Exam Preparatory Manual for Undergraduates

Medicine

2nd Edition

Archith Boloor
Ramadas Nayak

Foreword
Chakrapani M

HIGHLIGHTS
- Contains everything an undergraduate student of medicine would want to read before examination.
- Colorful clinical images and case scenarios included.
- Reader-friendly pattern. Easy-to-memorize format, interspersed with relevant, and commonly asked exam-questions in a question-answer format and covers all the questions appeared in university examinations till January 2018.
- Contains comprehensive information in compact boxes and figures, making it a ready reckoner before the examination.
- Covers all theory and most clinical scenarios. Management practices have been updated till March 2018.
- Includes recent advances, newer drugs and upcoming sections of geriatrics, immunology, and clinical pharmacology.
- Key points are highlighted. Richly illustrated in multicolor, including management algorithms, color coded as in etiology, management, etc.
- Exclusive coverage of high yielding points which is important for answering MCQs.
- Appendices provide reference values of common laboratory investigations and commonly used formulae.

Archith Boloor MBBS, MD (Internal Medicine) is a distinguished alumnus of the Manipal Academy of Higher Education. He is presently working as an Associate Professor, Department of Medicine, Kasturba Medical College, Manipal Academy of Higher Education, Mangaluru, Karnataka, India. He was adjudged the ‘Best Outgoing Student of the Year’ during his MBBS in Internal Medicine in the year 2008. He subsequently went on to pursue his passion for teaching and has distinguished himself as a teacher par excellence by winning several ‘Best Teacher Awards’ very early in his teaching career. He has added to his list of awards, a couple of awards in Best Audiovisual Teaching Methodology. With his unmatched zeal for teaching and his love of his students, he presents to his students this year a colorful, updated and much awaited Second Edition of the Exam Preparatory Manual for Undergraduates full of pictures from his everyday practice and never before seen algorithms which are a hallmark of his lucid and comprehensive classes. As is often said of his lectures, “attending his class is as good as reading 10 books in internal medicine”, so also this book will end your search for the ‘one single book in medicine’ that will give you everything you need to know for the medicine examination.

Ramadas Nayak MD, FRCP is also graduated from Myore Medical College, MYSR, Karnataka, India, in the year 1979 and completed his postgraduation in Pathology from Kasturba Medical College, Mangaluru, Karnataka, India. Presently, he is Professor and Head, Department of Pathology, Vennepoji Medical College, Vennepoji (affiliated to Vidyasagar University), Mangaluru. In his illustrious teaching career of 35 years, he was Head, Department of Pathology, Kasturba Medical College, Manipal Academy of Higher Education, Mangaluru, for a span of 5 years. Apart from publishing over 91 scientific papers in both national and international journals, he serves as an examiner for the undergraduate and postgraduate examinations in several universities. He has worked as project officer for Development of Cancer Atlas in India—a project conducted by Indian Council of Medical Research (ICMR) sponsored by World Health Organization (WHO). He was the editorial committee member of South Asia Edition of British Medical Journal. He is also the author of eight more books entitled Essentials in Hematology and Clinical Pathology, Textbook of Pathology and Genetics for Nurses, Rapid Review of Hematology, Exam Preparatory Manual for Undergraduates in Pathology, Exam Preparatory Manual for Undergraduates—Pathology for Dental Students, Textbook of Pathology for BPT Students, Textbook of Pathology for Allied Health Sciences and Histopathology Techniques and their Interpretation. Twice he secured ‘Good Teacher Award’ and eight times ‘Best Audiovisual Award’ in Kasturba Medical College, Mangaluru. Above all, he is loved and admired by his students.

Available at all medical bookstores
or buy online at www.jaypeebrothers.com

JAYPEE BROTHERS
Medical Publishers (P) Ltd.
www.jaypeebrothers.com

Join us on facebook.com/JaypeeMedicalPublishers

Sheiling Recommendation

MEDICINE

11th 710-52-11772-6714-7

11th 710-52-11772-6714-7
Internal medicine is expanding and evolving rapidly and there is a need for comprehensive yet simple textbook. Indian medical students have to be very competitive and up-to-date to excel in their fields. While a number of textbooks from foreign authors are available for the Indian students, they might not serve the purpose of preparing the students for the Indian examinations. A few Indian authors have accepted this challenge and have published textbooks oriented towards Indian medical examinations. Dr Archith Boloor realized this need many years ago and took up the challenge of publishing a textbook in internal medicine which was received well by the student community. Huge success of the first edition has prompted him to come out with the second edition of the book.

Dr Archith Boloor is an exceptionally gifted clinician and teacher. He has taken keen interest in medical education from his early days in the medical college and with more than a decade of experience in this field, he has been able to understand the needs of the students with regard to the medical examinations. He has received the Best Teacher Award at Kasturba Medical College, Mangaluru for many years.

The second edition of this compilation has seen qualitative improvements over the previous edition. While the contents of the book are comprehensive, presentation is simple. Clinical images, tables, boxes, algorithms and diagrams are simple and enhance the learning. This book will definitely be an essential learning tool for students of internal medicine.
Preface to the Second Edition

We have been extremely grateful for the positive response rendered towards the book, *Exam Preparatory Manual for Undergraduates—Medicine* and were thus, excited to undertake the challenge of developing a new edition. Surfing beyond plainly updating the literature, this second edition gifted us with the opportunity to further explore topics we ourselves have wrestled with as a student, teacher and teacher educator and also build an understanding of how we approach students and their texts.

In the year and a half following the release of the first edition of this book, we have received numerous feedbacks via e-mails and letters from readers who have given wonderful suggestions on how we could further upgrade the material. We had also built up a large file of ideas based on our own experiences in reading, writing and editing during this time. With the aid of all this information, we have completely revised the book.

In this second edition, the following changes and additions have been incorporated:

- Updated the literature, substantially reordered and updated the material according to the current guidelines in all chapters.
- Included clinical images for all commonly encountered medical conditions.
- Added X-rays, MRIs, CT scans and ECG images of common conditions with explanations.
- Treatment algorithms have been revised and updated.
- Topics regarding clinical trials and research methodology have been added.
- A full chapter on ‘common emergencies in medicine’ is included as a ready reckoner.
- With an eye to the book’s potential use as an aid for entrance preparation, high yield points are highlighted in each section
- The bibliography has been updated. Many new editions of books are referenced and updated references have been added.

We must hereby acknowledge those who have helped us with this new edition. We are especially grateful for the ongoing encouragement from our university, Manipal Academy of Higher Education (MAHE) and Yenepoya Medical College (Deemed to be University), Mangaluru, Karnataka, India. We would like to express our gratitude to Dr Ramdas M Pai (Chancellor), Dr HS Ballal (Pro-Chancellor), Dr H Vinod Bhat (Vice-Chancellor), Dr V Surendra Shetty and Dr Poornima Baliga (Pro Vice-Chancellor) of MAHE, for their continued support.

We profusely thank Dr Chakrapani M, for his support and for writing the foreword for this edition.

We would also like to extend our warm thanks to our esteemed colleagues/friends Dr Sheetal Raj, Dr Saritha Aadhi, Dr Sachin Vemula, Dr Kaushiki Kirty, Dr B Thinakar Mani, Dr Sibithooran Karmegan, Dr Vishnu B Chandran, Dr Narendran Krishnamoorthy, Dr Pradeep Krishna Chowdary, Dr Madhurya Mallavarapu, Dr Deepti Ajjangadi, Dr Ashwini Kamath, Dr Holla Subrava Krishna, and Dr Thomas Kuncheria, for their contributions with the clinical images and proofreading.

We humbly place on record our heartfelt gratitude to our students Dr Mishaal Talish, Dr Sidharth Herur, Dr Raghu RV, Dr Sriraksha R Nayak, Dr M Harsha Sagar, Dr Nikhil Kenny Thomas, Dr Vivek K Koushik, Dr Navyashree HC, Dr Padakant Anudeep Rao, Dr Laveena MariamJohn, Dr Ashwini MV, Dr Alister Joseph Thomas, and Dr Mohamed Faizan Thouseef, for their help in proofreading and correction.

We would further like to thank all our teachers, department colleagues, our current and former students and students from various colleges all over India, for their valuable suggestions and input.

Finally, we would like to acknowledge with gratitude, the support of our all family members, for their support and love, which has made us successful in our endeavors.

Students who have read the book before should find the revised edition more lucid and palatable, while those who have waited for scouts to carve the path will find the road paved and tested. Your suggestions are happily solicited for any improvements, if necessary.

Archith Boloor
Ramadas Nayak
Contents

1. NUTRITION AND ENVIRONMENTAL MEDICINE 1
   Vitamin A 1
   Vitamin B Complex 3
   Vitamin C 6
   Vitamin D 7
   Trace Elements 11
   Fluorosis 12
   Enteral and Parenteral Nutrition Support 12
   Protein-Energy Malnutrition 14
   Obesity 15
   Environmental Diseases 21
   Radiation Exposure 21
   Illness at High Altitude 22
   Heatstroke 23
   Drowning (Submersion Injuries) 27

2. ENDOCRINOLOGY 29
   Disorders of Pituitary and Hypothalamus 29
   Acromegaly 34
   Diabetes Insipidus 37
   Thyroid Disorders 39
   Thyrotoxicosis 41
   Hypothyroidism 46
   Thyroiditis 50
   Parathyroid Disorders 53
   Hypercalcemia 57
   Adrenal Gland Disorders 60
   Pheochromocytoma 70
   Gonadal Disorders 72

3. DIABETES MELLITUS 76
   Definition and Classification 76
   Pathogenesis 78
   Clinical Features of Diabetes Mellitus 81
   Diagnosis of Diabetes Mellitus 83
   Management of Diabetes Mellitus 85
   Oral Hypoglycemic (Glucose-Lowering) Drugs 86
   Insulin Therapy 90
   Diabetic Ketoacidosis 96
   Hyperglycemic Hyperosmolar State 99
   Hypoglycemia 101
   Chronic Complications of Diabetes 104
   Metabolic Syndrome 111

4. INFECTIOUS DISEASES 113
   Pyrexia (Fever) of Unknown Origin 113
   Strepococcal Infections 118
   Pneumococcal Infections 120
   Tetanus 122
Enteric Fever 128
Food Poisoning 130
Amebiasis 133
Cholera 136
Leprosy 137
Leptospirosis 142
Rickettsial Diseases 145
Viral Infections 146
Herpes Virus Infections 150
Dengue 156
Rabies 164
Fungal Infections 168
Opportunistic Mycoses 171
Malaria 173
Leishmaniasis 183
Cestodes (Tapeworms) 187
Filaria 194
Ectoparasites 196
Gonorrhea 199
Chlamydial Infections 202
Granuloma Inguinale (Donovanosis) 202
Syphilis 203
Nosocomial Infections (Hospital Infections) 207
Sepsis 211
Anti-infective Therapy 215

5. HIV INFECTION AND AIDS 220

Etiology 220
Pathogenesis of HIV Infection and AIDS 222
Natural History of HIV Infection 224
Important Infections and Presenting Problems in AIDS 226
Cancers in HIV 233
Diagnosis of HIV Infection or AIDS 233
Management of a Patient with HIV Infection 234
Postexposure Care of a Healthcare Worker 241

6. RESPIRATORY SYSTEM 244

Introduction, Basic Approach, Symptomatology and Investigations 244
Bronchial Asthma 252
Chronic Obstructive Pulmonary Disease 267
Pulmonary Tuberculosis 280
Antituberculous Drugs 289
Extrapulmonary Tuberculosis 296
Bronchiectasis 301
Lung Abscess 308
Pleural Effusion 312
Pneumothorax 321
Pneumonia 326
Diffuse Parenchymal Lung Disease/Interstitial Lung Disease 343
Occupational Lung Diseases 346
Lung Cancer (Bronchial Carcinoma) 349
Mediastinum 358
Respiratory Failure 360
Sleep Apnea/Hypopnea Syndrome 363
Acute Respiratory Distress Syndrome 367
Sarcoidosis 370
Hemoptysis 376
Dyspnea 379
Pulmonary Eosinophilic Syndromes 380
7. CARDIOLOGY

- Introduction and Symptomatology 384
- Arterial Pulse 388
- Jugular Venous Pressure 391
- Apical Impulse 395
- Heart Sounds 396
- Murmurs 400
- Conduction System of the Heart 404
- Electrocardiogram 404
- Ischemic Heart Disease 412
- Acute Coronary Syndrome 420
- Hypertension 433
- Rheumatic Heart Disease 443
- Mitral Stenosis 450
- Mitral Regurgitation 458
- Aortic Stenosis 463
- Aortic Regurgitation 466
- Infective Endocarditis 474
- Heart Failure 482
- Cardiac Arrhythmias 493
- Diseases of the Myocardium 505
- Congenital Heart Diseases 510
- Diseases of the Pericardium 518
- Pulmonary Hypertension 523
- Sudden Cardiac Death 524
- Cardiac Arrest 525
- Cor Pulmonale 528
- Diseases of Vessels 530
- Raynaud's Phenomenon and Raynaud's Disease 532
- Circulatory Failure: Shock 533
- Pulmonary Embolism and Venous Thrombosis 537
- Disorders of Blood Lipids and Lipoproteins 542
- Valsalva Maneuver 548

8. HEMATOLOGY

- Anemia 553
- Iron Deficiency Anemia 557
- Macrocytic Anemia 562
- Hemolytic Anemias 570
- Sickle Cell Disease 572
- Hereditary Spherocytosis 577
- Thalassemia Syndrome 577
- Glucose-6-Phosphate Dehydrogenase Deficiency 580
- Miscellaneous Anemias 581
- Non-neoplastic Disorders of WBC 589
- Acute Leukemias 592
- Chronic Myeloid Leukemia 600
- Chronic Lymphocytic Leukemia 604
- Myeloproliferative Neoplasms 606
- Plasma Cell Neoplasms 614
- Hodgkin Lymphoma 620
- Non-Hodgkin Lymphoma 622
- Immune Thrombocytopenic Purpura 635
- Thrombocytosis 638
- Hemophilia 638
- von Willebrand's Disease 641
- Microangiopathic Hemolytic States and Thrombocytopenias 642
- Disseminated Intravascular Coagulation 644
- Transfusion Medicine 646
Hematopoietic Stem Cell Transplantation 652
Drugs Used in Hematological Diseases 656
Spleen 662
Disorders of Heme Synthesis: The Porphyrias 664

9. RHEUMATOLOGY AND CONNECTIVE TISSUE DISORDERS 667
  Rheumatoid Arthritis 671
  Systemic Lupus Erythematosus 678
  Spondyloarthropathies (Spondyloarthritides) 684
  Vasculitis 690
  Osteoarthritis 697
  Systemic Sclerosis (Scleroderma) 699
  Sjögren's Syndrome 702
  Crystal Arthropathies 704
  Osteoporosis 708
  Antiphospholipid Antibody Syndrome 711
  Inflammatory Muscle Diseases 713

10. GASTROENTEROLOGY 716
  Symptomatology and Evaluation of Gastrointestinal Disease 716
  Gastrointestinal Bleeding 722
  Approach to Diarrhea 727
  Diseases of the Esophagus 731
  Gastroesophageal Reflux Disease 733
  Diseases of the Stomach and Duodenum 738
  Peptic Ulcer Disease 738
  Malabsorption Syndrome 746
  Irritable Bowel Syndrome 756
  Inflammatory Bowel Disease 762
  Probiotics and Prebiotics 773

11. HEPATOBILIARY SYSTEM 777
  Liver Function Tests 777
  Diagnostic Procedures 781
  Jaundice 783
  Congenital Nonhemolytic Hyperbilirubinemias 786
  Viral Hepatitis 788
  Chronic Hepatitis 796
  Acute Liver Failure 801
  Fatty Liver 803
  Non-alcoholic Fatty Liver Disease 803
  Alcoholic Liver Disease 805
  Cirrhosis 806
  Portal Hypertension 813
  Hepatic Encephalopathy 820
  Ascites 825
  Drug and Toxin-induced Hepatitis 834
  Hepatic Venous Outflow Tract Obstruction 834
  Hepatocellular Carcinoma 836
  Liver Transplantation 838
  Liver Abscess 839
  Metabolic Liver Disease 841
  Biliary Cirrhosis 845
  Noncirrhotic Portal Fibrosis 847

12. PANCREAS 850
  Acute Pancreatitis 850
  Chronic Pancreatitis 856
  Pancreatic Cancer 859
  Endocrine Tumors of Pancreas 861
### 13. KIDNEY

- Functional Anatomy of Kidney 864
- Approach to Renal Diseases 865
- Acute Kidney Injury (Acute Renal Failure) 871
- Glomerulonephritis 879
- Nephrotic Syndrome 883
- Tubulointerstitial Diseases 888
- Renal Tubular Acidosis 888
- Chronic Kidney Disease 890
- Cystic Diseases of Kidney 897
- Obstructive Uropathy 898
- Nephrolithiasis 898
- Urinary Tract Infections 901
- Acute Pyelonephritis 905
- Chronic Pyelonephritis 906
- Tuberculosis of the Urinary Tract 907
- Renal Replacement Therapies 908
- Renal Transplantation 912

### 14. FLUID AND ELECTROLYTE DISTURBANCES

- Volume Depletion (Hypovolemia) 916
- Disorders of Sodium Balance 917
- Disorders of Potassium Balance 924
- Acid-Base Balance 928
- Edema 934

### 15. NEUROLOGY

- Weakness and Paralysis 937
- Vertigo 939
- Abnormal Speech and Language 941
- Apraxia 942
- Agnosia 943
- Dysarthrias 943
- Headache 944
- Stroke and Cerebrovascular Disease 949
- Cerebral Venous Thrombosis 963
- Demyelinating Diseases 964
- Multiple Sclerosis 964
- Seizures and Epilepsy 966
- Meningitis 978
- Encephalitis 983
- Diseases of the Spinal Cord 984
- Motor Neuron Diseases 992
- Neurogenic Bladder 995
- Diseases of the Peripheral Nervous System 997
- Guillain-Barré Syndrome 1000
- Myasthenia Gravis 1002
- Diseases of Muscle 1004
- Disorders of Cerebellar Function 1006
- Parkinson’s Disease 1008
- Chorea 1014
- Tremor 1015
- Coma 1016
- Brain Death 1021
- Diseases of Cranial Nerves 1022
- Bell’s Palsy 1029
- Intracranial Pressure 1030
- Tumors of the Nervous System 1033
- Miscellaneous 1034
- Lathyrysm 1036
16. TOXICOLOGY
Clinical Assessment of Ingested Poison 1037
Organophosphate and Carbamate Poisoning 1041
Organochlorine Poisoning 1045
Snakebite 1045
Scorpion Bite 1048
Sedative Drug Poisoning 1049
Analgesic Poisoning 1051
Cyanide Poisoning 1053
Neurotoxic Plant Poisons 1054
Cardiotoxic Plant Poisons 1054
Gastrointestinal Toxic Plant Poisons 1055
Opioid Poisoning 1055
Aluminium Phosphide Poisoning 1057
Rodenticide Poisoning 1057

17. ONCOLOGY
Hallmarks of Cancer 1058
Cancer Treatment 1059
Oncologic Emergencies 1064
Investigations in Oncology 1066
Paraneoplastic Syndromes 1068
Positron Emission Tomography 1069
Oncogenic Viruses 1070

18. PSYCHIATRY
Psycho Pharmacology 1072
Electroconvulsive Therapy 1075
Mood Disorders 1076
Psychotic Disorders 1079
Schizophrenia 1080
Anxiety Disorders 1083
Obsessive-Compulsive Disorder 1084
Somatof orm Disorders 1085
Psychosomatic Disorder 1085
Conversion Disorder 1085
Factitious Disorder 1085
Impulse Disorders 1086
Delirium 1086
Alcohol Misuse and Dependence 1088
Substance-Related Disorders 1091
Sleep Disorders 1092
Eating Disorders 1096
Puerperal Disorders 1098
Nipah Virus Encephalitis 1098

