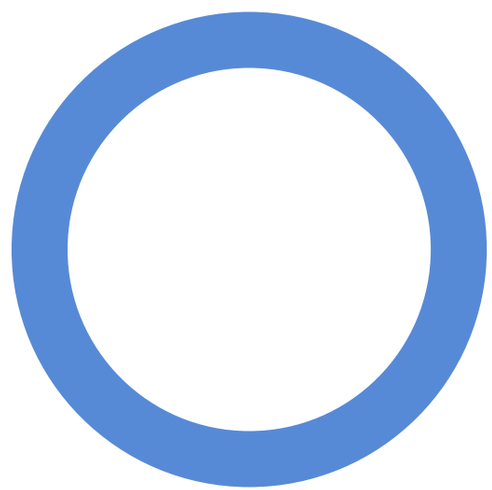
STANDARD TREATMENT GUIDELINES

DIABETES MELLITUS & ENDOCRINE DISEASES



DEPARTMENT OF HEALTH AND FAMILY WELFARE

GOVERNMENT OF KERALA

KERALA.HEALTH

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STANDARD TREATMENT GUIDELINES
for
DIABETES MELLITUS & ENDOCRINE DISEASES

Foreword

At the outset, I appreciate the work done by the respective thematic teams and coordination done by the DME. The Standard Treatment Guidelines (STG) were prepared and published in 2021 in the thick of the Covid pandemic. On the last page of these volumes the road map was mentioned. The few points are mentioned here for the recall.

"The Department of Health has been taking a systematic approach of creating and enabling multiple initiatives with a focus on prevention along with improving health care services. Health care service delivery is one of the most important services and is always seen as a barometer to assess the Governance. While it is important to develop infrastructure, an essential prerequisite is to develop systems and processes to bring in standardization in management of patient care. ……The foundation is laid and we take up the challenge to work on the unfinished agenda."

It was mentioned in the road map to have institutional mechanism to ensure updation of Standard Treatment Guidelines. The next step that was suggested was to do analysis of Karunya Arogya Suraksha Padhati (KASP) and standard treatment guidelines to work on developing a Balance Score Card to give information regarding compliance from the Hospitals and to build a "feedback loop" to improve. These initiatives remained at concept level on the last page! But following detailed discussions with Dr Vishwanathan, Director Medical Education, some of the foundational things were prioritized and given an impetus to take it to finality. In this journey, many committed doctors from various Medical Colleges of respective specialties participated. The previous coordination team members and experts were also consulted and they also participated in discussions and these Standard Treatment Guidelines are prepared.

The standard treatment guidelines will be made available in the Kerala Health portal (health.kerala.gov.in). This will enable the resource book availability not only to people within the state but to all in the country and outside our borders as well. I am confident that it will be used by students and practicing doctors. We request inputs based on the research from the Specialists and Experts. The teams shall continue to update and make any required changes in the STG by doing periodic updates.

The most important thing we all need to internalize is to have a shared vision and

work as a team to reach to a state of 'excellence'. If we take a look at the preparation of the Directorate Medical Education Management Information System, documents of each Medical Colleges, it provides information regarding 'what we are, what we do and what we aspire to do', pandemic preparedness, AMR accreditation and many more such initiatives taken on scale, which are all outcomes of collective TEAM work. This has laid a foundation for involving all the stakeholders including undergraduate and postgraduate students. This should encourage the teams in Medical Colleges to believe in themselves and build future initiatives on such a sound platform.

I express my sincere thanks to Dr Vishwanathan for his patience and bearing with relentless follow ups! I also take this opportunity to thank each and every team and their members and everyone from Directorate Medical Education and Medical Colleges who supported these initiatives.

I would like to express my sincere gratitude to all those who have contributed to publish these Standard Treatment Guidelines.

I wish all the success to DME team to make Kerala MCH as a premier knowledge hub in Medical Science.

Dr Rajan Khobragade IAS

Additional Chief Secretary
Health & Family Welfare and
AYUSH Department
Govt of Kerala.

Message

Patient care today demands evidence-based, standardized, and contextually relevant clinical practice. In this regard, the publication of the **Second Edition of the Standard Treatment Guidelines** marks an important step forward in strengthening the quality, consistency, and accountability of healthcare delivery in Kerala.

The first edition laid a strong foundation for uniform clinical practice across specialties and super specialties. Since then, advances in medical knowledge, evolving treatment modalities, and the growing need for periodic updating have made it essential to revisit and refine these guidelines. The present edition reflects this commitment to continuous improvement and clinical excellence.

I am pleased to note that subject experts from various disciplines of Government Medical Colleges, private institutions and professional bodies have contributed as resource persons in the preparation of these guidelines. Their academic expertise, practical insight, and dedicated involvement have greatly enriched this edition. I deeply appreciate the sincere efforts of all the conveners, contributors, and coordinators whose collective commitment and teamwork made this publication possible.

These guidelines will serve as a valuable reference for clinicians, teachers, trainees, and healthcare institutions, helping to promote evidence-based decision-making and improve patient outcomes. I am confident that this edition will further support standardization of care and contribute to the advancement of medical education and clinical practice in the State.

I congratulate everyone involved in this commendable effort and commend this publication to all healthcare professionals.

Dr. K. V. Viswanathan
Director of Medical Education
Government of Kerala

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Standard Treatment Guidelines in Diabetes Mellitus & Endocrine Diseases

2 sections

Section I

Diabetes Mellitus

Section II

Endocrine Diseases

Contents

Section - I
Diabetes Mellitus

Abbreviations

ASCVD	:	**Athero Sclerotic Cardio Vascular Disease**
CKD	:	**Chronic Kidney Disease**
DPP-4	:	**Dipeptidyl peptidase-4**
DPP-4-i	:	**DPP-4 inhibitor**
eGFR	:	**Estimated Glomerular Filtration Rate**
FPG	:	**Fasting Plasma Glucose**
FLP	:	**Fasting Lipid Profile**
GDM	:	**Gestational Diabetes Mellitus**
GLP-1	:	**Glucagon-like peptide-1**
GLP-1 RA	:	**GLP-1 receptor agonist**
HbA1C	:	**Glycated haemoglobin**
IM	:	**Intramuscular**
IV	:	**Intravenous**
MI	:	**Myocardial Infarction**
NPH	:	**Neutral Protamine Hagedorn**
NPO	:	**Nil Per Orally**
OGTT	:	**Oral Glucose Tolerance Test**
PG	:	**Plasma Glucose**
PPG	:	**Postprandial Plasma Glucose**
SC	:	**Subcutaneously**
SGLT2	:	**Sodium-Glucose co-transporter 2**
SGLT2-I	:	**SGLT2 inhibitor**
SU	:	**Sulfonylurea**
TDD	:	**Total Daily Dose**
TZD	:	**Thiazolidinedione**

1. The scope:

Diabetes mellitus is imposing a huge economic burden to the society. It is the leading cause of blindness, renal failure and amputation. Cardiovascular diseases are the important cause of death in diabetes patients. The risk factors identified are obesity, physical inactivity and unhealthy lifestyle along with the ethnic predisposition. Undetected and uncontrolled diabetes is a major challenge in the care of these patients. Management of diabetes must be based on a chronic care model and must be patient centred and team based with community participation in primary prevention, optimisation of management, prevention of complications and long-term care. The care plan must respect the customs, cultural background, needs and preferences of the society.

The standard treatment guideline for diabetes is designed to focus the secondary and tertiary care level management of diabetes mellitus.

The target group: Type 2, Type 1 and gestational diabetes and other causes of diabetes attending the treatment facilities provided by Government of Kerala in primary and tertiary care level centres

The objectives:

1. Detection and treatment of type 2 diabetes – early detection, advice on lifestyle modification, timely initiation of oral antidiabetic drugs, appropriate use of insulin, monitoring of glycemic control, screening of complications and other co-morbidities.
2. Detection and treatment of type 1diabetes – early detection and management including training on coping with disease and insulin use
3. Detection and care of diabetes in pregnancy including pre existing diabetes and gestational diabetes.

This document is intended to provide general guidelines for early diagnosis, management and follow up of patients with diabetes mellitus for improving patient care and also to plan strategies for prevention of type 2 diabetes mellitus in Kerala.

2. Diagnosis, classification, medical evaluation and investigations

2.1. Diagnosis of diabetes mellitus

Criteria for the diagnosis of diabetes

Fasting Plasma Glucose (FPG) ≥126 mg/dL

OR

2-h plasma glucose ≥200 mg/dL during an OGTT with 75g glucose

OR

A1C ≥6.5% *

OR

In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL

In asymptomatic subjects, to make the diagnosis, results should be confirmed by a repeat testing

*In situations where the quality control of HbA1c is uncertain, or not available clinician should preferably use plasma glucose for diagnosis of diabetes. Glucometers should not be used for establishing a diagnosis of diabetes mellitus

Diagnosis of Gestational Diabetes:

It is necessary to Test for Gestational Diabetes at 24 -28 weeks of Pregnancy (if not detected with Diabetes earlier) by 75 gm Oral GTT and **any value** above the following range must be diagnosed to have GDM and needs appropriate referral for management.

