GUIDELINES

For

GENERAL PRACTITIONERS

2024

Press record

First Edition

Printed by SARANA PRESS (Dr. Aung Kyaw Min)

249, Theinbyu Road, Mingalartaungnyunt Township, Yangon, Myanmar

2018

Cover Designer (Tun Zaw)

Inner Designer (Tun Zaw)

Second Edition

Digital Copy Printing (TMO)

249, Theinbyu Road, Mingalartaungnyunt Township, Yangon, Myanmar.

2024 April

Cover Designer (Tun Zaw & Win Zaw)

Inner Designer (TMO)

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recommendations for clinicians who are uncertain about how to proceed, overturn the beliefs of doctors accustomed to outdated practices, improve the consistency of care, and provide authoritative recommendations that reassure practitioners about the appropriateness of their treatment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**

LIST OF CONTRIBUTORS

1. *Aung Cho Myint, Prof*
2. *Aung Maw, Dr*
3. *Aye Aung, Prof*
4. *Aye Aye Than, Dr*
5. *Aye Aye Thein, Dr*
6. *Chit Soe, Prof*
7. *Hla Myat Nwe, Prof*
8. *Hla Myint Tun, Dr*
9. *Hlaing Mya Win, Prof*
10. *Hlaing Myint, Dr*
11. *Htay Win, Dr*
12. *Htin Aung Saw, Prof*
13. *Htun Lwin Nyein, Prof*
14. *Khin Hla Hla, Prof*
15. *Khin Hta Yi, Prof*
16. *Khin Mi Mi, Dr*
17. *Khin Ohnmar Khine, Prof*
18. *Khin Saw Than, Prof*
19. *Khine Khine Zaw, Prof*
20. *Khine Soe Win, Dr*
21. *Ko Ko, Prof*
22. *Kyaw Myint Naing, Prof*
23. *Kyaw Thu, Dr*
24. *Kyaw Zin Wai, Prof*
25. *Kyi Kyi Nyunt, Prof*
26. *Kyi Kyi Thinn, Prof*
27. *Kyin Htwe, Dr*
28. *Lin Htet, Dr*
29. *Lwin May Oo, Dr*
30. *Mar Mar Kyi, Prof*
31. *Maung Maung Sein, Prof*
32. *May Thandar Oo, Dr*
33. *Min Han, Prof*
34. *Min Yazar, Dr*
35. *Min Zaw Oo, Prof*
36. *Moe Naing, Dr*
37. *Moe Wint Aung, Prof*
38. *Mya Thae Han, Dr*
39. *Mya Win Hnit, Dr*
40. *Myint Thaung, Prof*
41. *Myo Khine, Dr*
42. *Myo Lwin Nyein, Prof*
43. *Myo Nyunt Aung, Dr*
44. *Myo Oo, Prof*
45. *Naing Oo, Prof*
46. *Nang Phyu Phyu Aung, Prof*
47. *Nwe Mar Tun, Prof*
48. *Nwe Nwe Aung, Dr*
49. *Nyein Moe Thaw, Dr*
50. *Phyu Phyu Khaing, Dr*
51. *Rai Mra, Prof*
52. *Samuel Kyaw Hla, Prof*
53. *Saw Win, Prof*
54. *Sein Way Lwin, Dr*
55. *Than Htike, Dr*
56. *Than Than Aung, A Prof*
57. *Than Than Aye, Prof*
58. *Thar Thar Oo, Dr*
59. *Thein Aung, Prof*
60. *Thein Myint, Prof*
61. *Thet Naing Maung, Dr*
62. *Thin Thin Nwe, Dr*
63. *Tin Aye, Dr*
64. *Tin Nyunt, Dr*
65. *Tin Tin Aye, Dr*
66. *Tin Tin Hla, Dr*
67. *Tint Tint Kyi, Prof*
68. *Vijay Kumar, Dr*
69. *Win Lwin Thein, Dr*
70. *Win Zaw, Dr*
71. *Yin Yin Soe, Prof*
72. *Yin Yin Zaw, Prof*
73. *Yu Yu Lwin, Dr*
74. *Zaw Lynn Aung, Prof*

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

HEMATOLOGY

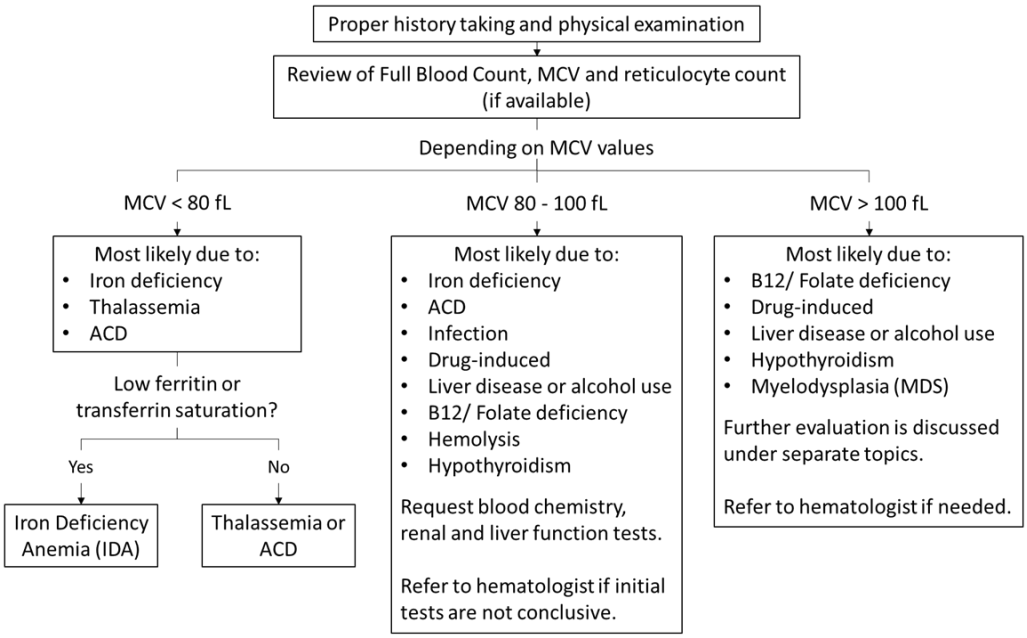
ANAEMIA

- Anaemia is defined by the World Health Organization (WHO) as a condition in which the number of red blood cells and their oxygen carrying capacity is insufficient to meet the body's physiologic needs. Hemoglobin (Hb) levels to diagnose anaemia varies according to age, sex, location (especially altitude) and smoking status. Generally, at sea level, anaemia can be diagnosed in men (15 years of age and above) if Hb is ≤ 12.9 g/dL; in non-pregnant women (≥ 15 years) if Hb is ≤ 11.9 g/dL; and in pregnant women if Hb is ≤ 10.9 g/dL.[1]
- Both Hb concentration and hematocrit (HCT), also known as packed cell volume (PCV), are commonly used to diagnose anaemia. The red blood cell (RBC) indices – such as mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC) and red cell distribution width (RDW) – are useful in detecting the underlying cause of anaemia. In Myanmar, Hb concentration is usually expressed in g/dL unit (it can be multiplied by 0.62 to convert to mmol/L).[2] HCT or PCV is usually reported in percentage.

Approach to Anaemia

- First of all, it is important to note that there are several conditions in which the ranges of Hb values provided by the laboratories may not apply. The causes of lower Hb values include pregnancy, old age and intense physical exercise whereas smoking, hemoconcentration and high altitude are the causes of higher Hb values. [2]
- The proper approach to diagnose anaemia divide patients into different categories and then the probability of particular diagnoses in each category are considered. The following figure is the simplified algorithm for evaluation of anaemia in ambulatory patients. [2]

Figure 1. Evaluation of anaemia in ambulatory patients



(ACD: anaemia of chronic disease; MCV: mean corpuscular volume)

ANAEMIA IN CHILDREN

- According to the World Bank data, the prevalence of anaemia among Myanmar children of 6 months to 5 years old was around **50%** in 2019.[3] The cut-off values of hemoglobin to define anaemia in children vary with age.
- The threshold to diagnose anaemia in children is HCT or Hb value at or below the 2.5th percentile for age and sex based upon normative data from healthy individuals, but that kind of data is still limited locally. Iron deficiency should be screened in children of **6 months to 6 years** old with Hb **<11 g/dL**, in **6 to 12 years** old children with Hb **<11.2 g/dL** and in children of **12 to <18 years** old with Hb **<11.4 g/dL (for girls)** or with Hb **<12.4 g/dL (for boys)**.[4]
- The first step of approach to anaemia in children is to detect whether the child has isolated anaemia or the other cell lines (white blood cells and platelets) are also affected. Then, the second step is to classify the anaemia according to MCV. Iron deficiency and thalassemia are the most common causes of microcytic anaemia in children. To differentiate IDA from thalassemia, the RDW index can be used: RDW is high in IDA and normal in thalassemia.[4]
- In children with normocytic anaemia, the following diagnoses should be considered first: hemolytic anaemia, blood loss, infection, medication, and anaemia of chronic disease. To differentiate between possible diagnoses, the reticulocyte count (RC) is helpful: high RC in blood loss (except acute blood loss: low RC) or hemolysis and low or normal RC in bone marrow suppression (e.g., due to infection, infiltrations or medications).[4]
- For the children with macrocytic anaemia, the common causes include the exposure to some drugs (e.g., antiseizure medications and immunosuppressives), vitamin B12 or folate deficiency, liver disease, hypothyroidism and aplastic anaemia. Children with Down syndrome can also present with isolated macrocytosis.[4]
- After narrowing down the possible underlying etiology/ pathology, further evaluation and confirmatory tests can be done accordingly:
    - Review medications and/ or diet history
    - Serum ferratin, iron, TIBC
    - Serum vitamin B12, folate levels
    - Infection screening tests
    - Serum indirect bilirubin, LDH and haptoglobin
    - Bone marrow aspirate/ biopsy (refer to hematology first).[4]