19. GENETICS
Common Genetic and Chromosomal Disorders 1099
Down Syndrome (Trisomy 21) 1101
Klinefelter’s Syndrome 1102
Turner’s Syndrome 1103
Mental Retardation/Insufficiency 1104
Inheritance 1104
Gene Therapy 1109
Human Genome Project 1110
Miscellaneous 1112
Polymerase Chain Reaction and its Applications 1114
Inborn Errors of Metabolism 1114
20. IMMUNOLOGY 1116
   Cytokines 1118
   Complement System 1119
   Immunodeficiency 1122
   Hypersensitivity Reactions 1125
   Autoimmunity 1131
   Transplantation Immunology 1133
   Immunomodulators 1134
   Adult Immunization 1136
   Amyloidosis 1139

21. GERIATRICS 1142
   Biology of Aging 1142
   Comprehensive Geriatric Assessment 1144
   Common Clinical Problems of Aging 1144
   Alzheimer's Disease 1146

22. DERMATOLOGY 1153
   Psoriasis 1154
   Lichen Planus 1157
   Acanthosis Nigricans 1158
   Eczema 1159
   Blistering (Bullous) Disorders of Skin 1162
   Reactive Disorders of Skin 1164
   Pigmentary Disorders of Skin 1166
   Skin Tumors 1169
   Phakomatoses 1171
   Disorders of Skin Appendages 1173
   Hair Disorders 1175
   Leg Ulcers 1176
   Xerostomia 1176
   Pruritus 1177
   Panniculitis 1177

23. CLINICAL PHARMACOLOGY 1179
   Adverse Drug Reaction 1179
   Drug Interaction 1181
   Drugs Used in Liver Disorder 1183
   Drugs Use in Kidney Disorders 1183
   Drugs Use in Pregnancy 1184
   Clinical Trials Basic Concepts 1184

24. EMERGENCIES IN MEDICAL PRACTICE 1188
   Management of Severe Hyperkalemia 1188
   Metabolic Acidosis 1189
   Hypoglycemia 1189
   Management of Acute Pulmonary Edema 1190
   Management of Severe Hypercalcemia 1190
   Tension Pneumothorax 1191
   Myxedema Coma 1191
   Thyrotoxic Crisis/Thyroid Storm 1192
   Acute Adrenal Insufficiency 1192
   Management of Status Epilepticus 1193
   Management of Coma 1193
   Management of Snake Bite 1194
   Management of Hypovolemia 1194
   Management of Shock 1194
   Ischemic Stroke 1195
   Hyperventilation 1196
   Acute Pulmonary Embolism 1196
Management of Hemoptysis 1196
Hypertensive Emergency/Crisis 1197
Severe Dehydration 1198
Management of Cardiac Arrest 1198
Management of Ventricular Fibrillation 1199
Upper Gastrointestinal Bleed 1199
Emergency Management of Acute Myocardial Infarction 1200
Organophosphate Poisoning 1200
Management of Anaphylaxis 1201
Management of Angina 1201
Management of Acute Severe Asthma 1202
Management of Diabetic Ketoacidosis 1203

APPENDICES 1205
Appendix 1: Laboratory Values of Clinical Importance and Routinely Used Formulae 1205
Appendix 2: Nervous System Examination Format 1211

BIBLIOGRAPHY 1219

INDEX 1221
Write short note on the normal arterial blood gas (ABG) levels.

Table 6.1 depicts normal arterial blood gas levels.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial oxygen tension (PaO₂)</td>
<td>90–104 mm Hg</td>
</tr>
<tr>
<td>Arterial carbon dioxide (PaCO₂)</td>
<td>35–45 mm Hg</td>
</tr>
<tr>
<td>Arterial oxygen saturation (SaO₂)</td>
<td>95 to 99%</td>
</tr>
<tr>
<td>Arterial blood pH (pH)</td>
<td>7.35–7.45 Units</td>
</tr>
<tr>
<td>Arterial bicarbonate (HCO₃⁻)</td>
<td>22–30 meq/L</td>
</tr>
<tr>
<td>Base excess (BE)</td>
<td>0 ± 2 mmol/L</td>
</tr>
</tbody>
</table>

Hypercapnic Encephalopathy

Write short essay/note on hypercapnic encephalopathy [Carbon dioxide (CO₂) narcosis].

**Definition**

- **Hypercapnia** is defined as a raised arterial carbon dioxide (PaCO₂) of 45 mm Hg (6 kPa) at rest.
- **Hypercapnic encephalopathy**: When PaCO₂ exceeds 90 mm Hg (12 kPa), severe hypercapnia causes confusion, progressive drowsiness and CO₂ narcosis.

**Causes of Hypercapnia (Table 6.2)**

Usually results from alveolar hypoventilation.

<table>
<thead>
<tr>
<th>Cause</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central depression of respiratory drive</td>
<td>Brain-stem lesions, Central sleep apnea, obesity hypoventilation, Sedatives: Morphone</td>
</tr>
<tr>
<td>Neuromuscular</td>
<td>Peripheral neuropathy, GB syndrome, poliomyelitis, Myasthenia gravis, Myopathies</td>
</tr>
</tbody>
</table>

**Clinical Features**

- **Headache**: Severe generalized or bilateral frontal or occipital headache (especially severe on waking up).
- **Depresses the level of consciousness**: Hypercapnia depresses the level of consciousness.
  - In mild cases, it produces intermittent drowsiness, indifference or inattention, reduction of psychomotor activity and forgetfulness.
– In severe cases, it causes mental dullness, drowsiness, confusion, seizures, stupor, and coma. If left untreated, acute hypercapnic respiratory failure can cause death.

**Signs (Box 6.1)**

**Investigations**

- **Arterial Blood Gas (ABG) study**: For confirmation of hypercapnia.
- **Other relevant investigations** depending on the underlying cause.

**Treatment**

- Mechanical ventilation with intermittent positive-pressure respirator. Non-invasive ventilation (NIV) may be sufficient in patients with mild symptoms. BiPAP: 8–12 cm H₂O (inspiratory pressure) and 3–5 cm H₂O (expiratory pressure).
- Treatment of the underlying cause. Respiratory stimulants (Doxapram, Medroxyprogesterone, Acetazolamide) are used with variable benefits.

**Precaution**: In chronic hypercapnia [e.g. chronic obstructive pulmonary disease (COPD)], oxygen should be administered in a controlled manner (about 2 L/minute) and morphine and other sedatives should be avoided.

**Hypoxemia**

**Definition**: Hypoxemia is defined as arterial oxygen tension (PaO₂) of less than 80 mm Hg (10.6 kPa) in a young healthy adult. As the age advances, the normal arterial oxygen tension (PaO₂) falls gradually.

### Causes of Hypoxemia (Table 6.3)

<table>
<thead>
<tr>
<th>Hypoventilation</th>
<th>Hypercapnia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central depression of respiratory drive: Brainstem lesions, central sleep apnea</td>
<td></td>
</tr>
<tr>
<td>Peripheral neuromuscular disease: Myasthenia gravis peripheral, neuropathy, myasthenia gravis, myopathies</td>
<td></td>
</tr>
<tr>
<td>Malfunctioning of mechanical ventilators</td>
<td></td>
</tr>
</tbody>
</table>

### Decreased inspired oxygen concentration

- High altitudes
- Malfunctioning of mechanical ventilators

Hypoxemia is rare due to reduced diffusion.

**Clinical Features**

- **Acute hypoxemia**: It closely resembles acute alcoholism and is characterized by impaired judgment and motor incoordination. On examination patient has tachypnea, cyanosis, cold peripheries, thready pulses, hypotension.
- **Chronic hypoxemia**: Of long-standing duration presents with fatigue, drowsiness, inattentiveness, apathy, delayed reaction time and reduced work capacity.
- **Consequences**: Centers in the brainstem gets affected and death may occur due to respiratory failure.

**Investigations**

- **Arterial Blood Gas (ABG) study**: For confirmation of hypoxemia.
- **Calculate the alveolar-arterial O₂ (PAO₂-PaO₂) gradient**: To differentiate various causes of hypoxemia.

**Treatment**: Treat the underlying cause or mechanism.

**Clubbing**

**Definition**: Clubbing (also called Hippocrates fingers) is defined as a selective bulbus enlargement of the distal segment of a digit (fingers and toes) due to an increase in connective tissue especially on the dorsal aspect resulting in loss of the onychonychial angle (Figs. 6.1A and B).
Mechanisms

Some of hypotheses are:

- **Role of platelets**: Megakaryocytes from the bone marrow normally break up to the platelets in the pulmonary capillaries. Whenever there are shunts or abnormal circulation (e.g. neoplasm), these megakaryocytes bypass the pulmonary capillaries and reach the systemic circulation. These megakaryocytes preferably lodge in the tips of the digits and locally release platelet derived growth factor (PDGF) and vascular endothelial growth factor (VEGF). These growth factors along with other mediators increase endothelial permeability and activate and cause proliferation of connective tissue cells (e.g. fibroblasts).

- **Humoral**: Unknown humoral substances dilate vessels in the fingertips (e.g. acromegaly)

- **Persistent hypoxia**: Causes opening of deep arteriovenous fistula in fingers (e.g. tetralogy of Fallot).

- **Reduced ferritin** in systemic circulation: Causes dilation of arteriovenous anastomoses.

- **Vagal theory**: Persistent vagal stimulation causes vasodilation and clubbing (e.g. lung carcinoma).

- **Toxic**: Subacute bacterial endocarditis (SABE).

- **Metabolic**: Thyrotoxicosis.

Grades of Clubbing (Table 6.4)

The process of clubbing usually takes years but in few conditions (e.g. lung abscess, empyema), it may develop quite fast.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Increased fluctuation due to softening of the nail bed (increased ballotability)</td>
</tr>
<tr>
<td>2</td>
<td>Loss of the normal &lt;165° onychodermal angle (Lovibond angle) between the nail bed and the nail fold (cuticula)</td>
</tr>
<tr>
<td>3</td>
<td>Thickening of the whole distal (end part of the) finger (resembling a parrot beak or drumstick)</td>
</tr>
<tr>
<td>4</td>
<td>Hypertrophic osteoarthropathy (Pain and tenderness at distal end of long bones due to subperiosteal new bone formation)</td>
</tr>
</tbody>
</table>

Causes (Table 6.5): Clubbing may be hereditary, idiopathic, or acquired and associated with a variety of disorders. Various methods of eliciting clubbing are listed in Box 6.2.

<table>
<thead>
<tr>
<th>Respiratory</th>
<th>Respiratory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neoplasms: Bronchogenic carcinoma (especially squamous cell carcinoma), metastasis to lung, mesothelioma</td>
<td></td>
</tr>
<tr>
<td>Suppurative lung disease: Bronchiectasis, lung abscess, cystic fibrosis, empyema</td>
<td></td>
</tr>
<tr>
<td>Asbestosis (with mesothelioma)</td>
<td></td>
</tr>
<tr>
<td>Sarcoïdosis</td>
<td></td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td></td>
</tr>
<tr>
<td>Pulmonary AV fistula</td>
<td></td>
</tr>
<tr>
<td>Interstitial lung diseases</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cardiovascular</th>
<th>Cardiovascular</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infective endocarditis</td>
<td></td>
</tr>
<tr>
<td>Cyanotic congenital heart diseases, atrial myxoma, Eisenmenger’s syndrome</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gastrointestinal</th>
<th>Gastrointestinal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inflammatory bowel disease (ulcerative colitis and Crohn’s disease)</td>
<td></td>
</tr>
<tr>
<td>Primary biliary cirrhosis</td>
<td></td>
</tr>
<tr>
<td>Hepatoma</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Miscellaneous</th>
<th>Miscellaneous</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Hereditary, idiopathic (pachydermoperiostitis or Touraine-Solente-Golé syndrome)</td>
<td></td>
</tr>
<tr>
<td>- Unidigital clubbing occurs in repeated trauma</td>
<td></td>
</tr>
</tbody>
</table>

Unilateral Clubbing

- Hemiplegia (long standing)

Vascular disease

- Aneurysm: Subclavian artery, brachiocephalic trunk
- Pre-subclavian coarctation of aorta (left-sided clubbing)
- Pancoast tumor
- Unilateral erythromelalgia
- AV fistula used for hemodialysis
- Infected arterial graft

Phalangeal depth ratio: It is defined by the ratio of digit’s depth measured at the junction between skin and nail (nail bed) and at the distal interphalangeal joint. Normally, the depth at distal interphalangeal joint is more than the depth at nail bed. In clubbing fingers, there is reversal of this ratio. A phalangeal depth ratio of over 1 indicates clubbing. It can be measured by a caliper or a digital photograph.
Pseudoclubbing: It is an increase in longitudinal curvature of the nail with loss of nail and nail plate material. It is characterized clinically by asymmetrical involvement of fingers and radiographically by resorption of the terminal tufts (acro-osteolysis). There is no over-growth of connective tissue as observed in clubbing.

Causes of pseudoclubbing: (1) Subungual tumor or cyst and (2) subperiosteal bone resorption (e.g., scleroderma, thyroid acropathy, vinyl chloride poisoning, acromegaly, hyperparathyroidism, leprosy, chronic renal failure, acrometastasis, etc.).

Primary hypertrophic osteoarthropathy (PHO), a rare hereditary disorder with digital clubbing, subperiosteal new bone formation, and arthropathy. It is associated with mutations in the 15-hydroxy-prostaglandin dehydrogenase (15-PGDH).

Abnormalities in Nails due to Systemic Diseases (Table 6.6)

Write short note/essay on abnormalities in nails due to systemic diseases.

Table 6.6: Abnormalities in nails due to systemic diseases.

<table>
<thead>
<tr>
<th>Abnormality and description</th>
<th>Associated systemic disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SHAPE OR GROWTH CHANGE</strong></td>
<td></td>
</tr>
<tr>
<td>Clubbing</td>
<td>Discussed above (Table 6.5)</td>
</tr>
<tr>
<td>Koilonychia: Spoon-shaped nails (transverse and longitudinal concavity)</td>
<td>Iron deficiency anemia, rarely in hemochromatosis, Raynaud's disease, SLE, hypothyroidism or hyperthyroidism</td>
</tr>
<tr>
<td>Pitting: Punctate depressions in nails</td>
<td>Psoriasis, Reiter's syndrome, pemphigus, lichen planus, alopecia areata, rheumatoid arthritis</td>
</tr>
<tr>
<td>Onycholysis: Distal nail plate separated from nail bed, white discoloration of the affected part of the nail</td>
<td>Psoriasis, local infection, hyperthyroidism, sarcoidosis, trauma, amyloidosis, connective tissue disorders, pellagra</td>
</tr>
<tr>
<td>Beau's lines: Transverse linear depressions over nails, move distally with the growth of nail</td>
<td>Any severe systemic illness that disrupts nail growth, Raynaud's disease, pemphigus, trauma</td>
</tr>
<tr>
<td>Onychomadesis: Proximal separation of nail plate from nail bed</td>
<td>Trauma, drug sensitivity, poor nutrition, pemphigus vulgaris, Kawasaki disease</td>
</tr>
<tr>
<td>Yellow nails: Nail has a 'heaped-up' or thickened appearance, yellow in color, with obliteration of lunula</td>
<td>Lymphedema, pleural effusion, immunodeficiency, bronchiectasis, sinusitis, rheumatoid arthritis, nephrotic syndrome, thyroiditis, tuberculosis, Raynaud's disease</td>
</tr>
<tr>
<td><strong>COLOR CHANGE</strong></td>
<td></td>
</tr>
<tr>
<td>Terry's (white) nails: Most of the nail plate turns white with obliteration of lunula, uniformly affects all nails</td>
<td>Liver failure, cirrhosis, diabetes mellitus, CHF, hyperthyroidism, malnutrition</td>
</tr>
<tr>
<td>Half-and-half nails (Lindsay's nails): Proximal portion of nail bed is white because of nail-bed edema (half-brown, half-white appearance)</td>
<td>Renal failure, HIV infection, Crohn's disease</td>
</tr>
<tr>
<td>Azure lunula (blue nails)</td>
<td>Hepatolenticular degeneration (Wilson's disease), silver poisoning, quinacrine therapy</td>
</tr>
<tr>
<td>Mees' lines: Transverse white bands affecting multiple nails, move distally with nail growth</td>
<td>Arsenic poisoning, Hodgkin's lymphoma, CHF, leprosy, malaria, chemotherapy</td>
</tr>
</tbody>
</table>

Box 6.2: Various methods of eliciting the signs of clubbing.

1. Lovibond's profile sign (Fig. 6.2A)
2. Curth's modified profile sign (Fig. 6.2B)
3. Fluctuation test
4. Schamroth's window test (Fig. 6.2C)
5. Phalangeal depth ratio

Figs. 6.2A to C: Various signs of clubbing.
### Abnormality and description

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Associated systemic disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Muehrcke's lines</strong></td>
<td>Specific for hypoalbuminemia of any cause</td>
</tr>
<tr>
<td><strong>Dark longitudinal streaks</strong></td>
<td>Melanoma, benign nevus, chemical staining, normal variant in darkly pigmented people</td>
</tr>
<tr>
<td><strong>Splinter hemorrhage</strong></td>
<td>Subacute bacterial endocarditis, SLE, rheumatoid arthritis, peptic ulcer disease, malignancies, oral contraceptive use, pregnancy, psoriasis, trauma</td>
</tr>
<tr>
<td><strong>Telangiectasia</strong></td>
<td>Rheumatoid arthritis, SLE, dermatomyositis, scleroderma</td>
</tr>
<tr>
<td><strong>Longitudinal striations</strong></td>
<td>Alopecia areata, vitiligo, atopic dermatitis, psoriasis</td>
</tr>
</tbody>
</table>

### Cyanosis (Fig. 6.3)

**Definition:** Bluish discoloration of the skin and mucous membrane. It results from an increased concentration of reduced hemoglobin/deoxyhemoglobin (>5 g/dL) or abnormal hemoglobin derivatives (e.g. methemoglobin, sulphydrylhemoglobin, etc.) in the capillary blood perfusing the area. Cyanosis is normally detected when the oxygen saturation (SaO₂) is <85%.

**Types of Cyanosis (Table 6.7)**

<table>
<thead>
<tr>
<th>Features</th>
<th>Central cyanosis</th>
<th>Peripheral cyanosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mechanism</strong></td>
<td>Inadequate oxygenation of systemic arterial blood (hypoxic hypoxia)</td>
<td>Sluggish peripheral circulation (stagnant hypoxia)</td>
</tr>
<tr>
<td><strong>Sites to look</strong></td>
<td>Tongue and oral mucosa</td>
<td>Acral: Tip of the nose, ear lobules, outer aspect of lips, finger tips, nail bed, extremities</td>
</tr>
<tr>
<td><strong>Associations</strong></td>
<td>Clubbing, polycythemia</td>
<td></td>
</tr>
<tr>
<td><strong>Extremities</strong></td>
<td>Warm</td>
<td>Cold</td>
</tr>
<tr>
<td><strong>Warming extremities</strong></td>
<td>No change</td>
<td>Cyanosis disappears</td>
</tr>
<tr>
<td><strong>Oxygen inhalation</strong></td>
<td>Slight improvement</td>
<td>No change</td>
</tr>
<tr>
<td><strong>ABG PaO₂</strong></td>
<td>Low &lt;85%</td>
<td>Normal 85–100%</td>
</tr>
<tr>
<td><strong>Pulse volume</strong></td>
<td>May be high</td>
<td>Usually low</td>
</tr>
<tr>
<td><strong>Dyspnea</strong></td>
<td>Usually present</td>
<td>Usually absent</td>
</tr>
<tr>
<td><strong>Exercise</strong></td>
<td>Worsens</td>
<td>May improve</td>
</tr>
</tbody>
</table>

**Causes of Cyanosis**

**Central cyanosis**

- **Cardiac**
  - Congenital cyanotic heart diseases (*Remember 5 'T's and 2 'E's'*): Transposition of great arteries, tetralogy of Fallot, truncus arteriosus, tricuspid valve abnormalities, total anomalous pulmonary venous return (TAPVR), Eisenmenger’s syndrome (cyanosis tardive) and Ebstein’s anomaly.
  - Acute pulmonary edema (due to left-sided heart failure).
- **Pulmonary**: Acute severe asthma, COPD, cor pulmonale, respiratory failure, respiratory depression, lobar and bronchopneumonia, tension pneumothorax, acute laryngeal edema, acute pulmonary embolism
- **High altitude** (due to low partial pressure of oxygen)
- **Polycythemia**
- **Enterogenous or pigment cyanosis**: Methemoglobinemia and sulphydrylhemoglobinemia.