Diagnosis of diabetes in pregnancy

A) Testing for GDM at 1st Antenatal visit**

After 75 g oral glucose, test 2 hr Plasma Glucose value)

Positive (2 hr PG ≥140 mg/dl) – manage as GDM

Negative(2 hr PG <140mg/dl) - Repeat Testing at 24-28 weeks

B) Testing for diabetes at 24-28 weeks

75 grams of glucose should be used for OGTT (Fasting 92 mg/dL, 1 hour 180 mg/dL and 2 hours 153 mg /dL of Plasma Glucose)

"National Guidelines for Diagnosis & Management of Gestational Diabetes Mellitus February 2018"

*** Including FPG and A1C at first antenatal visit will help to detect all subjects with pre-existing diabetes. Standard criteria for diagnosis of diabetes in non-pregnant adults may be used to diagnose overt diabetes in early pregnancy.*

Prediabetes is defined as FPG of 100–125 mg/dL, 2-hr OGTT of 140–199 mg/dL or A1C of 5.7–6.4%. All subjects with prediabetes must be provided with life style modification and repeat testing annually for early detection and management.

2.2. Classification of diabetes mellitus:

- Type 1 Diabetes mellitus
- Type 2 Diabetes mellitus

- Gestational Diabetes mellitus
- Other specific types – Diabetes in chronic calcific pancreatitis, monogenic diabetes etc.

2.3. Medical evaluation:

Every patient should receive a patient-centered comprehensive medical evaluation on first visit with adequate time given for education including interaction with patient and family to listen and sort out all their concerns. This will help in a successful enrolment into the management and regular follow up.

After confirming the diagnosis and classification of diabetes (may not be possible always in all patients on first contact), each patient must undergo:

1. Initial assessment
2. Assessment for complications
3. Assessment for co-morbidities
4. Develop a plan for a continuous care

Categorize the patient based on the age, gender, duration of diabetes, complications, co-morbidities, social support, and occupation, ability to monitor and then chart out an individualized care.

2.4. Investigations at diagnosis

- Fasting Plasma Glucose (FPG)
- Postprandial Plasma Glucose (PPG)
- Blood urea, Serum creatinine
- HbA1c (HPLC method if facilities are available – highly recommended)
- Fasting lipid profile (FLP)
- Urine albumin to creatinine ratio by dip stick test
- Dilated fundus (eye) examination should be organised at diagnosis in all type 2 diabetes patients, and after 5 years in type 1 diabetes.

Follow up care should be individualized and Fasting and Postprandial Plasma Glucose should be measured atleast monthly. HbA1c may be measured once in 6 months in patients with good glycemic control and once in 3 months in those with poor controls.

3. Management

1. Diet and life style management
2. Pharmacological management

3. Management of complications
4. Management of comorbidities

3.1 Diet & Lifestyle Management

Diet and life style management is the foundation of diabetes care. It must be reinforced in every visit and in every patient and should be taught to the entire family as and when possible. Diet in diabetes is the healthy balanced diet and must be incorporated into the normal dietary plan of the family.

3.1.1 Diet in diabetes

- Diet must be well balanced based on cultural beliefs and practices, and must be individualized. Dietary management is a continuous process.
- Calorie requirement must be based on a patient's body weight and physical activity. Total daily calorie intake of 30 Kcal /day for Normal BMI patients (25 Kcal /day for overweight and 35 Kcal /day for underweight category).
- There should be restricted intake of fried foods, refined sugar, maida, tubers (potato, yam, tapioca) and fruits like mango, jackfruit, Banana and pineapple.
- Complex carbohydrates are preferred to simple ones. Carbohydrates with low Glycemic Index should be advised.
- About 4 to 5 servings of vegetables and fruits in moderation should be included. This diet will help to ensure adequate fibre intake.
- Diet should include protein sources like pulses, egg white, fish and meat. Proteins need to be restricted only in patients with advanced Chronic Kidney Disease (CKD).
- Cooking oil must be used sparingly.
- Sugars, sweets and sweetened beverages must be avoided.
- Salt intake should be advised to be less than 5 gram per day.
- Smoking must be avoided.

3.1.2 Exercise in Diabetes

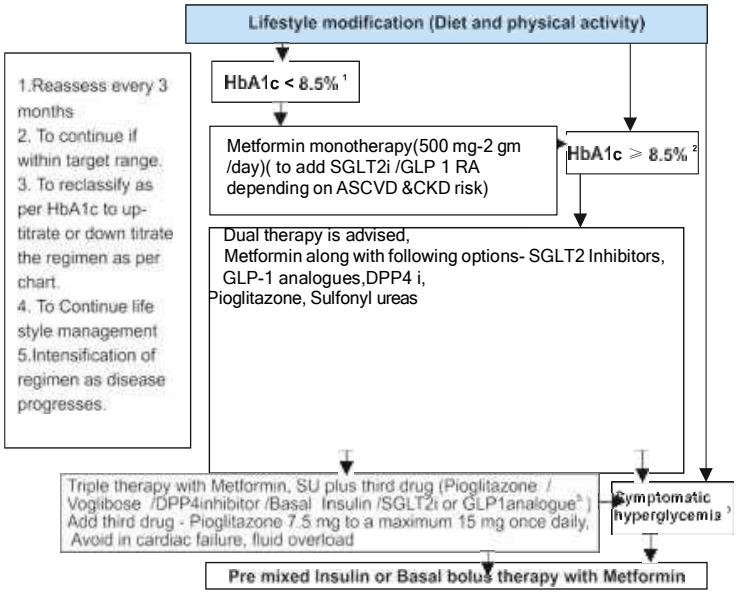
- It is advisable to have 30 minutes per day at least 5 days a week ie 150 minutes per week.
- In a person with long standing diabetes before advising on exercise, we have to assess the cardiac fitness, presence of peripheral occlusive vascular disease, peripheral neuropathy, foot problems, and visual disturbances including proliferative retinopathy and need to take decisions on an individual basis.

- Avoid strenuous exercise if blood glucose is> 250 mg/dl, <70 mg/dL, the patient has ketonuria or dehydration
- Appropriate foot wear must be used to avoid trauma to feet.

3.2 Pharmacological management:

Pharmacological management is started along with diet and lifestyle modification. If there is good glycemic control, continue the same and monitor every 3 months. Metformin can be initiated in the first visit itself after confirming the diagnosis

3.2.1 Treatment Algorithm for type 2 diabetes mellitus



1 If HbA1c is not available: use plasma glucose ,as HbA1C < 8.5% corresponds to average Plasma Glucose -200 mG/dL or Fasting 100-150 and PPPG 200-250 mG/Dl HbA1c ≥ 8.5% corresponds to average Plasma Glucose -230 mG/dL or Fasting 150-200 and PPPG 200-300 mG/dL

Glycemic goals are Preprandial / FPG - 80–130 mg/dL and 2 hrs PPPG less than180 mg/dL

3 Patients with symptomatic hyperglycemia, will benefit from Insulin as monotherapy (if with significant hyperglycemic symptoms and dehydration) or along with Metformin.

4 Dual therapy: After Metformin Options include

a) Pioglitazone Dose 7.5 mg daily to a maximum of 15 mg/day

b) SGLT2inhibitor – if CVD, Heart failure or CKD predominates; Avoid in seriously ill, dehydrated, and hospitalized patients.

c) GLP1analogue – If ASCVD predominates, in selected indications as per the discretion of treating clinicians

d) Voglibose if there is predominant Post prandial hyperglycemia. Dose 0.2 mg as once daily with major meal and up titrated to twice and thrice daily and then increase to 0.3 mg.

e) DPP4 Inhibitor in elderly, people on occupations with irregular meal timings and risk of Hypos.

f) Sulfonyl ureas – not preferred if risk of hypoglycemia

5 Triple therapy / with Insulin: If Plasma Glucose out of target and A1C ≥8.5 % after 3 months of dual therapy, a third drug must be added. If FPG is high, basal Insulin is a preferred option along with oral agents (half maximum dose of SUs and metformin of 1 g twice daily after food, or the SU is stopped and metformin alone continued)

Choosing the second drug after Metformin is based on many factors as listed below.

a) Cost, availability and experience – Options are SUs, Pioglitazone

b) Established ASCVD – GLP1 RA or SGLT2i

c) Established HF or CKD predominates: SGLT2i

d) Need to minimize hypoglycemia: DPP4i, GLP1 RA, SGLT2i, TZD

e) Promote weight loss: GLP1 RA, SGLT2i

3.2.2 Drug specific factors to choose the options in type 2 diabetes

Agent	Benefits	Side effects	Adverse effects	Dose
Metformin	Slight weight loss, No hypo	GI symptoms (rare)	Contraindicated in patients with estimated glomerular filtration rates<30 mL/minute/1.73 m2 Lactic acidosis, B12 deficiency	500 mg – 2000mg
SU (Glimiperide, Glipizide, Gliclazide)	Low cost and wide experience	Moderate to severe risk for hypoglycemia	· Weight gain · Heightened risk for hypoglycemia in patients with renal complications · May carry risk for ASCVD	Glimeperide-1-4 mg/ day Glipizide-2.5 to 10 mg once or divided Gliclazide-40 to 320 mg in divided doses
Pioglitazone	Low cost, no hypo	Fluid retention, weight gain		7.5mg -15 mg daily
Alpha-glucosidase inhibitors	Low cost, no hypo	Bloating, flatulence, diarrhea		Acarbose 25 -50 mg with food Voglibose 0.2-0.3 mg with food
DPP4i	Weight neutral, no hypos	Risk of acute pancreatitis		Sitagliptin 100 mg daily,

				Vildagliptin 50mg BD, Linagliptin 5 mg daily, Teniligliptin 20 mg daily

3.3 Insulin therapy in Diabetes

3.3.1 Indications of Insulin in Diabetes:

- Type 1 Diabetes
- At onset, if FPG is > 250 mg/dl,HbA1c >9 % inspite of multiple OADs and ketonuria, dehydration
- In stressful situations – Infections, Stroke, MI
- During pregnancy
- Peri-operative state
- Acute hyperglycemic complications eg: diabetic ketoacidosis, hyperosmolar coma
- Intolerance /Hypersensitivity to oral anti-diabetic agents – very rare