IRON DEFICIENCY ANAEMIA

- Iron deficiency anaemia (IDA) is the most common form of anaemia, accounting for nearly 50% of anaemia cases globally.[5] Iron deficiency is also the most common nutritional disorder worldwide. In Myanmar, it was recently estimated that about two in five pregnant women and one in three women of reproductive age (15- 49 years of age) could be iron deficient.[6, 7]

Management

- In a patient with anaemia, serum ferratin value lower than 45 ng/mL (or 45 mcg/L) can be used to diagnose iron deficiency, with the sensitivity of 85% and specificity of 92%. However, serum ferratin test is less accurate in patients with chronic kidney disease or any other inflammatory disorders. In such cases, additional tests – serum iron, transferrin saturation (TSAT) and C-reactive protein (CRP) – can be used to confirm the diagnosis of IDA.[8] According to a 2022 review, serum ferratin level cut-off for IDA is <100 mcg/L if there is inflammation and TSAT cut-off for IDA is <20%.[9]
- Investigations are based on the history and physical examination, including the rectal examination. If gastrointestinal (GI) bleeding is suspected, the esophagogastroduodenoscopy (OGDS) and

colonoscopy, small bowel biopsy, small bowel enema and the fecal occult blood test should be done.

- Typical findings of hematological investigations are as follows:
    - Microcytic, hypochromic red cells
    - Anisocytosis (variation in size), poikilocytosis (shape)- pencil-shaped rods
    - Low serum iron level
    - Raised iron-binding capacity and reduced transferrin saturations (TSAT)
    - Serum ferritin level low (the most useful index)
- As transferrin is a negative acute phase protein, it can be normal or reduced in patients with inflammatory disorders. Thus, it is better to check both serum ferratin level and TSAT in any case of inflammation.

Treatment

- Patients with IDA should be treated with the aim to refill iron stores and maintain hemoglobin to a normal level (for respective age and sex).[9]
- Evaluation and treatment of underlying causes of IDA is essential to achieve the above aim. For example, *Helicobacter pylori* infection is commonly associated with IDA and thus, *H. pylori* eradication therapy can improve the benefit of iron supplementation among infected patients. Besides, other nutritional deficiencies, covert blood loss and malabsorption syndromes should be excluded (if required resources are available) or treated accordingly if present.
- Iron supplementation: Oral iron, e.g., ferrous sulphate, can be given to most patients with IDA. The preferred dosing regimen is a single daily dose of 40- 60 mg or alternate-day dose of 80- 100 mg to optimize the absorption of elemental iron and lessen the side effects.[9]
- Hb should be increased by lg/dL per week. The response to treatment should be confirmed 2 to 3 weeks after starting. Treatment should be continued for 3 months after correction of the iron deficiency to allow replenishment of the iron stores.
- If a patient is not responding to one type of oral iron supplements, change to another formulation, or intravenous iron should be used as an alternative.[9]
- Sideroblastic anaemia should be considered if the patient has high serum ferritin with hypochromic microcytic anaemia and is not responding to iron.

Failure to respond

- In case of failure to respond to iron supplementation, the following causes should be considered: *H. pylori* infection (test/ treat), continuing bleeding, or non-compliance with iron supplements. Besides, the diagnosis should be reviewed: the patient may have anaemia mixed with other cell line disorders, or may have underlying chronic infection, vasculitis, rheumatoid arthritis (RA), malignancy or renal failure.

When to refer

- If the patient presents with dyspepsia and iron deficiency anaemia, refer him/her to gastroenterologist for gastroscopy.
- If Hb <11 g/dL in a man or <10 g/dL in a non-menstruating woman, refer him/ her for suspected lower GI cancer.
- Refer to hematologist for coordinated care if the patient fails to respond to iron supplementation and the initial tests for underlying causes are not conclusive.

Follow-up

- Once normal, monitor Hb, MCH, and MCV every 3months for 1 year, and then annually. Give further iron supplements if Hb, MCH, or MCV fall below normal levels. Investigate further if iron supplementation is unable to maintain Hb.

NON-ANEMIC IRON DEFICIENCY

- Iron deficiency without anaemia (low serum ferratin) is 3 times as common as iron deficiency anaemia but it is usually not recognized and treated. According to recent studies, iron deficiency (ID) is associated with colorectal cancers. Thus, in addition to giving iron supplements to replenish iron stores, iron deficient patients should be investigated for GI cancers, regardless of hemoglobin level.[10]

VITAMIN B12 DEFICIENCY

- Vitamin B12 is an essential cofactor for enzymes in DNA synthesis. It is found in animal liver & kidney, fish, chicken, meats, dairy products and eggs. Intrinsic factor is required for B12 absorption in the terminal ileum.
- Vitamin B12 is necessary for effective erythropoiesis, and it becomes deficient only when the hepatic stores are depleted. Vitamin B12 deficiency is usually defined as the value of serum B12 concentration <148 pmol/L (200 pg/mL). Sometimes, serum B12 levels may correlate poorly with deficiency, especially in pregnancy.[11]
- Prevalence of B12 deficiency is relatively low: ranging from <1% in children to about 6% in the elderly (>60 years of age), and the national data for B12 deficiency prevalence in Myanmar is still unknown.[12]
- The three main causes of B12 deficiency include autoimmune cause (pernicious anaemia), malabsorption (e.g., tapeworm infestation, bypass surgery or coeliac disease) and dietary insufficiency.[11]

PERNICIOUS ANAEMIA

- Pernicious anaemia (PA) is a rare autoimmune condition associated with gastric atrophy and anti-intrinsic factor antibodies or gastric parietal cell antibodies.
- Patients with PA have autoimmune gastritis due to antibodies to both parietal cells and intrinsic factor, which causes B12 deficiency and consequently, macrocytic megaloblastic anaemia.
- Although the prevalence of PA is very low (0.1%) in the community, it should be considered as a differential diagnosis if macrocytic anaemia is incidentally detected in the complete blood count (CBC) analysis.[13]

Management

- Generally, it is recommended to treat all people with confirmed vitamin B12 deficiency. In treating B12 deficiency, it is first to check whether the patient has the following conditions: symptomatic or severe anaemia (<8 g/dL), neurologic symptoms, possible malabsorption or concern about adherence or follow-up.[14]
- For patients with severe clinical features (mentioned above), treat with 1000 mcg hydroxocobalamin IM once daily or 1- 3 times weekly, then 1000 mcg per week for 4 weeks. If the neurological symptoms are improving but still present, the duration of initial treatment can be extended up to 3 months.
- To monitor for improvement in anaemia or resolution of neurological symptoms, close follow-up should be planned, and CBC (with reticulocyte count) should be repeated at 2 or 3 weeks. After initial treatment, maintenance therapy should be continued: either IM 1000 mcg hydroxocobalamin every 2 months, or oral/ sublingual methyl-cobalamin 1000 mcg daily. Then, CBC can be rechecked every 6 months for the first year, then yearly.[14]
- For patients without severe features, treat with 1000 mcg of hydroxocobalamin IM weekly for 4 weeks followed by 1000 mcg every 2 months; or treat with oral or sublingual methyl-cobalamin 1000 to 2000 mcg daily.[14]

- If the expected response to treatment is not achieved, the patient should be re-evaluated for other causes of anaemia and neurologic symptoms or the need to increase the dosing.
- If the cause of B12 deficiency is irreversible, the maintenance dose may be continued indefinitely.[14]
- Refer the patient if malabsorption or PA is suspected.[14]

FOLATE DEFICIENCY

- Folate is required for protein metabolism and synthesis of DNA and RNA. It is found in the highest concentrations in liver and yeast but is also in spinach, other green vegetables, nuts and fruits. The daily requirement for folate varies with age and pregnancy is the time when daily folate requirement is the highest (about 600 mcg per day).[14]
- The cut-off value for folate deficiency is defined as the serum folate less than 4.5 nmol/L (2 ng/mL).
- Both folate and B12 deficiencies may coexist in some cases and so serum B12 level should be checked together.
- The causes of folate deficiency include inadequate dietary intake, malabsorption, excess use (pregnancy & lactation, prematurity, malignancy and hemolysis) and drugs induced (anticonvulsant, trimethoprim).[14, 15]