**Peripheral cyanosis**

- **Low cardiac output**: Congestive heart failure.
- **Local vasoconstriction**: Cold, frostbite, Raynaud’s phenomenon, shock.
- **Arterial obstruction**: Peripheral vascular diseases (atherosclerosis, Buerger’s disease).
- **Venous obstruction**: Superior vena cava syndrome.
- **Hyperviscosity syndrome**: Multiple myeloma, polycythemia, macroglobulinemia.
- **Others**: Cryoglobulinemia, mitral stenosis.
Mixed cyanosis
- All causes of central cyanosis may also cause peripheral cyanosis
- Cardiogenic shock with pulmonary edema
- Congestive cardiac failure due to left sided heart failure
- Polycythemia (rarely).

Differential cyanosis: Cyanosis only in lower limbs seen in PDA with reversal of shunt.

Cyanosis only in upper limbs (reverse differential cyanosis): Coarctation of aorta (ductal type) with transposition of great arteries.

Cyanosis in left upper limb and both lower limbs: PDA with reversal of shunt and preductal coarctation of aorta

Intermittent cyanosis: Ebstein’s anomaly

Cyclical cyanosis: Bilateral choanal atresia

Orthocyanosis: Development of cyanosis only in upright position due to hypoxia occurring in erect posture. Seen in pulmonary arterio-venous malformation.

Cyanosis absent despite of sufficient reduced hemoglobin: In severe anemia, carbon monoxide poisoning.

Hyperoxia test (Cardiac vs Pulmonary cyanosis): After giving 100% oxygen for 10 minutes, a repeat ABG is done and if PaO₂ is <150 mm Hg then the cause is cardiac and if the PaO₂ improves to >200 mm Hg, the cause is respiratory.

Pseudocyanosis: Caused by metals (gold, silver, mercury, arsenic) and drugs (minocycline, phenothiazines, chloroquine, amiodarone).

Respiratory (Pulmonary) Function Tests (Table 6.8)

Q. Write short note on pulmonary function tests and give their clinical significance.
Q. Write short note on FEV₁ (Forced expiratory volume in one second).

### Table 6.8: Pulmonary function test (PFT).

<table>
<thead>
<tr>
<th>PFT Tracings have:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Four lung volumes</strong>: Tidal volume, inspiratory reserve volume, expiratory reserve volume, and residual volume</td>
</tr>
<tr>
<td><strong>Five capacities</strong>: Inspiratory capacity, expiratory capacity, vital capacity, functional residual capacity, and total lung capacity</td>
</tr>
<tr>
<td><strong>Flow-volume curves</strong></td>
</tr>
<tr>
<td><strong>Blood gases and pulse oximetry</strong></td>
</tr>
<tr>
<td><strong>Transfer factor (diffusion)</strong></td>
</tr>
<tr>
<td><strong>Exercise tests</strong></td>
</tr>
<tr>
<td><strong>Exhaled nitric oxide</strong></td>
</tr>
</tbody>
</table>

Abbreviations used in pulmonary function tests are presented in Table 6.9.

### Table 6.9: Abbreviations used in pulmonary function tests.

<table>
<thead>
<tr>
<th>Abbreviations</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC (Forced vital capacity)</td>
<td>Volume of air expired with a maximal effort after deep inspiration</td>
</tr>
<tr>
<td>FEV₁ (Forced expiratory volume in one second)</td>
<td>Volume of air expired in the first second after deep inspiration</td>
</tr>
<tr>
<td>VC (Vital capacity)</td>
<td>Maximum amount of air that can be expelled from the lungs after the deepest possible breath. TLC minus RV or maximum volume of air exhaled from maximal inspiratory level (60–70 mL/kg) (3100–4800 mL). VC decreases with age</td>
</tr>
<tr>
<td>PEF (Peak expiratory flow)</td>
<td>Volume of forcibly expired air during the first 10 seconds after deep inspiration</td>
</tr>
<tr>
<td>TLC (Total lung capacity)</td>
<td>Sum of all volume compartments or volume of air in lungs after maximum inspiration (4–6 L)</td>
</tr>
<tr>
<td>FRC (Functional residual capacity)</td>
<td>Sum of RV and ERV or the volume of air in the lungs at end-expiratory tidal position (30–35 mL/kg (2300–3300 mL)). Measured with multiple-breath closed-circuit helium dilution, multiple-breath open-circuit nitrogen washout, or body plethysmography. It cannot be measured by spirometry.</td>
</tr>
<tr>
<td>RV (Residual volume)</td>
<td>Volume of air remaining in lungs after maximum exhalation (20–25 mL/kg (1700–2100 mL)). It cannot be measured by spirometry. RV increases with age</td>
</tr>
<tr>
<td>IRV (Inspiratory reserve volume)</td>
<td>Maximum volume of air inhaled from the end-inspiratory tidal position (1900–3300 mL)</td>
</tr>
<tr>
<td>ERV (Expiratory reserve volume)</td>
<td>Maximum volume of air that can be exhaled from resting end-expiratory tidal position (700–1000 mL)</td>
</tr>
<tr>
<td>TV (Tidal volume)</td>
<td>Volume of air inhaled or exhaled with each breath during quiet breathing (6–8 mL/kg)</td>
</tr>
</tbody>
</table>

Contd...
**Measurement of Airway Obstruction (Fig. 6.4)**

**Ventilatory capacity**

Ventilatory capacity include **FEV₁** (volume of air expired in the first second after deep inspiration) and **FVC** (volume of air expired with a maximal effort after deep inspiration) and **PEF** (peak expiratory flow rate).

Normally, FEV₁/FVC ratio is around 75%.

**Patterns of abnormalities:**

i. **Obstructive ventilatory defect:** It is characterized by narrowing of airways during expiration (e.g. bronchial asthma, chronic bronchitis and emphysema). These disorders show **markedly reduced FEV₁**, **reduced or normal VC and reduced FEV₁/VC**. In airflow limitation, the FEV₁ is reduced as a percentage of FVC. With increasing airflow limitation FEV falls proportionately more than FVC, so the FEV₁/FVC ratio is reduced.

- **Reversibility of airflow limitation:** When FEV₁ is disproportionately reduced resulting in FEV₁/FVC ratios of less than 70%; spirometry should be repeated following inhaled short-acting β₂-adrenoceptor agonists (e.g. salbutamol). A large improvement in FEV₁ (over 400 mL) is seen in bronchial asthma and, to some extent, in chronic bronchitis.

ii. **Restrictive ventilatory defect:** In restrictive lung disease, **FEV₁ and FVC are reduced proportionately and the FEV₁/FVC ratio may be normal** or may even increase because of enhanced elastic recoil. This pattern is seen in interstitial inflammation and/or fibrosis that lead to progressive loss of lung volume.

**Peak expiratory flow rate (PEFR):**

- Peak flow meters are cheap and simpler than spirometer. Patient is asked to take a full inspiration to total lung capacity and then blow out forcefully into the peak flow meter. PEFR measures the volume of forcibly expired air during the first 10 seconds after deep inspiration. Reduced values are found in airflow obstruction and are not useful in assessing restrictive ventilatory defect. It is mainly useful for diagnosis, to monitor exacerbations and response to treatment in asthma.

**Lung volumes**

Lung volumes include total lung capacity (TLC) and residual volume (RV). Both can be measured by spirometry.

- **Total lung capacity** (TLC—the total amount of air in the lungs after taking the deepest breath possible).
- **Vital capacity (VC)** is the maximum amount of air that can be expelled from the lungs after the deepest possible breath is recorded separately. Patient is asked to make a full but unhurried (‘relaxed’) exhalation into the spirometer.
- **Residual volume (RV)** is the volume of air in the lungs at the end of full expiration. It is calculated by subtracting the VC (vital capacity) from the TLC (total lung capacity).

**Interpretation:**

- In obstructive lung disease, both TLC and RV are increased.
- In restrictive lung diseases (due to parenchymal lung disease), both TLC and RV are reduced.
- Extraparenchymal diseases with restriction during both inspiration and expiration (ankylosing spondylitis, kyphoscoliosis), RV is increased while TLC is reduced.

**Flow volume loops (Table 6.10 and Fig. 6.5)**

Flow volume loops measure flow rates against expired volume and shows the site of airflow limitation (obstruction) within the lung. At the start of expiration from TLC, maximum resistance is from the large airways. This affects the flow rate for the...
first 25% of the curve. As air is exhaled, lung volume reduces and the flow rate depends on the resistance offered by smaller airways.

- **FEV**$_1$ is the volume exhaled during the first second of the FVC maneuver. **Decreased in both obstructive and restrictive lung disorders.**
- **FEF 25–75%** is the mean expiratory flow during the middle half of the FVC maneuver; reflects flow through the small (<2 mm in diameter) airways.
- Interpretation of percent predicted: Normal (>79%), mild obstruction (60–79%), moderate obstruction (40–59%), severe obstruction (<40%).
- **FEV**$_1$/FVC is the ratio of FEV$_1$ to FVC × 100 (expressed as a percent); an important value because a reduction of this ratio from expected values is specific for obstructive rather than restrictive diseases. Normal value (FEV$_1$/FVC) is 75–85 %, <70% of predicted value in mild obstruction, <60% of predicted value in moderate obstruction and <50% of predicted value in severe obstruction.

**Spirometry Interpretation:** Obstructive versus restrictive defect (Table 6.11).

**Arterial blood gases (ABG) and oximetry** (refer Table 6.1)
These tests include measurement of (i) hydrogen ion (H$^+$) concentration, (ii) $P_{aO_2}$ and $P_{aCO_2}$, and (iii) oxygen saturation and bicarbonate concentration (derived from the above values) in an arterial blood. These are performed by automatic analyzers.

**Uses:** (1) To assess the degree and type of respiratory failure (for management of status asthmaticus and acute respiratory distress syndrome—ARDS) and (2) for measuring acid-based status.

**Tests for Gas Exchange Function**

a. **Alveolar-arterial $O_2$ tension gradient:**
- Sensitive indicator of detecting regional V/Q inequality
- It is the difference between the amount of the oxygen in the alveoli [i.e. the alveolar oxygen tension ($P_{aO_2}$)] and the amount of oxygen dissolved in the plasma ($P_{aO_2}$).

<table>
<thead>
<tr>
<th>Disease states</th>
<th>FVC</th>
<th>FEV$_1$</th>
<th>FEV$_1$/FVC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obstructive</td>
<td>Normal</td>
<td>Reduced</td>
<td>Reduced</td>
</tr>
<tr>
<td>Stiff lungs</td>
<td>Reduced</td>
<td>Reduced</td>
<td>Normal</td>
</tr>
<tr>
<td>Respiratory muscle weak</td>
<td>Reduced</td>
<td>Reduced</td>
<td>Normal</td>
</tr>
</tbody>
</table>

---

**Fig. 6.5:** Flow volume loop for common respiratory diseases.

**Table 6.10:** Flow volume loops in various disorders.

Disease states | FVC   | FEV$_1$ | FEV$_1$/FVC |
---------------|-------|---------|-------------|
Obstructive    | Normal| Reduced | Reduced     |
Stiff lungs    | Reduced| Reduced | Normal      |
Respiratory muscle weakness | Reduced| Reduced | Normal |
b. Dyspnea differentiation index (DDI):
   - To differentiate dyspnea due to respiratory/cardiac diseases
     \[
     DDI = \frac{PEFR \times PaCO_2}{1000}
     \]
   - DDI-Lower in respiratory pathology

c. Diffusing capacity of lung (DL): Defined as the rate at which gas enters into blood divided by its driving pressure.
   - The diffusing capacity for carbon monoxide (DLCO) is also known as the transfer factor. It measures the ability of the lungs to transfer gas from inhaled air in the alveoli to the red blood cells in pulmonary capillaries.
   - Diseases associated with reduced and increased gas transfer are listed in Table 6.12.

Tests for Cardiopulmonary Interactions
- Reflects gas exchange, ventilation, tissue O₂, CO₂.
- Qualitative: History, examination, ABG, stair climbing test
- Quantitative: 6 minute walk test.
  1. Stair climbing test: If able to climb 3 flights of stairs without stopping/dyspnea at his/her own pace-reduced morbidity and mortality. If not able to climb 2 flights: High-risk.
  2. 6 minute walk test: Gold standard. Cardiopulmonary reserve is measured by estimating maximum O₂ uptake (VO₂ Max) during exercise. Modified if patient cannot walk—bicycle/arm exercises. If patient is able to walk for >2000 feet during 6 min period VO₂ max >15 mL/kg/min, if 1080 feet in 1 min: VO₂ of 12 mL/kg/min. Simultaneously oximetry is done and if SpO₂ falls >4% high-risk.

Exhaled Nitric Oxide
- Nitric oxide is produced by the bronchial epithelium. Its production increases in asthma and other diseases associated with inflammation of airway.
- Measurement of exhaled NO may be helpful in asthma that is difficult to control. Measuring fractional exhaled nitric oxide (FeNO) helps to identify patients who are likely to benefit from treatment with corticosteroids. FeNO also predicts the likelihood of steroid responsiveness more consistently than spirometry, bronchodilator response, peak flow variation, or airway hyperresponsiveness to methacholine. A FeNO greater than 50 ppb in adults or greater than 35 ppb in children suggests eosinophilic airway inflammation.

BRONCHIAL ASTHMA

Define and classify bronchial asthma. Discuss the etiology, pathophysiology, clinical features, investigations, diagnosis, complications and management/treatment of bronchial asthma.

Definition
Definition: Asthma is a chronic inflammatory disorder of the airways (bronchial tree) in which breathing is periodically rendered difficult by widespread narrowing of the bronchi (reversible bronchoconstriction).
- It is clinically, characterized by recurrent episodes (paroxysms) of wheezing, breathlessness (dyspnea), tightness of the chest, and cough.

<table>
<thead>
<tr>
<th>Table 6.11: Spirometry interpretation—obstructive versus restrictive defect.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Obstructive disorders</strong></td>
</tr>
<tr>
<td>Limitation of expiratory airflow as airways cannot empty as rapidly compared to normal (e.g. narrowed airways from bronchospasm, inflammation, etc.)</td>
</tr>
<tr>
<td>• FVC normal or ↓</td>
</tr>
<tr>
<td>• FEV₁ (significantly decreased)</td>
</tr>
<tr>
<td>• FEV₁/FVC ↓ (&lt;0.7)</td>
</tr>
<tr>
<td>• TLC normal or ↑</td>
</tr>
<tr>
<td>Examples: Asthma, emphysema, cystic fibrosis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 6.12: Diseases associated with reduced and increased DLCO.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Reduced DLCO</strong> (ventilation is in excess of blood flow (a high VQ, - DEAD SPACE- “wasted air”))</td>
</tr>
<tr>
<td>• Emphysema, lung resection, pulmonary embolism, anemia</td>
</tr>
<tr>
<td>• Pulmonary fibrosis, sarcoidosis—increased thickness</td>
</tr>
</tbody>
</table>

Examples: Asthma, emphysema, cystic fibrosis

Examples: Interstitial fibrosis, scoliosis, obesity, lung resection, neuromuscular diseases, cystic fibrosis
Risk Factors

Endogenous factors
- Genetic predisposition: Major etiological factor in atopic asthma is genetic predisposition to type I hypersensitivity (atopy) reaction and exposure to environmental trigger. One of the susceptibility locus is on the chromosome 5 (5q) → several genes involved in regulation of IgE synthesis and mast cell and eosinophil growth and differentiation.
- Atopy: Atopic individuals tend to have higher serum IgE levels, and a positive family history of allergy is found in 50% of atopic individuals. Patients with asthma commonly suffer from other atopic diseases (e.g, allergic rhinitis, atopic dermatitis/eczema).
- Airway hyperresponsiveness: It is an abnormality in which there is excessive tendency for airways to contract (bronchoconstrictor) too easily in response to multiple inhaled triggers that usually does not have any effect on normal individuals.
- Gender and age: More common in boys than girls and, after puberty, women slightly more commonly than men. Most cases begin before the age of 25 years.

Environmental factors

Hygiene Hypothesis proposes that individuals with lack of infections in early childhood are more prone to asthma than children brought up on farms who are exposed to a high level of endotoxin. Intestinal parasite infection may also be associated with a decreased risk of asthma. Conversely, early childhood in a 'dirtier' environment (exposure to inhaled and ingested products of microorganisms) may allow the immune system to avoid developing allergic responses.

Pathogenesis (Pathophysiology) of Asthma

A. Airway inflammation
- Inflammation is chronic and involves many cell types and inflammatory mediators.
- Strong Th2 response: Genetic predisposition with susceptibility genes makes individuals prone to develop strong Th2 (type of T lymphocytes) reactions against environmental antigens (allergens).
- Th2 cells secrete cytokines: Which promote allergic inflammation and stimulate B cells to produce IgE.

Cells involved in the inflammatory response
Important cells involved in asthma are: Mast cells, eosinophils, dendritic cells (macrophages) and lymphocytes.
1. Mast cells
   - Early reaction is characterized by bronchoconstriction, increased mucus production, and vasodilation with increased vascular permeability (causes edema).
   - Late phase reaction: It is characterized by inflammation and airway remodeling.
2. Eosinophils
   - Mediators release from eosinophils: LTC4, and basic proteins such as major basic protein (MBP), eosinophil cationic protein (ECP) and eosinophils peroxidase (EPX). They are toxic to epithelial cells.
   - Corticosteroid rapidly decreases the number and reduces the activation of eosinophils.
   - Sputum eosinophilia is of diagnostic help and is a biomarker of response to therapy.
3. Dendritic cells and lymphocytes.
   They release prostaglandin, thromboxane, LTC4, LTB4 and platelet activating factor (PAF).

B. Airway Remodeling

Airway remodeling is the group of structural and functional changes in the bronchial wall due to repeated bouts of inflammation observed in chronic asthma.
- An increase in size and number (hypertrophy/hyperplasia) of the submucosal glands
- Hypertrophy and/or hyperplasia of the bronchial wall smooth muscle
- Increased vascularity
- Deposition of subepithelial collagen accompanied by fibrosis and thickening of the basement membrane.

Pathogenesis of asthma is summarized in Figure 6.6.
Clinical Features

Q. Write a short note on the clinical presentation of severe acute asthma (status asthmaticus).

- Clinical features are studied under three headings namely (1) episodic, (2) severe acute (status asthmaticus), and (3) chronic asthma.
- Usually, atopic individuals develop episodic asthma and non-atopic individuals develop chronic asthma.

1. Episodic Asthma

- Occurs as episodes with asymptomatic between asthmatic attacks.
- Frequency and duration of attacks vary.
- Present with relatively sudden onset of paroxysms of wheezing and dyspnea.
- May develop spontaneous or triggered by allergens, exercise or viral infections.
- It may be mild to severe and may last for hours, days or even weeks.

2. Severe Acute Asthma (Status Asthmaticus)

- It is the most severe form of asthma in which the severe acute paroxysm persists for days and even weeks.
- Presents with severe dyspnea and unproductive cough.
- During this attack, patients prefer an upright position fixing the shoulder girdle to assist the accessory muscles of respiration.
- Physical signs include sweating, central cyanosis, tachycardia and pulsus paradoxus. The bronchoconstriction and asthmatic symptoms does not respond despite the initial administration of standard acute asthma therapy.
- It may cause severe airflow obstruction leading to severe cyanosis and even death.

3. Chronic Asthma

- Chronic persistent symptoms and include chest tightness, wheeze and breathlessness on exertion.
- Characterized by episodes of spontaneous cough and wheeze worst during the night.
- Chronic productive cough with mucoid sputum, punctuated by recurrent attacks of purulent expectoration from frank infection. They are prone to repeated attacks of ‘severe acute asthma.’ Features sometimes resemble those of chronic bronchitis.