3.3.2 Insulin types, regimen, dose adjustments

Types of Insulin regimen

Basal only therapy (In type 2 Diabetes with oral drugs)

Basal Plus (Basal plus one or two bolus doses)

Basal Bolus therapy (Basal plus three bolus doses)

Pre mixed or split mix (mixing regular and NPH just before injecting) therapy

Available Insulin types

1. Short acting Insulin and rapid acting Insulin analogues as bolus Insulin
2. Intermediate acting and long acting Insulin as basal therapy
3. Pre mixed Insulins or insulin analogues (30/70; 25/75 and 50/50)
4. Insulin co-formulation (Insulin Aspart and Insulin Degludec)

Bolus Insulins – profile:

Insulin type	Onset	Peak activity	Duration of action
Regular Insulin	30-60 mts	2-3 hrs	5-8 hrs
Insulin lispro	5-15 mts	30-90 mts	5 hrs
Insulin Aspart	5-15 mts	30-90 mts	4-6 hrs
Insulin Glulisine	5-15 mts	30-90 mts	4-6 hrs

Basal Insulins – profile

Insulin type	Onset	Peak activity	Duration of action
NPH Insulin	1- 2 hrs	4-8 hrs	08-12 hrs
Insulin glargine	½ - 1 hr	No peak	20-24 hrs
Insulin Detemir	½ - 1 hr	No peak	16-24 hrs
Insulin degludec	½ - 1½ hrs	No peak	> 24hrs

How to adjust Insulin dose or which dose to adjust

Glucose out of target	Adjust this Insulin
Post BF / Pre lunch	Pre BF Rapid/Regular
Post lunch/Pre supper	Pre lunch Rapid/Regular or Morning NPH
Mid afternoon	Morning NPH or Detemir / Glargine
Post supper / Bed time	Pre supper Rapid/Regular
Early morning	Evening NPH / Detemir / Glargine

3.3.3 Initiating Insulin therapy

A short education session

- The need of glycemic control
- Why to start Insulin
- Hypoglycemia- what, when and how to recognize and manage
- Address all concerns about treatment. Insulin should never be started as a

punishment or a failure from the patient's side.

- Patient must be trained and this must be reinforced at every visit.

Basal only in Type 2 Diabetes

- Continue oral agents (half maximum dose of SUs and metformin in the dose of 2 g/day.
- In elderly patients and in those with long standing diabetes with complications, SUs are stopped, continuing metformin in the same dose) Intermediate acting (NPH) insulin administered once daily at 10.00 PM -given as

Total Daily Dose calculated by: Body weight in Kg x 0.2 IU of insulin and to a maximum of 20 IU SC.

- Monitor fasting plasma glucose and ask for any episode of hypoglycemia.
- Better options in patients with serious hypoglycemia will be long-acting Insulin analogues like Glargine, U300 Glargine, Detemir and Degludec.
- Continue if glycemic goals are achieved in 3 months or earlier, switch over to premixed or basal bolus regimen if glycemic goals are going out of target.

Pre mixed or basal bolus Insulin therapy

- All oral drugs are discontinued except Metformin. Consider continuing SGLT2 inhibitor according to CV or renal risk of the patient.
- Pre-mixed human insulin is introduced twice daily at a dosage of 0.2 IU/kg body weight.
- This is split into 2/3 in the morning and 1/3 in the evening, at 30 minutes before the morning and the evening meals.
- Premixed insulin may be titrated up gradually, to achieve the glycemic goal monitoring for hypoglycemia.
- If patients do not achieve this move to basal bolus therapy.
- Reassess after 3 months or earlier and the need for referral should be considered if goal is not achieved.
- Continue if glycemic goals are achieved in 3 months or earlier.

4. Monitoring and Glycemic targets

- A1c may be done once in 3-4 months to assess glycemic control and a minimum of once monthly plasma glucose (minimum of two values of fasting and postprandial) to emphasize lifestyle modification and drug compliance. If well controlled, may be followed up once in 3 months.

- A fasting capillary blood glucose of 80-130 mg/dL and post-prandial plasma glucose 140- 180 mg/dL in most measurements with an HbA1c <7% is the goal in most patients
- HbA1c target between 7.5% and 8% or higher for avoiding hypoglycemia is sought in the following patients
    1) Those with asymptomatic hypoglycemia
    2) With cognitive impairment
    3) CKD or severe CVD associated with multiple co morbidities
    4) Terminally ill with predicted short survival.
- Frequent plasma glucose measurements in different times of the day must be encouraged with documentation and must be reviewed in each hospital visit
- Glucose monitoring is mandatory in patients using Insulin.
- Self-monitoring of blood glucose (SMBG) for patients using insulin is recommended especially in situations such as frequent hypoglycemia, elderly, and other comorbidities or during acute illness, on multiple doses of Insulin and during pregnancy.
- More frequent plasma glucose testing needed
    1) Those who are having FPG > 140 and PPG > 200 mG/dL
    2) Those with frequent hypoglycemia and fluctuating glucose levels.
- All those patients with stable glycemic control must be followed up every month with a FPG and PPG.
- Perform A1C testing twice in a year in centres where facilities are provided.
- Continuous Glucose Monitoring may be reserved in difficult cases and for those selected patients on Insulin pumps considering the cost and availability.

5. Hypoglycemia training*:*

- Recognition and documentation of hypoglycemia is very important in clinical practice.
- All patients on planning to start SU or insulin must have received training on recognition and management of hypoglycemia and must be reinforced on every visit.
- Encourage to use **Personal Medical IDs** (with patient's name, address, phone number, emergency contact no, current treatment and hospital address with the message that "I am a person with diabetes on the following medications and if I am

found unconscious, please take me to the nearest hospital") to get appropriate emergency care if found unconscious.

Personal Medical IDs sample

തിരിച്ചറിയൽ രേഖ

പേര്: വയസ്സ്:

പുരുഷൻ / സ്ത്രീ:

മേൽവിലാസം:

ഫോൺ 1. :

ഫോൺ 2. :

ഞാൻ ഒരു പ്രമേഹരോഗിയാണ്. ഞാൻ ഇൻസുലിൻ / ഗുളികകൾ കഴിക്കുന്നുണ്ട്. എന്നെ അബോധാവസ്ഥയിലോ മറ്റു രോഗാവസ്ഥയിലോ കാണുകയാണെങ്കിൽ ദയവായി പഞ്ചസാര നൽകുകയും അടുത്ത ആശുപത്രിയിൽ എത്തിക്കുകയും ചെയ്യുമല്ലോ. ഇതു രക്തത്തിലെ പഞ്ചസാര കുറഞ്ഞതാകാൻ സാധ്യതയുണ്ട്.

Definitions for documentation and management:

- Hypoglycemia - Blood glucose < 70 mg/dL
- Clinically significant hypoglycemia <54 mg/dL
- Severe hypoglycemia - Any blood glucose level associated with severe cognitive impairment requiring external assistance for recovery in a diabetic with blood glucose < 70 mg/dL.

Causes: A missed meal, unusual physical exercise, inappropriate dose of insulin or OHA, liver, kidney diseases

Common Symptoms: sweating, trembling of hands, hunger, fatigue, nausea, rapid heart beat. Later: confusion, abnormal behavior, loss of consciousness, convulsions & death.

Early recognition and prompt treatment and measures for prevention must be the goal.

Hypoglycemia management:

Hypoglycemia treatment requires ingestion of glucose- or carbohydrate containing foods.

Rule of 15

Consume 15 gms of glucose or 1 tablespoon sugar; recheck blood glucose after 15 minutes, repeat if hypo continues. Once blood glucose returns to normal eat a small snack if next meal is more than an hour away. If unconscious, or cannot take orally, administer 50 ml of 50 % Dextrose IV and recheck blood glucose after 15 minutes.

Always assess and correct the precipitating cause.

6. Assessment of complications

a. Retinopathy - Once in an year from diagnosis in Type 2 DM and after 5 years of onset/11 yrs of age in Type 1 DM. Must be seen by an ophthalmologist and more frequently if suggested by the ophthalmlogist or patient complain of visual symptoms like eye pain, loss of vision or blurring

b. Nephropathy - Once in an year from diagnosis in Type 2 DM and after 5 years of onset//11 yrs of age in Type 1 DM. The test is Urine Albumin Creatinine ratio.

c. Neuropathy - Once a year from diagnosis in Type 2 DM and after 5 years of onset/11 yrs of age in Type 1 DM. Complete physical examination, specifically muscle wasting, ankle reflex, touch, pain sensation, vibration perception using 128 Hz tuning fork, 10 g monofilament for protective sensation.

d. Diabetic foot - Feet must be examined in every visit, neurological examination and staging of the feet and recognising high risk feet, with appropriate management and follow up strategy

7. Comprehensive management of co-morbidities

Obesity, Hypertension, Dyslipidemia, Addictions and Depression and Psychosocial stress must be addressed in every visit.Goal blood pressure

<130/80 mm of Hg

8. Management of Diabetes in Pregnancy (Pre-existing diabetes and GDM)

- Preconception counseling and planned pregnancy, ideally with an A1C of<6.5% without hypoglycemia.
- In the interest of maternal and fetal health, blood pressure must be documented and

in patients having chronic hypertension, BP must be controlled as normal as possible.

