GUIDELINES

For

GENERAL PRACTITIONERS

2024

Press record

First Edition

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FOREWORD

It is a great honor for me to write a foreword to Guidelines for General Practitioners by General Practitioners' society, Myanmar Medical Association (Central).

General practitioners are the primary health providers in the community looking after the majority of the people of our country. They are being trusted and depend upon by every families in the surrounding area where they practice. The first and foremost care by the General Practitioners are the most important for all the people.

Guidelines based on a critical appraisal of scientific evidence (evidence-based guidelines) clarify which interventions are of proved benefit and document the quality of the supporting data. They alert clinicians to interventions unsupported by good science, reinforce the importance and methods of critical appraisal, and call attention to ineffective, dangerous, and wasteful practices.

Clinical guidelines can improve the quality of clinical decisions. They offer explicit recommendations for clinicians who are uncertain about how to proceed, overturn the beliefs of doctors accustomed to outdated practices, improve the consistency of care, and provide authoritative recommendations that reassure practitioners about the appropriateness of their treatment policies.

The Myanmar Medical Association together with the GP society has been helping out with the CME and CPD program for the Member doctors both inhouse sessions and online courses. This guideline is one of the essential parts of this CPD for the GPs.

I would like to congratulate the GP society for their effort for producing this guideline and also, I would like to encourage them to review and updated regularly.

Professor Aye Aung
President
Myanmar Medical Association

April, 2024

PREFACE

We are writing this letter to express our sincerest gratitude and appreciation for the successful completion of the **second edition** of the **General Practitioners' Guidelines**. This accomplishment is the result of an exceptional collaborative effort, and we would like to extend our thanks to all those involved.

The General Practitioners' Guidelines has been an invaluable resource since its inception with the launch of the first edition in November 2017. As per the initial plan, the guidelines were intended to be updated every three years to ensure the most up-to-date information reaches Myanmar General Practitioners, enhancing their knowledge in primary healthcare and family health.

However, the unforeseen outbreak of the Covid-19 pandemic disrupted our plans and posed numerous challenges for the team. In-person meetings became impossible due to safety concerns, making it necessary for us to find alternative means of communication and collaboration. Despite the adversity faced, the team members demonstrated remarkable resilience and adaptability by utilizing online platforms and technology to continue the update process.

We would like to extend our deepest gratitude to the dedicated team members who persevered and worked tirelessly during these trying times. Their commitment, professionalism, and unwavering dedication to the project enabled us to overcome the obstacles posed by the pandemic and successfully complete the second edition of the guideline.

Furthermore, we would like to express our sincere appreciation to the specialist societies that actively contributed to the development of the guidelines. Their expertise and invaluable insights have ensured that the content remains current, accurate, and relevant, enabling our General Practitioners to provide the highest quality of care to their patients.

We would also like to extend our heartfelt thanks to the esteemed President of the Myanmar Medical Association, for their continuous support and guidance throughout this endeavor. Their leadership and unwavering commitment to advancing medical knowledge in Myanmar have been instrumental in the success of this Guidelines.

Moreover, the decision to distribute the guideline as electronic copies reflects our commitment to ensuring easy access for all Myanmar General Practitioners. By making it available in this format, we aim to facilitate the dissemination of updated knowledge, thus empowering our healthcare professionals to deliver the best possible care to the community.

In conclusion, we would like to express our deepest gratitude to all those who contributed to the development and distribution of the General Practitioners' Guidelines Second Edition. The unwavering supports and collective efforts have made a significant impact on enhancing primary healthcare and family health care in Myanmar.

Once again, thank you for your outstanding dedication, resilience, and invaluable contributions. We look forward to our continued collaboration in advancing medical knowledge and improving healthcare outcomes for all.

Dr Khine Soe Win and Dr Win Zaw April, 2024
General Practitioners' Society (Central)
Myanmar Medical Association

EDITORIAL

It is my privilege to inform you that our updated and revised edition of "**Guidelines for General Practitioners**" will be published very soon and it is my great pleasure to be the editor-in-chief of this guideline book. There are various reasons for revising and updating the previous edition.

This is the fact that some important topics, for example, malaria and family violence are missing in the first edition and some clinical practice guidelines like Diabetes Management have been changed during the interim period. Of course, this opportunity arises due to the emergence of COVID-19 in the world. As all you know, Medicine is an ever-changing science; we need to consider updating our guidelines at least five- yearly. Hence the time is up now!

Education is achieved by assimilating information from many resources and readers of this book can enhance their learning experience in terms of reflecting in their daily Family/General Practice. We all take immerse pride in contributing good educational resource dedicated to Myanmar General Practitioners. The editors and authors anticipate that the readers will both enjoy and profit from their work in preparing this volume.

Happy studying and learning,

Dr Win Lwin Thein
Editor-in chief
Vice President (GP Society)
April, 2024

ACKNOWLEDGEMENT

We would like to thank all our talented and hard-working colleagues who have contributed to the ongoing development of the **Guidelines for General Practitioners**.

Especially, we would like to highlight the significance of the second edition which appears when the family medicine development process in Myanmar is being idle. Many factors are impeding the developing process lately, which has been accelerated previously by the commitment of the MOHS, the medical universities, and the General Practitioners' Society before the COVID-19 pandemic started.

No one can deny that the Myanmar health care system is lacking a strong and effective primary care task force. The best solution to mend this defect is retraining the thousands of general practitioners who are working individually across the country. Here comes the role of family medicine to train these GPs and primary care doctors to be able to use its principles effectively and, in turn, strengthen primary care.

Many GPs are using some family medicine principles consciously or unconsciously in varying degree of competency. Person-centered care, continuity of care, and family-oriented care became the culture of most practices for a long time. But only a few GPs can enjoy the most effective coordinated care and seamless continuity of care with secondary and tertiary care providers. The reasons behind this would be the absence of standardization in general practitioners' service quality and unawareness of the value of family medicine practitioners by other specialties and the public.

To resolve this ambiguity, primary care doctors should be involved in the retraining programs and thereafter CME/CPD and other life-long-learning programs which prescribe family medicine curricula.

We also acknowledge the effort of the contributors to make this new edition more family medicine-oriented, in addition to the Family Medicine chapter at the beginning of the book. We genuinely believe that the new edition will be a better reference for the GP/FP who wants to practice quality primary care and for future family medicine programs in Myanmar.

Finally, we would like to thank all academic writers who contributed to the General Practice Guidelines-first edition. Without their kind support, this second edition could never have happened.

Regards,

Dr. Tin Aye and Dr. Kyaw Thu

General Practitioners' Society (Central), MMA **April, 2024**

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SYMBOLS AND ABBREVIATIONS

AAA abdominal aortic aneurysm
ABC airway, breathing, circulation
ABCD airway, breathing, circulation, dextrose
ABO A, B and O blood groups
ACE angiotensin-converting enzyme
ACEI angiotensin-converting enzyme inhibitor
ACTH adrenocorticotrophic hormone
ADHD attention deficit hyperactivity disorder
ADT adult diphtheria vaccine
AFP alpha-fetoprotein
AI aortic incompetence
AIDS acquired immunodeficiency syndrome
AIIRA angiotensin II (2) reuptake antagonist
AKF acute kidney failure
ALE average life expectancy
ALL acute lymphocytic leukaemia
ALP alkaline phosphatase
ALT alanine aminotransferase
AMI acute myocardial infarction
AML acute myeloid leukaemia
ANA antinuclear antibody
ANF antinuclear factor
AP anterior–posterior
APH ante-partum haemorrhage
ASD atrial septal defect
ASIS anterior superior iliac spine
ASOT antistreptolysin O titre
AST aspartate aminotransferase
AV atrioventricular
AZT azidothymidine
BCC basal cell carcinoma
BCG bacille Calmette-Guérin
BMD bone mass density
BMI body mass index
BP blood pressure
BPH benign prostatic hyperplasia
Ca carcinoma
CABG coronary artery bypass grafting
CAD coronary artery disease
CAP community acquired pneumonia
CBT cognitive behaviour therapy
CCF congestive cardiac failure
CCU coronary care unit
CD4 T helper cell
CD8 T suppressor cell
CDT combined diphtheria/tetanus vaccine
CEA carcinoembryonic antigen
CFS chronic fatigue syndrome
CHD coronary heart disease
CHF chronic heart failure
CIN cervical intraepithelial neoplasia
CK creatinine kinase
CKD chronic kidney disease
CKF chronic kidney failure
CML chronic myeloid leukaemia
CMV cytomegalovirus
CNS central nervous system
COAD chronic obstructive airways disease
COC combined oral contraceptive
COCP combined oral contraceptive pill
COPD chronic obstructive pulmonary disease
COX cyclooxygenase
CPA cardiopulmonary arrest
CPAP continuous positive airways pressure
CPK creatine phosphokinase
CPR cardiopulmonary resuscitation
CR controlled release
CREST calcinosis cutis; Raynaud's phenomenon; oesophageal involvement; sclerodactyly; telangiectasia
CRF chronic renal failure
CR(K)F chronic renal (kidney) failure
CRP C-reactive protein
CSF cerebrospinal fluid
CT computerised tomography
CTS carpal tunnel syndrome
CVA cerebrovascular accident
CVS cardiovascular system
CXR chest X-ray
DBP diastolic blood pressure
DC direct current
DHA docosahexaenoic acid
DI diabetes insipidus
DIC disseminated intravascular coagulation
dL decilitre
DMARDs disease modifying antirheumatic drugs
DNA deoxyribose-nucleic acid
DRABC defibrillation, resuscitation, airway, breathing, circulation
drug dosage bd—twice daily, tid/tds -three times daily, qid/qds -four times daily
ds double strand
DS double strength
DSM diagnostic and statistical manual (of mental disorders)
DU duodenal ulcer
DUB dysfunctional uterine bleeding
DVT deep venous thrombosis
EBM Epstein-Barr mononucleosis (glandular fever)
EBV Epstein-Barr virus
ECG electrocardiogram
ECT electroconvulsive therapy
EDD expected due date
EEG electroencephalogram
ELISA enzyme linked immunosorbent assay
ESRF end-stage renal failure
ESR(K)F end stage renal (kidney) failure
ERCP endoscopic retrograde cholangiopancreatography
esp. especially
ESR erythrocyte sedimentation rate
FB foreign body
FBE full blood count

FEV1 forced expiratory volume in 1 second
fL femtolitre = (1e–15) litre
FSH follicle stimulating hormone
FUO fever of undetermined origin
FVC forced vital capacity
g gram
GA general anaesthetic
GABHS group A beta-haemolytic streptococcus
GBS Guillain-Barré syndrome
GFR glomerular filtration rate
GI glycaemic index
GIT gastrointestinal tract
GLP glucagon-like peptide
GnRH gonadotrophin-releasing hormone
GO gastro-oesophageal
GORD gastro-oesophageal refl ux
GP general practitioner
G-6-PD glucose-6-phosphate
GU gastric ulcer
HAV hepatitis A virus
anti-HAV hepatitis A antibody
Hb haemoglobin
HbA haemoglobin A
anti-HBc hepatitis B core antibody
HBeAg hepatitis B e antigen
anti-HBs hepatitis B surface antibody
HBsAg hepatitis B surface antigen
HBV hepatitis B virus
HCG human chorionic gonadotropin
HCV hepatitis C virus
anti-HCV hepatitis C virus antibody
HDL high-density lipoprotein
HEV hepatitis E virus
HFM hand, foot and mouth
HFV hepatitis F virus
HGV hepatitis G virus
HIV human immunodeficiency virus
HNPCC hereditary nonpolyposis colorectal cancer
HPV human papilloma virus
HRT hormone replacement therapy
HSV herpes simplex viral infection
IBS irritable bowel syndrome
ICE ice, compression, elevation
ICS inhaled corticosteroid
ICS intercondylar separation
ICT immunochromatographic test
IDDM insulin dependent diabetes mellitus
IDU injecting drug user
IgE immunoglobulin E
IgG immunoglobulin G
IgM immunoglobulin M
IHD ischaemic heart disease
IM, IMI intramuscular injection
inc. including
IPPV intermittent positive pressure variation
IR internal rotation
ITP idiopathic (or immune) thrombocytopenia purpura
IUCD intrauterine contraceptive device
IUGR intrauterine growth retardation
IV intravenous
IVI intravenous injection
IVP intravenous pyelogram
IVU intravenous urogram
JCA juvenile chronic arthritis
JVP jugular venous pulse
KA keratoacanthoma
kg kilogram
KOH potassium hydroxide
LA local anaesthetic
LABA long acting beta agonist
LBBB left branch bundle block
LBO large bowel obstruction
LBP low back pain
LDH/LH lactic dehydrogenase
LDL low-density lipoprotein
LFTs liver function tests
LH luteinising hormone
LHRH luteinising hormone releasing hormone
LIF left iliac fossa
LMN lower motor neurone
LNG levonorgestrel
LRTI lower respiratory tract infection
LSD lysergic acid
LUQ left upper quadrant
LUTS lower urinary tract symptoms
LV left ventricular
LVH left ventricular hypertrophy
mane in morning
MAOI monoamine oxidase inhibitor
mcg microgram (also µg)
MCV mean corpuscular volume
MDI metered dose inhaler
MDR multi-drug resistant TB
MI myocardial infarction
MRCP magnetic resonance cholangiography
MRI magnetic resonance imaging
MS multiple sclerosis
MSM men who have sex with men
MSU midstream urine
N normal
NAD no abnormality detected
NGU non-gonococcal urethritis
NHL non-Hodgkin's lymphoma
NIDDM non-insulin dependent diabetes mellitus
nocte at night
NSAIDs non-steroidal anti-inflammatory drugs
NSU non-specific urethritis
(o) taken orally
OA osteoarthritis
OCP oral contraceptive pill
OGTT oral glucose tolerance test
OSA obstructive sleep apnoea
OTC over the counter
PA posterior–anterior
PAN polyarteritis nodosa
Pap Papanicolaou
pc after meals
PCA percutaneous continuous analgesia
PCB post coital bleeding

PCL posterior cruciate ligament
PCOS polycystic ovarian syndrome
PCP pneumocystis carinii pneumonia
PCR polymerase chain reaction
PCV packed cell volume
PDA patent ductus arteriosus
PEF peak expiratory flow
PEFR peak expiratory flow rate
PET pre-eclamptic toxaemia
PFT pulmonary function test
PH past history
PID pelvic inflammatory disease
PLISSIT permission: limited information: specific suggestion: intensive therapy
PMS premenstrual syndrome
PMT premenstrual tension
POP plaster of Paris
POP progestogen-only pill
PPI proton-pump inhibitor
PPROM preterm premature rupture of membranes
PR per rectum
prn as and when needed
PROM premature rupture of membranes
PSA prostate specific antigen
PSIS posterior superior iliac spine
PSVT paroxysmal supraventricular tachycardia
PT prothrombin time
PTC percutaneous transhepatic cholangiography
PU peptic ulcer
PUO pyrexia of undetermined origin
pv per vagina
qds, qid four times daily
RA rheumatoid arthritis
RBBB right branch bundle block
RBC red blood cell
RCT randomised controlled trial
RF rheumatic fever
Rh rhesus
RIB rest in bed
RICE rest, ice, compression, elevation
RIF right iliac fossa
RPR rapid plasma reagin
RR relative risk
RSV respiratory syncytial virus
RT reverse transcriptase
rtPA recombinant tissue plasminogen activator
SAH subarachnoid haemorrhage
SARS severe acute respiratory distress syndrome
SBE subacute bacterial endocarditis
SBO small bowel obstruction
SBP systolic blood pressure
SC/SCI subcutaneous/subcutaneous injection
SCC squamous cell carcinoma
SCG sodium cromoglycate
SIADH syndrome of secretion of inappropriate antidiuretic hormone
SIDS sudden infant death syndrome
SIJ sacroiliac joint
SL sublingual
SLE systemic lupus erythematosus
SLR straight leg raising
SND sensorineural deafness
SNHL sensorineural hearing loss
SNRI serotonin noradrenaline reuptake inhibitor
SOB shortness of breath
sp species
SR sustained release
SSRI selective serotonin reuptake inhibitor
SSS sick sinus syndrome
stat at once
STI sexually transmitted infection
SVC superior vena cava
SVT supraventricular tachycardia
T3 tri-iodothyronine
T4 thyroxine
TB tuberculosis
tds, tid three times daily
TENS transcutaneous electrical nerve stimulation
TFTs thyroid function tests
TG triglyceride
TIA transient ischaemic attack
TIBC total iron binding capacity
TM tympanic membrane
TMJ temporomandibular joint
TNF tissue necrosis factor
TOF tracheo-oesophageal fistula
TORCH toxoplasmosis, rubella, cytomegalovirus, herpes virus
TPHA Treponema pallidum haemoglutination test
TSE testicular self-examination
TSH thyroid-stimulating hormone
TT thrombin time
TV tidal volume
U units
UC ulcerative colitis
U & E urea and electrolytes
µg microgram
UMN upper motor neurone
URTI upper respiratory tract infection
US ultrasound
UTI urinary tract infection
U ultraviolet
VC vital capacity
VDRL Venereal Disease Reference Laboratory
VF ventricular fibrillation
VMA vanillyl mandelic acid
VSD ventricular septal defect
VT ventricular tachycardia
VUR vesico-ureteric reflux
VWD von Willebrand's disease
WBC white blood cells
WCC white cell count
WHO World Health Organization
WPW Wolff-Parkinson-White
XL sex linked

CHAPTER (6) ENDOCRINE PROBLEMS

1. Diabetes Mellitus
2. Thyroid Disorders
    a. Hypothyroidism
    b. Hyperthyroidism (Thyrotoxicosis)
    c. Thyroid crisis (Thyroid storm)
    d. Thyroid Nodules
    e. Thyroid Carcinoma
3. Pituitary Disorders
    a. Pituitary Tumours
    b. Over secretion of pituitary disorder
    c. Disorder of posterior pituitary disorders
    d. Adrenal disorder
    e. Primary Hyperaldosteronism
    f. Phaeochromocytoma
4. Calcium Disorders

DIABETES MELLITUS

Classification of diabetes mellitus

The features most useful in discrimination of type 1 diabetes include younger age at diagnosis (<35 years) with lower BMI (<25 kg/m^2), unintentional weight loss, ketoacidosis, and glucose >360 mg/dL at presentation.