Physical Signs

- During an attack:
  - Inspection: Increased respiratory rate with use accessory muscles of respiration.
  - Percussion: Hyperresonant percussion note over the lungs.
  - Auscultation
    - Breath sounds are vesicular with prolonged expiration.
    - High-pitched polyphonic expiratory and inspiratory rhonchi.
    - Very severe attacks may results in a silent chest which is ominous sign.
- In between the attacks: Chest may not reveal any abnormal physical signs.
- Chronic asthmatics: Usually reveal few scattered rhonchi.

Table 6.16 shows classification of asthma severity and initiating treatment in persons ≥ years of age.

Various Causes of Wheeze (Box 6.3)

Q. Write short essay/note on wheeze and its causes.

Investigations

The diagnosis is mainly clinical and based on a characteristic history. There is no single satisfactory diagnostic test for asthma.

1. Lung Function Tests

Pulmonary function tests useful in asthma are FEV₁, VC and PEFR.
- Spirometry: It is useful, especially in assessing reversibility. Simple spirometry useful in confirming the airflow limitation with a reduced FEV₁, FEV₁/FVC ratio, and PEF. Asthma can be diagnosed if there is greater than 15% improvement in FEV₁ or PEF following the inhalation of a bronchodilator.
- Peak expiratory flow rate (PEFR): It is useful in demonstrating the variable airflow limitation. PEFR measurements to be done on waking, prior to taking a bronchodilator and before bed after a bronchodilator. The diurnal variation in PEFR of more than 20% (the lowest values typically being recorded in the morning) is considered diagnostic. It is also provides good measure of disease severity.
Carbon monoxide (CO) transfer test: Increased in asthma.

Exercise tests: It used in the diagnosis of asthma in children. The child is asked to run for 6 minutes on a treadmill (heart rate should be above 160 beats per minute). A negative test does not rule out asthma.

Airway Responsiveness (AHR): AHR is sensitive but nonspecific. Histamine or methacholine bronchial provocation test:

- To detect the presence of airway hyperresponsiveness (a feature of asthma).
- Useful in patients whom cough is the only/main symptom and is useful in the differential diagnosis of chronic cough.
- Contraindicated on individuals who have poor lung function (FEV < 1.5 L) or a history of ‘brittle’ asthma.

Indirect challenge tests release of endogenous mediators that cause the contraction of airway smooth muscle. These include exercise eucapnic voluntary hyperpnea (EVH), ultrasonically nebulizer hypertonic saline and dry-powder mannitol.

2. Imaging

- Chest X-ray
  - Usually normal between attacks without any diagnostic features.
  - During an acute episode or in chronic severe disease there may hyperinflated lungs (overinflation).
  - May be helpful in excluding complications such as pneumothorax, lobar collapse (if mucus occludes large bronchus) or in detecting the pulmonary infiltrates associated with allergic bronchopulmonary aspergillosis.
- High-resolution computed tomography (CT): May show areas of bronchiectasis (complication) and thickening of the bronchial walls, but these changes are not diagnostic of asthma.

3. Measurement of Allergic Status

- Skin prick tests (SPT): SPT is performed by intradermal injections of common allergens (house dust mite, cat fur, grass pollen) and checking the development of a wheal and flare reaction. They are positive in allergic asthma and negative in intrinsic asthma.
- Elevated serum IgE levels: Measurement of total and allergen-specific IgE in serum may be seen.
4. **Blood and Sputum Tests**
   - Patients with asthma may show increased numbers of eosinophils (eosinophilia) in peripheral blood (>0.4 x 10⁹/L) but sputum eosinophils is a more specific diagnostic finding. Sputum examination may reveal Curschmann spirals, Creola bodies and Charcot-Leyden crystals. **Serum periostin** is also a marker of Th2 associated airway inflammation and a better predictor of airway eosinophilia than blood eosinophil counts or FENO.

5. **Exhaled Nitric Oxide (FENO)**
   - It is used as a noninvasive test to measure airway inflammation and as an index of efficacy of corticosteroid response in children (demonstration of insufficient response to anti-inflammatory therapy).

6. **Trial of Corticosteroids**
   - Patients with severe airflow limitation should be given a formal trial of corticosteroids. Prednisolone 30 mg orally/day is given for 2 weeks with lung function measured before and immediately after the course. A substantial improvement in FEV₁ (>15%) confirms the presence of a reversible airflow obstruction and indicates that the administration of inhaled steroids will be beneficial to the patient.

7. **Arterial Blood Gas Analysis**
   - Hypoxia and hypocarbia during acute attack
   - Hypercarbia during sever acute asthma.

**Differential Diagnosis of Asthma (Table 6.17)**

**Q** Give the differential diagnosis of a 45-year-old male presenting with acute breathlessness.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic obstructive pulmonary disease (COPD)</td>
<td>History of smoking, Less reversible airflow obstruction, Reduced DLCO (diffusing capacity of lung for carbon monoxide)</td>
</tr>
<tr>
<td>Bronchiectasis</td>
<td>May be secondary to many disorders, Copious purulent sputum, Computed tomography usually diagnostic</td>
</tr>
<tr>
<td>Reactive airways viral syndrome</td>
<td>Transient, usually resolves after several weeks</td>
</tr>
<tr>
<td>Rhinosinusitis</td>
<td>Nasal congestion and postnasal drip, Common comorbid illness accompanying asthma</td>
</tr>
<tr>
<td>Gastroesophageal reflux disease</td>
<td>Common comorbid illness accompanying asthma</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>Exertional dyspnea, Moist basilar rales, S₃ gallop, orthopnea, pink frothy/blood-tinged sputum, Echocardiography helpful</td>
</tr>
<tr>
<td>Laryngeal dysfunction</td>
<td>Stridor, May co-exist with asthma</td>
</tr>
<tr>
<td>Upper airway obstruction</td>
<td>May or may not exhibit stridor, Flow-volume loop may be helpful, Endoscopy diagnostic</td>
</tr>
<tr>
<td>Recurrent episodes of bronchospasm</td>
<td>Carcinoid tumors, recurrent pulmonary emboli, Churg Strauss syndrome</td>
</tr>
</tbody>
</table>

Differences between bronchial asthma and cardiac asthma are present in Table 6.18.

**Q** Write short essay/note on:
- Enumerate the drugs used in the treatment of chronic bronchial asthma.
- Management of acute severe asthma.
- List the drugs used for prophylaxis against asthma.
- Status asthmaticus.
- Long-term complications of asthma.

**Management**

Management is discussed under following headings namely:

**Avoid Identified Aggravating Factors/Allergens**
- This is important in the management of occupational asthma and atopic asthma.
- Avoid causative allergens such as pets, moulds and certain foodstuffs particularly in childhood.
- If it is due to single allergen, it is easy to reduce or avoid the exposure. However, when multiple allergens are responsible, avoidance is difficult.
Table 6.18: Differences between bronchial asthma and cardiac asthma.

<table>
<thead>
<tr>
<th>Features</th>
<th>Bronchial Asthma</th>
<th>Cardiac Asthma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathology</td>
<td>Bronchospasm</td>
<td>Pulmonary edema</td>
</tr>
<tr>
<td>Age</td>
<td>Young</td>
<td>Elderly (above 50–60 years)</td>
</tr>
<tr>
<td>Sex/gender</td>
<td>Both genders</td>
<td>Mostly male</td>
</tr>
<tr>
<td>Past history</td>
<td>Of eczema, urticaria (allergy) susceptibility to cold, allergy to pollen, groundnuts, eggs</td>
<td>No history of allergy, history of left ventricular failure, right ventricular failure</td>
</tr>
<tr>
<td>Family history</td>
<td>Other family members may have similar disease</td>
<td>Hypertension may run in families</td>
</tr>
<tr>
<td>Personal history</td>
<td>Highly sensitive individual</td>
<td>Nil</td>
</tr>
<tr>
<td>Onset</td>
<td>Acute, usually in early hours of morning or late hours of night</td>
<td>Acute usually at midnight (very specific) 2 to 3 hours after sleep</td>
</tr>
</tbody>
</table>

**Symptoms**

<table>
<thead>
<tr>
<th>Respiratory</th>
<th>Expiratory wheeze present</th>
<th>Basal crepitations and sweating present</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyanosis</td>
<td>Present during acute severe asthma</td>
<td>Cyanosis present</td>
</tr>
<tr>
<td>Pulse rate</td>
<td>May be high</td>
<td>Very high (may be pulsus alternans)</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>Normal or slightly more systolic</td>
<td>BP usually high</td>
</tr>
<tr>
<td>Heart sounds</td>
<td>Heart sounds are distant</td>
<td>S3, Gallop rhythm may be present</td>
</tr>
</tbody>
</table>

**On examination**

Control of Risk Factors Causing Exacerbation

The rapid identification and removal of extrinsic causes of asthma and risk factors that exacerbate asthma should be done.

- Active and passive smoking should be avoided.
- Control if there is associated rhinitis and GERD (gastroesophageal reflux disease).
- Control obesity.
- Individuals intolerant to aspirin should avoid NSAIDs.
- Avoid inadequate use of inhaled corticosteroids.
- Avoid overuse of inhaled short acting β-agonists (e.g. more than one canister of 200 doses/month).
- Follow proper inhalation techniques.

Desensitization or Immunotherapy

Desensitization is performed by repeated subcutaneous injections of gradually increasing doses of the extracts of allergen(s). However, its benefit is doubtful. GINA 2017 recommends adding SLIT (sublingual immunotherapy) in adult HDM (house dust mite)-sensitive patients with allergic rhinitis who have exacerbations despite ICS treatment, provided FEV1 is 70% predicted.

Drug Therapy (Table 6.19)

Drug therapy is used to control or suppress clinical manifestations.

The drugs useful in asthma can be divided into bronchodilators (rapidly relieve of symptoms through relaxation of airway smooth muscle), and controllers (inhibit the underlying inflammatory process).

**Bronchodilators**

1. **β2-adrenoreceptor agonists**
   - **β-adrenoreceptor:** There are two types of β-adrenoreceptor namely, β1 and β2-adrenoreceptors. β1-adrenoreceptors are expressed in the heart and β2-adrenoreceptors are widely expressed in the airways (in bronchial smooth muscles).
   - **β2-adrenoreceptors agonists** (β2-agonists) can be divided into short-acting β2-agonists (SABAs) (e.g. salbutamol, levalbutamol, and terbutaline) and long-acting β2-agonists (LABAs) (e.g. bambuterol, salmeterol and formoterol).
   - **a. Catecholamines:** Catecholamines used are adrenaline, isoprenaline and isoetharine.
     - **Adrenaline:** Most commonly used agent in this group. However, it is not a β2-selective and produces significant undesirable cardiovascular side effects. The usual dose is 0.3–0.5 mL of a 1:1000 solution administered subcutaneously. It may be repeated thrice at an interval of 20 minutes. They are useful in children.

**Table 6.19: Drugs useful in asthma.**

<table>
<thead>
<tr>
<th>Bronchodilators</th>
<th>Controllers</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-adrenoreceptor agonists</td>
<td>Inhaled Corticosteroids</td>
</tr>
<tr>
<td>Methylxanthines</td>
<td>Systemic Corticosteroids</td>
</tr>
<tr>
<td>Anticholinergics</td>
<td>Steroid-sparing therapies, cromones</td>
</tr>
<tr>
<td></td>
<td>antileukotrienes</td>
</tr>
</tbody>
</table>

**Anti-IgE Immunotherapy**

Alternative Therapies

Miscellaneous agents, SLIT
b. **Salbutamol, levosalbutamol, terbutaline, fenoterol**: These drugs are highly selective for β₂-adrenoreceptors and act predominantly on the respiratory tract.
- **Powerful and rapidly but short acting** bronchodilators that relaxes bronchial smooth muscles.
- **Routes of administration**: They are active by inhalation, oral, intravenous, subcutaneous route of administration, but the preferred route is inhalation. Inhalation is extremely effective, since, it rapidly decreases airflow obstruction. Intravenous administration has no advantages over inhalation. Other routes of administration are preferred avoided and reserved for selected indications.
  - **Dose**:  
    - Salbutamol: 2–4 mg thrice a day orally or two puffs of 100 μg each as required.  
    - Terbutaline: 2.5–5 mg thrice a day or two puffs of 100 μg each as required.  
    - Levosalbutamol: Two puffs of 50 μg each as required.  
  - **Side effects**: Main untoward effects are tremor and palpitation. Prolonged use of β₂-adrenoreceptor agonists are preferable avoided because they worsen bronchial hyper-responsiveness. Tachycardia which is less with levosalbutamol compared to salbutamol.

c. **Bambuterol**: It is a long acting β₂-adrenoreceptor agonist which is converted into terbutaline in the body.
- **Dose**: 10–20 mg once in a day orally.
- **Side effects**: More than inhaled β-agonists and include tachycardia, palpitations and tremors.

d. **Salmeterol and formoterol**: They are highly selective, potent and long-acting β₂-adrenoreceptor agonist. They are given once or twice a day by inhalation (either as aerosol or dry powder).
- **Uses**: Routinely used in place of short-acting β₂-stimulants when the patient requires regular β₂-stimulant therapy. Not to be used as monotherapy but to be used as add on therapy along with ICS (inhaled corticosteroids) when the response to ICS is suboptimal.
- **Salmeterol** has a slow onset of action whereas formoterol has a rapid action. Hence, formoterol is suitable for immediate control of symptoms as well.
- **Dose**:  
  - Salmeterol: Two puffs of 25 μg each two to three times a day.  
  - Formoterol: Two puffs of 6 μg each one to three times a day.

### Q. Write a short note on action of methylxanthines.

**2. Methylxanthines**

They are of little value as monotherapy but they are beneficial as add-on therapy in patients not controlled with inhaled corticosteroids (ICS). Methylxanthines as an add-on therapy are less effective than long-acting inhaled β₂-agonists.

**a. Theophylline**
- Theophylline is a medium-potency bronchodilator.
- **Actions**: i) improve the movement of airway mucus, ii) improves diaphragm contractility and iii) reduces the release of mediators.  
  - **Route of administration**: Intravenous, oral or as suppository. Therapeutic plasma concentrations of theophylline range from 10 to 20 μg/mL. However, the dose required to achieve this concentration varies from patient to patient.
  - **Type of preparation**:  
    - **Dose**: Usual dose is 100–200 mg (of plain preparation) three times/day, and 300 mg twice/day or 450–600 mg once/day for sustained-release preparation.  
    - **Side effects**: Nervousness, nausea, vomiting, anorexia and headache. When plasma levels exceed 30 μg/mL, seizures and cardiac arrhythmias can occur.
  - **Precautions**: Theophylline (and aminophylline) clearance is decreased in elderly, liver disease, congestive heart failure, and with concurrent use of erythromycin, allopurinol and cimetidine. Its clearance is increased with concurrent use of phenobarbitone and phenytoin, and in smokers.

### Q. Write short essay/note on adverse effects of and precautions in using aminophylline.

**b. Aminophylline**
- Aminophylline is a bronchodilator that is effective when given orally, intravenously and as a suppository. The preferred route of administration is intravenous and may have some role in the management of status asthmaticus (severe acute asthma).
- **Mechanism of action**: Bronchodilator effect is by inhibition of phosphodiesterases in airway smooth-muscle cells which increases cyclic AMP.
- **Dose**: Loading dose of 5 mg/kg given slowly intravenously over 20 minutes. This is followed by a maintenance dose of 0.5 mg/kg/hour delivered as a continuous intravenous infusion. Patients already on theophylline, loading dose is preferably withheld or in extreme cases given in a reduced amount at 0.5 mg/kg.
  - **Dose**: Rapid infusion of the bolus can lead to sudden death due to cardiac arrhythmias.
- **Sodium cromoglycate**: Useful in children with atopic asthma and in few cases of non-atopic asthma. Sodium cromoglycate is administered as an inhalation. Therapy is started between the attacks or in periods of relative remission. If there is no response within 4 to 6 weeks, the drug can be discontinued.
- **Nedocromil sodium**: It is given as an inhalation at a dose of 4 mg two to four times daily.
- **Ketotifen** is not a chromone. It is an antihistaminic that inhibits release of mediators. It is useful in the prophylactic treatment of asthma at a dose 1–2 mg twice daily by mouth. The main side effects are drowsiness and weight gain.

4. **Anticholinergics**

**Q. Write short note/essay on tiotropium/ipratropium bromide uses and side effects.**

- Anticholinergics such as atropine sulfate and atropine methyl nitrate were previously used, but they are presently not used because of their systemic side effects.
- Currently used anticholinergics are **ipratropium bromide and tiotropium**. These are non-adsorbable quaternary ammonium compounds with minimal side effects. These are administered as aerosol or in dry-powder form. Ipratropium is also given as nebulization solution.
- **Uses**: They are useful in two situations:
  1. Patients with co-existent heart disease, in whom methylxanthines and β2-adrenoreceptor agonists causes significant tachycardia.
  2. In refractory cases, bronchodilator action of β2-adrenoreceptor agonists is enhanced by the addition of ipratropium bromide or tiotropium.
- **Dose**:
  - **Ipratropium**: Two puffs of 20 µg each four times/day.
  - **Tiotropium**: Two puffs of 9 µg each once a day.
  - **Ipratropium**: 250–500 µg nebulization; may be repeated if necessary.
- **Side effects**: Dryness of mouth and bitter taste.

5. **Leukotriene modifiers**

- These include leukotriene receptor antagonists—**LTRAs** (montelukast, zafirlukast, pranlukast) and 5-lipoxygenase inhibitors (Zileuton).
- **Uses**: Used as add on therapy.
  - In patients who do not respond to the conventional agents.
  - In patients who require high doses of inhaled steroids (ICS). They can be used as a second choice to inhaled corticosteroids in mild persistent asthma.
- **Dose**:
  - **Zafirlukast**: 20 mg BID
  - **Montelukast**: 10 mg once a day in the evening.
- **Side effects**: Uncommon and include headache, abdominal pain, skin rashes, angioedema, pulmonary eosinophilia and arthralgia. Zileuton may cause liver damage.

Anti-IgE—**Monoclonal Antibodies**

- **Omalizumab**, recombinant humanized monoclonal antibody against IgE that neutralizes/chelates free circulating IgE without binding to cell-bound IgE. It prevents the binding of circulating IgE to receptors on mast cells and basophils, and decrease release of mediators. Thus, it inhibits IgE-mediated reactions. Monoclonal antibodies (mepolizumab and reslizumab) against interleukin-5 (IL-5), a potent chemoattractant for eosinophils, are indicated for the treatment of severe eosinophilic asthma poorly controlled with conventional therapy.
- **Useful in patients with allergic asthma.**
- **Disadvantage**: Treatment is very expensive. Patients should be given a 3- to 4-month trial of therapy to show objective benefit.
- **Administration**: Given as a subcutaneous injection once every 2–4 weeks, depending on total serum IgE level and body weight.
- **Side effects**: No significant side effects, very rarely can produce anaphylaxis.
- **Anti-TNF therapy** (infliximab or etanercept): May be beneficial in severe corticosteroid refractory asthma.

**Miscellaneous**

Proton pump inhibitor (PPI) may be used in patients with symptomatic gastroesophageal reflux disease and suboptimally controlled asthma.

**Bronchial Thermoplasty**

- Invasive procedure for severe asthma. In this therapy, controlled thermal energy is delivered to the airway wall during a series of bronchoscopies. It results in a prolonged reduction in airway smooth muscle mass. But patient still needs to use their asthma-maintenance medications after the procedure.
- **Risks**: Lung collapse, bleeding and additional breathing problems, mostly related to the bronchoscope.
- **Benefits**: Patient may use rescue inhalers less often and are able to engage strenuous physical activity than before.

**General Measures in Asthmatics**

- **Avoid**:
  - Opiates, sedatives and tranquilizers in acutely-ill patients with asthma.
  - β-blockers and parasympathetic agonists in asthmatics.
- **Expectorants and mucolytic agents** have no significant role in the management of bronchial asthma.
**Prevention/treatment of exercise-induced asthma**
- Prevention of episode by the inhalation of 2 metered doses of salbutamol or terbutaline a few minutes before exercise. However, regular use may lead to loss of their effect.
- Regular use of sodium cromoglycate or leukotriene modifiers is often needed. Additional use of inhaled \( \beta_2 \)-adrenoreceptor agonists may be necessary before exercise.