- Potentially teratogenic medications (ACE inhibitors, statins, etc.) should be avoided in sexually active women of childbearing age and planning pregnancy or who are not using reliable contraception.
- Insulin is the treatment of choice in pregnancy as all oral agents lack long term safety data.

Glycemic goals for pregnant women (in Type 1, type 2 and GDM) must be individualized but as close to optimum targets avoiding hypoglycemic episodes.

Optimum glycemic targets in pregnancy are

Fasting ≤95 mg/dL and

Either One-hour postprandial≤ 140 mg/dLor

Two-hour postprandial ≤ 120 mg/dL without producing hypoglycaemia.

9. Insulin in hospitalised patients

Uncontrolled hyperglycemia in hospitalized patients with or without a previous diagnosis of diabetes is associated with adverse outcomes and longer length of hospital stay.

This could be due to

- Preexisting diabetes
- Undiagnosed diabetes
- Stress induced hyperglycemia

For management of hyperglycemia, the hospitalized patients can be categorized into two broad categories:

(1) **Non-ICU patients**

(2) **ICU patients**

9.1 Management of hyperglycemia in hospital

9.1.1 Non-ICU Patients

Non-critical patients are less likely to receive adequate attention for hyperglycemia per se. Use of insulin does not necessarily commit patients to chronic insulin therapy as outpatients, and this should be discussed with patients to allay any potential anxiety. If the A1C value indicates the need for chronic insulin therapy, it is a good opportunity to begin discussion and training as soon as possible.

The preferred glycemic targets

- Premeal blood glucose (BG) (80-130 mg/dL)
- 1-2 h post prandial plasma glucose – 140- 180 mg/dL
- Avoiding hypoglycemia.

Targets should be less stringent for the elderly and patients with significant medical comorbidity or limited life expectancy.

Basal bolus insulin regimen is the preferred option in non critically ill patients. This is considered the physiologic approach as it addresses the three components of insulin requirement: basal (what is required in the fasting state), nutritional (what is required for peripheral glucose disposal following a meal), and supplemental (what is required for unexpected glucose elevations).

Components of Basal Bolus Insulin therapy is provided as:

- Basal insulin – NPH / Glargine or Degludec
- Prandial/Bolus (meal time) insulin – Regular Insulin or Rapid acting Insulin analogues (Aspart, Lispro, Glulisine, Fiasp)
- Correction (supplemental) insulin - Regular Insulin or Rapid acting Insulin analogues (Aspart, Lispro, Glulisine, Fiasp)
  - Noncritically ill inpatients on enteral nutrition should be preferably managed with insulin.
  - Insulin analogs should be preferred in indoor patients as they are associated with less hypoglycemia, better therapeutic outcomes, and are more flexible to use. But Human regular insulin can also be used as bolus insulin as it is the one still widely available with long experience and used in India.
  - NPH is better than glargine in inpatient setting as frequent adjustments are possible with NPH and not with glargine. As NPH insulin has a pronounced and variable peak and should be avoided during hospitalization in patients with high risk of hypos or who are not eating reliably.
  - **Sliding scale is not recommended.** It should be emphasized that using a correction scale insulin regimen alone, also known as **"sliding scale"** is not appropriate to treat sustained hyperglycemia (> 140 mg/dl).
  - Bolus insulin should be withheld when patients are NPO or when premeal glucose levels are < 70 mg/dL

Prescribing insulin in non ICU patients

- Estimating patients' total daily insulin requirement, or total daily dose (TDD),

is the first step in ordering insulin.

- For patients who were on insulin before admission, the best indicator of insulin requirement is their TDD before admission.
- Patients with an elevated A1C value may require an increase, and those whose glycemia was too tightly controlled or those who were admitted with hypoglycemia may require a reduction in their prehospitalization TDD.

Table 1 is a simple guide to calculate the intial dose if previous requirement is not known.

Table 1. Determining a TDD for Insulin - Naive Patients	
TDD estimation	Patient characteristics
0.3 units/kg body weight	Underweight, Older age, renal insufficiency, on Hemodialysis
0.4 units/kg body weight	Normal weight
0.5 units/kg body weight	Overweight
≥ 0.6 units/kg body weight	Obese, Insulin resistant, Glucocorticoid

- Studies in both type 1 and type 2 diabetes have consistently shown that optimal glycemic control can be achieved with subcutaneous insulin in patients who are eating normally when approximately 50% of their TDD is provided as basal insulin, and 50% is provided as bolus insulin.
- Mealtime doses may need to be adjusted daily based on patients' anticipated caloric intake and to withhold if patients are not eating or if their premeal glucose level is < 70 mg/dl. . Faster Insulin analogue can be given after food in such situations.
- For patients who are eating unreliably, rapid-acting analog insulin can be ordered to be given immediately after they have eaten, and the mealtime dose can then be adjusted to match their actual intake (e.g., reducing the dose by 50% if only half of the food on the tray was consumed).
- Correction insulin requirements depend on individuals' insulin sensitivity. The type of correction insulin (eg, short acting or rapid acting) should be the

same as the premeal insulin used.

Table 2. Sample Order for Subcutaneous Insulin in a Hospitalized Patient

Sample: Basal/bolus insulin dose calculation for a patient weighing 80 kg with a BMI of 28 kg/m2 and normal renal function	
Step 1	**TDD calculation** TDD = 0.5 units/kg body weight × 80 = 40 units
Step 2	**Basal insulin dose calculation** Basal insulin dose = 50% of TDD = 50% of 40 units = 20 units glargine / NPH
Step 3	**Bolus insulin dose calculation** Bolus insulin dose per meal = (50% of TDD)/3= (50% of 40 units)/3 = 20/3 = 6.3 units, or ~ 6 units of rapid-acting insulin before each meal. If the patient or nurse estimates that the patient is only eating 50% of the food on the tray, a reduced dose of 3 units should be ordered instead of the full dose of 6 units
Step 4	**Correction scale estimation** Correction Insulin for BG≥150 mg/dL, is prescribed based on a graded scale of 1 to 4 IU for each increment of 50 mg/dL based on insulin sensitivity and it is preferable to start with 1IU/50 mg/dL increment

Blood glucose monitoring

BG testing is mandatory for every patient on admission and at least two readings in the next 24 hours to rule out hyperglycemia.

HbA1c should be obtained in patients with hyperglycemia without prior history of DM and with persistent hyperglycemia of uncertain etiology. This test is unreliable in patients receiving massive blood transfusions, severe anemia, and hemolysis.

Point of care monitoring of blood glucose is to be done preferably with capillary method.

In cases of hypotension, hypothermia, shock, use of vasoconstrictors and vasopressors, glucose values will fluctuate and glucometer reading may be

incorrect. Hence, use of venous sampling must be used instead of glucometer readings as it may be unreliable in these conditions.

Initial monitoring should be done on an hourly basis for patients on IV insulin infusion. Interval of testing can be increased when three consecutive readings are consistently around the target by monitoring 3 premeal glucose.

9.1.2 ICU Patients

Glycemic control in critically ill patients is a challenge, as these patients invariably have multiorgan dysfunction and are at high risk of hypoglycemia. The only acceptable modality of treatment is continuous IV insulin infusion, which should be initiated when BG levels are greater than 180 mg/dL.

- Any blood glucose >140 mg/dL is hyperglycemia and needs close monitoring.
- Insulin therapy should be initiated for treatment of persistent hyperglycemia starting at a threshold ≥180 mg/dL (10.0 mmol/L).
- Once insulin therapy is started, a target glucose range of 140–180 mg/dL (7.8–10.0 mmol/L) is recommended for the majority of critically ill patients and noncritically ill patients.
- Only IV insulin is recommended. (Table 3)
- Regular insulin or rapid-acting insulin analogs (aspart, lispro, and glulisine) can be used as IV infusion.
- Titration of insulin dose can be done according to blood glucose level (Table 4).
- Transition to subcutaneous insulin from IV insulin should have an overlapping period of 1–2 hour. The overlap can be reduced to 15–30 min if rapid acting analogs are used.

Table 3: Suggested protocol for insulin infusion in ICU

Preparation	50 units of regular insulin dissolved in 50 mL normal saline (NS) in a 50 mL disposable syringe
Mode of administration	IV infusion with an electronic syringe pump/ infusion pumps
Primary target	To maintain blood glucose level within a predefined target 140 – 180 mg/dL
Achieving	Blood glucose to be controlled gradually in case

control	of severe hyperglycemia by titrating the dose of IV insulin
Pre requisite	Initially 15–20 mL of solution should be flushed through plastic tubing to saturate the insulin binding sites in the tubing
Targets	Dose should be adjusted as per the levels of blood glucose
Monitoring	Either by capillary blood glucose or from the venous site/central line

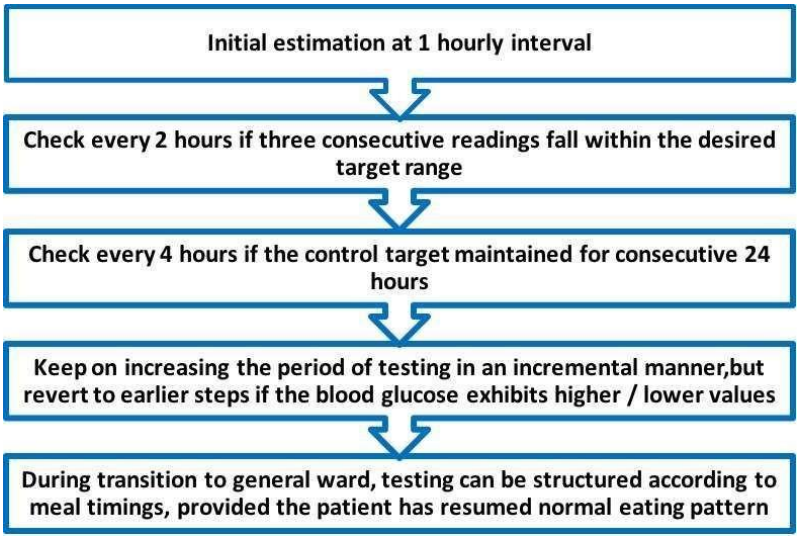
Table 4: Titration of insulin dose according to blood glucose (BG) levels

Blood glucose levels (mg/dL)	Dosage of insulin infusion
<100	No insulin
100-149	1-1.5u/hr
150-199	2.0 u/hr
200-249	2.5u/hr
250-299	3.0 u/hr
300-349	3.5u/hr
350-400	4.0 u/hr

For any further increase in BG, duty doctor needs to decide the rate on individual basis. If BG does not fall more than 10%, insulin can be increased to 1.5 times the normal dose.