Type 1 diabetes	Type 2 diabetes	Specific types of diabetes due to other causes	Gestational diabetes mellitus
• Due to autoimmune β-cell destruction, usually leading to absolute insulin deficiency, including (LADA)	• non-autoimmune progressive loss of adequate β-cell insulin secretion frequently on the background of insulin resistance and • metabolic syndrome	• Monogenic diabetes syndromes (neonatal diabetes and MODY) • Diseases of the exocrine pancreas (cystic fibrosis and pancreatitis) • Drug- or chemical-induced diabetes (glucocorticoid use, in the treatment of HIV/AIDS, or after organ transplantation	• Diabetes diagnosed in the second or third trimester of pregnancy that was not clearly overt diabetes prior to gestation

LADA = latent autoimmune diabetes of adulthood, MODY = maturity-onset diabetes of the young

Criteria for screening for diabetes or prediabetes in asymptomatic adults

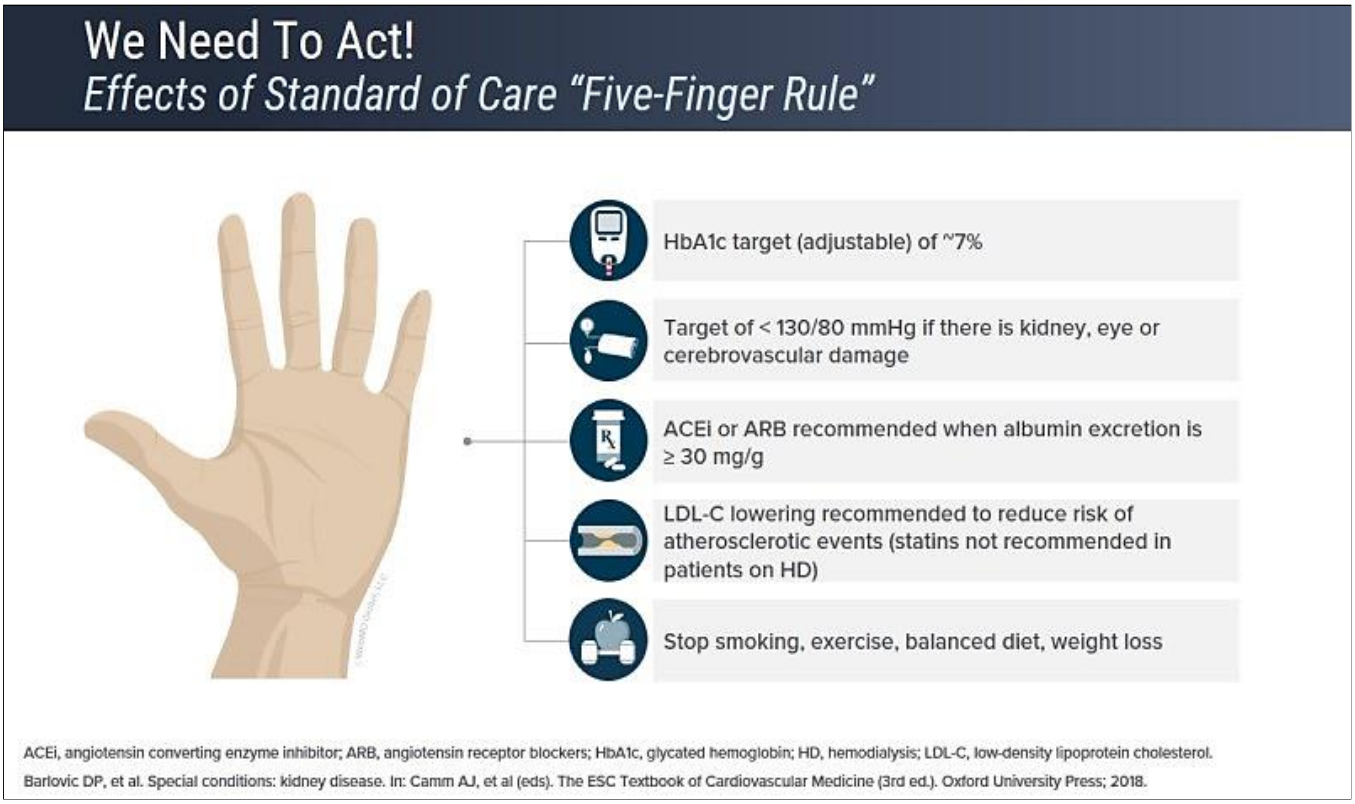
1. Adults with overweight or obesity (BMI ≥ 25 kg/m^2 or ≥ 23 kg/m^2 in Asian American individuals) who have one or more of the following risk factors: - First-degree relative with diabetes - High-risk race/ethnicity (e.g., African American, Latino, Native American, Asian American, Pacific Islander) - History of CVD - Hypertension (≥ 140/90 mmHg or on therapy for hypertension) - HDL cholesterol level <35 mg/dL (0.90 mmol/L) and/or a triglyceride level >250 mg/dL (2.82 mmol/L) - Individuals with polycystic ovary syndrome - Physical inactivity -Other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans)
2. People with prediabetes should be tested yearly
3. People who were diagnosed with GDM should have lifelong testing at least every 3 years
4. For all other people, testing should begin at age 35 years.
5. People with HIV

Criteria for the diagnosis of diabetes and prediabetes

CRITERIA FOR THE DIAGNOSIS OF DIABETES
FPG ≥ 126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h.*
OR
2-h PG ≥ 200 mg/dL (11.1 mmol/L) during OGTT.

The test should be performed as described by WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water. *
OR
A1C ≥ 6.5% (48 mmol/mol). The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay. *
OR
In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥ 200 mg/dL (11.1 mmol/L).
CRITERIA FOR THE DIAGNOSIS OF PREDIABETES
FPG 100 mg/dL (5.6 mmol/L) to 125 mg/dL (6.9 mmol/L) (IFG)
OR
2-h PG during 75-g OGTT 140 mg/dL (7.8 mmol/L) to 199 mg/dL (11.0 mmol/L) (IGT)
OR
A1C 5.7–6.4% (39–47 mmol/mol)

DCCT = Diabetes Control and Complications Trial; FPG = fasting plasma glucose; OGTT= oral glucose tolerance test; NGSP= National Glycohemoglobin Standardization Program; WHO = World Health Organization; 2-h PG = 2-h plasma glucose; IFG = impaired fasting glucose; IGT, impaired glucose tolerance. *In the absence of unequivocal hyperglycemia, diagnosis requires two abnormal test results from the same sample or in two separate test samples.



Diabetic Treatment Strategy in Family Medicine Clinic	
A	**A**ssess Glycaemic Status, Hb**A**1c
B	**B**MI **B**P (Hypertension)
C	**C**VD Risk Assessment, **C**holesterol
D	**D**etection of Comorbidity and Complications Working **D**iagnosis
E	**E**vidence-Based, Updated Management Patient **E**mpowerment

Comprehensive medical evaluation and assessment of comorbidities

	Initial visit	3-monthly OR Every follow-up visit	At annual visit
Physical examination			
Weight	✓	✓	✓
Waist circumference	✓	✓	✓
BMI	✓		✓
BP	✓	✓	✓
Eye			
Visual acuity	✓		✓
Fundoscopy/Fundus camera	✓	If indicated	✓
Feet			✓
Pulses/ABI	✓	If indicated	✓
Neuropathy	✓	If indicated	✓
Dental check-up	✓		✓
ECG	✓	If indicated	✓
Laboratory investigations			
HbA1C	✓	✓	✓
Lipid profile	✓	If indicated	✓
Creatinine, urea + eGFR	✓	✓	✓
Urine microscopy	✓	If indicated	✓
spot morning UACR	✓	If indicated	
LFT (AST, ALT)	✓	✓	✓

✓ = conduct test

GLYCEMIC TARGET

HbA1c	**<7%***
Pre-prandial Glucose	**80 - 130 mg/dl***
Post-prandial Glucose	**<180 mg/dl***

*More or less stringent individualized glycemic target should be based on duration of diabetes, age/life expectancy, comorbid conditions, known CVD or advanced microvascular complications, hypoglycemia unawareness, and individualized considerations.

PHARMACOLOGIC APPROACHES TO GLYCEMIC TREATMENT

1. *Glycemic management of out patients*

Lifestyle modification to all patients ††

↓

Glycemic management

HbA1c <8.5% OR FPG <150 mg/dl, RBS <250 mg/dl	**HbA1c 8.5 - 10.0% OR FPG 150 – 250 mg/dl, RBS 250 – 350 mg/dl**	**HbA1c >10.0% OR FPG >250 mg/dl, RBS >350 mg/dl**
Mono therapy	**Dual combination therapy**	**Triple combination therapy++ or Insulin if osmotic symptoms or weight loss present**
Follow-up with Blood Glucose level after 2-4 weeks. •Optimize dose of OAD/ addition of another OAD in subsequent 2-4 weeks. •HbA1c every 3-6 months.	Follow-up with Blood Glucose level after 2-4 weeks. •Optimize dose of OAD/ addition of another OAD in subsequent 2-4 weeks. •HbA1c every 3-6 months.	Follow-up with Blood Glucose level after 2-4 weeks, •Optimize dose of OAD/ addition of another OAD in subsequent 2-4 weeks. •HbA1c every 3-6 months.
If Blood Glucose level is satisfactory and/or HbA1c reach individualized target, continue therapy.*	If Blood Glucose level is satisfactory and/or HbA1c reach individualized target, continue therapy.*	If Blood Glucose level is satisfactory and/or HbA1c reach individualized target, continue therapy.*

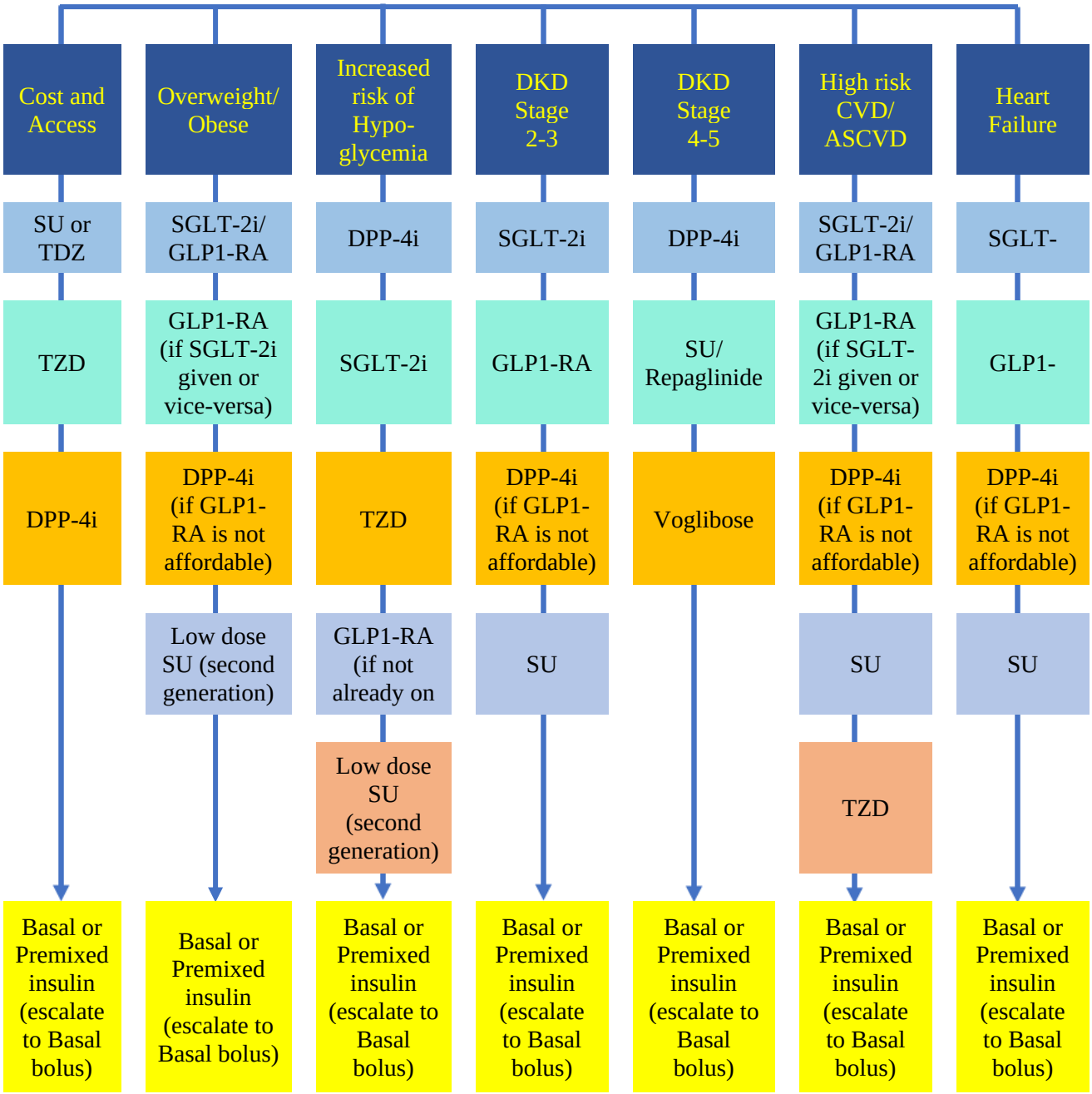
†† 150 min or more of moderate- to vigorous-intensity aerobic activity per week, spread over at least 3 days/week, with no more than 2 consecutive days without activity

++Rescue Therapy: For symptomatic hyperglycemia, consider insulin or sulfonylurea and review when blood glucose has been achieved
**If Blood glucose level and HbA1c is discordant, look for the reasons of discordance or seek advice from Endocrinologists*

Use of glucose-lowering medications in the management of type 2 diabetes

LIFESTYLE MODIFICATION + METFORMIN
Unless intolerant or contraindicated/ ½ dose at DKD stage 3B, stop at DKD stage 4-5)

If HbA1c does not reach individualized target/Blood Glucose level is not satisfactory



**In terms of choosing between SGLT-2i or GLP1-RA, SGLT-2i should be prioritized according to Myanmar situation.*
**DKD Stage 1-3: eGFR >30 ml/min DKD Stage 4-5: eGFR <30 ml/min*
**Sulfonylurea and Repaglinide should not be used together because of similar site of action*

Oral Anti- diabetic drugs and injectable non-Insulin Agents

Drugs	Formulation	Minimum dose	Maximum dose
Biguanides			
Metformin SR	500/750/850/1000 mg	Initial dose: 500 mg OD	850 mg TDS 2000 mg OD
Metformin	500/850/1000 mg	Initial dose 500 mg OD	Usual: 850 BD/100 BD Exception: 1000 TDS
Sulphonylureas			
Gliclazide	80 mg	40 mg OD	160 mg BD
Gliclazide MR	60/30 mg	30 mg OD	120 mg OD
Glipizide	5 mg	2.5 mg OD	10 mg OD
Glimepiride	2/3 mg	1 mg OD	8 mg OD
Meglitinides			
Repaglinide	0.5/1/2 mg	0.5 mg with main meal	4 mg with main meals (not exceeding 16 mg daily)
Nateglinide	60/120 mg	60 mg with meals	180 mg with meals
α-glucosidase inhibitor			
Acarbose	50/100 mg	Initial dose 50 mg OD Usual dose: 50-100 mg take at 1st bite of main meals	100 mg TDS
Voglibose	0.2/0.3 mg	0.2 mg TDS (with meal)	0.3 mg TDS (with meals)
Thiazolidinedione			
Pioglitazone	15/30 mg	15 mg OD	45 mg OD
DPP4-inhibitors			
Sitagliptin	25/50/100 mg	25 mg OD	100 mg OD
Vildagliptin	50 mg	50 mg OD	50 mg OD
Teneligliptin	20/40 mg	20 mg OD	40 mg OD
Linagliptin	5 mg	5 mg OD	5 mg OD
SGLPT2-inhibitors			
Dapagliflozin	5/10 mg	5 mg OD	10 mg OD
Canagliflozin	100/300 mg	100 mg OD	300 mg OD
Empagliflozin	10/25 mg	10 mg OD	25 mg OD
GLP1-RA			
Liraglutide	6 mg/ml	0.6 mg OD	1.8 mg OD

Efficacy of Anti-diabetic Drugs

	MET	SU	GLN	AGI	TZD	DPP4-i	SGLT2-i	GLP1-RA	Insulin
HbA1c ↓%	1.0-1.5	0.4-1.6	1.0-1.2	0.5-0.8	0.5-1.4	0.5-0.8	0.2-0.8	0.5-1.4	>1.5
FPG vs. PPG	FPG	Both	PPG	PPG	FPG	Both	Both	Both	Both
Hypoglycemia	↔	↑↑	↑	↔	↔	↔	↔	↔	↑↑
Weight change	↓	↑↑	↑	↔	↑↑	↔	↓-↓↓	↓↓	↑↑
GI symptoms	↑↑	↔	↔	↑↑	↔	↑	↔	↑↑	↔
CHF	↔	↔	↔	↔	↑	↔	↓↓	↔	↔
CVD	↓	↔	↔	↔	↔	↔	↓↓	↓↓	↔
Bone loss	↔	↔	↔	↔	↑	↔	↔	↔	↔
DKD	Avoid*	Hypo	Hypo	↔	Fluid retent[n]	Dose adjust[m]	↓↓[a]	↓↑	

**Avoid if eGFR <30ml/min/1.73m²; ↑avoid if eGFR <15ml/min/1.73m²; a SGLT2-i can be used until dialysis is initiated and has proven reno-protection although glucose-lowering efficacy is reduced.*

Increased risk | *Mild-moderate risk* | *Neutral* | *Possible benefit* | *Beneficial*

Dosage of oral anti-diabetic drugs in Renal Failure

Generic Name	Usual dose*	Dose adjustment in renal failure			
		Mild (CKD 2) (GFR 60-89)	Moderate (CKD 3) (GFR 30-59)	Severe (CKD 4-5) (GFR <30)	
Biguanide					
Metformin	500-1000 mg BD	Continue	45-60: No dose adjustment	Avoid	
Metformin SR	500-100 mg BD 750 mg TDS 850 mg BD		<45: 50% dose reduction		
Sulphonylurea*					
Gliclazide	80 mg OD – 160 mg BD	No dose adjustment		Caution	
Gliclazide MR	30-120 mg OD	No dose adjustment		Caution	
Glimepiride	1-8 mg OD	Initiate with 1 mg OD		≥15: Caution	<15: Avoid
Glipizide	2.5 mg OD – 10 mg BD	No dose adjustment		Caution	
Meglitinides					
Repaglinide	0.5-4 mg TDS	No dose adjustment		Initiate at 0.5 mg with meals	
Nateglinide	60-120 mg TDS	No dose adjustment		Initiate at 60 mg with meals	
α-glucosidase inhibitor					
Acarbose	25-100 mg TDS			Avoid	
Voglibose	0.2-0.3 mg TDS	No dose adjustment			
Thiazolidinedione					
Pioglitazone	15-45 mg OD	No dose adjustment (caution with fluid retention risk)			
DPP4-inhibitors					
Sitagliptin	100 mg OD	No dose adjustment	≥50: No dose adjustment	25 mg OD	
			30-<50: 50 mg OD		
Vildagliptin	50 mg OD-BD	No dose adjustment	≥50: No dose adjustment		
			<50: 50 mg OD (limited data)		
Teneligliptin	20-40 mg OD	No dose adjustment			
Linagliptin	2.5-5 mg OD	No dose adjustment			
GLP1-RA					
Liraglutide	1.2 to 1.8 mg OD (Initial 0.6 mg OD x one week)	No dose adjustment	No dose adjustment	≥15: No dose adjustment	<15: Avoid
SGLPT2-inhibitors					
Dapagliflozin	5-10 mg OD	No dose adjustment	45-60: No dose adjustment	Avoid Exception: can give up to eGFR 25 in HF and CKD	
			<45: not recommended in DM		
Canagliflozin	100-300 mg OD	No dose adjustment	45-60: 100 mg OD	Avoid	
Empagliflozin	10-25 mg OD	No dose adjustment			

Dose should be adjusted based on frequent monitoring to balance goals of glycemic control with avoiding hypoglycaemia.

