glucocorticoids in treatment, the interruption or non-standard treatment with oral antidiabetic drugs (OAD) in isolation wards [59]. Reasons for glucose fluctuation in patients with diabetes and COVID-19 has shown in **Figure 6.4.**

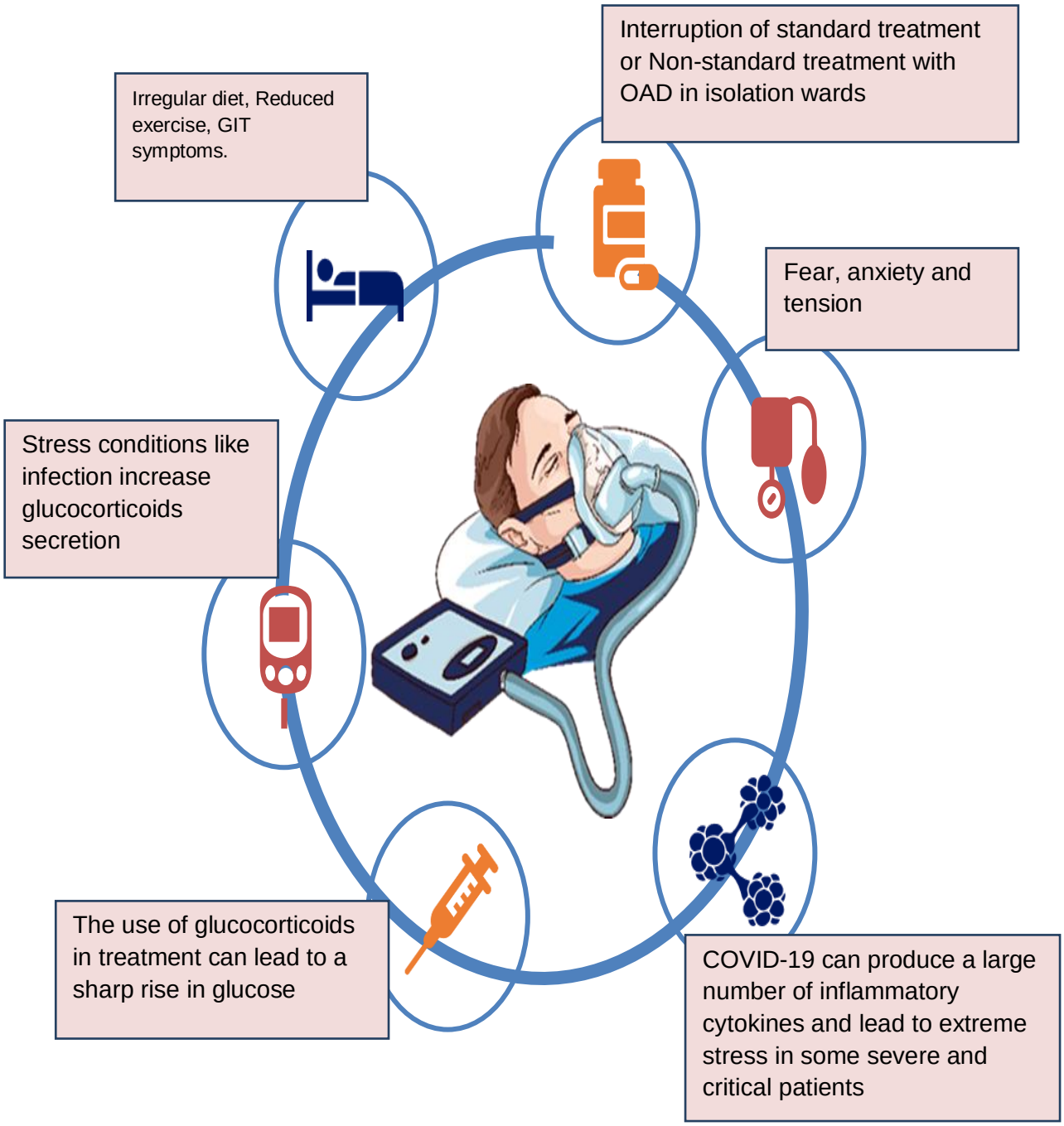


Figure 6.4. Reasons for glucose fluctuation in patients with diabetes and COVID-19. Adapted from **Alshaikh A et al. [59]**

Glycaemic testing and control should be recommended for all COVID-19 patients even if they do not have pre-existing diabetes, as most COVID-19 patients are prone to glucose metabolic disorders. All patients with COVID-19 disease and diabetes require continuous, reliable and intensive glycemic control as suggested in the **Table 6.2** [59]**.** Recommendations for glycemic target are not uniform by different organizations. HCPs may follow the recommendations of ACEDB guideline to manage their patients at home and hospital settings. They are also encouraged to follow recommendations regarding glycemic control from various organizations such as WHO, the CDC, IDF, ADA, etc.

Table 6.2. Glycemia Target in Patients with COVID-19

	Level of control		
	High	**Medium**	**Low**
Fasting/Premeal (mmol/l)	4.4 - 6.1	6.1 - 7.8	7.8 - 10.0
2h post prandial (mmol/l)	6.1 - 7.8	7.8 - 10.0	7.8 - 13.9
Target patient group	Mild and moderately severe COVID-19 non-elderly patient.	Mild and moderately severe COVID-19 elderly patients, Patient using glucocorticoid.	Severe COVID-19 & critically ill, Hypoglycemia intolerable, Patients with severe CVD, Patients with organ dysfunction.

6.6. Admission hyperglycemia is a bad prognostic factor

Evidence in the COVID-19 pandemic shows that hyperglycemia in people with diabetes worsens the prognosis and increases the risk of death [60,61]. In addition, it is emerging that particularly the hyperglycemia at the admission in the hospital is a very bad prognostic factor suggesting that hyperglycemia in the very early phase of the disease may play a particular role in determining the seriousness of the prognosis [60,61]. Zhang Y et al. [62] assessed the association of comorbid diabetes and FBG on admission with the fatality of COVID-19 using Cox proportional hazard model and found that both diabetes and FBG was an independent risk factor for death in COVID-19 patients, after adjusting for age, CVD, CKD and laboratory markers **(Table 6.3).**

There are at least two reasons why hyperglycemia, particularly an acute one, can be very dangerous during the SARSCoV-2 infection. One is that an acute increase of glycemia is accompanied by a huge increase of inflammatory mediators [63]. Clearly, knowing the role of the ‘‘cytokines storm” in the COVID-19 this is an effect that must be avoided. Another reason seems to be related to the binding of SARS-CoV-2 to ACE2 [64]. The glycosylation of ACE2 induced by hyperglycemia is needed for the linkage of the virus to this cellular receptor. Therefore, high and aberrantly glycosylated ACE2 in the tissue in uncontrolled hyperglycemia could favor the cellular intrusion of SARS-CoV2, thus leading to a higher propensity to COVID-19 infection and a higher disease severity. It is also likely that it is the amount of glycosylated ACE2 receptor, and not simply the amount of ACE2 alone, that is responsible for virus binding and fusion [64].

Therefore, it is conceivable that rapid normalization of hyperglycemia may results in a decrease of inflammatory cytokines release and in a lower ACE2 binding capacity for the virus. These two facts consistently might help in improving the prognosis in people affected by SARS-CoV-2 [65].

Table 6.3. Associations of diabetes and FBG with fatality of COVID-19 (Adapted from Zhang Y, et al. [62]

	Model I[a]		**Model II[b]**		**Model III[c]**	
Variable	AHR (95% CI)	P	AHR (95% CI)	P	AHR (95% CI)	P
DM	2.80 (1.01,7.80)	0.048	2.840 (1.01, 8.01)	0.048	3.64 (1.09, 12.21)	0.036
FBG (mmol/L)	1.14 (1.06,1.22)	<0.001	1.142 (1.07, 1.23)	<0.001	1.19 (1.08, 1.31)	<0.001

AHR, adjusted hazard ratio; CI, confidence interval; DM, diabetes mellitus; FBG, fasting blood glucose; a: Adjusted for age; b: Additionally adjusted for preexisting CVD and CKD; c: Additionally adjusted for inflammatory biomarkers (leucocytes, neutrophils, lymphocyte, eosinophil, NLR, neutrophil-to-lymphocyte ratio; C-reactive protein, procalcitonin).

In a retrospective study [66] of COVID-19 patients admitted in two hospitals of Wuhan, China, the association between FBG on admission and the 28-day mortality of COVID-19 patients without previously diagnosed diabetes was examined. In this study the elevated FBG (≥7.0 mmol/l) at admission was independently associated with increased 28-day mortality and percentages of in-hospital complications in COVID-19 patients without previous diagnosis of diabetes.

6.7 Management of diabetes with COVID-19 in hospital

Management of diabetes today has been addressed as an exciting confusion [67]. Considering the fast spread of the ‘‘Corona Virus Disease 2019 (COVID-19)” due to the ‘‘Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)”, there is currently a considerable debate on several important topics related to the most appropriate way to manage people with diabetes during this pandemic, including the susceptibility to this new infection, the severity of the complications, as well as the role of the drugs to use for the glycemic control [68].

An international panel of experts in the field of diabetes and endocrinology to provide some guidance and practical recommendations for the management of diabetes during the pandemic have compiled a simple flowchart for the metabolic screening and management of patients with COVID-19 and diabetes or at risk for metabolic disease [9]. This includes recommendations regarding both the need for primary prevention of diabetes as well as the avoidance of severe sequelae of diabetes triggered by unidentified or poorly managed diabetes (**Figure 6.5**).

Infection prevention and control (IPC) is a critical and integral part of clinical management of patients and should be initiated immediately at the point of entry of the patient to hospital (typically the Emergency Department). Standard precautions should always be routinely applied in all areas of health care facilities. Standard precautions include hand hygiene; use of PPE to avoid direct contact with patients’ blood, body fluids, secretions (including respiratory secretions) and non-intact skin. It also includes prevention of needle-stick or sharps injury; safe waste management; cleaning and disinfection of equipment; and cleaning of the environment [69]. Prevention and control measures for COVID - 19 infection has been described in details in Chapter 11 of this guideline.

Consensus recommendations for management of diabetes in COVID-19

Out-patient care

- Prevention of infection in diabetes
- Sensitization of patients with diabetes for the importance of optimal metabolic control
- Optimization of current therapy if appropriate
- Caution with premature discontinuation of established therapy
- Utilization of Telemedicine and Connected Health models if possible,

In-patient or intensive care unit

- Monitor for new onset diabetes in infected patients (in-patient care)
- Management of infected patients with diabetes (intensive care unit)
  - Plasma glucose monitoring, electrolytes, pH, blood ketones, or β-hydroxybutyrate
  - Liberal indication for early intravenous insulin therapy in severe courses (ARDS, hyperinflammation) for exact titration, avoiding variable subcutaneous resorption, and management of commonly seen very high insulin consumption

Therapeutic aims

- Plasma glucose concentration: 4–8 mmol/L (72–144 mg/dL) * (Out-patient care)
- Plasma glucose concentration: 4–10 mmol/L (72–180 mg/dL) * (In-patient or ICU)
- HbA1c: † less than 53 mmol/mol (7%)
- CGM/FGM targets
  - TIR (3·9–10 mmol/l): more than 70% (>50% in frail and older people)
  - Hypoglycemia (<3.9 mmol/l): less than 4% (<1% in frail and older people)

6.7.1 Outpatient management of diabetes with COVID-19

The algorithm (**Figure 6.6**) for outpatient diabetes management with prioritization for specialist diabetes department during covid-19 pandemic developed by the NHS London Clinical Networks [70] may be followed.

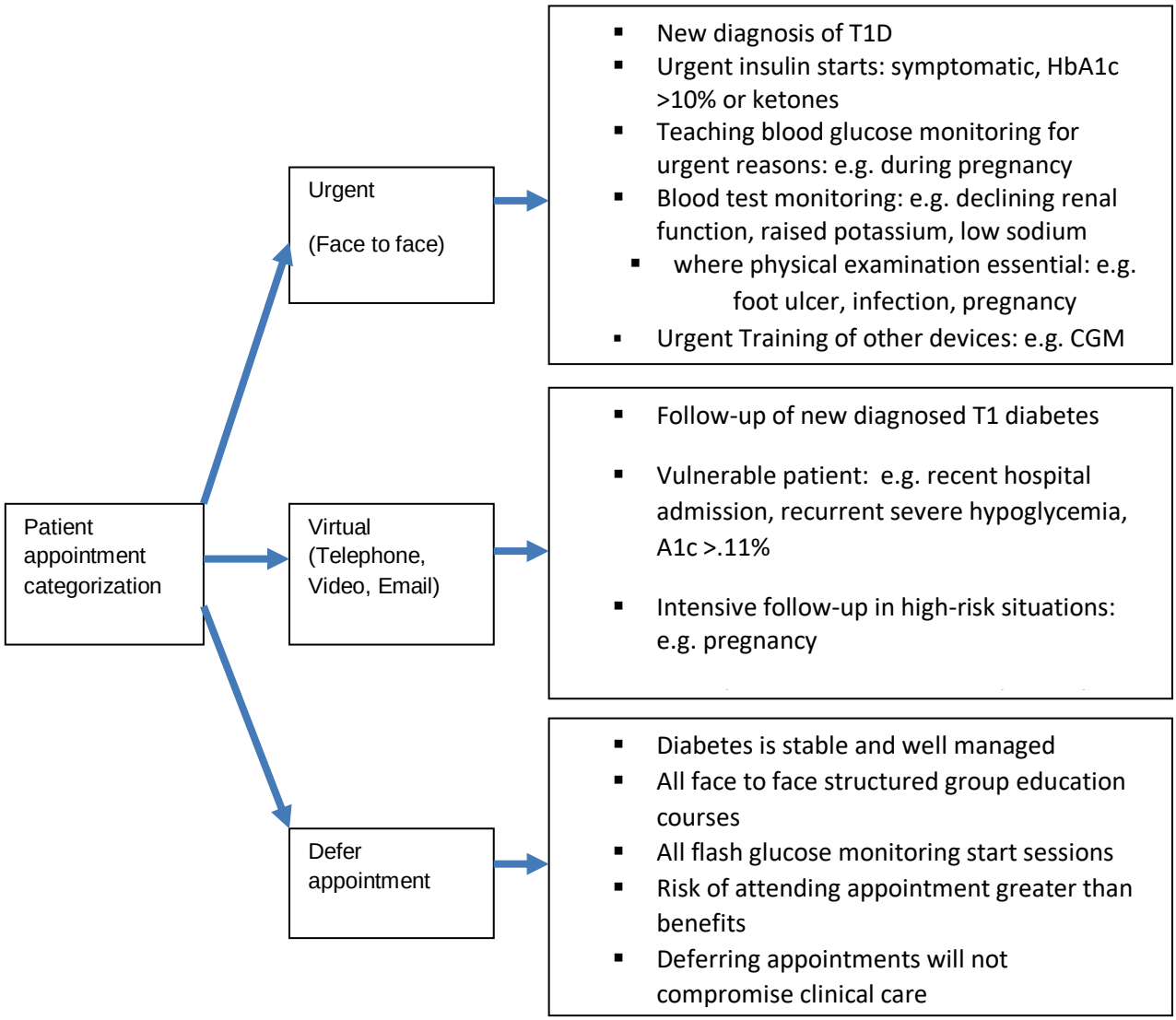


Fig. 6.6. Outpatient appointment prioritization for specialist diabetes departments during the coronavirus pandemic. Adapted from NHS London Clinical Networks [70].

6.7.2 Inpatient management of diabetes with COVID-19

Among hospitalized patients, both hyperglycemia and hypoglycemia are associated with adverse outcomes, including death [45,71,72]. Therefore, careful management of inpatients with diabetes has direct and immediate benefits.

Hospital management of diabetes is facilitated by a dedicated specialized diabetes management team service applying well-developed standards, and careful transition out of the hospital to prearranged outpatient management. Appropriately trained specialists or specialty teams may reduce length of stay, improve glycemic control, reduce the need for readmission, save the costs and improve outcomes [73-76]. High-quality hospital care for diabetes requires standards for care delivery, which are best to start implementation on admission (**Box 6.2)**. The maximum level of care needs to be determined by the admitting doctor, as COVID-19 can develop quickly. If the first assigned doctor is a junior doctor, the level of care should be consulted with the specialist in charge [77].

Box 6.2. HOSPITAL CARE DELIVERY STANDARDS: Recommendations
❖ Perform a random blood glucose test on all patients with diabetes admitted to the hospital, if not performed before admission. ❖ Perform an A1C test on all patients with diabetes or hyperglycemia (blood glucose >140 mg/dL [7.8 mmol/L]) admitted to the hospital, if not performed in the prior 3 months. ❖ Insulin is "the treatment of choice" in a hospitalized patient, if not indicated otherwise. ❖ Insulin should be administered using validated protocols that allow for predefined adjustments in the insulin dosage based on glycemic fluctuations.

A. Checklist for admission

Once the emergency department doctor has decided to admit a patient of diabetes with COVID-19 to the hospital, the following checklists should be completed to ensure that adequate preparations have been done for admission **(Box 6.3)**.

Box 6.3. Checklist for admission
i) Brief medical history taken and physical examination performed, ABC checked. **ii) Emergency treatments given and patient's response checked:** Example: oxygen therapy, insertion of peripheral IV canola (use appropriate antisepsis for the skin to prevent catheter-related infections), initial fluid therapy (and vasopressors if in shock). **iii) Essential diagnostic tests obtained:** Example: complete blood cell count, chemistry panel, glucose, chest radiograph, upper respiratory tract specimens for viral testing and blood sample for culture (when possible, before first dose of antimicrobials); but do not delay antimicrobials. **iv) First dose of antibiotics given, if required.** **v) The level of care the patient needs determined:** Example: ICU, high dependency unit, wards. **vi) Infection prevention and control measures the patient needs determined.** **vii) Verbal communication with ward staff completed to ensure continuity of care.** **viii) Patient prepared for safe transfer.** **ix) Patient's party has been adequately informed about the diagnosis, current status and possible prognosis of patient.** **x) All documentations kept completed.**
A, Airway; B, Breathing; C, Circulation

B. Diagnostic evaluation

The diagnosis of COVID-19 with new coronavirus SARS-CoV-2 is obtained by a Reverse Transcription Polymerase Chain Reaction (RT-PCR) analysis of a pharyngeal swab. Hospitalized patients should be monitored, from arrival at the hospital with Early Warning Score (vitals including blood pressure, pulse rate, respiratory rate, oxygen saturation, temperature and responsiveness score) and a thorough physical examination must be performed [77].

The optimal pulmonary imaging technique for people with COVID-19 is yet to be defined. Initial evaluation may include chest x-ray, ultrasound, or if indicated, computerized tomography (CT). Electrocardiogram (ECG) should be performed if indicated. Laboratory testing includes a complete blood count (CBC) with differential and a metabolic profile, including liver and renal function tests. Measurements of inflammatory markers such as C-reactive protein (CRP), D-dimer, and ferritin, while not part of standard care, may have prognostic value. The diagnostic work-up is summarized in **Figure 6.7** [77].

Common laboratory findings of COVID-19 include leukopenia and lymphopenia. Other laboratory abnormalities have included elevations in aminotransferase levels, C-reactive protein, D-dimer, ferritin, and lactate dehydrogenase [78,79]. Abnormalities in chest X-ray vary, but typically reveal bilateral multi-focal opacities. Abnormalities seen in computed tomography (CT) of the chest also vary, but typically reveal bilateral peripheral groundglass opacities with the development of areas of consolidation later in the clinical course [79]. Imaging may be normal early in infection and can be abnormal in the absence of symptoms. It is recommended that diagnostic samples are obtained at initial contact with the patient and before the patient is moved to the general ward.

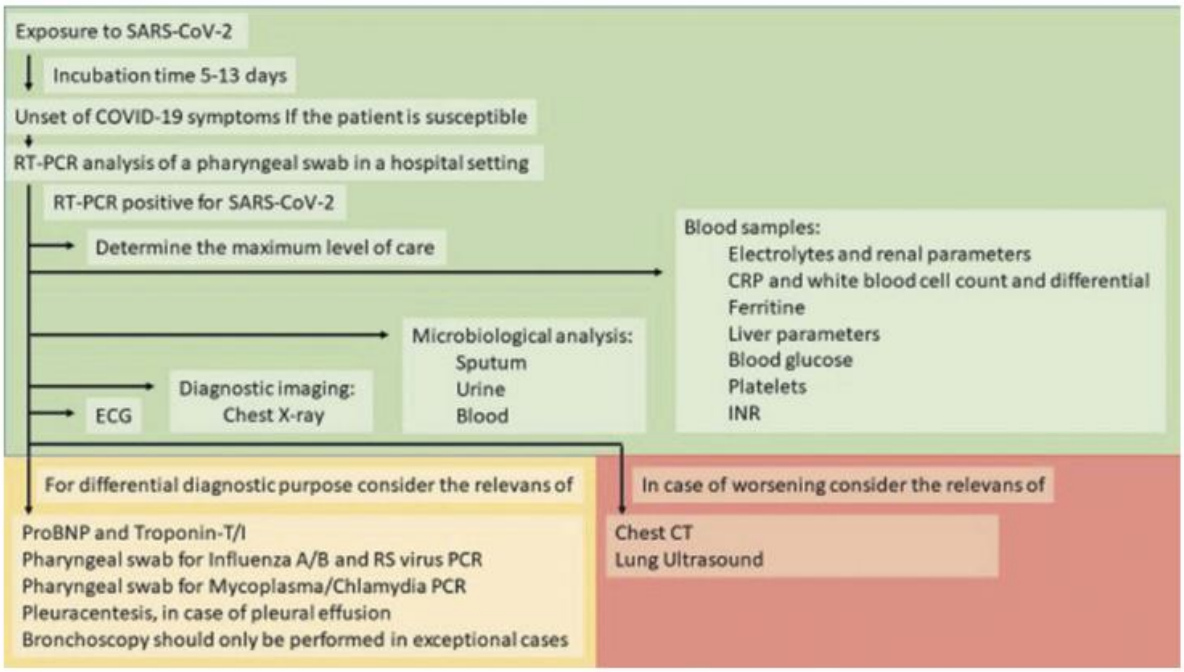


Figure 6.7. Summary of diagnostic workup for hospitalized COVID-19 patients. Adapted from Jeschke KN et al. [77].

C. Antidiabetic treatment in hospitalized patients with COVID-19

In most instances, insulin is the preferred treatment for hyperglycemia in hospitalized patients [45]. However, in certain circumstances, it may be appropriate to continue oral glucose-lowering medications [80]. In our perspective, an insulin regimen with basal insulin or a basal plus bolus with or without correction components is the preferred treatment for noncritically ill hospitalized patients either with poor or good oral intake. Continuous intravenous insulin infusion regimen is the preferred treatment for all critically ill hospitalized patients [45]. Regimens using insulin analogs and human insulin result in similar glycemic control in the hospital setting [81]. Department of Endocrinology, All India Institute of Medical Science [82] developed a clinical guidance on antihyperglycemic treatment initiation and titration in diabetes patients with COVID 19. With some modifications those has been depicted in **Table 6.4**.

Table 6.4. Clinical guidance on antihyperglycemic treatment initiation and titration in patients with COVID-19 and diabetes:

Clinical presentation	Blood glucose level (mg/dL)	Recommendations
Detected to have hyperglycemia at admission or on starting steroids or DKA/HHS	Pre-meal : <140 and Post-meal : <180	Healthy diet. Monitor BG levels
	Pre-meal : ≥140 and/or Post-meal : ≥180	Monitor BG levels Medical Nutrition Therapy (MNT)
	Pre-meal :140-180 and/or Post-meal :180-250	Start Tab Metformin 500 mg Plus DPP4i 50 mg BD*
	Pre-meal : ≥180 and/or Post-meal : ≥250	Start on basal + bolus insulin
	Pre-meal : ≥300 and/or Post-meal : ≥400	Start on IV insulin infusion
	Lab findings of DKA/HHS	Start on IV insulin infusion (DKA/HHS protocol)
Patient on OAD at admission/during follow-up Or DKA/HHS	Pre-meal : <140 and Post-meal : <180	Continue existing OAD*
	Pre-meal : ≥140 and/or Post-meal : ≥180	Up titrate OAD*
	Pre-meal : ≥180 and/or Post-meal : ≥250	Start on basal + bolus insulin
	Just FPG : ≥140	Add basal insulin at bed time
	Pre-meal : ≥300 and/or Post-meal : ≥400	Start on IV insulin infusion
	Lab findings of DKA/HHS	Start on IV insulin infusion (DKA/HHS protocol)
On basal bolus regimen at admission/during follow-up or DKA/HHS	Pre-meal : <140 and Post-meal : <180	Continue basal bolus regimen**
	Pre-meal : ≥140 and/or Post-meal : ≥180	Optimize insulin doses
	Pre-meal : ≥300 and/or Post-meal : ≥400	Start on IV insulin infusion
	Lab findings of DKA/HHS	Start on IV insulin infusion (DKA/HHS protocol)
Patient is NPO	BG level (2 hourly): If ≥3 values ≥180	Start on IV insulin infusion

* OAD to be initiated/continued only in stable, orally eating, mild COVID-19 cases without any contraindications for their use and the clinician's judgement about individual patient and their perspective would be applied to take decision.

** Continue existing basal bolus regimen if there are no episodes of hypoglycemia.

BG: Blood glucose; DKA: Diabetic ketoacidosis; HHS: Hyperglycemic hyperosmolar state; IV: Intravenous; NPO: Nothing by mouth; OAD: Oral antihyperglycemic drug.

I. Insulin Therapy [82]

a. Basal-bolus regimen (preferred to only basal or to only bolus regimen).

i) Total daily dose (TDD) = 0.4 units/kg/day (In case of age > 65 yr, nephropathy or liver disease, use 0.2 units/kg/day).

ii) Total daily dose may be divided equally into 4 doses (25% each): 3 doses are for bolus insulin (Regular/Rapid/Fast acting insulin before breakfast, lunch and dinner) and 1 dose for basal insulin (Intermediate- or long-acting insulin before dinner/at bed time.)

iii) Total daily dose may be divided into 2 basal bolus doses in the proportion of 50/50, 70/30, 75/25 or 80/20 as the individual patient demanded.

iv) Other basal bolus combination regimen may also be used according to the individual need.

v) Use split-dose combination regimen while patient is in hospital.

vi) Start mixed-dose combination regimen one or two days before discharge, if feasible.

b. Intravenous insulin infusion (III)

Indications for the use of III:

When blood glucose is persistently above 180 mg/dl (3 or more values) under the following circumstances: -

i) Diabetic Ketoacidosis (DKA) or/and Hyperglycemic Hyperosmolar state (HHS).

ii) Severe hyperglycemia at onset (Pre-meal BG level ≥300 mg/dl and post-meal BG level ≥400 mg/dl).

iii) Critically ill as in sepsis and septic shock.

iv) Patient is NPO or has erratic diet (in time and content).

v) Uncontrolled hyperglycemia despite multiple subcutaneous insulin injection (MSII) use or hyperglycaemia resistant to MSII (Insulin requirements > 2 units/kg).

Protocol for Intravenous insulin infusion (III):

A simple protocol for III, modifiable as necessary is shown in **Table 6.5**.

Table 6.5. Simplified protocol for Intravenous Insulin Infusion (III)

Infusion preparation	Starting dose of insulin	Glycemic targets BG (mg/dl)	Insulin infusion rate (IIR) (iu /hr)	Expected rate of fall of BG (mg/dl)/h	Further titration of IIR	Monitoring of BG	Monitoring of serum potassium
50 units regular /rapid /fast acting insulin in 50ml NS (1unit/ml)	0.05-0.1 iu/kg bd. wt. /hour.	To achieve & maintain 140 to 180 for most patients. Tighter target to 110-180 if safe. Relaxed target up to 220, if necessary.	Calculation of initial insulin infusion rate: BG (mg/dl) divided by 100. Variation is expected.	initially 50-100, till it reaches the target. If rate of BG change is >100 or <50 consider increasing or decreasing the infusion rate.	Based on: a. current BG level, b. target BG level, c. Rate of BG change in previous hour. d. Other factors	2 hourly Initially; 4 hourly, when BG values are stable and in target.	6 hourly if patient is NPO; 12 hourly if patient is taking orally

c. To switch to basal bolus regimen from III

The following steps are to be followed to switch to basal bolus regimen from III: -

i) Consult endocrinologist/ diabetologist to switch to basal bolus regimen (if available).

ii) Switch to basal bolus regimen from insulin infusion when BG levels are adequately controlled for last 24 hours, patient is taking orally well or on Ryle's tube feeds and is hemodynamically stable.

iii) Calculate TDD based on insulin infusion requirements for the last 24 hours: TDD = 80% of the total daily insulin requirement on intravenous infusion in the last 24 hours.

iv) Once you have the TDD, calculate the doses of bolus and basal insulin according to the individual patient's requirement as described above.

v) Insulin infusion has to be overlapped with basal bolus regimen for 60 minutes before stopping. That means, basal bolus regimen should be started 60 minutes before stopping insulin infusion. Don't stop insulin infusion abruptly.

II. Noninsulin Therapies

The safety and efficacy of noninsulin glucose-lowering therapies in the hospital setting is an area of active research [83]. Several recent randomized trials have demonstrated the potential effectiveness of glucagon-like peptide 1 receptor agonists and dipeptidyl peptidase 4 inhibitors in specific groups of hospitalized patients [84-86]. Sodium–glucose transporter 2 (SGLT2) inhibitors should be avoided in cases of severe illness, in patients with ketonemia or ketonuria, and during prolonged fasting and surgical procedures [87]. Until safety and effectiveness are established, SGLT2 inhibitors are not recommended for routine in-hospital use. The use of metformin and GLP-1 receptor agonists (GLP-1 RA) should be reviewed and stopped if acute gastrointestinal illness is present, as these medicines may further aggravate dehydration and hypovolaemia [88,89]. Dehydration can lead to develop serious side effects with metformin, SGLT2i and GLP-1 RA [90].

Potential metabolically interfering effects of noninsulin antidiabetic drugs in suspected or confirmed COVID-19 patients with type 2 diabetes and the recommendation for their use has been discussed in brief in **Table 6.6.**

D. Bedside blood glucose monitoring

In hospitalized patients with diabetes who are eating, glucose monitoring should be performed before and after meals; in those not eating, glucose monitoring is advised every 4–6 h [45]. More frequent blood glucose testing ranging from every 30 min to every 2 h is the required standard for safe use of intravenous insulin. Safety standards for blood glucose monitoring that prohibit the sharing of lancets, other testing materials, and needles are mandatory [92].

Capillary BG should be monitored and maintained as a chart as shown in **Table 6.7**. Good practice dictates that any glucose result that does not correlate with the patient's clinical status should be confirmed through measurement of a serum sample in the clinical laboratory. Real-time continuous glucose monitoring (CGM) provides frequent measurements of interstitial glucose levels, as well as direction and magnitude of glucose trends including detection of more incidence of hypoglycemia. However, at present, there are insufficient data on clinical outcomes, safety, or cost effectiveness to recommend widespread use of CGM in hospitalized patients [93].

Table 6.6. Recommendations for the use of noninsulin antidiabetic drugs in suspected or confirmed COVID-19 patients with type 2 diabetes.

Class of drugs	Considerations for use during COVID-19	Recommendations for practice
Biguanide [8,9,88,90] Example: Metformin	Risk of lactic acidosis in hypoxia and acute illness.	• Stop if severely ill with hemodynamic instability or hypoxia. • Stop the drugs if patient is admitted to hospital. • Renal function should be carefully monitored for acute kidney injury.
Sodium-glucose-co-transporter2 inhibitors (SGLT2i) [8,9,87,88-90] Example: Canagliflozin, Dapagliflozin, Empagliflozin	Increased risk of dehydration and euglycemic ketoacidosis. May present with abdominal pain, nausea, vomiting, fatigue or metabolic acidosis.	• Stop if oral intake is not tolerated or severely ill. • Patients should avoid initiating therapy during respiratory illness. • Renal function should be carefully monitored for acute kidney injury.
Glucagon-like peptide-1 receptor agonists (GLP-1 RA) [8,9,84,85,90] Example: Albiglutide, Dulaglutide, Exenatide Liraglutide, Semaglutide	Gastrointestinal side effects and risk of aspiration. Dehydration may lead to a serious illness	• Stop in severely ill patients. • Adequate fluid intake and regular meals should be encouraged • Patients should be closely monitored.
Dipeptidyl peptidase-4 inhibitors (DPP4i) [8,9,86,91] Example: Linagliptin, Sitagliptin, Vildagliptin	Low risk of hypoglycemia; possible to use for a wide range of renal function.	• Generally, well tolerated and may be continued in non-critically ill patients
Sulfonylureas [8] Example: Glimepiride, Glyburide, Glipizide	Risk of hypoglycaemia if oral intake is poor.	• Stop if unable to maintain regular oral food intake or at risk of hypoglycaemia.
Thiazolidinedione [8] Example: Pioglitazone	Risk of fluid retention and oedema.	• Stop if severely ill with haemodynamic instability, or hepatic or cardiac dysfunction.