Management

- Initial screening test is the CBC with blood film report. If macrocytic anaemia is found, serum B12 and folate levels should be detected.
- If the levels of serum B12 and folate are in the borderline range, methylmalonic acid (MMA) and homocysteine levels can be checked (if local resources are available).
- In folate deficiency, both serum B12 and MMA levels are normal and only homocysteine level is raised, while B12 deficiency shows elevated MMA and homocysteine levels.[15]
- All patients with folate deficiency should be evaluated for possible underlying causes and treated accordingly.
- Usual treatment for folate deficiency is oral folic acid 1- 5 mg daily for 1- 4 months if the cause of deficiency is reversible.
- For those with chronic or irreversible cause of folate deficiency, folic acid supplementation should be continued for long-term.
- For individuals with macrocytic anaemia, vitamin B12 should be given together with folic acid before the laboratory results are available.
- Besides, vitamin B12 should also be administered to those who develop neurologic symptoms after taking folic acid.[14]
- In addition to supplementation, it is important to encourage all patients with folate deficiency to eat more fruits and vegetables.[15]
- If the folate deficiency is due to malabsorption, further evaluation should be done to confirm the cause of malabsorption and in even such case, folic acid 5 mg daily dose is sufficient. For prevention of folate deficiency, the individuals, who have severe malnutrition, chronic haemolytic anaemia, renal dialysis or other diseases with high cellular turnover, can take oral folic acid 1 to 5 mg daily.[14]

Folate supplements in pregnancy

- As the folate requirement is the highest during pregnancy, it is recommended to provide folic acid tablet 0.4 mg once a day to all women of childbearing age, starting at least one month before planning conception and continuing throughout pregnancy to prevent neural tube defect as well as to fulfill the growth and developmental needs of the fetus.
- High dose prophylaxis (folic acid 1- 4 mg daily) should be prescribed if there is any personal or family history of neural tube defect in either parent or first degree relative of either parent (*high risk*), or if the mother has coeliac disease, diabetes, obesity (BMI >30), or is taking anticonvulsants (*moderate risk*).[16]

ANAEMIA OF CHRONIC DISEASE

- Anaemia of chronic disease (ACD), also known as anaemia of chronic inflammation, is the most common cause of anaemia in hospitalized patients.[17]
- Due to the increasing prevalence of chronic communicable and non-communicable diseases, the number of people with ACD is rising in the community.
- ACD is usually a type of normocytic anaemia, but it can become hypochromic microcytic anaemia over a period of time.[18]

Management

- The main aims of management are to detect and treat underlying disorders, such as chronic infections, chronic kidney disease, and hematologic or other malignancies, and to improve hemoglobin concentration of blood.[18]
- The following laboratory tests should be done in patients with ACD:
    - Complete blood count, reticulocyte count and peripheral blood film report
    - Iron studies: serum iron (low), TIBC (low) and ferritin (normal or high);
    - Liver function tests: serum bilirubin, ALT, AST and alkaline phosphatase;
    - Renal function tests (serum creatinine & eGFR), together with blood glucose test;
    - Serum lactate dehydrogenase (LDH) test and if needed, serum electrophoresis.
- After proper history taking and physical examination of patients with ACD, together with the results of initial tests, any recently diagnosed chronic diseases or inflammatory conditions should be treated accordingly. Since ageing is a pro-inflammatory process, some of the elderly patients may have unexplained anaemia, even after detailed investigations. It is also important to provide cancer screening tests, appropriate to the patient's age (if resources are available).[18, 19]
- Erythropoiesis-stimulating agents (ESAs) are not commonly used now and generally reserved for patients with chronic kidney disease (CKD), inflammatory bowel disease or rheumatologic disorders who are not responding to iron supplementation. This is because some studies have reported that ESAs could increase the mortality due to increased risk of thromboembolism.[19]
- Although iron supplementation is not usually prescribed in ACD, it can be given to those with absolute iron deficiency.
- Oral or parenteral iron can also be used together with erythropoietin to reach the target hemoglobin concentration (10- 12 g/dL) in some patients with functional iron deficiency.[18, 19]
- Transfusion of packed red cells should be given only for those with severely symptomatic or life-threatening anaemia.
- For symptomatic patients, the hemoglobin threshold for transfusion is 10 g/dL for ill patients with acute myocardial ischemia or hemodynamic instability, and 7- 8 g/dL for hemodynamically stable patients in hospitals.[19]

When to refer

- Patients with ACD should be referred for admission to a hospital if they are severely symptomatic, when there is acute drop in Hb/ HCT, if transfusion is needed or if detailed or invasive investigations are required.[18]

HAEMOLYTIC ANAEMIA

- Hemolytic anaemia is a type of normocytic anaemia due to premature RBC and hemoglobin breakdown. Hemolytic anaemia can be classified based on severity (mild to life-threatening), chronicity (acute to chronic), or etiology (hereditary or acquired).[20]
- The causes of hemolytic anaemia include:
    - Hereditary/ Genetic (intrinsic) RBC defects:
    - Hemoglobinopathies (e.g., Sickle cell disease and Thalassemia)
    - Abnormalities of RBC membrane (e.g., Hereditary spherocytosis and elliptocytosis)
    - RBC enzyme disorders (e.g., glucose-6-phosphate dehydrogenase (G6PD) deficiency)
    - Immune-mediated (extrinsic) causes:
    - Warm autoimmune hemolytic anaemia (AIHA)
    - Cold agglutinin disease
    - Drug-induced (or toxin-induced) hemolytic anaemia
    - Systemic diseases (infections including COVID-19, liver disease, renal disease)
- Less common causes:
    - Microangiopathic hemolytic anaemia (e.g., thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome)
    - Hemolytic transfusion reactions
    - Paroxysmal nocturnal hemoglobinuria (PNH)[20]

Approach to Hemolytic Anaemia

- General principles for evaluation of anaemia should be followed when approaching to patients with hemolytic anaemia.
- The clinical features of hemolysis (such as jaundice, dark urine, splenomegaly, increased reticulocyte count, different sizes and shapes of RBC on peripheral smear, elevated indirect bilirubin and increased serum LDH) are usually seen in many patients with hemolytic anaemia.[20]
- All children with unexplained hemolytic anaemia should be referred immediately to pediatric hematologist because of the increased risk of developing acute life-threatening hemolysis.[21]
- For adult patients with hemolytic anaemia, it is first to exclude the conditions for immediate medical attention: hemodynamic instability (rapid thready pulse with signs of pending shock), active bleeding, acute thrombosis, acute kidney injury, Hb level <7 g/dL, and schistocytes on blood film. If any of the above conditions are detected, the primary care physician can provide pre-hospital emergency care to stabilize the patient and refer him/ her to hospital immediately.[20]
- If there is no urgent conditions, the next step is to check whether the patient received a transfusion within the last four weeks. If ‘yes’, the patient should be evaluated for acute and delayed transfusion reactions. Refer the patient to a hematologist (or an internal medicine specialist).[20]
- If there is no transfusion history, the other causes of hemolysis should be evaluated based on history, examination, blood film report and direct antiglobulin (Coombs) test (if available).[20, 21]
- Management of hemolytic anaemia will vary according to the underlying cause and every patient should have consultation with a hematologist.

HAEMOGLOBINOPATHY

THALASSAEMIA

- Thalassaemia (or thalassemia) is a group of inherited (autosomal recessive) hemoglobinopathies with impaired production of normal alpha- or beta-globin chains, leading to ineffective erythropoiesis, hemolysis, and anaemia.[22]
- Prevalence of alpha thalassemia is higher in Asian countries than that of beta thalassemia. Hemoglobin E (HbE) is also prevalent in South-East Asia.[23]
- In Myanmar, alpha thalassemia is the most common hemoglobinopathy (10% - 56.9%) followed by HbE (1% - 28.3%) and beta thalassemia (0.5% - 4%).[24]

Approach to Thalassemia Patients

- Evaluation of a suspected case of thalassemia usually starts with CBC and peripheral blood film. In all patients with low Hb and reduced MCV (microcytic anaemia), iron deficiency should be excluded first with iron studies (mainly serum ferratin level), before confirming the diagnosis of thalassemia. The findings of peripheral blood film seen in thalassemia patients are as follows:
    - Hypochromic and microcytic cells
    - Aniso-poikilocytosis
    - Increased percentage of reticulocytes
    - Target cells, and
    - Heinz bodies.[23]
- Patients with the above findings, especially all pregnant mothers with microcytic anaemia, should be tested with hemoglobin electrophoresis (if resources are available).
- However, hemoglobin electrophoresis should not be repeated in patients who have a prior result and who do not require therapeutic intervention or monitoring of hemoglobin variant levels.[22]

Management

- Management depends on the type and severity of thalassemia. The overview of management includes treatment of anaemia, reduction of ineffective erythropoiesis, prevention of excess iron stores and treatment of complications due to iron overload.[22, 23]
- Patients with alpha-thalassemia trait (normal HbA_2) and those with beta-thalassemia trait (increased HbA_2) are usually asymptomatic and do not require any treatment (as long as they have hemoglobin level >7 g/dL). [22, 23]
- Patients with alpha-thalassemia intermedia (deletional HbH disease) can require treatment for mild to moderate anaemia, ineffective erythropoiesis and skeletal abnormalities.
- In patients with more severe phenotype (non-deletional HbH disease), transfusion therapy is usually required.[22] They should be referred urgently to hematologists (or to internist or pediatrician if there is no hematologist in some rural areas).
- Alpha-thalassemia major (with Hb Bart's disease) is usually fatal (hydrops fetalis).[22] The babies with this phenotype are almost impossible to survive in the local setting of Myanmar.
- Patients with beta-thalassemia intermedia may sometimes need transfusions and should be referred to a specialist, too.[22]
- Patients with beta-thalassemia major, similar to those with other types of transfusion-dependent thalassemia (TDT) (e.g., severe HbE/beta thalassemia and non-deletional HbH disease), require regular transfusions, usually every two to five weeks. All patients with TDT should be referred to a hematologist.[22]