**Assessment of asthma control (Table 6.20)**
- Features which suggest that asthma is under control are listed in Box 6.4.
- Complications of asthma is mentioned in Box 6.5.

**Box 6.4: Features of controlled asthma.**
- Daytime symptoms develop two times or less/week
- No limitation of daily activities including exercise
- No awakening in the night due to symptoms
- Need for short-acting \( \beta \)-agonists twice or less/week
- No exacerbations

**Box 6.5: Complications of asthma.**
- Pneumonia
- Collapse of part or all of the lung
- Respiratory failure
- Status asthmaticus

**Global Initiative for Asthma (GINA) Severity Grades (refer Table 6.22)**
- **Severe asthma:**
  - It is an asthma which requires treatment with high dose inhaled corticosteroids and long-acting \( \beta_2 \)-agonist and/or leukotriene receptor antagonists for the previous year or systemic corticosteroids for \( \geq 50\% \) of the previous year to prevent from becoming uncontrolled asthma or
  - Asthma which remains uncontrolled despite this therapy.

**Table 6.20: Assessment of asthma control.**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Controlled asthma</th>
<th>Partly controlled asthma</th>
<th>Uncontrolled asthma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daytime symptoms more than twice/week</td>
<td>No</td>
<td>Any 1 or 2 characteristics present</td>
<td>Any 3 or more characteristics partly controlled asthma</td>
</tr>
<tr>
<td>Limitation of activities due to asthma</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nocturnal symptoms/awakening due to asthma</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Need for reliever/rescue medicine more than twice/week</td>
<td>No</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Stepwise Management of Chronic Asthma (Table 6.21 and Fig. 6.7)**

**Q. Write short essay/note on step care management of bronchial asthma.**

All asthmatics should be educated regarding self-monitoring and correct use of inhalers.

**Table 6.21: Stepwise management of asthma.**

<table>
<thead>
<tr>
<th>Step</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 1: (only for intermittent/less frequent symptoms)</td>
<td>Short-acting inhaled ( \beta )-agonist as required (required in all steps)</td>
</tr>
<tr>
<td>Step 2: Daily symptoms</td>
<td><strong>Regular inhaled preventer therapy</strong></td>
</tr>
<tr>
<td></td>
<td>• Low-dose inhaled corticosteroids up to 800 ( \mu )g daily OR</td>
</tr>
<tr>
<td></td>
<td>• Leukotriene receptor antagonists (LTRA), (if patient develops side effects to inhaled corticosteroids), SLIT (Sublingual immunotherapy)</td>
</tr>
<tr>
<td>Step 3: Severe symptoms</td>
<td><strong>Inhaled corticosteroids and long-acting inhaled ( \beta_2 )-agonist</strong></td>
</tr>
<tr>
<td></td>
<td>• Continue low-dose inhaled corticosteroids plus long-acting ( \beta_2 )-agonist OR</td>
</tr>
<tr>
<td></td>
<td>• Medium or high dose inhaled corticosteroids OR</td>
</tr>
<tr>
<td></td>
<td>• Low-dose inhaled corticosteroids plus leukotriene receptor antagonists (LTRA), OR</td>
</tr>
<tr>
<td></td>
<td>• Low-dose inhaled corticosteroids plus sustained-release oral theophylline</td>
</tr>
<tr>
<td>Step 4: Severe symptoms uncontrolled with high dose inhaled corticosteroids</td>
<td><strong>High dose inhaled corticosteroid and regular bronchodilators</strong></td>
</tr>
<tr>
<td>Step 5: Severe symptoms deteriorating</td>
<td><strong>Regular oral corticosteroids</strong></td>
</tr>
<tr>
<td>Step 6: Severe symptoms deteriorating in spite of prednisolone</td>
<td><strong>Hospital admission</strong></td>
</tr>
</tbody>
</table>
Fig. 6.7: Stepwise management of asthma in adults.

- Once the patient is on treatment for several months, asthma severity can be assessed by using step-wise criteria.
  - Mild asthma: Well controlled with step 1 and 2.
  - Moderate asthma: Controlled with step 3 treatment
  - Severe asthma: Needs step 4 or 5 treatment to prevent it to progress to uncontrolled asthma.

Step-down Therapy
Once asthma is controlled, the dose of inhaled (or oral) corticosteroid should be reduced to the lowest dose at which effective control of asthma is maintained.

The Control-based Asthma Management Cycle GINA 2017 (Fig. 6.8)

Treatment of Severe Acute Asthma (Status Asthmaticus)

- Write short essay/note on management of status asthmaticus.

Acute severe asthma is the term used for an exacerbation of asthma that has not been controlled by the use of standard medication.

Treatment at Home
- Give high concentrations of oxygen (40–60%) through a mask if available.
- Bronchodilator therapy: Any one of the following should be given.
  - Nebulized salbutamol 5 mg or terbutaline 10 mg every 20 minutes for 3 doses.
  - Salbutamol/terbutaline through metered-dose inhalers (four to eight puffs with a spacer every 20 minutes for 3 doses), followed by 4–8 puffs every 2–4 hours.
- Corticosteroids
  - Give IV hydrocortisone sodium succinate 200 mg.
  - Give oral prednisolone 60 mg.
- Admit to hospital if there is no response within 1 hour or if patient becomes drowsy.
Management in Hospital

Initial assessment: Take brief history, perform rapid examination of the patient and assess the severity (Table 6.22). Administer high concentration of oxygen (40–60%).

<table>
<thead>
<tr>
<th></th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Respiratory arrest imminent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breathless</td>
<td>Walking</td>
<td>Taking</td>
<td>At rest</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lying down possible</td>
<td>Taking</td>
<td>Hunched forward</td>
<td></td>
</tr>
<tr>
<td>Talking in</td>
<td>Sentences</td>
<td>Phrases</td>
<td>Words</td>
<td></td>
</tr>
<tr>
<td>Alertness</td>
<td>Possibly agitated</td>
<td>Usually agitated</td>
<td>Usually agitated</td>
<td>Drowsy or confused</td>
</tr>
<tr>
<td>Respiratory rate</td>
<td>Increased</td>
<td>Increased</td>
<td>Usually</td>
<td>Paradoxical thoracoabdominal movement</td>
</tr>
<tr>
<td>Accessory muscles/</td>
<td>Usually not</td>
<td>Usually</td>
<td>Usually</td>
<td></td>
</tr>
<tr>
<td>suprasternal retraction</td>
<td></td>
<td></td>
<td>Paradoxical thoracoabdominal movement</td>
<td></td>
</tr>
<tr>
<td>Wheeze</td>
<td>Moderate</td>
<td>Loud</td>
<td>Usually loud</td>
<td>Absent</td>
</tr>
<tr>
<td>Pulse/min</td>
<td>&lt;100</td>
<td>100–120</td>
<td>&gt;120</td>
<td>Bradycardia</td>
</tr>
<tr>
<td>Pulsus paradoxus</td>
<td>Absent</td>
<td>May be present</td>
<td>Often present</td>
<td>Possibly absent due to muscle fatigue</td>
</tr>
<tr>
<td>PEF after bronchodilator</td>
<td>&gt;80%</td>
<td>Approx. 60–80%</td>
<td>&lt;60%</td>
<td></td>
</tr>
</tbody>
</table>


Management Algorithm of Acute Asthma (Flowchart 6.1)

Exacerbations of Asthma

Q. Write short essay on management of acute severe asthma.

- Precipitating factors of exacerbations: Viral infections (most common), others include moulds, pollens and air pollution.

Treatment of Mild-to-Moderate Exacerbation

- \( \beta_2 \)-agonists (via inhaler or nebulizer) every 20 minutes for 3 doses (as mentioned above).
- Oral corticosteroids if there is no immediate response.
- Patient is reassessed every hour.

Treatment of Severe Exacerbation

- Give high concentration of oxygen (40–60%).
- Bronchodilators
- Administer nebulized (in oxygen) salbutamol (5 mg) or terbutaline (10 mg) or levosalbutamol (1.25–2.5 mg) immediately and may be repeated after a few minutes if there is no response.
- \( \beta_2 \)-agonist (subcutaneously or intravenously) are indicated in patients with excessive cough, too weak to inspire adequately or moribund.
- Terbutaline is administered subcutaneously (0.25–0.5 mg) or intravenously (0.1–10 µg/kg/minute).
- Epinephrine (adrenaline) may be administered in children and young adults. Adult dose is 0.2–0.5 mg as 1:1000 solution subcutaneously every 20 minutes
- Add nebulized ipratropium bromide 0.5 mg to nebulized salbutamol 5 mg/terbutaline 10 mg to those patients who do not respond within 15–30 minutes. It can be repeated every 20 minutes for 3 doses.
- Aminophylline can be given intravenously to those patients who do not respond to nebulized bronchodilators. Give a loading dose of 5 mg/kg/hour as an infusion.
- Corticosteroids
- In severely ill patients, hydrocortisone sodium succinate 100 mg is administered intravenously at presentation and then repeated 4–6 hourly for 24 hours.
- Antibiotics are indicated only if there is respiratory infection.
- Role of magnesium sulfate either intravenously or by nebulization is not clear.
- If no improvement with above measures, perform endotracheal intubation and mechanical ventilation.
- Indications for intubation: Cardiac or respiratory arrest, severe hypoxia (\( \text{PaO}_2 < 60 \text{ mm Hg} \)), hypercapnia (\( \text{PaCO}_2 > 50 \text{ mm Hg} \)), acidosis (\( \text{pH} < 7.3 \)), exhaustion or deterioration in mental status.
- NIV (non-invasive ventilation) using continuous positive pressure of BiPAP machines and tight fitting face mask reduces the work of breathing without intubation. It is useful in assisting breathing. It is used in a cooperative and alert patient who has impending respiratory failure but does not require immediate intubation.
Treatment with 70–80% helium with oxygen may be useful, since it reduces airway resistance and improves efficacy of bronchodilators.

Assessment of response to treatment is done by noting the patient distress, respiratory rate, FEV₁, heart rate, presence of pulsus paradoxus and serial arterial blood gas (ABG) studies.

More severe cases should remain in hospital for 2–5 days with regular monitoring of oxygen saturation and peak flow rates. Bronchial thermoplasty may be beneficial for moderate to severe persistent asthma. This reduces the mass of airway smooth muscle, reducing bronchoconstriction.

**Occupational Asthma**

**Q.** Write a short note on occupational asthma.

Occupational asthma is relatively common.

**Etiology**

- It is a type of asthma caused by specific occupational sensitizer (proteins or glycopeptide). Often associated with allergic rhinitis/conjunctivitis.
- Once the individual is sensitized, subsequent low exposure is capable of producing specific IgE antibodies and can induce asthma.
- Latency period between first exposure to sensitizer and onset of work-related symptoms can range from weeks to years.
- Triggering occupational agents include: Fumes (epoxy resins, plastics), organic and chemical dusts (wood, cotton, platinum), gases (toluene diisocyanate), animal allergens, plants and plant products (flours and cereals) and other chemicals (formaldehyde, penicillin products). Work-exacerbated asthma is defined as preexisting or concurrent asthma that subjectively worsens in the workplace.
Investigations

- **Chest X-ray:** Findings are nonspecific. It may show diffuse micronodular shadowing with the subsequent development of streaky shadows, particularly in the upper zones. Very advanced cases produce honeycomb lung.
- **High resolution computed tomography (HRCT):** Shows reticular and nodular changes with ground-glass opacity.
- **Blood:** Raised ESR and neutrophilia (especially in acute form). Eosinophil counts and IgE levels are usually normal.
- **Lung function tests:** Show a restrictive ventilatory defect with normal FEV₁: FVC ratio. Diffusion capacity for carbon monoxide may be significantly impaired in chronic cases.
- **Precipitating antibodies:** In the serum against offending agent indicates the evidence of exposure, but not disease.
- **Bronchoscopy with bronchoalveolar lavage (BAL):** Although not a specific, BAL shows increased T-lymphocytes and granulocytes. Most often, CD4:CD8 ratio <1 (normal is about 0.9–2.5). In sarcoidosis, it is usually above 3.5.
- **Lung biopsy:** May show chronic inflammatory cells, ill-defined non-caseating granulomas and fibrosis in late stages.
- **Provocation test:** If about 4–10 hours after exposure to the inhaled antigen, there is respiratory or systemic findings (e.g. fever, leukocytosis); reduced diffusing capacity, diminished VC (vital capacity), or both; increased radiographic abnormalities; worsening alveolar-arterial oxygen pressure suggests a positive response.

Treatment

- **Prevention:** It should be the aim and can be achieved by identification and avoidance of the offending antigen.
- **Corticosteroids:** Because acute form is usually a self-limited disease treatment is not necessary. However, corticosteroid has some role in subacute and chronic forms. Prednisolone in large doses (1 mg/kg/day) orally for 1–2 weeks, followed by gradual tapering over the next 4–6 weeks. It may achieve regression during the early stages but not those with established fibrosis.
- **Oxygen therapy** in severely hypoxemic individuals. Symptomatic bronchodilator therapy.

Drug-induced Asthma

**Drugs Implicated**

- Most common due to aspirin (aspirin-induced asthma, AIA) followed by ibuprofen, indomethacin, naproxen, phenylbutazone, mefenamic acid. About 10% of asthma patients are aspirin-sensitive
- **Drugs that can cause bronchospasm:** Adenosine, prostaglandin analogues, BBs (beta-blockers), cholinergic drugs, streptomycin, pentazocine, penicilllin.
- **Non-pharmaceutical agents:** Tartrazine (coloring agent), sulfating agents (preservatives in food/medicines)

**Mechanism:** Decreased production of prostaglandin E₂ (PGE₂) and enhanced production of leukotriene B₄ (LTB₄).

**Associations:** Nasal polyps, vasomotor rhinitis, hyperplastic rhinosinusitis (Samter’s triad).

**Aspirin-induced Asthma (AIA):** Two distinct forms:
- **Cutaneous form:** Associated with urticaria and angioedema
- **Respiratory form:** Resulting in rhinoconjunctivitis and bronchospasm.

**Diagnosis:** Bronchial Challenge with aspirin.

**Drug treatment of AIA:** Treat the underlying asthma and the strict avoidance of aspirin and cross-reacting NSAIDs. Acetaminophen and selective COX2 inhibitors are safe.

CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

**Q.** Write short essay/note on COPD (chronic obstructive pulmonary disease), COLD (chronic obstructive lung disease) or COAD (chronic obstructive airway disease).

**Introduction**

COPD is also known as chronic obstructive lung disease (COLD), chronic obstructive airway disease (COAD), chronic airflow limitation (CAL) and chronic obstructive respiratory disease (CORD).

**Definition**

- COPD is a **preventable and treatable pulmonary disease** associated with some **significant extrapulmonary effects** that may contribute to the severity in individual patients.
- Pulmonary disease is characterized by **airflow limitation** which is **not fully reversible**.
- The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lung to various noxious particles or gases.
Conditions included under COPD: Disease is considered COPD, only if chronic airflow obstruction occurs.
- **Emphysema**: An anatomically defined condition characterized by abnormal and permanent enlargement of the airspaces distal to the terminal bronchioles. It is accompanied by destruction of the airspace walls, without obvious fibrosis (i.e. there is no fibrosis visible to the naked eye).
- **Chronic bronchitis**: It is defined as a chronic productive cough for three months in each of two successive years in a patient in whom other causes of chronic cough (e.g. bronchiectasis) have been excluded.
- **Small airways disease**: A condition in which small bronchioles are narrowed.

**Pathogenesis**
- **Major physiologic change** in the COPD is **airflow limitation**. It can develop due to both small airway obstruction and emphysema. The small airways may become narrowed by cells (hyperplasia and accumulation), mucus, and fibrosis.
- Activation of transforming growth factor-β (TGF-β) contributes to airway fibrosis, whereas absence of TGF-β may produce parenchymal inflammation and emphysema. The mechanism involved in emphysema is better understood than small airway obstruction.

**Chronic Bronchitis**

**Q. Define chronic bronchitis. Describe the etiology, pathology, clinical features, investigations, course, prognosis, treatment and complications of chronic bronchitis.**

**Q. Discuss the etiology, pathology, clinical features, investigations, course, prognosis, treatment and complications of chronic obstructive pulmonary disease.**

**Incidence**
- **Age and gender**: Occurs during **middle and late adult life**. It is more common in **males than in females**.
- More common in **smokers than in non-smokers**. Also more often develops in urban than in rural dwellers.

**Types of Chronic Bronchitis**: (1) Simple chronic bronchitis; (2) chronic mucopurulent bronchitis; (3) chronic asthmatic bronchitis; and (4) chronic obstructive bronchitis.

**Etiology**

**Risk Factors (Table 6.24)**

**Q. Write short note on risk factors of chronic obstructive pulmonary disease.**

**Smoking and COPD**

- **Cigarette smoking**: It is the most important risk factor for the development of COPD. The risk of developing COPD relates to both the amount and the duration of smoking. However, only about 15–20% of smokers develop clinically significant COPD. This suggests that genetic predisposition and environmental factors play a role in the pathogenesis.
- **Second-hand smoke**: Environmental tobacco smoke that is inhaled involuntarily or passively by someone who is not smoking.
- **Environmental tobacco smoke** is generated from the side stream (the burning end) of a cigarette, pipe or cigar or from the exhaled mainstream (the smoke puffed out by smokers) of cigarettes, pipes, and cigars.
- **Abnormalities due to smoking**: Cigarette smoking is associated with a variety of abnormalities of the respiratory system that predispose to the development of chronic bronchitis. These include:
  - Sluggishness of movement of cilia.
  - Bronchoconstriction brought through constriction of smooth muscle
  - Hypertrophy and hyperplasia of mucus secreting glands. The **ratio of the thickness of the mucous gland layer to the thickness of the bronchial wall** between the base of the surface epithelium and the inner limit of the cartilage plates is called Reid index. It is useful for detecting the increase in the size and number of the mucus glands. Reid index (normally 0.44 ± 0.094) is increased in chronic bronchitis (>0.51). There is a direct correlation between the value of Reid Index and the volume of daily sputum production by the patient.
  - Release of proteolytic enzymes from polymorphonuclear leucocytes and release of inflammatory mediators in lungs.
  - Inhibits the function of alveolar macrophages.
  - Adverse effect on surfactant and favors overdistension of the lungs.

**Table 6.24: Risk factor for COPD.**

<table>
<thead>
<tr>
<th>Environmental</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tobacco smoke</td>
</tr>
<tr>
<td>Indoor air pollution. Cooking with biomass fuels</td>
</tr>
<tr>
<td>Toxic industrial inhalants: Occupational dust exposure (e.g. coal dust, silica and cadmium)</td>
</tr>
<tr>
<td>Respiratory infections: Recurrent infection; HIV infection (associated with emphysema), previous tuberculosis</td>
</tr>
<tr>
<td>Low birth weight and bronchopulmonary dysplasia</td>
</tr>
<tr>
<td>Lung growth: Childhood infections or maternal smoking may affect growth of lung during childhood</td>
</tr>
<tr>
<td>Low socioeconomic status, antioxidant deficiency</td>
</tr>
<tr>
<td>Cannabis smoking</td>
</tr>
</tbody>
</table>

**Host factors**
- Genetic factors: α1-antiproteinase deficiency TGF Beta 1 polymorphism, Serpine 2 gene expression.
- Airway hyper-reactivity
**Respiratory System**

**Pathogenesis (Flowchart 6.2)**

Major physiologic change in COPD is airflow limitation. It can result from both small airway obstruction and emphysema.