Table 6.7. Example of SMBG (Self-Monitoring of Capillary Blood Glucose) Chart

Date	BBF	2h-ABF	BL	2h-AL	BD	2h-AD	1-3 am	Remarks
11.09.20	106							
12.09.20	5.9							
13.09.20								
14.09.20								
15.09.20								
16.09.20								
17.09.20								

Note: No need to write unit of glucose measurements in the Table. Just write the figure of measurements (In case of mg/dl, no decimal is required; in case of mmol/l, just one decimal is the rule) as shown as an example. It is to make the chart presentable at a glance. Always use a glucometer with reliable and good rapport, and test strips before the date of expiry. BBF, Before breakfast; 2h-ABF, 2-hour after breakfast; BL, Before lunch; 2h-AL, 2-hour after lunch; BD, Before dinner; 2h-AD, 2-hour after dinner.

6.7.3 Specific therapeutic agents for treatment of COVID-19

A number of investigational agents and drugs that are approved for other indications are currently being studied in clinical trials for the treatment of COVID-19 and associated complications. Data from randomized controlled trials, prospective and retrospective observational cohorts, and case series studies are rapidly emerging. The COVID-19 Treatment Guidelines Panel [94] reviewed the most recent clinical data and provided recommendations for the use of investigational agents and drugs as Antiviral, Immune-Based, and Adjunctive Therapy for the treatment of COVID-19 and associated complications.

A. Antiviral therapy under evaluation for the treatment of covid-19

On the 22nd October the US Food and Drug Administration (FDA) approved Remdesivir, the first drug approved to treat COVID-19, for use in adults and pediatric patients 12 years of age and older and weighing at least 40 kg (about 88 pounds) requiring hospitalization [95].

COVID-19 Treatment Guidelines Panel of NIH [94] provides recommendations for the treatment of COVID-19 based on the severity of disease. It includes recommendations for the use of Remdesivir, an antiviral agent that targets SARS-CoV-2, and dexamethasone, a corticosteroid that reduces inflammation **(Figure 6.8).** The Panel recommends against the use of Chloroquine/Hydroxychloroquine with or without Azithromycin, Lopinavir/Ritonavir and Ivermectin for the treatment of COVID-19, except in a clinical trial.

B. I**mmune-based therapy under evaluation for treatment of covid-19**

Considering the hyperactive inflammatory effects of SARSCoV-2, agents that modulate the immune response are being explored as adjunctive treatments for the management of moderate to critical COVID-19 [96]. These agents include human blood-derived products and immunomodulatory therapies. Some human blood-derived products are obtained from individuals who have recovered from SARS-CoV-2 infection (e.g., convalescent plasma, immunoglobulin products) [97,98]. These heterogenous products are postulated to have either direct antiviral properties, such as with convalescent plasma, and/ or immunomodulatory

effects like those noted with mesenchymal stem cells [99]. Additionally, neutralizing monoclonal antibodies directed against SARS-CoV-2 have been developed and are under investigation in clinical trials [100]. Other agents in this group include therapeutics currently approved for the treatment of other immune and/or inflammatory syndromes. These agents include corticosteroids (e.g., glucocorticoids),[101] which as a class possess a broad array of mechanisms to abrogate systemic inflammation, and more targeted anti-inflammatory treatments such as interleukin inhibitors [102,103], interferons [104], kinase inhibitors [105] and others. Recommendations of the COVID-19 Treatment Guidelines Panel's [94] for their use has been described in **Figure 6.9A** and **Figure 6.9B**.

Figure 6.8. Recommendations for antiviral treatment of patients with COVID-19. Adapted from NIH COVID-19 Treatment Guidelines Panel [94].

Summary Recommendations

- There are insufficient data for the COVID-19 Treatment Guidelines Panel (the Panel) to recommend either for or against the use of the following blood-derived products for the treatment of COVID-19:
  - **COVID-19 convalescent plasma**
  - **Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) immunoglobulins**
- The Panel **recommends against** the use of the following blood-derived products for the treatment of COVID-19, except in a clinical trial:
  - **Mesenchymal stem cells (AII)**
  - **Non-SARS-CoV-2-specific intravenous immunoglobulins (IVIG) (AIII)**. This recommendation should not preclude the use of IVIG when it is otherwise indicated for the treatment of complications that arise during the course of COVID-19.

Rating of Recommendations: A = Strong; B = Moderate; C = Optional

Rating of Evidence: I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies; III = Expert opinion

Figure 6.9A Blood-Derived Products Under Evaluation for the Treatment of COVID-19 (Last Updated: July 17, 2020). Adapted from NIH COVID-19 Treatment Guidelines Panel [94].

Summary Recommendations

Dexamethasone

- On the basis of the preliminary report from the Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial, the COVID-19 Treatment Guidelines Panel (the Panel) recommends using **dexamethasone** 6 mg per day for up to 10 days or until hospital discharge, whichever comes first, for the treatment of COVID-19 in hospitalized patients who are mechanically ventilated **(AI)** and in hospitalized patients who require supplemental oxygen but who are not mechanically ventilated **(BI)**.
- The Panel **recommends against** using **dexamethasone** for the treatment of COVID-19 in patients who do not require supplemental oxygen **(AI)**.
- If dexamethasone is not available, the Panel recommends using alternative glucocorticoids such as **prednisone**, **methylprednisolone**, or **hydrocortisone** **(AIII)**.

Other Immunomodulators

There are insufficient data for the Panel to recommend either for or against the use of the following immunomodulators for the treatment of COVID-19:

- Interleukin (IL)-1 inhibitors (e.g., **anakinra**)
- **Interferon beta** for the treatment of early (i.e., <7 days from symptom onset) mild and moderate COVID-19.

The Panel **recommends against** the use of the following immunomodulators for the treatment of COVID-19, except in a clinical trial:

- Anti-IL-6 receptor monoclonal antibodies (e.g., **sarilumab**, **tocilizumab**) or anti-IL-6 monoclonal antibody (**siltuximab**) **(BI)**.
- **Interferons (alfa or beta)** for the treatment of severely or critically ill patients with COVID-19 **(AIII)**.
- Bruton's tyrosine kinase inhibitors (e.g., **acalabrutinib**, **ibrutinib**, **zanubrutinib**) and Janus kinase inhibitors (e.g., **baricitinib**, **ruxolitinib**, **tofacitinib**) **(AIII)**.

Rating of Recommendations: A = Strong; B = Moderate; C = Optional

Rating of Evidence: I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies; III = Expert opinion

Anti-HTN

Figure 6.9B Immunomodulators Under Evaluation for the Treatment of COVID-19 (Last Updated: August 27, 2020). Adapted from NIH COVID-19 Treatment Guidelines Panel [94].

6.7.5 Use of other drugs

Anti-HTN

Figure 6.9B Immunomodulators Under Evaluation for the Treatment of COVID-19 (Last Updated: August 27, 2020). Adapted from NIH COVID-19 Treatment Guidelines Panel [94].

C. Adjunctive Therapy

In addition to the antiviral medications and the immune-based therapies for the treatment of COVID-19, adjunctive therapies are frequently used in patients to prevent and/or treat the infection or its complications. Some of these agents are being studied in clinical trials. Infection with SARS-CoV-2 is associated with a prothrombotic state and an increased incidence of thromboembolic disease. NIH COVID-19 Treatment Guidelines Panel [94] recommended antithrombotic therapy for the care of individuals who were receiving antithrombotic agents before they acquired SARS-CoV-2 and those who need these therapies to prevent or treat thromboembolic events during course of the infection as shown in **Figure 6.10**.

Some clinicians advocate for the use of vitamin and mineral supplements to treat respiratory viral infections. At present, there are insufficient data to recommend either for or against the use of vitamin C, vitamin D or Zinc for the prevention and treatment of COVID-19 [94]. The NIH COVID-19 Treatment Guidelines Panel [94] recommends against using zinc supplementation above the recommended dietary allowance for the prevention of COVID-19, except in a clinical trial.

Summary Recommendations

Laboratory Testing:

• In non-hospitalized patients with COVID-19, there are currently no data to support the measurement of coagulation markers (e.g., D-dimers, prothrombin time, platelet count, fibrinogen) (AIII).

• In hospitalized patients with COVID-19, hematologic and coagulation parameters are commonly measured, although there are currently insufficient data to recommend for or against using this data to guide management decisions (BIII).

Chronic Anticoagulant and Antiplatelet Therapy:

• Patients who are receiving anticoagulant or antiplatelet therapies for underlying conditions should continue these medications if they receive a diagnosis of COVID-19 (AIII).

Venous Thromboembolism Prophylaxis and Screening:

• For non-hospitalized patients with COVID-19, anticoagulants and antiplatelet therapy should not be initiated for prevention of venous thromboembolism (VTE) or arterial thrombosis unless there are other indications (AIII).

• Hospitalized adults with COVID-19 should receive VTE prophylaxis per the standard of care for other hospitalized adults (AIII). A diagnosis of COVID-19 should not influence a pediatrician's recommendations about VTE prophylaxis in hospitalized children (BIII). Anticoagulant or antiplatelet therapy should not be used to prevent arterial thrombosis outside of the usual standard of care for patients without COVID-19 (AIII).

• Reported incidence of VTE in hospitalized patients with COVID-19 varies. There are currently insufficient data to recommend for or against the use of thrombolytics or increasing anticoagulant doses for VTE prophylaxis in hospitalized COVID-19 patients outside the setting of a clinical trial (BIII).

• Hospitalized patients with COVID-19 should not routinely be discharged on VTE prophylaxis (AIII). Using Food and Drug Administration-approved regimens, extended VTE prophylaxis can be considered in patients who are at low risk for bleeding and high risk for VTE as per protocols for patients without COVID-19 (see text for details on defining atrisk patients) (BI).

• There are currently insufficient data to recommend for or against routine deep vein thrombosis screening in COVID-19 patients without signs or symptoms of VTE, regardless of the status of their coagulation markers (BIII).

• For hospitalized COVID-19 patients, the possibility of thromboembolic disease should be evaluated in the event of rapid deterioration of pulmonary, cardiac, or neurological function, or of sudden, localized loss of peripheral perfusion (AIII).

Treatment:

• Patients with COVID-19 who experience an incident thromboembolic event or who are highly suspected to have thromboembolic disease at a time when imaging is not possible should be managed with therapeutic doses of anticoagulant therapy as per the standard of care for patients without COVID-19 (AIII).

• Patients with COVID-19 who require extracorporeal membrane oxygenation or continuous renal replacement therapy or who have thrombosis of catheters or extracorporeal filters should be treated with antithrombotic therapy per the standard institutional protocols for those without COVID-19 (AIII).

Special Considerations During Pregnancy and Lactation:

• Management of anticoagulation therapy during labor and delivery requires specialized care and planning and should be managed similarly in pregnant patients with COVID-19 as other conditions that require anticoagulation in pregnancy (AIII).

• Unfractionated heparin, low molecular weight heparin, and warfarin do not accumulate in breast milk and do not induce an anticoagulant effect in the newborn; therefore, they can be used in breastfeeding women with or without COVID-19 who require VTE prophylaxis or treatment (AIII). In contrast, direct-acting oral anticoagulants are not routinely recommended due to lack of safety data (AIII).

Rating of Recommendations: A = Strong; B = Moderate; C = Optional

Rating of Evidence: I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies; III = Expert opinion.

Figure 6.10. Antithrombotic Therapy in Patients with COVID-19 Last Updated: May 12, 2020. Adapted from NIH COVID-19 Treatment Guidelines Panel [94].

6.7.4 Considerations for use of concomitant medications in patients with covid-19

A. Anti-hypertensive drugs

Hypertension predisposes a poor outcome of COVID-19 [106]. It has been speculated that specific antihypertensive drugs may underlie this association [107]. In particular, angiotensin-converting enzyme inhibitors (ACE-Is) and angiotensin II receptor blockers (ARBs) may up-regulate ACE2—the receptor used by SARS-CoV-2 to enter host cells—which has been suggested to lead to an increased risk of infection [107]. However, by limiting the effects of angiotensin II, ACE2 could also protect against a more severe COVID-19 infection [108]. **Figure 6.11** showed classic and non-classic renin-angiotensin system (RAS) with its interaction with SARS-COV-2 and the site of action of ACE inhibitors, and the Angiotensin Receptor Blockers [109].

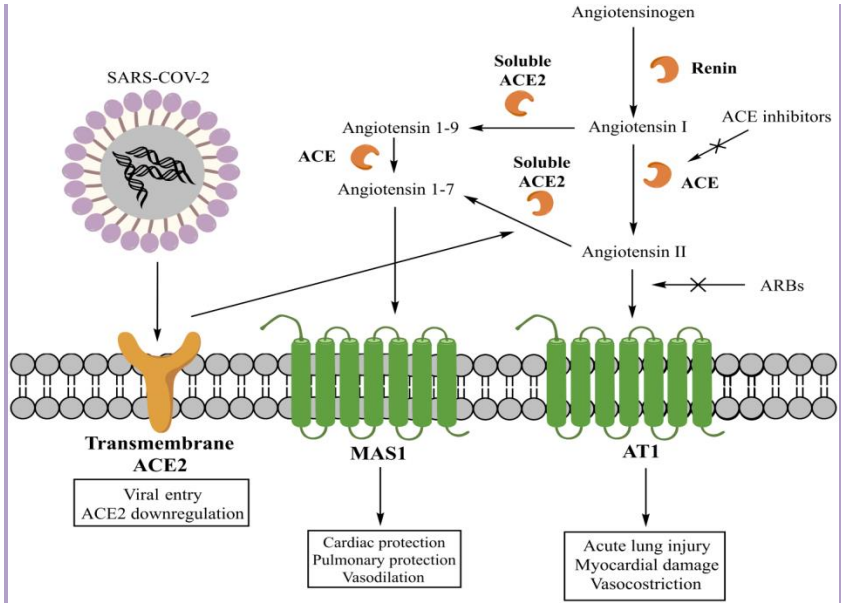


Figure 6.11. Classic and non-classic renin-angiotensin system (RAS) and its interaction with SARS-COV-2. The site of action of ACE inhibitors, and the Angiotensin Receptor Blockers (ARBs). Adapted from Mascolo A, et al [109]. ACE, Angiotensin-Converting-Enzyme; ARBs, Angiotensin Receptor Blockers; AT1, Angiotensin receptor1; MAS1, MAS receptor1.

In a study to observe the relationship between hypertension and severity of COVID-19 Pinto-Sietsma SJ et al. [110] found no evidence for adverse outcomes in severely affected COVID-19 patients those used ARBs prior to admission. The use of beta-blockers was associated with a significantly better outcome, whereas the use of calcium channel blockers was associated with poorer outcomes (**Figure 6.12**). However, to date, there is no sound evidence from clinical studies that replacing ACEIs/ARBs with other antihypertensive drugs is associated

with beneficial effects on either the prevention of COVID-19 or the prognosis for infected patients [111].

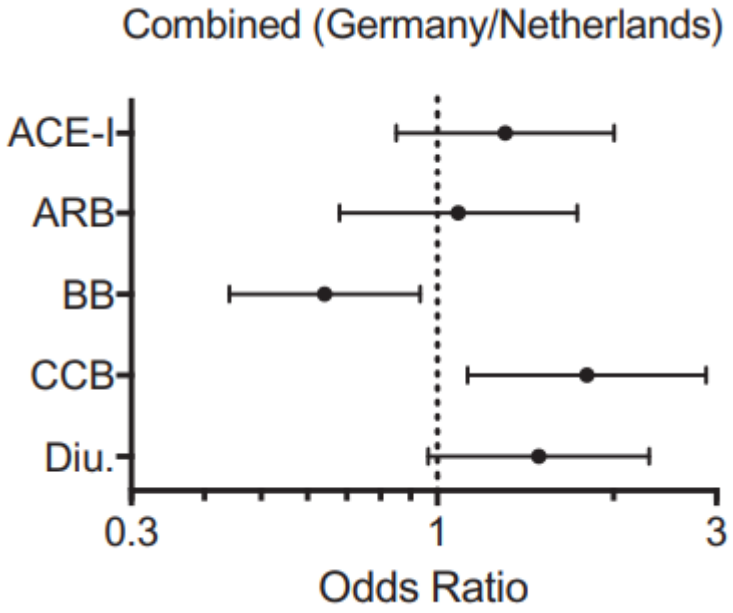


Figure 6.12. Association between antihypertensive drugs used and outcomes in the two cohorts combined, corrected for age, sex, and diabetes. An odds ratio >1 indicates a higher chance of treatment in an intensive care unit or death (error bars indicate 95% confidence limits; ACE-I, ACE inhibitor; ARB, angiotensin receptor blocker; BB, beta-blocker; CCB, calcium channel blocker; Diu, diuretic). Adapted from Pinto-Sietsma SJ et al. [110].

In a case-control study in Italy, Gnavi R et al [112] showed no increased risk of being infected by SARS-COV-2 in patients treated with RAS inhibitors. A Korean nationwide population-based cohort study [113] showed no difference for mortality between RAS inhibitors users and non-users (adjusted odds ratio, 0.88; 95% CI, 0.53 to 1.44). A retrospective, multi-center study demonstrated a lower risk of COVID-19 mortality in hospital patients with hypertension and COVID-19 who received ACE inhibitor/ARB compared to those who did not receive an ACE inhibitor/ARB (adjusted HR, 0.37; 95% CI, 0.15 to 0.89) [114].

American Diabetes Association (ADA) [115] recommended ACE inhibitors and angiotensin receptor blockers for treatment of hypertension as this drug classes demonstrated to reduce cardiovascular events in patients with diabetes. ADA also recommended ACE inhibitors and angiotensin receptor blockers as the first-line treatment for hypertension in patients with diabetes and chronic kidney disease (CKD).

International Scientific Societies including WHO have expressed their opinion on the use of RAS inhibitors, highlighting the absence of evidence suggesting an eventual discontinuation of ACE-inhibitors, or ARBs in patients with COVID-19. Therefore, they recommend to continue the treatment with the usual anti-hypertensive agent in patients with COVID-19

[94,116-122]. Therapy may need to be adjusted based on general considerations for patients with acute illness, with particular reference to maintaining normal blood pressure and renal function [119].

B. **HMG-CoA Reductase Inhibitors (Statins)**

At present, there is no direct evidence for or against continuation of statins in patients with diabetes and COVID-19. There are preliminary reports of raised liver enzymes and muscle enzymes associated with COVID-19 although severe liver disease or rhabdomyolysis are not characteristic [123]. Given the close links between diabetes and cardiovascular disease, persons with COVID-19 who are prescribed statin therapy for the treatment or prevention of cardiovascular disease should continue these medications [9,94]. However, an individualized decision considering the indication for statin therapy as well as possible drug interactions with antiviral agents has been suggested.

C. Antiplatelet drugs

There is no clear evidence of risks associated with continuing aspirin. Although myocardial injury is a well-known serious manifestation of COVID-19, acute myocardial ischemia is not clearly described. Concerns of atherosclerotic plaque accidents and increased acute ischemic strokes exist [124,125]. Until further data are available, it would be appropriate to continue aspirin for patients with indication for secondary prevention unless specific individual concerns such as gastrointestinal bleeding are noted [8].

D. Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

NIH COVID-19 Treatment Guidelines Panel recommended that persons with COVID-19 who are taking NSAIDs for a comorbid condition should continue therapy as previously directed by their physician [94]. The Panel recommended that there be no difference in the use of antipyretic strategies (e.g., with acetaminophen or NSAIDs) between patients with or without COVID-19. However, if patient is dehydrated, these medicines can cause injury to the kidneys (Examples include ibuprofen, naproxen) [90].

E. Corticosteroids for chronic users

• Oral corticosteroid therapy that was used prior to COVID-19 diagnosis for another underlying condition (e.g., primary or secondary adrenal insufficiency, rheumatological diseases) should not be discontinued. On a case-by-case basis, supplemental or stress-dose steroids may be indicated [94].

• Inhaled corticosteroids that are used daily for patients with asthma and chronic obstructive pulmonary disease for control of airway inflammation should not be discontinued in patients with COVID-19 [94].

F. Corticosteroids in pregnancy

• In pregnancy, given the potential benefit of decrease in maternal mortality and the low risk of fetal adverse effects for this short course of therapy, using dexamethasone in pregnant women with COVID-19 who are mechanically ventilated or who require supplemental oxygen but who are not mechanically ventilated (BIII) is recommended [94].

G. Anti-bacterial agents

Antibacterial agents are of no use against viral infections; however, they are useful in the treatment of suspected/verified secondary bacterial infections. A previous study showed that 50% of patients who died of COVID-19 had secondary infection, whereas only 1% of patients who survived had had a secondary infection ($p < 0.0001$) and septic shock was seen in70% vs. 0% in the respective groups [126]. There are no solid data on which microorganisms are most prevalent in secondary infections. However, it is reasonable to believe that bacterial infections are most prevalent, and variable within the patient population, co-dependent on both pulmonary (e.g. bronchiectasis and COPD) and other chronic comorbidities (e.g. diabetes, treatment with immunosuppressants). As such, there is reason to believe that secondary bacterial infections are important for disease development and the patient's prognosis. It is therefore recommended that at any given time, at admission or during hospitalization, if a secondary bacterial infection is suspected, antibiotic treatment should be initiated. Treatment should be broad-spectrum, as the most common etiology of secondary infections inCOVID-19 is yet unknown, and since secondary infections are often caused by bacteria resistant to small-spectrum antibiotics. The diagnostic work-up does not differ from that in other patients; suspected bacterial infection and relevant material for microbiological investigation should be secured before the start of anti-biotic treatment. The most frequent infection is probably pneumonia. Furthermore, disease progression in case of secondary bacterial infection has been rapid. COVID-19 with severe pneumonia should be treated with IV antibiotics. For COVID-19 uncomplicated pneumonia, oral antibiotics may be given [127].

The empiric recommendation [77,128] is therefore:

Piperacillin/Tazobactam 4g +0,5 g x 3

Cefuroxim 1,5 g x 3, in case of allergy to penicillin.

Meropenem 1 g x 3, in case of previous treatment failure.

Remember to adjust the dosage of antibiotics in case of renal failure.

6.7.5. Hypoglycemia and its management.

Hypoglycemia is the major limiting factor in the glycemic management of diabetes. Hypoglycemia in hospitalized patients is categorized by blood glucose concentration and clinical correlates. Recommendations regarding the classification and definition of hypoglycemia are outlined in **Table 6.8** [129,130].

Table 6.8. Classification of hypoglycemia

	Glycemic criteria/description	
Level 1	Glucose <70 mg/dL (3.9 mmol/L) and =/>54 mg/dL (3.0 mmol/L)	recognized as the threshold for neuroendocrine responses to falling glucose in people without diabetes.
Level 2	Glucose <54 mg/dL (3.0 mmol/L)	the threshold at which neuroglycopenic symptoms begin to occur and requires immediate action to resolve the hypoglycemic event
Level 3	A severe event characterized by altered mental and/or physical status requiring assistance for treatment of hypoglycemia, and immediate correction of low blood glucose.	
Adapted from ADA [130].		

A hypoglycemia management protocol should be adopted and implemented by each hospital. A plan for preventing and treating hypoglycemia should be established for each patient. Episodes of hypoglycemia in the hospital should be documented in the medical record and tracked. A treatment regimen to combat acute hypoglycemia is depicted in **Figure 6.13.**

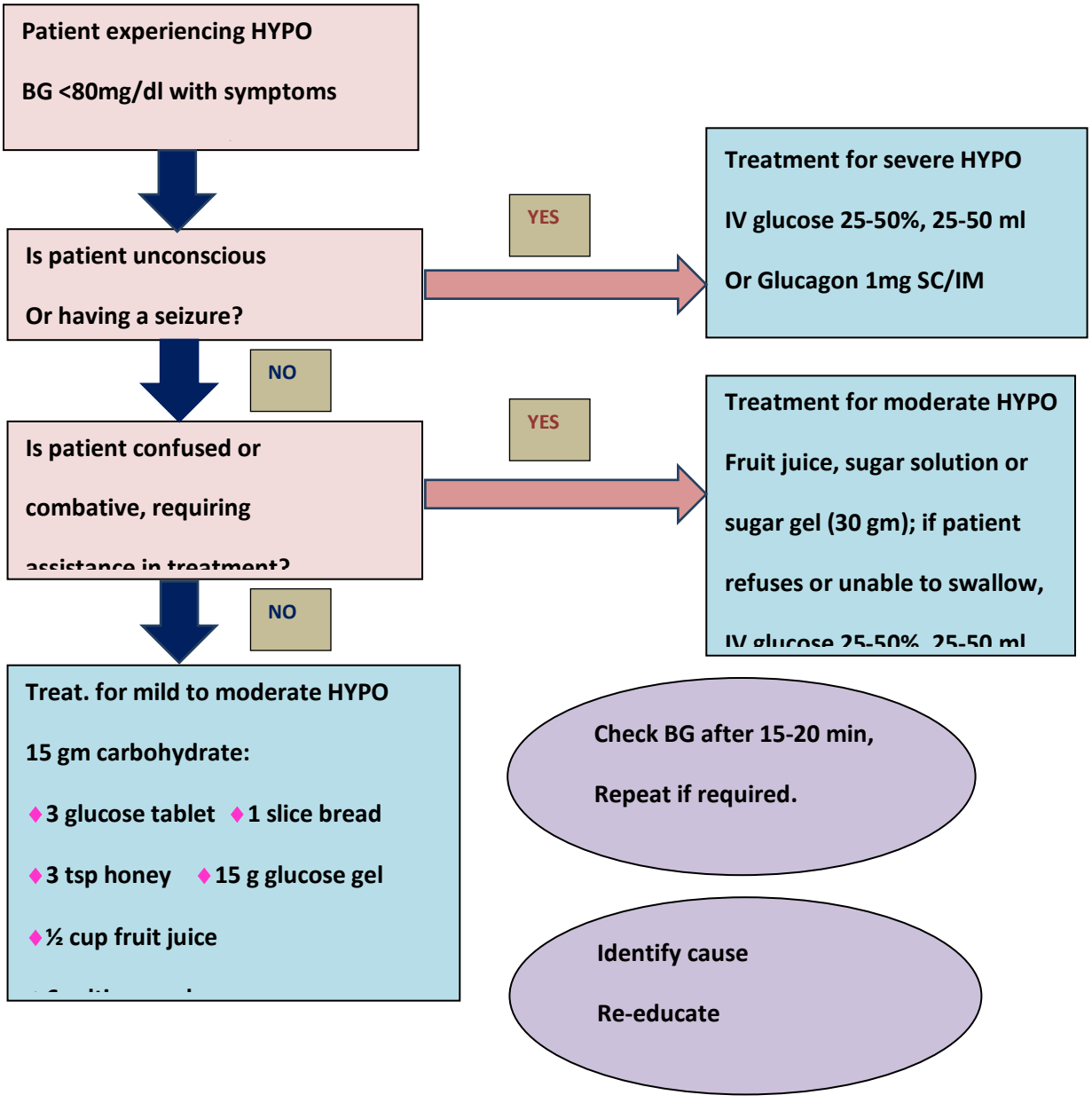


Fig. 6.13. A treatment regimen for acute hypoglycemia

6.7.6. Consideration for certain special populations with diabetes and COVID-19

Most patients of type 2 diabetes with COVID-19 infection have other components of the metabolic syndrome including hypertension, and cardiovascular disease and dyslipidaemia. Therefore, continuation with an appropriate antihypertensive, cardiovascular and lipid-lowering regimen in all these patients is of crucial importance and discussed above in brief.

There are certain subgroups of people with diabetes infected with COVID-19 who might require specific consideration. Critical COVID-19 illness has been shown to be significantly more prevalent in elderly patients with worse prognosis. [131]. Although children with COVID-19 may have less severe disease overall than adults with COVID-19, the recently described multisystem inflammatory syndrome in children (MIS-C) requires further study [132-136]. Data are also emerging on the clinical course of COVID-19 in pregnant patients, pregnancy outcomes in the setting of COVID-19, and vertical transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [137-140]. Special considerations should be given for transplant recipients [141-144], patients with cancer [145-150], persons with HIV [151-154], and patients with other immunocompromised conditions [94], as some of these patients may be at increased risk of serious complications as a result of COVID-19.

There is no scope for detail discussions on the management of diabetes and COVID-19 among these special population in this section. However, principles of management of diabetes is not different from others. The interested readers may consult the related references cited above in the text.

6.7.7. Treatment of critically ill patients

There is no scope here to discuss in details the treatment of COVID-19 associated with severe disease that requires intensive care unit management. Management of severe COVID-19 is not different from management of most viral pneumonia causing respiratory failure [155]. Management of diabetes in those patients has been described elsewhere in this chapter. Summary of caring for critically ill patients with COVID-19 has been described in **Figure 6.14.**

Caring for critically ill patients with COVID-19 is based on the usual management of viral pneumonia with respiratory failure with additional precautions to reduce risk of transmission.
Usual critical care
Many patients with severe COVID-19 develop acute respiratory distress syndrome (ARDS). Evidence-based guidelines for ARDS in the context of COVID-19 include treatments such as • Conservative intravenous fluid strategies • Empirical early antibiotics for possible bacterial pneumonia • Consideration for early invasive ventilation usual critical care • Lung-protective ventilation strategies • Periodic prone positioning during mechanical ventilation • Consideration of extracorporeal membrane oxygenation
Modifications to usual critical care
• Admission of patients with suspected disease to private rooms when possible • Use of medical face masks for symptomatic patients during assessment and transfer • Maintain distancing of at least 2 m between patients • Caution when using high-flow nasal oxygen or noninvasive ventilation due to risk of dispersion of aerosolized virus in the health care environment with poorly fitting masks • Clinicians involved with aerosol-generating procedures should use additional airborne precautions including N95 respirators and eye protection
Facility planning
• Ensure staff have updated training in infection prevention and control including PPE. • Planning at local and regional levels for a potential surge in the need for critical care resources
COVID-19–specific considerations
• Antiviral or immunomodulatory therapies for treatment of COVID-19 should be considered as up dated recommendations by authentic organizations. • Patients should be asked to participate in clinical trials of supportive or targeted therapies.
Figure 6.14 Summary of Caring for Critically Ill Patients With COVID-19

The principal feature of patients with severe disease is the development of ARDS: a syndrome characterized by acute onset of hypoxemic respiratory failure with bilateral infiltrates. Evidence based treatment guidelines for ARDS should be followed, including conservative fluid strategies for patients without shock following initial resuscitation, empirical early antibiotics for suspected bacterial co-infection until a specific diagnosis is made, lung-protective ventilation, prone positioning, and consideration of extracorporeal membrane oxygenation for refractory hypoxemia [156]. In settings to invasive ventilation or prior to patients developing severe hypoxemic respiratory failure, there may be a role for high-flow nasal oxygen or noninvasive ventilation [157].

Septic shock and specific organ dysfunction such as acute kidney injury appear to occur in a significant proportion of patients with COVID19–related critical illness and are associated with increasing mortality with management recommendations following available evidence-based guidelines [158]. While no antiviral or immunomodulatory therapies for COVID-19 have yet proven effective, a majority of severely ill patients described to date have received

numerous potentially targeted therapies—most commonly neuraminidase inhibitors and corticosteroids—and a minority of patients have been enrolled in clinical trials [159].

6.7.8 Palliative care

Palliative care aims to optimize function and to enhance quality of life for patients with serious and life-limiting illnesses. It focuses on reducing the burden of symptoms, and supporting patients and caregivers. Recommendations for palliative care for patients withCOVID-19 does not differ from recommendations in general. We, therefore, recommend the use of local guidelines or to consult the comprehensive overview of "Palliative Care in Respiratory Disease", published by European Respiratory Society [160]. However, special care should be taken of patients' relatives who due to the risk of spreading disease do not have the usual possibilities for being with their loved ones.

6.7.9. Discharge criteria for confirmed COVID-19 cases from hospital and Follow-up

When deciding on criteria for hospital discharge of COVID-19 patients, health authorities should take into account several factors such as the existing capacity of the healthcare system, home facilities for individual patients, laboratory diagnostic resources, and the prevailing epidemiological situation.

After reviewing the existing clinical guidance, protocols from national and international organizations, and peer-reviewed publications, the European Centre for Disease Prevention and Control (ECDC) [161] provided an overview of recommendations for the de-isolation of COVID-19 patients of the national bodies in countries that have experienced local transmissions of SARS-CoV-2 as presented in the **Table 6.9**. It suggests criteria to be considered when deciding whether a confirmed COVID-19 case can be safely (i.e. without being infectious) discharged from hospital.

- Despite of some differences in practice, a consensus exists to combine a) the evidence for viral RNA clearance from the upper respiratory tract with b) the clinical resolution of symptoms.
- At least two upper respiratory tract samples negative for SARS-CoV-2, collected at ≥24-hourintervals are recommended to document SARS-CoV-2clearance.
- For symptomatic patients after the resolution of symptoms, samples should be collected at least seven days after the onset or after >3 days without fever.
- For asymptomatic SARS-CoV-2-infected persons, the tests to document virus clearance should be taken at a minimum of 14 days after the initial positive test.
- Italy indicates that serology tests to document IgG antibody specific to SARS-CoV-2 will be of value.

All patients discharged for home should be instructed to return to hospital if they develop any worsening of illness.