Role of primary care physicians

- Being the primary care physicians in the community, family physicians (FP) and general practitioners (GP) can be part of the multi-disciplinary management team for thalassemia patients, especially those from sub-urban or rural areas, who cannot frequently visit the hematology clinics.
- FP/ GP can help thalassemia patients in the following ways:
    - Monitoring for any side-effects from iron chelation therapy,
    - Addressing any physical and psychosocial problems related to the patients and their families which can affect the treatment outcomes,
    - Monitoring for any complications of thalassemia and transfusion-related complications,
    - Coordinating with specialists and providing treatments for cardiac complications, endocrine disorders, leg ulcers (if any), osteoporosis, transfusion-related infections, prophylactic anticoagulation (in high-risk patients for thrombosis), and
    - Providing reproductive health care and family planning for those in child-conceiving age.[22]

GLUCOSE-6-PHOSPHATE DEHYDROGENASE (G6PD) DEFICIENCY

- Glucose-6-phosphate dehydrogenase (G6PD) is an intracellular enzyme found in every cell and it plays a significant role in prevention of cell damage from oxidation processes due to reactive oxygen species.
- G6PD deficiency is an X-linked recessive disorder, in which boys are mostly affected and girls are usually the carriers. It is the most common enzyme disorder of RBC detected in nearly 500 million people globally.[26, 27]
- Most forms of G6PD are mild and G6PD deficient people do not usually have any symptoms. Symptoms develop when they are either exposed to certain foods or drugs (*See the prevention section below*), when they are severely ill, or when exposed to noxious substances. Symptoms may develop when rapid breakdown of RBCs occurs and usually disappear when the offending food or drug is stopped.
- Typical presenting symptoms include acute onset of pallor, jaundice and dark-colored urine with sudden fall in Hb levels by 3- 4 g/dL, after a few hours or days of exposure to the triggering factors.[27]

Diagnosis

- When patients present themselves with acute jaundice and pallor, G6PD deficiency should be considered as a possible differential diagnosis, since prevalence of G6PD deficiency can be as high as 30% in some ethnic groups of Myanmar.
- In children, most cases are not detected until the child develops a health problem.[28]

Investigation for G6PD deficiency

- It should be done in the following cases:
    - Neonatal jaundice;
    - Unexplained hemolytic anaemia after exclusion of other possible causes;
    - Asymptomatic patients from high-risk populations before prescribing certain drugs, and
    - Asymptomatic family members of G6PD deficient patients (if needed).[27]
- Screening for G6PD deficiency can be done with qualitative G6PD assay. If the screening test is positive, it should be confirmed by quantitative G6PD assay at the reference laboratories.
- Timing for the G6PD enzyme assays is also important.
- The test may be false-positive in patients during the time of acute hemolysis because the RBCs with reduced G6PD enzyme activity have hemolyzed and are not be measured in the G6PD assay. Thus, if the screening test is negative and G6PD deficiency is still suspected, then the G6PD assay should be repeated about 3 months after the resolution of hemolysis.[27]

Treatment

- For the majority of cases, treatment is as simple as avoiding the triggering factors. Severely ill children may need hospitalization, oxygen support and intravenous fluids.
- In neonatal jaundice, treatment for those with G6PD deficiency is similar to treating those without deficiency.
- Mild cases do not usually require treatment; intermediate cases are treated by phototherapy and severe cases may need therapeutic plasma exchange.[27]
- Most of the neonatal jaundice cases are now diagnosed and treated in hospitals and hence, it is less likely to see such cases in primary care clinics.
- Treatment for acute hemolysis include the removal of any possible causes as soon as possible, adequate hydration, and transfusion for severe anaemia.
- Mild cases of hemolysis due to G6PD deficiency are usually self-limiting and may recover soon after discontinuation of the trigger for hemolysis.

- For moderate cases, supportive treatment to maintain adequate hydration and to improve symptoms should be given and transfusion will be required for those with severe hemolysis and sudden pallor.[27,28]

When to refer

- Immediately refer the patient to a general physician or hematologist if he/ she experiences:
  - severe exhaustion or pale skin or any of the persisting symptoms become worse;
  - very dark, red, red-brown, brownish or tea colored urine; and
  - urine output has noticeably reduced recently (oliguria or anuria).

Prevention

- It is important to avoid the foods and drugs below.
  - Antibiotics: Sulphonamides, Co-trimoxazole (Septrin), Dapsone, Chloramphenicol,
  - Nitrofurantoin, Nalidixic acid, Fluoroquinolones
  - Antimalarials: Chloroquine, Hydroxychloroquine, Primaquine, Quinine, Mepacrine
  - Chemicals: Moth Balls, naphthalene, Methylene blue
  - Food: Fava beans - also called broad beans
  - Other drugs: Aspirin, Phenacetin, Sulphasalazine, Methyldopa, Hydralazine, Quinidine, Large doses of Vitamin C, Procainamide, Rasburicase and some chemotherapy agents
- Tips to help patient get the most from a visit to healthcare provider:
  - Know the reason for their visit and what they want to happen;
  - Before their visit, write down questions they want answered;
  - Bring someone to help them ask questions and remember what their provider tells them;
  - During the visit, write down the name of a new diagnosis, and any new medicines, treatments, or tests;
  - Also write down any new instructions their provider gives them;
  - Know why a new medicine or treatment is prescribed, how it will help them, and what the side effects are;
  - Ask if their condition can be treated in other ways;
  - Know why a test or procedure is recommended and what the results could mean;
  - Know what to expect if they do not take the medicine or have the test or procedure;
  - If they have a follow-up appointment, write down the date, time, and purpose for that visit;
  - Know how they can contact their provider if they have questions.

APLASTIC ANAEMIA

- Aplastic anaemia is a rare disorder of bone marrow failure characterized by pancytopenia and bone marrow aplasia. Its incidence is as low as about two per million per year and nearly half of all diagnosed cases are usually younger than 30 years of age.
- The causes of aplastic anaemia include certain drugs (phenytoin, carbamazepine, sulfonamides, indomethacin, methimazole, propylthiouracil), toxins, ionizing radiation and infection.
- Primary care physicians may often find bicytopenia or pancytopenia incidentally in CBC and blood film reports. In such cases, possible causes of aplastic anaemia should be excluded and the patients with pancytopenia should be referred urgently to a hematologist.
- Treatment depends on the underlying cause and severity, and the patients should be under the care of hematologist.
- Supportive treatment involves transfusions and prophylaxis/treatment of infection.
- Definitive treatment includes the hemopoietic cell transplant and the immunosuppressive therapy.[29]

HAEMOPHILIA

- Hemophilia is the X-linked recessive disorder which causes prolonged bleeding due to deficiency of certain clotting factors. Common types include haemophilia A (factor VIII deficiency) and haemophilia B (factor IX deficiency- Christmas disease).[30]

Diagnosis

- The important point in diagnosis and evaluation is to differentiate haemophilia from other bleeding disorders as well as to confirm the severity and type of haemophilia. Severity of haemophilia can be classified as mild, moderate and severe based on the residual factor level as follows:
    - mild haemophilia with factor level between >5% and <40% of normal;
    - moderate haemophilia with factor level between ≥1% and ≤5%; and
    - severe haemophilia with factor level <1%.[31]
- In all patients with prolonged bleeding, haemophilia should be included in the list of differential diagnoses and personal bleeding history and family history should be taken thoroughly.
- Initial tests for all suspected cases of haemophilia include the prothrombin time (PT), activated partial thromboplastin time (aPTT), and platelet count.
- In moderate and severe hemophilia, the PT and platelet count are normal with prolonged aPTT while those with mild hemophilia (Hemophilia B) can have normal aPTT. Thus, for those with isolated prolonged aPTT (which corrects in mixing studies) and those with normal PT, aPTT and platelet count who have a relevant clinical history or family history for hemophilia should be tested for factor activity levels.[31]
- In every individual with suspected hemorrhagic disorders, screening tests for HIV, Hepatitis B and Hepatitis C infections should be ordered to get the baseline status before transfusions and to provide vaccination for Hepatitis B if not previously vaccinated.
- Low platelet count should suspect HIV infection associated with immune thrombocytopenic purpura (ITP).

Management

- The management of haemophilia includes the treatment of acute bleeding and prophylaxis.[30]
- It is important to follow the guidelines for management of hemophilia (3rd edition) published by the World Federation of Hemophilia (WFH) and individualized care should be provided (based on the available resources).
- During an acute bleeding episode,
    - patient should be immediately admitted to a hospital with hematology unit for transfusion of clotting factor concentrates (CFCs), even if the diagnostic tests are pending.
    - The transfusion of factor VIII concentrate (FVIII) for Hemophilia A or factor IX concentrate (FIX) for Hemophilia B must be done as soon as possible after bleeding has started.
    - In areas where CFCs are not available, fresh frozen plasma and cryoprecipitate can be provided as emergency care.
    - Symptomatic treatment includes proper rest, adequate analgesia and physiotherapy for bleeding into muscles/ joints (hematoma).[30]

Prophylaxis

- The WFH recommends regular long-term prophylaxis (regular factor infusions) as the standard of care for hemophilia patients. Even in resource-limited setting, the use of less intensive prophylaxis should be considered because it is more effective than on-demand therapy.[32]
- Tranexamic acid can be used to prevent or control superficial soft tissue and mucosal bleeds, and for invasive dental procedures (pre- and post-operatively). It can be given orally (25 mg/kg/dose) 3-4 times daily or by IV infusion (10 mg/kg/dose) 2-3 times daily.