If BG is < 70 mg/dL, administer 50 mL of dextrose (25 g), check blood glucose at 15 minutes and repeat if hypoglycaemia persists. If blood glucose increases to more than 100 mg/dL, start insulin infusion after 1 hour at a lower dose.

Monitoring of blood glucose in ICU



Transition from intravenous to subcutaneous basal bolus insulin

IV insulin provides basal insulin for critically ill patients who are not on oral feeds.

Once oral feeds are started, meal time bolus insulin should be the best option to cover meal related hikes in blood glucose. Therefore, it is best to change to subcutaneous basal/bolus insulin once patient starts having oral feeds.

Intravenous insulin infusion should be continued for at least 3-4 hours after the basal Insulin dose is administered and starting the meal time bolus dose. It can be discontinued sooner after the basal Insulin is given if rapid-acting Insulin analogs provided as a mealtime bolus dose.

The basal insulin dose can be estimated by calculating the total IV insulin requirement for 24 hours while the patient was not eating or as 50% of the TDD if patient is taking orally.

During transition from IV to subcutaneous insulin, a reduction in the basal dose by 20–30 % to account for decreasing requirements has been found to be safe and effective.

Table 5: Sample Conversion From IV to Basal/Bolus Insulin

Sample: Basal/bolus insulin dose calculation for a patient started on diet who required 2 units/hour of insulin overnight while NPO	
Step 1	Basal dose calculation: 1. Patient's hourly insulin infusion rate while NPO = 2 units/hour 2. 24-hour basal insulin dose during stress = 24 × hourly infusion rate = 24 × 2 = 48 units 3. Adjusted basal dose accounting for stress reduction = 2/3 × 24-hour basal rate = 2/3 × 48 = 32 units of Basal insulin
Step 2	TDD calculation TDD = dose is 2 × adjusted basal dose = 2 × 32 = 64 units
Step 3	Mealtime bolus dose calculation Patient just started to eat, so 10% of basal dose can be started with each meal = 0.1 × 32 = 3 units with each meal
Step 4	Correctional scale estimation (See below)

Calculation of Correction dose (1800 for analogues and 1500 for conventional insulin)

Correction Factor = 1800 ÷Total Daily Insulin Dose

= Reduction of blood glucose in mg/dl with 1 unit of insulin Example:

To calculate the correction factor for the total daily insulin dose of 40 units

Correction Factor = 1800 ÷ TDD(40 units) = 45 mg/dL.

This means that 1 unitof insulin will decrease the blood glucose by 45 mg/dl. **For all practical purposes, we can use the correction factor as 1 unit of rapid acting/regular insulin will drop the blood glucose by 40-50 mg/dl.**

9.1.3 Special situations

1. Patient on steroids

Due to sustained hyperglycemia especially during post-prandial period, susceptible glucocorticoid users can be treated with adding and titration of meal-time insulin.

For patients already on insulin, 20% increment in total daily insulin dose at the time of high-dose glucocorticoid initiation is a reasonable step.

2. Patients on Enteral Nutrition

- Insulin analogs should be preferred to control hyperglycemia in indoor patients on enteral nutrition
- Basal plus multiple subcutaneous prandial boluses are to be preferred over Sliding scale.

3. Patients Receiving Parenteral Nutrition

- Intravenous insulin infusion is the preferred treatment for control of hyperglycemia in patients receiving parenteral nutrition
- Glucose targets should be based on the severity of underlying illness

4. Peripartum Control of Hyperglycemia

- Insulin is the preferred therapy in pregnancy complicated by diabetes.
- Regular insulin or rapid-acting insulin analogs—aspart and lispro are approved for use in pregnancy.
- NPH or Detemir are the approved basal insulins.
- Patients in active labor should be on glucose, IV insulin plus potassium infusion to prevent hypokalemia, hypoglycemia as well as ketosis.
- Incremental insulin dose is required for pregnant females receiving long-acting glucocorticoid for fetal maturity

9.1.4 Discharge and outdoor management of patients with diabetes

Transition Regime: Discharge should be done only after stabilization of blood glucose levels. It is prudent to follow a practical plan of switching over to SC insulin based on the most recent IV insulin requirement before planning discharge.

The patient should be provided a simplified treatment plan including drug regime and its appropriate use, BG monitoring schedule, hypoglycemic symptoms and their management, and contact number of primary care physician whom they can contact during any major complaint or emergency.

Patients should be shifted to more convenient insulin regimes, such as premixed insulin twice daily, if possible, before discharge from hospital, and the concordance of meals and SC insulin should be ensured.

They should be monitored on this regime for a few days in hospital if possible, and the first follow-up should be done within 10–14 days time period. The discharge card will take into consideration the following points.

- Discharge plan for every patient
- Diagnosis
- Dose requirements
- Patient preferences
- Education
- Plan next follow up visit

9.2 Prevention of diabetes

Screen all high risk subjects attending our health care facility and every opportunity to diagnose early must be utilised at all levels of care.

Targeting high risk groups:

1. Age more than 30 years
2. Obese children& young adults
3. Higher waist circumference
4. Family history of diabetes
5. Women with history of GDM & PCOD
6. History of hypertension

If the screening test and the diagnostic test are the same will be cost effective and hence FPG is appropriate if possible. It must be repeated every 3 years and yearly if more than one risk factors are present.

Education and community empowerment programs must be incorporated as and when possible.

9.3 Further reading

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Section - II

Endocrine Diseases

Abbreviations

ACTH	**:**	**Adreno-cortico trophic hormone**
ASCVD	**:**	**Athero Sclerotic Cardio Vascular Disease BG Blood Glucose**
CKD	**:**	**Chronic Kidney Disease**
CMV	**:**	**Cytomegalovirus**
DPP-4	**:**	**Dipeptidyl peptidase-4**
DPP-4-i	**:**	**DPP-4 inhibitor**
eGFR	**:**	**Estimated Glomerular Filtration Rate**
GLP-1 RA	**:**	**GLP-1 receptor agonist**
GLP-1	**:**	**Glucagon-like peptide-1**
HbA1C	**:**	**Glycated haemoglobin**
HIV	**:**	**Human Immunodeficiency Virus**
IM	**:**	**Intramuscular**
IV	**:**	**Intravenous**
NPH	**:**	**Neutral Protamine Hagedorn**
NPO	**:**	**Nil Per Orally**
PRL	**:**	**Prolactin**
SC	**:**	**Subcutaneously**
SGLT2	**:**	**Sodium-Glucose co-transporter 2**
SGLT2-I	**:**	**SGLT2 inhibitor**
SU	**:**	**Sulfonylurea**
T3	**:**	**Serum Triiodothyronine**
T4	**:**	**Serum Thyroxine**
TDD	**:**	**Total Daily Dose**
TSH	**:**	**Thyroid Stimulating Hormone**
TZD	**:**	**Thiazolidinedione**

Introduction

This volume of Standard Treatment Guidelines includes selected topics in the area of Endocrinology and Metabolism and this includes:

1. Diagnosis and management of Diabetes mellitus
2. Management of in hospital hyperglycemia
3. Hypothyroidism
4. Thyrotoxicosis
5. Cushing's syndrome
6. Adrenal insufficiency
7. Hyperprolactinemia

Scope:

Diabetes mellitus is the major clinical condition we are going to face in clinical practice and we need to address it in all levels from primary prevention, early diagnosis, management, screening and management of complications. Patient and community empowerment is also a challenge in patient care. Other topics also selected to address the common endocrine problems in clinical practice.

The team has prepared the STGs jointly trying to incorporate the current knowledge and to suit our patient population at large. Definitely the clinician has to use their practical knowledge and judgement to suit the best care for an individual patient. There are six chapters in this volume to make it easy to refer. We are tried to incorporate algorithms and tables to make it user friendly.

1. Hypothyroidism

1.1. Introduction

Hypothyroidism is a clinical disorder characterized by insufficient thyroid hormone and may arise from primary hypothyroidism, due to intrinsic failure of the thyroid gland, or central hypothyroidism, resulting from inadequate stimulation of the thyroid gland by the hypothalamus or pituitary.

Hypothyroidism can be overt; with decrease in serum thyroxine (T4) levels and a compensatory increase in thyroid stimulating hormone (TSH) or subclinical hypothyroidism in which TSH is mildly elevated with normal serum T4 levels.