Table 6.9. Comparison of current guidelines on de-isolation of COVID-19 cases	
Guidelines	**Discharge criteria for hospitalized cases**
Ministero della salute, Consiglio Superiore di Sanità, Italy (28 February2020)	A COVID-19 patient can be considered cured after the resolution of symptoms and 2 negative tests for SARS-CoV-2 at 24-hourintervals. For patients who clinically recover earlier than 7 days after onset, an interval of 7 days between the first and the final test is advised. Note: Virus clearance is defined as viral RNA disappearance from bodily fluids of symptomatic and asymptomatic persons, accompanied by appearance of specific IgG.
China CDC Diagnosis and treatment protocol for COVID-19 patients (trial version 7, revised)	Patients meeting the following criteria can be discharged: • Afebrile for >3 days, • Improved respiratory symptoms, • Pulmonary imaging shows obvious absorption of inflammation, and • Nucleic acid tests negative for respiratory tract pathogen twice consecutively (sampling interval ≥24 hours). After discharge, patients are recommended to continue 14 days of isolation management and health monitoring, wear a mask, live in a single room with good ventilation, reduce close contact with family members, eat separately, keep hands clean and avoid outdoor activities. It is recommended that discharged patients should have follow-up visits after 2 and 4 weeks.
National Centre for Infectious Diseases (NCID) Singapore De-isolation of COVID-19 suspect cases. Link: https://academic.oup.com/cid/article/71/15/883/5758073	Discharge patient with advisory and clinic follow-up if indicated and with daily wellness calls until day 14 after last possible exposure, under the following conditions: • Afebrile ≥24 hours, • 2 respiratory samples tested negative for SARS-CoV-2by PCR in ≥24 hours, • Day of illness from onset ≥6 days • OR • Alternative etiology found (e.g. influenza, bacteremia) • OR • Not a close contact of a COVID-19 case • Does not require in-patient care for other reasons.
CDC US A Interim guidance for discontinuation of transmission-based precautions and disposition of hospitalized patients with COVID-19. Link: https://www.cdc.gov/coronavirus/2019-ncov/hcp/disposition-hospitalized-patients.html	Negative rRT-PCR results from at least 2 consecutive sets of nasopharyngeal and throat swabs collected ≥ 24hours apart from a patient with COVID-19 (a total of four negative specimens) AND resolution of fever, without use of antipyretic medication, improvement in illness signs and symptoms. Note: decision to be taken on a case-by-case basis in consultation with clinicians and public health officials.

6.8. Lifestyle management and diabetes self-management education and support (DSMES) in the context of the COVID-19 pandemic

Effective behavior management and psychological well-being are foundational to achieving treatment goals for people with diabetes [162,163]. Essential to achieving these goals are diabetes self-management education and support (DSMES), medical nutrition therapy (MNT), routine physical activity, smoking cessation counseling when needed, and psychosocial care. Evaluation during routine and emergency care should include not only assessment of medical health but also behavioral and mental health outcomes, especially during times of deterioration in health and well-being, as occurs in SARS-CoV-2 infection.

Nutrition intervention and therapy needs to be considered as an integral part of the approach to patient of SARS-CoV-2 infection in the general healthcare, as well as in the hospital care setting. Many chronic diseases such as diabetes and cardiovascular diseases and their clustering in polymorbid individuals [164] as well as older age per se [165] are very commonly associated with high risk and prevalence of malnutrition and worse outcomes.

Acute respiratory complications that are reported to require prolonged ICU stays are a major cause of morbidity and mortality in COVID-19 patients. ICU stays, and particularly their longer duration, are well-documented causes of malnutrition, with loss of skeletal muscle mass and function which in turn may lead to poor quality of life, disability and morbidities long after ICU discharge [166]. Causes of ICU- and disease related malnutrition include reduced mobility, catabolic changes particularly in skeletal muscle as well as reduced food intake, all of which may be exacerbated in older adults. In addition, inflammation and sepsis may further and primarily contribute to enhance all the above alterations in the presence of SARS-CoV-2 infections. Most importantly, appropriate nutritional assessment and treatment are well-documented to effectively reduce complications and improve relevant clinical outcomes under various conditions including ICU stays, hospitalization, several chronic diseases and in older adults [164-166]. Based on the above observations, prevention, diagnosis and treatment of malnutrition should be considered in the management of COVID-19 patients to improve both short- and long-term prognosis.

The European Society for Clinical Nutrition and Metabolism (ESPEN) [167] provided concise experts statements and practical guidance for nutritional management of COVID-19 patients, with regard to those in the ICU setting or in the presence of older age and polymorbidity (**Figure 6.15**), which are all independently associated with malnutrition and its negative impact on patient survival. Health care providers are required to train on how to address the nutritional aspects of these patients.

DSMES services facilitate the knowledge, decision-making, and skills mastery necessary for optimal diabetes self-care and incorporate the needs, goals, and life experiences of the person with diabetes. DSMES are based on evidence of benefit [163,168]. Specifically, DSMES helps people with diabetes to identify and implement effective self-management strategies and cope with diabetes at four critical time points [163] – at diagnosis, annually, when complicating factors arise (as in COVID -19), and when transitions in care occur (as at the time of discharge from hospital after recovery from COVID-19). DSMES should include appropriate skills needed after discharge, such as medication dosing and administration, glucose monitoring, and recognition and treatment of hypoglycemia with a special focus on sick-day-rules.

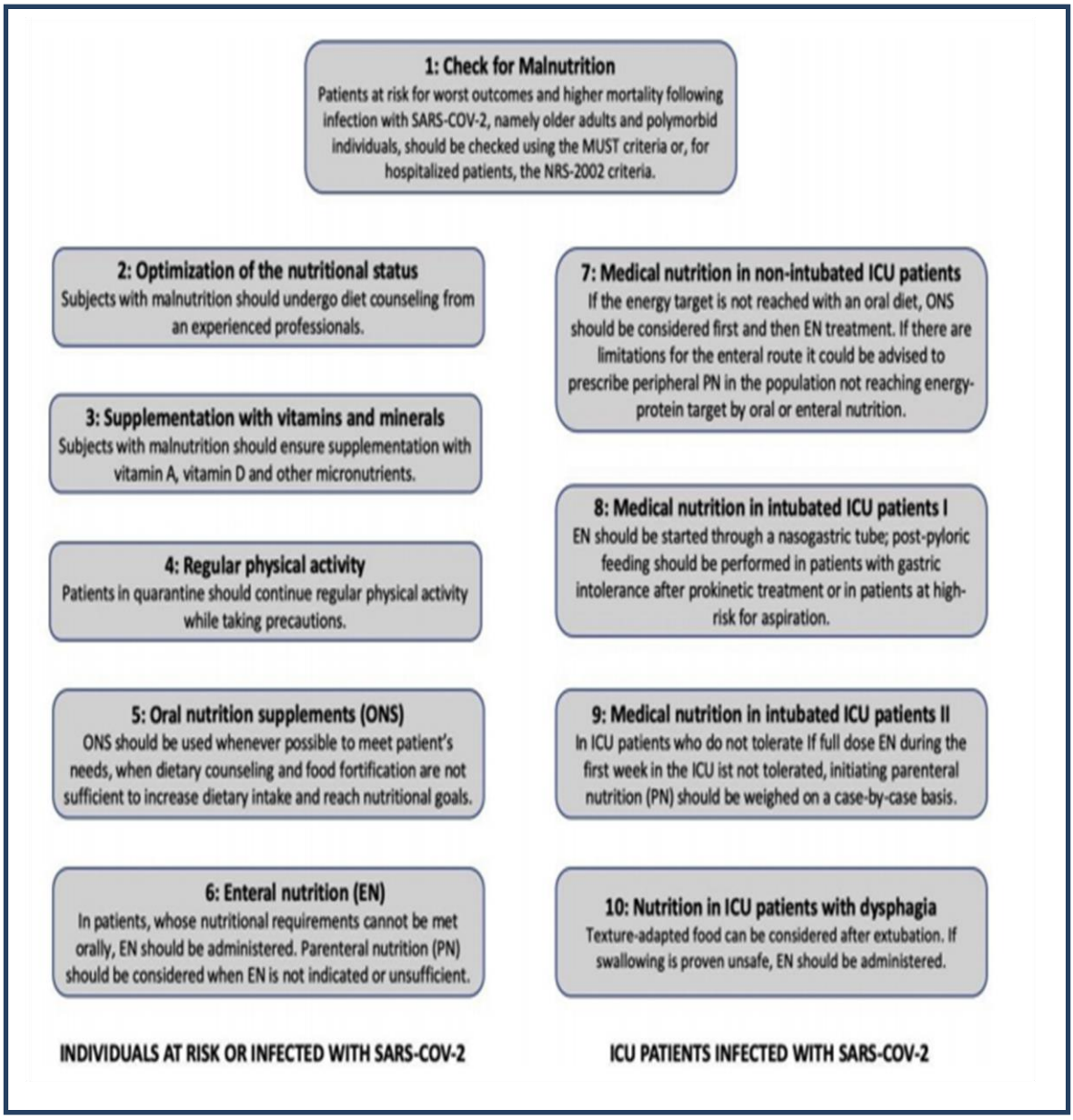


Figure 6.15. Nutritional management in individuals at risk for severe COVID-19, in subjects suffering from COVID-19 and in COVID-19 ICU patients requiring ventilation. Adapted from Barazzoni R et al. [167].

At the time of this writing the available evidence suggests that smoking is associated with increased severity of disease and death in hospitalized COVID-19 patients. Although likely related to severity, there is no evidence to quantify the risk to smokers of hospitalization with COVID-19 or of infection by SARS-CoV-2 was found in the peer-reviewed literature [169]. WHO recommends that tobacco users stop using tobacco [169]. WHO recommended population-based studies to address these questions.

Complex environmental, social, behavioral, and emotional factors, known as psychosocial factors, influence living with diabetes, both type 1 and type 2, and achieving satisfactory medical outcomes and psychological well-being [170]. The individuals with diabetes and their families are challenged with complex, multifaceted issues when integrating diabetes care into daily life [171]. Emotional well-being is an important part of diabetes care and self-management. Psychological and social problems can impair the individual's [171,172] or family's [173] ability to carry out diabetes care tasks and therefore potentially compromise health status. A systematic review and meta-analysis showed that psychosocial interventions significantly improved A1C (standardized mean difference –0.29%) and mental health outcomes [174].

Existing evidence clearly showed the most relevant and profound psychological impact of the COVID-19 outbreaks on the general population [175-177]. **Figure 6.16** summarized the most relevant psychological reactions in the general population related to COVID-19 infection.

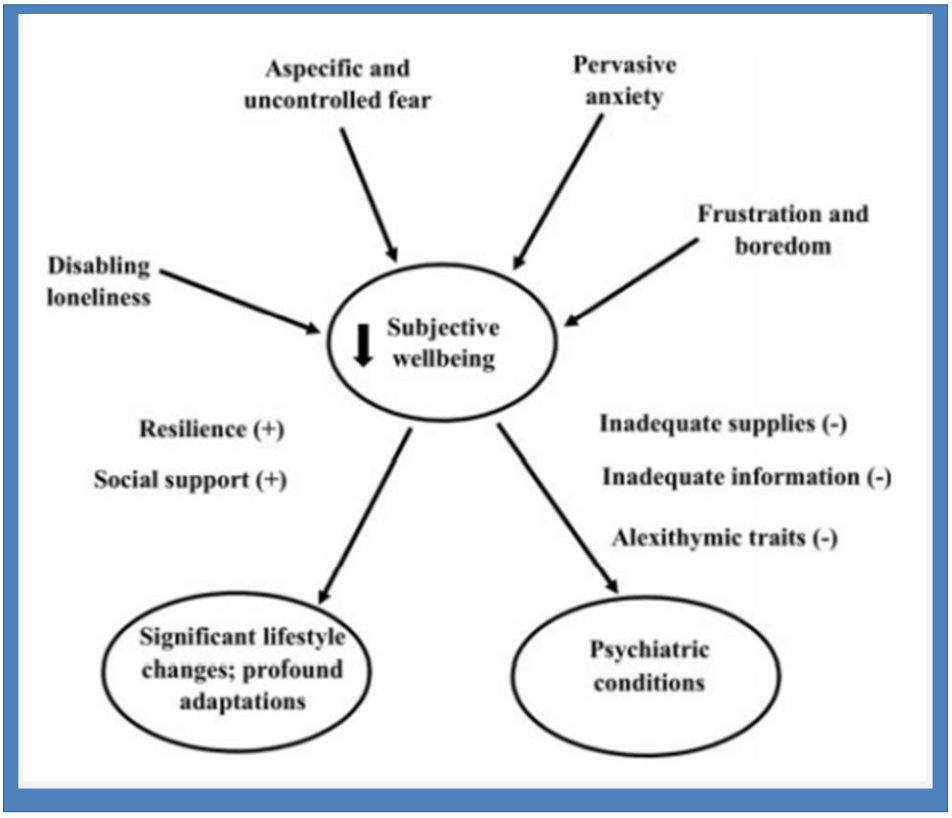


Figure 6.16. Summary of the most relevant psychological reactions in the general population related to COVID-19 infection.

Although non-specific and uncontrolled, fears related to infection, pervasive anxiety, frustration and boredom, as well as loneliness have been hypothesized to impair subjective

wellbeing and quality of life. Resilience and enhanced social support are protective factors that may help with regard to lifestyle changes and re-adaptation mechanisms [175,176].

The Inter Agency Standing Committee (IASC) for "mental health and psychosocial support" (MHPSS) in Emergency Settings [178] recommends in their guideline that multiple levels of interventions be integrated within outbreak response activities. These levels align with a spectrum of mental health and psychosocial needs and are represented in a pyramid of interventions (**Figure 6.17**) ranging from embedding social and cultural considerations in basic services, to providing specialized services for individuals with more severe conditions. Core principles include: do no harm, promote human rights and equality, use participatory approaches, build on existing resources and capacities, adopt multi-layered interventions and work with integrated support systems.

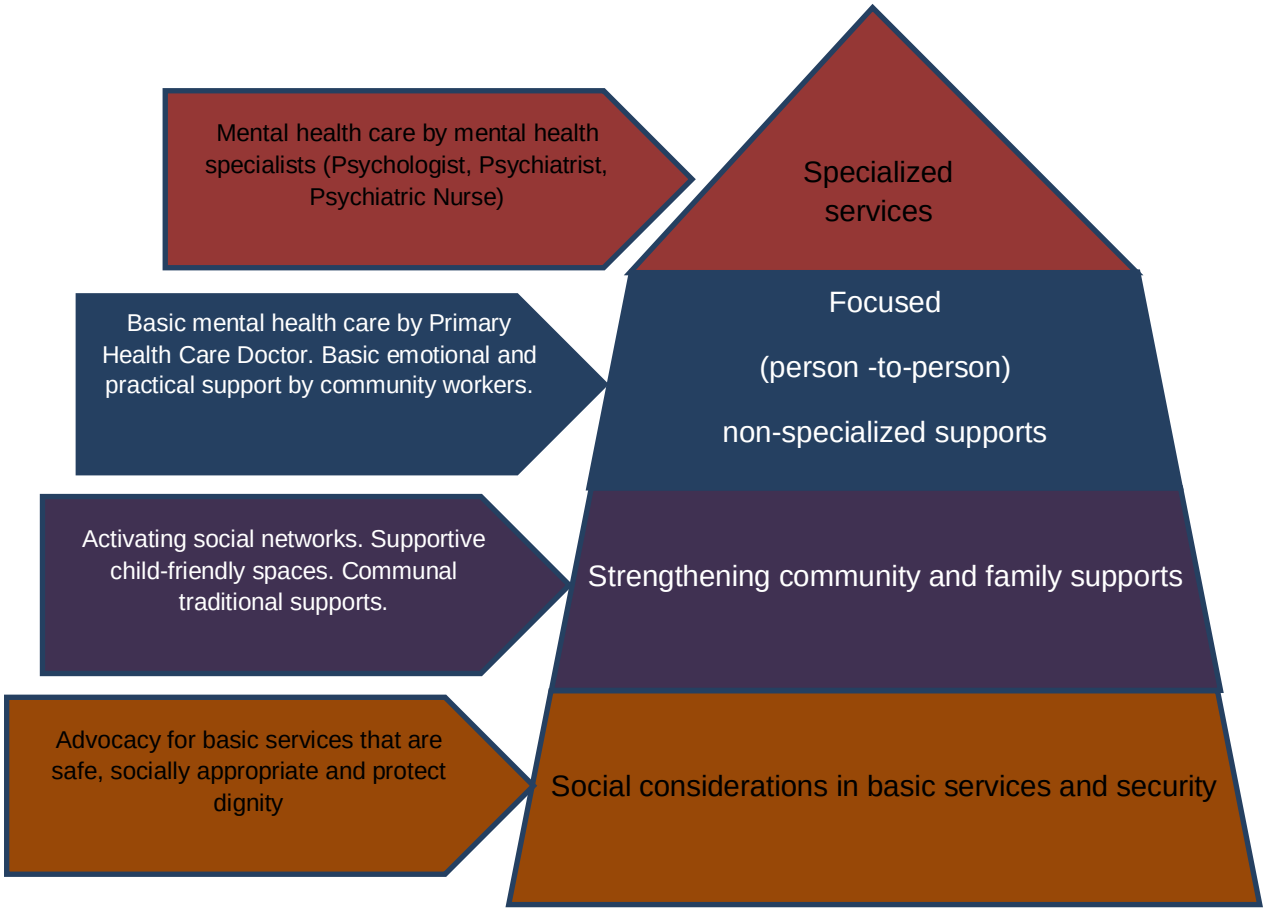


Figure 6.17. Intervention pyramid for mental health and psychosocial support. Adapted from IASC (MHPSS) [178].

As part of its public health response, WHO [179] has worked and developed a set of materials on the mental health and psychosocial support for COVID-19 pandemic as shown in **Figure 6.18**.

Figure 6.18. Coping with stress during the 2019-nCoV outbreak. Adapted from WHO [179].

6.9. Summary

In summary, the COVID-19 pandemic is a huge challenge for diabetic patients and diabetologists, but it can be also an opportunity to improve physician–patient communication for better management of the disease in this novel and unfamiliar era of social distancing, isolation, and quarantine. Diabetic patients need special attention and care, since it seems that their disease is associated with increased severity of symptoms, complications and mortality with COVID-19. A summary of management of diabetes and COVID-19 in hospital settings has been shown **Figure 6.19.**

Diabetes and COVID-19						
Glycemic control						Comorbidity control
Asymptomatic infection		Symptomatic non-severe illness		Severe illness		Cautious use of ACEI/ARBs, statins, aspirin
Home/hospital care		Hospital care		ICU care		Prevent secondary bacterial infections
Continue usual therapy		Usual therapy with caution		MDI of insulin		? Specific therapies: antivirals, immunomodulators
		? Withhold SGLT2i & other OADs		IVI insulin for critically ill		
		± Insulin				

Note: Owing to limited evidence and risk of dehydration and its consequences, lactic acidosis and euglycemic ketoacidosis, oral antidiabetic drugs should be used with caution particularly in hospitalized patients or it may be advisable to discontinue those until recovering from acute illness and/or until further evidence is available. Insulin is safe, provided glycemic status is regularly monitored and treatment is adjusted. IVI, intravenous infusion; MDI, multiple daily injections; OAD, oral antidiabetic drugs.

Figure 6.19. A summary of management of diabetes and COVID-19 in hospital settings

A physician with expertise in diabetes management should treat the hospitalized patient. Appropriately trained specialists or specialty teams may reduce length of stay, improve glycemic control, and improve outcomes.

References

1. COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. Updated: September 01, 2020. Available at https://www.covid19treatmentguidelines.nih.gov/. Accessed September 06, 2020

2. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72,314 cases From the Chinese Center for Disease Control and Prevention. JAMA. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32091533.

3. Centers for Disease Control and Prevention (CDC). Coronavirus Disease 2019 (COVID-19). People Who Are at Increased Risk for Severe Illness. Updated June 25, 2020, Available from: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-at-increased-risk.html?

4. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020;395(10223):497-506.

5. Alqahtani JS, Oyelade T, Aldhahir AM, Alghamdi SM, Almehmadi M, Alqahtani AS, et al. Prevalence, Severity and Mortality Associated with COPD and Smoking in Patients with COVID-19: A Rapid Systematic Review and Meta-Analysis. PLoS One. 2020;15(5):e0233147.

6. World Health Organization. WHO statement: Tobacco use and COVID-19 . May 11, 2020 Statement. Geneva. Available from: (https://www.who.int/news-room/detail/11-05-2020-who-statement-tobacco-use-and-covid-19 (Accessed September 06, 2020).

7. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020;395(10229):1054-62.

8. Katulanda P, Dissanayake HA, Ranathunga I, Ratnasamy V, Wijewickrama PSA, Yogendranathan N. Prevention and management of COVID-19 among patients with diabetes: an appraisal of the literature. Diabetologia https://doi.org/10.1007/s00125-020-05164-x

9. Bornstein SR, Rubino F, Khunti K, Mingrone G, Hopkins D, Birkenfeld AL. Practical recommendations for the management of diabetes in patients with COVID-19. Lancet Diabetes Endocrinol 2020; 8: 546–50. Published Online April 23, 2020 https://doi.org/10.1016/ S2213-8587(20)30152-2. Accessed 10 Sep2020.

10. Remuzzi A, Remuzzi G. COVID-19 and Italy: what next? Lancet 2020; 395: 1225–28.

11. Kornum JB, Thomsen RW, Riis A, Lervang HH, Schonheyder HC, Sorensen HT (2007) Type 2 diabetes and pneumonia outcomes: a population-based cohort study. Diabetes Care 30(9):2251–2257. https://doi.org/10.2337/dc06-2417

12. Yang JK, Feng Y, Yuan MY et al. Plasma glucose levels and diabetes are independent predictors for mortality and morbidity in patients with SARS. Diabet Med 2006; 23(6):623 –628. https://doi.org/10. 1111/j.1464-5491.2006.01861.x

13. Yang YM, Hsu CY, Lai CC et al. Impact of comorbidity on fatality rate of patients with Middle East respiratory syndrome. Sci Rep 2017;7(1):11307. https://doi.org/10.1038/s41598-017-10402-1

14. Allard R, Leclerc P, Tremblay C, Tannenbaum TN. Diabetes and the severity of pandemic influenza A (H1N1) infection. Diabetes Care 2010;33(7):1491–1493. https://doi.org/10.2337/dc09- 2215

15. Yang X, Yu Y, Xu J, Shu H, Liu H, Wu Y, et al. Clinical course and outcomes of critically ill patients with SARSCoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med. 2020. doi: 10.1016/S2213-2600(20)30079-5

16. Novel Coronavirus Pneumonia Emergency Response Epidemiology Team. Vital surveillances: the epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19)—China, 2020. China CDC Weekly. Available at: http://weekly.chinacdc.cn/en/article/id/e53946e2-c6c4-41e9-9a9b-fea8db1a8f51. Accessed 20 April, 2020.

17. Huang Y-T, Lee Y-C, Hsiao C-J. Hospitalization for ambulatory-care-sensitive conditions in Taiwan following the SARS outbreak: A population-based interrupted time series study. Formos Med Assoc. 2009;108(5):386-394. doi: 10.1016/S0929-6646(09)60082-6.

18. Chan-Yeung M, Xu R-H. SARS: epidemiology. Respirology. 2003;8(s1):S9-S14. doi: 10.1046/j.1440-1843.2003.00518.x

19. Morra ME, Van Thanh L, Kamel MG, Ghazy AA, Altibi AM, Dat LM, et al. Clinical outcomes of current medical approaches for Middle East respiratory syndrome: A systematic review and meta analysis. Rev Med Virol. 2018;28(3):e1977. doi: 10.1002/rmv.1977.

20. Guo W, Li M, Dong Y et al. Diabetes is a risk factor for the progression and prognosis of COVID-19. Diabetes Metab Res Rev 2020;e3319. doi:https://doi.org/10.1002/dmrr.3319

21. American Diabetes Association (2020). How COVID-19 affects people with diabetes. Available from: https://www.diabetes.org/ coronavirus-covid-19/how-coronavirus-impacts-people-withdiabetes. Accessed 8 Sep 2020.

22. Zhou J, Tan J. Diabetes patients with COVID-19 need better care. Metabolism. 2020; https://doi.org/10.1016/j. metabol.2020.154216

23. Bogun M, and Inzucchi SE. Inpatient Management of Diabetes and Hyperglycemia. Clin Ther. 2013;35: 724–733. Available from: http://dx.doi.org/10.1016/j.clinthera.2013.04.008.

24. Krinsley JS. Association between hyperglycemia and increased hospital mortality in a heterogeneous population of critically ill patients. Mayo Clin Proc. 2003;782:1471– 1478.

25. Jafar N, Edriss H, Nugent K. The effect of short-term hyperglycemia on the innate immune system. Am J Med Sci 2016;351:201e11.

26. Guo W, Li M, Dong Y, Zhou H, Zhang Z, Tian C, et al. Diabetes is a risk factor for the progression and prognosis of COVID-19. Diabetes Metab Res Rev 2020 Apr 7:e3319.

27. Dunn E, Grant P. Type 2 diabetes: an atherothrombotic syndrome. Curr Mol Med 2005;5:323e32.

28. Hussain A, Bhowmik B, do Vale Moreira NC. COVID-19 and diabetes: knowledge in progress. Diabetes Res Clin Pract 2020;162:108142.

29. Pal R, Bhansali A. COVID-19, diabetes mellitus and ACE2: the conundrum. Diabetes Res Clin Pract 2020. 108132.

30. Yang JK, Feng Y, Yuan MY, Yuan SY, Fu HJ, Wu BY, et al. Plasma glucose levels and diabetes are independent predictors for mortality and morbidity in patients with SARS. Diabet Med 2006;23:623e8.

31. Yang JK, Lin S-S, Ji X-J, Guo L-M. Binding of SARS coronavirus to its receptor damages islets and causes acute diabetes. Acta Diabetol 2010 Sep;47:193e9.

32. Kassir R. Risk of COVID-19 for patients with obesity. Obes Rev [Internet] 2020;21:e13034. https://doi.org/10.1111/obr.13034

33. Liamis G. Diabetes mellitus and electrolyte disorders. World J Clin Cases 2014;2:488.

34. Carter SJ, Baranauskas MN, Fly AD. Considerations for obesity, vitamin D, and physical activity amidst the COVID-19 pandemic. Obesity [Internet] 2020 [cited 2020 Apr 28]; Available from: https://onlinelibrary.wiley.com/doi/abs/ 10.1002/oby.22838.

35. Szymczak-Pajor I, Sliwinska A. Analysis of association between vitamin D deficiency and insulin resistance. Nutrients 2019;11:794.

36. Epperla N, McKiernan F. Iatrogenic Cushing syndrome and adrenal insufficiency during concomitant therapy with ritonavir and fluticasone. SpringerPlus [Internet] 2015;4:455 [cited 2020 Apr 28];4(1). Available from: http:// www.springerplus.com/content/4/1/455.

37. Sallard E, Lescure F-X, Yazdanpanah Y, Mentre F, Peiffer-Smadja N. Type 1 interferons as a potential treatment against COVID-19. Antivir Res 2020;178. 104791.

38. Gautret P, Lagier J-C, Parola P, Hoang VT, Meddeb L, Mailhe M, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents 2020: 105949. 105949.

39. Iqbal A, Prince LR, Novodvorsky P, Bernjak A, Thomas MR, Birch L, et al. Effect of hypoglycemia on inflammatory responses and the response to low-dose endotoxemia in humans. J Clin Endocrinol Metab 2019;104:1187e99.

40. Pal R, Bhadada SK. COVID-19 and diabetes mellitus: An unholy interaction of two pandemics. Diabetes & Metabolic Syndrome: Clinical Research & Reviews 2020;14:513-517. https://doi.org/10.1016/j.dsx.2020.04.049

41. Stoian AP, Banerjee Y, Rizvi AA, and Rizzo M. Diabetes and the COVID-19 Pandemic: How Insights from Recent Experience Might Guide Future Management (Commentary). Metabolic Syndrome and Related Disorders 2020;18(4):173-75. Available from: DOI: 10.1089/met.2020.0037 (Accessed on September 06, 2020)

42. Centers for Disease Control and Prevention (CDC). Coronavirus Disease 2019 (COVID-19). Interim Clinical Guidance for Management of Patients with Confirmed Coronavirus Disease (COVID-19). **Revisions were made on April 3, 2020.**

43. Petrilli CM, Jones SA, Yang J, Rajagopalan H, O'Donnell L, Chernyak Y, et al. Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: prospective cohort study. BMJ 2020;369:m1966 http://dx.doi.org/10.1136/bmj.m1966

44. Clement S, Braithwaite SS, Magee MF, et al.; Diabetes in Hospitals Writing Committee. Management of diabetes and hyperglycemia in hospitals [published corrections appear in Diabetes Care 2004;27:856 and Diabetes Care 2004;27:1255]. Diabetes Care 2004;27:553– 591.

45. Moghissi ES, Korytkowski MT, DiNardo M, et al.; American Association of Clinical Endocrinologists; American Diabetes Association. American Association of Clinical Endocrinologists and American Diabetes Association consensus statement on inpatient glycemic control. Diabetes Care 2009;32:1119–1131.

46. CritchleyJA, Carey IM, Harris T, DeWilde S, Hosking FJ, and Cook DG. Glycemic Control and Risk of Infections Among People With Type 1 or Type 2 Diabetes in a Large Primary Care Cohort Study. Diabetes Care 2018;41:2127–2135. Available from: https://doi.org/10.2337/dc18-0287.

47. Akirov A, Grossman A, Shochat T, Shimon I. Mortality among hospitalized patients with hypoglycemia: insulin related and noninsulin related. J Clin Endocrinol Metab 2017;102: 416–424.

48. Bragg F, Holmes MV, Iona A et al (2017) Association between diabetes and cause-specific mortality in rural and urban areas of China. JAMA 317(3):280–289. https://doi.org/10.1001/jama. 2016.19720

49. Gregg EW, Cheng YJ, Srinivasan M et al. Trends in cause-specific mortality among adults with and without diagnosed diabetes in the USA: an epidemiological analysis of linked national survey and vital statistics data. Lancet 2018;391(10138):2430–2440. https://doi.org/10.1016/s0140-6736(18)30314-3

50. Pearson-Stuttard J, Blundell S, Harris T, Cook DG, Critchley J. Diabetes and infection: assessing the association with glycaemic control in population-based studies. Lancet Diabetes Endocrinol 2016;4(2):148–158. https://doi.org/10.1016/s2213-8587(15) 00379-4

51. Rao Kondapally Seshasai S, Kaptoge S, Thompson A et al. Diabetes mellitus, fasting glucose, and risk of cause-specific death. N Engl J Med 2011;364(9):829–841. https://doi.org/10.1056/ NEJMoa1008862

52. Ehrlich SF, Quesenberry CP Jr, Van Den Eeden SK, Shan J, Ferrara A. Patients diagnosed with diabetes are at increased risk for asthma, chronic obstructive pulmonary disease, pulmonary fibrosis, and pneumonia but not lung cancer. Diabetes Care 2010;33(1):55–60. https://doi.org/10.2337/dc09-0880

53. Lepper PM, Ott S, Nuesch E et al. Serum glucose levels for predicting death in patients admitted to hospital for community acquired pneumonia: prospective cohort study. BMJ 2012;344:e3397. https://doi.org/10.1136/bmj.e3397

54. McAlister FA, Majumdar SR, Blitz S, Rowe BH, Romney J, Marrie TJ. The relation between hyperglycemia and outcomes in 2, 471 patients admitted to the hospital with community-acquired pneumonia. Diabetes Care 2005;28(4):810–815. https://doi.org/10.2337/diacare.28.4.810

55. Yang JK, Feng Y, Yuan MY et al.Plasma glucose levels and diabetes are independent predictors for mortality and morbidity in patients with SARS. Diabet Med 2006;23(6):623–628. https://doi.org/10. 1111/j.1464-5491.2006.01861.x

56. Alanazi KH, Abedi GR, Midgley CM et al. Diabetes mellitus, hypertension, and death among 32 patients with MERSCoV infection, Saudi Arabia. Emerg Infect Dis 2020;26(1):166–168. https://doi.org/10.3201/eid2601.190952

57. Bode B, Garrett V, Messler J et al. Glycemic characteristics and clinical outcomes of COVID-19 patients hospitalized in the United States. J Diabetes Sci Technol 2020:193229682092446. https:// doi.org/10.1177/1932296820924469

58. Zhu L, She ZG, Cheng X, Guo J, Zhang BH, Li H, et al. Association of blood glucose control and outcomes in patients with COVID-19 and pre-existing type 2 diabetes. Cell Metab 2020;31(6):1068–1077.e3. https://doi.org/10. 1016/j.cmet.2020.04.021

59. Alshaikh A, Alsifri S, Alhozali A, Mosli H, Zawawi T, Mira S, et al. Saudi Scientific Diabetes Society Position Statement: Management of Diabetes Mellitus in the Pandemic of COVID-19. International Journal of Clinical Medicine 2020;11:199-206. https://doi.org/10.4236/ijcm.2020.115020

60. Bode B, Garrett V, Messler J, McFarland R, Crowe J, Booth R, et al. Glycemic characteristics and clinical outcomes of COVID-19 patients hospitalized in the United States. J Diabetes Sci Technol; 2020 [in press]. https://www. bloomberg.com/press-releases/2020-04-17/covid-19

61. Iacobellis G, Penaherrera CA, Bermudez LE, Mizrachi EB. Admission hyperglycemia and radiological findings of SARSCOv2 in patients with and without diabetes. Diab Res Clin Pract 2020;164:108185.