- ***However, tranexamic acid is contraindicated in patients with hemophilia B receiving prothrombin complex concentrates.***[32]
- Desmopressin (DDAVP)- increases the plasma level of factor VIII (but not factor IX) and can be used, under close supervision, as a treatment option for mild or moderate hemophilia A.[32]
- Prophylaxis with standard half-life clotting factor:
    - for Hemophilia A, 10-15 IU FVIII/kg (low-dose) or 15-25 IU FVIII/kg (intermediate-dose) 3 days per week;
    - for Hemophilia B, 10-15 (low-dose) or 20-40 IU FIX/kg (intermediate-dose) twice a week.
- Prophylaxis is essential to prevent joint damage in children with haemophilia.
- The dose of prophylactic therapy can be increased if the patient still experience some breakthrough bleeds and high-dose prophylaxis can be used if the resources are available in the local area.[32]

VON WILLEBRAND DISEASE (VWD)

- Von Willebrand disease (VWD) is a common bleeding disorder, affecting up to 1% of population in the United States.
- Bleeding in VWD patients is usually a mild problem with an excellent prognosis.
- There are three types of VWD:
    - autosomal dominant type 1
    - autosomal dominant type 2 (type 2A is the most common variant) and
    - autosomal recessive type 3 (with severe bleeding).[33]
- Regarding the local incidence, there were only nineteen patients with VWD reported in 2018 and hence majority of people with VWD may still remain undiagnosed in Myanmar.[34]
- Most people with VWD are asymptomatic and only a small percentage of them presents with recurrent bruising, prolonged bleeding from skin cuts or from mucosal surfaces (e.g., menorrhagia and epistaxis). They can be diagnosed after proper evaluation and investigations. In severe cases, bleeding may occur in joints. Bleeding tendency can be exacerbated by aspirin.[33]

Diagnosis

- CBC shows normal platelets.
- Coagulation screening results will be as follows: increased bleeding time, normal PT and normal/ prolonged aPTT (aPTT may be prolonged if there is associated factor VIII deficiency).
- Von Willebrand (VW) factor antigen test is indicated for quantitative defect.
- VW factor activity test can be done for quantitative defect.
- VW factor level <30% is required to confirm the diagnosis.[33]

Management

- Refer to a hematologist in easily accessible areas for the patients.
- Mild cases are managed with tranexamic acid and desmopressin (DDAVP) trial.
- Type 1 VWD patients generally have good response to DDAVP trial, while type 3 VWD does not response.
- Severe cases (those with type 3 VWD or severe variants of type 1 & 2) may require VW factor replacement therapy.[33]

THROMBOCYTOPENIC PURPURA

- Bleeding is inevitable if platelet count decrease to <5-10 x 10^9/L. Purpura due to thrombocytopenia can be classified into two groups as follows:
    - ***Non-immune thrombocytopenic purpura***
        - caused by conditions that damage the bone marrow, e.g., drugs (chemotherapy), aplastic anaemia, leukemia, myeloproliferative disorders
    - ***Immune thrombocytopenic purpura***
        - Primary immune thrombocytopenic purpura (ITP) or
        - Secondary to SLE, transfusions or drug reactions (drug-induced ITP).

IMMUNE THROMBOCYTOPENIC PURPURA

- Immune thrombocytopenic purpura (ITP) is an acquired autoimmune disorder caused by anti-platelet antibodies.
- Most patients with thrombocytopenia may be asymptomatic and underdiagnosed.
- Patients with ITP can present with skin/ mucosal bleeding and low platelet count.[35]

Diagnosis

- ITP is the diagnosis of exclusion – meaning all other possible causes of thrombocytopenia should be excluded before confirming the diagnosis of ITP.
- Clinical presentations of acute ITP include generalized purpura in otherwise healthy children, easy bruising, oral mucosal bleeds, epistaxis, conjunctival hemorrhage, menorrhagia or hematuria.[35]
- Initial investigations for suspected cases of ITP include
    - CBC,
    - peripheral blood film,
    - reticulocyte count,
    - direct antiglobulin test and
    - serum immunoglobulin levels (if available).
- For further evaluation and diagnosis, refer any children with suspected ITP to a pediatric hematologist, and adult patients with isolated thrombocytopenia should also consult with a hematologist.
- Bone marrow examination of ITP patients will reveal normal marrow with normal or increased megakaryocytes.
- Platelet Coomb's test can detect anti-platelet antibodies fixed on the platelets of the patient.[35, 36]

Management

- The aim of ITP management is to prevent or treat significant bleeding, and not just to merely increase the platelet count.
- In managing patients with ITP, it is first to consider whether each patient is indicated for treatment. Then, the next step is to determine the urgency of treatment.[37]
- The risk of severe bleeding is highest in those with:
    - previous bleeding history,
    - older age >60 years, and
    - platelet count <10,000/microliter.
- The indications for specific therapy are based on the rapid clinical assessment which includes the following points:
    - Bleeding site, acuity and severity (if bleeding is present at the time of assessment),
    - Platelet count (Severe or critical bleeding occurs with platelets <20,000/microliter),

    - Other bleeding risk factors,
    - Previous treatments given for bleeding or thrombocytopenia and their effectiveness
    - Treatment given for the current bleeding episode
- All patients with suspected ITP, who have high risk of severe or critical bleeding or who present with bleeding, should be urgently referred to a hospital with a hematology unit.
- Most patients with minor bleeding or asymptomatic patients may not require any treatment, however, they should be scheduled for regular follow-up and informed about the risks of bleeding and treatment plan if there is acute bleeding.[37]
- ITP often resolves spontaneously within 3 months in children, but a minority of children can develop chronic ITP (thrombocytopenia >12 months since presentation) and they should be referred to a pediatric hematologist for further evaluation and management.[38]
- Patients with critical bleeding, which includes ***intracranial, intraspinal, intraocular, retroperitoneal, pericardial, or intramuscular bleeding with compartment syndrome,*** require immediate treatment with platelet transfusion, intravenous immune globulin (IVIG) infusion, glucocorticoids and other necessary treatments.
- Patients with severe bleeding, which causes reduction in Hb of ≥2 g/dL or requires blood transfusion (≥2 units) but do not have features of critical bleeding, will need urgent treatment with IVIG, glucocorticoids and other supportive care.[37]
- Antifibrinolytic therapy is useful for mucosal bleeding (oral, gastrointestinal, or gynecologic). Tranexamic acid can be given orally (1 g three to four times per day) or intravenously (10 mg/kg three times a day).[37]
- In managing patients with ITP, it is also important to detect and treat the underlying conditions which can cause secondary ITP. The causes of secondary ITP include:
    - ***Autoimmune diseases:*** Antiphospholipid syndrome, Systemic lupus erythematosus, Rheumatoid arthritis, Inflammatory bowel disease
    - ***Immunodeficiency:*** HIV, Selective IgA deficiency, Common variable immune deficiency
    - ***Infections:*** Cytomegalovirus (CMV), Hepatitis C virus, Varicella zoster virus, *H. pylori*
    - ***Lymphoma and Chronic lymphocytic leukemia (CLL)***
    - ***Alemtuzumab or some other monoclonal antibodies, and***
    - ***Mumps, measles and rubella (MMR) vaccine***
- There are some reported cases of ITP with COVID-19 vaccination. However, the risk is low and individuals with ITP can also receive COVID-19 vaccines after consultation with a hematologist. In patients with acute flare of ITP, doctors should postpone the vaccination until the flare is controlled.[37]

LEUKEMIA

- Leukemia is a group of hematological malignancies caused by an acquired malignant transformation in the haemopoietic stem cells.
- Acute leukemia has a rapidly fatal course if untreated, while chronic leukemia has a variable chronic course with an inevitable fatal outcome.
- Globally, the estimated number of deaths due to leukemia was over 334,000 in the year 2019.[39]

ACUTE LEUKEMIA

- Patients with acute leukemia usually have blast cells >20% in the peripheral blood smear or bone marrow.
- Acute leukemia is more commonly diagnosed in children and adolescents than in adults.[40]

ACUTE LYMPHOBLASTIC LEUKEMIA

- Acute lymphoblastic leukemia (ALL), or recently called lymphoblastic lymphoma (LBL), is the most common malignancy in children. It accounts for about 30% of all childhood cancers.[41]
- Clinical signs and symptoms of ALL/ LBL are non-specific and may be difficult to differentiate with other diagnoses. The common clinical findings in patients with ALL/ LBL include:
    - Hepatomegaly and/ or splenomegaly (the most common signs in >60% of the patients);
    - Lymphadenopathy (in about 50% of the patients);
    - Fever (in >50% of the patients): either due to infection or leukemia itself;
    - Hematologic abnormalities: bleeding with reduced platelet count, features of anaemia (pallor or fatigue) and low, normal or high white cell count (WCC >50,000/microL in 20%); and
    - Musculoskeletal pain: the affected child can present with a limp or refusal to bear weight.