INSULIN THERAPY

Indications for Insulin therapy in T2DM

- Newly diagnosed patients (with severe osmotic symptoms) if
  - ✓ *RBS >300mg/dl or*
  - ✓ *FBS >250mg/dl or*
  - ✓ *HbA1c of ≥ 10%*
- Acute clinical conditions (e.g. AMI, Sepsis, Severe Pneumonia, Extensive Koch's Lung etc.)
- Pregnancy (pre-pregnant or GDM)
- Diabetes patients already on OAD therapy (Poor glycaemic control despite maximal tolerable dose of two or three OADs over three months, with HbA1c >7%)

↓

Start Basal Insulin
Starting dose: 10 units (0.2 units/kg/day)
Continue lifestyle management + other anti-diabetic agents

↓

Repeat HbA1c 3 monthly

Target HbA1c reached → Continue basal insulin, Repeat HbA1c

↓

Titration based insulin

If above HbA1c target

↓

Pre-mixed Insulin
TDD = 0.5 units/kg/day (or) unit per unit at the same total insulin dose
Premixed insulin before breakfast and dinner

Basal Bolus Insulin

Basal Insulin Therapy

BASAL INSULIN

Intermediate acting (Insulin N): NPH insulin (*Insulatard, Insunova N, Wolsulin N, Gensulin N*)

Long-acting Analogue (Insulin G): Insulin Glargine (*Glaritus, Insunova G, Lantus*)
Detemir (*Levemir*)

- *Basal insulin is best starting insulin choice.*
- *Intermediate and long-acting insulin are comparable in HbA1c lowering effect but less hypoglycaemia with long-acting analogue insulin.*
- *Start one of the intermediate-acting or long-acting insulins listed above at bedtime.*
- *When starting basal insulin: Continue OAD*
- *Note: if NPH causes nocturnal hypoglycaemia, consider switching NPH to long-acting insulin.*
- *Let the patient know that food intake is not recommended with basal insulin.*
- *Before up-titrating the dose, check the diet first and correct accordingly.*

↓

STARTING DOSE:
Start dose: 10 units (0.2 units/kg/day)

↓

TITRATE:

Adjust insulin doses after 3 consecutive FBS values obtained (every 3 – 7 days)

- <80 mg/dL (>1 value) → reduce dose by 2 units
- 80 – 130 mg/dL (all value) → maintain current dose
- >130 mg/dL (>1 value, no hypos) → increase by 2 units

Maximum dose for basal insulin = 0.5/kg/day. If needing more than that, change to other regimen.

↓

Assess adequacy of basal insulin dose

Consider clinical signals of overbasalization (e.g. Basal insulin >0.5 units/kg/day, elevated bedtime-morning and/or post-preprandial differential, hypoglycaemia (aware or unaware), high variability) and need for adjunctive therapies

↓

Once fasting glucose at goal, evaluate post-meal glucose pattern

PREMIXED INSULIN THERAPY

PREMIXED INSULIN

Conventional: Combination of short and intermediate acting (30% short + 70% NPH)
(*Mixtard 30, Insunova 30/70, Wolsulin 30/70, Gensulin M30*)

Analogue: Combination of rapid acting & protaminated analogue (*Novomix 30*),
Combination of Aspart 30% & Degludec 70% (*Ryzodeg*)

1. Premixed insulin is an option for patients who are unable to do multiple injections and who have fixed meal schedules.
2. Premixed insulin is more likely to cause hypoglycemia compared to basal and prandial insulins.
3. Start one of the mixed insulins listed above. Given twice daily, before breakfast and before dinner (or before other meals depending on the main meals, food intake and lifestyle). For analogue insulin, can increase to three times daily before each meal if not well controlled with twice daily regimen.
4. Analogue insulins should be just before meal. Conventional insulin needs to be taken 30 minutes before meals.
5. When starting pre-mixed insulin: Stop secretagogues. Continue metformin. Stop all other insulins.
6. Before up-titrating the dose, check the diet first and correct accordingly.

↓

STARTING DOSE:

Total Daily dose: 0.5 units/kg/day (or) unit per unit at the same total insulin dose

Conventional: Morning 2/3, Evening 1/3
Analogue: Morning 50%, Evening 50%

↓

TITRATE

Adjust insulin doses after 3 consecutive days blood glucose values obtained (every 3 – 7 days)

- <80 mg/dL (>1 value) → reduce dose by 2 units
- 80 – 130 mg/dL (all value) → maintain current dose
- >130 mg/dL (>1 value, no hypos) → increase by 2 units

- Pre-lunch and Pre-dinner blood glucose determines morning premixed dose adjustment.
- Bedtime and Pre-breakfast blood glucose determines evening premixed dose adjustment

Screening and management of complications

(A) Cardiovascular Disease and Risk Management

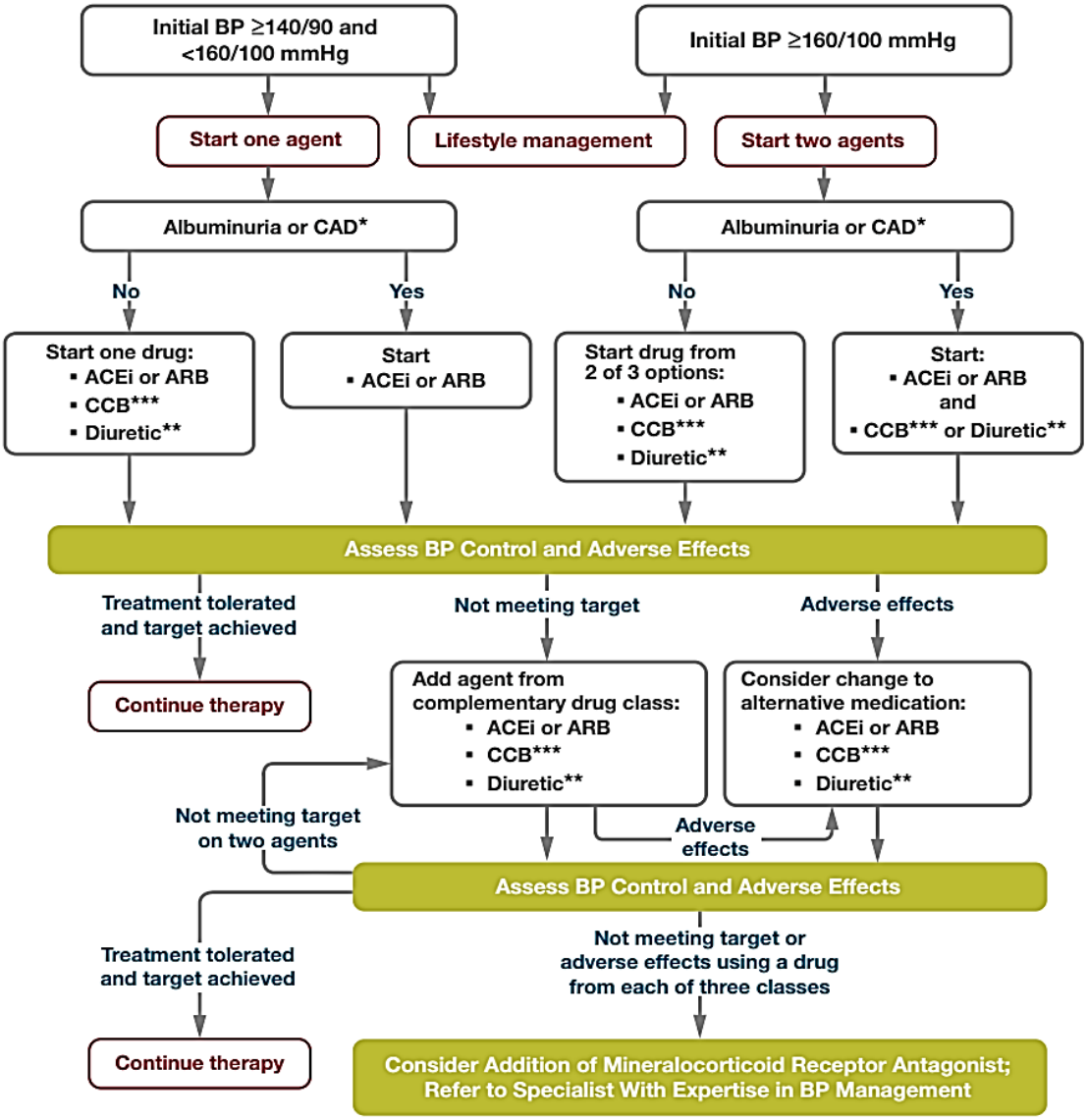
Atherosclerotic cardiovascular disease (ASCVD)—defined as coronary heart disease (CHD), cerebrovascular disease, or peripheral arterial disease presumed to be of atherosclerotic origin—is the leading cause of morbidity and mortality for individuals with diabetes.

Cardiovascular Disease Screening	
Consider investigations for coronary artery disease (eg ECG, CT coronary calcium score, pharmacologic stressed ECHO) in the presence of any of the following: 1. atypical cardiac symptoms (e.g., unexplained dyspnea, chest discomfort); 2. signs or symptoms of associated vascular disease including carotid bruits, transient ischemic attack, stroke, claudication, or peripheral arterial disease; 3. electrocardiogram abnormalities (e.g., Q waves).	
Treatment of Cardiovascular Disease	
Lifestyle	Intensive lifestyle intervention focusing on weight loss (Preferably >10%)
Glucose lowering therapies	• SGLT 2 inhibitor or GLP 1 receptor agonist with demonstrated CV disease benefit is recommended in people with T2DM who have established CV disease or established heart failure with either preserved or reduced ejection fraction or established CKD or multiple risk factors for ASCVD.
ACEI/ARB/ MRA	• For people with T2DM and CKD with albuminuria treated with maximum tolerated doses of ACEI or ARB, addition of MRA is recommended to improve CV outcomes and reduce the risk of CKD progression. • In people with known ASCVD, particularly coronary artery disease, ACE inhibitor or ARB therapy is recommended to reduce the risk of cardiovascular events
Beta blocker	• In prior myocardial infarction or heart failure with reduced EF (beta-blocker with proven CV outcomes benefit)

Hypertension/BP control

BP monitoring	At every routine clinical visit
How to diagnose?	Systolic blood pressure ≥ 130 mmHg or a diastolic blood pressure ≥ 80 mmHg based on an average of ≥ 2 measurements obtained on ≥ 2 occasions (1-2 week apart) Individuals with BP ≥ 180/110 mmHg and cardiovascular disease could be diagnosed with hypertension at a single visit.
Threshold for pharmacologic therapy	Confirmed office-based blood pressure ≥130/80 mmHg
Blood pressure target/goal	<130/80 mmHg. Multiple-drug therapy is generally required to achieve blood pressure targets in DM.

Recommendations for the Treatment of Hypertension in People with Diabetes



*An ACEi or ARB is suggested to treat hypertension for people with coronary artery disease (CAD) or urine albumin-to-creatinine ratio (ACR) 30–299 mg/g creatinine and strongly recommended for individuals with urine albumin-to-creatinine ratio ≥ 300 mg/g creatinine.

**Thiazide-like diuretic; long-acting agents shown to reduce cardiovascular events, such as chlorthalidone and indapamide, are preferred.

***Dihydropyridine calcium channel blocker (CCB)

For patients treated with an ACEi, ARB or diuretic, serum creatinine/estimated glomerular filtration rate and serum potassium levels should be monitored at least annually.

LIPID MANAGEMENT

When to Obtain a Lipid Profile (total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides)?	
1. at the time of diagnosis 2. at the initial medical evaluation, and at least every 5 years thereafter in patients <40 years of age	3. immediately before initiating statin therapy 4. 4–12 weeks after initiation of statin therapy, 5. after any change in dose of statin therapy

Primary Prevention	
For aged 40–75 years • **without ASCVD risk*** → moderate-intensity statin therapy in addition to lifestyle therapy • **with one or more ASCVD risks*** → use high intensity statin therapy with target LDL cholesterol goal of <70 mg/dL • with multiple ASCVD risks* and LDL cholesterol >70 mg/dL → may be reasonable to add ezetimibe to maximum tolerated statin therapy.	**For aged 20–39 years with** • additional ASCVD risks* → may be reasonable to initiate statin therapy in addition to lifestyle **For aged >75 years** • if already on statin therapy, it is reasonable to continue statin treatment • if not already on statin therapy, it is reasonable to initiate moderate-intensity statin therapy after discussion of potential benefits and risks
Secondary Prevention	
For people of all ages with diabetes and ASCVD, • **high intensity statin** therapy should be added to lifestyle therapy. • Target LDL cholesterol: reduction of >50% from baseline and goal of <55 mg/dL. • If lipid goal is not achieved on maximum tolerated statin therapy, add ezetimibe.	
Treatment of other Lipoprotein	
• For individuals with fasting TG levels ≥ 500 mg/dL, evaluate for secondary causes of hypertriglyceridemia and consider medical therapy (fibric acid derivatives and/or fish oil) and reduction in dietary fat to reduce the risk of acute pancreatitis. • In individuals with ASCVD or other CV risk factors on a statin with controlled LDL cholesterol but elevated TG (135–499 mg/dL), the addition of icosapent ethyl can be considered to reduce CV risk.	

High-Intensity Statin Therapy Lowers LDL by ≥50% from baseline	**Moderate-Intensity Statin Therapy** Lowers LDL by 30 - 49% from baseline
Atorvastatin 40-80 mg Rosuvastatin 20-40 mg	Atorvastatin 10-20 mg Rosuvastatin 5-10 mg Pitavastatin 2-4 mg

*ASCVD risk (family history of CVD, obesity, hypertension, smoking, dyslipidemia, or albuminuria)

ANTI-PLATELET THERAPY

Primary prevention
• May be consider in patient **aged ≥50 years** and at least one additional **major CV risk factor** (family history of premature ASCVD, hypertension, dyslipidemia, smoking, or CKD/albuminuria) who are not at increased risk of bleeding (e.g., older age, anemia, renal disease)

Secondary prevention	
1. Use **aspirin** therapy (75–162 mg/day) in all patients with ASCVD. In documented aspirin allergy, clopidogrel should be use. 2. **Dual antiplatelet therapy** (with low-dose aspirin and clopidogrel,) is reasonable for a year after ACS and may have benefits beyond this period. 3. Long-term treatment with dual antiplatelet therapy should be considered for individuals with prior coronary intervention, high ischemic risk, and low bleeding risk.	4. **Combination therapy with aspirin plus low-dose rivaroxaban** (2.5 mg twice daily) should be considered for individuals with stable coronary and/or peripheral artery disease and low bleeding risk to prevent major adverse limb and cardiovascular events

CHRONIC KIDNEY DISEASE AND RISK MANAGEMENT

Diagnosis of Diabetic Kidney Disease (DKD)

DKD is usually clinical diagnosis based on serum creatinine for eGFR ≤ 60 ml/min or 2 or 3 out of 3 UACR ≥ 2.0 mg/mmol at 3 months in the absence of signs or symptoms of other primary causes of kidney damage.

Screening

At least annually

→ urinary albumin (e.g., spot urinary albumin-to-creatinine Ratio-UACR)

→ estimated glomerular filtration rate(eGFR) should be assessed.

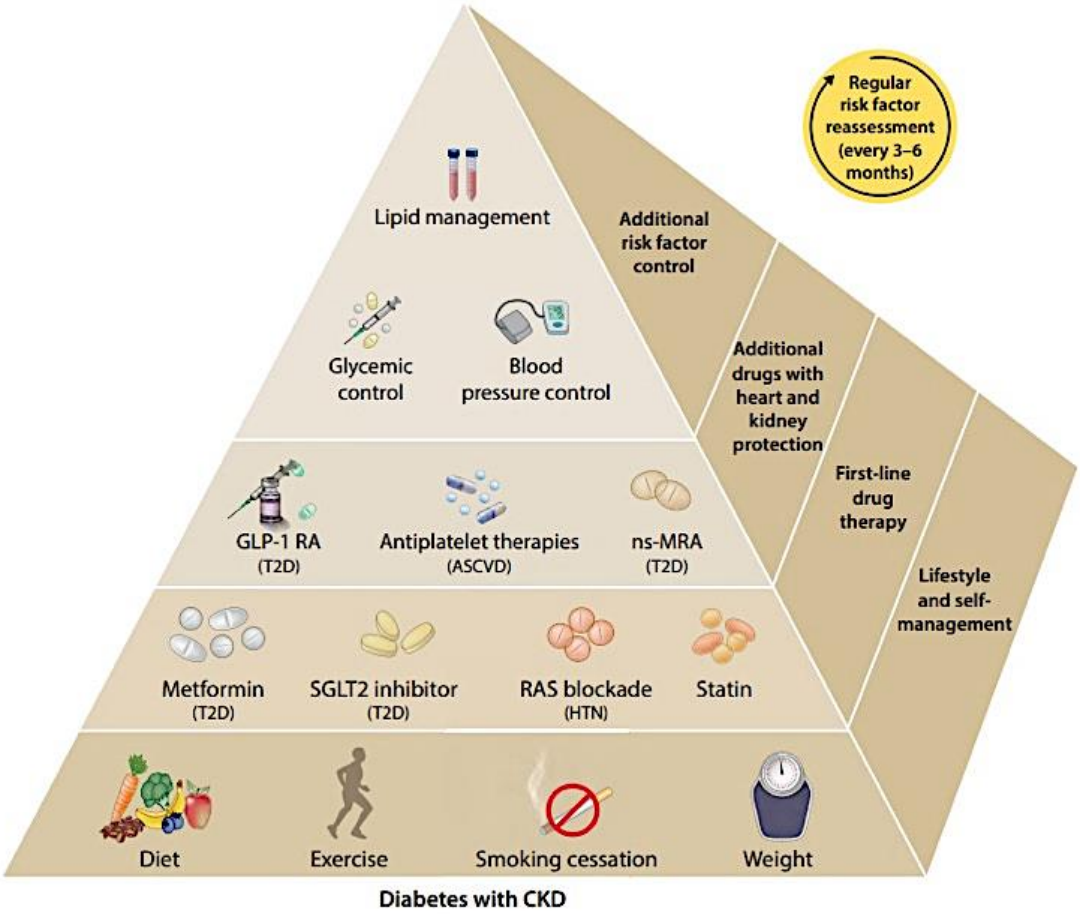
When to Screen

→ Type 1 diabetes with duration of >5 years

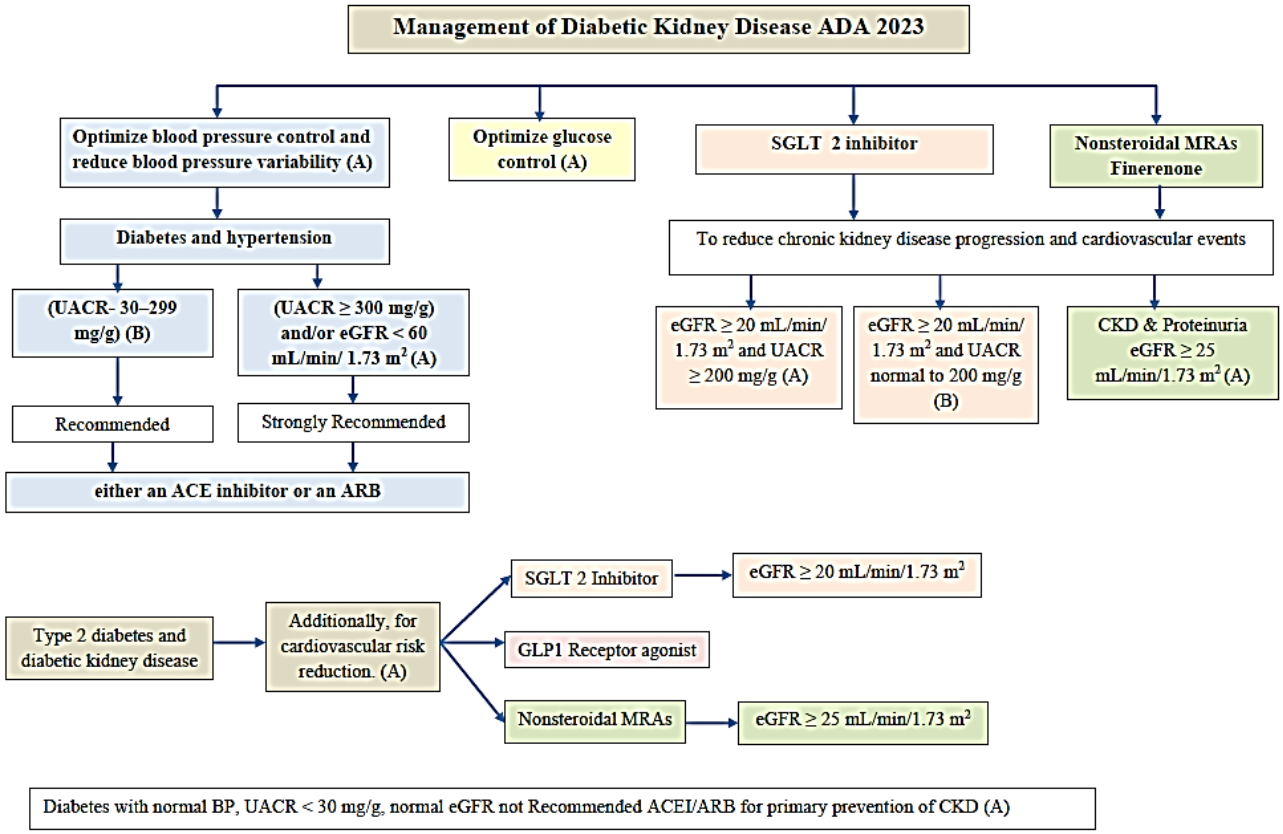
→ Type 2 diabetes regardless of treatment.