62. Zhang Y, Cui Y, Shen M, Zhang J, Liu B, Dai M, et al. Comorbid Diabetes Mellitus was Associated with Poorer Prognosis in Patients with COVID-19: A Retrospective Cohort Study. Available at https://www.medrxiv.org/content/10.1101/2020.03.24.20042358v1 . Accessed 12 Aug 2020.

63. Ceriello A, Zarich SW, Testa R. Lowering glucose to prevent adverse cardiovascular outcomes in a critical care setting. J Am Coll Cardiol 2009;53(5 Suppl):S9–S13.

64. Brufsky A. Hyperglycemia, hydroxychloroquine, and the COVID-19 epidemic. J Med Virol 2020. https://doi.org/10.1002/ jmv.25887.

65. Ceriello A. Hyperglycemia and the worse prognosis of COVID-19. Why a fast blood glucose control should be mandatory (Editorial). Diab Res Clin Pract 2020;163:108186. https://doi.org/10.1016/j.diabres.2020.108186

66. Wang S, Ma P, Zhang S, Song S, Wang Z, & Ma1 Y. Fasting blood glucose at admission is an independent predictor for 28-day mortality in patients with COVID-19 without previous diagnosis of diabetes: a multi-centre retrospective study. Diabetologia 2020 (10 July). https://doi.org/10.1007/s00125-020-05209-1. Accessed 10 Sep 2020.

67. Ceriello A. Management of diabetes today: An exciting confusion. Diabetes Res Clin Pract 2020;162:108129. https:// doi.org/10.1016/j.diabres.2020.108129.

68. Bhadada SK. Should anti-diabetic medications be reconsidered amid COVID-19 pandemic?. Diabetes Res Clin Pract 2020. https://doi.org/10.1016/j.diabres.2020.108146.

69. Ministry of Health & Family Welfare (Government of India). Directorate General of Health Services (EMR Division). Guidelines on Clinical Management of COVID – 19. pp 5. 17th March 2020. Available at:

https://www.mohfw.gov.in/pdf/GuidelinesonClinicalManagementofCOVID1912020.pdf. Accessed 20 Sep 2020.

70. NHS London Clinical Networks. Outpatient appointment prioritization for specialist diabetes departments during the coronavirus pandemic (Date approved 26.03.20). Available from: https://www.england.nhs.uk/london/wp-content/uploads/sites/8/2020/04/4.-Covid-19-Diabetes-Outpatient-Appointment-Prioritisation-Crib-Sheet-27032020.pdf

71. Clement S, Braithwaite SS, Magee MF, et al. Diabetes in Hospitals Writing Committee. Management of diabetes and hyperglycemia in hospitals Diabetes Care 2004;27:553–591.

72. McCoy RG, Van Houten HK, Ziegenfuss JY, Shah ND, Wermers RA, Smith SA. Increased mortality of patients with diabetes reporting severe hypoglycemia. Diabetes Care 2012;35:1897–1901.

73. Wang YJ, Seggelke S, Hawkins RM, et al. Impact of glucose management team on outcomes of hospitalization in patients with type 2 diabetes admitted to the medical service. Endocr Pract 2016;22:1401–1405.

74. Bansal V, Mottalib A, Pawar TK, et al. Inpatient diabetes management by specialized diabetes team versus primary service team in non-critical care units: impact on 30-day readmission rate and hospital cost. BMJ Open Diabetes Res Care 2018;6:e000460

75, American Diabetes Association. 15. Diabetes care in the hospital: Standards of Medical Care in Diabetes-2020. Diabetes Care 2020;43(Suppl.1):S193-S202.

76. Draznin B, Gilden J, Golden SH, et al.; PRIDE investigators. Pathways to quality inpatient management of hyperglycemia and diabetes: a call to action. Diabetes Care 2013;36:1807–1814.

77. Jeschke KN, Bonnesen B, Hansen EF, Jensen JUS, Lapperre TS, Weinreich UM, et al. Guideline for the management of COVID-19 patients during hospital admission in a non-intensive care setting. European Clinical Respiratory Journal 2020;7(1):1761677. Available from: DOI:10.1080/20018525.2020.1761677. Accessed 20 Oct 2020.

78. Research Society for the Study of Diabetes in India (RSSDI). Guidance for People with Diabetes on COVID - 19 for Healthcare Professionals. March 2020. Available at https://rssdi.in/newwebsite/pdfdata/Covid-19-Guidance-Healthcare-Professionals.pdf.

Accessed 11 Sep 2020.

79. Shi H, Han X, Jiang N, et al. Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study. Lancet Infect Dis. 2020;20(4):425-434. Available at: https://www.ncbi.nlm.nih.gov/ pubmed/32105637.

80. Maynard G, Wesorick DH, O'Malley C, Inzucchi SE; Society of Hospital Medicine Glycemic Control Task Force. Subcutaneous insulin order sets and protocols: effective design and implementation strategies. J Hosp Med 2008; 3(Suppl.):29–41.

81. Bueno E, Benitez A, Rufinelli JV, et al. Basal bolus regimen with insulin analogues versus human insulin in medical patients with type 2 diabetes: a randomized controlled trial in Latin America. Endocr Pract 2015;21:807–813.

82. All India Institute of Medical Science. Department of Endocrinology. Clinical Guidance on Antihyperglycemic Treatment Initiation and Titration in Patients with COVID 19 and Diabetes. Version 1.0. The 6th July, 2020. Available at: https://covid.aiims.edu/protocols-for-management-of-people-with-diabetes-in-covid-facilities/. Accessed on 06 Sep 2020.

83. Pasquel FJ, Fayfman M, Umpierrez GE. Debate on insulin vs non-insulin use in the hospital setting- is it time to revise the guidelines for the management of inpatient diabetes? Curr Diab Rep 2019;19:65.

84. Fushimi N, Shibuya T, Yoshida Y, Ito S, Hachiya H, Mori A. Dulaglutide-combined basal plus correction insulin therapy contributes to ideal glycemic control in non-critical hospitalized patients. J Diabetes Investig. 5 June 2019 [Epub ahead of print]. DOI:10.1111/jdi.13093

85. Fayfman M, Galindo RJ, Rubin DJ, et al. A randomized controlled trial on the safety and efficacy of exenatide therapy for the inpatient management of general medicine and surgery patients with type 2 diabetes. Diabetes Care 2019;42:450–456.

86. Vellanki P, Rasouli N, Baldwin D, et al.; Linagliptin Inpatient Research Group. Glycaemic efficacy and safety of linagliptin compared to basal-bolus insulin regimen in patients with type 2 diabetes undergoing non-cardiac surgery: a multicenter randomized clinical trial. Diabetes Obes Metab. 20 November 2018 [Epub ahead of print]. DOI: 10.1111/dom.13587

87. Umpierrez G & Korytkowski M. Diabetic emergencies — ketoacidosis, hyperglycaemic hyperosmolar state and hypoglycaemia (Review). *Nature Reviews Endocrinology 2016;* **12:**222–232.

88. Australian Diabetes Educators Association. Sick day management of adults with type 2 diabetes. Canberra: Australian Diabetes Educators Association, 2014.

89. Australian Diabetes Society, New Zealand Society for the Study of Diabetes. Alert update January 2020: Periprocedural diabetic ketoacidosis (DKA) with SGLT2 inhibitor use. Available at https:// diabetessociety.com.au/documents/ADS_DKA_SGLT2i_Alert_ update_2020.pdf [Accessed 7 April 2020].

90. NHS London Clinical Networks. Sick day rules: how to manage Type 2 diabetes if you become unwell with coronavirus and what to do with your medication. Updated 06.04.2020. Available from at: https://www.england.nhs.uk/london/wp-content/uploads/sites/8/2020/04/3.-Covid-19-Type-2-Sick-Day-Rules-Crib-Sheet-06042020.pdf

91. Mohan V, Ramesh J. Managing diabetes and COVID-19: A national strategic framework. Int J Non-Commun Dis [serial online] 2020 [cited 2020 Sep 6];5:58-62. Available from: http://www.ijncd.org/text.asp?2020/5/2/58/288257

92. Cobaugh DJ, Maynard G, Cooper L, et al. Enhancing insulin-use safety in hospitals: practical recommendations from an ASHP Foundation expert consensus panel. Am J Health Syst Pharm 2013;70:1404–1413.

93. Wallia A, Umpierrez GE, Rushakoff RJ, et al.; DTS Continuous Glucose Monitoring in the Hospital Panel. Consensus statement on inpatient use of continuous glucose monitoring. J Diabetes Sci Technol 2017;11:1036–1044.

94. COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. Last Updated: October 9, 2020. Available at https://www.covid19treatmentguidelines.nih.gov/. Accessed 3 Nov 2020.

95. Food and Drug Administration (FDA). FDA's approval of Veklury (remdesivir) for the treatment of COVID-19—The Science of Safety and Effectiveness. Availble at https://www.fda.gov/drugs/drug-safety-and-availability/fdas-approval-veklury-remdesivir-treatment-covid-19-science-safety-and-effectiveness. Accessed on 24 October 2020.

96. Zhong J, Tang J, Ye C, Dong L. The immunology of COVID-19: is immune modulation an option for treatment? Lancet Rheumatology. 2020;2(7):e438-e436. Available at: https://www.theLancet.com/journals/ lanrhe/article/PIIS2665-9913(20)30120-X/fulltext#seccestitle10.

97. Wang X, Guo X, Xin Q, et al. Neutralizing antibodies responses to SARS-CoV-2 in COVID-19 inpatients and convalescent patients. medRxiv. 2020;Preprint. Available at: https://www.medrxiv.org/ content/10.1101/2020.04.15.20065623v

98. Mair-Jenkins J, Saavedra-Campos M, Baillie JK, et al. The effectiveness of convalescent plasma and hyperimmune immunoglobulin for the treatment of severe acute respiratory infections of viral etiology: a systematic review and exploratory meta-analysis. J Infect Dis. 2015;211(1):80-90. Available at: https://www. ncbi.nlm.nih.gov/pubmed/25030060.

99. Shetty AK. Mesenchymal stem cell infusion shows promise for combating coronavirus (COVID-19)-induced pneumonia. Aging Dis. 2020;11(2):462-464. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32257554.

100. Marovich M, Mascola JR, Cohen MS. Monoclonal antibodies for prevention and treatment of COVID-19. JAMA. 2020.

Available at: https://www.ncbi.nlm.nih.gov/pubmed/32539093.

101. Horby P, Shen Lim W, Emberson J, et al. Effect of dexamethasone in hospitalized patients with COVID-19: preliminary report. medRxiv. 2020;Preprint. Available at: https://www.medrxiv.org/ content/10.1101/2020.06.22.20137273v1.

102. Shakoory B, Carcillo JA, Chatham WW, et al. Interleukin-1 receptor blockade is associated with reduced mortality in sepsis patients with features of macrophage activation syndrome: reanalysis of a prior Phase III trial. Crit Care Med. 2016;44(2):275-281. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26584195.

103. Xu X, Han M, Li T, et al. Effective treatment of severe COVID-19 patients with tocilizumab. Proc Natl Acad Sci USA. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32350134.

104. Zhou Q, Wei X, Xiang X, et al. Interferon-a2b treatment for COVID-19. medRxiv. 2020;Preprint.

Available at: https://www.medrxiv.org/content/10.1101/2020.04.06.20042580v1.

105. Cao Y, Wei J, Zou L, et al. Ruxolitinib in treatment of severe coronavirus disease 2019 (COVID-19): a multicenter, single-blind, randomized controlled trial. J Allergy Clin Immunol. 2020;146(1):137-146.

Available at: https://www.ncbi.nlm.nih.gov/pubmed/32470486.

106. Guan W-J , Ni Z-Y , Hu Y , Liang W-H , Ou C-Q , He J-X et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med 2020;382:1708–1720.

107. Fang L , Karakiulakis G , Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? Lancet Respir Med 2020;8:e21.

108. Imai Y , Kuba K , Rao S , Huan Y , Guo F , Guan B , et al. Angiotensin-converting enzyme 2 protects from severe acute lung failure. Nature. 2005;436:112–116.

109. Mascolo A, Scavone C, Rafaniello C, Ferrajolo C, Racagni G, Berrino L, et al. Renin-Angiotensin System and Coronavirus Disease 2019: A Narrative Review. Front. Cardiovasc. Med. 2020;7:143. Available at: doi: 10.3389/fcvm.2020.00143. Accessed on 28 September 2020.

110. Pinto-Sietsma SJ, Flossdorf M, Buchholz VR, Offerhaus J, Bleijendaal H, Beudel M, et al. Antihypertensive drugs in COVID-19 infection. European Heart Journal - Cardiovascular Pharmacotherapy. Available at: https://academic.oup.com/ehjcvp/advance-article/doi/10.1093/ehjcvp/pvaa058/5851726. Accessed on 28 September 2020.

111. Trifrò G, Crisafulli S, Andò G, Racagni G, Drago F (on behalf of the Italian Society of Pharmacology). Should Patients Receiving ACE Inhibitors or Angiotensin Receptor Blockers be Switched to Other Antihypertensive Drugs to Prevent or Improve Prognosis of Novel Coronavirus Disease 2019 (COVID-19)? Drug Safety 2020 (17 April). Available from: https://doi.org/10.1007/s40264-020-00935-2.

112. Gnavi R, Demaria M, Roberta P, Dalmasso M, Ricceri F, Costa G. Therapy with agents acting on the renin-angiotensin system and risk of severe acute respiratory syndrome coronavirus 2 infection. Clin Infect Dis. (2020) 174:30–3. doi: 10.1093/cid/ciaa634

113. Jung SY, Choi JC, You SH, Kim WY. Association of renin-angiotensinaldosterone system inhibitors with COVID-19-related outcomes in korea: a nationwide population-based cohort study. Clin Infect Dis. (2020) 22:ciaa624. doi: 10.1093/cid/ciaa624

114. Zhang P, Zhu L, Cai J, Lei F, Qin JJ, Xie J, et al. Association of inpatient use of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers with mortality among patients with hypertension hospitalized with COVID-19. Circ Res. (2020) 126:1671–81. doi: 10.1161/CIRCRESAHA.120.317242

115. American Diabetes Association. Cardiovascular disease and risk management: Standard of Medical Care in Diabetes-2020. Diabetes Care 2020;43(Suppl.1):S111-S134.

116. American Heart Association. HFSA/ACC/AHA statement addresses concerns Re: Using RAAS antagonists in COVID-19. (2020). Available online at: https://

www.acc.org/latest-in-cardiology/articles/2020/03/17/08/59/hfsa-acc-ahastatement-addresses-concerns-re-using-raas-antagonists-in-covid-19 (accessed April 20, 2020).

117. European Society of Cardiology. Position Statement of the ESC Council on Hypertension on ACE-Inhibitors and Angiotensin Receptor Blockers. (2020). Available online at: https://www.escardio.org/Councils/Councilon-Hypertension-(CHT)/News/position-statement-of-the-esc-council-onhypertension-on-ace-inhibitors-and-ang (accessed April 20, 2020).

118. European Society of Hypertension. Statement of the European Society of Hypertension (ESH) on hypertension, Renin Angiotensin System blockers and COVID-19 March 19th 2020. 2020. Available from: https://www.eshonline.org/spotlights/esh-stabt ement-on-COVID-19/

119. International Society of Hypertension. A statement from the International Society of Hypertension on COVID-19. 2020. Available from: https://ish-world.com/news/a/A-statement-from-the-Inter national-Society-of-Hypertension-on-COVID-19/

120. Italian Society of Hypertension. Farmaci antiipertensivi e rischio di COVID19. Il comunicato della SIIA | SIIA. Available at: https://siia.it/notiziesiia/farmaci-antiipertensivi-e-rischio-di-covid-19-il-comunicato-della-siia/. Accessed 28 October 2020.

121. WHO. Clinical of management of COVID-19. Interim Guidance. Updated 27 May 2020. Available at: https://www.who.int/publications/i/item/clinical-management-of-covid-19. Accessed 12 August 2020.

122. European Medicines Agency. EMA advises continued use of medicines for hypertension, heart or kidney disease during COVID-19 pandemic. 2020. Available from: https://www.ema.europa.eu/en/ news/ema-advises-continued-use-medicines-hypertension-heart -kidney-disease-during-COVID-19-pandemic.

123. Bangash MN, Patel J, Parekh D. COVID-19 and the liver: little cause for concern. Lancet Gastroenterol Hepatol 2020. https://doi. org/10.1016/S2468-1253(20)30084-4

124. Driggin E, Madhavan MV, Bikdeli B et al. Cardiovascular considerations for patients, health care workers, and health systems during the coronavirus disease 2019 (COVID-19) pandemic. J Am Coll Cardiol 2020. https://doi.org/10.1016/j.jacc.2020.03.031

125. Li Y, Wang M, Zhou Y et al. Acute cerebrovascular disease following COVID-19: a single center, retrospective, observational study. SSRN 2020. https://doi.org/10.2139/ssrn.3550025

126. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet.2020;395:1054–1062.

127. World Health Organization. Clinical care for severe acute respiratory infection (toolkit). COVID-19 adaptation. Available at: Geneva: World Health Organization; 2020 (WHO/2019- nCoV/SARI_toolkit/2020.1).

128. Alhazzani W, Møller MH, Arabi YM, Loeb M, Gong MN, Fan E, et al. Surviving Sepsis Campaign: guidelines on the management of critically ill adults with Coronavirus

Disease 2019 (COVID-19). Intensive Care Med (2020) 46:854–887. Available at: https://doi.org/10.1007/s00134-020-06022-5. Accessed 20 September 2020.

129. Agiostratidou G, Anhalt H, Ball D, et al. Standardizing clinically meaningful outcome measures beyond HbA1c for type 1 diabetes: a consensus report of the American Association of Clinical Endocrinologists, the American Association of Diabetes Educators, the American Diabetes Association, the Endocrine Society, JDRF International, The Leona M. and Harry B. Helmsley Charitable Trust, the Pediatric Endocrine Society, and the T1D Exchange. Diabetes Care 2017;40:1622–1630.
130. American Diabetes Association. 6. Glycemic targets: Standards of Medical Care in Diabetesd2020. Diabetes Care 2020; 43(Suppl. 1):S66–S76.
131. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet.2020;395:1054–1062
132. Centers for Disease Control and Prevention. Coronavirus Disease 2019 in Children—United States, February 12–April 2, 2020. 2020. Available at: https://www.cdc.gov/mmwr/volumes/69/wr/mm6914e4.htm. Accessed June 5, 2020.
133. Cui X, Zhang T, Zheng J, et al. Children with coronavirus disease 2019 (covid-19): a review of demographic, clinical, laboratory and imaging features in 2,597 pediatric patients. J Med Virol. 2020. Available at: https:// www.ncbi.nlm.nih.gov/pubmed/32418216.
134. Chiotos K, Hayes M, Kimberlin DW, et al. Multicenter initial guidance on use of antivirals for children with COVID-19/SARS-CoV-2. J Pediatric Infect Dis Soc. 2020. Available at: https://www.ncbi.nlm.nih.gov/ pubmed/32318706.
135. Royal College of Paediatrics and Child Health. Guidance: Paediatric multisystem inflammatory syndrome temporally associated with COVID-19. 2020. Available at: https://www.rcpch.ac.uk/sites/default/files/2020-05/ COVID-19-Paediatric-multisystem-%20inflammatory%20syndrome-20200501.pdf. Accessed May 28, 2020.
136. Verdoni L, Mazza A, Gervasoni A, et al. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. Lancet. 2020. Available at: https://www.ncbi. nlm.nih.gov/pubmed/32410760.
137. Centers for Disease Control and Prevention. Considerations for inpatient obstetric healthcare settings. 2020. Available at: https://www.cdc.gov/coronavirus/2019-ncov/hcp/inpatient-obstetric-healthcare-guidance.html. Accessed August 26, 2020.
138. The American College of Obstetricians and Gynecologists. Novel coronavirus 2019 (COVID-19): practice advisory. August 2020. Available at: https://www.acog.org/clinical/clinical-guidance/practice-advisory/ articles/2020/03/novel-coronavirus-2019. Accessed August 26, 2020.
139. Society for Maternal-Fetal Medicine. Coronavirus (COVID-19) and Pregnancy: What Maternal Fetal Medicine Subspecialists Need to Know. July 2020. https://s3.amazonaws.com/cdn.smfm.org/media/2468/ COVID19-What_MFMs_need_to_know_revision_7-23-20_(final).PDF. Accessed August 26, 2020.

140. The American College of Obstetricians and Gynecologists. COVID-19 FAQs for Obstetricians-Gynecologists, Obstetrics. 2020. Available at: https://www.acog.org/clinical-information/physician-faqs/covid-19-faqs-for-obgyns-obstetrics. Accessed August 26, 2020.

141. Fix OK, Hameed B, Fontana RJ, et al. Clinical best practice advice for hepatology and liver transplant providers during the COVID-19 pandemic: AASLD Expert Panel consensus statement. Hepatology. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32298473.

142. American Society of Transplantation. COVID-19 resources for transplant community. 2020. Available at: https://www.covid19treatmentguidelines.nih.gov/contact-us/. Accessed June 26, 2020.

143. American Society for Transplantation and Cellular Therapy. ASTCT interim patient guidelines April 20, 2020. 2020. Available at: https://www.astct.org/viewdocument/astct-interim-patient-guidelinesap?CommunityKey=d3949d84-3440-45f4-8142-90ea05adb0e5&tab=librarydocuments. Accessed July 2, 2020.

144. Elens L, Langman LJ, Hesselink DA, et al. Pharmacologic treatment of transplant recipients infected with SARS-CoV-2: considerations regarding therapeutic drug monitoring and drug-drug interactions. Ther Drug Monit. 2020;42(3):360-368. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32304488.

145. American Society of Clinical Oncology. ASCO Special Report: A guide to cancer care delivery during the COVID-19 pandemic. 2020. Available at: https://www.asco.org/sites/new-www.asco.org/files/contentfiles/2020-ASCO-Guide-Cancer-COVID19.pdf. Accessed August 17, 2020

146. American Society for Radiation Oncology. COVID-19 recommendations and information: COVID-19 clinical guidance. 2020. Available at: https://www.astro.org/Daily-Practice/COVID-19-Recommendations-andInformation/Clinical-Guidance. Accessed August 3, 2020.

147. Yahalom J, Dabaja BS, Ricardi U, et al. ILROG emergency guidelines for radiation therapy of hematological malignancies during the COVID-19 pandemic. Blood. 2020;135(21):1829-1832. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32275740.

148. American Society of Hematology. COVID-19 and hodgkin lymphoma: frequently asked questions. 2020. Available at: https://www.hematology.org/covid-19/covid-19-and-hodgkin-lymphoma. Accessed August 3, 2020.

149. National Comprehensive Cancer Network. NCCN hematopoietic growth factors: short-term recommendations specific to issues with COVID-19 (SARS-CoV-2). 2020. Available at: https://www.nccn.org/covid-19/pdf/ HGF_COVID-19.pdf. Accessed: August 3, 2020

150. American Society of Clinical Oncology. COVID-19 patient care information: cancer treatment & supportive care. 2020. Available at: https://www.asco.org/asco-coronavirus-resources/care-individuals-cancer-duringcovid-19/cancer-treatment-supportive-care. Accessed August 3, 2020.

151. Byrd KM, Beckwith CG, Garland JM, et al. SARS-CoV-2 and HIV coinfection: clinical experience from Rhode Island, United States. J Int AIDS Soc. 2020;23(7):e25573. Available at: https://www.ncbi.nlm.nih.gov/ pubmed/32657527.

152. Bhaskaran K, Rentsch CT, MacKenna B, et al. HIV infection and COVID-19 death: population-based cohort analysis of UK primary care data and linked national death registrations within the OpenSAFELY platform. medRxiv. 2020. Available at: https://www.medrxiv.org/content/10.1101/2020.08.07.20169490v1.

153. Geretti A, Stockdale A, Kelly S, et al. Outcomes of COVID-19 related hospitalisation among people with HIV in the ISARIC WHO Clinical Characterisation Protocol UK Protocol: prospective observational study. medRxiv. 2020. Available at: https://www.medrxiv.org/content/10.1101/2020.08.07.20170449v1.

154. Dandachi D, Geiger G, Montgomery MW, et al. Characteristics, comorbidities, and outcomes in a multicenter registry of patients with HIV and coronavirus disease-19. Clin Infect Dis. 2020. Available at: https://www. ncbi.nlm.nih.gov/pubmed/32905581.

155. Murthy S, Gomersall CD, Fowler RA. Care for CriticallyIll Patients With COVID-19. JAMA 2020;323(15):1499-1500. Available from: https:// doi: 10.1001/jama.2020.3633. Accessed 12 Sep 2020.

156. Fan E, Del Sorbo L, Goligher EC, et al. An official American Thoracic Society/European Society of Intensive Care Medicine/Society of Critical Care Medicine clinical practice guideline: mechanical ventilation in adult patients with acute respiratory distress syndrome. Am J Respir Crit Care Med.2017;195(9):1253-1263.

157. Alraddadi BM, Qushmaq I, Al-Hameed FM, et al. Noninvasive ventilation in critically ill patients with the Middle East respiratory syndrome. Influenza Other Respir Viruses 2019;13(4):382-390.

158. De Backer D, Dorman T. Surviving Sepsis Guidelines: a continuous move toward better care of patients with sepsis. JAMA. 2017;317(8):807-808.

159. COVID-19 case record form. Available at: https://isaric.tghn.org/novel-coronavirus/. Accessed 2 March 2020.

160. Bausewein C, Currow DC, Johnson MJ, editors. Palliative care in respiratory disease. Eur Respir Soc.2016. DOI:10.1183/2312508X.erm7316

161. European Centre for Disease Prevention and Control. Novel coronavirus (SARS-CoV-2): Discharge criteria for confirmed COVID-19 cases from the hospital. ECDC Technical Report. Available at: https://www.ecdc.europa.eu/sites/default/files/documents/COVID-19-Discharge-criteria.pdf. Accessed 8 November 2020.

162. Young-Hyman D, de Groot M, Hill-Briggs F, Gonzalez JS, Hood K, Peyrot M. Psychosocial care for people with diabetes: a position statement of the American Diabetes Association. Diabetes Care 2016;39:2126–2140.

163. Powers MA, Bardsley J, Cypress M, et al. Diabetes self-management education and support in type 2 diabetes: a joint position statement of the American Diabetes Association, the American Association of Diabetes Educators, and the Academy of Nutrition and Dietetics. Diabetes Care 2015;38:1372–1382.

164. Gomes F, Schuetz P, Bounoure L, Austin P, Ballesteros-Pomar M, Cederholm T, et al. ESPEN guideline on nutritional support for polymorbid internal medicine patients. Clin Nutr 2018;37:336e53.

165. Volkert D, Beck AM, Cederholm T, Cruz-Jentoft A, Goisser S, Hooper L, et al. ESPEN guideline on clinical nutrition and hydration in geriatrics. Clin Nutr 2019;38:10e47.

166. Singer P, Blaser AR, Berger MM, Alhazzani W, Calder PC, Casaer MP, et al. ESPEN guideline on clinical nutrition in the intensive care unit. Clin Nutr 2019;38:48e79.

167. Barazzoni R, Bischoff SC, Breda J, Wickramasinghe K, Krznaric Z, Nitzan D, et al. ESPEN expert statements and practical guidance for nutritional management of individuals with SARS-CoV-2 infection (Editorial). Clinical Nutrition 2020;39:1631-1638. Available at: https://doi.org/10.1016/j.clnu.2020.03.022.

168. Beck J, Greenwood DA, Blanton L, et al.; 2017 Standards Revision Task Force. 2017 National Standards for Diabetes Self-Management Education and Support. Diabetes Care 2017;40:1409–1419.

169. WHO. Smoking and COVID-19 (Scientific Brief). 30 June 2020. Available at: https://www.who.int/news-room/commentaries/detail/smoking-and-covid-19. Accessed 9 November 2020.

170. American Diabetes Association. 5. Facilitating behavior change and wellbeing to improve health outcomes: Standards of Medical Care in Diabetes -2020. Diabetes Care 2020;43(Suppl. 1):S48–S65.

171. Beck J, Greenwood DA, Blanton L, et al.; 2017 Standards Revision Task Force. 2017 National Standards for Diabetes Self-Management Education and Support. Diabetes Care 2017;40: 1409–1419.

172. Anderson RJ, Grigsby AB, Freedland KE, et al. Anxiety and poor glycemic control: a meta-analytic review of the literature. Int J Psychiatry Med 2002;32:235–247.

173. Kovacs Burns K, Nicolucci A, Holt RIG, et al.; DAWN2 Study Group. Diabetes Attitudes, Wishes and Needs second study (DAWN2): cross-national benchmarking indicators for family members living with people with diabetes. Diabet Med 2013;30:778– 788.

174. Harkness E, Macdonald W, Valderas J, Coventry P, Gask L, Bower P. Identifying psychosocial interventions that improve both physical and mental health in patients with diabetes: a systematic review and meta-analysis. Diabetes Care 2010;33:926–930.

175. Wang J, Wang JX, Yang GS. The Psychological Impact of COVID-19 on Chinese Individuals. Yonsei Med J 2020; 61: 438–40.

176. Khan S, Siddique R, Li H, Ali A, Shereen MA, Bashir N, et al. Impact of coronavirus outbreak on psychological health. J Glob Health 2020; 10:010331.

177. Torales J, O'Higgins M, Castaldelli-Maia JM, Ventriglio A. The outbreak of COVID-19 coronavirus and its impact on global mental health. Int J Soc Psychiatry 2020; 66:317–320.

178. Inter Agency Standing Committee (IASC). IASC Reference Group on MHPSS in Emergency Settings. Addressing mental health and psychosocial aspects of covid-19

outbreak. Interim Briefing Note (Version 1.5) last up dated February 2020. Available at: https://interagencystandingcommittee.org/system/files/2020-03/IASC%20Interim%20Briefing%20Note%20on%20COVID-19%20Outbreak%20Readiness%20and%20Response%20Operations%20-%20MHPSS_0.pdf

179. World Health Organization (WHO). Coronavirus disease (COVID-19) outbreak. Mental health and COVID-19. Available at: https://www.euro.who.int/en/health-topics/health-emergencies/coronavirus-covid-19/publications-and-technical-guidance/noncommunicable-diseases/mental-health-and-covid-19. Accessed 10 November 2020.

Chapter 7

Pharmacological Management of Diabetes Mellitus in COVID-19

Dr. Md. Shah Emran

7.1: Fluctuations of blood Glucose level

It has been found that inflammatory cytokines, stress, changes in food intake and exercise, respiratory distress, glucocorticoid administration, low blood pressure, nonstandard self medication of diabetes by the patients, insulin resistance render the patients to have wide fluctuation of blood sugar in COVID-19 patients. The mechanism of action of drugs used in diabetes management and disease severity guides the choice of appropriate antidiabetic drugs. So modifications in the pharmacological treatment of Diabetes in COVID-19 patients are imperative (1)

7.2: Glycemic Targets

As has already mentioned in section 3 clinical categorization of patients as in table-1 guide choosing appropriate drugs, regimens and glycemic targets in managing COVID-19 patients

7.2.1:

Clinical classification scheme of COVID-19 patients(2)

Severity class	Clinical features
Mild	Mild flue like symptoms, No respiratory distress, normal oxygen saturation, no imaging signs of pneumonia
Moderate	Respiratory distress with radiological evidence of pneumonia but respiratory rate <30/min, Oxygen saturation> 93%, CRB-65 score 0
Severe	All /any of the followings: 1. Respiratory distress with rate > 30/min 2. Oxygen saturation ≤ 93% 3. FiO_2 / PaO_2 ≤ 300 mmHg
Critical	All/any of the followings 1.Respiratory failure, ARDS 2.Shock 3.Evidences of organ failure 4.Oxygen saturation is maintained by mechanical ventilation

Footnote: CRB-65 scoring counts 1 each for the presence of confusion,respiratory rate >30/min, blood pressure Systolic<90/diastolic <60 mmHg, age ≥ 65

Strict blood glucose control as in table-2 is recommended for mild ,nonelderly moderate cases

Elderly moderate cases and patients on glucocorticoid should have medium or less stringent glycemic targets

Similarly severe, critical, patients with co morbidities like stroke, IHD, organ dysfunction and who are prone to develop hypoglycemia should have less stringent blood glucose targets

7.2.2: Therapeutic glycemic targets

Table 2: Levels of blood sugar control

	Strict	Moderate	Less stringent
FPG (mmol/L)	4.4	6.1	7.8
PPG (mmol/L)	7.8	10	13.9

7.3: Therapeutic Principle of Glucose Management in Patients with COVID-19

Insulin is the preferred choice in diabetics with severe infection. For non-critical patients, insulin s/c injection is recommended. For critical patients IV insulin or CSII is recommended. In case of Diabetic ketoacidosis and hyperglycemic hyperosmolar state IV insulin treatment should be started in combination with adequate fluid infusion. If the clinical condition is stable and eating pattern is regular, patients can continue OAD treatment as before COVID-19 infection. NPH and long-acting insulins are recommended during glucocorticoid treatment. Measureing 7 point blood glucose during insulin treatment is recommended (1)

7.4: Management Plan of Diabetes according to Severity of COVID-19 infection

Severity of COVID-19 can be determined as shown above in table-1

7.4.1: Mild cases

There is no need to adjust the original regime too much. Both OAD and insulin treatment can be maintained as the patient was taking before COVID-19 infection. The progress of COVID-19 can be rapidly worsen with hyperglycemia, thus, it is strongly recommended to increase the frequency of glucose monitoring, and consult with physicians to adjust treatment regime whenever needed even in diabetes patients with mild COVID-19

7.4.2: Moderate cases

Original treatment regime is to be maintained if patient's cognitive condition, appetite and glucose control are within normal range. In patients with obvious COVID-19 symptoms who cannot eat regularly, OAD is to be switched to insulin, preferably short acting analogue insulin. Premix insulin regime is to be switched to basal-bolus regime or insulin pump for better flexibility of glucose management. In hypoglycemia prone patient, analogue insulins are better than human insulin.