- **Irritants cause inflammation → infiltration by CD8 + T-lymphocytes, macrophages and neutrophils.**
- **Hypersecretion of mucus**
  - **Hyperplasia/hypertrophy of the submucosal glands in large airways (trachea and bronchi):** Develops as response to inhaled **environmental irritants** and **proteases released from neutrophils** (e.g. elastase and cathepsin). This leads to **hypersecretion of mucus.**
  - **Marked increase of goblet cells in small airways (small bronchi and bronchioles):** They produce excessive mucus → mucus plugging of bronchial lumen → inflammation and fibrosis of bronchial wall → **leads to airway obstruction.**

**Clinical Features**

**History:** Most common three symptoms in COPD are impressive history of cough, sputum production, and exertional dyspnea (breathlessness).

- **Cough:** Initially, the cough is present only in the winter seasons (often referred as ‘winter cough’ or ‘smoker’s cough’), especially in the mornings (‘morning cough’). Later, cough increases in frequency, severity and duration.
- **Sputum:** Usually scanty, mucoid and more in the mornings. It may be occasionally blood-stained (hemoptysis) or frankly purulent (‘mucopurulent relapse’).
- **Breathlessness:** It is **relatively insidious in onset** and is due to airflow obstruction. It is aggravated by infection; excessive smoking and adverse atmospheric conditions. Breathlessness severity can be assessed by the modified MRC dyspnea scale (Table 6.25).

**Other symptoms:** Fever during mucopurulent relapses, wheezing and tightness in the chest.

**Physical signs**

- Patient is usually overweight.
- In the early stages, patients are entirely normal on physical examination. At rest, there is no respiratory distress, respiratory rate is normal and accessory muscles of respiration are not acting.
- **Auscultation:** (i) Vesicular breath sounds with prolonged expiration; (ii) inspiratory and expiratory rhonchi; and (iii) crepitations that either disappear or change in location and intensity after coughing; (iv) forced expiratory time >4 sec.

**Table 6.25: Modified Medical Research Council (mMRC) scale for dyspnea.**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No breathless except on strenuous exercise</td>
</tr>
<tr>
<td>1</td>
<td>Breathless when hurrying on the level or walking up a slight hill</td>
</tr>
<tr>
<td>2</td>
<td>Walks slower than people of same age on the level ground because of breathlessness or has to stop for breath while walking at his own pace on the level ground</td>
</tr>
<tr>
<td>3</td>
<td>Stops for breath after walking 100 meters or after a few minutes on the level ground</td>
</tr>
<tr>
<td>4</td>
<td>Too breathless to leave the house or gets breathless while dressing or undressing</td>
</tr>
</tbody>
</table>
- **Secondary polycythemia**: Due to hypoxemia which stimulates erythropoiesis.
- **Pulmonary hypertension and right ventricular failure (cor pulmonale)**
- Pneumonia
- Tuberculosis
- Lung cancer
- Pneumothorax (emphysema)
- Deep vein thrombosis
- Pulmonary embolism

**Pathogenesis of Complications (Flowchart 6.3)**

**Management**

**General measures**
- Regular exercises and management of nutritional status.
- Weight loss, if the patient is obese.

**Reducing exposure to noxious particles and gases that cause bronchial irritation**
- **Smoking cessation**: Stop smoking completely and this may be aided by bupropion (a noradrenergic antidepressant) nicotine replacement therapy (by gum, transdermal patch lozenge inhaler or nasal spray) or varenicline [partial agonist of the nicotinic acetylcholine receptor (nAChR) subtype alpha4beta2].
- **Reduce smoke**: Reducing the risk from indoor and outdoor air pollution. Reduce exposure to smoke from biomass fuel, particularly among women and children.
- **Avoid**: Dusty and smoke-laden atmospheres.

**Drug therapy (Table 6.28)**

Used both for the short-term management of exacerbations and for the long-term relief of symptoms. However, none of the medications for COPD reduce the rate of decline of lung functions.

- **Bronchodilators**: They are central to the management of breathlessness.
  - **β2-Adrenergic agonists**: The inhaled route is preferred.
    - **Mild disease**: Short-acting agents namely salbutamol 200 µg or terbutaline 500 µg 6 hourly.
    - **Moderate-to-severe disease**: Long-acting agents such as salmeterol 50 µg twice daily or formoterol (12 µg powder inhaled twice daily) or indacaterol (150–300 µg daily) achieve bronchodilation and also reduce the incidence of infective exacerbations. LABAs include salmeterol, formoterol, arformoterol, indacaterol, vilanterol, and olodaterol; all are beta-2 selective.
  - **Antimuscarinic (anticholinergic) drugs**: More prolonged and greater bronchodilatation is achieved by adding ipratropium bromide (40–80 µg 6 hourly) or tiotropium bromide (18 µg once a day) or oxitropium (200 µg twice daily) in severe disease.
    - Oral long-acting theophylline or doxophylline may be beneficial in selected cases. Umeclidinium, aclidinium, glycopyrronium are newer long acting anticholinergic drugs available.
- **Phosphodiesterase type 4 inhibitors**: Roflumilast is an inhibitor with anti-inflammatory properties. It may be used as an adjunct to bronchodilators. Weight loss is a significant side effect.

**Flowchart 6.3: Pathogenesis of complications of chronic bronchitis.**
Table 6.28: Drug therapy in chronic bronchitis.

<table>
<thead>
<tr>
<th><strong>Beta&lt;sub&gt;2&lt;/sub&gt;-agonists</strong></th>
<th><strong>Methylxanthines</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Short-acting beta&lt;sub&gt;2&lt;/sub&gt;-agonists (SABA)</td>
<td>• Inhaled corticosteroids (ICS)</td>
</tr>
<tr>
<td>• Long-acting beta&lt;sub&gt;2&lt;/sub&gt;-agonists (LABA)</td>
<td>• Combination long-acting beta&lt;sub&gt;2&lt;/sub&gt;-agonists + corticosteroids in one inhaler</td>
</tr>
<tr>
<td><strong>Anticholinergics/muscarinic antagonists</strong></td>
<td><strong>Systemic corticosteroids</strong></td>
</tr>
<tr>
<td>• Short-acting anticholinergics (SAMA)</td>
<td>• Phosphodiesterase-4 inhibitors</td>
</tr>
<tr>
<td>• Long-acting anticholinergics (LAMA)</td>
<td><strong>Combination short-acting beta&lt;sub&gt;2&lt;/sub&gt;-agonists + anticholinergic in one inhaler</strong></td>
</tr>
<tr>
<td><strong>Acebrophylline:</strong> An airway mucoregulator and anti-inflammatory agent.</td>
<td></td>
</tr>
</tbody>
</table>

**Corticosteroids**

- Inhaled corticosteroids (ICS) reduce the frequency and severity of exacerbations, and are used in moderately severe COPD. These include beclomethasone, budesonide, fluticasone, ciclesonide, flunisolide, beclametasone.
- Oral corticosteroids are useful during exacerbations and should be avoided as a maintenance therapy because it may lead to osteoporosis and impaired skeletal muscle function.

**Respiratory infections**

- **Treatment of infection:** Bacterial infection precipitates exacerbations. Azithromycin (has both anti-inflammatory and antimicrobial properties) administered daily to subjects with a history of exacerbation in the past 6 months may reduce the exacerbation. If patient develops purulent (yellow or green) sputum oral tetracycline or ampicillin 250 mg 6 hourly or cotrimoxazole 960 mg 12 hourly for 10 days should be given. If there is no response, sputum culture and sensitivity is done and the antibiotic is changed accordingly.

- **Prevention of infection:** Patients with COPD should receive vaccination with polyvalent pneumococcal and influenza vaccines.

**Symptomatic measures**

- **Antimucolytic agents:** They reduce viscosity of sputum and can reduce the number of acute exacerbations and total number of days of disability. Mucolytic agents include bromhexine, N-acetylcysteine carbocysteine, ambroxol and erdosteine can be tried.

- **Antitussives:** Regular use of antitussives to control cough in stable COPD is not recommended.

**Chest physiotherapy.**

**Pulmonary rehabilitation**

- It is an individually designed treatment program consisting of education and cardiovascular conditioning (reverse muscular and cardiovascular dysfunction).
- Program includes breathing technique, chest physiotherapy, postural drainage, activities of daily living (work simplification, energy conservation) and exercise conditioning (upper and lower extremity).

**Oxygen therapy**

**Write short note on oxygen therapy in chronic obstructive pulmonary disease (COPD).**

**Long-term domiciliary oxygen therapy (LTOT)**

- **Aim of therapy:** To increase the PaO<sub>2</sub> to at least 8 kPa (60 mm Hg) or SaO<sub>2</sub> to at least 90%. It is administered through nasal cannulae for at least 15 hours per day at a low-dose (2 L/minute).
- **Indications:** in COPD patient with exertional hypoxemia or nocturnal hypoxemia.
- Daytime PaO<sub>2</sub> ≤55 mm Hg at rest or oxygen saturation ≤ 88% with or without hypercapnia during a period of clinical stability OR
- Daytime PaO<sub>2</sub> between 56 and 59 mm Hg or oxygen saturation > 88% in the presence of secondary polycythaemia, nocturnal hypoxemia, peripheral edema or evidence of pulmonary hypertension.
- **Benefits:** LTOT has significant benefits and reduces mortality rates in selected patients. It decreases pulmonary hypertension and prolongs life in hypoxemic COPD patients with right heart failure. It also reduces polycythemia, pulmonary artery pressures, dyspnea, and hypoxemia during sleep and reduced nocturnal arrhythmias.

- **Treatment of pulmonary hypertension:** by long-term oxygen therapy, sildenafil, bosentan synthetic prostacyclin (epoprostenol).

**Pharmacologic therapy in COPD depending on severity is presented in Figure 6.9.**

**Surgical treatments**

**Lung volume reduction surgery (LVRS)** is more efficacious than medical therapy among patients with upper-lobe predominant emphysema and low exercise capacity.

In appropriately selected patients with very severe COPD, lung transplantation has been shown to improve quality of life and functional capacity.
**Acute Exacerbations of COPD**

- **Definition:** An event in the natural course of the COPD characterized by a change in the patient’s baseline dyspnea, cough, and/or sputum that is beyond normal day-to-day variations. It is acute in onset, and may warrant a change in regular medication in a patient with underlying COPD.

- **Causes of exacerbation:** (1) Infection of the tracheobronchial tree, and (2) air pollution. In about one-third of cases, no cause can be identified.

- **Trigging factors:** Infections by bacteria, viruses or a change in air quality.

**Q. Write short note/essay on management of a case of acute exacerbation of chronic bronchitis.**

### Treatment of Severe Acute Exacerbations

**Oxygen**

- Adequate oxygenation (i.e. to achieve an oxygen saturation of 88–92%) must be assured.
- **Method of administration:** By nasal catheter or through a facemask equipped to control the inspired oxygen fraction. Venture masks are preferred because they permit a precise fraction of inspired oxygen (FiO₂).

**Bronchodilators**
Nebulized short-acting β₂-agonists (salbutamol 2.5 mg every 20 minutes for initial 1–2 hours) and/or anticholinergic agent (ipratropium bromide 0.5 mg) should be given. Intravenous aminophylline may be added, if the patient fails to respond to the above treatment.

**Antibiotics**

- **Indications:** Patients with: (1) increase in sputum purulence, sputum volume, or (2) breathlessness (dyspnea), or (3) those requiring mechanical ventilation.
- **Most common organisms during exacerbations:** *S. pneumoniae, H influenza* and *M. catarrhalis*. Risk factors for *P. aeruginosa* infection include recent hospitalization, frequent antibiotics use and severe exacerbation.
- **Antibiotics used:**
  - **Outpatient:** Doxycycline, cotrimoxazole or amoxicillin–clavulanate can be given. Patients older than 65 years given one of the newer fluoroquinolones (levofloxacin, gemifloxacin, moxifloxacin).
  - **Hospitalized patients:** Intravenous antibiotics (azithromycin or fluoroquinolone or a third-generation cephalosporin-like ceftriaxone or cefotaxime).
  - **Severe exacerbations:** Third-generation cephalosporin plus a fluoroquinolone or an aminoglycoside.

**Corticosteroids**
Intravenous or oral corticosteroids shorten the recovery time, improve lung functions (FEV₁) and hypoxemia.

**Diuretics**
Given to patients with gross right ventricular failure.

**Respiratory stimulants**
May be used when there is no response to the conventional agents. Doxapram in the dose of 1.5–4 mg/minute as infusion is the most often used agent. Other respiratory stimulants are almitrine, nikethamide, medroxy progesterone and acetazolamide.

**Mechanical Ventilatory Support**

- **Noninvasive positive airway pressure ventilation (NIPPV)**
  - NIPPV is by using tight-fitting facemask to deliver BIPAP.
- **Invasive (conventional) ventilation**
  - It is administered via an endotracheal tube.
Management of associated co-morbidities
It is necessary to manage co-morbidities because they are responsible for mortality and hospitalization.

GOLD staging for severity of COPD and management (Fig. 6.10)
It is used for both chronic bronchitis and emphysema.

Emphysema
The word ‘emphysema’ literally means inflation or distension with air. Emphysema can be classified depending on the organ or structure involved as:

- **Pulmonary emphysema** (refer below)
- **Compensatory emphysema/hyperinflation**
  - It is characterized by dilatation of alveoli without destruction of septal walls. It develops as a compensatory response to loss of extensive lung substance elsewhere (e.g., removal of a diseased lung or lobe).
- **Mediastinal emphysema** (Fig. 6.11)
  - It occurs as a result of entry of air rapidly into the mediastinum following rupture of over distended alveoli as in severe bronchial asthma, rupture of emphysematous bulla (during coughing) and rupture of esophagus.
  - Severe mediastinal emphysema can lead to cardiac tamponade.
  - **Auscultation:** It may reveal a crunching sound (mediastinal crunch).
- **Subcutaneous emphysema** (Fig. 6.11)
  - It is characterized by the entry of air into subcutaneous tissue.
  - **Causes:** Penetrating chest injuries, fracture of ribs of intercostals tube introduction.
  - On palpation, it produces a characteristic crepitation or crackling sensation.
  - **Treatment:** Not needed because the air will get absorbed slowly. In severe cases, subcutaneous incisions may be necessary to relieve pressure.

Discuss the etiology, pathology, clinical features, investigations, complications and management of pulmonary emphysema.

Write short essay/note on definition and various types of emphysema.

**Definition:** Emphysema (pulmonary) is a chronic lung disease characterized by abnormal irreversible (permanent) dilatation of the airspaces distal to the terminal bronchiole. This is associated with destruction of their walls but without obvious fibrosis.

**Types of Emphysema/Classification (Figs. 6.12A and B)**
Emphysema is classified according to its anatomic distribution (location of the lesions) within the lobule into four major types: (1) Centriacinar, (2) panacinar, (3) paraseptal, and (4) irregular.
1. **Centriacinar (centrilobular) emphysema:**
   - Dilatation involves the central or proximal parts of the acini (formed by respiratory bronchioles), whereas distal alveoli are spared.
   - Common and severe in the upper lobes, especially in the apical segments.
   - Association: Occurs in heavy smokers and in association with chronic bronchitis and coalworkers’ pneumoconiosis.

2. **Panacinar (panlobular) emphysema:**
   - All the airspaces beyond terminal bronchiole are more or less uniformly/equally dilated.
   - Site: More common in the lower lobes, and is usually most severe at the bases.
   - Associated with $\alpha_1$-antitrypsin ($\alpha_1$-AT) deficiency.

3. **Distal acinar (paraseptal) emphysema:**
   - Dilatation affects the distal airspace at the periphery of the lobule and the proximal portion is normal.
   - It is found near the pleura. Dilated spaces of more than 1 cm in size are known as bullae which may rupture and cause spontaneous pneumothorax.
   - It occurs adjacent to areas of fibrosis, scarring, or atelectasis.

4. **Irregular (scar or cicatricial) emphysema**
   - Acinus is irregularly involved and may be asymptomatic.
   - Most common form of emphysema.
   - Occurs near the scar and is commonly found around old healed inflammatory process such as tuberculous scars.

**Etiology and Pathogenesis (Fig. 6.13)**

- Write short essay/note on etiological factors for emphysema.

The major event in emphysema is destruction of alveolar wall.
- **Mechanism that checks the destruction of alveolar wall:** These include: (1) Antielastases (e.g. $\alpha_1$-antitrypsin) and (2) antioxidants. If these two mechanisms are defective → results in (1) protease-antiprotease imbalance (e.g. $\alpha_1$-antitrypsin deficiency) and (2) imbalance between oxidants and antioxidants.
  - Unchecked inflammation and proteolysis: Develops due to deficiency of the above protective mechanism.
- **Genetic factors**
  - Write short note on $\alpha_1$-antitrypsin deficiency.
    - Deficiency of $\alpha_1$-antitrypsin: It is inherited as autosomal recessive, which exhibits polymorphism → tendency to develop emphysema. $\alpha_1$-antitrypsin is a major inhibitor of proteases (particularly elastase). It is normally present...
in serum, tissue fluids, and macrophages and a balance is maintained between protease and antiproteases. During inflammation, protease (proteolytic enzyme) is secreted by neutrophils and digests the connective tissue of the lung. α1-antitrypsin is a protease inhibitor (antiprotease), preventing this proteolytic digestion. Hence, a deficiency or absence of α1-antitrypsin results in the proteolytic destruction of lung. These patients develop severe panacinar emphysema.

**Clinical Features**

Manifestations appear late until at least one-third of the functioning pulmonary parenchyma is damaged.
- **Dyspnea** is the most striking feature that begins insidiously and steadily progresses ultimately ending in breathlessness on trivial exertion and even at rest.
- **Cough and expectoration** of scanty mucoid sputum.
- **Weight loss**, weakness, anorexia and lethargy is common with advanced disease.

**Physical findings**

**General**: Body build is asthenic, short and thick neck, neck veins may appear distend during expiration and collapse during inspiration. Patient leans forwards, extending the arms to brace himself during sitting posture.

**Respiratory**
- **Inspection**
  - Patient appears **distressed** and **tachypneic, hypertrophy of accessory muscles of respiration** (sternomastoid and scalene muscles), length of the trachea above the suprasternal notch is reduced, apical impulse is invisible or feeble
  - **During inspiration**: **Tracheal descent exaggerated** (Campbell's sign), excavation of the suprasternal and supraclavicular fossae, **indrawing of the costal margins**.
  - **Expiration**: **Prolonged through pursed lips** (purse-lip breathing) and beginning of expiration with a **grunting sound**.
  - **Chest**: Cylindrical or barrel like (barrel-shaped chest), anteroposterior diameter of the chest is markedly increased. Whole chest is in a fixed state of full inspiration. Ribs are placed more horizontally and widely. Chest expansion diminished symmetrically. Thoracic kyphosis is exaggerated and the subcostal angle is widened.

**Fig. 6.13**: Pathogenesis of emphysema. Exposure to environmental toxins (e.g. cigarette smoke) causes inflammatory reaction, cell death and proteolysis of extracellular matrix (ECM). α1-antitrypsin (α1-AT) deficiency also results in increased degradation of ECM.

(IL-8: interleukin 8; TNF: tumor necrosis factor)
- **Dahl Sign**: Above the knee, patches of hyperpigmentation or bruising caused by constant ‘tenting’ position of hands or elbows.
- **Hoover’s sign**: Briefly, during inspiration a paradoxical medial movement of the chest. The ‘subcostal angle’ is the angle between the xiphoid process and the right or left costal margin. Normally, during inhalation the chest expands laterally, increasing this angle. When the diaphragms are flattened (as in COPD), inhalation paradoxically causes the angle to decrease.
- **Harrison’s sulcus**: A horizontal groove where the diaphragm attaches to the ribs; associated with chronic asthma, COPD, and rickets.

**Percussion**: Hyper-resonant percussion note over the lungs, reduced cardiac dullness, and liver dullness is pushed down or absent. Tidal percussion is negative.

**Auscultation**: Diminished intensity of the breath sound, breath sounds are vesicular with prolonged expiration. Scattered, faint, high-pitched, end-expiratory rhonchi may be audible.