Treatment

Kidney-Heart Risk Factor Management



Management of Diabetic Kidney Disease



For people with non–dialysis dependent stage 3 or higher CKD, dietary protein intake should be aimed to a target level of 0.8 g/kg body weight per day.

For patients on dialysis, higher levels of dietary protein intake should be considered since protein energy wasting is a major problem in some individuals on dialysis.

Referral to Nephrologist

1. *Continuously increasing urinary albumin levels*
2. *Continuously decreasing eGFR and if the eGFR rate is <30 mL/min/1.73 m²*
3. *Uncertainty about the etiology of kidney disease*
4. *Difficult management issues*
5. *Rapidly progressing kidney disease.*
6. *Haematuria*
7. *Resistant hypertension (failure to achieve target BP despite 3 antihypertensive agents including a diuretic)*

RETINOPATHY, NEUROPATHY, AND FOOT CARE

Diabetic retinopathy

Definition
Diabetic retinopathy is clinically defined, diagnosed and treated based on the extent of retinal vascular disease detected by ophthalmoscopy
Screening
• Adults with **type 1** diabetes → within **5 years** after the onset of diabetes • Patients with **type 2** diabetes→ **at the time of the diabetes diagnosis** • If there is no evidence of retinopathy for one or more annual eye exams and glycemia is well controlled, then screening every 1–2 years may be considered. →If any level of diabetic retinopathy is present, subsequent dilated retinal examinations should be repeated at least annually by an ophthalmologist or optometrist. →If retinopathy is progressing or sight-threatening, then examinations will be required more frequently.
Treatment
- Optimize glycemic control to reduce the risk or slow the progression of diabetic retinopathy. - Optimize blood pressure and serum lipid control to reduce the risk or slow the progression of diabetic retinopathy. - The presence of retinopathy is **NOT a contraindication to aspirin** therapy for cardioprotection, as aspirin does not increase the risk of retinal hemorrhage

Urgency of referral	**Ocular features**
Emergency (same day referral)	Sudden severe visual loss Symptoms or sign of acute retinal detachment
Appointment within 1 week	Presence of retinal new vessels Retinal hemorrhage Viterous hemorrhage Rubeosis iridis
Appointment within 4 weeks	Unexplained drop in visual acuity Any form of maculopathy Severe NPDR Worsening retinopathy

NPDR = non proliferative diabetic retinopathy

Diabetic neuropathy and foot care

Screening of neuropathy

- ***Type 2 Diabetes patients at diagnosis***
- ***Type 1 Diabetes 5 year after diagnosis***
- ***And then Annually thereafter***

Neuropathic Pain

Positive Symptoms **(Due to excessive activities)**	
Symptoms	Definition
Spontaneous pain	Painful sensations felt with no evident stimulus
Allodynia	Pain due to a stimulus that does not normally provoke pain

	(eg, touching, movement, cold, heat)
Hyperalgesia	An increased response to a stimulus that is normally painful (eg, cold, heat, pinprick)
Dysesthesia	An unpleasant abnormal sensation, whether spontaneous or evoked (eg, shooting sensation)
Paresthesia	An abnormal sensation, whether spontaneous or evoked (eg, tingling, buzzing, vibrating sensations)

Negative Symptoms (Due to deficit of function)	
Symptoms	**Definition**
Hypoesthesia	Diminished sensitivity to stimulation
Anesthesia	A total loss of sensation (especially tactile sensitivity)
Hypoalgesia	Diminished pain in response to a normally painful stimulus
Analgesia	Absence of pain in response to stimulation that would normally be painful

Diagnosis of Diabetic Peripheral Neuropathy

1. History
2. Neurological Examination- Pinprick, Temperature, Vibration, 10 g monofilament test, Distal Reflexes
3. Rule out other causes – B12 deficiency, Hypothyroid, Uremic Syndrome, Peripheral Vascular Disease

Treatments

STEP – 1	**Initiate treatment with one or more first-line treatments** α2δ ligands (gabapentin, pregabalin) SNRIs (duloxetine, venlafaxine) TCAs* (nortriptyline, desipramine)
↓	
STEP – 2	If there is partial pain relief, add another first-line medication If there is no or inadequate pain relief, switch to another first-line medication
↓	
STEP – 3	If first-line medications alone and in combination fail, consider second-line medications (opioids, tramadol) or third-line medications (bupropion, citalopram, paroxetine, carbamazepine, lamotrigine, oxcarbazepine, topiramate, valproic acid, topical capsaicin, dextromethorphan, memantine, mexiletine) or referral to pain specialist.

FOOT CARE

Perform a comprehensive foot evaluation at least annually to identify risk factors for ulcers and amputations.

History Taking	**Examination**
Prior history of ulceration, amputation, Charcot foot, angioplasty or vascular surgery - cigarette smoking - retinopathy - renal disease	1. *look skin, foot deformities* 2. *Neurological assessment (10-g monofilament testing with at least one other assessment: pinprick, temperature, vibration),* 3. *Vascular assessment- pulses in the legs and feet. capillary refill time, rubor on*

- assess current symptoms of neuropathy (pain, burning, numbness) - vascular disease (leg fatigue, claudication).	*dependency, pallor on elevation, and venous filling time.* 4. *Multidisciplinary approach - for individuals with foot ulcers and high-risk feet* 5. *Provide general preventive foot self-care education to all people with diabetes*
Referral Criteria to do ankle–brachial index and for further vascular assessment	**Refer to Foot care Specialist.**
1. *history of leg fatigue, claudication, and rest pain relieved with dependency* 2. *decreased or absent pedal pulses*	1. *Smoker* 2. *history of prior lower-extremity complications,* 3. *loss of protective sensation,* 4. *structural abnormalities, or peripheral arterial disease*

International working group on the Diabetic Foot risk stratification system and corresponding foot screening frequency

Category	Ulcer risk	Characteristic	Examination frequency
0	Very low	No LOPS & No PAD	Annually
1	Low	LOPS or PAD	Every 6-12 month
2	Moderate	LOPS + PAD or LOPS + Foot deformity, or PAD + Foot deformity	Every 3-6 month
3	High	LOPS or PAD and one or more of the following - H/O foot ulcer - Amputation - ESRD	Every 1-3 month

LOPS = loss of position sensation, PAD = Peripheral artery disease

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THYROID PROBLEMS

HYPOTHYROIDISM

Hypothyroidism is the syndrome caused by thyroid hormone deficiency

Common, in women, with a prevalence of about 2% (compared with 0.1% for men).
The prevalence of subclinical hypothyroidism is about 7.5% in women and 3% in men, and increases with age.
Congenital hypothyroidism is one of the most common congenital defects (about 1 in 5000 births).

Causes of hypothyroidism

Primary Hypothyroidism (>95% of cases)

- ***Chronic lymphocytic (Hashimoto's) thyroiditis***
- ***Radioactive iodine treatment or external neck radiation***
- ***Thyroidectomy***
- ***Transient (during recovery from painless thyroiditis or subacute thyroiditis***
- **Drugs (amiodarone, lithium, interferon-α and interferon-β, interleukin-2, thalidomide, bexarotene, and sunitinib, thionamide drugs etc;)**
- ***Severe iodine deficiency***
- ***Congenital hypothyroidism***

Secondary (Central) Hypothyroidism

- ***Any Pituitary or Hypothalamic causes***

Others

- ***Consumptive hypothyroidism due to vascular tumours expressing deiodinase***

Diagnosis

Clinical features

Symptoms	Signs
Cold intolerance	Delayed tendon reflex relaxation
Lethargy, fatigue	Facial and periorbital puffiness
Weight gain (modest)	Bradycardia
Dry skin, hair loss	Poor memory, dementia
Constipation	Non pitting oedema (Myxedema)
Myalgia, arthralgia	Pleural and pericardial effusion
Menorrhagia	Carpel tunnel syndrome
Hoarseness of voice	Deafness
	Hypoventilation, Hypothermia

- The most specific findings are cold intolerance (feeling cold when others are comfortable) and delayed relaxation of tendon reflexes.
- Hypothyroidism does not cause marked obesity.
- Laboratory findings may include hyponatremia and elevated plasma levels of cholesterol, triglycerides, and creatine kinase.
- Primary hypothyroidism may cause hyperprolactinemia.
- The electrocardiogram (ECG) may show low voltage and T- wave abnormalities

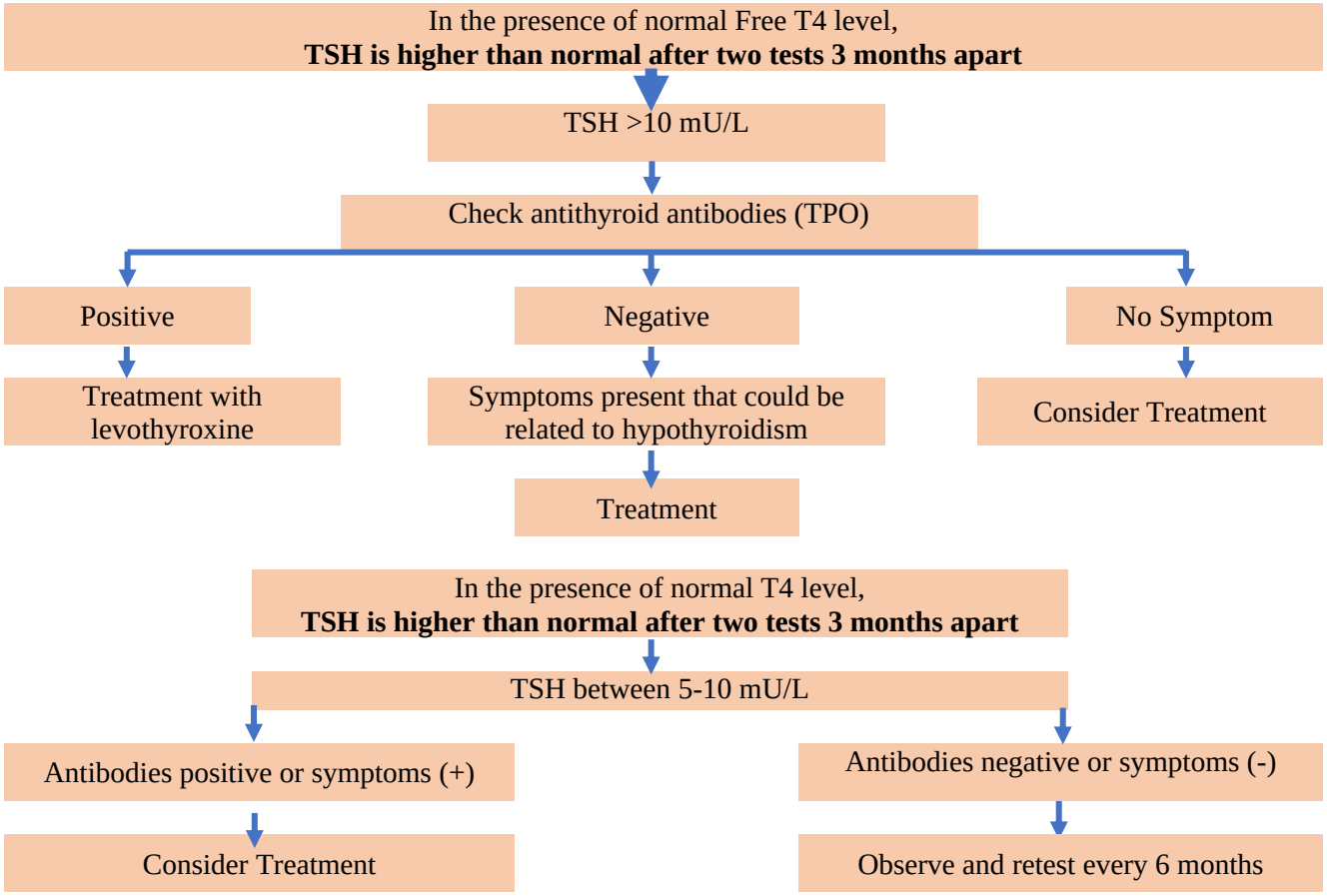
Clinical scoring systems should not be used to diagnose hypothyroidism

Investigations (Thyroid function test)	
Free T4 & TSH	
Primary hypothyroidism (T4 ↓, TSH ↑)	
Plasma TSH is the best initial diagnostic test. A normal value excludes primary hypothyroidism, and a markedly elevated value (>20 µU/mL) confirms the diagnosis	
Secondary hypothyroidism (T4 ↓ TSH → ↑) Procced MRI-brain	
Plasma TSH levels are usually within the reference range in secondary hypothyroidism and cannot be used alone to make this diagnosis. Plasma free T_4should be measured.	
Subclinical hypothyroidism (T4 →, TSH ↑)	
Anti-thyroid peroxi- dase antibody (TPOAb) measurements should be considered	
Hypothyroid in pregnancy	
Total or free T4, TSH (Trimester specific value of TSH)	
Nonthyroidal illness	
Mild elevation of plasma TSH (<20 µU/mL) may be caused by nonthyroidal illness.The test should be repeated with measurement of plasma free T_4 to confirm the diagnosis.	
Anti TPO measurement	
Primary hypothyroid (To confirm Dx- Hashimoto) Subclinical hypothyroidism To identify autoimmune thyroiditis	
Treatment	
Levothyroxine	
1.6 mcg/kg orally daily, and most patients require doses between 75 and 150 mcg daily	
How to take	
Levothyroxine should be taken 60 minutes before a meal, since dietary fiber and soy products interfere with its absorption. It should not be taken together with medications that inhibit its absorption including calcium or iron supplements, cholestyramine, sucralfate, and aluminum hydroxide.	
Initiation of therapy	
Young healthy adult	1.6 mcg/kg daily.
Elderly	50 ug/day
Cardiac disease	25-50 ug/day
Monitoring	
Primary Hypothyroid	
Plasma TSH after 6-8 weeks	Dose adjustment 12-25 ug at 6-8 weeks until TSH normal
After TSH normal	Annual TSH measurement
Secondary hypothyroidism	
plasma TSH cannot be used to adjust therapy	to maintain the plasma free T_4 near the middle of the reference range
Side effects	
Iatrogenic hyperthyroidism, Atrial fibrillation, osteoporosis	
Problems with treatment – Difficult to achieve a dose to normalize TSH	
Poor or erratic medication compliance Drugs interaction Pregnancy	

Gradual failure of endogenous thyroid function (Eg. After RAI treatment of hyperthyroid)

Special situations

Subclinical hypothyroidism



Hypothyroid in pregnancy

In pregnancy, the upper limit of the normal range should be based on trimester-specific ranges for that laboratory.
If trimester-specific reference ranges for TSH are not available in the laboratory, the following upper normal reference ranges are recommended:

1st trimester- 2.5 mIU/L
second trimester- 3.0 mIU/L
third trimester- 3.5 mIU/L

LT4 therapy is recommended for

- TPOAb-positive women with a TSH greater than the pregnancy-specific reference range
- TPOAb-negative women with a TSH greater than 10.0 mU/L

Hypothyroid in severely ill patient

In severe nonthyroidal illness, the diagnosis of hypothyroidism may be difficult
Plasma TSH is the best initial diagnostic test. A normal TSH value is strong evidence that the patient is euthyroid
Marked elevation of plasma TSH (>20 μ U/mL) establishes the diagnosis of primary hypothyroidism.
Moderate elevations of plasma TSH (<20 μ U/mL) may occur in euthyroid patients with nonthyroidal illness and are not specific for hypothyroidism

When to refer

A nodular thyroid, suspicious thyroid nodules, or compressive symptoms
Pregnancy
Underlying cardiac disorders
Age younger than 18 years
Secondary or tertiary hypothyroidism
Unusual constellation of thyroid function test
Inability to maintain TSH in the target range
Unresponsiveness to treatment

Myxoedema coma

Myxedema coma is a severe and life-threatening form of de-compensated hypothyroidism with an underlying precipitating factor.
The mortality rates may be as high as 25–60% even with best possible treatment.
It is a medical emergency and requires immediate specialist input.
Definition: Severe Hypothyroidism with

- Altered mental state
- Hypothermia
- Other organ failure
- Typically triggered by underlying illness or event

Clinical features: Usual symptoms & signs of hypothyroidism, Plus:

- Hypothermia (80 % of cases)
  - If temp: is normal, consider infection present
- Hypotension / bradycardia
- Hypoventilation / respiratory failure
- Ileus
- Depressed mental status

Laboratory Abnormalities
Hyponatraemia
Hypoglycaemia
Anaemia
Elevated creatinine
Elevated creatinine kinase
Elevated transaminases
Hypercapnoea
Hypoventilation
Hyperlipidaemia
Leucopenia
Respiratory acidosis
Elevated aPTT

Treatment of myxedema crisis should be prompt and multi-dimensional with attention to the following principles:
(a) intensive care treatment with ventilator support, central venous pressure monitoring, and pulmonary capillary wedge pressure if feasible in patients with cardiac disease,
(b) appropriate fluid management and correction of hypotension and dyselectrolytemia,
(c) aggressive management of precipitating factors and steroid supplementation if required,
(d) thyroid hormone replacement.

- Initial thyroid hormone replacement for myxedema coma should be levothyroxine given intravenously.
- A loading dose of 200–400 lg of levothyroxine may be given, with lower doses given for smaller or older patients and those with a history of coronary disease or arrhythmia.

Prolong bleeding time	• A daily replacement dose of 1.6lg/kg body weight, reduced to 75% as long as it is being intravenously administered, can be given thereafter.