7.4.3: Severe and critical cases

Intravenous insulin is the best choice. For patients on renal replacement therapy (CRRT), the proportion of glucose and insulin in the replacement solution should be increased or decreased according to blood glucose level to avoid hypoglycemia and severe glucose fluctuations (3)

7.5: Common Anti-diabetic drugs and COVID-19

Class Comments

Metformin	• Not recommended in • Severe/critical patients • Patients with gastrointestinal symptoms • Patients with low oxygen saturation
Secretagogue	• Recommended in • Mild/moderate patients using glucocorticoid • Short-acting agents used in early stage • Middle/long-acting agents to control FPG and/or PPG
α-glucosidase inhibitors	• Can be used to control PPG • Not recommended in severe/critical patients • Not recommended in patients with gastrointestinal symptoms
Thiazolidindione	• Expected to reduce insulin response-related inflammation • Can be used during the process of glucocorticoid Treatment (Madhu 7) • Regime should be adjusted according to treatment effect
DPP-4i	• Low risk of hypoglycemia • Possible to use for a wide range of renal dysfunction • ?May have some anti inflammatory property • Reduce DPP4-mediated immune dysregulation (Madhu 5,6)
SGLT-2i	• Increased risk of dehydration and euglycemic Ketoacidosis (Madhu5,6) • Stop if oral intake is not tolerated or severely ill • Not recommended for COVID-19 patients having stress reaction at different levels
Insulin and analogues	Generally considered safe in treating diabetes Hypoglycemia is serious compliacation Routes of delivery depends on the severity of COVID-19 infection
GLP-1 receptor agonists	Can cause GI symptoms Recent reports on salutary effects on COVID is not confirmed

7.6: Management plan on types and special groups of Diabetes with COVID 19

7.6.1: Type-1 DM

- Basal bolus/basal plus or Insulin pump if available treatment is suggested.
- Insulin analogues are recommended as first choice.
- Insulin treatment regimen needs to be individualized

7.6.2: Type 2DM

- For mild COVID-19 patients on OAD no change is needed if glycemic control is achieved
- For patients treated by glucocorticoids subcutaneous/IV insulin treatment is recommended
- For critical patients IV insulin is recommended.

7.6.3: Glucocorticoid-associated diabetes

- As glucocorticoid-induced hyperglycemia usually more pronounced between lunch and bed time, monitoring blood sugar in this period is emphasized. .
- Insulin treatment is recommended.

7.6.4: Glucose Management of Children and Adolescents

- In children, frequent blood glucose monitoring (4 - 7 times /day) is needed.
- Individualize exercise program.
- Ensure energy requirement in (kcal/day) as calculated (70 -100) + 1000 with carbohydrate: 50% - 55%, fat: 25% - 35% and protein: 15% - 20%.
- Adjustment should be made for physical activity and stress of the children.
- Target of blood glucose control is HbA1c < 7.5% (4).
- Look for DKA and hypoglycemia in the earliest possible time.

7.7: Key Recommendations

- More frequent glucose monitoring is recommended for COVID patient.
- Initiate Insulin therapy earlier as the disease worsens.
- Severe and critical patient should be treated by IV insulin.
- For patients on NPO, ratio of glucose to insulin is 2 - 4 G glucose per unit insulin
- Large dose of glucocorticoids for long time can lead to diabetes mellitus in previously nondiabetics.
- Discontinuation of glucocorticoid without decreasing antidiabetic dose can cause hypoglycemia
- New and clear evidences of diabetic medications on COVID-19 should be incorporated in treating diabetes in COVID-19
- Pregnant women, children and diabetes with comorbidities are better treated with insulin
- In principle, it is recommended to measure blood glucose 7 times a day

Reference:

1. Türk Diyabet Cemiyeti (2020) Expert Recommendation on Glucose Management Strategies of Diabetes Combine with COVID-19. Journal of Clinical Internal Medicine, 37, 215-219.
2. Leng, Z., Zhu, R., Hou, W., Feng, Y., Yang, Y., Han, Q., et al. (2020) Transplantation of ACE2-Mesenchymal Stem Cells Improves the Outcome of Patients withCOVID-19 Pneumonia. Aging and Disease, 11, 216-228.https://doi.org/10.14336/AD.2020.0228
3. (2020) Expert Recommendation on Home-Based Management of Diabetes in Children and Adolescents during the Period of COVID-19 Epidemic Prevention and Control. Chinese Journal of Diabetes, 12.
4. Smart, C.E., Annan, F., Bruno, L.P.C., Higgins, L.A. and Acerini, C.L. (2014) Nutritional Management in Children and Adolescents with Diabetes. Pediatric Diabetes,15, 135-153. https://doi.org/10.1111/pedi.12175
5. Bornstein SR, Rubino F, Khunti K, Mingrone G, Hopkins D,Birkenfeld AL, et al. Practical recommendations for the management of diabetes in patients with COVID-19. Lancet Diabetes Endocrinol.2020.https://doi.org/10.1016/S2213-8587(20)30152-2.
6. Paul R, Bhadada SK. Should anti-diabetic medications be reconsidered amid COVID-19 pandemic? Diabetes Res Clin Pract.2020;163:108146.

7.8: Glycemic management after recovery from COVID 19

During diabetes management in hospital with COVID 19 insulin is the preferred treatment
Insulin should be continued for at least six weeks after discharge, because patient cannot take oral food adequately

They should do SMBG; BBF, 2hrs after breakfast, 2hrs after lunch, and before dinner per day initially
Maintain contact with endocrinologist to modify insulin dose and schedule at least initial few days
Patients who were on OAD prior to hospital stay; they can be shifted to OAD after six weeks
As physical wellbeing resume, they can start physical exercise

It should be emphasized that existing influenza and pneumococcal vaccines should be taken as recommended by diabetic patients

Endocrinologist should deliver diabetes care more innovatively and increasingly use telemedicine to be in touch with the diabetic patient while keeping face-to-face consultations to a minimum.
This will ensure maximum benefit with minimum risk.

Let us prepare for all the new post COVID challenges in diabetes care even as we remain alert to newer lessons that are constantly emerging and will help us organize our practice.

References:

1. International Journal of Diabetes in Developing Countries https://doi.org/10.1007/s13410-020-00831-6
2. Diabetes UK Guidelines for the management of diabetes services and patients during the COVID-19 pandemic 2020. DIABETIC Medicine: DOI: 10.1111/dme.14316

Chapter 8

Glycemic management after recovery from COVID-19

Dr. Md. Shah Emran

- During diabetes management in hospital with COVID 19 insulin is the preferred treatment
- Insulin should be continued for at least six weeks after discharge, because patient cannot take oral food adequately
- They should do SMBG; BBF, 2hrs after breakfast, 2hrs after lunch, and before dinner per day initially
- Maintain contact with endocrinologist to modify insulin dose and schedule at least initial few days
- Patients who were on OAD prior to hospital stay; they can be shifted to OAD after six weeks
- As physical wellbeing resume, they can start physical exercise
- It should be emphasized that existing influenza and pneumococcal vaccines should be taken as recommended by diabetic patients
- Endocrinologist should deliver diabetes care more innovatively and increasingly use telemedicine to be in touch with the diabetic patient while keeping face-to-face consultations to a minimum.
- This will ensure maximum benefit with minimum risk.
- Let us prepare for all the new post COVID challenges in diabetes care even as we remain alert to newer lessons that are constantly emerging and will help us organize our practice.

References

1. International Journal of Diabetes in Developing Countries https://doi.org/10.1007 /s13410-020-00831-6
2. Diabetes UK Guidelines for the management of diabetes services and patients during the COVID-19 pandemic 2020. DIABETIC Medicine: DOI: 10.1111/dme.14316

Chapter 9

Management of diabetes in pregnancy during COVID-19 pandemic

Dr. Farhana Akter

9.1. Covid-19 pandemic and pregnancy in diabetes

Pregnant people might be at an increased risk for severe illness from COVID-19 compared to non-pregnant people. Additionally, there may be an increased risk of adverse pregnancy outcomes, such as preterm birth, among pregnant people with COVID-19 [1].The anatomical structure of the respiratory system is changed during pregnancy, and the virus transmitted by droplets and aerosols is more easily inhaled by pregnant women and is difficult to remove [2].Furthermore, the prognosis is worse after infection when compared with non -pregnant women. Changes in reproductive hormones and immune systems during pregnancy collectively make them more susceptible to certain infections. More importantly, angiotensin-converting enzyme (ACE)-2, the SARS-CoV-2 receptor, has been proven highly increased during pregnancy, which may contribute to the susceptibility to SARS-CoV-2 [3].In the context of the COVID-19 pandemic, widespread anecdotal evidence suggests that both clinicians and pregnant women are increasingly unwilling to recommend or undergo the OGTT. This is based on valid concerns regarding travel, the possible need for two visits, and the time (up to 3 h) spent in the potentially infectious environment of specimen collection centers. Further, a GDM diagnosis generally involves additional health service visits for diabetes education, glucose monitoring review, and fetal ultrasonography, all of which carry exposure risks during a pandemic [4]. During COVID-19 pandemic, there will be temporary changes to the recommended process of diagnostic testing for gestational diabetes during pregnancy and for postnatal checks in women who have had gestational diabetes [5]. The rationales for the suggestion of these temporary measures were: shortening the screening test process to reduce risk of exposure to COVID-19 in laboratories; reducing the burden on pathology centers, diabetes care providers and obstetric team; minimizing the number of visits and duration of stay in the hospital for pregnant women; and reducing in-person visit by replacing such visits with remote communication with patients [2].

9.1.1. Pregnancy co-morbidities and COVID-19 infection:

It is important to consider the potential impact of pre-existing hyperglycemia and hypertension on the outcome of COVID-19 in pregnant women. Currently, there are higher risks of infection and poorer outcomes, including very high mortality, among the elderly population and those with co-morbidities such as hypertension and diabetes in this global pandemic. One in seven pregnancies is impacted by hyperglycemia and one in ten is impacted by hypertension. The stress of infection, accompanied by severe anxiety and use of high doses of corticosteroids, has the potential to worsen glycemic control and could enhance the risk of secondary infections [6].

9.1.2. Epidemiology of COVID-19 and pregnancy in diabetes:

To date, no review has comprehensively evaluated the comparative data concerning pregnant and recently pregnant women and non-pregnant women with covid-19. Moreover, the sampling frames in primary studies have varied, ranging from universal SARS-CoV-2 testing for all pregnant women admitted to hospital [7,8] to symptom based testing [9,10].Testing strategies have also differed within and between countries, with diagnosis in many early studies based on epidemiological risk assessment and clinical features without confirmed infection, which need to be considered in the analysis [11].

Limitations in the external and internal validity of studies make it challenging for guideline developers and policy makers to make evidence based recommendations for the management of pregnant and recently pregnant women with covid-19.The overall rate of covid-19 diagnosis in pregnant and recently pregnant women attending or admitted to hospital for any reason was 10% , In US All prevalence rate for covid-19 greater than 15%, one in 10 pregnant or recently pregnant women who are attending or admitted to hospital for any reason are diagnosed as having suspected or confirmed covid-19, although the rates vary by sampling strategy [12].

9.1.3: Effects of COVID-19 on pregnancy, mother and neonate:

Most pregnant women will experience only mild or moderate cold/flu-like symptoms. Cough, fever, shortness of breath, headache and anosmia are other relevant symptoms [13]. Fever is common in COVID-19-infected patients. Previous data have demonstrated that maternal fever in early pregnancy can cause congenital structural abnormalities involving the neural tube, heart, kidney, and other organs [14, 15, 16]. More severe symptoms which suggest pneumonia and marked hypoxia are widely described with COVID-19 in older people, the immunosuppressed and those with chronic conditions suchas diabetes, cancer or chronic lung disease. It has been reported that viral pneumonia in pregnant women is associated with an increased risk of preterm birth, fetal growth restriction (FGR), and perinatal mortality [17]. The symptoms of severe infection are no different in pregnant women and early identification and assessment for prompt supportive treatment is the key. There have also been case reports of women with severe COVID-19 infection at the time of birth who have required ventilation and ECMO, and of maternal death [18].The overall numbers are small. There's no evidence right now that COVID-19 causes problems with a baby's development or an increased risk of miscarriage. Few cases of neonatal COVID-19 infections have been reported but both were most likely an outcome of postnatal transmission [19].

9.1.4. Vertical transmission of infection to newborn of COVID-19 suspected or confirmed mother:

Based on previous observations of pregnant women with MERS and SARS, although limited in number, intrauterine corona virus transmission from mother to fetus has never been confirmed [3]. At this point in the global pandemic of COVID-19 infection, currently there is no evidence for intrauterine vertical transmission of COVID-19 from infected pregnant mothers to their fetuses [20]. While this is reassuring, larger data are needed to firmly rule out trans-placental vertical transmission.

9.1.5. Effects of pregnancy on COVID-19:

Pregnancy is a physiological state that predisposes women to viral respiratory infection. Due to the physiological changes in the immune and cardiopulmonary systems, pregnant women are more likely to develop severe illness after infection with respiratory viruses. Pregnancy may also modify the clinical manifestation, for example lymphocytopenia may be even more marked [19].

9.2: Definition, classification, diagnosis and screening of pregnancy in diabetes:

9.2.1: Definition:

Diabetes in pregnancy may be either Pre-existing Diabetes or Gestational diabetes mellitus (GDM). GDM is defined as hyperglycemia with onset or first recognition during pregnancy, at severity less than those occur in overt diabetes [21]. GDM is a high-risk condition with adverse maternal and neonatal outcomes. Offspring of mothers with GDM are at risk for development of obesity and abnormal glucose metabolism during childhood, adolescence, and adulthood. Having fetal hyperinsulinism is a risk factor for development of both obesity and abnormal glucose metabolism, and might be implicated in pathophysiology [22, 23].
Diabetes confers significantly greater maternal and fetal risk largely related to the degree of hyperglycemia but also related to chronic complications and comorbidities of diabetes. In general, specific risks of diabetes in pregnancy include spontaneous abortion, fetal anomalies, preeclampsia, fetal demise, macrosomia, neonatal hypoglycemia, hyperbilirubinemia, and neonatal respiratory distress syndrome, among others. In addition, diabetes in pregnancy may increase the risk of obesity, hypertension, and type 2 diabetes in offspring later in life [24, 25].

9.2.2: Diagnosis and screening:

Assess risk of gestational diabetes using risk factors in a healthy population. At the booking appointment, determine the following risk factors for gestational diabetes:

• BMI above 30 kg/m2
• previous macrosomic baby weighing 4.5 kg or above
• previous gestational diabetes
• family history of diabetes (first-degree relative with diabetes)
• minority ethnic family origin with a high prevalence of diabetes [26.]

GDM diagnosis can be accomplished with either of two strategies:

1. The “one-step” 75-g OGTT derived from the IADPSG criteria or
2. The older “two-step” approach with a 50-g (nonfasting) screen followed by a 100-g OGTT for those who screen positive, based on the work of Carpenter and Coustan’s interpretation of the older O’Sullivan [27] criteria.
The screening and diagnostic work-up of GDM has been described in Box 9.1

Box 9.1. The screening and diagnostic work-up of GDM

One-step strategy

Perform a 75-g OGTT, with plasma glucose measurement when patient is fasting and at 1 and 2 h, at 24–28 weeks of gestation in women not previously diagnosed with diabetes.

The OGTT should be performed in the morning after an overnight fast of at least 8 h.

One abnormal value, not two become sufficient to make the diagnosis of GDM.[28].

So, GDM diagnosis is made when any of the following plasma glucose values are met or exceeded:

Fasting : 92 mg/dL (5.1 mmol/L)
1 h : 180 mg/dL (10.0 mmol/L)
2 h : 153 mg/dL (8.5 mmol/L)

Two-step strategy

Step 1: Perform a 50-g GLT (nonfasting), with plasma glucose measurement at 1 h, at 24–28 weeks of gestation in women not previously diagnosed with diabetes.

If the plasma glucose level measured 1 h after the load is ≥130, 135, or 140 mg/dL (7.2, 7.5, or 7.8 mmol/L, respectively), proceed to a 100-g OGTT.

Step 2: The 100-g OGTT should be performed when the patient is fasting.

The diagnosis of GDM is made when at least two* of the following four plasma glucose levels (measured fasting and at 1, 2, and 3 h during OGTT) are met or exceeded (Carpenter-Coustan criteria) [29].

Fasting : 95 mg/dL (5.3 mmol/L)
1 h : 180 mg/dL (10.0 mmol/L)
2 h : 155 mg/dL (8.6 mmol/L)
3 h : 140 mg/dL (7.8 mmol/L)

GDM, gestational diabetes mellitus; GLT, glucose load test; OGTT, oral glucose tolerance test.IADPSG, International Association of Diabetes and Pregnancy Study Groups

* American College of Obstetricians and Gynecologists notes that one elevated value can be used for diagnosis [30].

9.2.3. Diagnosis and screening of GDM during COVID-19 pandemic [31].

In an evolving pandemic with a highly infectious virus, screening OGTTs involve high exposure risks and health service burden. The routine use of OGTTs for GDM screening needs to be carefully considered in the context of local pandemic impact including community transmission rates. Where it is no longer safe or feasible current evidence does not support a single alternative test. We thus propose a strategy that utilizes alternative simpler tests and mitigation 'safety-nets' balancing GDM detection with minimizing of health service burden and viral exposure of women (Fig.: 9.1)

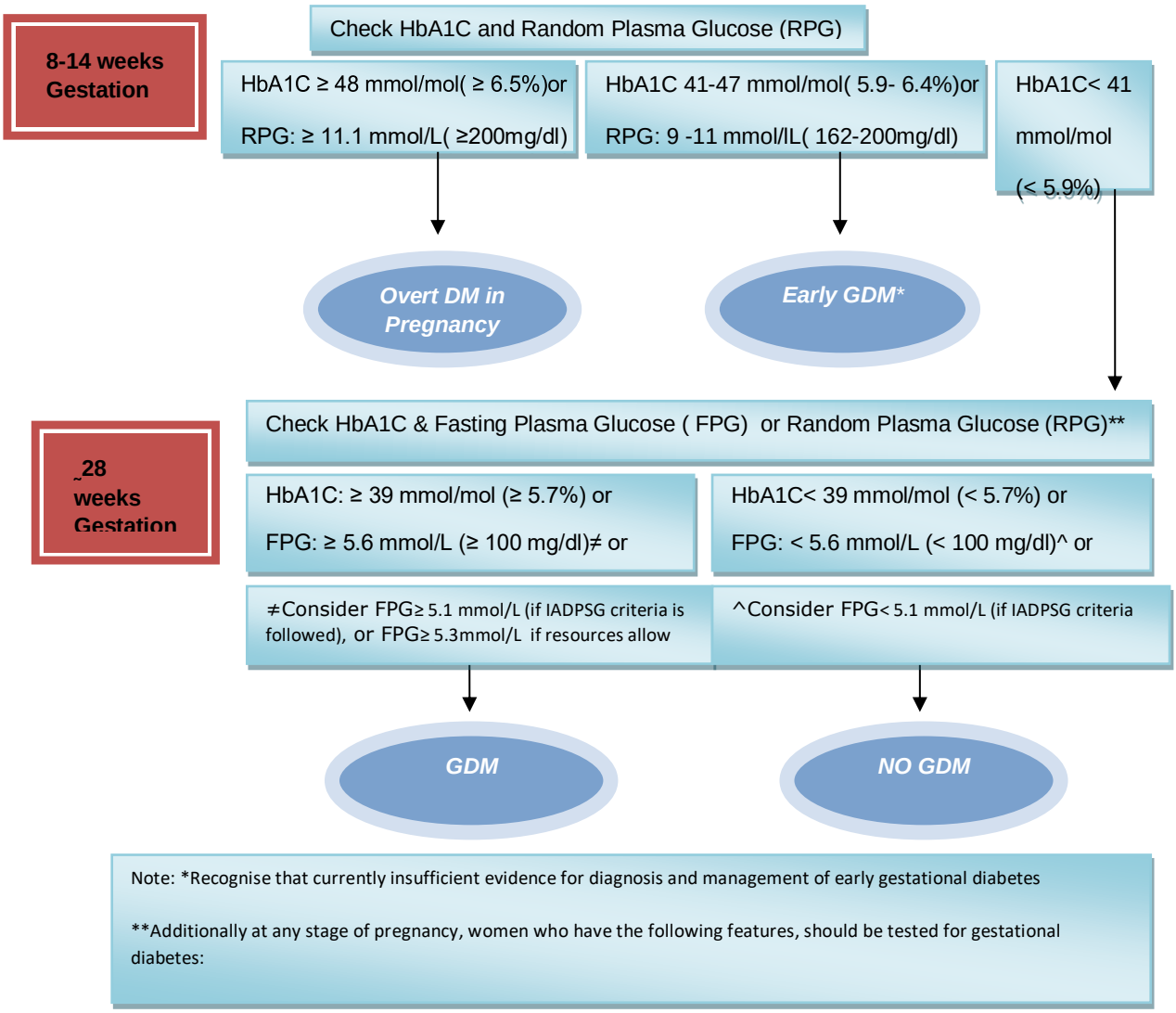


Fig- 9.1: Screening for gestational diabetes mellitus in women with risk factors during the evolving COVID-19 pandemic. Figure adapted from the Royal College of Obstetricians and Gynaecologists' Guidance for maternal medicine in the evolving coronavirus (COVID19) pandemic [32].

9.2.3.1: Early screening for GDM:

Early screening for GDM is primarily designed to identify women who had undetected diabetes before pregnancy, given the risks of undiagnosed (largely type 2) diabetes in pregnancy. At booking, HbA1c and RPG can be performed in addition to usual booking bloods, to detect the highest risk groups [31]. We suggest the following thresholds and actions: (Table 9.1)

HbA1c ≥48 mmol/mol (≥6.5%) *or* RPG ≥11.1 mmol/L (≥200 mg/dL): treat as pre-existing diabetes.HbA1c 41–47 mmol/mol (5.9–6.4%) *or* RPG 9–11 mmol/L (162–200 mg/dL): consider managing using the GDM pathway.

9.2.3.2: Screening blood tests for GDM at 24–28 weeks:

HbA1c ≥39 mmol/mol (≥5.7%) or FPG ≥5.6 mmol/L (≥100 mg/dL) or RBG ≥9 mmol/L (≥162 mg/dL): treat as GDM

Table 9.1: Screening for GDM at early and at 24–28 weeks of gestation:

Time of screening	Diagnostic thresholds	Actions
At early screening	HbA1c ≥6.5% *or* RPG ≥11.1 mmol/L (≥200 mg/dL)	Treat as pre-existing diabetes.
	HbA1c 5.9–6.4% *or* RPG 9–11 mmol/L (162–200 mg/dL)	Consider managing using the GDM pathway
At 24–28 weeks	HbA1c ≥5.7% *or* FPG ≥5.6 mmol/L (≥100 mg/dL) *or* RPG ≥9 mmol/L (≥162 mg/dL)	Treat as GDM

9.2.3.3: Diagnosis and monitoring in women with past GDM:

Women with a history of GDM have a high risk of subsequent GDM and of T2DM. The risk of GDM in a subsequent pregnancy is approximately 50%, or up to 80% in some series [33,34, 35].We therefore suggest that booking blood tests should be completed as outlined above, to detect pre-existing overt diabetes or early GDM where HbA1c, FPG or RPG thresholds are exceeded. If resources allow, healthcare services may consider regular glucose monitoring of women with a history of GDM, without the need for testing at 24–28 weeks, combined with early lifestyle interventions.

9.2.3.4: Ongoing monitoring for complications of any GDM missed in routine care:

Women that have previously had a normal GDM screening test, should be re-screened for GDM or commence routine glucose monitoring as per GDM protocols, if any of the following features are identified at any time during pregnancy: heavy glycosuria (≥2+ glucose); symptoms of diabetes (e.g. thirst, polydipsia/polyuria, nocturia); large-for-gestational-age fetus or polyhydramnios on ultrasound [31].

9.3. Pre-pregnancy counseling:

According to recent guidelines from the American College of Obstetricians and Gynecologists, there is "no clear answer," as to whether or not couples should delay attempts to get pregnant. Individuals should make their own decisions based on their unique needs, desires, and values. Issues to consider include potential risks to pregnant individuals and their fetuses due to COVID-19, resource limitations, the social and financial effects of COVID-19 on an individual, and other factors [36]. So, this is an extremely personal decision and couples should make upon consulting their physicians. At any time, but now more than ever, it's important for people to make an informed decision on whether or not to try to conceive. The most important point to realize is that there are still a lot of unknowns on how COVID-19 affects pregnancy, fetal development and newborn babies. COVID-19 has only been around for several months. Mental health also plays an important role throughout this process.

9.4. Management of diabetes in pregnancy with suspected or conformed COVID-19:

9.4.1: Lifestyle management:

After diagnosis, treatment starts with medical nutrition therapy, physical activity, and weight management depending on pre-gestational weight [4].Women with preexisting Diabetes should titrate insulin dose to reach target along with dietary readjustment and exercise as directed.

9.4.1.1: Medical nutrition therapy:

Medical nutritional therapy is the keystone of treating GDM as it maintains desired glycemic goals in 80-90% of GDM women. The optimal dietary prescription would be a diet that provides adequate nutrition to support fetal and maternal well-being, while maintaining normoglycemia with absence of ketones, and achieving appropriate weight gain in pregnancy.

9.4.1.2: Physical Exercise:

Exercise has been shown to improve glycemic control in GDM. Daily moderate exercise for 30 minutes or more is recommended for a woman with GDM, if she has no medical or obstetrics contraindications. Advising GDM patients to walk briskly, or do arm exercises while seated in a chair for at least 10 minutes after each meal facilitates in reducing post-meal glucose rise, and help in achieving glycemic goal. Patients can perform their exercise at home as far as possible, lockdown should not be an excuse to refrain from exercise.

9.4.1.3: Smoking cessation:

Smoking during pregnancy is the leading modifiable risk factor for poor birth outcomes, including stillbirth, miscarriage and pre-term birth [37].Smoking during pregnancy contributes to increased respiratory conditions among children and the World Health Organization has highlighted that exposure to secondhand smoke is a major cause of bronchitis, pneumonia, coughing and wheezing and asthma attacks in children [38]. Preliminary evidence indicates that smokers who contract the new coronavirus (COVID-19) have more severe symptoms [39]. One survey from China has found that smokers with COVID19 are 14 times more likely to develop severe disease [40]. As a precautionary measure, pregnant women are classed as a group at risk of severe illness with COVID-19. It is vitally important that we help smokers to quit. Secondhand smoke exposure also elevates risks, so it is important that smokers are supported to maintain a smoke free home and pregnant women are not exposed to secondhand smoke in the home.

9.4.1.4: Coping with psychological stress:

Pregnant women are at an increased risk for anxiety and depression; once they have been defined with suspected/probable/confirmed COVID-19 infection they may exhibit varying degrees of psychiatric symptoms that are detrimental to maternal and fetal health [41]. Mother/baby separation may impede early bonding as well as establishment of lactation [42].These factors will inevitably cause additional stress for mothers in the postpartum period. Healthcare providers should pay attention to a patient's mental health, including promptly assessing her sleep patterns and sources of anxiety, depression, and even suicidal ideation. A perinatal psychiatrist should be consulted when necessary.

9.4.2: Pharmacological intervention:

If the medical nutrition therapy and exercise fail to achieve glycemic goals for a woman with GDM, insulin therapy should be initiated. Insulin therapy is the primary pharmacological treatment. The type and timing of insulin should be chosen based on the specific blood glucose elevation [43].

9.5. Antenatal care:

9.5.1: Antenatal visits, Physical checkup and laboratory tests:

A flowchart detailing the suggested care for women with GDM is given below (Fig.: 9.2). All women diagnosed with GDM should have an appointment with the diabetes midwife/nurse, who will provide training in the use of a glucose meter. Where feasible, this should be done remotely via video call. This visit should also be used as an opportunity to provide women with dietetic information and contact details of the dietician, where one is available. Women should be followed-up remotely in the week after the meter training by the diabetes midwife/nurse and for all appointments where home capillary blood sugar levels are to be checked by the diabetes team. Women should be provided with clear guidance on who to contact if they have >3 abnormal blood glucose levels in a week or >10-15% of all readings – this will usually be the diabetes antenatal team [32]. Antenatal care for pregnant women with GDM should, wherever possible, minimize the need for hospital-based care, support public health measures concerning physical distancing and self-isolation and reduce health service burden.

Retinal screening services were targeted at the highest risk women (proliferative and previously treated proliferative retinopathy, pre- proliferative retinopathy, or maculopathy, those without retinal screening in past 2 years [44].

9.5.2: Specific management of suspected, probable, or confirmed cases of COVID-19 in pregnancy:

Patient be managed initially by designated tertiary hospitals with effective isolation facilities and protection equipment. Suspected/probable cases should be treated in isolation and confirmed cases should be managed in a negative pressure isolation room, although it is recognized that these may be unavailable in many units. In general, critically ill confirmed cases should be admitted to a negative pressure isolation room in an ICU[45].If negative pressure isolation rooms are not available, patients should be isolated in single rooms or grouped together once COVID-19 infection has been confirmed. Chest CT scanning has high sensitivity for diagnosis of COVID-19 [46]. In a pregnant woman with suspected COVID-19 infection, a chest CT scan may be considered as a primary tool for the detection of COVID-19 in epidemic areas. Informed consent should be obtained and a radiation shield applied over the gravid uterus.

Maternal surveillance: Maintain fluid and electrolyte balance; symptomatic treatment, such as antipyretic, anti-diarrheal medicines. Close and vigilant monitoring of vital signs and oxygen saturation level to minimize maternal hypoxia; conduct arterial blood-gas analysis; repeat chest imaging (when indicated); regular evaluation of complete blood count, renal and liver function testing, and coagulation testing. If antiviral treatment is to be considered, this should be done following careful discussion with virologists; pregnant patients should be counseled thoroughly on the potential adverse effects of antiviral treatment for the patient herself as well as for the risk of FGR. Monitoring for bacterial infection (blood culture, midstream or catheterized specimen urine microscopy and culture) should be done, with timely use of appropriate antibiotics when there is evidence of secondary bacterial infection. Severe pneumonia is associated with a high maternal and perinatal mortality rate, therefore aggressive treatment is required, including supporting measures with hydration and oxygen therapy. Consideration for the use of low molecular weight heparin in severe cases; however, its efficacy in improving the outcomes of severe COVID-19 pneumonia requires further investigation before formal recommendation [6]

Fetal surveillance: Undertake cardiotocography (CTG) for fetal heart rate (FHR) monitoring when gestational age is beyond the limit of viability based on local practice (23–28 weeks).

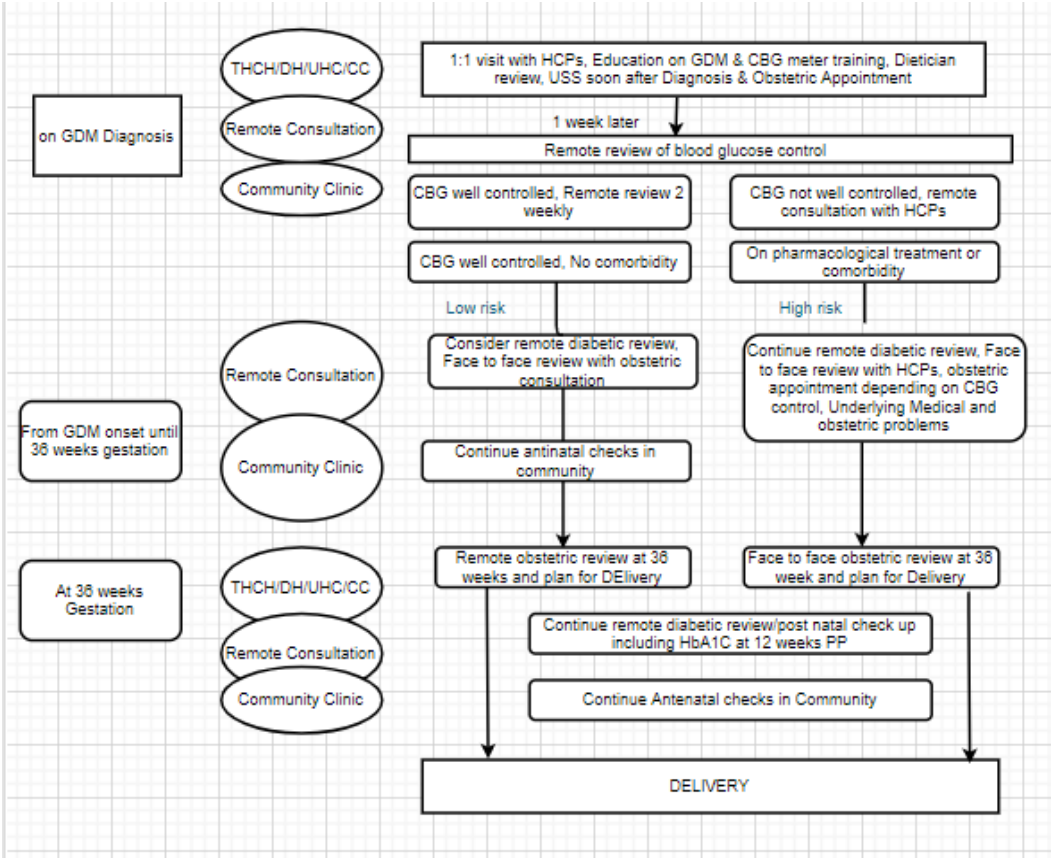


Figure: 9.2: Management of women with GDM–the suggested patient pathway after a diagnosis of GDM during the COVID-19 pandemic. THC: Tertiary health care, DH: District Hospital, UHC: Upazilla Health Complex, GDM: gestational diabetes mellitus; CBG: capillary blood glucose; USS: ultrasound scan; PP: postpartum. Figure adapted from Thangaratinam S, et al. [31] (modified).