1.1.1. Causes

- Auto immune thyroiditis (Hashimotos thyroiditis)
- Thyroidectomy

- Subacute thyroiditis
- External irradiation
- Medications (antithyroid drugs, amiodarone, lithium, bexarotene, tyrosine kinase inhibitors and interferon)
- Infiltrative diseases
- Central (Pituitary/hypothalamic) hypothyroidism
- Congenital defects
- Endemic (iodine deficient) goiter

1.1.2. Signs and Symptoms of Hypothyroidism

Symptoms	Signs
Tiredness, weakness	Dry, coarse skin
Dry skin	Cool Peripheral Extremities
Hair loss	Puffy face, hand and feet
Difficulty in concentrating or poor Memory	Delayed relaxation of ankle jerk
Constipation	
Weight gain with poor appetite	
Dyspnoea	
Hoarse Voice	
Menorrhagia (Later	

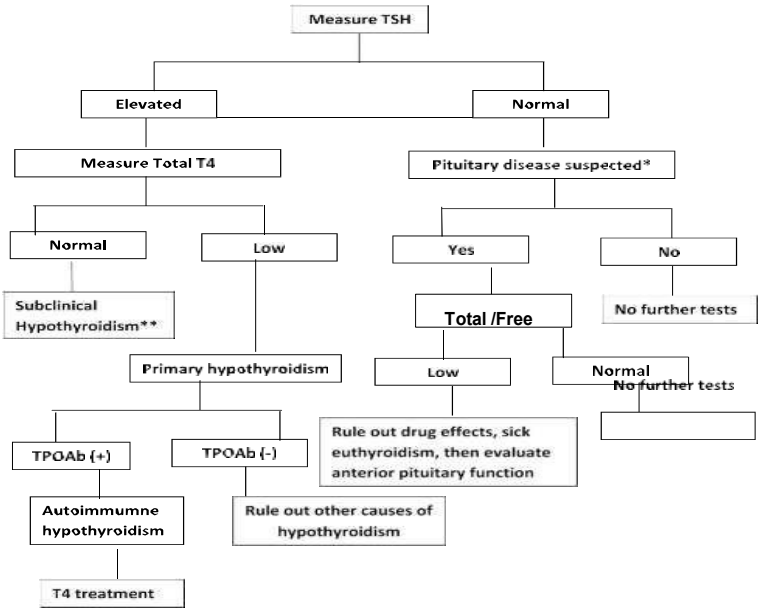
oligomenorrhoea or amenorrhoea) Paraesthesia Impaired Hearing	

1.1.3. Diagnosis

- Clinical signs and symptoms
- Laboratory test – T3, T4 & TSH
- Sub clinical hypothyroidism- Normal T3, Normal T4, Increased TSH. Patients with subclinical hypothyroidism should have repeat testing of T4, TSH after 6-8 weeks. An anti-TPO antibody can be considered in subjects with subclinical hypothyroidism.

Overt Hypothyroidism – Low T3, Low T4 and Increased TSH

1.1.4. Diagnosis



1.2. Hypothyroidism in pregnancy

Both subclinical and overt hypothyroidism results in adverse foetal and maternal outcome during pregnancy. Hypothyroidism is associated with an increased risk of obstetric problems like spontaneous abortion, hypertensive disorders of pregnancy, placental abruption, foetal distress, increased caesarean sections, postpartum haemorrhage, preterm birth, low birth weight, perinatal death and foetal goitre. Screening for thyroid dysfunction is preferable in pregnancy.

Treatment

Levothyroxine is the preferred drug

Dose- 0.6 to 1.6 microgram /kg/day, as single morning dose on empty stomach.

- In healthy young patients start with a higher dose and in elderly patients start with a lower dose. In subjects with cardiac disease, start at a lower dose and titrate up gradually.

  The goal TSH of treatment of primary hypothyroidism is normal TSH levels, including in pregnancy. Treatment decisions should be guided by trimester-specific, pregnancy-based TSH reference intervals, preferably derived from local population-specific normative data, when such reference ranges are available.

- In suspected central hypothyroidism, cortisol axis should be assessed before starting treatment with Thyroxine.

Monitoring the treatment

Six to eight weeks after changing the treatment and once target is achieved on a stable dose, once in an year - TSH

Pregnancy: Once in 4 weeks in first trimester, 6 – 8 weeks in second and third trimester –T4 & TSH.

Subclinical hypothyroidism is not a contraindication for surgery.

Overt, uncorrected hypothyroidism carries a high risk for surgery. Therefore, in elective cases euthyroid status may be achieved before taking up for procedure.

Indications for Referral

1. Not responding to standard treatment
2. Central hypothyroidism.

2. Thyrotoxicosis

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Thyrotoxicosis is defined as the state of thyroid hormone excess and is not synonymous with *hyperthyroidism*, which is the result of excessive thyroid function.

2.1. Etiology

Causes of thyroid hormone excess include

1) Hyperthyroidism (Graves' disease, toxic multinodular goiter [MNG], toxic adenoma, iodine excess)
2) Thyroid destruction (subacute thyroiditis, silent thyroiditis, amiodarone, radiation)
3) Extrathyroidal sources of thyroid hormone (thyrotoxicosis factitia, struma ovarii, functioning follicular carcinoma metastasis)
4) Secondary hyperthyroidism (TSH-secreting pituitary adenoma, thyroid hormone resistance syndrome, human chorionic gonadotropin [hCG]-secreting tumors, gestational thyrotoxicosis).

Graves' disease, caused by stimulating TSH-receptor antibodies, is the most common cause of thyrotoxicosis and accounts for 60–80% of cases.

2.1.1. Clinical Features

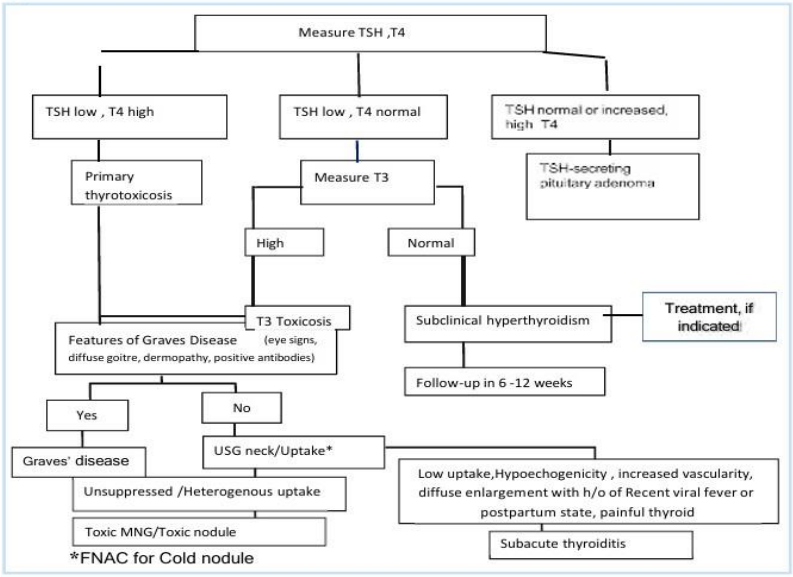
Symptoms include nervousness, irritability, heat intolerance, excessive sweating, palpitations, fatigue and weakness, weight loss with increased appetite, frequent bowel movements, and oligomenorrhea. Pts are anxious, restless, and fidgety. Eyelid retraction and lid lag may be present. Cardiovascular findings include tachycardia, systolic hypertension, systolic murmur, and atrial fibrillation. A fine tremor, hyperreflexia, and proximal muscle weakness also may be present. In the elderly, the classic signs of thyrotoxicosis may not be apparent, the main manifestations being weight loss and fatigue ("apathetic thyrotoxicosis"). In Graves' disease, infiltrative ophthalmopathy (with variable degrees of proptosis, periorbital swelling, and ophthalmoplegia) and dermopathy (pretibial myxedema) also may be found. Thyrotoxic crisis, or thyroid storm presents as a life-threatening exacerbation of hyperthyroidism, and can be accompanied by fever, delirium, seizures, arrhythmias, coma, vomiting, diarrhea, and jaundice.

2.1.2. Diagnosis

Serum TSH is a sensitive marker of thyrotoxicosis. Supression of TSH is caused by Graves' disease, autonomous thyroid nodules, thyroiditis, and exogenous levothyroxine treatment. All patients with hyperthyroidism should have at least T4 (or Free T4) and TSH done.

Thyroid scintigraphy (RAI/Technitium) may be required to distinguish the various etiologies: high uptake in Graves' disease and nodular disease versus low uptake in thyroid destruction, iodine excess, and extrathyroidal sources of thyroid hormone.

2.1.2.1. Algorithm for diagnosis



2.2. Treatment

2.2.1. Graves' disease

Graves' disease may be treated with antithyroid drugs or radioiodine. Thyroidectomy is rarely indicated. The main antithyroid drugs are methimazole or carbimazole and propylthiouracil. Carbimazole is preferred in most patients because of easier dosing. The initial dose of Carbimazole commonly employed in moderate thyrotoxicosis is 20 to 30 mg daily in divided doses until the patient is euthyroid and then a maintenance dose of 5 to 10 mg once daily can be employed. Thyroid function tests should be checked 3–4 weeks after initiation of treatment, with adjustments to maintain a normal T4 level. TSH levels often remain supressed for several months and therefore do not provide a sensitive index for treatment response. The common side effects are rash, urticaria, fever, and arthralgia. Uncommon but major side effects include hepatitis, an SLE-like syndrome and agranulocytosis. WBC count testing is indicated in patients with sore throat and fever. Propranolol or longer- acting beta blockers such as atenolol may be useful at the start of treatment to control adrenergic symptoms until euthyroidism is reached. Radioiodine can also be used as initial treatment or in patients who do not undergo remission after 12-18 months of antithyroid drug therapy. In patients with good

remission, regular follow up is essential. If symptoms relapses, the treatment options are,

1. Prolonged medical treatment
2. Radio Iodine ablation. Surgery is considered in cases of suspected malignancy, large goitre with compressive symptoms or resistance to large doses of antithyroid drugs. Progressive exophthalmos with chemosis, ophthalmoplegia, or vision loss is treated with large doses of steroids. In thyroid storm, large doses of PTU or methimazole / carbimazole should be administered followed by saturated solution of KI along with propranolol and dexamethasone. Any underlying precipitating cause should be identified and treated.