THYROTOXICOSIS

Hyperthyroidism	Thyrotoxicosis
Due to an inappropriately high synthesis and secretion of thyroid hormone (TH) by the thyroid	A clinical state that results from inappropriately high thyroid hormone action in tissues generally due to inappropriately high tissue thyroid hormone levels

Causes of thyrotoxicosis

Thyrotoxicosis assicated with a normal or elevated radioactive iodine (RAI) uptake over the neck[a]

- *GD*
- *TA or TMNG*
- *Trophoblastic disease*
- *Thyroid-stimulating hormone (TSH)-producing pituitary adenomas*
- *Resistance to thyroid hormone (T_3 receptor β mutation [THRB])[b]*

Thyrotoxicosis associated with a near-absent RAI uptake over the neck

- *Painless (silent) thyroiditis*
- *Amiodarone-induced thyroiditis*
- *Subacute (granulomatous, deQuervain's) thyroiditis*
- *Palpation thyroiditis*
- *Iatrogenic thyrotoxicosis*
- *Factitious ingestion of thyroid hormone*
- *Struma ovarii*
- *Acute thyroiditis*
- *Extensive metastaese from follicular thyroid cancer*

[a] In iodine-induced or iodine-exposed hyperthyroidism (including amiodarone type 1), the uptake may be low.
[b] Patients are not uniformly clinically hyperthyroid.

Common symptoms

- Nervousness
- Anxiety
- Increased perspiration
- Heat intolerance
- Hyperactivity
- Palpitations

Common signs

- Tachycardia or atrial arrhythmia
- Systolic hypertension
- wide pulse pressure
- Warm, moist, smooth skin
- Lid lag
- Stare
- Hand tremor
- Muscle weakness
- Weight loss despite increased appetite
- oligomenorrhea

Presentations of thyrotoxicosis

Younger patients tend to exhibit symptoms of sympathetic activation (e.g., anxiety, hyperactivity, tremor)
Older patients have more cardiovascular symptoms (e.g., dyspnoea, atrial fibrillation) and unexplained weight loss
Patients with Grave's disease often have more marked symptoms than patients with thyrotoxicosis from other causes
Ophthalmopathy (e.g., periorbital oedema, diplopia, or proptosis) and pretibial myxoedema dermopathy specifically occur with Grave's disease
Elevated thyroid hormone levels associated with subacute thyroiditis may occur as part of a post-viral syndrome (subacute granulomatous thyroiditis) or within a year of the end of a pregnancy (postpartum subacute thyroiditis)

Investigations and Diagnosis

Thyroid function test	**To find out the aetiology of thyrotoxicosis**
The most reliable screening measure of thyroid function is the thyroid-stimulating hormone (TSH) level. ***Hyperthyroidism and thyrotoxicosis*** - suppressed TSH & elevated T3 and FT4 ***Milder hyperthyroidism*** - elevation of T3 only with a suppressed TSH ***Subclinical hyperthyroidism*** - decreased TSH and normal T3 and FT4	• ***TSH-receptor antibody (TRAb)***: 63-81% of Grave's disease; diagnostic & specific for GD • ***^{123}I or ^{99m}Tc pertechnetate uptake scan*** (when clinically suggests TA or TMNG or Subacute thyroiditis) • ***Thyroidal blood flow on USG***

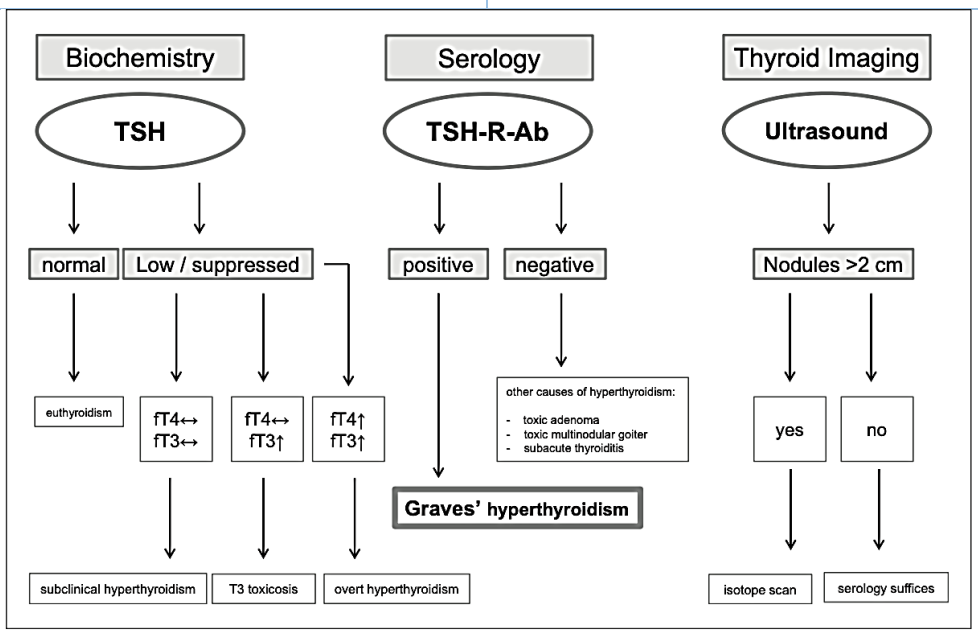


Fig. 1. Algorithm for investigating a patient with suspected Graves' hyperthyroidism.

Treatment

Symptomatic management (Beta-adrenergic blockade)	Propranolol (20–40 mg 6 h) or longer acting (i.e., atenolol/bisoprolol) recommended in all with symptomatic thyrotoxicosis, especially • Elderly • Resting HR >90/minute or • Coexistent cardiovascular disease If not tolerate or severe asthma, CCB (verapamil or diltiazem) can be used.
Grave's disease	▪ *Patients with newly diagnosed Graves' hyperthyroidism should be treated with ATD. RAI therapy or thyroidectomy may be considered in patients who prefer this approach.* ▪ *Methimazole (MMI) or Carbimazole (CBZ) should be used in every non-pregnant patient.* ▪ *The initial dose of MMI: 10–30 mg once daily depending on severity of hyperthyroidism (CBZ 15–40 mg/day).* ▪ *Propylthiouracil (PTU): 100 mg TID, divided doses throughout the course.* ▪ *Gradually reduced (titration regimen) as thyrotoxicosis improves.* ▪ *Patients should be informed of potential side effects of ATD and the necessity of informing the physician promptly if they should develop jaundice, light-colored stools, dark urine, fever, pharyngitis, or cystitis.* ▪ *In patients taking ATD, a differential white blood cell count should be obtained during febrile illness and/or pharyngitis, and liver function should be assessed in those who experience jaundice, light-colored stools, or dark urine.*
	Table: Advert effects if anti-thyroid drugs
	Common (1.0-5.0%) - *Skin rash* - *Urticaria* - *Arthralgia, Polyarthritis* - *Fever,* - *Mild Leukopenia* **Rare (0.2-1.0%)** - *Gastrointestinal* - *Abnormalities of taste and smell* - *Agranulocytosis* **Very rare (<0.1%)** - *Aplastic anaemia (PTU, CBZ)* - *Thrombocytopenia (PTU, CBZ)* - *Vasculitis, lupus-like, ANCA + (PTU)* - *Hepatitis (PTU)* - *Hypoglycaemia (Anti-insulin Abs, PTU)* - *Cholestatic Jaundice (CBZ, MMI)*
	PTU= propylthiouracil, MMI = methimazole, CBZ = carbimazole, ANCA = anti-neutrophil cytoplasmic antibody
	▪ *MMI is administered for 12–18 months then discontinued if the TSH and TRAb are normal.* ▪ *Measurement of TRAb levels prior to stopping ATD therapy is recommended, as it aids in predicting which patients can be weaned from the medication, with normal levels indicating a greater chance of remission.* ▪ *Patients with persistently high TRAb at 12–18 months can continue MMI therapy, repeating the TRAb measurement after an additional 12 months, or opt for RAI or thyroidectomy.*

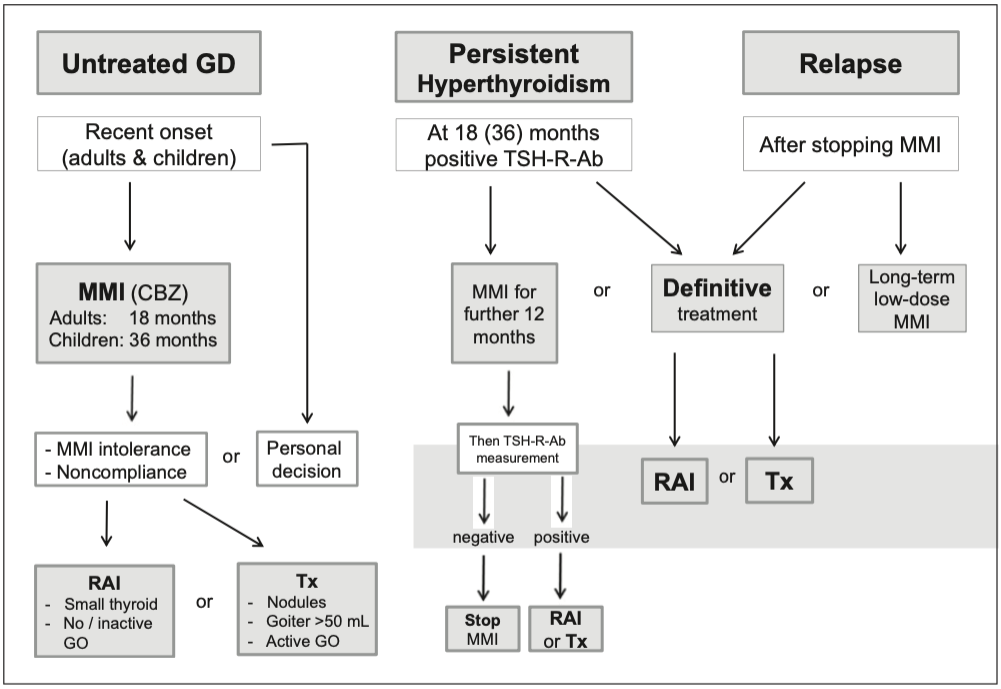
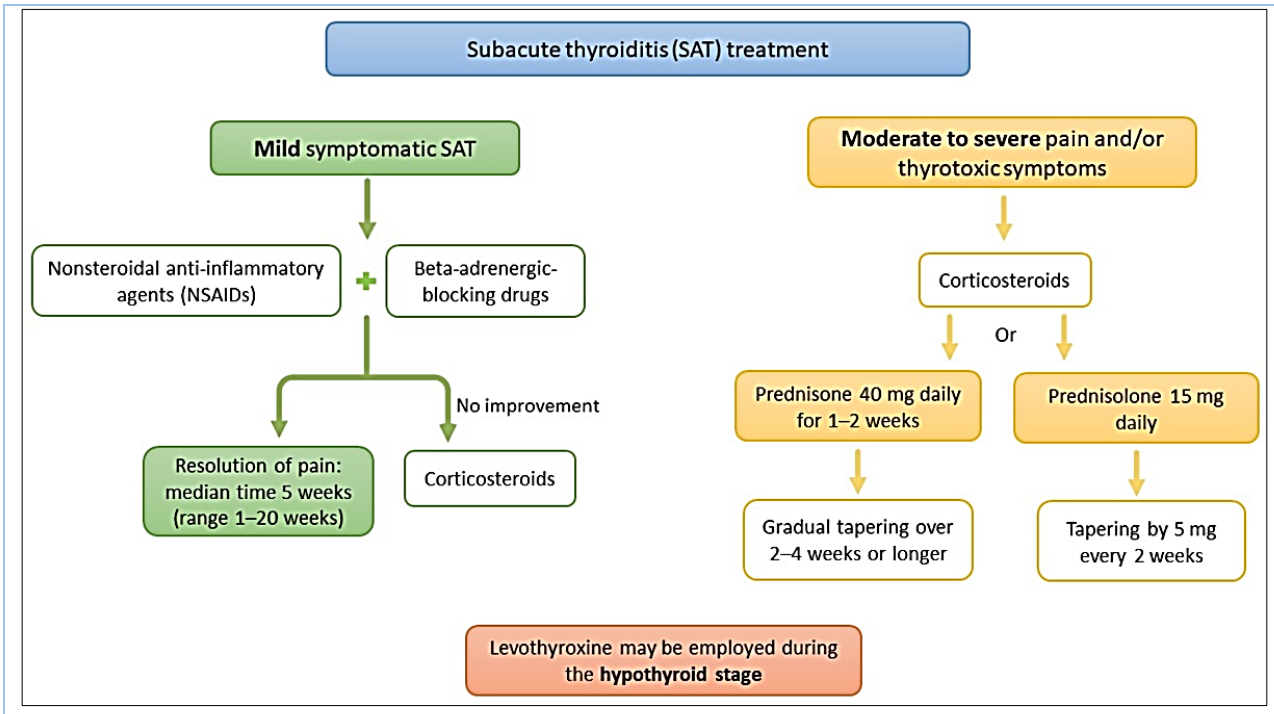


Fig. 2. Algorithm for the management of a patient with Graves' hyperthyroidism. GD, Graves' disease; MMI, methimazole; CBZ, carbimazole; GO, Graves' orbitopathy; RAI, radioactive iodine; Tx, total thyroidectomy.

Toxic nodular goitre	Control hyperthyroidism with antithyroid drugs, then surgery or RAI. Long term remissions on antithyroid drugs in a toxic nodular goitre are rare.
Subacute thyroiditis (SAT)	▪ Thyrotoxicosis temporary following surge of thyroxine after viral-type illness ▪ Self-resolving, and the treatment is also symptom relief. ▪ Pain &/or tenderness over the goitre (esp. on swallowing) & fever. ▪ Rest, analgesics (aspirin 600mg (po) 4-6 hourly) and soft foods. ▪ beta-blockers can be used to control symptoms ▪ Rarely, when pain is severe, corticosteroids may be used. ▪ Antithyroid drugs not indicated.



When to refer

- Doubt about the diagnosis
- Severe hyperthyroidism, especially if there is coexisting thyrocardiac disease
- Pregnant patients with hyperthyroidism
- Progression of exophthalmos
- Ideally all cases

THYROID CRISIS (THYROID STORM)

- *Rare disorder characterized by multisystem involvement*
- *Mortality rates in the range of 8%–25% in modern series*
- *Clinical features are marked anxiety, weight loss, weakness, proximal muscle weakness, hyperpyrexia, tachycardia (>150/ minute), heart failure and arrhythmias.*
- *It is usually precipitated by surgery or an infection in an undiagnosed patient.*
- *Dx made clinically in severely thyrotoxic patient + systemic decompensation.*
- *Referral is required for urgent intensive hospital management.*

2.

THYROID NODULES AND THYROID CARCINOMAS

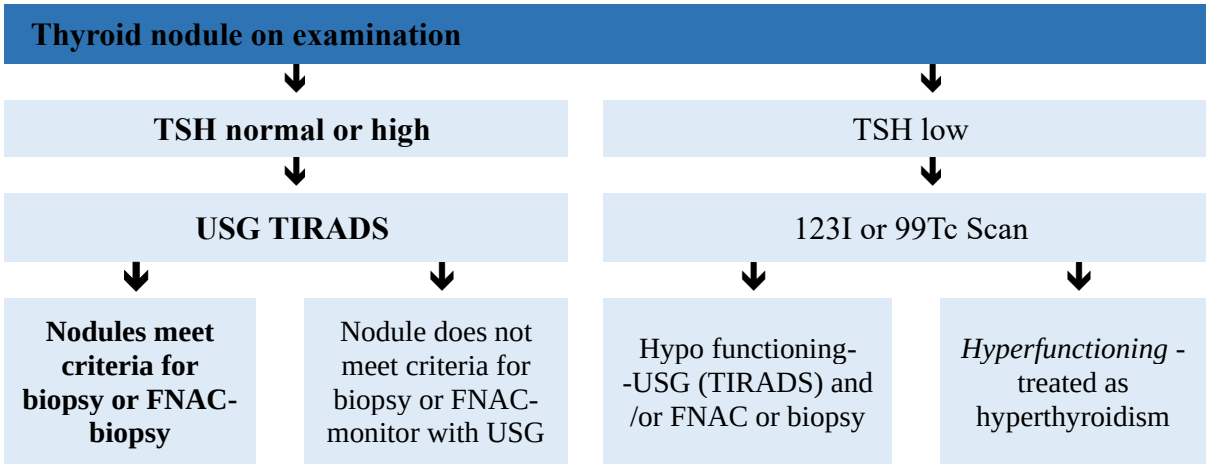
Prevalence of palpable thyroid nodules are 5% in women and 1 % in men in iodine sufficient part of the world (ATA 2015)
Thyroid cancers are found in 7 -15 % of cases depending on age, sex, radiation exposure history, family history and other factors
Differentiated thyroid cancer (DTC), which includes papillary and follicular cancer, comprises the vast majority (>90%) of all thyroid cancers and <3 % are poorly differentiated tumors

Risk factors for Malignancy

1. Prior irradiation
2. Family history
3. Male sex
4. Nodules in individuals age less than 15 year and above 45 year
5. Symptoms of invasiveness: development of hoarseness, progressive dysphagia or dyspnea

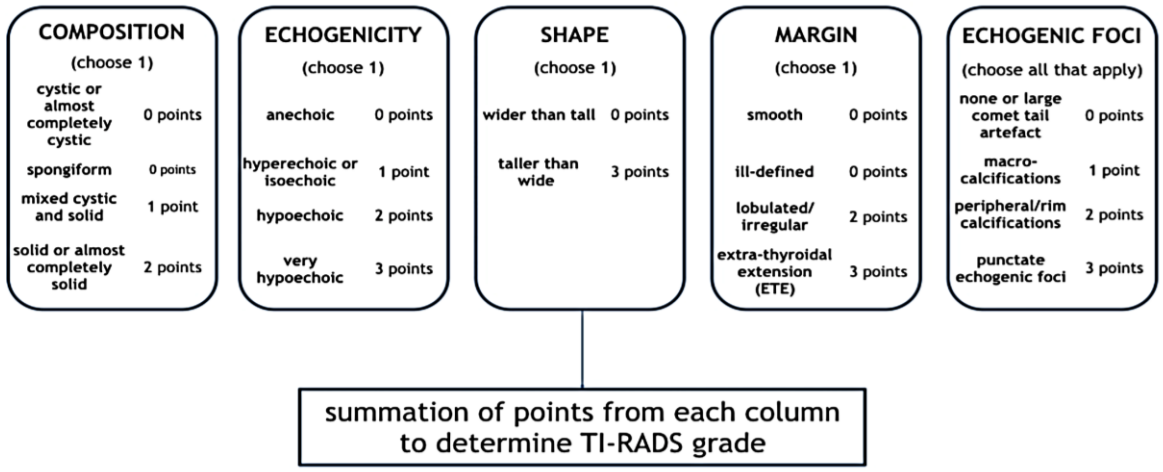
Investigations of Thyroid nodules

1. Ultrasound imaging by TIRADS
2. Thyroid function tests (TSH)



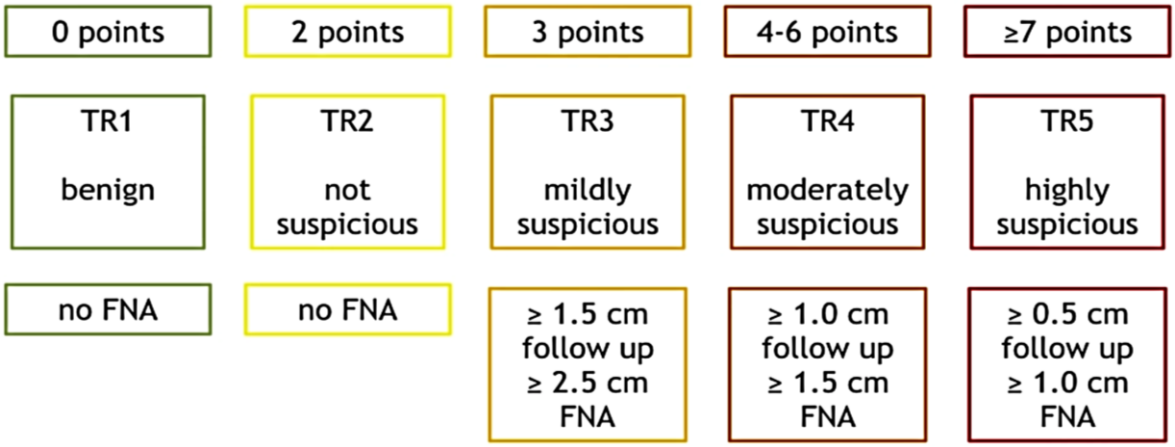
Thyroid USG (TIRADS)