9.5.3: Glycemic targets and self-monitoring of blood glucose (SMBG)

9.5.3.1: Glycemic Target:

The level of glycemic target in pregnancy is shown in Table 9.2.

Table 9.2: Glycemic targets during diabetes in pregnancy:

Plasma Glucose/HbA1C	Target
Fasting plasma glucose	<95 mg/dL (5.3 mmol/L)
AND EITHER	
One-hour postprandial glucose	<140 mg/dL (7.8 mmol/L)
OR	
Two-hour postprandial glucose	<120 mg/dL (6.7 mmol/L)
HbA1C	< 6%

9.5.3.2: Blood glucose monitoring:

Women are instructed to carry out self-monitoring of blood glucose (SMBG) 4 times a day, fasting glucose (upon awakening), and one or 2 hour post-meals (after the first bite of a meal) [43].

9.6: Intrapartum management during labour and delivery:

All pregnant women with or recovering from COVID-19 should be provided with counseling and information related to the potential risk of adverse pregnancy outcomes. Pregnant women have continued to deliver their babies in hospital settings with minimal disruption. The use of birthing pools during labor should be avoided in confirmed or suspected cases of COVID-19, given the potential risk of infection via feces [44]. Mode of birth should be individualized, based on obstetric indications and the woman's preferences. WHO recommends that induction of labour and caesarean section should only be undertaken when medically justified and based on maternal and fetal condition. Suspected COVID-19 infection is not an indication for cesarean section, unless the woman's respiratory condition demands urgent delivery, or pregnant women have other indications. If caesarean section is indicated, the procedure should be performed in a negative pressure isolation operating room.

9.7: Postpartum management and neonatal care:

9. 7.1: Postpartum management of woman:

Mother/baby separation may impede early bonding as well as establishment of lactation. These factors will inevitably cause additional stress for mothers in the postpartum period. Unless there is a reasonable suspicion of postpartum type 2 diabetes, postpartum follow-up testing, most likely using an OGTT, should be delayed until either the pandemic has been controlled or another pregnancy is contemplated [4].

9.7.2: Management of newborn:

Regarding neonatal management of suspected, probable, and confirmed cases of maternal COVID-19 infection, the umbilical cord should be clamped promptly and the neonate should be transferred to the resuscitation area for assessment by the attending pediatric team. There is insufficient evidence regarding whether delayed cord clamping increases the risk of infection to the newborn via direct contact [48].In units in which delayed cord clamping is recommended, clinicians should consider carefully whether this practice should be continued [49].

9.8. Covid -19 and Breast feeding:

Relatively few cases have been reported of infants confirmed with COVID-19; those that have been reported experienced mild illness. There is currently insufficient evidence regarding the safety of breastfeeding and the need for mother/baby separation. Except in the sickest women with COVID-19 infections (i.e., those requiring respiratory support or intensive care admission), the benefits of breast feeding outweigh any potential transmission risks [44]. Some pictorial presentation as recommended by WHO [50] regarding Breast feeding advice during covid-19 pandemic has been depicted in figure 9.3, 9.4, 9.5, 9.6 , 9.7, 9.8 and figure 9.9.

9.9: Contraception during Covid-19:

Long-acting reversible contraceptives – IUDs and implants – are highly effective and safe, and may be considered first-line for women with gestational diabetes. If access to postnatal long acting reversible contraception is limited, postpartum medroxyprogesterone (Depo-Provera) injections are offered, before hospital discharge [44]

Figure 9.3 Breast feeding and covid-19. Adapted from WHO [50]

Figure 9.4 Breast feeding by mothers infected with Covid -19. Adapted from WHO [50]

Figure 9.5 Breastfeeding by severely ill mother with covid-19. Adapted from WHO [50]

Figure 9.6 Alternate approach of breastfeeding when covid-19 infected mothers are too unwell to breastfeed or express breast milk. Adapted from WHO [50]

Figure 9.7 Basic support in stressful situation of covid-19 infected mothers and infants. Adapted from WHO [50]

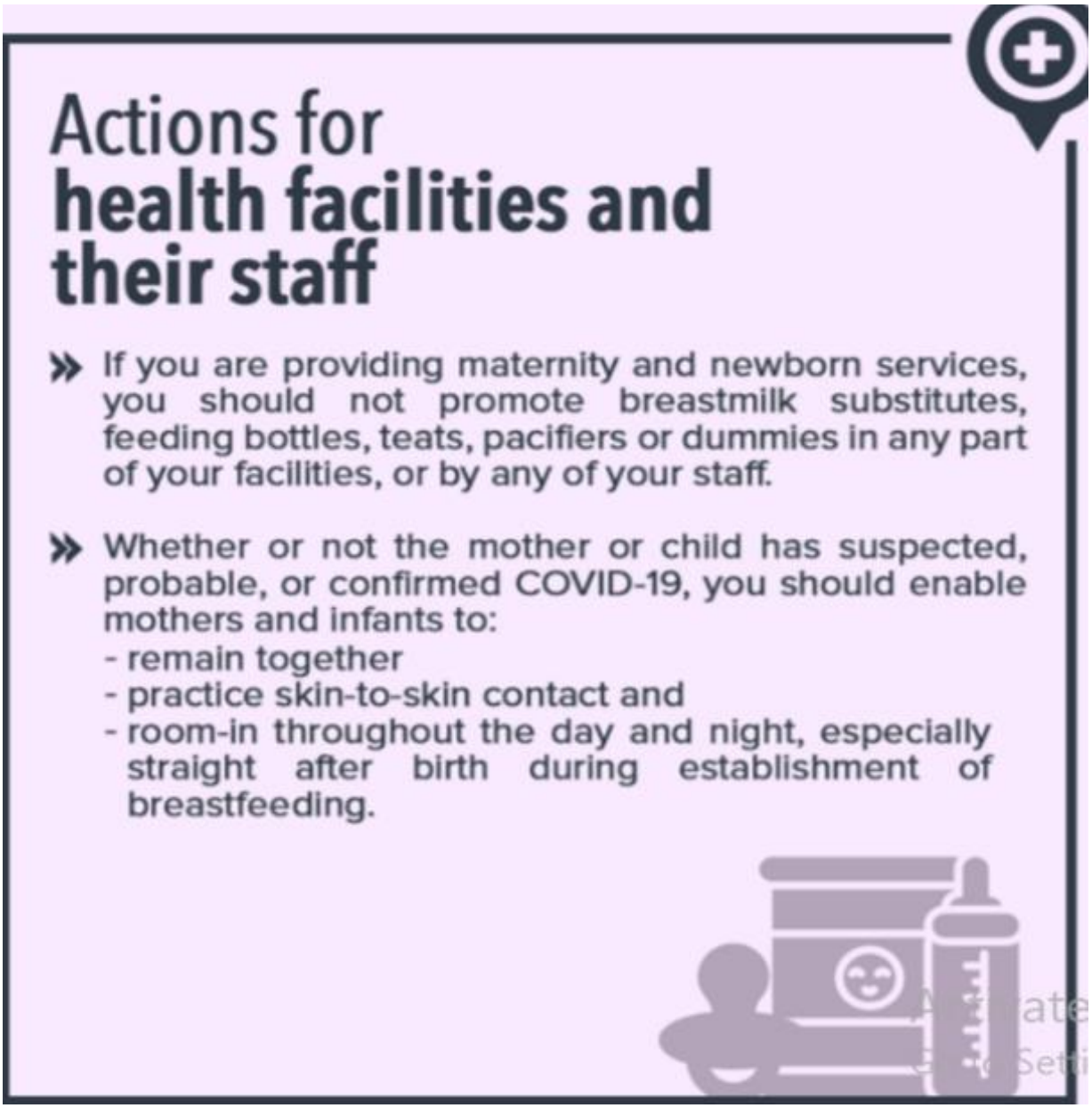


Figure 9.8 Actions for health facilities and their staff. Adapted from WHO [50]

Figure 9.9: Counselling, psychosocial support and standard infant feeding guidelines. Adapted from WHO [50]

9.10: Conclusion:

We suggest pragmatic options for screening, diagnosis and management of pregnancy during the pandemic with emphasis on risk-stratified approaches and in the context of local practice and facilities available. Management strategies should focus on changes to care prompted by the pandemic.

References:

1. Centers for Disease Control and Prevention. Coronavirus Disease 2019 (COVID-19): Considerations for Inpatient Obstetric Healthcare Settings (Updated May 20, 2020). Available from: https://www.cdc.gov/coronavirus/2019-ncov/hcp/inpatient-obstetric-healthcare-guidance.html
2. Nouhjah S, Jahanfar S, Shahbazian H. Temporary changes in clinical guidelines of gestational diabetes screening and management during COVID-19 outbreak: A narrative review. Diabetes & Metabolic Syndrome: Clinical Research & Reviews.2020;14: 939-942.
3. Zhao X, Jiang Y, Zhao Y, Xi H, Liu C, Qu F et al. Analysis of the susceptibility to COVID-19 in pregnancy and recommendations on potential drug screening. European Journal of Clinical Microbiology & Infectious Diseaseshttps://doi.org/10.1007/s10096-020-03897-6.
4. McIntyre HD, Moses RG. The Diagnosis and Management of Gestational Diabetes Mellitus in the Context of the COVID-19 Pandemic. Diabetes Care 2020;43:1433–1434 | https://doi.org/10.2337/dci20-0026.
5. Australasian Diabetes in Pregnancy Society, Australian Diabetes Society, Australian Diabetes Educators Association, Diabetes Australia. Diagnostic testing for gestational diabetes mellitus (GDM) during the COVID 19 pandemic: antenatal and postnatal testing advice. Accessed 5 April 2020. Available from https://www.adips.org/documents/ COVID-19GDM Diagnosis 030420ADIPSADSADEADA for Website.
6. International Federation Gynecology and Obstetrics (FIGO). Non-Communicable Diseases and COVID-19: Statement from the FIGO Committee on Pregnancy and NCDs. Available at www.figo.org accessed at 30 march 2020.
7. Breslin N, Baptiste C, Gyamfi-Bannerman C et al. Coronavirus disease 2019 infection among asymptomatic and symptomatic pregnant women: Two weeks of confirmed presentations to an affiliated pair of New York City hospitals. Am J ObstetGynecol MFM 2020;2:100118.
8. Vintzileos WS, Muscat J, Hoffmann E et al. Screening all pregnant women admitted to labor and delivery for the virus responsible for coronavirus disease 2019. Am J ObstetGynecol 2020;223:284-6.
9. Xu L, Yang Q, Shi H et al. Clinical presentations and outcomes of SARS-CoV-2 infected pneumonia in pregnant women and health status of their neonates. Sci Bull (Beijing) 2020;65: 1537-42.

10. Blitz MJ, Grunebaum A, Tekbali A et al. Intensive care unit admissions for pregnant and nonpregnant women with coronavirus disease 2019. Am J ObstetGynecol 2020; 22(3):290-1.

11. Chin Med J (Engl). Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Trial Version 7)2020 May 5;133(9):1087–1095. doi: 10.1097/CM9.0000000000000819.

12. Allotey J, Stallings E, Bonet M, Yap M, Chatterjee S, Kew T et al. Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy: living systematic review and meta-analysis. the bmj | BMJ 2020;370:m3320 | doi: 10.1136/bmj.m3320.

13. Royal College of Obstetricians & Gynaecologists :Coronavirus (COVID-19) Infection in Pregnancy Information for healthcare professionals, Version 11. Available from: https://www.rcog.org.uk/ en/guidelines-research-services/guidelines/coronavirus-pregnancy.

14. Vallejo V, Ilagan JG. A Postpartum Death Due to Coronavirus Disease 2019 (COVID-19) in the United States. ObstetGynecol 2020 doi: 10.1097/AOG.0000000000003950.

15.Hantoushzadeh S, Shamshirsaz AA, Aleyasin A et al. Maternal Death Due to COVID-19 Disease. American journal of obstetrics and gynecology 2020 doi: 10.1016/j.ajog.2020.04.030.

16. Karami P, Naghavi M, Feyzi A et al. Mortality of a pregnant patient diagnosed with COVID-19: A case report with clinical, radiological, and histopathological findings. Travel Med Infect Dis 2020:101665. doi: 10.1016/j.tmaid.2020.101665.

17. Henderson J, Gao H, Redshaw M. Experiencing maternity care: the care received and perceptions of women from different ethnic groups. BMC Pregnancy Childbirth 2013; 13(1):196. doi: 10.1186/1471-2393-13-196.

18. Knight M, Bunch K, Vousden N, et al. Characteristics and outcomes of pregnant women admitted to hospital with confirmed SARS-CoV-2 infection in UK: national population based cohort study. BMJ 2020;369:m2107. doi: 10.1136/bmj.m2107.

19. Poon LC, Yang H, Kapur A, Melamed N, Dao B, Divakar H et al. Global interim guidance on coronavirus disease 2019 (COVID-19) during pregnancy and puerperium from FIGO and allied partners: Information for healthcare professionals. Int J GynecolObstet 2020; 149: 273–286. DOI: 10.1002/ijgo.13156.

20. Zarchia MK, Neamatzadeh H, Dastgheib SA, Abbasi H, Mirjalilid SR, Behforouz A et al. Vertical Transmission of Coronavirus Disease 19 (COVID-19)from Infected Pregnant Mothers to Neonates: A Review. Fetal and Pediatric Pathologyhttps://doi.org/10.1080/15513815.2020.174712.

21. Metzger BE. International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. Diabetes Care.2010; 33(3):676-82.

22. Hillier TA, Pedula KL, Schmidt MM, Mullen JA, Charles MA, Pettitt DJ. Childhood obesity and metabolic imprinting: the ongoing effects of maternal hyperglycemia. Diabetes Care 2007; 30(9):2287-92.

23. Metzger BE. Long-term outcomes in mothers diagnosed with gestational diabetes mellitus and their offspring. ClinObstetGynecol 2007;50(4):972-9.

24. Dabelea D, Hanson RL, Lindsay RS, et al. Intrauterine exposure to diabetes conveys risks for type 2 diabetes and obesity: a study of discordant sibships. Diabetes 2000;49:2208–2211.

25. Holmes VA, Young IS, Patterson CC, et al.; Diabetes and Pre-eclampsia Intervention Trial Study Group. Optimal glycemic control, preeclampsia, and gestational hypertension in women with type 1 diabetes in the Diabetes and Pre-eclampsia Intervention Trial. Diabetes Care 2011;34:1683–1688.

26. National Institute for Health and Care Excellence. Diabetes in Pregnancy: Management from Preconception to the Postnatal Period (NICE Guideline [NG3]). London 25 February, 2015. www.nice.org.uk/guidance/ng3.

27.O'Sullivan J, Mahan C. Criteria for the oral glucose tolerance test in pregnancy. *Diabetes* 1964;**13**:278–285.

28. Sacks DA, Hadden DR, Maresh M, et al.; HAPO Study Cooperative Research Group.Frequency of gestational diabetes mellitus at collaborating centers based on IADPSG consensus panel-recommended criteria: the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study. *Diabetes Care* 2012;**35**:526–528.

29. Carpenter MW, Coustan DR. Criteria for screening tests for gestational diabetes. Am J ObstetGynecol1982;144:768–77.

30. Committee on Practice Bulletins—Obstetrics. Practice Bulletin No. 190: gestational diabetes mellitus. *ObstetGynecol* 2018;**131**:e49–e64.

31.Thangaratinam S, Cooray SD, Sukumar N, Huda MSB, Devlieger R, Benhalima K, et al. Clinical Practice Guidance. Endocrinology in the time of COVID-19:Diagnosis and management of gestational diabetes mellitus. European Journal of Endocrinology.2020; 183: G49–G56.

32. Royal College of Obstetricians and Gynaecologists. Guidance for Maternal Medicine in the Evolving coronavirus (COVID-19) Pandemic – Information for Healthcare Professionals ch. 30/03/2020, pp. 1–40. London: RCOG, 2020.

33. Khambalia AZ, Ford JB, Nassar N, Shand AW, McElduff A & Roberts CL. Occurrence and recurrence of diabetes in pregnancy. Diabetic Medicine.2013 30 452–456. https://doi.org/10.1111/ dme.12124.

34. Kim C, Berger DK, Chamany S. Recurrence of gestational diabetes mellitus: a systematic review. Diabetes Care 2007 30 1314–1319. https://doi.org/10.2337/dc06-2517 .

35. Schwartz N, Green MS, Yefet E & Nachum Z. Modifiable risk factors for gestational diabetes recurrence.Endocrine.2016;54;714–722. https://doi.org/10.1007/s12020-016-1087-2.

36. American College of Obstetricians and Gynecologists (ACOG). COVID-19 FAQs for obstetricians-gynecologists, gynecology: Should individuals delay attempts to become pregnant during COVID-19 pandemic? REVISED. *Last updated September 28, 2020.* Available at: https://www.acog.org/clinical-information/physician-faqs/covid19-faqs-for-ob-gyns-gynecology. Accessed 19 Oct 2020.

37. Smoking in Pregnancy Challenge Group. Review of the Challenge. 2018.

38. International Consultation on Environmental Tobacco Smoke (ETS) and Child Health. Consultation Report, WHO, 1999.

39. Vardavas C. Nikitara K. COVID-19 and Smoking: A systematic review of the evidence. Tob. Induc. Dis. 2020;18(March):20.

40. Liu W. Tao Z-W. Lei W. Ming-Li Y. Kui L. Ling Z. Analysis of factors associated with disease outcomes in hospitalized patients with 2019 novel coronavirus disease. Chinese Medical Journal: February 28, 2020.

41.Dørheim SK, Bjorvatn B, Eberhard-Gran M. Insomnia and depressive symptoms in late pregnancy: A population-based study. *Behav Sleep Med*. 2012;**10**:152–166.

42.Chua M, Lee J, Sulaiman S, Tan HK. From the frontlines of COVID-19 – How prepared are we as obstetricians: A commentary. *BJOG*. 2020; [Epub ahead of print].

43. Alfadhli EM. Gestational diabetes mellitus. Saudi Med J 2015;36(4):399-406.

44. Murphy HR. Managing Diabetes in Pregnancy Before, During, and After COVID-19 Diabetes Technology &Therapeutics 2020;22(6):454-61.

45. Maxwell C, McGeer A, Tai KFY, Sermer M. No 225-Management guidelines for obstetric patients and neonates born to mothers with suspected or probable severe acute respiratory syndrome (SARS). J ObstetGynaecol Can. 2017;39:e130–e137.

46. Zhao W, Zhong Z, Xie X, Yu Q, Liu J. Relation between chest CT findings and clinical conditions of coronavirus disease (COVID-19) pneumonia: A multicenter study. AJR Am J Roentgenol. 2020:1–6 [Epub ahead of print.

47. American Diabetes Association. 14. Management of diabetes in pregnancy: standards of medical care in Diabetes-2020. Diabetes Care 2020; 43(Suppl.1):S183–S192. https://doi.org/10.2337/dc20-S014.

48. Yang H, Wang C, Poon LC. Novel coronavirus infection and pregnancy. *Ultrasound Obstet Gynecol*. 2020; [Epub ahead of print].

49.Global interim guidance on coronavirus disease 2019 (COVID-19) during pregnancy and puerperium from FIGO and allied partners: Information for healthcare professionals Liona C. Poon Huixia Yang Anil Kapur Nir Melamed Blami Dao Hema Divakar H. David McIntyre Anne B. Kihara Diogo Ayres-de-Campos Enrico M. Ferrazzi Gian Carlo Di Renzo Moshe Hod.

50.World Health Organisation, Breastfeeding advice during the COVID-19 outbreak http://www.emro.who.int/noncommunicablediseases/campaigns/breastfeeding-advice-during-the-covid-19-outbreak.html.

Chapter 10

Management of endocrine and metabolic disorders during COVID- 19 pandemic

Dr. Moinul Islam

The novel coronavirus of 2019 causes the illness known as coronavirus disease-19 (COVID-19) and is responsible for the unprecedented pandemic starting in 2020. Research is emerging that patients with some endocrine and metabolic conditions be at higher risk of acquiring COVID-19 and/or developing complications from the disease. At this moment we are all in the midst of national and locally driven crisis management plans that understandably impacting our routine practice as well as acute care management. So we fell that it will be time of the essence to highlight the common practical problems of our discipline that we are facing every day in this moment. Herein, we have summarized the best possible management strategies of common endocrine disorders amid the constraints imposed by the ongoing COVID-19 pandemic.

10.1: Thyroid disease and coronavirus (COVID-19)

Hypo and hyperthyroidism are two common thyroid dysfunction which are usually treated in an outpatient setting and their management is heavily reliant on biochemical testing, imaging and nuclear medicine procedures. Moreover, some of the commonly used therapies may pose diagnostic and therapeutic challenges for healthcare practitioners and patients during this COVID situation[1].

10.1.1: How will COVID-19 and thyroid dysfunction impact each other?

There is no evidence that patients with existing autoimmune thyroid disease are more susceptible to contracting viral illnesses including infection with SARS-CoV-2 or that they are at risk of developing more severe COVID-19 disease. But patients with Graves' ophthalmopathy who are actively undergoing immunosuppressive therapy, are likely to be at increased risk of developing severe corona virus infection [2].

10.1.2: Does control of thyroid disease affect infection risk?

There is no evidence that those with poorly controlled thyroid disease are more likely to contract viral infections in general. However, it is possible that patients with uncontrolled thyroid disease (especially thyrotoxicosis) may be at higher risk of complications (for example thyroid storm) from any infection. We strongly recommend that patients with thyroid disease continue taking their thyroid medication(s) to reduce this risk [2].

10.1.3: Management of hyperthyroidism:

10.1.3.1: How can we diagnose a patient with hyperthyroidism?

Hyperthyroidism should be diagnosed on the basis of clinical suspicion and characteristic biochemical feature. To identify the underlying an etiology, thyroid ultrasonography and TSH-receptor antibodies (TRAb) would be the important tools (if resources are available) as isotope scanning very difficult to perform during the COVID-19 crisis. Evaluation of a thyroid nodule can usually be postponed, unless indicating a high-risk for malignancy [1].

10.1.3.2: How can we treat a patient with hyperthyroidism?

Management of hyperthyroidism usually requires frequent monitoring of thyroid function test. Currently, or in the future, it may be difficult or impossible to perform such biochemical monitoring; in this exceptional circumstance, block & replace regimen (BRRs) would be the most ideal initial therapy for new or relapsed hyperthyroidism patients[2]. Start carbimazole (20-40 mg/d) or methimazole (15-30 mg/d) and continue for 4 to 6 weeks. Then add levothyroxine (75mcg od if BW $\leq$ 55kg; 100mcg od if BW > 55kg); while continue the carbimazole (40mg/d) or methimazole (30mg/d) for all patients. After 6 months, assessment in endocrinology clinic based on thyroid status with re-evaluation of available treatment option. If patients develop significant symptoms during this period, thyroid function should be tested and discuss with an endocrinologist for further management [1].

10.1.3.3: Are individuals taking antithyroid drugs at higher risk of infection?

Antithyroid drugs are not known to increase the risk of infection with COVID-19 or developing more severe disease, unless they result in neutropenia. COVID-19 infected patients can continue ATDs unless neutrophil count of $<1.0 \times 10^9$/L). Lymphopenia is not an indication to stop ATDs [2].

10.1.3.4: How should we advise patients who are at risk of neutropenia due to ATD therapy?

Symptoms of neutropenia may overlap with symptoms of COVID-19 infection. We recommend that patients on antithyroid drugs (ATDs) with any symptoms suggestive of neutropenia should STOP the ATD and have an urgent complete blood count (CBC) to be performed. If it is not possible to check CBC then stop ATD at the onset of onset of symptoms suggestive of neutropenia. Restart one week later if symptoms have resolved. If symptoms worsen during the period off ATDs or recur after recommencing the drug, the patient should seek urgent medical attention[2].

10.1.3.5: How should we advise patients on steroid treatment for thyroid eye disease?

Graves's ophthalmopathy patients on steroid at immunosuppressive dosages or other immunosuppressive agents are at very high risk of severe illness from coronavirus and should be advised to self-isolate [2].

10.1.3.6: Should we advise hyperthyroidism patients for surgery or radioiodine therapy?

- **Surgical treatment of hyperthyroidism:** Elective surgical procedures have been postponed in most countries for benign disease during this outbreak. But uncontrolled thyrotoxicosis patients who have developed significant adverse effects from antithyroid drugs may require urgent thyroid surgery[2].
- **Radioiodine therapy for hyperthyroidism:** Elective radioiodine therapy has been postponed in most countries both for benign and for malignant thyroid diseases. But it is crucial to identify patients who have undergone 131-I treatment for hyperthyroidism in the earlier months of COVID -19 pandemic and to adopt a low threshold for commencing levothyroxine therapy if hypothyroid symptoms develop [2].

10.1.4: Management of hypothyroidism:

- We do not suggest any particular changes in diagnosis and treatment of hypothyroidism during the COVID -19 crisis [3]. Patient should continue the same form and dosage of levothyroxine therapy. Regular blood test monitoring may be difficult, but when patients on thyroid hormone replacement feel significantly unwell or if there are significant weight changes, thyroid function testing (preferably TSH and FT4) is recommended [1].

10.1.5: How can we manage thyroid dysfunction (hypo or hyperthyroidism) during pregnancy?

10.1.5.1: Pregnant women with hypothyroidism:

Pregnant women are at increased risk of developing more severe COVID-19 disease [4]. Expecting mothers with hypothyroidism should continue the levothyroxine by doubling the current dose on 2 days in a week as soon as the pregnancy test become positive. Ideally, thyroid function should be checked on a regular basis [4, 5]. But considering the present situation the frequency of testing may be reduced in whom thyroid function is stably controlled [1].

10.1.5.2: Pregnant women with hyperthyroidism:

The usual principles of treatment with ATD, preferably with propylthiouracil before and in the first trimester of pregnancy, should be adhered to and the lowest possible dose of ATDs should be used [6]. Measurement of TRAb and regular thyroid function testing is advised in those treated with ATDs, available resources and infrastructure allowing [1].

10.1.6: How should we manage sub-acute thyroiditis (SAT) during COVID-19 pandemic?

Several case report has published relating the thyroiditis and SARS-CoV-2 [7]. We suggest for a physical consultation (as potential for harm may outweigh the risk of pandemic with appropriate precaution) and management as per standard treatment protocols [8].

10.1.7: What should be appropriate advice for patients with thyroid cancer?

Surgery should be done with no delay in patients with significant symptoms and/or rapidly progressive disease. But for 'low risk' patients, surgery may be delayed until for a favorable time to proceed [9].Many centres ceased radioactive iodine treatment in the early days of the pandemic due to a combination of increased admissions and COVID-19 safety concerns. In most cases, radioiodine therapy is not urgent and can be safely delayed [9].

10.1.8: What should be the appropriate advice for patients with thyroid nodule?

- **Euthyroid nodular goiter with benign sonological features:** Defer FNAC. Educate the patient for symptoms and signs of obstruction or malignancy. Follow-up with teleconsultation if any of the above symptomatology is present [8].
- **Euthyroid thyroid nodule with suspicious/malignant sonology:** Consider for serum calcitonin. If nodule <1 cm in size with sonological features of malignancy, consider deferring FNAC following a risk-benefit discussion with the patient. For lesions ≥1 cm and those with high-risk feature PTMC, a physical consultation may be considered and decision on FNAC may be discussed [8].

10.1.9: How should endocrine services for thyroid dysfunction be remodeled in the acute crisis?

- **Telephone and video consultations:**

  Endocrinologists can provide support in the form of advice and guidance letters, telephone advice, virtual outpatient clinics or face-to - face appointments, as dictated by the clinical urgency and availability of staff resources.

- **Remote monitoring services:**

  These services would be helpful for patients on a prolonged course or long-term ant thyroid drugs, for those on thyroid hormone replacement for endogenous or iatrogenic hypothyroidism and for close follow-up of patients who have undergone radioactive iodine treatment. These services should continue if staff are available to perform them.

- **Face-to-face appointments:**

We suggest only for the following patients group: new-onset or worsening thyroid eye disease, those with enlarging goiters causing symptoms of obstruction and patients who are not responding to standard treatment measures [1].

References:

1. Boelaert K, Visser WE, Taylor PN, Moran C, Léger J & Persani L. Clinical Practice Guidance. Endocrinology in the time of COVID-19: Management of hyperthyroidism and hypothyroidism. Eur J Endocrinol. 2020; 183 (2):G33–G39.
2. British Thyroid Association (BTA) and the Society for Endocrinology (SfE). BTA/SFE statement regarding issues specific to thyroid dysfunction during the COVID -19 pandemic. Available from https://www.british-thyroidassociation.org/sandbox/bta2016/ management-of-thyroid-dysfunction-during-covid-19_final.pdf (Accessed 3 Sep 2020).
3. Rajput R, Agarwal A, Ganie MA, Bal CS, Sharma DC, Seshadri K, Puttiyaveettil J, Kotwal N, Kumar KMP, Jayakumar RV, Bajaj S, Joshi S, Chowdhury S, & Ghosh S. Coronavirus disease 2019 and thyroid disease: Position statement of Indian Thyroid Society. Thyroid Research & Practice. 2020; 17(1):P4-6.
4. RCOG. Coronavirus (COVID-19) Infection in Pregnancy. Information for healthcare professionals. Version 11: Published Friday 24 July 2020. Available from https: //www.rcog.org.uk/globalassets/documents/guidelines/2020-04-17-coronavirus-covid-19-infection-in-pregnancy.pdf.
5. Alexander EK, Pearce EN, Brent GA, Brown RS, Chen H, Dosiou C, Grobman WA, Laurberg P, Lazarus JH, Mandel SJ et al. 2017 Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease During pregnancy and the postpartum. Thyroid. 2017; 27:315–389. (https://doi.org/10.1089/ thy.2016.0457).

6. Korevaar TIM, Medici M, Visser TJ & Peeters RP. Thyroid disease in pregnancy: new insights in diagnosis and clinical management. Nature Reviews: Endocrinology. 2017; 13:610-622. (https://doi.org/10.1038/nrendo.2017.93).
7. Muller I, Cannavaro D, Dazzi D, Covelli D, Mantovani G, Muscatello A et al. SARS-CoV-2 related atypical thyroiditis. THE LANCET Diabetes & Endocrinology. September 01, 2020; 8(9):P739-741.
8. John M, Veetil VM. Management of thyroid diseases during pandemic: A narrative review. Thyroid Res Pract. 2020;17(2):62-9.
9. Thyroid Cancer Forum UK, the Society for Endocrinology and the British Thyroid Association. Thyroid cancer and coronavirus (COVID-19). Available from. https://www.btf-thyroid.org/thyroid-cancer-and-coronavirus [Accessed on 29 Aug 2020].

10.2: Adrenal gland disorder and COVID-19

Data published so far have not considered the possibility of direct aggression towards the adrenal gland by this virus in previously healthy subjects [1]. Viral, bacterial and fungal sepsis may cause hemorrhage, necrosis or thrombosis at the adrenal level with consequent acute hypoadrenalism. Moreover, recent findings have indicated the possibility of venous thrombo-embolism in COVID-19 patients [2]. Thus, it has to be considered that an acute adrenal insufficiency may also be due to a thrombotic event at the adrenal level in COVID-19 patients. This could cause an acute adrenal insufficiency with consequent shock and worsening to severe respiratory distress. A timely screening for HPA axis function could allow adequate replacement therapy avoiding severe shock[3]. SARS (and COVID-19) might affect the hypothalamic pituitary-adrenal (HPA) axis as well. Hypothalamic and pituitary tissues do express ACE2 and can therefore be viral targets. Nevertheless, frank central hypocortisolism has never been documented in patients with active SARS (or COVID-19)[4].

10.2.1: Adrenal insufficiency and COVID-19

10.2.1.1: What is mean by adrenal insufficiency?