**Investigations**
- **Chest X-ray** (Fig. 6.14)
  - **PA view**: Features include low set, flat diaphragm, translucent lung field, long and narrow heart (‘tubular heart’), loss of peripheral vascular markings, prominent pulmonary artery shadows at the hilum and bullae.
  - **Lateral view**: Large retrosternal translucency.
- **Computed tomography**: Can identify emphysema with certainty.
- **Pulmonary function tests** (Table 6.29)
- **Arterial blood gas studies**: Slightly reduced PaO₂ and normal or mildly elevated PaCO₂.

**Complications**
Emphysema progresses steadily and gradually.

**Write short note on pulmonary bullae.**
1. **Pulmonary bullae**
   - They represent inflated thin-walled spaces produced due to the rupture of alveolar walls.
   - May be single or multiple, small or large and resembles an amulet.
   - Usually located in the subpleural region along the anterior borders of lungs.
   - **Complications**: A subpleural bulla may rupture producing spontaneous pneumothorax. Large bullae can interfere with pulmonary ventilation.
2. **Respiratory failure**: Type I and type II respiratory failure can occur.
3. **Pulmonary hypertension and right heart failure** *(cor pulmonale)*: These are late complications and right ventricular failure in emphysema is usually a terminal event.
4. **Severe weight loss**: Leading to emaciation can occur.

**Treatment**: Treatment similar as described for COPD (refer pages 271-3).
- No specific treatment for established case of emphysema. Bronchodilators and steroids may be helpful in few patients.
- **Prevention of progression**: Cessation of smoking and avoidance of occupational exposure.
- **Treatment of aggravating factors and complications**: Treatment of infections, respiratory failure and right heart failure.
- **Physiotherapy**
- **Surgical therapy**: Ablation of giant bullae, lung volume reduction surgery reduced hyperinflation of one or both lungs and/or laser resection.
- **Heart and lung transplantation**: In young patients with severe emphysema due to α₁-antitrypsin deficiency.

**Blue Bloaters (Fig. 6.15A)**

**What are blue bloaters?**
It is a distinctive clinical pattern seen in chronic bronchitis, the characteristics of which are:
- Marked/heavy cyanosis (‘blue’) and peripheral edema (‘bloated’) and secondary polycythemia.
- Current evidence demonstrates that most patients have elements of both bronchitis and emphysema and by physical examination cannot reliably differentiate ‘blue bloaters’ from ‘pink puffers.’
**Pink Puffers (Fig. 6.15B)**

**Q. What are pink puffers?**
- It is a distinctive clinical pattern seen in emphysema of lung.
- Patients are thin and noncyanotic at rest (hence ‘pink’).
- They have marked dyspnea (‘puffer’) and have prominent use of accessory muscle. They develop steadily progressive dyspnea.

**Differences between emphysema and chronic bronchitis (Table 6.30)**

**Q. What are the differentiating features of emphysema and chronic bronchitis?**

**Table 6.30: Differences between emphysema and chronic bronchitis.**

<table>
<thead>
<tr>
<th>Feature</th>
<th>Emphysema</th>
<th>Chronic bronchitis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical features</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>Severe</td>
<td>Mild to moderate</td>
</tr>
<tr>
<td>Cough</td>
<td>Develops after dyspnea starts</td>
<td>Frequent, develops before dyspnea starts</td>
</tr>
<tr>
<td>Sputum—amount and nature</td>
<td>Scanty, mucoid</td>
<td>Copious, purulent</td>
</tr>
<tr>
<td>Frequency of mucopurulent relapses</td>
<td>Less</td>
<td>More</td>
</tr>
<tr>
<td>Cyanosis</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
<td>Late and mild</td>
<td>Early and severe</td>
</tr>
<tr>
<td>Right ventricular failure and respiratory failure</td>
<td>Late and often terminal</td>
<td>Repeated episodes</td>
</tr>
<tr>
<td>Mechanism of airway obstruction</td>
<td>Loss of elastic recoil</td>
<td>Decreased airway lumen due to mucus and inflammation</td>
</tr>
<tr>
<td><strong>Investigations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematocrit (PCV)</td>
<td>Normal</td>
<td>Increased</td>
</tr>
<tr>
<td>PaO₂</td>
<td>Normal to low ‘pink puffer’</td>
<td>Low ‘blue bloater’</td>
</tr>
<tr>
<td>PaCO₂</td>
<td>Normal mildly increased</td>
<td>High (&gt;40)</td>
</tr>
<tr>
<td>FEV₁</td>
<td>Decreased</td>
<td>Decreased</td>
</tr>
<tr>
<td>Diffusing capacity</td>
<td>Reduced</td>
<td>Normal</td>
</tr>
<tr>
<td>Chest X-ray</td>
<td>Features of hyperinflation, bullae and tubular heart</td>
<td>Increased bronchovascular markings and cardiomegaly</td>
</tr>
<tr>
<td>Elastic recoil</td>
<td>Decreased</td>
<td>Normal</td>
</tr>
<tr>
<td>Airway resistance</td>
<td>Normal to slightly increased</td>
<td>Increased</td>
</tr>
<tr>
<td>Cor pulmonale</td>
<td>Late, mild</td>
<td>Early, marked</td>
</tr>
<tr>
<td>Prognosis</td>
<td>Good</td>
<td>Poor</td>
</tr>
</tbody>
</table>

**Figs. 6.15A and B:** (A) Blue bloater (in chronic bronchitis) versus; (B) Pink puffer (in emphysema).
Asthma COPD Overlap Syndrome (ACOS)

**Major Criteria for ACOS:**
- Characterized by persistent airflow limitation with several features usually associated with asthma and several features usually associated with COPD.
- History or evidence of atopy (e.g. hay fever, elevated total IgE).
- Age 40 years or more
- Smoking >10 pack-years, post-bronchodilator FEV₁ <80% predicted and FEV₁/FVC <70%.
- A ≥15% increase in FEV₁ or ≥12% and ≥200 mL increase in FEV₁ post-bronchodilator treatment with albuterol would be a minor criteria.

PULMONARY TUBERCULOSIS

MYCOBACTERIA

Classification

**Write short note on classification of mycobacteria and give an account of disease produced by them.**

Mycobacteria are classified into three groups:
1. *Mycobacterium tuberculosis* complex (*M. tuberculosis, M. bovis and M. africanum*).
2. *Mycobacterium leprae*.
3. Atypical mycobacteria or non-tuberculous mycobacteria (NTM) or mycobacteria other than tuberculosis (MOTT).

**Write short note on mycobacteria other than tuberculosis (MOTT)/non-tuberculous mycobacteria (NTM).**

- MOTT or NTM are ubiquitous in the environment. They occur in soil and water and are not usually pathogenic due to their lack of virulence. Therefore, their isolation from a site that is not normally sterile (e.g. sputum, skin or urine) does not constitute proof of disease. Groups of atypical *Mycobacterium* are listed in Table 6.33.
- Patients with NTM lung disease often have predisposing disease of the lung (e.g. COPD, bronchiectasis, cystic fibrosis, pneumoconiosis, etc.).

- *Mycobacterium avium intracellulare*
  - Also known as MAC (*Mycobacterium avium* complex).
  - Most common non-tuberculous mycobacterial infection associated with AIDS.
  - Symptoms include fever, swollen lymph nodes, diarrhea, fatigue, weight loss and shortness of breath.
  - May develop into pulmonary MAC.
- *Mycobacterium marinum* causes infections of skin and swimming pool granuloma.
- *Mycobacterium ulcerans* cause skin infections.
- *Mycobacterium kansasii* causes lung disease.

Therapeutic options in atypical mycobacterial infections (Table 6.34)

<table>
<thead>
<tr>
<th>Atypical mycobacteria</th>
<th>Therapeutic options</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAC (Mycobacterium avium complex)</td>
<td>Clarithromycin or azithromycin + ethambutol + rifampin</td>
</tr>
<tr>
<td><em>M. xenopi</em></td>
<td>Rifampin + ethambutol + INH</td>
</tr>
<tr>
<td><em>M. kansasii</em></td>
<td>Rifampin + ethambutol should be treated for at least 18 months</td>
</tr>
<tr>
<td><em>M. malmoense</em></td>
<td>Rifampin or ethambutol</td>
</tr>
<tr>
<td><em>M. marinum</em></td>
<td>Rifampin or clarithromycin + ethambutol 2–3 months. Treatment with other antibiotics should be for at least two months</td>
</tr>
<tr>
<td>Rapid growers</td>
<td>Doxycycline, amikacin, imipenem, quinolones, sulfonamides, cefoxitin, clarithromycin</td>
</tr>
<tr>
<td><em>Mycobacterium chelonae</em></td>
<td>Clarithromycin in combination with another agent, sometimes surgical excision is the best approach</td>
</tr>
</tbody>
</table>
TUBERCULOSIS
Tuberculosis (also called Koch’s disease) is a communicable, chronic granulomatous disease caused by Mycobacterium tuberculosis.

Tuberculosis (TB) is caused by four main mycobacterial species collectively termed Mycobacterium tuberculosis complex (MTb): (1) Mycobacterium tuberculosis (reservoir human), (2) Mycobacterium bovis (reservoir cattle), (3) Mycobacterium africanum and (4) Mycobacterium microti. These are obligate aerobes and facultative intracellular pathogens which usually infect mononuclear phagocytes.

- **Majority of tuberculosis are due to Mycobacterium tuberculosis hominis** (human strain). The source of infection is patients suffering from active open case of tuberculosis.
- **Oropharyngeal and intestinal tuberculosis can be due to drinking of milk contaminated by M. bovis** (bovine strain) from infected cows. Routine pasteurization has almost eliminated this source of infection.
- **M. avium and intracellulare are non-pathogenic to normal individuals. They cause infection in patients suffering from AIDS.**

Characteristics of Mycobacteria

- **Write short note on acid-fast bacilli.**
  - It is an aerobic, slender, and rod-shaped bacteria. It measures 2 to 10 μm in length.
  - It has a high lipid content in the cell wall which makes it difficult to stain, but **once stained resists decolorization by acids and alcohol.** Hence, it is termed as acid-fast bacilli (AFB), because once stained by carbol fuchsin (present in Ziehl-Neelsen stain), it is not decolorized by acid and alcohol. Acid fast organisms and structures are listed in Table 6.35.

Epidemiology

- Tuberculosis is common in India. High incidence of tuberculosis is observed with poverty, overcrowding, and chronic debilitating illness. As per WHO 2016, there are an estimated 10.4 million new TB cases worldwide, 10% of which were people living with HIV. TB statistics for India for 2016 give an estimated incidence figure of 2.79 million cases of TB for India. An estimated 1.7 million people died from TB, including nearly 400,000 people who were co-infected with HIV.
- **Diseases associated with increased risk of tuberculosis include diabetes mellitus, Hodgkin lymphoma, malnutrition, immunosuppression, alcoholism, chronic lung disease (e.g. silicosis), and chronic renal failure.**
- **HIV is the most important risk factor.**

Determinants of Virulence

- **Three genes:** (1) kagG-encodes catalase, (2) rpo V-signs factor (initiates transcription of many enzymes) and (3) erp-encodes a protein required for multiplication.
  - **NRAMP-1 gene:** NRAMP1 is a transmembrane protein (a product of NRAMP1 gene) **inhibits microbial growth** and it determines the susceptibility to tuberculosis. In individuals with polymorphisms in the NRAMP1 (natural resistance-associated macrophage protein 1) gene, tuberculosis may progress due to the absence of an effective immune response.

Mode of Transmission

- **Inhalation:** It is the most common mode of transmission. Source of organisms is an active open case of tuberculosis to a susceptible individual. Infection spread by the inhalation of respiratory droplet from other infected patients.
- **Ingestion:** Tuberculosis may be transmitted by drinking nonpasteurized milk from infected cows contaminated with M. bovis. It causes oropharyngeal and intestinal tuberculosis. Nowadays, the ingestion mode of transmission occurs when a patient with open case of tuberculosis swallows the infected sputum results in tuberculosis of intestine.
- **Inoculation:** It is extremely rare and may develop during postmortem examination, while cuts resulting from handling tuberculous infected organs.

Primary Tuberculosis

- **Discuss the pathogenesis, pathology, clinical manifestations and diagnosis of primary pulmonary tuberculosis.**
- **Write short essay/note on primary complex of Ranke and Ghon's complex/features of primary tuberculosis.**

Initial infection that occurs on first exposure to the organism (Mycobacterium tuberculosis) in an unsensitized (previously unexposed tuberculin-negative) individual is known as primary tuberculosis. First infection of the lung caused by the tubercle bacillus is termed as primary pulmonary tuberculosis.
Morphology

Gross
- **Site**: In the lungs, post-primary (secondary) tuberculosis usually involves the **apex of the upper lobes** of one or both lungs, **within 1 to 2 cm of the apical pleura**. It commonly involves apical and posterior segments of the upper lobe or apical segment of the lower lobe. This predilection may be due to good ventilation, decreased blood and lymphatic supply of these regions in the erect posture, and the oxygen tension that favors survival of the strictly aerobic tubercle bacilli.
- **Appearance**: **Initially small focus** (less than **2 cm in diameter**) of consolidation, sharply circumscribed, firm, and **gray-white to yellow** in color. The central caseated liquefied material of a tuberculous primary lesion may be discharged into a bronchus and forms a tuberculous cavity in the lung.
- **Regional lymph nodes involvement is not as prominent as that seen in primary tuberculosis.**

**Fate of Secondary Tuberculosis (Fig. 6.16)**

**Healing**: In immunocompetent individuals, localized, apical, focus may **heal with fibrosis and calcification** rarely ossification.

**Progress**: It may occur along several different pathways.
- **Progressive pulmonary tuberculosis**: It occurs mainly in the elderly and immunosuppressed. Apical lesion may expand into surrounding lung and may erode into bronchi and vessels.
  - **Erosion into bronchi**: It leads to release of the central area of caseous necrosis → resulting in a ragged, irregular **apical cavity** surrounded by fibrous tissue. This produces an **important source of infection**, because when the patient coughs, sputum contains bacteria.
  - **Erosion of blood vessels**: It may result in hemoptysis.
- **Spread of infection**: If the treatment is inadequate or if host defenses are impaired, the infection may spread via: 1) airways, 2) lymphatics or 3) blood vessels.
  - **Local/direct spread**: Tuberculosis can directly spread to the surrounding tissue. In the lung local spread to the pleura may result in serous **pleural effusions**, **tuberculous empyema**, or **obliterative fibrous pleuritis**.
  - **Spread through bronchi/airways**: It may produce tuberculous pneumonia.

![Fig. 6.16: Progress and complications of secondary tuberculosis of lung.](image-url)
Classical physical signs of consolidation (dullness to percussion), cavitation, fibrosis, bronchiectasis, pleural effusion or pneumothorax may be present.

Cavernous bronchial breathing with post-tussive suction may be heard if there is a superficial collapsible cavity.

There may be bronchial breathing in the upper part and localized wheeze due to local tuberculous bronchitis or pressure by a lymph node on a bronchus may be heard. In chronic tuberculosis when accompanied by fibrosis may show evidence of volume loss and mediastinal shift.

Extrapulmonary manifestations depend on the organ/system involved.

Conditions/diseases that favor reactivation/reinfection of tuberculosis are presented in Table 6.37.

Investigations

Q. Write short note on diagnosis, investigations of pulmonary tuberculosis.

Presence of an unexplained cough for more than 2–3 weeks, particularly in regions where TB is prevalent, or typical chest X-ray changes, should prompt for further investigation.

Blood examination

- Anemia: Moderate degree
- White cell count: Usually normal or below normal
- ESR: Usually raised.
- Other findings:
  - Serum electrolytes: Hyponatremia and hyperkalemia may be observed in severe disease.
  - Liver function tests: Occasionally may be impaired.

Radiological examination

- For practical purposes, a normal chest radiograph excludes the diagnosis of pulmonary tuberculosis (Fig. 6.17).

Radiological Features of Pulmonary Tuberculosis (Table 6.38)

Q. Write short note on the radiological features of pulmonary tuberculosis.

For all practical purposes, a normal chest radiograph excludes the diagnosis of pulmonary tuberculosis.

- Radiological findings: It shows ill-defined opacification in one or both of the upper lobes. As the disease progresses features of consolidation, collapse and cavitation develop to varying degrees (Fig. 6.18). It is often difficult to distinguish between active from quiescent form of tuberculosis on radiological criteria alone, but the presence of a miliary pattern or cavitation favors active disease.
In extensive disease, collapse may cause significant displacement of the trachea and mediastinum. Occasionally, a caseous lymph node may drain into an adjoining bronchus, resulting in tuberculous pneumonia.

**CT chest:** It may be useful in evaluating parenchymal and lymph node lesions. It may show **tree in bud appearance** (Fig. 6.18).

**18F-FDG PET scans and 11C-choline PET scans may be done in few selected patients.**

**Sputum examination**

- **Direct microscopic examination of sputum:** It remains the most important first step investigation in pulmonary TB. Three specimens of sputum should be examined and if two of these smears are positive, diagnosis of TB is certain.
  - A **first spot specimen:** Obtained when the patient presents himself.
  - An **early morning specimen:** When the patient returns with an early morning specimen.
  - A **second spot specimen:** When the patient returns with an early morning specimen.

- **Revised WHO definition of a new sputum smear-positive case of pulmonary tuberculosis:** Presence of at least one acid fast bacillus in at least one sputum sample in countries with a well-functioning external quality-assurance system. Presently, WHO recommends that the number of sputum specimens to be examined for screening of tuberculosis cases can be **reduced from three to two**, in places (i) where a well-functioning external quality-assurance system exists, (ii) where the workload is very high and (iii) human resources are scarce.

- **Stain:** Rapid identification of the presence of tubercle bacilli by immediate stains is essential and should be done within 24 hours. The most effective stains are the Ziehl–Neelsen and rhodamine–auramine. Auramine-rhodamine staining is more sensitive (though less specific) than Ziehl–Neelsen.

- **Culture of sputum:** A positive sputum smear is sufficient for the presumptive diagnosis of TB, but definitive diagnosis requires culture of tubercle bacillus. Smear-negative sputum should also be cultured.

- **Culture media:** It may be
  - Liquid/broth culture (Middlebrook 7H12) or the non-radiometric mycobacteria growth indicator tube (MGIT)): Faster growth (1–3 weeks) occurs in liquid media. The BACTEC radiometric growth detection method detects mycobacterial growth by measuring the liberation of $^{14}$CO$_2$ following metabolism of $^{14}$C-labeled substrate present in the medium. The growth can be detected in 4–8 days.
  - Solid media (Löwenstein–Jensen slopes): MTB grows slowly and may take between 4 and 6 weeks.

- **Drug sensitivity testing:** Should be done in selected cases. It is important in patients with a previous history of TB, treatment failure or chronic disease, and in those who are resident in or have visited an area of high prevalence of resistance, or who are HIV-positive. Using liquid culture in the presence of antimycobacterial drugs (usually first line therapy initially) establishes the drug sensitivity for that strain and usually takes approximately 3 weeks.

- **Nucleic acid amplification (NAA) tests:** The Amplified Mycobacterium tuberculosis Direct (MTD) test and the Gene Xpert MTB/RIF test. NAA is more sensitive than smear but less sensitive than culture, as few as 1 to 10 organisms/mL may give a positive result. Resistance to rifampin can be detected by Xpert MTB/RIF or MTBDRplus, resistance to isoniazid can be detected by MTBDRplus.

**Other investigations**

- **Laryngeal swab,** early morning gastric lavage and bronchoalveolar lavage samples can be used for detecting AFB.

- **Tuberculin test:** It is used for diagnosis but is less valuable. However, this test may be negative in patients with active tuberculosis associated with malnutrition or other diseases. It may be positive in patients without active tuberculosis. Strongly positive test favors tuberculosis, where as a negative test does not exclude tuberculosis.