Diagram



Source: ACR White Paper 2017

Diagram



Source: ACR White Paper 2017

From findings on USG or USG guided FNA

- **Follicular neoplasm- 80% of these nodules-benign & 20 %- thyroid carcinoma**
- **Papillary carcinoma- accuracy of FNA approaches 100 %**

General features of thyroid cancers derived from follicular and para-follicular cells

Type	Prevalence	Age (years)	Distant Metastasis	5 years survival rate
Papillary	85-90%	20-50	5-7%	>90%
Follicular	<10%	40-60	20%	>90%
Poorly differentiated	<5%	50-60	20-80%	>50%
Anaplastic	1-2%	60-80	20-50%	1-17%
Medullary thyroid carcinoma	1-2%	40-50	10-15%	65-89%

Preoperative staging with diagnostic imaging and laboratory tests

- USG (Neck)
- CT/ MRI/ PET
- serum Tg or anti-Tg

Treatment of Thyroid carcinoma (DTC)

- Surgery
  - For cytology "diagnostic of" or "suspicious for" papillary thyroid cancer, surgery is recommended.
  - If FNAB cytology is indeterminate, use of molecular markers such as BRAF, RAS, RET/PTC, Pax8-PPARɣ, or galectin-3 may be considered to guide management
  - Iodine-123 (^{123}I) thyroid scan - considered if the cytology report documents a follicular neoplasm, especially TSH -in the low-normal range
- Tumor >1 cm and <4 cm, no extrathyroidal extension-Total Thyroidectomy
- Tumor >4 cm, or with gross extrathyroidal extension _ Near total _Total Thyroidectomy

An alternative active surveillance management approach can be considered in:

A) patients with very low risk tumors
B) patients at high surgical risk because of co-morbid conditions,
C) patients expected to have a relatively short remaining life span

Follow p after Surgery after FNA

DTC (PTC, FTC)
↓
TSH, Tg, USG
↓
RAI Therapy
Life-long T4 with Risk Assessment

MTC
↓
Assessment of associated MEN's $
↓
Follow up
Calcitonin, CEA

Long term management

1. Repeat RAI scan 6-12 months after ablation & every 2 years thereafter
2. Tg- every 6-12 months for at least 5 years

3. Annual measurement of unstimulated Tg and periodic neck USG
4. A patient who has had a thyroidectomy without parathyroid preservation requires vitamin D and calcium supplementation for life.
5. Patients require lifelong thyroid hormone replacement therapy, especially after total thyroidectomy (levothyroxine in a dosage of 2.5-3.5 mcg/kg/d)

Standard Treatment of Thyroid Cancer

Thyroid Nodules – Physical Examinations and USG (TIRADS) / and FNAC

↓

FNAC finding - Thyroid Ca

↓

Total Thyroidectomy

↓

RAI Ablation - detect and destroy any metastasis and residual tissue in the thyroid.

↓

Suppression Therapy -Minimum T4 to suppress TSH without thyrotoxicosis

- *TSH target - <0.1 mU/L in High-risk TC*
- *TSH -0.1-0.5 in intermediate risk TC*
- *TSH -0.5- 2 mU/L in Low-risk TC*

↓

Whole body Scan, USG, Tg assay -to detect any metastasis and residual tissue in the thyroid.

References

3. *American Thyroid Association (ATA) (2015)*
4. *National Comprehensive Cancer Network (NCCN) (2014)*
5. *European Society for Medical Oncology (ESMO)*
6. *American Association of Clinical Endocrinologists/Association of Medicine Endocrinologist /European Thyroid Association (AACE/AME/ETA)*

PITUITARY DISORDERS

Pituitary Tumours

Types of Pituitary tumours	Symptoms	Investigation	Treatment
- Prolactinomas (49%) - Acromegaly (12%) - Cushing's $ (7%) - TSHomas (<1%) - Non-functioning adenoma (28%) - Incidental tumours (~10%) - Pituitary carcinoma very rare (<0.1%)	*Mass effects* - Headache, nausea and vomiting - Visual field defects (uni- or bitemporal quadrantanopia or hemianopia) - Ophthalmoplegia - Apoplexy (rarely) - May also manifest symptoms of pituitary hormone deficiencies or overproduction, depending on the size and type of tumour	Refer to endocrinologists/ physicians to proceed - Pituitary imaging: MRI/CT - Visual assessment - Pituitary function assessment	Refer to neurosurgeons for Transphenoidal surgery Based on the type and size of the tumour, - observation - medical therapy, or - radiation therapy may be possible treatment options

PITUITARY HORMONE DEFICIENCIES (HYPOPITUITARISM)

- Hypopituitarism refers to either partial or complete deficiency of anterior and/or posterior pituitary hormones.

Common Causes

- *Sellar and parasellar tumours (e.g. pituitary adenomas, craniopharyngiomas, meningiomas, 2° deposits (e.g. breast, lung))*
- *Surgery to remove a pituitary tumour*
- *Radiotherapy for pituitary, cranial, nasopharyngeal tumours*
- *Vascular: Pituitary infarction (apoplexy), Subarachnoid haemorrhage (SAH), or severe blood loss during childbirth (Sheehan's Syndrome)*
- *Infection (e.g. tuberculosis (TB))*
- *Traumatic brain injury (TBI)*

Signs and symptoms of hypopituitarism

- The signs and symptoms vary from person to person, depending on which pituitary hormones are affected and to what degree. They usually develop gradually and can get worse over time but develop suddenly for others. These are listed in the Fact Sheet.

FACT SHEET – HYPOPITUITARISM

Deficient Hormone	Symptoms	Investigation	Hormone Replacement Therapy
Adreno cortico-trophic hormone (ACTH)	Pale, ↓BP, dizziness, tiredness, weight loss, stomach pain, depression, low tolerance to stresses, reduced QOL	- 8–9 AM cortisol levels (perform at least 18–24 hours after the last hydrocortisone (HC) dose) -a corticotropin stimulation test	- HC, usually 15–20 mg total daily dose/ Prednisolone (3.75-10 mg) in single or divided doses to be taken the highest dose in the morning at awakening - treat patients with suspected adrenal crisis due to secondary AI with an immediate parenteral injection of 50–100 mg HC
Thyroid Stimulating Hormone (TSH)	Weight gain, lethargy, cold intolerance, constipation, dry skin	- fT4 level↓ with ↓or ↔ TSH usually	- L-T4 in doses (~1.6 µg/kg/d) sufficient to achieve serum fT4 levels in the mid to upper half of the reference range - dose adjustments based on clinical context, age, and fT4 levels
Follicle Stimulating Hormone (FSH) / Luteinising Hormone (LH) in ♀	Irregular or loss of periods, low libido, hot flushes, vaginal dryness (pain during sex), sleep disturbance	-estradiol (E2), FSH, and LH	- hormone replacement therapy in premenopausal women with central hypogonadism, provided there are no contraindications
FSH/LH in ♂	Erectile dysfunction, low libido (sex drive), low sperm count, infertility, loss of facial and body hair	- serum Testosterone (T), FSH, and LH (in the absence of illness and before 10 AM after overnight fast)	-T replacement for adult males in order to prevent anemia related to T deficiency; reduce fat mass and improve bone mineral density (BMD), libido, sexual function, energy levels, sense of wellbeing, and muscle mass and strength
Growth Hormone (GH)	Lack of growth and sexual development (in children), excessive tiredness, muscle weakness, ↓bone density, ↑body fat, ↓QOL	- IGF-1 level - GH stimulation testing	- GH replacement to those patients with proven GHD and no contraindications

PITUITARY HORMONE OVERPRODUCTION

Prolactinoma

Definition

A prolactinoma is a benign pituitary tumor causing hyperprolactinaemia.

Epidemiology

- *Prolactinomas are the commonest functioning pituitary tumour.*
- *(microprolactinomas >macroprolactinomas),*

- ♀ *preponderance of microprolactinomas*

Clinical features

- ***Hyperprolactinaemia (microadenomas <1cm and macroadenomas ≥1cm)***
  - *Galactorrhoea (up to 90% ♀, <10% ♂)*
  - *♀ : presents with menstrual disturbance (up to 95%)—amenorrhoea, oligomenorrhoea, or with infertility and reduced libido*
  - *♂ : presents with loss of libido and/or erectile dysfunction*
  - *a long-term risk of ↓ BMD*
  - ***Mass effects (macroadenomas only)***
  - *Headaches and visual field defects (usually uni- or bitemporal field defects)*
  - *Hypopituitarism*
  - *Invasion of the cavernous sinus may lead to cranial nerve palsies and even temporal lobe epilepsy.*
- ***Other Causes of Hyperprolactinaemia***
  - *Physiological: Pregnancy, Stress*
  - *Pituitary Stalk section—head injury*
  - *Cranial irradiation.*
  - *Drug treatment: metoclopramide, domperidone. Opiates. Cocaine.*
  - *Neuroleptics: haloperidol, chlorpromazine, risperidone. Antidepressants: tricyclics amitriptyline, SSRIs, MAOIs, Protease inhibitors (PIs): ritonavir, indinavir,*
  - *Others: Oestrogens, omeprazole, H_2 antagonists,*
  - *Metabolic: Hypothyroidism, CRF, Severe liver disease, PCOS*
  - *'Idiopathic' hyperprolactinaemia*

Investigations

- ***Serum Prolactin (PRL):*** *Serum PRL <2000mU/L- a tumour—either a microprolactinoma or a non-functioning macroadenoma compressing the pituitary stalk. Serum PRL >3000mU/L - diagnostic of a macroprolactinoma.*
- ***Imaging:*** *MRI*

Management

- ***(Refer to endocrinologist/physician for medical therapy and neurosurgeons for operation)***
- ***Drug therapy****—dopamine agonists:*
  - ***Cabergoline****: 0.25 mg 2 times a week*
  - ***Bromocriptine****: 1.25-2.5 mg once a day, may increase the dose by 2.5 mg every 2 to 7 days as needed and tolerated (maximum dose- 10 mg/day)*
  - *Side effects: nausea, vomiting, stomach upset or pain, constipation, dizziness,*
  - *psychological manifestations: impulse control disorders (viz. Hypersexuality, Compulsive shopping, Compulsive eating, Pathological gambling),*
  - *Cardiac valvulopathy - risk appears to be low in prolactinoma patients on standard doses of cabergoline (<2mg/week)*
- ***Surgery****:* ***Transsphenoidal surgery*** *indicated for patients who are resistant to, or intolerant of, dopamine agonist treatment.*
- ***Radiotherapy*** *useful in the treatment of macroprolactinomas once the tumour has been shrunken away from the chiasm, only if the tumour is resistant.*

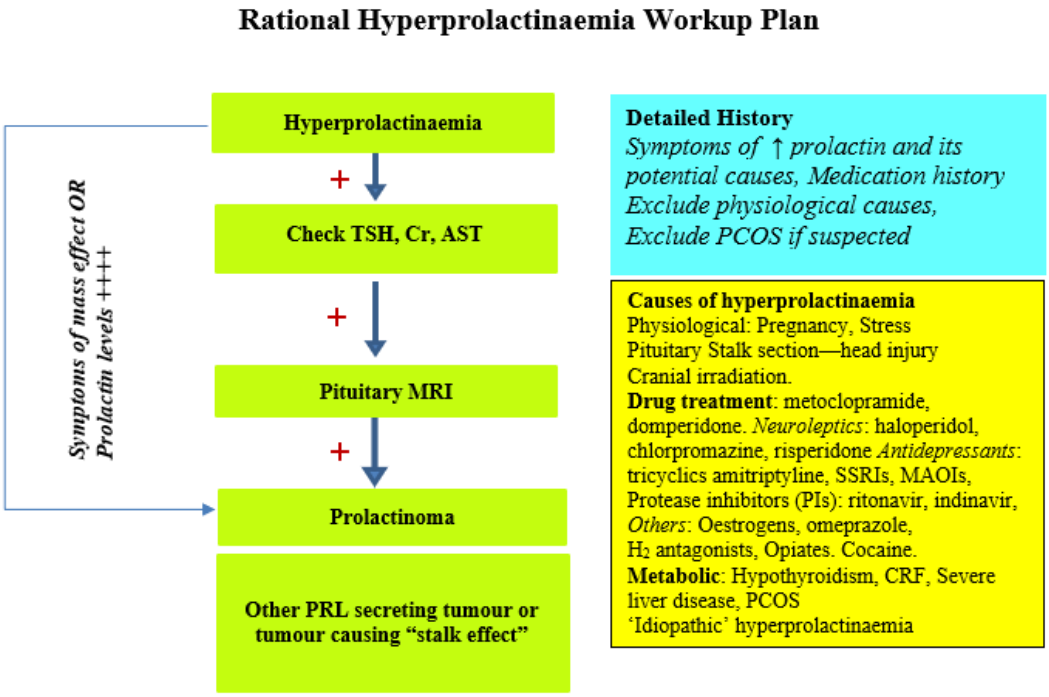


Figure 1. Algorithm for investigating hyperprolactinaemia.

OVER-SECRETION PITUITARY DISORDERS

	Acromegaly	*8. Cushing's disease*
Definition	*Acromegaly is the clinical condition resulting from prolonged excessive GH, and hence IGF-1 secretion in adults.*	*Cushing's disease is the clinical condition resulting from excess cortisol secretion due to pituitary adenoma.*
Epidemiology	• *Rare. Equal sex distribution. Mean age at diagnosis 49 years.* • *Prevalence 40–86 cases/million population.* *13.*	• *Rare; annual incidence ~2/million.* • *More common in ♀ (♀:♂, 3–15:1).* • *Age—most commonly, 20–40 years.*

Causes	**Causes of acromegaly**
	• *Pituitary adenoma (>99% of cases):*
	  ○ *Macroadenomas 60–80%*
	  ○ *Microadenomas 20–40%*
	• *GHRH secretion:*
	  ○ *Hypothalamic secretion.*
	  ○ *Ectopic GHRH e.g. carcinoid tumour (pancreas, lung) or other neuroendocrine tumours (NETs)*
	• *Ectopic GH secretion. Very rare (e.g. pancreatic islet cell tumour, lymphoreticulosis)*
		Causes of Cushing's syndrome
		• *Pseudo-Cushing's syndrome:*
		  ○ *Alcoholism*
		  ○ *Severe depression 1%*
		• *ACTH-dependent:*
		  ○ ***Pituitary adenoma 68% (Cushing's disease)***
		  ○ *Ectopic CRH/ACTH secretion ~12%*
		• *ACTH-independent:*
		  ○ *Adrenal adenoma 10%*
		  ○ *Adrenal carcinoma 8%*
		  ○ *Nodular (macro- or micro-) hyperplasia 1%*
		  ○ *Carney complex*
		• *Exogenous steroids*

Clinical features	***Symptoms*** • *↑ sweating—>80% of patients* • *Headaches—independent of tumour effect* • *Tiredness and lethargy* • *Joint pains. Change in ring or shoe size.* **Signs** • *Facial appearance. Coarse features, oily skin, frontal bossing, enlarged nose, deep nasolabial furrows, prognathism, and ↑ interdental separation* • *Deep voice* • *Tongue enlargement—macroglossia* • *Enlargement of hands and feet, osteoarthritis (OA), generalized myopathy*	• *Facial appearance—round plethoric complexion, acne and hirsutism, thinning of scalp hair* • *Weight gain—truncal obesity, buffalo hump, supraclavicular fat pads* • *Skin—thin and fragile due to loss of SC tissue, purple striae on abdomen, breasts, thighs, and axillae, easy bruising, tinea versicolor, occasionally pigmentation due to ACTH.* • *Proximal muscle weakness.* • *Mood disturbance—labile, depression, insomnia, psychosis* • *Menstrual disturbance* • *Low libido and impotence* • *High incidence of venous thromboembolism (VTE)*

	Acromegaly	*8. Cushing's disease*
	• *Entrapment neuropathies such as carpal tunnel syndrome (40% of patients)* • *Goitre and other organomegaly—liver, heart, kidney* *18.* **Complications** • *Hypertension (40%).* • *Insulin resistance and impaired glucose tolerance (40%)/DM (20%).* • *Obstructive sleep apnoea* • *↑ risk of colonic polyps and colonic carcinoma* • *CVD and cerebrovascular disease.* • *CCF and possible ↑ prevalence of regurgitant valvular heart disease.* • *Higher frequency of vertebral fractures.* **Effects of tumour** • *Visual field defects.* • *Hypopituitarism.*	• *Overall mortality greater* • *Growth arrest in children* **Associated features** • *Hypertension (>50%)* • *Impaired glucose tolerance (IGT)/DM (30%).* • *Osteopenia and osteoporosis (leading to fractures of spine and ribs).* • *Vascular disease due to metabolic syndrome.* • *Susceptibility to infections.*
. ***Investigations***	• *IGF-1.* • *GH Oral glucose tolerance test (OGTT)* • *MRI pituitary* • *Pituitary function testing*	• *Overnight dexamethasone suppression test* • *24h Urinary Free Cortisol* • *Low-dose dexamethasone suppression test* • *ACTH*
. ***Management***	Refer to endocrinologist/ physician	Refer to endocrinologist/ physician

DISORDERS OF POSTERIOR PITUITARY HORMONES

DIABETES INSIPIDUS AND SIADH

Diabetes insipidus	SIADH
High urine output	Low urine output
Low level of ADH	High level of ADH
Hypernatremia	Hyponatremia
Dehydrated	Over hydrated
Lose too much fluid	Retain too much fluid

DIABETES INSIPIDUS

Definition	Impaired secretion of vasopressin (antidiuretic hormone) from the posterior pituitary
Clinical features	polyuria, nocturia and compensatory polydipsia resulting in the passage of 3-20 L of dilute urine per day.
Causes	• Postoperative (hypothalamic- pituitary), transient only • Cranial DI - tumours, infections and infiltrations. • Nephrogenic DI - insensitive to vasopressin. (e.g. lithium, hypercalcaemia, pyelonephritis, hydronephrosis)
Diagnostic criteria	Serum Sodium >145mEq/L **AND** Serum osmolality >295 mOsm/ kg **AND** Urine Osmolality <300 mOsm/ kg

SIADH

Definition	SIADH is a disorder of impaired water excretion caused by the inability to suppress the secretion of antidiuretic hormone (ADH). Results in impaired water excretion, and subsequently hyponatremia and hypo-osmolality.
Clinical features	STADH: signs and symptoms → Decreased/low urine output Signs of hyponatremia: lethargy, apathy, disorientation, muscle cramps, anorexia, agitation Signs of water toxicity: nausea, vomiting, personality changes, confused, combative If Na <110 mEq/L, seizures, bulbar palsies, hypothermia, stupor, coma
Causes	Malignant disease - Bronchogenic carcinoma Pulmonary disorders - Viral and bacterial pneumonias ,Tuberculosis Neurologic disorders – Encephalitis, Meningitis

	Trauma Stroke Alcohol withdrawal HIV/AIDS
Diagnostic Criteria	• Decreased serum osmolality (<275 mOsm/kg) • Urine osmolality >100 mOsm/kg in the setting of serum hypotonicity • In the setting of normal dietary sodium intake, urine sodium >40 mmol/L • Normal thyroid, adrenal, renal, cardiac function • No recent use of diuretics
Treatment	Fluid restriction and referral to endocrine team

Approach to a patient with high urine output

High urine output (>4ml/kg/hr)

↓

Rule out other causes of polyuria
- osmotic diuresis secondary to mannitol hyperglycaemia
- diuretics
- appropriate diuresis following large IV fluid load intra operatively
- large volumes of contrast media during angiography/embolisation

↓

SEND
Serum Sodium
Serum Osmolality
Urine Sodium Urine Osmolality/Urine Specific Gravity

↓

SERUM SODIUM HIGH >145 mmol/l
Has the serum Na risen rapidly with the diuresis?
Is the serum osmolality >295?
Is there a negative fluid balance?
Is the urine colourless with a very low urine Na?
If all 4 criteria are met then polyuria is probably Diabetes Insipidus, contact Endocrine team.