We define, primary adrenal insufficiency (PAI) as a loss of function of the adrenal itself, mostly due to autoimmune adrenalitis or other causes including congenital adrenal hyperplasia, bilateral adrenalectomy and adrenoleukodystrophy. Secondary adrenal insufficiency (SAI) applies to hypothalamic or pituitary disease or due to chronic exogenous glucocorticoid therapy for treatment of other conditions.

10.2.1.2: Are individuals with adrenal insufficiency at higher risk of infection?

Patients with adrenal insufficiency (both primary and secondary) are at increased risk of COVID -19 [5, 6].They also have higher risk of development of adrenal crisis to be triggered by the infection [7, 8].

10.2.1.3: How should we manage patients with an established diagnosis of adrenal insufficiency?

A. General measures:

Patients with adrenal insufficiency just like patients with diabetes mellitus, need to be extra cautious amid the ongoing pandemic. We highlight the need for education (sick day rules that is increase their usual glucocorticoid replacement doses during intercurrent illness, stringent social distancing rules), equipment (sufficient glucocorticoid supplies, steroid emergency self-injection kit) and empowerment (steroid emergency card, COVID-19 guidelines) to prevent adrenal crises. Self-management support can be facilitated and communicated by mailshot, video, text, email phone call or videoconferencing, as appropriate [9].

B. Glucocorticoid therapy for adrenal insufficiency (AI) patients with suspected or confirmed COVID-19:

Adrenal crisis is a life-threatening medical condition and remains an important cause of death in patients with AI. We recommended that if patients with adrenal insufficiency develops signs and symptoms suggestive of COVID-19 should seek medical advice regarding the management of suspected or confirmed COVID19 infection along with sick day rules for steroid therapy either over the internet or by a phone call [10]. In the presence of any warning signs or an inability to administer oral glucocorticoid doses, we recommend that patients should immediately seek an Emergency service and receive 100 mg hydrocortisone by intravenous injection [11]. We recommended that if adrenal insufficiency patients develop COVID-19 -related ARDS, their glucocorticoid replacement should never be interrupted, but continued at a major stress dose (200 mg/24 h) until clinical improvement [12].

Patients with AI requiring high dose steroid are more prone to develop hyperosmolar hyperglycemic state or diabetic ketoacidosis. We recommended here to frequent monitoring of blood glucose and basal bolus therapy of insulin for blood glucose control. For the patients who develop hyperglycemic emergencies, we recommended to use standard insulin infusion therapy.

Recommendation of glucocorticoid therapy for adrenal insufficiency (AI) patients with suspected or confirmed COVID-19 diagnosis (Table 1)[9, 10 & 12].

Table 1. Glucocorticoid therapy for adrenal insufficiency (AI) in patients with suspected or confirmed COVID-19.

Clinical scenario	Suggested management
Mild symptoms:	
Signs and symptoms suggestive of COVID-19 (fever, cough, sore throat, loss of sense of smell or taste, body ache, fatigue, diarrhoea)	Start hydrocortisone 20 mg orally 6 hourly. Patients on modified release hydrocortisone should switch to immediate release hydrocortisone and take 20 mg orally 6 hourly.
	5–15 mg daily prednisolone should split into 10 mg prednisolone every 12 h. If on >15 mg prednisolone; should continue their usual dose but split into two equal doses of at least 10 mg each.
	If on fludrocortisone, continue at usual dose (0.05-0.1mg/day)
	Take paracetamol 1000 mg every 6 h for fever
	Rest, drink regularly and monitor urine output
	Request medical advice on the suspected COVID-19 infection
Warning symptoms:	
Dizziness, intense thirst, drowsiness, confusion, lethargy; vomiting; severe diarrhea, breathlessness, respiratory rate >24/min	Immediately inject 100 mg hydrocortisone (IV/ IM) and emergency search for treatment and transfer to Hospital
	If patients cannot be taken or kept in hospital, then they should take 50 mg hydrocortisone every 6 h orally (if possible IV) at home.
Clinical scenario	**Suggested management**
At hospital:	
	Hydrocortisone 100 mg IV injection followed by continuous iv infusion of 200 mg hydrocortisone/24 h (alternatively 50 mg/ 6 h IV or IM bolus injection).
	Pause fludrocortisone
	Continuous IV fluid resuscitation with isotonic saline; regularly check blood glucose, urea and electrolytes.
At clinical improvement:	Gradual tapering of stress dose hydrocortisone down to double regular replacement dose at time of discharge (endocrinologist to advise). Re-start usual fludrocortisone dose in adults when total daily hydrocortisone dose <50 mg

10.2.1.4: How should we follow -up the adrenal insufficiency patients during COVID crisis?

We recommend that otherwise healthy patients should be followed-up at intervals of 6–12 months by telephone or videoconferencing. Investigations should be reserved for patients with clinical signs of hypotension. Glucocorticoid replacement therapy is based on the patient's clinical performance and ability to cope with daily stress [13].

References:

1. Isidori AM, Arnaldi G, Boscaro M, Falorni A, Giordano C, Giordano R, et al. COVID-19 infection and glucocorticoids: update from the Italian Society of Endocrinology Expert Opinion on steroid replacement in adrenal insufciency. J Endocrinol Invest. 2020. https://doi.org/10.1007/s40618-020-01266-w 4.

2. Porfidia A, Pola R. Venous thromboembolism in COVID-19 patients. Journal of Thrombosis and Haemostasis. 2020 Jun 1; 18(6). https://doi.org/10.1111/jth.14842.

3. Bellastella G, Maiorino MI, & Esposito K. Endocrine complications of COVID-19: what happens to the thyroid and adrenal glands? J Endocrinol Invest. 2020. https://doi.org/10.1007/s40618-020-01311-8.
4. Pal R. COVID-19, hypothalamo-pituitary-adrenal axis and clinical implications. Endocrine. 2020 April 28; 68: 251-252. https://doi.org/10.1007/s12020-020-02325-1.

5. Tresoldi AS, Sumilo D, Perrins M, Toulis KA, Prete A, Reddy N, Wass JAH, Arlt W & Nirantharakumar K. Increased infection risk in Addison's disease and congenital adrenal hyperplasia. J Clin Endocrinol Metab. 2020 February 1; 105(2). (https://doi. org/10.1210/clinem/dgz006.
6. Stewart PM, Biller BM, Marelli C, Gunnarsson C, Ryan MP & Johannsson G. Exploring inpatient hospitalizations and morbidity in patients with adrenal insufficiency. J Clin Endocrinol Metab. 2016; 101: 4843–4850. (https://doi.org/10.1210/ jc.2016-2221).

7. Arlt W & Society for Endocrinology Clinical Committee. Society for Endocrinology Endocrine Emergency Guidance: emergency management of acute adrenal insufficiency (adrenal crisis) in adult patients. Endocrine Connection. 2016; 5(5): G1–G3. (https://doi. org/10.1530/EC-16-0054)

8. Allolio B. Extensive expertise in endocrinology: adrenal crisis. European Journal of Endocrinology. 2015; 172(3): 115–124. (https://doi. org/10.1530/EJE-14-0824).
9. Arlt W, Baldeweg SE, Simon HS, Pearce SHS & Simpson HL. Clinical Practice guidance. Endocrinology in the time of COVID- 19: Management of adrenal insufficiency. Eur J Endocrinol. 2020 July; 183 (1):G25-G32. doi: 10.1530/EJE-20-0361.
10. Almeida MQ, Mendonca BB. Adrenal Insufficiency and Glucocorticoid Use During the COVID-19 Pandemic. Clinics. 2020; 75:e2022. DOI: 10.6061/clinics/2020/e2022.
11. Pal R, & Bhadada, SK. Managing common endocrine disorders amid COVID-19 pandemic. Diabetes & Metabolic Syndrome: Clinical Research & Reviews. 2020 June; 14(5):767-771. https://doi.org/10.1016/j.dsx.2020.05.050.
12. Prete A, Taylor AE, Bancos I, Smith DJ, Foster MA, Kohler S, etal. Prevention of Adrenal Crisis: Cortisol Responses to Major Stress Compared to Stress Dose Hydrocortisone Delivery. J Clin Endocrinol Metab. 2020 July; 105(7):dgaa133. doi:10.1210/clinem/dgaa133.
13. Bancos I, Hahner S, Tomlinson J & Arlt W. Diagnosis and management of adrenal insufficiency. Lancet: Diabetes and Endocrinology. 2015; 3:216–226. (https://doi.org/10.1016/S2213- 8587(14)70142-1).

10.2.2: Management Cushing's syndrome during COVID-19

10.2.2.1: Are Cushing's syndrome patients at higher risk of infection?

Patients with active Cushing's syndrome (CS) are immunocompromised and are at a high risk of viral and other infections [1]. So rapid normalization of cortisol secretion [2] and active management of diabetes and hypertension are needed to minimize the risk of infection [3].

10.2.2.2: How should we diagnose Cushing's syndrome?

We suggest to investigate a patients with typical features of Cushing's syndrome [4]. If clinical features are mild, or in doubt, investigation should be deferred for 3 to 6 months after a repeat clinical assessment and/or until SARS-CoV-2 viral prevalence has significantly diminished. Those with moderate and severe clinical disease must be investigated and managed urgently.

Patients with adrenal incidentaloma should only be investigated for hypercortisolism at times of high SARS-CoV-2 viral prevalence if radiological features suggest adrenocortical cancer or clinical signs suggest moderate to severe Cushing's syndrome [5].

We suggest to do overnight dexamethasone suppression test, 24-h urinary free cortisol along with basal plasma ACTH at the beginning of the investigation. Salivary cortisol tests should be avoided.

Then we should go for CT scan of thorax, abdomen and pelvis to identify adrenocortical cancer or ectopic ACTH syndrome that may need urgent surgery.

We defer to do pituitary MRI unless there is visual compromise. As our target is to postpone surgical intervention and to start medical treatment for at least 3-6 months during this high prevalence of COVID infection [2].

10.2.2.3: What should be the treatment protocol of Cushing's syndrome patients during this COVID crisis?

We suggest medical therapy as a first line of treatment protocol and steroidogenesis inhibitors will remain the mainstay of therapy. Wherever available, metyrapone may be preferred over ketoconazole considering its faster onset of action and less drug-drug interactions. In the absence of provisions for frequent biochemical monitoring, a 'block-and replace' regimen may be preferred when using steroidogenesis inhibitors [6]. The suggested full 'block and replace' regime[2] with regular telephone monitoring of symptoms is shown in Table 2.

Table 2. 'Block-and replace' regimen for Cushing's syndrome patients during COVID crisis.

<table>
<tr><td colspan="4">Medication:</td></tr>
<tr><td>Block</td><td>Day 1 to 3</td><td>Day 4 to 6</td><td>Day 7 Onwards</td></tr>
<tr><td>Metyrapone or</td><td>500mg TID</td><td>1000mg TID</td><td>1000mg QID</td></tr>
<tr><td>Ketoconazole</td><td>200mg TID</td><td>400mg TID</td><td>400mg TID</td></tr>
<tr><td>Replacement</td><td>Glucocorticoids</td><td colspan="2">Added as for adrenal insufficiency</td></tr>
<tr><td rowspan="2">Hydrocortisone
Or</td><td></td><td colspan="2" rowspan="2">20-30mg in divided doses 2-3 times daily</td></tr>
<tr><td></td></tr>
<tr><td rowspan="2">Dexamethasone
Or</td><td></td><td colspan="2" rowspan="2">0.2-0.5mg OD</td></tr>
<tr><td></td></tr>
<tr><td>Prednisolone</td><td></td><td colspan="2">3-7.5mg OD</td></tr>
</table>

Monitoring:

1. 9.00am serum cortisol pre-dose of Metyrapone or Ketoconazole or Glucocorticoid- aim for lowest possible number and/or

2. 24 hour UFC- Switch Hydrocortisone to Dexamethasone or Prednisolone day before and day of collection- aim for lowest possible number

3. While adequate block confirmed continue medications with intermittent or no monitoring during COVID-19 crisis

Co-morbidities should be treated as for standard of care. Patients with severe Cushing's syndrome should receive prophylaxis for Pneumocystis jivoreci wit co-trimoxazole. It is recommended that treatment with low molecular weight heparin be given until definitive treatment has been achieved, especially in patients with moderate to severe disease [7].If a patient on medical treatment for Cushing's syndrome is infected by SARS-C0V-2, it is recommended that stress doses of glucocorticoid are given [2].

We prefer to avoid surgical intervention until COVID situation improved. But surgery may be considered in the following situations: visual symptoms, intolerance or failure of medical therapy and cushing's syndrome due to cancer where risk and benefit ratio should be checked[8,9].

References:

1. AACE Position statement: coronavirus (COVID-19) and people with adrenal insufficiency and Cushing's syndrome. [Internet]. Cited 2020 May 22]. Available from: https://www.aace.com/recent-news-and-updates/aace-positionstatement-coronavirus-covid-19-and-people-adrenal.

2. Newell-Price J, Nieman L, Reincke M, Tabarin A. Clinical Practice Guidance. Endocrinology in the time of COVID-19: Management of Cushing's syndrome. Eur J Endocrinol. 2020; 183(1):G1-G7. [cited 2020 May 27]; Available from: https://eje.bioscientifica.com/view/journals/eje/aop/eje-20-0352/eje-20-0352.xml.
3. Pal R, Bhadada SK. COVID-19 and non-communicable diseases. Postgrad Med J. 2020 Jul; 96(1137):429-430.

4. Nieman LK, Biller BM, Findling JW, Newell-Price J, Savage MO, Stewart PM & Montori VM. The diagnosis of Cushing's syndrome: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2008; 93 1526–1540. (https://doi. org/10.1210/jc.2008-0125].
5. Fassnacht M, Arlt W, Bancos I, Dralle H, Newell-Price J, Sahdev A, Tabarin A, Terzolo M, Tsagarakis S & Dekkers OM. Management of adrenal incidentalomas: European Society of Endocrinology Clinical Practice Guideline in collaboration with the European Network for the Study of Adrenal Tumors. Eur J Endocrinol. 2016; 175:G1–G34. (https://doi.org/10.1530/EJE-16-0467).
6. Young J, Bertherat J, Vantyghem MC, Chabre O, Senoussi S, Chadarevian R, et al. Hepatic safety of ketoconazole in Cushing's syndrome: results of a Compassionate Use Programme in France. Eur J Endocrinol. 2018; 178:447-58.

7. Nieman LK, Biller BM, Findling JW, Murad MH, Newell-Price J, Savage MO, Tabarin A & Endocrine Society. Treatment of Cushing's syndrome: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2015; 100(8):2807–2831. (https://doi.org/10.1210/jc.2015-1818).
8. Patel ZM, Fernandez-Miranda J, Hwang PH, Nayak JM, Dodd RL, Sajjadi H & Jackler RK Precautions for endoscopic transnasal skull base surgery during the covid-19 pandemic. Neurosurgery 2020 In press. (https://doi.org/10.1093/neuros/nyaa125).
9. NICE Guidelines NG161. COVID-19 rapid guideline: delivery of systemic anticancer treatments, 2020. (available at: https://www.nice.org.uk/guidance/ng161).

10.3: Management of pituitary tumors during COVID-19

10.3.1: What is the impact of COVID-19 on patients with pituitary tumors?

Currently there is no evidence that pituitary tumors per se affect the immune system, apart from corticotropinomas [1]. Nevertheless, a number of patients with pituitary tumors have co-morbidities that can portend a poor prognosis in COVID-19 (e.g. hypopituitarism, diabetes mellitus, hypertension, obesity, cardiovascular diseases) [2].

10.3.2: What will be the treatment protocol in patients with preexisting (or known) pituitary conditions?

As our aim is to defer surgery so far possible; medical therapy will be our choice of treatment until otherwise. Electrolyte and water imbalances can occur in COVID-19 infection due to insensible loss caused by high fever and tachypnea, gastrointestinal loss such as vomiting and diarrhea, as well as the inability to take adequate fluids due to an impaired level of consciousness [3]. Hypokalemia had been documented which has been attributed to upregulation of the RAAS by degradation of ACE2 by SARS-CoV-2 with increased renal loss of potassium [4]. Clinicians must be vigilant regarding possible electrolyte imbalances and should titrate any corticosteroid or desmopressin doses according to serum sodium, and osmolality. Convert to parenteral form of desmopressin (IV/IM) if intranasal route is not feasible [3]. Table 3 shows Desmopressin dose equivalents.

Table 3. Desmopressin dose equivalents

Tablets	**Spray**	**Injections**
100 µg	2.5 µg	NA
200 µg	5.0 µg	<0.5 µg
400 µg	10.0 µg	<1.0 µg

Patients with acromegaly having no compressive symptoms can be managed in the interim period with long acting somatostatin-receptor ligands (SRLs), pegvisomant and/or dopamine agonists. Dose titration and follow up can be done through virtual clinics. Injectable long-acting SRLs are preferable but pegvisomant or dopamine agonist at high doses may also applicable.

IGF-I measurement whenever it can be safely arranged [5]. Regarding growth hormone deficiency, Continue on the same dose of growth hormone in those with established growth hormone deficiency [5].

Hyperprolactinemia and Macroprolactinoma causing visual compromise should be initially treated with dopamine agonists, preferably cabergoline. Dose titration should be based on tolerability of the agents and improvement of symptoms. Follow up of visual dysfunction should be done 2 -3 weeks after initiation of treatment by virtual visits or by formal visual field assessment [5].

In hypogonadism, temporary discontinuation of testosterone may be possible if medication is not available or changing to an alternative is possible (e.g. intramuscular injections to testosterone gel). Estrogen may be Convert to transdermal formulations as the thrombosis risk is lower with transdermal compared to oral oestrogen [6].

References:

1. Stewart PM, Biller BMK, Marelli C, Gunnarsson C, Ryan MP, Johannsson G. Exploring inpatient hospitalizations and morbidity in patients with adrenal insufficiency. J Clin Endocrinol Metab. 2016; 101:4843-50.https://doi.org/10.1210/jc.2016-2221.
2. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X et al. Clinical course and risk factors for mortality of adult in patients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020 395 1054–1062. (https://doi.org/10.1016/S0140-6736(20)30566-3).
3. Baldeweg SE, Ball S, Brooke A, Gleeson HK, Levy MJ, Prentice M, et al. Society for endocrinology clinical guidance: Inpatient management of cranial diabetes insipidus. Endocr Connect. 2018; 7(7):G8-G11.doi:10.1530/EC-18-0154.
4. Chen dong, Li X, song qifa, Hu C, Su F, Dai J. Hypokalemia and Clinical Implications in Patients with Coronavirus Disease 2019 (COVID-19). medRxiv. January 2020:2020.02.27.20028530. doi:10.1101/2020.02.27.20028530].
5. Fleseriu M, Karavitaki N, Dekkers OM. Clinical Practice Guidance. Endocrinology in the time of COVID-19: management of pituitary tumours. Eur J Endocrinol. 2020; 183(1):G17-G23.[cited 2020 May, 27]; Available from: https://eje.bioscientifica.com/view/journals/eje/aop/eje-20-0473/eje-20 0473.xml.
6. Somasundaram NP, Ranathunga I, Ratnasamy V, Alwis Wijewickrama PS, Dissanayake HA, Yogendranathan N, et al. The Impact of SARS-Cov-2 Virus Infection on the Endocrine System. Journal of the Endocrine Society. 2020; bvaa082. https://doi.org/10.1210/jendso/bvaa082.

10.4: COVID-19 and parathyroid conditions

10.4.1: Are hypo- or hyper-parathyroidism patients more susceptible to COVID-19 infection than other people?

Although there is no evidence that primary hyper- or hypo-parathyroidism are risk factors for COVID-19. Patients with chronic renal impairment and parathyroid dysfunction may be at risk for COVID-19 due to the underlying renal disease [1].

10.4.2: How should we manage hypoparathyroidism?

Patients with hypoparathyroidism should continue calcium and active vitamin D supplements. The availability of calcium supplements must be ensured to prevent life-threatening complications of hypocalcemia. Patients should have access to their endocrine service provider if they develop symptoms of hypocalcemia, and treatment should be given based on the symptoms and signs, pending laboratory confirmation of hypocalcemia. Similarly, hypomagnesemia should be corrected for optimal calcium and vitamin D metabolism. In addition, they should be made conversant with the sick-day guidelines, specially the need to double the dose of calcium/vitamin D during periods of stressful situations [2].

10.4.3: How should we manage hyperparathyroidism?

Patients with diagnosed primary hyperparathyroidism (PHPT) can be managed conservatively and surgery can be defer until the patient is severely symptomatic and/or serum calcium >3.25 mmol/l. Patients should be educated to maintain good a hydration status at home. Patients with PHPT developing COVID- 19 need to be cautious about insensible fluid loss (fever, tachypnea) and should increase fluid intake accordingly. Severe hypercalcemia may necessitate hospital admission and start treatment with parenteral fluids. However, overzealous fluid administration should be avoided asit can increase the chances of acute respiratory distress syndrome. Pharmacological modalities like calcitonin, zoledronic acid and denosumab can be safely used [3].

10.4.4: What is the current the recommendation for vitamin D in COVID-19?

Six medical societies from across the globe are emphasizing the importance of individuals obtaining the daily recommended dose of vitamin D, especially given the impact of the COVID-19 pandemic on outdoor time. The statement, "Joint Guidance on Vitamin D in the Era of COVID-19," is supported by the American Society for Bone and Mineral Research (ASBMR), the Endocrine Society, and the American Association of Clinical Endocrinologists (AACE), among others. They

felt the need to clarify the recommendations for clinicians. Central to the guidance is the recommendation to directly expose the skin to sunlight for 15-30 minutes per day, while taking care to avoid sunburn. The statement noted that "Vitamin D is very safe when taken at reasonable dosages and is important for musculoskeletal health. Levels are likely to decline as individuals reduce outside activity (sun exposure) during the pandemic." It adds, "most older and younger adults can safely take 400-1000 IU daily to keep vitamin D levels within the optimal range as recommended by [the US] Institute of Medicine guidelines."

Over recent months, the role of vitamin D in relation to prevention of COVID-19 has been the subject of intense debate. Now, these societies have joined forces and endorsed evidence-based guidance to clarify the issue around obtaining the daily recommended dosage of vitamin D. During the pandemic, orders to stay at home meant individuals were likely to spend less time outdoors and have less opportunity to draw their vitamin D directly from sunlight, which is its main source, other than a limited number of foods or as a dietary supplement, the societies explain. However, they acknowledge that the role of vitamin D in COVID-19 remains unclear. Research to date suggests that vitamin D may play a role in enhancing the immune response, and given prior work demonstrating a role for the activated form of vitamin D [1,25(OH)2D] in immune responses, but further research into vitamin D supplementation in COVID -19 disease is warranted. Trials to date have been observational and there have been no randomized controlled trials from which firm conclusions about causal relationships can be drawn. Observational studies suggest associations between low vitamin D concentrations and higher rates of COVID-19 infection[4].

References:

1. Somasundaram NP, Ranathunga I, Ratnasamy V, Alwis Wijewickrama PS, Dissanayake HA, Yogendranathan N, et al. The Impact of SARS-Cov-2 Virus Infection on the Endocrine System. Journal of the Endocrine Society. 2020; bvaa082. https://doi.org/10.1210/ jendso/bvaa082.
2. Bhadada S, Sridhar S, Rao S, Bhansali A, Singh R. Do we need sick-day guidelines for hypoparathyroidism? Indian J Endocrinol Metab. 2012; 16:489.
3. Gittoes NJ, Criseno S, Appelman-Dijkstra NM, Bollerslev J, Canalis E, Rejnmark L, et al. Endocrinology in the time of COVID-19: management of calcium disorders and osteoporosis [Internet] Eur J Endocrinol. 2020 May [cited 2020 May 27]; Available from, https://eje.bioscientifica.com/view/ journals/eje/aop/eje-20-0385/eje-20-0385.xml.
4. Joint guidance on vitamin D in the era of covid -19 from the ASBMR, AACE, ENDOCRINE SOCIETY, ECTS, NOF and IOF. Published July 9,2020.

10.5: COVID-19 and Osteoporosis

10.5.1: Is osteoporosis therapy and aggravates risk of COVID-19 infection?

There is no evidence that any osteoporosis therapy increases the risk or severity of COVID -19 infection or alters the disease course. However, COVID -19 is considering as an increased risk for hypercoagulable state[1, 2]. Caution should be used for estrogen and raloxifene, as both of them may modestly increase thrombotic risk[3, 4].

10.5.2: Diagnosis of osteoporosis:

2020AACE Diagnosis of Osteoporosis in Postmenopausal Women

1. T-score −2.5 or below in the lumbar spine, femoral neck, total proximal femur, or 1/3 radius
2. Low-trauma spine or hip fracture (regardless of bone mineral density)
3. T-score between −1.0 and −2.5 and a fragility fracture of proximal

   humerus, pelvis, or distal forearm 4. T -score between −1.0 and −2.5 and high FRAX® (or if available, TBS-adjusted FRAX®) fracture probability based on country-specific thresholds.

[Abbreviations: AACE = American Association of Clinical Endocrinologists; FRAX® = fracture risk assessment tool; TBS = trabecular bone score.]

Bone mineral density (BMD) examinations may need to be postponed. Pre-treatment labs (such as calcium, 25 -hydroxyvitamin D, and/or creatinine) can be avoided if labs within the preceding year were normal and it is the clinical judgement of the medical provider that a patient's health has been stable. However, laboratory evaluation is recommended for patients with fluctuating renal function and those who are at higher risk of developing hypocalcemia, such as those with malabsorptive disorders, hypoparathyroidism, chronic kidney disease stage 4 or 5 or taking loop diuretics [5].

10.5.3: Management of osteoporosis

General Recommendation:

- The initiation of oral bisphosphonate therapy can be done via telephone or video visit and should not be delayed in patients at high risk for fracture (for example: in patients who have recently sustained an osteoporotic fragility fracture).
- Patients who are already taking osteoporosis medications should continue to receive ongoing medications including oral and intravenous (IV) bisphosphonates, denosumab, estrogen, raloxifene, teriparatide, abaloparatide, and romosozumab.
- If parenteral osteoporosis treatments that are not self-administered (e.g. IV bisphosphonates, denosumab, or romosozumab) is not possible then alternative delivery method should be sought (Off-site clinic/ home delivery and administration/ self-injection of denosumab (and/or romosozumab)/ drive-through administration of denosumab and/or romosozumab) [5].
- Supplemental doses of calcium (1200mg/day) and vitamin D (800-1000 IU/day) should be continued in patients with post-menopausal osteoporosis. Patients with osteoporosis should be advised to engage in regular home based exercise to improve the quality of life and muscle mass in older individuals [6]. Preventing falls and remaining fracture free are critical.

10.5.4: Management of patients when injectable osteoporosis medications are not feasible to receive during the COVID-19 pandemic

We recommend to switch oral bisphosphonate therapy in certain circumstances with the goal to resume the original osteoporosis treatment plan once circumstances allow.

- **Denosumab:** If there is discontinuation of treatment of denosumab more than 7 months, strongly consider to switch to oral bisphosphonate if possible (such as weekly alendronate). For patients with underlying gastrointestinal disorders, such as gastroesophageal reflux disease (GERD), achalasia or active peptic ulcer disease, consider monthly ibandronate or weekly/monthly risedronate. For patients with chronic renal insufficiency [estimated glomerular filtration rate (eGFR) levels < 30-35 mL/min], consider an off-label regimen of lower dose oral bisphosphonate (e.g. alendronate 35 mg weekly, or alendronate 70 mg every 2 weeks).

- **Teriparatide or abaloparatide:** For patients in whom continued treatment with teriparatide or abaloparatide is not feasible, consider a delay in treatment. If this delay exceeds 2 -3 months, consider a temporary transition to oral bisphosphonate.
- **Romosozumab:** For patients in whom continued treatment with romosozumab is not feasible, consider a delay in treatment. If this delay exceeds 2-3 months, consider a temporary transition to oral bisphosphonate.
- **Intravenous (IV) bisphosphonates:** For patients in whom continued treatment with intravenous (IV) bisphosphonates is not feasible, delays of even several months are unlikely to be harmful [5].

References:

1. Terpos E, Ntanasis-Stathopoulos I, Elalamy I, Kastritis E, Sergentanis TN, Politou M, Psaltopoulou T, Gerotziafas G, Dimopoulos MA. Hematological findings and complications of COVID-19. Am J Hematol. 2020 Apr 13. doi: 10.1002/ajh.25829. [Epub ahead of print]

2. Spiezia L, Boscolo A, Poletto F, Cerruti L, Tiberio I, Campello E, Navalesi P, Simioni P. COVID19 related severe hypercoagulability in patients admitted to intensive care unit for acute respiratory failure. Thromb Haemost. 2020 Apr 21. doi: 10.1055/s-0040- 1710018. [Epub ahead of print].

3. https://www.accessdata.fda.gov/drugsatfda_docs/label/2007/022042lbl.pdf.

https://www.accessdata.fda.gov/drugsatfda_docs/label/2006/004782s147lbl.pdf.

4.

5. Joint guidance on osteoporosis management from the American Society for Bone and Mineral Research (ASBMR), American Association of Clinical Endocrinologists (AACE), Endocrine Society, European Calcified Tissue Society (ECTS) and National Osteoporosis Foundation (NOF). Published May7, 2020. Accessed May 8,2020.https://www.endocrine.org//media/endocrine/files/membership/joint-statement-on-covid19-and-osteoporosis-final.pdf.

6. Papaioannou A, Adachi JD, Winegard K, Ferko N, Parkinson W, Cook RJ, et al. Efficacy of home-based exercise for improving quality of life among elderly women with symptomatic osteoporosis-related vertebral fractures. Osteoporos Int. 2003; 14:677-82.

10.6: COVID-19 and Obesity

Obesity is one of the most important conditions that increases exponentially the mortality risk of the SARS-CoV-2 patients[1]. The Center for Disease Control and Prevention (CDC) determined obesity as one of the most important groups with higher risk for severe illness [2]. Patients under age 60 years who were overweight were twice as likely to be hospitalized as their leaner counterparts, while those with obesity were three times as likely to need intensive care support. These findings contribute to the growing body of evidence that obesity and other chronic conditions likely predispose an individual to increased risks associated with contraction of infectious diseases [3]. Based on currently available information and clinical expertise, the Centers for Disease Control and Prevention has identified severe obesity (ie, BMI 40 kg/m2) as a common clinical risk factor for worse prognosis and higher mortality in patients with coronavirus disease 2019 (COVID-19) infection [4].

10.6.1: Why might people with obesity be at higher risk?

The obese demonstrate insulin resistance and over activity of the renin-angiotensin-aldosterone system (RAAS), which is implicated with worse outcomes in COVID-19 infection [5]. The ACE2 expression in adipose tissue is higher than that in the lung, a major target organ affected by COVID-19 [6], suggesting that adipose tissue may be more vulnerable to COVID-19 infection. Moreover, obesity, along with low PA/fitness, is the leading cause of T2DM, and T2DM is also causally linked with elevated ACE2 expression [7]. Cell`s expressing ACE2 are also connected to progression of idiopathic pulmonary fibrosis [8].

10.6.2: What may be the potential obesity implications in the mechanism of severe infection in COVID-19?

- Obesity is linked with respiratory difficulties such as sleep apnoea, obesity hypoventiliation syndrome, asthma and cardiovascular disease which can impair oxygen levels in the blood.
- Obesity is associated with a significantly dysregulated immune system and impaired response to both bacterial and viral illness.
- Many people with obesity also have other chronic diseases such as diabetes or high blood pressure.
- Hypercoagulability and a tendency to thromboembolic disease.
- Obesity is linked with inflammation, which may cause a more severe inflammatory reaction in the lungs with COVID-19 infection[9].

10.6.3: What are steps should be taken to reduce the Risk?

Recognition of risk factors is a critical first step to determine prevention strategies. It's also a key factor in targeting high-risk populations for potential therapeutics. So a partnership between patients and doctors will require not only to deals with the medical side of obesity, but also to take a deep dive into the mental and emotional impact of obesity. The National Institute of Diabetes and Digestive and Kidney Disease (NIDDK) explains that common treatments for obesity include:

- Losing weight through healthy eating
- Being more physically active
- Making other lifestyle changes

When it comes to dietary modifications, sticking with an eating plan is often more important than the type of plan you're following. In other words, find something that works for you and make it a lifestyle change [10]

10.6.4: The 10TT counseling method to lose weight in overweight and obese patients.

Family and Community Health reviews the Ten Top Tips (10TT) weight loss counseling method, which is a quick and easy intervention for patients to lose weight and possibly prevent COVID-19 complications [11].

Box 1. Summary of Ten Top Tips (10TT)

- ❖ Develop a meal routine
- ❖ Eat reduced fat foods
- ❖ Walk for weight loss
- ❖ Pack a healthy snack
- ❖ Look at food labels
- ❖ Be mindful of portion sizes
- ❖ Get up on your feet
- ❖ Remember that drinks have calories
- ❖ Focus on food when eating
- ❖ Eat at least five portions of fruits and vegetables daily

Summary of 10TT is shown in Box 1:

Regarding exercise, peoples may benefit from more structure interventions such as formal weight management programs, weight loss medicines [10]. Ensure that any policies and restrictions that are put in place to limit the spread of COVID also allow for people to be physically active in open spaces, while still maintaining adequate social distancing[12].

Healthy weight loss, according to the CDC, should be gradual and steady. In fact, lose about 1 to 2 pounds per week are more successful at keeping weight off. Make sure to get the green light from your doctor before engaging in physical activity.