Diagnosis

- Diagnosis of ALL/ LBL in children requires a high level of clinical suspicion since major clinical findings are not specific.
- The laboratory tests for suspected patients with ALL/ LBL includes the ***complete blood count (CBC) and differential count, peripheral blood smear, and bone marrow examination***.
- If lymphadenopathy is the first or main clinical finding, diagnostic evaluation should start with the excisional or core needle biopsy of the suspected lymph node.[41]
- The morphologic evaluation of cells from a peripheral blood film, bone marrow or other affected tissues (e.g., lymph nodes) together with immunophenotyping and karyotyping are usually required to confirm the diagnosis of ALL/ LBL. Thus, all suspected patients should be referred to a hemato-oncologist (or pediatric oncologist) for detailed investigations to confirm the diagnosis.[41]

Treatment

- Treatment of ALL/ LBL includes multidrug regimen divided into different phases, namely induction, consolidation or intensification and maintenance therapy.
- The treatment protocols may vary based on the immunophenotype and risk category and it usually takes about two or three years to complete the treatment.[42]
- All patients with suspected or confirmed ALL/ LBL should be referred to an oncologist (hemato-oncologist) on the same day to receive all necessary investigations and specific treatments.
- At the time of diagnosis, majority of the patients with ALL/ LBL require supportive care with transfusion, treatment for infections with broad-spectrum antibiotics, and treatment for metabolic changes due to fast cellular turnover (e.g., allopurinol can be used for hyperuricemia to prevent tumor lysis syndrome in ALL/ LBL patients).[42]

ACUTE MYELOID LEUKEMIA

- Acute myeloid leukemia (AML) is characterized by the clonal proliferation of myeloid precursor cells. It is the most common form of acute leukemia in adults.
- The incidence of AML increases with age and the median age at the time of presentation is approximately 68 years.[40, 43]
- The risk factors for AML consist of environmental factors such as:
    - exposure to smoking, radiation, chemicals or
    - previous chemotherapy/ radiotherapy and
    - genetic factors such as trisomy 21 (Down syndrome), Fanconi anaemia and Bloom's syndrome.[43]
- Most patients may not exactly know the onset of AML because they only experience subtle and non-specific symptoms (e.g., fatigue and weakness) at the beginning of the disease, probably several weeks or months before diagnosis.
- Common presenting features of AML are as follows:
    - Fatigue – in the majority of patients;
    - Pallor and weakness;
    - Fever, almost always due to infections;
    - Hemorrhage – gingival bleeding, epistaxis, ecchymoses, or menorrhagia, and
    - Any combination of the above clinical signs and symptoms.[43]

Diagnosis

- Similar to ALL/ LBL, the initial laboratory tests for patients with suspected AML include CBC, peripheral blood smear and reticulocyte count.
- CBC results may be normal or shows reduced Hb and platelet counts and WCC may vary (20% of patients have WCC >100,000/microliter; 25- 40% have WCC <5000/microL).
- Provisional diagnosis of AML can be made if there are ***any myeloid precursor cells detected in the peripheral blood smear examination***.
- To confirm the diagnosis of AML, ***evidence of bone marrow infiltration*** (from adequate bone marrow aspiration and biopsy) as well as ***demonstration of myeloid cells*** (with the presence of Auer rods, cytochemical reaction for myeloperoxidase or presence of myeloid markers in immuno-phenotyping) are required.[43]
- Impairment of renal function can be found in patients with AML if the WCC is very high. Mediastinal mass and/or lytic bone lesions may be detected in chest X-ray of some patients.

Management

- All suspected cases of AML should be referred to a hemato-oncologist within one day for early diagnosis and treatment.
- The management of AML ***aims to control disease activity and to achieve complete remission, if possible.*** The individual goals of treatment should be made by share decision-making by patients, their family members and clinicians.[44, 45]
- Pretreatment evaluation should include:
    - thorough history taking,
    - physical examination, and
    - the following laboratory tests:
    - CBC with differential count,
    - coagulation studies,
    - serum chemistries and viral serologies.
- Flow cytometry (immunophenotyping), karyotyping and molecular analysis (if needed) will be required to classify the subtypes of AML.[44]
- The ideal treatment outline for AML patients consists of
    - induction therapy (for complete remission),

    - followed by consolidation and/ or maintenance therapy to strengthen the remission and increase response duration.
- Before starting the definitive treatment, it is recommended to take time to prepare the patients physically and psychosocially to stabilize them and also to determine the best treatment option for individual patients.[44]
- AML is the most common indication for allogenic hemopoietic cell transplantation (HCT).
- Finding and matching with possible donors, specific indications, timing of HCT and preparation for HCT should be consulted with the experienced hemato-oncologists in well-equipped tertiary hospitals.[44]

Prognosis of Acute Leukemia

- Prognosis of acute leukemia varies significantly according to
    - the subtypes of ALL and AML,
    - chromosomal abnormalities,
    - genetic mutations,
    - age and
    - presenting features at the time of diagnosis,
    - underlying comorbid conditions (multimorbidity), and
    - treatment responses.[40]
- Due to the availability of newer therapies and person-centered comprehensive care, overall five-year survival rate of patients with acute leukemia has increased up to nearly 70%.[40,46]
- Prognosis is usually poor if any prognostic factors listed in Table-1 are present.

Table-1. Poor prognostic factors for Acute Leukemia

For ALL/ LBL[47]	**For AML[48]**
Personal: Age ≤1 year (infants) or ≥10 years at diagnosis	Personal: older age (>55 yrs.) and poor performance status (due to comorbidities)
Cytogenetics*: t(9:22)/BCR::ABL1, t(4:11), Hypodiploidy, etc.	Cytogenetics*: t(6;9), t(9:22), del(5q), complex karyotype, monosomal karyotype, etc.
T-cell immunophenotype	Acute promyelocytic leukemia (PML-RARA)
White cell count >50,000/microL; CNS or testicular involvement at diagnosis	Therapy-related AML; prior myelodysplastic syndrome or other hematological disorder
Delayed disappearance/ reappearance of measurable residual disease (MRD)	[Role of MRD detection is still unclear in AML prognosis]

** for detailed information, check the two cited references; CNS: central nervous system*

CHRONIC LEUKEMIA AND MYELOPROLIFERATION

CHRONIC LYMPHOCYTIC LEUKEMIA

- Chronic lymphocytic leukemia (CLL) is the most common form of leukemia in the western hemisphere. It is commonly detected in the elderly, with the median age of 70 years.
- CLL has pathologic and immunophenotypic features identical to small lymphocytic lymphoma (SLL).
- When the disease manifestations are primarily in the blood, it is diagnosed as CLL while SLL is diagnosed when the primary involvement is nodal.[49, 50]

Diagnosis

- Many patients with CLL are asymptomatic and they usually present with an incidental finding in CBC result showing abnormal lymphocytosis.

- On physical examination, up to 90% of such patients may have ***localized or generalized lymphadenopathy,*** most commonly found in triangles of neck, supraclavicular and axillary region. ***Spleen*** can be palpable in 25 to 55% of the patients and ***hepatomegaly*** is found at the time of diagnosis in 15- 25% of cases.[49, 50]
- Skin is the most common non-lymphoid tissue that is already infiltrated by CLL cells at the time of diagnosis. Thus, it is important to examine the skin for any skin lesions ***(leukemia cutis)***, and if present, can refer the patient for skin biopsy.[49]
- The initial investigations include ***CBC and peripheral blood smear***. The threshold of absolute lymphocyte count for diagnosis of CLL is >5 x 10^9/L of B lymphocytes and it can be as high as >100 x 10^9/L in some cases. The peripheral blood film usually shows small lymphocytes with a darkly stained nucleus and narrow rim of basophilic cytoplasm, and smear cells or smudge cells can also be detected.[49, 50]
- ***Immunophenotyping*** by flow cytometry is essential for the diagnosis of CLL.
- The three main immunophenotypic findings of CLL include:
    - expression of B-cell associated antigens (CD19, CD20, CD23),
    - expression of CD5 and
    - expression of low levels of surface membrane immunoglobulin.
- Bone marrow aspirate and biopsy are not usually needed for CLL diagnosis.[49]

Management

- Refer to a hematologist, depending on age and clinical state of the patient
- Once diagnosis has been confirmed, well patients with low levels of lymphocytosis are often managed in primary care with regular FBC and clinical review (at least every 6 months).
- Treat any infections promptly.
- Refer to a hematologist for expert management if any of the following is present:
    - Symptomatic disease (fevers, sweats, weight loss);
    - Lymphadenopathy and/or hepatosplenomegaly;
    - Rising lymphocyte count (increase >50% in 2 months or doubling time of <6 months);
    - Anaemia or thrombocytopenia
- Splenectomy is indicated in patients with massive symptomatic splenomegaly and refractory cytopenia. It should be consulted with a hematologist.
- Explain the diagnosis of CLL, its benign nature and often good prognosis (>10 years).
- Stem-cell transplantation may have a role in carefully selected patients.