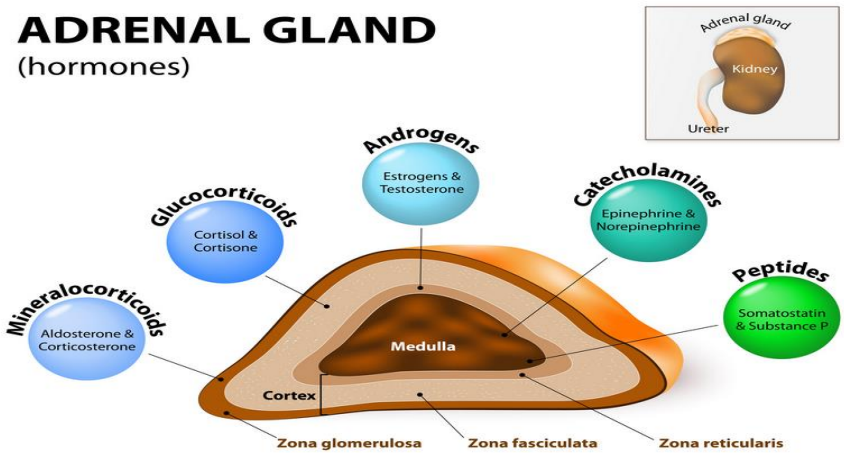
The points of difference between Diabetes Insipidus & SIADH have been summarized below.

Characteristics	Diabetes Insipidus	SIADH
Definition	A disorder of water and salt metabolism marked by heavy urination and intense thirst.	A disorder in which increased levels of a hormone causes the body to retain water.
ADH	Inadequate ADH	Excess ADH
Types	2 forms of DI include Cranial diabetes insipidus (CDI) Nephrogenic diabetes insipidus (NDI)	4 forms include Type A SIADH, Type B SIADH, Type C SIADH and Type D SIADH
Urinary Output (Osmolarity)	Higher urinary output (polyuria)	Lower urinary output (Oliguria)
Sodium content	High	Low

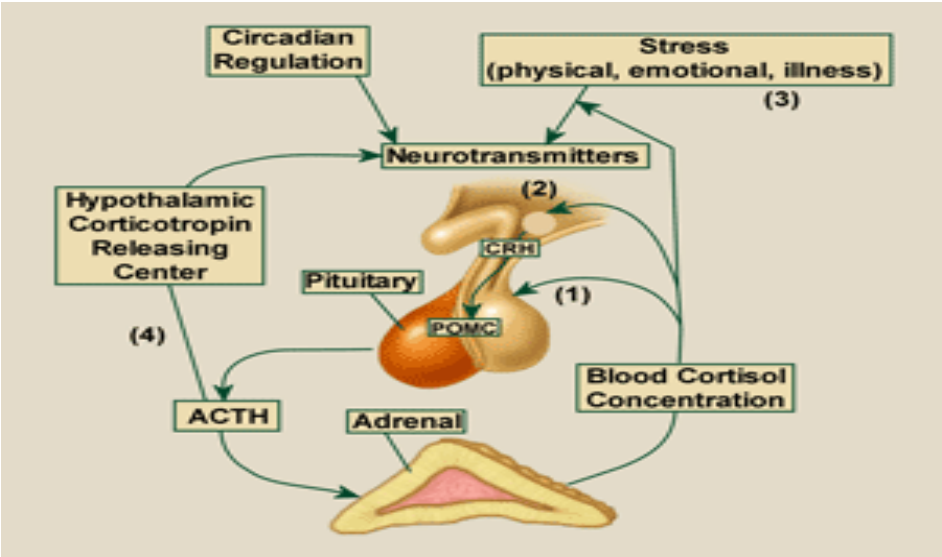
Risk	Hypovolemic shock	Seizures
Plasma volume	Euvolemic	Euvolemic or slightly hypervolemic
Diagnostic criteria	Diagnostic criteria Serum Sodium >145mEq/L AND Serum osmolality >295 mOsm/ kg AND Urine Osmolality <300 mOsm/ kg	• Concentrated urine Na >20 mmol/L • Hyponatremia <125 mmol/L • Plasma osmolarity <260 mmol/kg In the absence of hypokalaemia, oedema or diuretics
Treatment	Vasopressin/ Desmopressin Chlorpropamide/HCTZ	Normal saline Fluid restriction Demeclocycline

ADRENAL DISORDERS

- The adrenal glands are located on the top of the kidneys
- The adrenal glands are made up of two parts, the cortex and the medulla
- The adrenal cortex, zona glomerulosa layer produces aldosterone, zona fascicular and reticularis layer produce cortisol and androgen



Hypothalamo–pituitary–adrenal axis (HPA axis)



	Adrenal Insufficiency (AI)	Cushing's Syndrome
Definition	Adrenal insufficiency is a chronic medical condition in which the adrenal glands do not produce enough of the necessary hormones (cortisol and aldosterone) to respond to stressors such as illness and injury	○ Cushing's syndrome comprises a large group of signs and symptoms, results from chronic exposure to excess glucocorticoids, which can be from either exogenous corticosteroids or

	Adrenal Insufficiency (AI)	Cushing's Syndrome
		endogenous source of cortisol
Epidemiology	Rare Prevalence - 5 in 10,000 Usually effects 30-50 years old, but can be seen in all ages Affects women more frequently than men	○ Estimated incidence of 0·2–5·0 per million people per year ○ A prevalence of 39–79 per million in various populations ○ Median age of onset/diagnosis was 41·4 years ○ Female-to-male ratio of 3:1
Causes	Primary (high ACTH) Addison's disease • Autoimmune (80%) (sporadic or polyglandular failure, APS1 and APS2) • Adrenal infection (TB, HIV, CMV, cryptococcosis, histoplasmosis, coccidioidomycosis) • Adrenal infiltration (Metastases, lymphomas, sarcoidosis, amyloidosis, hemochromatosis) • Bilateral adrenalectomy • Adrenoleukodystrophy (ALD) Secondary (low ACTH) • Pituitary tumors (endocrine adenomas, rarely carcinoma) • Mass lesions affecting the HP region (craniopharyngioma, meningioma, metastases) • Pituitary irradiation • Pituitary apoplexy/hemorrhage • Pituitary infiltration (TB, actinomycosis, sarcoidosis, Wegener's granulomatosis, metastases) • Glucocorticoid-induced AI (long-term administration of exogenous glucocorticoids)	○ Exogenous / Iatrogenic (Oral, injection or inhaled steroid) • the most common cause of Cushing's syndrome ○ Endogenous • ACTH dependent (80%) • Pituitary adenoma (Cushing's disease) • Ectopic ACTH or CRH secreting tumor • ACTH independent (20%) • Adrenal adenoma • Adrenal carcinoma
Clinical features	Symptoms and Signs Caused by Glucocorticoid Deficiency: • Chronic fatigue • Weight loss, anorexia • Myalgia, joint pain	○ Symptoms and Signs Caused by Glucocorticoid Excess: • Facial appearance— round plethoric complexion, acne and hirsutism, thinning of scalp hair

	Adrenal Insufficiency (AI)	Cushing's Syndrome
	• Low blood pressure, postural hypotension • Fever • Anemia, eosinophilia and lymphocytosis • Hypoglycemia, Hyponatremia due to loss of feedback inhibition of ADH release • Symptoms and Signs Caused by Mineralocorticoid Deficiency (Primary AI Only) • Abdominal pain, nausea, vomiting • Dizziness, postural hypotension • Salt craving • Low blood pressure, postural hypotension • Hyponatremia • Hyperkalemia • Hyperpigmentation, especially mucous membranes of mouth and hard palate, skin creases of hands • Signs and Symptoms Caused by Adrenal Androgen Deficiency • Lack of energy • Dry and itchy skin (in women) • Loss of libido (in women) • Loss of axillary and pubic hair (in women)	• Weight gain—truncal obesity, buffalo hump, supraclavicular fat pads • Skin—thin and fragile due to loss of SC tissue, purple striae on abdomen, breasts, thighs, and axillae, easy bruising, tinea versicolor, occasionally pigmentation due to ACTH. • Proximal muscle weakness. • Mood disturbance—labile, depression, insomnia, psychosis • Menstrual disturbance • Low libido and impotence • High incidence of venous thromboembolism (VTE) • Overall mortality greater • Growth arrest in children • Associated features • Hypertension (>50%) • Impaired glucose tolerance (IGT)/DM (30%). • Osteopenia and osteoporosis (leading to fractures of spine and ribs). • Vascular disease due to metabolic syndrome. • Susceptibility to infections.
Investigations	• Morning cortisol level (8:00 AM) • Random cortisol in ill patient • ACTH level • ACTH stimulation test • DHEAS • Adrenal Autoantibodies • Anti-21-OH-hydroxylase antibody (80%) • ACA—adrenal cortex antibody	• Overnight dexamethasone suppression test (1mg DST) • 24h Urinary Free Cortisol (UFC) (at least two measurements) • Late night salivary cortisol (two measurements) • Low-dose dexamethasone suppression test (2mg/day for 48 hr) • ACTH
Diagnosis	• Low basal serum cortisol: Highly likely if serum cortisol <138 nmol/L (5µg/dl) • Elevated plasma ACTH: >2-foldover URL • Corticotropin stimulation test:250µg iv, cortisol at baseline and after 30 min) for confirmation - peak cortisol below 500–550 nmol/l (18µg/dl)	• Serum cortisol greater than 1.8 g/dl (50 nmol/liter) after 1 mg dexamethasone (1-mg DST) • UFC greater than the normal range • Late-night salivary cortisol greater than 145 ng/dl
Management	• Glucocorticoid replacement therapy • Hydrocortisone (15 –25 mg), 2-3 times divided daily	• In exogenous Cushing's syndrome, gradual withdrawal of the glucocorticoid is

	Adrenal Insufficiency (AI)	Cushing's Syndrome
	• Prednisolone (3-5 mg) once or twice daily • Do not use dexamethaxone • Monitor energy level, BP, body weight, sign of Cushing • No biochemical or hormonal monitoring recommended • Mineralocorticoid replacement • fludrocortisone in confirmed aldosterone down, starting with 100µg/d • Monitor clinical sign, electrolytes and plasma renin • DHEA replacement therapy • Treating depression, low energy and libido • Initial dose 25–50 mg • Discontinue after 6 months if no benefit • Measurement of DHEAS	important because most patients on long-term therapy will have some degree of HPA-axis suppression with resultant adrenal insufficiency if therapy is abruptly discontinued • In ACTH-independent Cushing's syndrome, Patients should be referred for adrenalectomy • In ACTH-dependent Cushing's disease, a transsphenoidal microadenectomy is the treatment of choice for patients with a clearly circumscribed pituitary microadenoma
Sick day rules for patients with known AI	• Double the normal dose of hydrocortisone for a fever of more than 37.5 C or for infection/sepsis requiring antibiotic. • For severe nausea (often with headache), take 20mg hydrocortisone orally and sip rehydration/electrolyte fluids • On vomiting, use the emergency injection (100mg hydrocortisone) immediately. Then call a doctor, saying Addison's emergency.	• Refer to endocrinologist/ physician

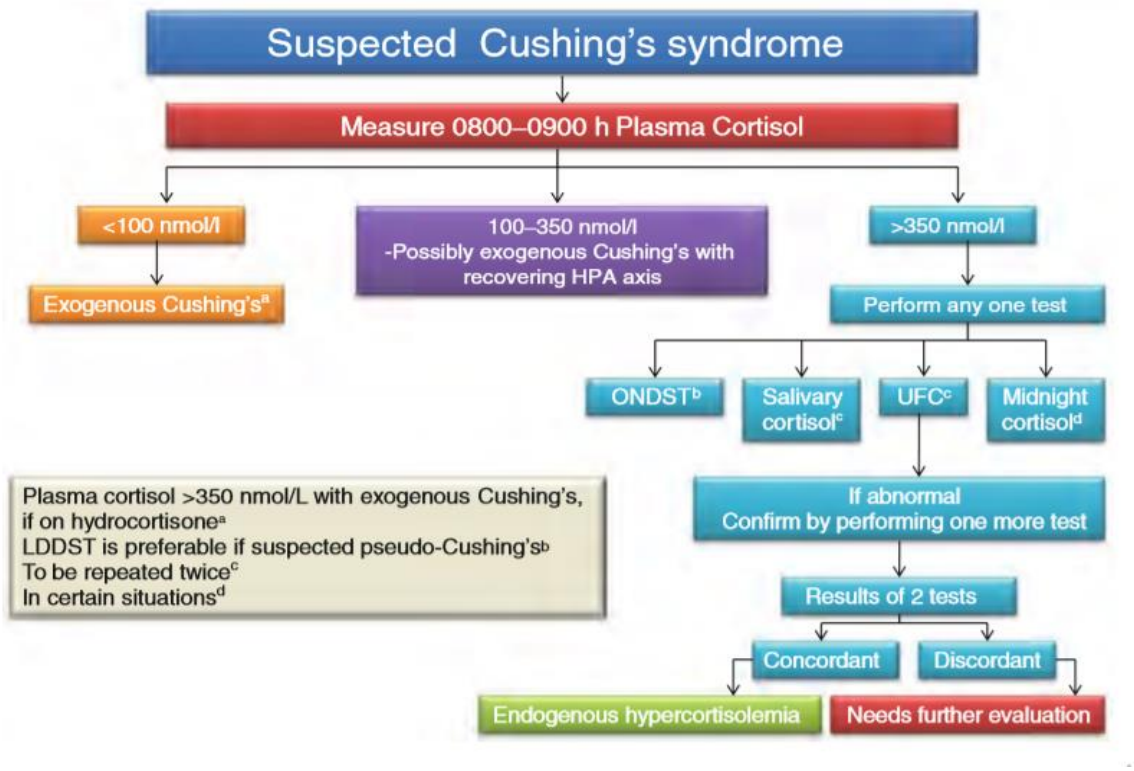
ADDISONIAN CRISIS

- It is a life-threatening medical emergency condition
- Severe hypotension (shock)
- Unexplained fever, diarrhea, vomiting
- Hyperkalemia
- Hyponatremia
- Hypoglycemia
- Could cause coma and death
- Precipitated by infection, surgery or intercurrent disease

Acute Management of Addisonian Crisis

- IV fluid (normal saline 1L/h) - Infusion rate 1 litre per hour until SBP >100mg Hg, then reduced rate according to clinical state
- IV Hydrocortisone 100 mg bolus then 200 mg over 24h (infusion or multiple injections (50mg 6hrly) until GI symptoms improve then start oral therapy

- If hypoglycaemic (blood glucose <4.0 mmol/L) -100ml 20% dextrose over 10-15 minutes stat and Intravenous infusion 10% dextrose at 100ml/hr if hypoglycaemia persists, Monitor blood glucose hourly
- Mineralocorticoid replacement can be initiated once the daily hydrocortisone dose has been reduced to <50 mg
- Treat Precipitating causes



Algorithm for withdrawal from chronic GC (Exogenous Cushing/GC induced

Step 1 Decrease glucocorticoid dose from supraphysiologic to physiologic

↓

Step 2 Switch to a.m. hydrocortisone or alternate day therapy

↓

Step 3 Measure morning cortisol level

<3µg/dl	3-20 µg/dl	>20 µg/dl
Patient adrenally insufficient. Continue glucocorticoid. Retest in 4-6 weeks	Need further testing • *Insulin tolerance test* • *CRH stim* • *Cortisol stim* • *Metarapone test*	Recover HPA axis Can withdraw glucocorticoid therapy

Physiologic dose of prednisolone 5-7.5mg/day

PRIMARY HYPERALDOSTERONISM

Primary hyperaldosteronism is due to unilateral or bilateral cortical adrenal hyperproduction of aldosterone. It may be caused by adenoma, hyperplasia or carcinoma of adrenal gland. Among them, aldosterone producing macro or micro adenoma called Conn's syndrome is most common one.

When to suspect Conn's syndrome

- Resistant hypertension
- Patients with BP ≥150 (systolic) and /or 100(diastolic) on ≥3 measurements
- Hypertension and hypokalemia
- Hypertension and adrenal incidentaloma
- Hypertension and sleep apnoea syndrome
- Hypertension and a family history of early onset hypertension or stroke (before 40 years of age)
- Hypertensive first degree relatives of patients with primary aldosteronism
- Hypertension with atrial fibrillation

How to diagnose Conn's syndrome

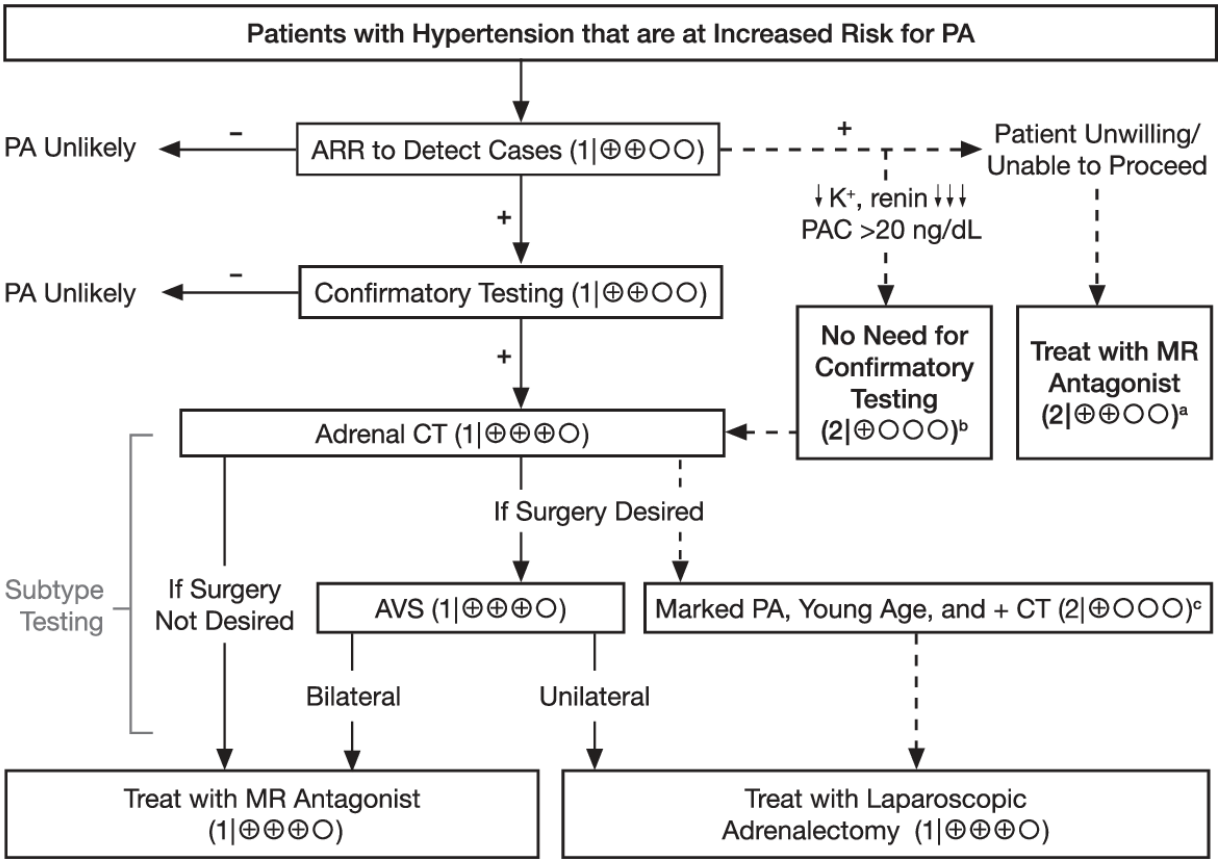
- For screening, Aldosterone Renin Ratio (ARR) need to be done. Before ARR, the following drugs that affect ARR need to be stopped for at least four weeks.