Once you're cleared for working out, follow the Physical Activity Guidelines which recommend for adults, should do at least 150 minutes to 300 minutes of moderate-intensity (30 to 60 minutes, five days a week), 75 minutes to 150 minutes a week (15 to 30 minutes, 5 days a week) of vigorous-intensity aerobic physical activity or an equivalent combination of both [13].

10.6.5: How can we cope with stress during the time of COVID-19?

Mix up your quarantine routine with a walk, a conversation with a good friend, a puzzle, a book, yoga, tai chi, meditation, a board game, something creative or indulging in a favorite hobby. But be careful from passive stress relievers (surfing the internet, watching TV and playing video games). Indeed, too much screen time could potentially worsen obesity as it distracts from opportunities to be active and mindful [14].

10.6.6: What may be the therapeutic considerations for people with obesity and COVID-19?

Glucagon like peptide-1 analogues

GLP1 and GLP1 analogues have been shown to be beneficial for the treatment of chronic inflammatory diseases such as nonalcoholic fatty liver disease [15], atherosclerosis [16], and neurodegenerative disorders [17]. Taken together, these findings suggest that GLP1 analogues have a protective role against atherosclerosis that is mediated by a dampening of the inflammatory pathways [18].Therefore, alleviation of inflammatory processes in the vascular system by these agents is a rationale for the recommendation to prescribe GLP1 analogues during the COVID-19 pandemic.

Dipeptidyl peptidase-4 enzyme and inhibitors

DPP4 inhibitors have both positive and negative effects on the immune system. For example, the use of DPP4 inhibitors was reported to increase the rate of certain types of infection [19], but basic and clinical studies support its anti-inflammatory properties [20]. At present, there is insufficient evidence either for or against the use of DPP4 inhibitors in patients with DM and COVID-19 [21].

ACE2 and potential therapeutic implications

Despite uncertainties regarding RAAS inhibitors on the infectivity of SARS-CoV-2, there is clear potential for harm related to the withdrawal of RAAS inhibitors in patients concerned that RAAS inhibitors may be harmful in those with an unstable status, such as heart failure [22] or myocardial infarction [23]. Experts strongly recommend that patients should not stop taking their RAAS inhibitor during the COVID-19 pandemic [24].

Hydroxymethylglutaryl-CoA reductase inhibitors

These data support the favorable effects of statins on respiratory diseases [25]. Statin therapy should be continued during the COVID-19 pandemic if there is no definite contraindication.

References:

1. Goumenou M, Sarigiannis D, Tsatsakis A, Anesti O, Docea AO, Petrakis D, Tsoukalas D, Kostoff R, Rakitskii V, Spandidos DA, et al. COVID 19 in Northern Italy: An integrative overview of factors possibly influencing the sharp increase of the outbreak (Review). Mol Med Rep. 2020; 22: 20-32.
2. Centers for Disease Control and Prevention (CDC): Coronavirus Disease 2019 (COVID-19). People who are at higher risk for severe illness. https://www.cdc.gov/coronavirus/2019-ncov/ need-extra-precautions/groups-at-higher-risk.html. Accessed April 15, 2020.
3. Petrilli CM, Jones SA, Yang J, et al. Factors associated with hospitalization and critical illness among 4,103 patients with Covid-19 disease in New York City: Prospective cohort study. Br Med J. 2020; 369: m1966. doi:10.1101/2020.04.08.20057794.
4. Centers for Disease Control and Prevention. Coronavirus disease 2019 (COVID-19). Groups at higher risk for severe illness. https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/groups-at-higher-risk.html. Accessed April 20, 2020.
5. Bornstein SR, Dalan R, Hopkins D, Mingrone G, Boehm BO. Endocrine and metabolic link to coronavirus infection. Nat Rev Endocrinol. 2020; 16(6):297-298.
6. Jia X, Yin C, Lu S, et al. Two things about COVID-19 might need attention. Preprints. 2020:2020020315. https://doi.org/10. 20944/preprints202002.0315.v1
7. Rao S, Lau A, So H-C. Exploring diseases/traits and blood proteins causally related to expression of ACE2, the putative receptor of 2019-nCov: a Mendelian randomization analysis highlights tentative relevance of diabetes-related traits [preprint May 12, 2020]. medRxiv, https://doi.org/10.1101/2020.03.04. 20031237.
8. Kruglikov IL, Schere PE. The role of adipocytes and adipocytelike cells in the severity of COVID-19 infections [published online ahead of print April 27, 2020]. Obesity (Silver Spring), https:// doi.org/10.1002/oby.22856.

9. O'Shea D, & Gaynor k. Obesity and COVID - 19: National Obesity. Management Clinical Programme. Association for the Study of Obesity on the Island of Ireland (ASOI). Sep 7,2020.
10. NIDDK. Treatment for Overweight and Obesity. Updated February, 2018.
11. Burr K, Roberson KB, Onsomu EO, Yancu CN, Pritchard R. Evaluating Ten Top Tips (10TT): Brief Dietary and Physical Activity Counseling in Rural Overweight and Obese Adults. Family & community health. 2020; 43(2):106-117.
12. World Obesity Federation. Obesity and COVID-19 policy statement. 2020.
13. DHHS. Physical Activity Guidelines for Americans. 2018.
14. Obesity Medicine Association. https://obesitymedicine.org/obesity-algorithm/. Accessed March 24, 2020.
15. Wang XC, Gusdon AM, Liu H, Qu S. Effects of glucagonlike peptide-1 receptor agonists on non-alcoholic fatty liver disease and inflammation. World J Gastroenterol .2014;20: 14821-30.
16. Lim S, Lee GY, Park HS, Lee DH, Tae Jung O, Kyoung Min K, et al. Attenuation of carotid neointimal formation after direct delivery of a recombinant adenovirus expressing glucagon-like peptide-1 in diabetic rats. Cardiovasc Res. 2017; 113:183-94.
17. Athauda D, Maclagan K, Skene SS, Bajwa-Joseph M, Letchford D, Chowdhury K, et al. Exenatide once weekly versus placebo in Parkinson's disease: a randomised, double-blind, placebo-controlled trial. Lancet 2017;390:1664-75.
18. Lim S, Kim KM, Nauck MA. Glucagon-like peptide-1 receptor agonists and cardiovascular events: class effects versus individual patterns. Trends Endocrinol Metab. 2018; 29:238-48.
19. Gorricho J, Garjón J, Alonso A, Celaya MC, Saiz LC, Erviti J, et al. Use of oral antidiabetic agents and risk of communityacquired pneumonia: a nested case-control study. Br J Clin Pharmacol. 2017;83:2034-44.
20. Lim S, Choi SH, Shin H, Cho BJ, Park HS, Ahn BY, et al. Effect of a dipeptidyl peptidase-IV inhibitor, des- fluoro-sitagliptin, on neointimal formation after balloon injury in rats. PLoS One. 2012; 7:e35007.
21. Iacobellis G. COVID-19 and diabetes: can DPP4 inhibition play a role? Diabetes Res Clin Pract. 2020; 162:108125.
22. Pflugfelder PW, Baird MG, Tonkon MJ, DiBianco R, Pitt B. Clinical consequences of angiotensin-converting enzyme inhibitor withdrawal in chronic heart failure: a double-blind, placebo-controlled study of quinapril: the Quinapril Heart Failure Trial Investigators. J Am Coll Cardiol. 1993;22:1557- 63.
23. Indications for ACE inhibitors in the early treatment of acute myocardial infarction: systematic overview of individual data from 100,000 patients in randomized trials. ACE Inhibitor Myocardial Infarction Collaborative Group. Circulation. 1998;97:2202-12.
24. Danser AH, Epstein M, Batlle D. Renin-angiotensin system blockers and the COVID-19 pandemic: at present there is no evidence to abandon renin-angiotensin system blockers. Hypertension. 2020;75:1382-5.
25. Frost FJ, Petersen H, Tollestrup K, Skipper B. Influenza and COPD mortality protection as pleiotropic, dose-dependent effects of statins. Chest. 2007; 131:1006-12.

Chapter 11

Measures for prevention and control of COVID-19 pandemic

Dr.Palash Kumar Chanda

In response to COVID-19 pandemic, World Health Organization (WHO) [1], Center for Disease Control and Prevention (CDC) [2], International Diabetes Federation [3], American Diabetes Association [4] and many other organizations [5,6] recommended a comprehensive set of measures to implement, calibrated to the local context and epidemiology of the disease. Special preventive and control measures are recommended for healthcare personals (HCPs) who are the frontline warriors and are playing critical role to combat COVID-19 globally.

Till date, there is no therapeutic drug or vaccine to cure or to prevent COVID-19. Multiple trials for drugs and vaccines are ongoing, some are very near to the successful outcome [7].

Our goal is to control COVID-19 by slowing down transmission of the virus and preventing associated illness and death. Essential measures in general and for the HCPs is to be discussed under the following headings: -

11.1. General measures for prevention and control of COVID-19

11.2. Prevention and control recommendations for healthcare personals during covid-19 pandemic

11.3. Special consideration for healthcare personals (HCPs) with older age and comorbidities

11.1. General measures for prevention and control of COVID-19

Till today general preventive measures upholding as superior initial stage that is recommended by different authorized international bodies for all people. CDC recommended simple 5 steps to follow for all people in general those are depicted in figure 1 [8]

Figure 1: 5 steps to follow for prevention in covid-19 pandemic. Adopted by CDC

11.1.1: Certain others measures should also followed by general people. [9]

The general preventive rules are given below

- Specifically wash your hands before eating or preparing foods and touching your face
- Wash your hands after using rest room, leaving public place, handling mask, after caring sick person, after touching pets or animals
- Do not touch your mouth, face and eyes with unwashed hands
- Avoid close contact as much as possible and prohibit handshaking and hugging from other
- If any family member sick try to maintain 6 feet distance, if not possibly then strictly follow the hand washing rules
- Always try to keep 2 arm length distance from other people outside of your home
- Always try to avoid crowded place

- People should wear cloth masks to avoid infection and it is not necessary that surgical masks are mandatory and masks are not substitute to social distancing
- Cleaning of frequently touched surfaces daily should be a norm for all like tables, doorknobs, light switches, handles, phones, keyboards, toilets, sinks etc.
- Monitoring of health status such as development of fever, cough, shortness of breath and if so stay in home and if needed consultation with physician should be done

11.2. Prevention and control recommendations for healthcare personnel during covid-19 pandemic

Healthcare personnel poses 3.4 fold higher risk of COVID-19 infection because of more frequent exposure to COVID-19 cases and may contribute to the spread of COVID-19 in healthcare institutions [10]

Recommended Preventive and control measures for the healthcare providers are discussed under the following headings

11.2.1: Routine healthcare delivery during COVID-19 pandemic [11]

A) Implementation of telehealth and nurse directed triage protocol:

- Continue telehealth services to provide high quality patient care and limit the transmission of COVID-19 in the healthcare facilities
- Before giving scheduled appointment symptoms regarding COVID-19 should be ascertain by trained nurse directed triage protocol

B) Screen and Triage Everyone Entering a Healthcare Facility for Signs and Symptoms of COVID-19:

- Screening strategies should be adopted for patients, visitors and healthcare providers entering into the healthcare facilities each time by
    a) Actively taking their temperature and documentation of symptoms consistent with COVID-19 where fever is defined as temp ≥100˚F or subjective feeling
    b) Asking them whether they have been advised to self-quarantine due to exposure

C) Vital steps to ensure that everyone adheres to source control measures:

- Different post or signs should be given at the entrance, waiting areas, elevators, cafeterias to provide instructions in appropriate languages about wearing masks and how and when to perform hand hygiene
- Proper supplies of alcohol based hand sanitizers, tissues at the entrances, waiting rooms and patient check-ins
- Education sessions for patients, visitors and health care providers regularly about the importance of performing hand hygiene

D) Immediate management of patients with symptoms of COVID-19 or who has been advised to self-quarantine:

- Health care provider should notify superior authority
- Visitors should be restricted from entering the facility
- Patient should be isolated in examination room with the door closed
- If room is not available patient should be kept in a well-ventilated area with maintaining social distance and adequate supplies of hand sanitizers, tissues

E) Protocol for healthcare professionals at working place

- Strictly follow social distancing, cough etiquette, hand hygiene
- Face mask should be worn all the time including in break rooms
- Surgical mask or respirators are preferred
- To minimize source of infection same mask should be continued over the whole duty hours
- After removing face mask hand hygiene must be done and then wearing cloth face mask can leave the facility at the end of their shift

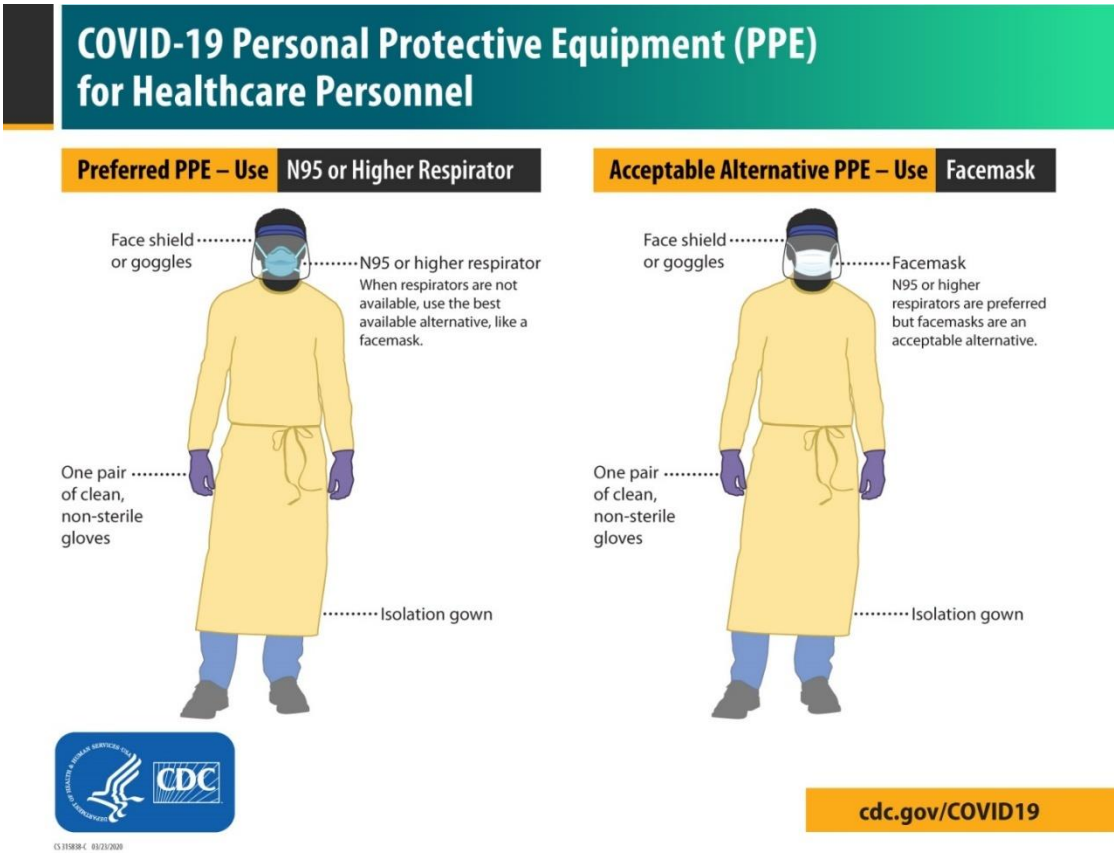
11.2.2: Recommendations for healthcare professionals when caring with suspected or confirmed case of COVID-19: [11]

- Establish reporting within and between healthcare facilities and local authority
- Triage patients needing hospitalization, if not home care must be advised
- If admission needed try to keep that patient in a single well ventilated room with attached bathroom and the door should always be closed
- Strictly isolate aerosol generating room
- Health care professionals must be dedicated to do duties in isolation ward during their shift
- Accommodation for healthcare professionals should be done in same room in the facility around their duty time
- Limit transport patients from the isolation room and all the procedures should be confined in that room like imaging

- Before any consultation with other department patient details must be incorporated to that department to limit transmission
- Patients must be advised to use mask and if not possible covering of face with tissues should be encouraged
- Health care personnel entering the isolation room should use personal protective equipment as shown in figure 2

Figure 2: COVID-19 Personal Protective Equipment (PPE) for Healthcare Personnel

Adopted from Centers for Disease Control (CDC), available at cdc.gov/COVID-19



- Healthcare personnel must follow hand hygiene before and after caring patient and obviously in each steps of doffing of personal protective equipment
- Regular training of healthcare professional regarding PPE must be applied by the authority
- Along with PPE protection of eye is mandatory either by goggles or face shield with proper decontamination procedure
- In aerosol generating procedure healthcare professionals must wear N95 or equivalent or higher level respirator, eye protection, gloves and gown
- At that time minimum personnel should be applied to limit transmission
- Prompt cleaning and disinfecting the procedure room
- After ending of shift proper decontamination should be done depicted as figure 3

Figure 3: Decontamination for yourself and others. Adopted from Centers for Disease Control, available at emergency.cdc.gov/radiation[12]

11.3. Special consideration for healthcare personals (HCPs) with older age and comorbidities:

Individuals with non-communicable diseases (NCDs) are susceptible to communicable diseases (CDs) as documented in the current COVID-19 pandemic as well as previous viral and bacterial infections. While CD epidemics are ‘‘fast and furious,” the pandemics of NCDs, such as diabetes, and hypertension are silent, ‘‘slow-motion” killers with far greater tolls on mortality, disability, and costs [13] . The co-occurrence of diabetes with CDs predicts greater severity, and death, as we see with COVID-19 [14]. Those who are older [15] and having other comorbidities like ischemic heart disease, chronic obstructive pulmonary disease, severe obesity (BMI $\geq$ 40 kg/m^2), hypothyroidism and cancers [15,16] are at higher risk to develop complications of COVID-19 [15,16].

HCPs with older age and comorbidities should remain in special considerations in this pandemic situation. Besides general preventive measures additional recommendations are added to keep them safe as well as their families. Recommended measures will be discussed in the following headings:

11.3.1: Special considerations for healthcare professionals with older age:

In the setting of COVID-19 infection increasing age has high mortality and morbidity rates and associated comorbidities accelerate the mortality and morbidity rates. [17] In USA 8 out of 10 COVID-19 deaths are 65 years old and older. [18] So, health care personnel with older age need special considerations at this covid-19 era both in personal life and at health care facility to safe them and their family

Recommended considerations for healthcare personnel with older age are as follows in general: [18]

- Visit with your friends and family **outdoors**, when possible. If this is not feasible, make sure the room or space is well-ventilated (for example, open windows or doors) and large enough to accommodate social distancing
- Arrange tables and chairs to allow for social distancing. People from the same household can be in groups together and don't need to be 6 feet apart from each other
- Consider activities where social distancing can be maintained, like sidewalk chalk art or yard games
- Try to avoid close contact with your visitors. For example, don't shake hands, elbow bump, or hug. Instead wave and verbally greet them
- If possible, avoid others who are not wearing masks or ask others around you to wear masks
- Consider keeping a list of people you visited or who visited you and when the visit occurred. This will help with contract tracing if someone becomes sick
- Try to be physically active and practicing healthy habits to cope with stress
- For comorbidities continuation of current medications, adequate storage of medications for at least one month
- Strictly isolated if feel sick and telephonic consultations should be done

Recommended considerations for healthcare personnel with older age at health care facility:

- Health care facilities could absorb health care personnel to free younger ones with more robust immune systems to transition to clinical work [19]
- In critical care wards, virtual rounds with senior physicians could allow social distancing while ensuring their continued guidance of younger colleagues[19]

- Similarly, in medicine wards, vulnerable clinicians could do “virtual rounds” by checking electronic medical records and receiving information directly from residents and interns[19]
- Senior physicians in emergency departments and critical care units could also leverage their skills to train others on procedures such as intubation and management of severe respiratory failure for those working in hospitals[19]
- Those who are older than 55 to 65 years should avoid to contact with infected person [20]
- Strictly avoid procedures that produce aerosolized aerodigestive products [20]
- If possible working from home by utilization of teleconferencing for meetings and discussions should be adopted [21]
- Flexible electronic learning (e-learning) can be utilized for uninterrupted academic activities [21]
- Conduction of academic examinations may also be done by video conferencing[21]

11.3.2: Special considerations for healthcare personals with co-morbidities:

As stated previously HCPs suffering from diabetes mellitus and/or obesity will fall in more vulnerable groups. So, in this pandemic era they should maintain additional measures besides general preventive measures as stated before [22]

It is important to note that although lockdowns and advocacy to stay at home are an essential part of COVID-19 pandemic containment measures, these may have negative consequences on
individuals with diabetes. This will curtail the regular diabetes clinic consultations, will limit sunlight exposure, affect the maintenance of physical activity as well as alter the dietary habit. [22]

[22] Cuschieri S, Grech S. COVID-19 and diabetes: The why, the what and the how. J Diabetes Complications. 2020;34(9):107637. doi:10.1016/j.jdiacomp.2020.107637

So, special measures needed for them. It is unlikely that everyone is able to take every precaution but every precaution that is taken makes a difference.

JDRF beyond type1 alliance recommended some behavior changes for those suffering from diabetes mellitus. [23]

Recommended specific measures are:

BEHAVIOR CHANGE RECOMMENDATIONS

Shared Goal	**Individual Behaviors**
Elevated average blood sugar levels in individuals with diabetes is a risk factor for more severe COVID-19 outcomes - *set yourself up for success with diabetes management.*	● Test blood sugar levels more often; your body may be reacting differently under these new circumstances. Maintain a routine of physical movement and blood sugar friendly eating. ● Contact your doctor or health professionals by phone/telehealth if possible for personal diabetes management advice, especially if your blood glucose numbers are consistently out of range. ● Familiarize yourself with how to check for ketones. If you have adequate supplies, check for ketones regularly regardless of blood sugar levels. ● Secure a sufficient amount of your standard management supplies as well as supplies to check ketones and treat severe hypoglycemia (glucagon). ● Lean on your community for help – none of these behaviors are easy, and we all need support. Look into diabetes online communities.
Being overweight/obese and smoking are risk factors for more severe COVID-19 outcomes, in addition to elevated blood glucose levels - *maximize baseline physical and mental health to improve physical immunity.*	● If you smoke or vape, stop now. ● If overweight, work toward a healthier weight. ● Prepare meals at home using whole foods and stay hydrated. ● Be sure to exercise, in your home or in an outdoor area where you can easily maintain distance from others. ● Get a sufficient amount of quality sleep - most adults need 7+ hours per night, children need more (at least 9). ● Reach out to others to stay in touch virtually, especially those who may need help. ● Check in with your mental health, including substance use and other potentially harmful habits. If you are struggling with mental health, seek online help.

BEHAVIOR CHANGE RECOMMENDATIONS

Shared Goal	Individual Behaviors
Many are returning to work and school - *make environments as safe as possible.*	• Work from home as much as you can. Look into modifications in work procedures to keep 2 meters / 6 feet distance from others. Adjust your schedule to avoid high-traffic times. • If you manage a work or school environment, ensure precautions are being set up for vulnerable individuals. Advocate for flexible work options for high-risk individuals.
Early detection of COVID-19 or other health issues can be life saving - *if you get sick, get treated quickly.*	• Measure temperature daily with a thermometer and take heart rate with a watch. Track any changes. • Never stop taking insulin or other medications, even when you become sick. Discuss insulin, metformin, or other medication dosage changes with a doctor. • Make sure you have a diabetes-specific sick day management plan ready, just in case. • Know the warning signs of diabetic ketoacidosis (DKA) and seek immediate medical attention for symptoms including fruity smelling breath, vomiting, weight loss, dehydration, confusion, and hyperventilation.
Basic precautions save lives - *continue strict personal hygiene habits.*	• Wash hands every time you come into contact with an out-of-home item or place. • Wear a cloth mask or face covering any time you're within 2 meters/6 feet of individuals outside your home. • Avoid prolonged exposure to aerosolized particles - e.g. indoor spaces with low ventilation, especially featuring loud conversation or singing • Regularly disinfect high-touch surfaces in your home, cough or sneeze into your elbow or a tissue, and avoid touching your face.
Social distancing works - *continue to minimize physical interaction with others.*	• Minimize contact with individuals outside your household. Maintain a distance of at least 2 meters / 6 ft from others. • Minimize trips outside of your home - shop weekly if your budget allows, get groceries delivered if you can, and seek routine medical care from home, utilizing telehealth and mail-order pharmacy options. • Adjust schedule to avoid busy times in public places. Take advantage of dedicated shopping times for vulnerable individuals if available.

[23] JDRF - Beyond Type 1 Alliance: Behavior Change Guidelines for Organization and Community Leaders (Updated August 27, 2020) available at: Coronavirusdiabetes.org

References:

1. World Health Organization (WHO). Infection prevention and control during health care when novel coronavirus (nCoV) infection is suspected, interim guidance: WHO; 2020.

   Available from: https://www.who.int/publications-detail/infection-prevention-and-control-during-health-care-when-novelcoronavirus-(ncov)-infection-is-suspected-20200125.

2. Centers for Disease Control and Prevention. Transmission-based precautions: US CDC; 2016 [updated 7January 2016; cited 2020 24 June]. Available from: https://www.cdc.gov/infectioncontrol/basics/transmissionbased-precautions.html.

3. International Diabetes Federation (IDF). COVID-19 outbreak n.d. https://www.idf.org/our-network/regions-members/europe/europe-news/196-information-on-corona-virus-disease-2019-covid-19-outbreak-and-guidance-for-people-with-diabetes.html (accessed March 30, 2020).

4. American Diabetes Association. Diabetes and coronavirus (COVID-19).

   Available at: https://www.diabetes.org/coronavirus-covid-19/take-everyday-precautions-for-coronavirus

5. European Centre for Disease prevention and Control. Infection prevention and control and preparedness for COVID-19 in healthcare settings - third update Stockholm: ECDC; 2020 [updated 13 May; cited 2020 24 June]. Available from: https://www.ecdc.europa.eu/en/publications-data/infection-prevention-and-control-andpreparedness-covid-19-healthcare-settings.

6. DIABETES CANADA. COVID-19 (coronavirus).

   Available at: https://www.diabetes.ca/campaigns/covid-19-(coronavirus)-and-diabetes

7. Lu, Chih-Chiaa; Chen, Mei-Yua; Lee, Wan-Shina; Chang, Yuh-Liha,b,

   * Potential therapeutic agents against COVID-19: What we know so far, Journal of the Chinese Medical Association: June 2020 -Volume 83 - Issue 6 - p 534-536 doi:10.1097/JCMA.0000000000000318

8. Coronavirus disease 2019 [COVID-19] Factsheet-CDC (updated June9, 2020) Available at: www.cdc.gov> 2019-ncov>downloads>community

9. Centers for Disease Control and Prevention. How to protect yourself and others. 2020 [internet publication].
   Available at:www.cdc.gov/coronavirus/2019-ncov/prevent-getting-sick/prevention.html 2020

10. European Centre for Disease Prevention and Control. ECDC technical report-

Infection prevention and control for COVID-19 in healthcare settings - first update 12 March 2020 https://www.ecdc.europa.eu/sites/default/files/documents/COVID-19-infection-prevention-andcontrol-healthcare-settings-march-2020.pdf (March 12, 2020; date last accessed).

11. As health care facilities begin to relax restrictions on healthcare services provided to patients (e.g. restarting elective procedures). So, in accordance with guidance from local and state officials, there are precautions that should remain in place for all staffs in every healthcare facility.

Additional recommendations are there for health care providers and for health care facilities

12. Center for Disease Control and Prevention (CDC). Interim infection prevention and control recommendations for healthcare personnel during the coronavirus disease 2019 (COVID-19) pandemic (Interim Guidance, Updated July 15, 2020).

13. Siegel KR, Narayan KM V, Hancock C. Silent killers amidst the fast and the furious. https://www.healthaffairs.org/do/10. 1377/hblog20150507.047514/full/.

14. Drucker DJ. Coronavirus infections and type 2 diabetes shared pathways with therapeutic implications. Endocrine Rev. https://doi.org/10.1210/endrev/bnaa011.

15. Alexander G. Obukhov, Bruce R. Stevens, Ram Prasad, Sergio Li Calzi, Michael E. Boulton, Mohan K. Raizada, Gavin Y. Oudit, Maria B. Grant

Diabetes Sep 2020, 69 (9) 1875-1886; DOI: 10.2337/dbi20-0019

16. Hans Henri P Kluge et al, DOI:https://doi.org/10.1016/S0140-6736(20)31067-9 (published May 08, 2020)

17. Fallon A, Dukelow T, Kennelly SP, O'Neill D. COVID-19 in nursing homes.

QJM. 2020; 113(6):391-392. doi:10.1093/qjmed/hcaa136

18. Centers for Disease Control and Prevention (CDC) coronavirus disease 2019 (COVID-19)

Available at: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/older-adults.html

19. Protect older and vulnerable health care workers from Covid-19
By Aaron Kofman and Alfonso Hernandez-Romieu /March 25, 2020
Available at: **https://www.statnews.com/2020/03/25/protect-older-and-vulnerable-health-care-workers-from-covid-19/**

20. Kowalski, LP, Sanabria, A, Ridge, JA, et al. COVID-19 pandemic: Effects and evidence-based recommendations for otolaryngology and head and neck surgery practice. *Head & Neck*. 2020; 42: 1259– 1267. https://doi.org/10.1002/hed.26164

21. Stawicki SP, Jeanmonod R, Miller AC, et al. The 2019-2020 Novel Coronavirus (Severe Acute Respiratory Syndrome Coronavirus 2) Pandemic: A Joint American College of Academic International Medicine-World Academic Council of Emergency Medicine Multidisciplinary COVID-19 Working Group Consensus Paper. *J Glob Infect Dis*. 2020;12(2):47-93. Published 2020 May 22. doi:10.4103/jgid.jgid_86_20

22. Cuschieri S, Grech S. COVID-19 and diabetes: The why, the what and the how. J Diabetes Complications. 2020;34(9):107637. doi:10.1016/j.jdiacomp.2020.107637

23. JDRF - Beyond Type 1 Alliance: Behavior Change Guidelines for Organization and Community Leaders (Updated August 27, 2020) available at: Coronavirusdiabetes.org

Annex 1. ACEDB CPG-DM & COVID-19 Guideline Committee Members

Portfolio	Name	Affiliation/Working place
Chairman	Prof. Md. Nazrul Islam Siddiqui	Professor & Head (Rtd.), Department of Endocrinology, Mymensingh Medical College, Mymensingh.
Member Secretary (1)	Dr. Ajit Kumar Paul	Associate Professor, Department of Endocrinology, Mainamoti Medical College, Comilla.
Member Secretary (2)	Dr. Indrajit Prasad	Associate Professor, Department of Endocrinology, Dhaka Medical College, Dhaka.
Members	Dr. Md. Shah Emran	Associate Professor & Head, Department of Endocrinology Sylhet MAG Osmani Medical College, Sylhet.
	Dr. Md. Qamrul Hassan	Associate Professor, Department of Endocrinology, Rangpur Medical College, Rangpur.
	Dr. Farhana Akter	Associate Prof. & Head , Department of Endocrinology , Chittagong Medical College, Chittagong.
	Dr. Md. Anowar Hossain	Associate Prof. & Head, Department of Endocrinology Shahed Sayed Nazrul Islam Medical College, Kishoreganj.
	Dr. Moinul Islam	Assistant Professor, Dept. of Endocrinology, Dhaka Medical College, Dhaka.
	Dr. Mirza Sharifuzzaman	Assistant Professor Dept. of Endocrinology, Dhaka Medical College, Dhaka.
	Dr. Abu Jar Gaffar	Consultant Endocrinologist, Naogaon Medical College, Naogaon.
	Dr. Palash Kumar Chanda	Assistant Registrar , Department of Endocrinology Mymensingh Medical College Hospital, Mymensingh.

Annex 2. ACEDB CPG-DM & COVID-19 Review Committee

Members

Portfolio	Name	Affiliation/Working place
Chairman	Prof Abdus Saleque Mollah	Professor & Head (Rtd.), Department of Endocrinology, Chittagong Medical College, Chittagong.
Member Secretary	Prof Md. Abdul Jalil Ansari	Professor & Head, Department of Endocrinology, Shahabuddin Medical College, Dhaka.
Members	Prof. Md. Farid Uddin	Professor and Founder Chairman, Department of Endocrinology, BSMMU, Dhaka.
	Prof Sayed Shahidul Islam	Professor, Department of Endocrinology, Sylhet Women's Medical College, Sylhet.
	Prof. Md. Ruhul Amin	Professor & Head, Department of Endocrinology, Dhaka Medical College, Dhaka.
	Dr. AKM Aminul Islam	Associate Professor, Department of Endocrinology, Col. Malek Medical College, Manikganj.
	Dr. Mashfiqul Hasan	Assistant Professor, Department of Endocrinology National Institute of Neuroscience, Dhaka.

ACEDB CLINICAL PRACTICE GUIDELINE FOR THE TREATMENT OF DIABETES, ENDOCRINE AND METABOLIC DISEASES IN PATIENTS WITH COVID-19

ASSOCIATION OF CLINICAL ENDOCRINEOLOGIST AND DIABETOLOGIST OF BANGLADESH