2.2.2. Toxic nodular hyperthyroidism (Toxic multi nodular goitre & Toxic adenoma)

Medical therapy using antithyroid drugs and betablockers can normalise thyroid function but it is not an optimal long-term treatment. Radio-iodine is the treatment of choice for toxic adenoma. Large toxic adenomas and MNG needs surgery in most of the clinical situations.

2.2.3. Subacute thyroiditis

Aspirin or NSAIDS are sufficient to control symptoms in most cases. Steroids may be used if patients fail to respond to NSAIDS. Symptoms of thyrotoxicosis improve spontaneously but may be controlled by beta blockers ; antithyroid drugs play no role in treatment of thyrotoxic phase. Levothyroxine replacement may be needed if the hypothyroid phase is prolonged/symptomatic. Thyroid function should be monitored every 2-4 weeks using TSH and T4 levels.

2.2.4. Thyrotoxicosis in pregnancy

- Physiological changes in pregnancy should be considered while interpreting TFT especially in the first trimister. Normal T3& T4 levels in pregnancy are 1 ½ times upper limit of normal of nonpregnant levels by around 16th week of gestation.
- TSH will normally be low/ suppressed in first trimester because of the effect of HCG.
- Getstational thyrotoxicosis is diagnosed in presence of hyperemesis, elevated T3 T4 and suppressed TSH and requires only symptomatic treatment.
- A denovo diagnosis of Grave's disease in the first trimester should be suspected when there are clinical features like ophthalmopathy, goitre and dermopathy and confirmed by serial testing of TFTs and TSH R antibodies.
- Pre existing thyrotoxicosis on Carbimazole coming with pregnancy

- In stable disease – Change to PTU in smallest possible dose to maintain upper normal level of FT4/T4. Convert initially using the equivalence of 10 mg of Carbimazole =100 mg of PTU.
- 2^{nd} & 3^{rd} trimester – Change to Carbimazole after first trimester
- In postpartum breast feeding – Minimum dose of Carbimazole to maintain upper normal level of FT4/T4
- Fetal heart rate and Goitre should be monitored throughout antenatally. Neonatal thyroid assessment is mandatory.

2.3. Who needs referral

1) Patients with unsupressed TSH in the setting of elevated T4.
2) Failure to achieve remission in Grave's disease despite treatment with antithyroid drugs for upto 18 months.
3) Progressive or severe exophthalmos despite treatment.
4) Symptoms and signs of thyroid crisis.
5) Thyrotoxicosis during pregnancy

3. Hyperprolactinemia

3.1. Introduction

Prolactin is unique among the pituitary hormones in that the predominant central control mechanism is inhibitory, reflecting dopamine-mediated suppression of PRL release. Prolactin acts to induce and maintain lactation and decrease reproductive function and drive.

3.1.1. Etiology:

Physiological causes	Pathological causes
Pregnancy, Nursing, Nipple stimulation, Sexual intercourse, Stress (surgery, hypoglycemia, myocardial infarction, syncope, trauma, venesection), sleep, exercise, Food ingestion	1) Pituitary disease (Prolactinomas, Mixed GH/PRL or ACTH/PRL secreting adenomas, intrasellartumours causing stalk compression (non secretor adenomas, germinoma, meningioma, glioma,

Pharmacological causes 1) Dopamine receptor antagonists – a. Antipsychotics [Phenothiazines, Butyrophenones, Thioxanthenes, Risperidone, Sulpiride) b. Antiemetics [Metoclopramide, Domperidone 2) Dopamine depleting agents α- Methyl Dopa, Reserpine 3) Antidepressants a. Tricyclic antidepressants b. Selective Serotonin Receptor Inhibitors 4) Hormones: Estrogens (high dose), Antiandrogens 5) Opiates 6) Verapamil 7) Cimetidine (intravenous)	metastasis), intrasellar cyst, Rathke's cleft cyst. 2) Hypothalamic and pituitary stalk disease a. Granulomatous diseases (sarcoidosis, tuberculosis, eosinophilic granuloma) b. Tumours (craniopharyngioma, hamartoma, glioma, germinoma, metastasis) c. Cranial irradiation d. Pituitary stalk section e. Empty sella f. Vascular (aneurysm, arteriovenous malformation) g. Lymphocytic hypophysitis 3) Others a. Primary hypothyroidism, Chronic Renal Failure, Cirrhosis, Chest wall trauma (including surgery, herpes zoster), seizures, Polycystic Ovary Syndrome, Ectopic secretion of PRL (bronchogenic sarcoma, hypernephroma)

3.1.2. Clinical Features

In women, amenorrhea, galactorrhea, and infertility are the hallmarks of hyperprolactinemia.

Galactorrhea, the inappropriate discharge of milk –containing fluid from the breast, is considered abnormal if it persists longer than 6 months after cessation of breast-feeding.

In men, symptoms of hypogonadism or mass effects are the usual presenting

symptoms, and galactorrhea is rare.

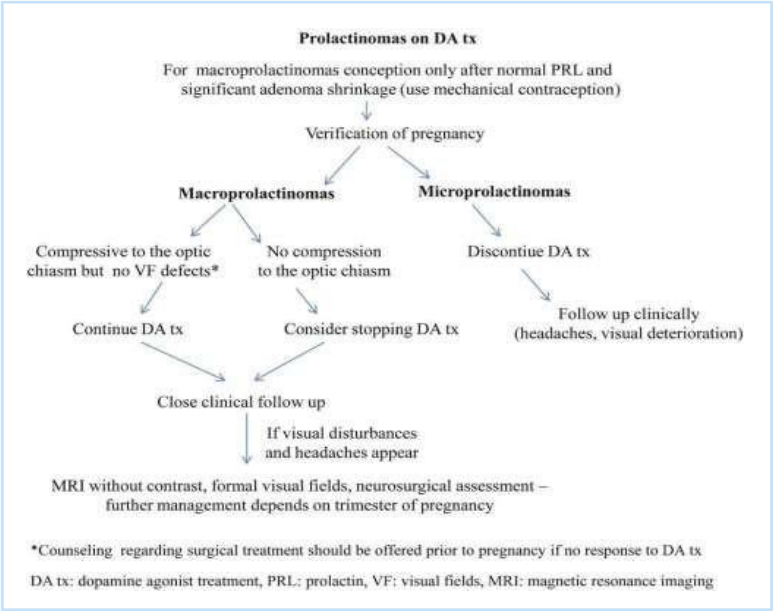
3.1.3. Diagnosis

1) Pooled sample levels (preferably 3 samples in 30 minutes intervals but at least two) should be measured.
2) When clinical suspicion is high, measurement of levels on several different occasions may be required.
3) If hyperprolactinemia is present, nonneoplastic causes should be excluded (e.g., pregnancy test, hypothyroidism, chronic renal failure, chronic liver disease, medications).Even in such cases, if the level exceeds more than100ng/ml, further evaluation is needed.
4) A pituitary MRI should be performed if the underlying cause of PRL elevation is unknown.
5) Pituitary macroadenoma needs further evaluation of other pituitary hormonal axis and visual field testing.

3.1.4. Treatment

1) If the patient is taking a medication that is known to cause hyperprolactinemia, the drug should be withdrawn, if possible.
2) Medical therapy with a dopamine agonist is indicated in microprolactinomas for control of symptomatic galactorrhea, for restoration of gonadal function, or when fertility is desired. Dopamine agonist therapy for macroprolactinomas generally results in both adenoma shrinkage and reduction of PRL levels.
3) Cabergoline and bromocriptine are the two most frequently used dopamine agonists. Cabergoline is started at a dose of 0.25 – 0.5 mg weekly once and then the dose is modified depending on the clinical and biochemical response. The response is assessed 6-8 weeks after starting or modifying treatment.
4) The dosage of Bromocriptine – 1.25mg – 2.5 mg daily preferably at bed time.
5) In patients with microadenomas successfully treated (good clinical response, normal PRL), therapy may be withdrawn after 2 years, followed by careful clinical monitoring for recurrence.

3.1.5. Prolactinomas management in pregnancy:



3.2. When to refer

1. Discordance between biochemical and clinical parameters
2. Not responding to conventional treatment for 6 months
3. Patients planning for pregnancy
4. Patients while on treatment presenting with severe headache, ocular palsies, other neurological defects, CSF rhinorrhoea
5. Macroprolactinomas

4. Cushing's syndrome

4.1. Introduction

Cushing's syndrome is caused by chronic exposure to excess of either endogenous cortisol or exogenous glucocorticoids. Most common cause is exogenous Cushing's syndrome caused by iatrogenic administration of synthetic glucocorticoids.