Drugs	Effect on ARR
• ACEI	• Decrease
• ARB	• Decrease
• MRB (aldosterone)	• Decrease
• Diuretics	• Decrease
• CCB	• Normal or increase
• NSAID	• Normal or increase
• Beta blockers	• Normal or increase
• Clonidine	• Normal or increase
• Methyldopa	• Normal or increase

- When ARR test is positive, confirmatory test should be done and refer to Endocrinologist for them.
- After confirming the diagnosis, imaging with contrast CT with adrenal protocol or MRI need to be done for localization.
- Adrenal venous sampling for lateralization can be done if tumour is bilateral or sugery is desired.

Treatment

- For unilateral disease and surgery is desired, unilateral adrenalectomy can be done.
- For bilateral disease or surgery is not indicated, mineralocorticoid receptor antagonists should be given to control the deleterious effect of aldosterone on cardiovascular system.


Patients with Hypertension that are at Increased Risk for PA
PA Unlikely
–
ARR to Detect Cases (1|⊕⊕○○)
+
Patient Unwilling/
Unable to Proceed
↓K+, renin ↓↓↓
PAC >20 ng/dL
+
PA Unlikely
–
Confirmatory Testing (1|⊕⊕○○)
+
No Need for
Confirmatory
Testing
(2|⊕○○○)b
Treat with MR
Antagonist
(2|⊕⊕○○)a
Adrenal CT (1|⊕⊕⊕○)
If Surgery Desired
Subtype
Testing
If Surgery
Not Desired
AVS (1|⊕⊕⊕○)
Marked PA, Young Age, and + CT (2|⊕○○○)c
Bilateral
Unilateral
Treat with MR Antagonist
(1|⊕⊕⊕○)
Treat with Laparoscopic
Adrenalectomy (1|⊕⊕⊕○)

PHEOCHROMOCYTOMA

- Pheochromocytoma is a tumour arising from adrenomedullary chromaffin cells that commonly produces one or more catecholamines such as epinephrine, norepinephrine and dopamine.

When to suspect Pheochromocytoma

If the patient has signs and symptoms of Pheochromocytoma and the following score can be used.

• Pallor	+1 point
• Hyperhidrosis	+1 point
• Palpitaitons	+1 point
• Tremor	+1 point
• Nausea	+1 point
• BMI <25	+1 point
• Heart rate of 85bpm or higher	+1 point
• BMI >30	-1 point

If score is 3 or more, the probability is 5.8 folds higher.

- Other signs and symptoms are postural hypotension, anxiety, panic attack, sense of doom, weakness, abdominal or chest pain, constipation, fasting hyperglycemia, paresthesia, flushing, dyspnoea and visual disturbances.
- In some patients, signs and symptoms appear and lead to crisis after taking following drugs.

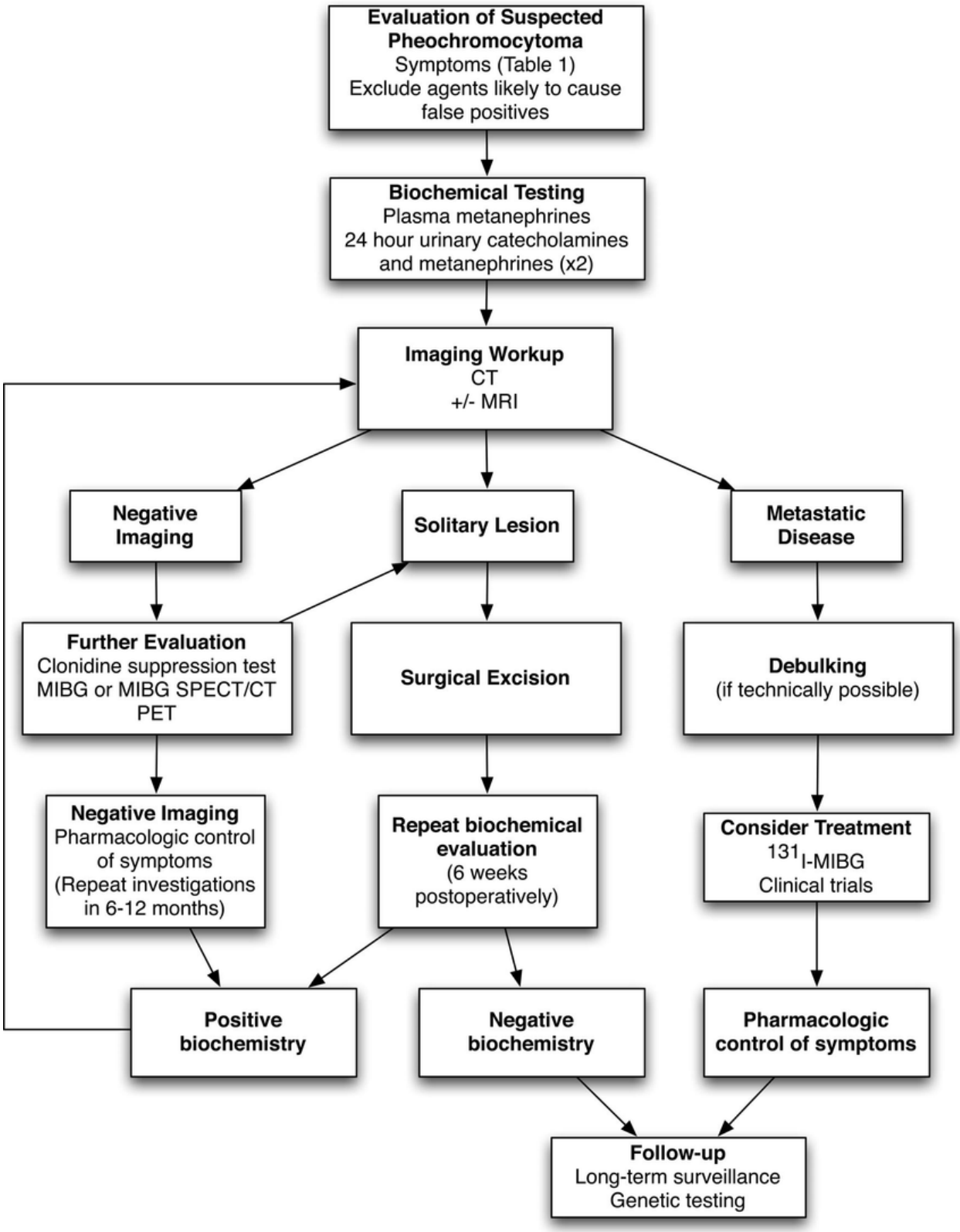
Dopamine receptor antagonists	Metoclopramide, chlorpromazine
Beta adrenergic receptor blockers	Propranolol, sotalol, timolol, labetolol
Sympathomimetics	Ephedrine, fenfluramine, phentermine
Opoid analgesics	Morphine, pethidine, tramadol
Norepinephrine reuptake inhibitors	Amitriptyline, imipramine
Serotonin reuptake inhibitors	Paroxetine, fluoxetine
Monoamine oxidase inhibitors	Phenelzine
Corticosteroids	Dexamethasone, prednisolone, hydrocortisone
Peptides	ACTH, glucagon
Neuromuscular blocking agents	Succinylcholine, tubocurarine, atracurium

How to diagnose Pheochromocytoma

1. 1.Gold standard is measurement of plasma free metanephrines by using liquid chromatography with tandem mass spectrometry method. Supine position for at least 20 minutes is required before taking blood. More than 2 folds increase above reference interval upper cut off is high suspicion. Major medications that may cause falsely elevated tests are acetaminophen, methyldopa, tricyclic antidepressant, phenoxybenzamine, sulphasalazine, cocaine and levodopa. Physiological stress associated with extreme illness may have effect on the test. So, confirmation with clonidine suppression test need to be done for above conditions.
2. Imaging studies with contrast CT with adrenal protocol or MRI can be done for localization.
3. Genetic testing with shared decision making.

Treatment

1. Surgery is treatment of choice.
2. Before surgery, alpha-adrenoreceptor blockade should be given for 2 to 14 days to prevent cardiovascular emergency and crisis. Blood pressure target before surgery is <130/80 mmHg and heart rate target before surgery is 60 to 70 bpm in a seated position and 70 to 80 bpm for upright position. Phenoxybenzamine is best and doxazosin can be used. Beta blockers should not be used before alpha blockade.



PHEOCHROMOCYTOMA CRISIS

When to suspect crisis

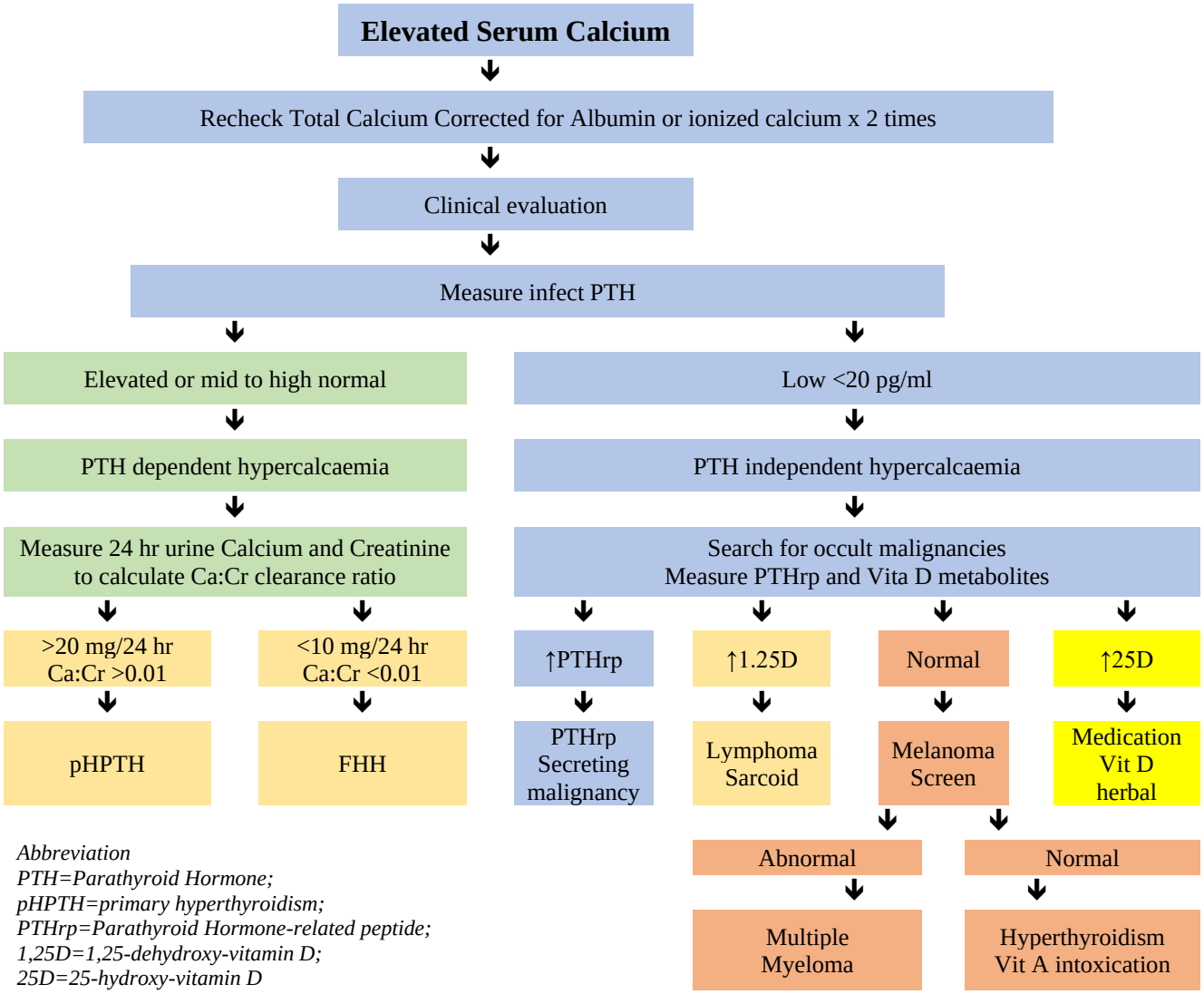
- Unexplained shock or left ventricular failure
- Multiorgan failure
- Hypertensive crisis
- Unexplained lactic acidosis especially if also febrile.
- When crisis is suspected, refer to endocrinologist.

CALCIUM DISORDER

	Hypercalcemia	Hypocalcemia
Definition	Corrected calcium >10.5 mg/dl (2.63mmol/L)	Corrected calcium<8.8 mg/dl (2.2mmol/L)
Causes	Common • Hyperparathyroidism: • Primary • Tertiary • Malignancy • Humoral hypercalcaemia • Multiple myeloma • Bony metastases Uncommon • Familial hypocalciuric hypercalcemia • Sarcoidosis and other granulomatous diseases • Thiazide diuretics • Lithium • Immobilization • Vitamin D intoxication • Hyperthyroidism • Renal failure • Addison's disease • Vitamin A intoxication	Hypoparathyroidism Destruction of parathyroid glands: • Surgical. • Autoimmune. • Radiation. • Infiltration. Failure of parathyroid development: • Isolated, e.g. X-linked. • With other abnormalities, e.g. di George syndrome (with thymic aplasia, immunodeficiency, and cardiac anomalies). Failure of PTH secretion: • Magnesium deficiency. • Overactivity of Ca-sensing r/c Failure of PTH action: • Pseudohypoparathyroidism—due to G protein abnormality. Failure of release of calcium from bone Osteomalacia: • Vitamin D deficiency. • Vitamin D resistance. • Renal failure. Inhibition of bone resorption: • Drugs linked to hypocalcaemia, e.g. cisplatin, calcitonin, PO PO4, • IV bisphosphonates, denosumab. • ↑ uptake of Ca into bone: • Osteoblastic metastases (e.g. prostate). • Hungry bone syndrome. • Imatinib mesylate Complexing of calcium from the circulation • ↑albumin-binding in alkalosis. • Acute pancreatitis:

		• Formation of Ca soaps from autodigestion of fat. • Abnormal PTH and vitamin D metabolism. • PO4 infusion. • Multiple blood transfusions—complexing by citrate.
Clinical features	**Renal** • Polyuria • Polydipsia • Stones GI • Anorexia • Vomiting • Constipation • Abdominal pain CNS • Confusion • Lethargy • Depression Other • Pruritus • Sore eyes	Acute • Neuromuscular irritability (Tetany) • Paresthesias (peri-oral, extremities) • Muscle twitching • Carpopedal spasm • Trousseau's sign • Chvostek's sign • Seizures • Laryngospasm • Bronchospasm Cardiac Prolong QT interval Hypotension Heart failure Arrhythmia Papilledema Chronic • Ectopic calcification (basal ganglia) • Extrapyramidal signs • Parkinsonism • Dementia • Subcapsular cataracts • Abnormal dentation • Dry skin
Evaluation	• Careful history and physical examination • Repeat serum calcium • Calculate corrected calcium level if needed or check ionized calcium • Stop causative medication if possible and recheck again	• repeat the measurement to confirm that there is a true decrease in the serum calcium concentration • corrected calcium • serum calcium to add by 0.8 mg/dL (0.2 mmol/L) for every 1 g/dL (10 g/L) fall in the serum albumin concentration
Investigations	• intact parathyroid hormone • magnesium • U & E, creatinine • phosphate • vitamin D • alkaline phosphatase.	• intact parathyroid hormone • magnesium • U & E, creatinine • phosphate • vitamin D • alkaline phosphatase.
Management	Management in hospital Moderate hypercalcemia (<3.5 mmol/L, <14 mg/dl)	Management in hospital • (Corrected calcium ≤7.5mg/dl, 1.9mmol/L and symptomatic)

	• Rehydration • Normal saline 4-6 L/day Recheck serum calcium after 24 hours • If >3 mmol/L (12 mg/dl) → treat as severe hypercalcemia Severe Hypercalcemia ≥ 3.5 mmol/L (≥14mg/dl) • IV Bisphosphonate If Malignancy • IVI Zoledronic acid 4 mg in NS 100cc over 15 minutes If not Malignancy • IVI Pamidronate (in 100 ml-500 ml NS over 2 hours) • 60-90 mg if adjusted Ca >3 mmol/L • 30-60 mg if adjusted Ca <3 mmol/L Recheck serum calcium after 48 hours Calcium >4 mmol/L (≥16 mg/dl) • SC inj Calcitonin 100 units 3 times per day for 24-48 hours If no response in 5 days after adequate hydration and Pamidronate • consider giving Zoledronic Acid 4 mg in 50 ml saline over 15 minutes. *Refer to Endocrinologist	• Initially, 10–20mL of 10% calcium gluconate diluted in 50–100mL of • 5% glucose and infused over about 10min. Repeat if symptoms not resolved. Cardiac monitoring is advisable. In order to maintain the plasma Ca, a Ca infusion is required; • 100mL of 10% calcium gluconate (ten vials) should be added to 1L of saline • or glucose solution and infused at 50–100mL/h. The plasma Ca should be checked regularly (not less than 6-hourly), and the infusion rate adjusted in response to the change in concentration. **Oral calcium** supplementation • 1 to 2 g of elemental calcium given as calcium carbonate or calcium citrate daily, in divided doses. As an example, calcium carbonate is 40 percent elemental calcium, so that 1250 mg of calcium carbonate contains 500 mg of elemental calcium. oral magnesium, • typically, 300 to 400 mg daily divided into three doses For patients with acute hypoparathyroidism, • calcitriol (in a dose of 0.25 to 0.5 mcg twice daily) and oral calcium (1 to 4 g of elemental calcium carbonate daily in divided doses) should be initiated as soon as possible. *Refer to Endocrinologist



Abbreviation
PTH=Parathyroid Hormone;
pHPTH=primary hyperthyroidism;
PTHrp=Parathyroid Hormone-related peptide;
1,25D=1,25-dehydroxy-vitamin D;
25D=25-hydroxy-vitamin D

Management of Primary Hyper-Parathyroidism