CHRONIC MYELOID LEUKEMIA

- Chronic myeloid leukemia (CML) is the myeloproliferative disorder caused by uncontrolled proliferation of mature and premature granulocytes with relatively normal differentiation.
- CML accounts for approximately 20% of leukemias in adults, with the median age of 50 years at the time of presentation.[51]
- Nearly half of patients with CML are initially asymptomatic and they can be incidentally detected with routine blood tests.
- Non-specific systemic symptoms such as fatigue, weight loss and excessive sweating, and bleeding due to platelet dysfunction are common in symptomatic patients.[51]

Diagnosis

- If CBC result shows marked leukocytosis (>50 x 10^9/L) with/ without anaemia and if numerous granulocytes (from myeloblasts to segmented neutrophils) are found in peripheral blood smear, CML should be suspected.
- The diagnosis of CML is confirmed by cytogenetic analysis (***demonstration of Philadelphia chromosome BCR::ABL1 fusion gene***).[51]

Management

- **Refer urgently to a hematologist** (by using teleconsultation service in remote areas).
- Treatment is determined by the phase of the disease.
- Initial treatment is BCR::ABL1 tyrosine kinase inhibitors (TKI) if there is no contraindication.
- Other medications like hydroxyurea and interferons may be used sometimes.
- Allogeneic hematopoietic cell transplantation (HCT) can be considered for medically fit patients if there is a suitable donor.[51]

LYMPHOMA

NON-HODGKIN'S LYMPHOMA

- Non-Hodgkin's lymphoma (NHL) is a group of hematologic malignancies which includes all lymphomas without Reed-Sternberg cells.
- NHL can be found in all ages and socioeconomic status.[52]
- The clinical features and presenting symptoms may vary based on different histologic types of NHL and sites of involvement.
- Typical presentations of NHL can be divided into two groups as follows:
    - ***Aggressive NHLs*** usually present with constitutional symptoms ("B" symptoms) such as fever, weight loss and night sweats; rapidly growing mass; and tumor lysis syndrome.
    - ***Indolent cases*** often present with slow-growing lymph nodes over several months or years, hepatomegaly, splenomegaly, with/ without cytopenia.[52]

Diagnosis

- Initial investigations are the CBC with differential count, coagulation tests, serum electrolytes, renal function (blood urea nitrogen & creatinine) and liver function tests, serum LDH and uric acid.
- CBC may be normal if there is no bone marrow involvement. Increased LDH may be associated with poor prognosis.[52]
- In patients with suspected NHL, a biopsy should be taken from an involved lymph node.
- The patients should not recently take glucocorticoids before biopsy, as steroids are lymphocytolytic. Diffuse large B cell lymphoma (DLBCL) is the most common histologic subtype.[52]

Management

- All patients with suspected NHLs should be urgently referred to an oncologist or hematologist for diagnosis confirmation, pretreatment evaluation, staging and specific treatments.[52]
- Fitness for treatment can be evaluated by clinical examination and performance status.[52]
- Serum protein electrophoresis should be done in selected cases.[52]
- Infection screening: for HIV in all patients and for HBV and HCV in some cases.[52]
- Imaging can be done depending on the histologic subtypes.[52]

Prognosis

- The prognosis of NHL varies widely between different histopathological types.
- DLBCL can be cured in nearly 50% of patients with current standard therapy, especially for those who have complete remission with the first-line treatment.
- Younger, fitter patients with less widespread disease do better.
- Socioeconomic conditions, performance status and underlying comorbidities can also influence the prognosis to a certain extent.
- Poor prognostic factors are as follows:
    - Age >60 years,
    - Increased serum LDH,
    - Eastern Cooperative Oncology Group (ECOG) performance status ≥2,
    - Clinical stage III or IV, and
    - >1 extranodal disease stie.[53]

HODGKIN'S LYMPHOMA

- Hodgkin's lymphoma (HL) is a relatively rare lymphoid malignancy characterized by the histologic finding of multi-nucleated Reed-Sternberg cells mixed with non-neoplastic inflammatory cells.
- HL can be divided into two main types:
    - Classic HL (90%)- Reed Sternberg cells are present; and
    - Nodular lymphocyte predominant HL (NLPHL).[54]
- Typically, the majority of patients with classic HL present with asymptomatic/ painless lymph node enlargement or an incidental finding of a mass in chest X-ray (CXR).
- About 40% of patients also develop systemic "B" symptoms such as fever, weight loss and night sweats.[54]
- In 60-80% of cases, lymphadenopathy is found in the neck (cervical nodes) or supraclavicular region. Mediastinal nodes are sometimes involved in about 60% of cases.
- Bone marrow and liver involvement as extranodal sites are less common in classic HL.[54]

Diagnosis

- Initial investigations for all patients should include:
    - Complete blood count (CBC) with differential count and erythrocyte sedimentation rate (ESR),
    - Serum electrolytes, renal and liver function tests and serum albumin, and
    - HIV testing,
    - Serum LDH and uric acid.[54]
- Classic HL should be suspected in any patients with lymphadenopathy or mediastinal mass on CXR.
- Imaging can be used to find out potential sites for lymph node biopsy and for other organ involvement. PET/CT is used for staging.[54]

Staging

- Staging for Hodgkin's lymphoma is important for specific treatment and prognosis.
- Ann Arbor staging is summarized in Table-2.
- Recently there is another modified staging, known as Lugano classification, derived from Ann Arbor staging.[55]

Table-2. Staging (Ann Arbor Staging)

Stage	Description
Stage I	Confine to single lymph node region.
Stage II	Involvement of two or more nodal area on the same side of diaphragm
Stage III	Involvement of nodes on both side of diaphragm
Stage IV	Spread beyond lymph nodes (e.g.; liver or bone marrow)
Each stage is either: A: no systemic symptoms except pruritus or B: presence of B symptoms: weight loss >30% in last 6 months, unexplained fever >38°C, sweating (needing change of clothes) Localized extranodal extension does not advance stage but is indicated subscripted 'E'.	

Management

- All patients with classic HL or NLPHL should be consulted with a hemato-oncologist for diagnostic confirmation, pretreatment evaluation, staging and specific treatments.[56]
- For patients with ***early staging,*** treatment should be aimed for eradication of the disease.[56]
- For ***Stage I and II patients***, combination of chemotherapy and involved-field radiotherapy can be used for higher disease-free survival.[56]

- For patients with ***advanced classic HL*** (stage III or IV), combination chemotherapy with ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) is the treatment of choice.[57]
- Patients should receive individualized treatment from the specialist team.[56]
- One month after the completion of planned treatment, the patients should be evaluated for treatment response and regularly followed for any relapse.[56]

Prognosis

- Prognosis of HL depends on several factors, including
    - age at onset,
    - staging,
    - WCC,
    - serum LDH,
    - albumin and hemoglobin level.
- Nodular sclerosis type of classic HL has better prognosis than other types of HL. 5-year overall survival of early stages of HL (Stage 1 and 2A) is nearly 90% while that of advanced HL (Stage 4) is about 60%.[58]

References

1. *World Health Organization (WHO). Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity. Vitamin and Mineral Nutrition Information System. Geneva, World Health Organization, 2011 (WHO/NMH/NHD/MNM/11.1). https://apps.who.int/iris/bitstream/handle/10665/85839/WHO_NMH_NHD_MNM_11.1_eng.pdf*
2. *Means RT Jr, Brodsky, RA. Diagnostic Approach to Anaemia in Adults. In: UpToDate, Post, TW (Ed), UpToDate, Waltham, MA, 2022. Accessed August 7, 2022.*
3. *World Bank. Prevalence of anaemia among children (% of children ages 6-59 months) – Myanmar. World Health Organization, Global Health Observatory Data Repository/World Health Statistics. Accessed September 12, 2022. https://data.worldbank.org/indicator/SH.ANM.CHLD.ZS?locations=MM.*
4. *Powers JM, Sandoval C. Approach to the child with anaemia. In: UpToDate, Post, TW (Ed), UpToDate, Waltham, MA, 2022. Accessed September 12, 2022.*
5. *Stoltzfus RJ. Iron deficiency: global prevalence and consequences. Food Nutr Bull. 2003 Dec;24(4 Suppl):S99-103. doi: 10.1177/15648265030244S206. PMID: 17016951.*
6. *United Nations Children's Fund. Ministry of Health and Sports and UNICEF present Frameworks of Action for Complementary Feeding and Maternal Nutrition in Myanmar. Published February 14, 2020. Accessed August 7, 2022. https://www.unicef.org/myanmar/press-releases/ministry-health-and-sports-and-unicef-present-frameworks-action-complementary*
7. *United Nations Children's Fund. The State of the World's Children 2021: On My Mind – Promoting, protecting and caring for children's mental health, UNICEF, New York, October 2021.*
8. *Sonoda, K. Iron Deficiency Anaemia: Guidelines from the American Gastroenterological Association. American Family Physician. August 2021;104(2):211-212.*
9. *Kumar A, Sharma E, Marley A, et al. Iron deficiency anaemia: pathophysiology, assessment, practical management. BMJ Open Gastroenterology 2022;9:e000759. doi: 10.1136/bmjgast-2021-000759*
10. *Majeed T, Solomon J, Ali RS, Chitsabesan P. Non-anaemic iron deficiency should be investigated with the same priority as iron deficiency anaemia in fast-track colorectal clinics-retrospective cohort study. J Gastrointest Oncol. 2020 Aug;11(4):609-615. doi: 10.21037/jgo-19-451.*
11. *Ankar A, Kumar A. Vitamin B12 Deficiency. [Updated 2022 Jun 5]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK441923.*
12. *Allen LH. How common is vitamin B-12 deficiency?, The American Journal of Clinical Nutrition, Volume 89, Issue 2, February 2009, Pages 693S–696S, https://doi.org/10.3945/ajcn.2008.26947A*
13. *Rodriguez NM, Shackelford K. Pernicious Anaemia. [Updated 2022 Jul 4]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK540989.*
14. *Means RT Jr, Fairfield KM. Treatment of vitamin B12 and folate deficiencies. In: UpToDate, Post, TW*