Endogenous Cushing's is further divided into:

- *ACTH –dependent*

Pituitary adenoma secreting ACTH

Ectopic ACTH syndrome

- *Non-ACTH dependent*

Adrenal adenoma

Adrenal carcinoma

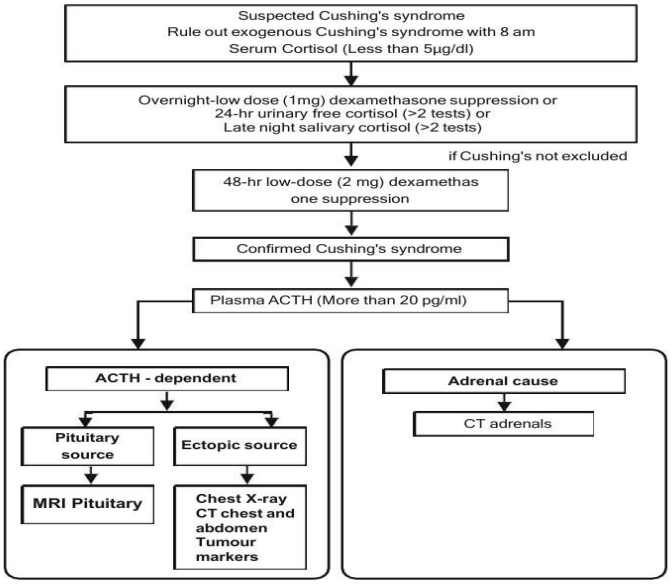
- **Other rare causes -** Adrenal hyperplasia Either Macronodular adrenal hyperplasia or Micronodular Hyperplasia (Ex – Primary Pigmented nodular adrenocortical disease)

4.1.1. Clinical features

Centripetal obesity, wide purple striae, hirsuitism, easy bruisability, proximal myopathy, hypertension, personality changes, fractures. Hyperpigmentation is seen in ACTH dependent cases. Hypokalemia and metabolic alkalosis is more pronounced in ectopic ACTH production. Hypertension, diabetes, osteoporosis are non-specific features associated with cortisol excess.

4.1.2. Diagnosis of Cushing syndrome: Flow chart is given below

Sequence of investigations in suspected spontaneous Cushing's syndrome



4.1.3. Management:

Uncontrolled hypercorticolism carries a poor prognosis, and treatment of Cushing's syndrome is therefore necessary. Trans-sphenoidal surgery for pituitary ACTH secreting microadenomas is curative in 70–80% when performed by a highly experienced surgeon, but long-term follow-up is required because these tumors

may recur. Radiation therapy may be used when a surgical cure is not achieved. Therapy of adrenal adenoma or carcinoma requires surgical excision. If the source of ACTH cannot be resected, medical management with ketoconazole, Levoketoconazole , Mifepristone, metyrapone, or mitotane may relieve manifestations of cortisol excess. Newer drugs like osilodrostat which specifically inhibit 11 beta hydroxylase enzyme type 1 helps in disease control.

4.2. When to refer:

All cases of endogenous Cushing's syndrome

5. Adrenal Insufficiency

5.1. Introduction

Adrenal insufficiency (AI) is one of the endocrine emergencies which may be rapidly life threatening. Adrenal hormones include glucocorticoids, mineralocorticoids, sex steroids and catecholamines (Adrenaline and Noradrenaline). Glucocorticoid secretion is regulated by Adreno- corticotrophic hormone (ACTH) from pituitary whereas mineralocorticoid regulation is via the renin angiotensin system. In primary adrenal insufficiency (PAI) (diseases affecting the adrenal itself) both glucocorticoid and mineralocorticoid deficiency is seen whereas in secondary adrenal insufficiency (SAI) (Pituitary/ hypothalamic dysfunction) only glucocorticoid deficiency is seen.

5.1.1. Etiology

Major reasons for PAI include adrenal tuberculosis and autoimmune adrenalitis. Other reasons include viral (CMV/HIV), fungal infections, metastatic and infiltrative diseases, adrenal haemorrhage, adrenalectomy and certain congenital diseases. Autoimmune adrenalitis may be accompanied by autoimmune diseases involving other endocrine glands (thyroid, endocrine pancreas, gonads, parathyroids etc) as well as other organs (pernicious anemia). Exogenous steroid withdrawal is the most common reason for secondary adrenal insufficiency followed by pituitary tumours, apoplexy, pituitary surgery or irradiation, Sheehan's Syndrome and some genetic disorders.

5.1.2. Clinical features of Primary AI and those of adrenal crisis are listed in the table below.

Feature	Frequency %
Weakness Tiredness, fatigue	100
Anorexia	100

Nausea	86
Vomiting	75
Abdominal Pain	31
Salt craving	16
Postural dizziness	12
Weight loss	100
Hyperpigmentation	94
BP<110 mm Hg	90
Hyponatremia	88
Hyperkalemia	88

5.1.3. Clinical and laboratory features of Adrenal Crisis

Dehydration, Hypotension or shock out of proportion to the severity of current illness
Nausea and vomiting with history of weight loss and anorexia
Abdominal pain (acute abdomen)
Unexplained hypoglycaemia
Hyponatremia, hyperkalemia, azotemia hypercalcemia or eosinophilia
Hyperpigmentation or vitiligo
Other endocrine deficiencies like hypothyroidism, gonadal failure or hypophysitis

5.1.4. Recommendations

5.1.4.1. Diagnosis

1) A very low serum cortisol (< 3µg/dl) at the expected diurnal peak (8 am) may

be considered diagnostic of adrenal insufficiency in a patient who is not currently on steroid supplementation.

2) For patients who are clinically suspected to have AI but serum cortisol levels are between 3-14.5 µg/dl an ACTH stimulation test should be done to exclude the condition.

3) Procedure for ACTH stimulation test: Take a basal cortisol value irrespective of the time of the day and Inject Synacthen 250 µg IV or IM collect serum sample for Serum cortisol after 30 min and again after one hour. If synacthen is not available, long acting ACTH 30 iu s/c may be used with samples for cortisol drawn at 60 and 90 minutes.

4) Any value more than 18 µg/dl during an ACTH stimulation test rules out Adrenal insufficiency and peak value less than this cut off is considered diagnostic of AI.

5) During acute illness an unstimulated level less than 15 µg/dl is considered to be low and a stimulated value more than 33 µg/dl or a rise in cortisol by 9 µg/dl is considered normal.

6) Differentiation between primary and secondary AI is done on basis of Serum ACTH levels. In primary AI Serum ACTH is usually elevated many timesthe upper limit of normal (at least two fold) whereas in Secondary AI it may be normal (inappropriately) or low.

7) For etiological diagnosis further evaluation is warranted.

5.1.5. Treatment

1) For an adult patient who is not seriously ill the treatment may be started with a physiological replacement dose of hydrocortisone 15 to 20 mg/ day in divided doses or prednisolone 5 to 7.5 mg/ day.

2) Patients with primary adrenal insufficiency require mineralocorticoid supplementation (fludrocortisone 50 to 100 mcg/day)

3) In children hydrocortisone is recommended.

4) During acute illnesses the doses of glucocorticoid needs to be escalated. For any illness like a mild infection, injury, vomiting /diarrhoea the steroid dose can be doubled for 2-3 days.

5) For patients experiencing hypotension or loss of consciousness IV hydrocortisone needs to be given at a dose of 100 mg Stat and then 50 to 100 mg IV Q6 h and then tapered back to maintenance doses once the illness has settled. If there is no IV access, IM hydrocortisone can be given.

6) Any elective or emergency procedures of a major nature (general anaesthesia) require preoperative steroid escalation. Injection Hydrocortisone 100 mg IV should be given 30 min prior to induction and should be continued Q6h for first 48 hours after which it can be rapidly tapered by 50 % per day. Minor procedures like endoscopy, cataract surgery, dental extraction etc may be given one single dose of 100 mg hydrocortisone IV before the procedure.

7) Injection Hydrocortisone 100 mg IV should be given 30 min prior to induction and should be continued Q6h for first 48 hours after which it can be rapidly tapered by 50 % per day.

8) AI patients require at least half-yearly to yearly regular follow up.

9) Identification cards with diagnosis and emergency medications should be carried by the patient.

5.1.6. Monitoring

Clinical weight, blood pressure, Cushingoid features, growth monitoring in children
Biochemical: Monitoring of sodium, potassium, plasma glucose

5.2. Treatment of adrenal crisis (Acute adrenal insufficiency)

5.2.1. Emergency Measures

1) Establish IV access with a large gauge needle.

2) Draw blood for immediate serum electrolytes and glucose and routine measurement of plasma cortisol and ACTH. Do not wait for the laboratory results.

3) Infuse 2-3 litters of 0.9 % NaCl solution or Dextrose Normal Saline (5% & 0.9%) as fast as possible. Monitor for fluid overload (Jugular venous pressure or central venous pressure or bilateral basal crepitations), reduce infusion rate if indicated.

4) Inject Hydrocortisone 100 mg IV every sixth hourly.

5) Use supportive measures as indicated.

5.2.2. Subacute measures after stabilization of the patient

1) Continue 0.9% NaCl at a slower rate75-100 ml/hr for the next 24 hours.

2) Search for and treat the precipitating cause of adrenal insufficiency

3) Perform an ACTH Stimulation test if the patient is not previously known to have adrenal insufficiency.

4) Determine the type of adrenal insufficiency and consider imaging if appropriate.

5) Taper glucocorticoids to maintenance doses over 1-3 days if precipitating illness permits

6) Begin mineralocorticoid (fludrocortisone) supplementation (0.1 mg/day) inpatients with primary adrenal insufficiency only

5.3. Indications for Referral

All cases of adrenal insufficiency for etiological diagnosis and long-term management.