(Ed), UpToDate, Waltham, MA, 2022. Accessed September 19, 2022.
15. *Khan KM, Jialal I. Folic Acid Deficiency. [Updated 2022 Jun 27]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK535377.*
16. *Goetzl LM. Folic acid supplementation in pregnancy. In: UpToDate, Post, TW (Ed), UpToDate, Waltham, MA, 2022. Accessed September 19, 2022.*
17. *Badireddy M, Baradhi KM. Chronic Anaemia. [Updated 2022 May 8]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK534803.*
18. *Madu AJ, Ughasoro MD. Anaemia of Chronic Disease: An In-Depth Review. Med Princ Pract. 2017;26(1):1-9. doi: 10.1159/000452104. Epub 2016 Sep 28. PMID: 27756061; PMCID: PMC5588399.*
19. *Camaschella C, Weiss G. Anaemia of chronic disease/anaemia of inflammation. In: UpToDate, Post, TW (Ed), UpToDate, Waltham, MA, 2022. Accessed September 20, 2022.*
20. *Barcellini W. Diagnosis of hemolytic anaemia in adults. In: UpToDate, Post, TW (Ed), UpToDate, Waltham, MA, 2022. Accessed September 24, 2022.*
21. *Despotovic JM. Overview of hemolytic anaemias in children. In: UpToDate, Post, TW (Ed), UpToDate, Waltham, MA, 2022. Accessed September 24, 2022.*
22. *Baird DC, Batten SH, Sparks SK. Alpha- and Beta-thalassemia: Rapid Evidence Review. Am Fam Physician. 2022;105(3):272-280. https://www.aafp.org/pubs/afp/issues/2022/0300/p272.html*
23. *Bajwa H, Basit H. Thalassemia. [Updated 2022 Jun 7]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK545151.*
24. *Win S. Epidemiology and current status of case management of Thalassemia in Myanmar – Country Report. Myanmar Medical Journal. December 2016;58(4):43-51.*
25. *Benz EJ Jr, Angelucci E. Management of thalassemia. In: UpToDate, Post, TW (Ed), UpToDate, Waltham, MA, 2022. Accessed September 22, 2022.*
26. *Richardson SR, O'Malley GF. Glucose 6 Phosphate Dehydrogenase Deficiency. [Updated 2022 Jun 21]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK470315.*
27. *Glader B. Diagnosis and management of glucose-6-phosphate dehydrogenase (G6PD) deficiency. In: UpToDate, Post, TW (Ed), UpToDate, Waltham, MA, 2022. Accessed September 24, 2022.*
28. *Li Q, Yang F, Liu R, Luo L, Yang Y, Zhang L, Liu H, Zhang W, Fan Z, Yang Z, Cui L, He Y. Prevalence and Molecular Characterization of Glucose-6-Phosphate Dehydrogenase Deficiency at the China-Myanmar Border. PLoS One. 2015 Jul 30;10(7):e0134593. doi: 10.1371/journal.pone.0134593. Erratum in: PLoS One. 2015;10(9):e0138038. PMID: 26226515; PMCID: PMC4520570.*
29. *Moore CA, Krishnan K. Aplastic Anaemia. [Updated 2022 Jul 18]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK534212.*
30. *Mehta P, Reddivari AKR. Hemophilia. [Updated 2022 Jun 11]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK551607.*
31. *Hoots WK, Shapiro AD. Clinical manifestations and diagnosis of hemophilia. In: UpToDate, Post, TW (Ed), UpToDate, Waltham, MA, 2022. Accessed September 27, 2022.*
32. *Srivastava A, Santagostino E, Dougall A, et al. WFH Guidelines for the Management of Hemophilia, 3rd edition. Haemophilia. 2020:26(Suppl 6):1-158. https://doi.org/10.1111/hae.14046.*
33. *Sabih A, Babiker HM. Von Willebrand Disease. [Updated 2022 Jul 10]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK459222.*
34. *World Federation of Hemophilia. Report on the Annual Global Survey 2018. 2019. Available from: https://www1.wfh.org/publications/files/pdf-1731.pdf. Assessed September 27, 2022.*
35. *Justiz Vaillant AA, Gupta N. ITP-Immune Thrombocytopenic Purpura. [Updated 2022 Jul 8]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK537240*
36. *Bussel, JB. Immune thrombocytopenia (ITP) in children: Clinical features and diagnosis. In: UpToDate, Post, TW (Ed), UpToDate, Waltham, MA, 2022. Accessed September 29, 2022.*
37. *Arnold DM, Cuker A, Kelton JG. Initial treatment of immune thrombocytopenia (ITP) in adults. In: UpToDate, Post, TW (Ed), UpToDate, Waltham, MA, 2022. Accessed September 29, 2022.*

38. *Bussel, JB. Immune thrombocytopenia (ITP) in children: Management of chronic disease. In: UpToDate, Post, TW (Ed), UpToDate, Waltham, MA, 2022. Accessed September 29, 2022.*
39. *Sharma, R., Jani, C. Mapping incidence and mortality of leukemia and its subtypes in 21 world regions in last three decades and projections to 2030. Ann Hematol 101, 1523–1534 (2022). https://doi.org/10.1007/s00277-022-04843-6*
40. *Chennamadhavuni A, Lyengar V, Shimanovsky A. Leukemia. [Updated 2022 May 4]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK560490*
41. *Horton TM, Steuber CP, Aster JC. Overview of the clinical presentation and diagnosis of acute lymphoblastic leukemia/lymphoma in children. In: UpToDate, Post, TW (Ed), UpToDate, Waltham, MA, 2022. Accessed September 29, 2022.*
42. *Horton TM, Steuber CP. Overview of the treatment of acute lymphoblastic leukemia/lymphoma in children and adolescents. In: UpToDate, Post, TW (Ed), UpToDate, Waltham, MA, 2022. Accessed September 29, 2022.*
43. *Schiffer CA, Gurbuxani S. Clinical manifestations, pathologic features, and diagnosis of acute myeloid leukemia. In: UpToDate, Post, TW (Ed), UpToDate, Waltham, MA, 2022. Accessed September 30, 2022.*
44. *Döhner H, Wei AH, Appelbaum FR, et al. Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN. Blood. 2022;140(12):1345-1377. doi:10.1182/blood.2022016867*
45. *Kolitz JE. Overview of acute myeloid leukemia in adults. In: UpToDate, Post, TW (Ed), UpToDate, Waltham, MA, 2022. Accessed September 30, 2022.*
46. *The Cancer.Net Editorial Board. Leukemia - Acute Myeloid - AML: Statistics. April 2022. Available from https://www.cancer.net/cancer-types/leukemia-acute-myeloid-aml/statistics. Accessed September 30, 2022.*
47. *Horton TM. Prognostic factors and risk group stratification for acute lymphoblastic leukemia/lymphoblastic lymphoma in children and adolescents. In: UpToDate, Post, TW (Ed), UpToDate, Waltham, MA, 2022. Accessed September 30, 2022.*
48. *Schiffer CA. Prognosis of acute myeloid leukemia. In: UpToDate, Post, TW (Ed), UpToDate, Waltham, MA, 2022. Accessed September 30, 2022.*
49. *Rai KR, Stilgenbauer S, Aster JC. Clinical features and diagnosis of chronic lymphocytic leukemia/small lymphocytic lymphoma. In: UpToDate, Post, TW (Ed), UpToDate, Waltham, MA, 2022. Accessed September 30, 2022.*
50. *Mukkamalla SKR, Taneja A, Malipeddi D, et al. Chronic Lymphocytic Leukemia. [Updated 2022 Jul 4]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK470433*
51. *Etten RAV. Clinical manifestations and diagnosis of chronic myeloid leukemia. In: UpToDate, Post, TW (Ed), UpToDate, Waltham, MA, 2022. Accessed September 30, 2022.*
52. *Freedman AS, Friedberg JW, Aster JC. Clinical presentation and initial evaluation of non-Hodgkin lymphoma. In: UpToDate, Post, TW (Ed), UpToDate, Waltham, MA, 2022. Accessed September 30, 2022.*
53. *Freedman AS, Aster JC. Prognosis of diffuse large B cell lymphoma. In: UpToDate, Post, TW (Ed), UpToDate, Waltham, MA, 2022. Accessed October 1, 2022.*
54. *LaCasce AS, Ng AK, Aster JC. Clinical presentation and diagnosis of classic Hodgkin lymphoma in adults. In: UpToDate, Post, TW (Ed), UpToDate, Waltham, MA, 2022. Accessed October 1, 2022.*
55. *McClain KL, Kamdar K. Overview of Hodgkin lymphoma in children and adolescents. In: UpToDate, Post, TW (Ed), UpToDate, Waltham, MA, 2022. Accessed October 1, 2022.*
56. *Hoppe RT, LaCasce AS. Treatment of favorable prognosis early (stage I-II) classic Hodgkin lymphoma. In: UpToDate, Post, TW (Ed), UpToDate, Waltham, MA, 2022. Accessed October 1, 2022.*
57. *Yahalom J, LaCasce AS. Initial treatment of advanced (stage III-IV) classic Hodgkin lymphoma. In: UpToDate, Post, TW (Ed), UpToDate, Waltham, MA, 2022. Accessed October 1, 2022.*
58. *Kaseb H, Babiker HM. Hodgkin Lymphoma. [Updated 2022 Jul 10]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK499969.*