---

**Table 6.38: Radiological features of tuberculosis of lung.**

<table>
<thead>
<tr>
<th>Radiological shadows that strongly suggest tuberculosis</th>
<th>Radiological shadows that may be due to tuberculosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Patchy or nodular shadows in the upper zone (on one or both sides)</td>
<td>• Oval or round single shadow (tuberculoma)</td>
</tr>
<tr>
<td>• Cavitation (especially if more than one)</td>
<td>• Hilar and mediastinal shadows (due to enlarged lymph nodes)</td>
</tr>
<tr>
<td>• Calcified lesion</td>
<td>• Diffuse small nodular shadows (miliary tuberculosis)</td>
</tr>
<tr>
<td>• Pleural effusion/thickening</td>
<td></td>
</tr>
</tbody>
</table>

**Fig. 6.18:** Tree in bud appearance of tuberculosis on CT.
Write short note on newer methods of diagnosis of tuberculosis.

• Interferon gamma release assays (IGRAs)
  - IGRAs are in vitro tests of cellular immunity. These assays measure cell-mediated immune response by quantifying interferon gamma (IFN-γ) released by T cells in response to stimulation by Mycobacterium tuberculosis specific antigens. These specific antigens include early secretory antigenic target-6 (ESAT-6) and culture filtrate protein-10 (CFP10).
  - The test does not differentiate between active and latent infection. This test requires high cost and trained personnel.

• Other methods of diagnosis
  - MGIT (Mycobacteria growth indicator tube) method: In this method, growth is detected by a non-radioactive detection system using fluorochromes for detection and drug screening.
  - Identification by mycolic acids using high-pressure liquid chromatography.
  - ELISA testing for IgM and IgA: It is commonly used but has low specificity.
  - Mycobacterial-specific phages (reporter phages) to detect luciferase gene. It can be used to detect drug-resistant isolates.

Causes of Hemoptysis in Pulmonary Tuberculosis

Q. List the causes of hemoptysis in pulmonary tuberculosis.

• Hemoptysis from a pulmonary cavity
  - Rasmussen’s aneurysm: Blood vessels traversing a tuberculous cavity can undergo changes due to inflammatory and necrosis. Over a period of time these vessels may develop aneurysmal dilatation (Rasmussen’s aneurysm). These aneurysms may rupture resulting in hemoptysis.
  - Allergic response of vessel: Occasionally, intense allergic response to antigens of tubercle bacilli can damage the walls of the blood vessels in and around the tuberculous cavities leading to hemoptysis.

• Hemoptysis from endobronchial tuberculosis
  - Tuberculosis of endobronchial region may be surrounded by vessels with small aneurysmal dilatation. Rupture of these aneurysms can produce hemoptysis.
  - Occasionally, sloughing of the part of the granuloma may result in hemoptysis.

• Hemoptysis as a sequel of pulmonary tuberculosis
  - Open-healed cavities: A tuberculous cavity may persist as a sequelae following chemotherapy which are designated as 'open-healed cavities'/INH cysts. The aneurysmal dilations of vessels may also persist in these open-healed cavities which can rupture producing hemoptysis.
  - Post-tuberculous bronchiectasis: The upper lobe bronchiectasis is common sequelae of pulmonary tuberculosis. This may be characterized by repeated attacks of hemoptysis without sputum production (bronchiectasis sicca or dry bronchiectasis).
  - Broncholith: Calcification in a primary/Gohn focus or lymph node may be extruded into a bronchus as a ‘broncholith’ and can cause hemoptysis. Hemothorax may also result from the broncholith eroding through blood vessels.
  - Aspergilloma: Treated and healed tuberculous cavities may sometimes remain open and can be infected by the fungus Aspergillus fumigatus. This may produce a fungal ball (aspergilloma) in the cavity and can present as severe hemoptysis.

• Hemoptysis due to scar carcinoma.

Tuberculin Skin Test

Q. Write a short note on tuberculin test/Mantoux test?

First infection with mycobacteria leads to development of delayed hypersensitivity to M. tuberculosis antigens (tuberculin) and this is detected by the tuberculin skin test.

Tuberculins: There are two commonly used tuberculins in present use:
1. PPD-S has been adopted as the international standard for PPD of mammalian tuberculin.
2. PPD-RT23 is widely used in epidemiological studies throughout the world.

Mantoux test (Fig. 6.19): It is ideal to begin the test with 5 IU PPD-S or 1 or 2 IU PPD-RT23.

Method

• Select an area of skin at the junction of the mid and upper thirds of flexure surface of the left forearm.
• Skin is cleaned with soap and water and allowed to dry.
• Using a tuberculin syringe and an intradermal needle, inject 0.1 mL of the tuberculin solution strictly intradermally. It should result in papule in the skin measuring 5–6 mm in diameter.
Reading and Interpreting the Result

- The test is read after 48–72 hours.
- If a reaction has taken place, there will be an area of erythema (redness) and an area of induration (thickening) of the skin. Measure the diameter of induration across the transverse axis of the arm. The reaction is considered positive if an area of induration of the skin of 10 mm diameter or more at the site of injection of PPD. The amount of erythema (redness) present is not important. Induration ≥5 mm is considered as positive in patients with HIV infection (or risk factors for HIV infection, but unknown status), recent close contact to person with known active TB, patients with chest X-ray consistent with prior TB, patients with organ transplants and other immunosuppressed patient.

Significance

- **Positive tuberculin test:** Indicates T-cell–mediated immunity to mycobacterial antigens. A strongly positive test is particularly valuable in children, especially very young children and favors the diagnosis of tuberculosis.
- **False-negative reactions:** If the diameter of induration is below 10 mm, the test is considered negative. But a negative test does not exclude tuberculosis. It is seen in certain viral infections, sarcoidosis, malnutrition, Hodgkin lymphoma, immunosuppression, and overwhelming active tuberculous disease, HIV infection, measles, chickenpox, glandular fever (infectious mononucleosis), cancer, corticosteroids and similar drugs.
- **False-positive reactions:** It seen in infection by atypical mycobacteria or prior vaccination with BCG (Bacillus Calmette-Guerin) or lymphoma. Most infants immunized with BCG at birth have a negative tuberculin test by 1–2 years. In infants immunized after 1 year, the tuberculin reaction often remains positive for some years. It may also be positive in NTM infections.

Latent Tuberculosis

**Describe latent tuberculosis infection (LTBI).**
- In the majority of individuals infected by *Mycobacterium tuberculosis*, the immune system contains the infection and the patient develops cell mediated immune memory to the bacteria. These individuals do not currently have active tuberculosis disease. This is termed latent tuberculosis.
- Individuals with latent tuberculosis are at risk of progression to active tuberculosis. About 5–10% is the lifetime risk of progression. The increased risk of progression from latent tuberculosis to active tuberculosis is during the first two years after infection. Groups of individuals at high-risk of tuberculosis infection are listed in Table 6.39.

Groups at increased risk of progression to active tuberculosis are listed in Table 6.40.

Screening for Latent Tuberculosis

- Tuberculin skin test
- T-cell IGRAs.

Prophylaxis (to Prevent Development of Active Tuberculosis)

Refer tuberculosis prophylaxis on page 301.

**ANTITUBERCULOUS DRUGS (ATDS)**

**Write short note on the terms ’bactericidal action’ and ’sterilizing action’ in relation to antituberculous drugs.**

- **Bactericidal action:** It is the capacity of antituberculous drugs to rapidly kill large numbers of actively metabolizing bacilli. Most of the antituberculous drugs (except thiacetazone and PAS) are bactericidal. Isoniazid is the most potent bactericidal. Ethambutol is bacteriostatic at low doses and bactericidal at high doses.
- **Sterilizing action:** It is the capacity of antituberculous drugs to kill special populations of slowly or intermittently metabolizing semi-dormant bacilli (so-called ’persisters’), e.g. rifampicin and pyrazinamide.

**Write short essay/note on:**
- Management of pulmonary tuberculosis, antituberculous drugs and their dosages in adults.
- List the first and second line antituberculous drugs. Explain the rationale for using a multidrug regime.
- Bactericidal drugs used in the treatment of tuberculosis.
Classification of Antituberculous Drugs (Table 6.41)

First Line Antituberculous Drugs

- **Isoniazid (INH)**
  - It is primarily tuberculocidal drug.
  - **Mechanism of action:** Inhibition of mycolic acid cell wall synthesis via O2 dependent pathways (e.g. catalase-peroxidase reaction). Bactericidal against rapidly multiplying and bacteriostatic against resting bacilli.
  - **Active against both extracellular and intracellular organisms.** Resistance occurs spontaneously in 1 in 10^5 bacilli.
  - **Pharmacokinetics:**
    - Excreted in urine: Decrease dose if creatinine clearance <30 mL/minute.
    - Slow vs. rapid acetylators (t ½)
  - **Adverse effects:**
    - Peripheral neuropathy: Commoner in slow acetylators, diabetic, alcoholics, malnourished patients
      - Prevention: Pyridoxine 10 mg/day.
      - INH neurotoxicity is treated by pyridoxine 100 mg/day. Convulsions should be treated by IV pyridoxine 100 mg.
      - Other TB-related drugs that cause peripheral neuropathy: Pyridoxine, ethambutol and cycloserine.
    - Hepatitis
      - Increased risk: Age >35 years, alcohol abuse, rapid acetylators, co-administration of rifampin, pyrazinamide, HIV infection, chronic hepatitis B, pregnant females, immediate postpartum (3 months).
      - Dose related and is reversible on stopping the drug.
    - Others: Idiosyncratic reactions, SLE, gynecomastia acne, rash, anemia psychosis, memory impairment, optic neuritis (atrophy).

- **Rifampin**
  - Semisynthetic derivative of rifamycin B obtained from *Streptomyces mediterranei*.
  - **Mechanism of action:** Inhibition DNA-dependent RNA synthesis. Bactericidal against both extracellular and intercellular organisms.
  - **Adverse effects Patients have discolored (orange) body secretions,** hepatitis, thrombocytopenic purpura, respiratory syndrome, shock, renal failure (azotemia). Minor effects are:
    - Cutaneous (red man) syndrome: Flushing, pruritis, rash (especially face and scalp). Exfoliative dermatitis is more frequent in HIV-positive TB patients
    - Influenza-like (Flu) syndrome
    - Abdominal syndrome: Pseudomembranous colitis (especially rifabutin).
  - **Newer rifampicin-related antitubercular agents**
    - **Rifabutin**
      - **Actions:** It is related to rifampin. Active against rifampicin-resistant *M.tuberculosis*; more active than rifampicin against *M. avium* intracellulare complex/NTM; longer t ½; extent of absorption unchanged with food; recommended instead of rifampicin in patients on pulmonary infections.
      - **Dose:** It is recommended for tuberculosis in HIV-infected patients who are on protease inhibitors. Dose is 150 mg/day.
      - **Adverse effects:** GI distress, rash, myalgias and insomnia, Flu-like syndrome, anterior uveitis, leukopenia, skin discoloration and hepatitis. Patients also have discolored (orange) body secretions.
    - **Rifapentine**
      - **Features:** It is lipophilic and has longer duration of action. Mycobacteria resistant to rifampicin are also resistance to this drug. May be used in the treatment of pulmonary tuberculosis in place of rifampicin. Higher likelihood of relapse, but lower risk of adverse effects and less frequent administration than with rifampicin
      - **Dose:** 600 mg once or twice a week
      - **Side effects:** Similar to rifampicin.
Q. Write short essay/note on uses of rifampin.

Uses of rifampin is listed in Box 6.6.

3. Pyrazinamide
   - Chemically similar to INH.
   - **Mechanism of action**: Inhibition of mycolic acid cell wall synthesis and resembles INH. Bactericidal to slowly metabolizing bacilli in phagosome/granuloma. Most effective in acidic pH (<6.0).
   - **Adverse effects**
     - Hepatotoxicity: Dose dependent
     - Arthralgias, polyarthralgias (especially shoulders) are common. Arthralgias are not related to the serum uric acid level.
     - Hyperuricemia is common due to inhibition of uric acid secretion by kidney. Development of new-onset gout is rare, but pre-existing gout may be exacerbated.

4. Ethambutol
   Q. Write short essay/note on ethambutol.
   - **Mechanism of action** (MOA): Inhibits arabinose (arabinosyl transferase) involved in arabinogalactan synthesis. Bacteriostatic.
   - Excreted in urine (Dose reduction required for patients with creatinine clearance < 50 mL/min).
   - **Adverse effects**
     a. **Retrobulbar neuritis**: Dose-dependent. Usually occurs after many months of treatment. Manifests with reduced visual acuity, central scotoma, disturbance of red-green discrimination (loss of ability to see green). Permanent blindness may develop if not discontinued.
     b. Others: Hyperuricemia, peripheral sensory neuropathy.

5. Streptomycin
   - It is an aminoglycoside, bactericidal antibiotic derived from *Streptomyces griseus*.
   - **Adverse effects**
     a. **Otoxicity, cochlear and vestibular damage, deafness and neuromuscular blockage**: Dosage should be reduced if headache, vomiting, vertigo and tinnitus occur. Avoid in young children.
     b. **Renal damage-nephrotoxicity** (non oliguric renal failure): Dosage must be reduced by half immediately if (1) urinary output falls, (2) if albuminuria occurs or (3) if tubular casts are detected in the urine.
     c. **Others**: Rare and include hemolytic anemia, aplastic anemia, agranulocytosis, thrombocytopenia and lupoid reactions.

**Mode of Action of First-Line Antituberculous Drugs**

In a tuberculous lesion (particularly in a cavitary lesion), mycobacteria exist in several foci (Table 6.42).

**Second Line Antituberculous Drugs**

Q. Write short note on second line antituberculous drugs.

- **Ethionamide**: Structurally related to INH and acts by inhibiting the mycolic acid synthesis. It is effective against bacilli resistant to other drugs and are effective in infections due to atypical mycobacteria. It is effective against both intracellular and extracellular organisms.
- **Cycloserine**: Mainly bacteriostatic and acts by inhibiting the synthesis of the bacterial cell wall. It is effective against bacilli resistant to INH or streptomycin and against atypical mycobacteria. Antitubercular activity is less than that of these two drugs.
- **Fluroquinolones**: Ciprofloxacin, ofloxacine, levofloxacine, moxifloxacine and gatifloxacine are active against *M. tuberculosis*, even in cases resistant to other drugs. Given orally or IV. Useful in treating infections resistant to standard drugs and in relapse cases.
- **Capreomycin**: It is bactericidal and its mechanism of action, pharmacokinetics and adverse reactions are similar to those of streptomycin. Administer with caution in presence of renal impairment.
- **Kanamycin and amikacin**: Both are bactericidal and are active against bacilli resistant to streptomycin, INH and cycloserine.
- **Macrolides**: Newer macrolides azithromycin and clarithromycin also have action against tubercular bacilli. They are used to treat typical mycobacterial infection as well as in relapse cases.
- **Initial phase:** Lasts for 2 to 3 months and aimed to rapidly kill majority of mycobacteria. The symptoms resolve, sputum becomes negative and the patient becomes non-infectious.

- **Continuation phase:** It lasts for 4 to 6 months during which the remaining bacilli are eliminated so that relapse does not occur.

Advantages of short course of chemotherapy is mentioned in Box 6.8.

**WHO (2009) Definitions**

- **New case:** A patient who has never had been treated for TB or not had anti-TB drugs for less than one month. New case may have positive or negative bacteriology and may have tuberculosis at any anatomical site.

- **Previously treated case:** It is defined as a newly registered episode of TB in a patient who has received one month or more of anti-TB drugs in the past. A culture and drug sensitivity test should be done before starting treatment. It is also referred to as ‘retreatment cases’ and forms a heterogeneous group composed of several subcategories:
  - **Relapse:** A patient who has been previously treated for TB and was declared cured and is now been diagnosed bacteriologically positive tuberculous case (either a true relapse or a new episode of TB caused by reinfection).
  - **Treatment after failure:** A patient who have been previously treated for TB and whose treatment failed at the end of course of treatment. The sputum smear or culture is positive at 5 months or later during treatment. This includes patients who have a multidrug-resistance strain at any point of time during the treatment.
  - **Treatment after loss to follow-up patients** have previously been treated for TB and were declared lost to follow-up at the end of their most recent course of treatment (previously known as treatment after default patients) and now has bacteriologically positive tuberculosis.
  - **Treatment after default:** A patient who returns to treatment with positive bacteriology, following interruption of treatment for two months or more.
  - **Other:** All cases which does not fit the above definitions. It includes patients who are sputum smear-positive at the end of a re-treatment regimen (previously defined as chronic cases) and who may be resistant to the first-line drugs.

**Categories of Diagnosis and Treatment**

Treatment regimen for tuberculosis is presented in Table 6.44.

### Table 6.44: Treatment regimen for tuberculosis.

<table>
<thead>
<tr>
<th>A. DOTS (Directly observed treatment, short course)</th>
<th>Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. New (Category 1)</td>
<td></td>
</tr>
<tr>
<td>Earlier CATEGORY I</td>
<td></td>
</tr>
<tr>
<td>New smear-positive patients</td>
<td></td>
</tr>
<tr>
<td>New smear negative pulmonary TB with extensive parenchymal invasion</td>
<td>2 months (HRZE) + 4 months (HRE)</td>
</tr>
<tr>
<td>Severe concomitant HIV disease; or</td>
<td>Duration: 6 months</td>
</tr>
<tr>
<td>New cases of severe forms of extrapulmonary TB</td>
<td></td>
</tr>
<tr>
<td>Earlier CATEGORY III</td>
<td></td>
</tr>
<tr>
<td>New cases of smear negative pulmonary TB</td>
<td></td>
</tr>
<tr>
<td>Less severe forms of extrapulmonary TB</td>
<td></td>
</tr>
<tr>
<td>2. Previously Treated (Category 2)</td>
<td></td>
</tr>
<tr>
<td>Earlier CATEGORY II includes previously treated sputum smear-positive pulmonary TB</td>
<td>2 months (HRZES) followed by 1 month (HRZE), followed by 5 months (HRE)</td>
</tr>
<tr>
<td>Relapse</td>
<td>Duration: 8 months</td>
</tr>
<tr>
<td>Treatment after interruption</td>
<td></td>
</tr>
<tr>
<td>Treatment failure</td>
<td></td>
</tr>
</tbody>
</table>

| B. DOTS PLUS                                        |         |
| 1. Earlier CATEGORY IV                              |         |
| Includes MDR and chronic TB cases (still sputum-positive after supervised retreatment) | 6–9 months (KM LVX, ETO CS, Z, E) followed by 18 months (LVX, ETO, CS, E) |
| Duration: 24–27 months                              |         |
| 2. Earlier CATEGORY V                               |         |
| Extensively Drug Resistant TB (XDR TB)              |         |
| 6–12 months intensive phase followed by 18 months continuation phase (Capreomycin, PAS, Moxifloxacin, Clofazamine, Linezolid, Amoxicillin/clavulnate, Clarithromycin, Thiacetazone) | Duration: 24–30 months |

| C. NON DOTS                                         |         |
| Rare TB patients may need non-rifampicin and non-pyrazinamide regimen | 2 SHE + 10 HE OR 12 HE |

**Note:** Since 2017 the thrice weekly regimen has been changed daily regimen.

(H: isoniazid; R: rifampin; Z: pyrazinamide; E: ethambutol; S: streptomycin; KM: kanamycin; LVX: levofloxacin; ETO: etionamide; CS: cyclosporine; PLHIV: people living with HIV)
Prim ary drug resistance and initial drug resistance
- Primary drug resistance
  - It develops in patients who have not received any antituberculous chemotherapy before or received it for less than 1 month.
  - Cause: Infection by drug resistant organism from another patient with secondary resistance due to inadequate chemotherapy.
- Initial drug resistance: When it is impossible to obtain a reliable history of previous chemotherapy from a new drug resistant patient, it is better to term it has initial drug resistance. This covers both true primary and undisclosed acquired resistance.
- Secondary or acquired drug resistance: Resistance to one or more antituberculous drugs, usually due to incorrect chemotherapy.
- Natural drug resistance: Mycobacterial strains which have never been exposed to any antibacterial drug are called 'wild strains.' Thus, natural drug resistant strain is a wild strain resistant to a particular drug but never having any contact with it. Thus, neither the patient with naturally resistant bacilli nor his source of infection has had chemotherapy in the past.
- Transient drug resistance: A positive culture of bacilli may be resistant to one or more (rarely two) drugs of a regimen during the course of successful chemotherapy. This may be due to resistant organisms for unknown reasons outlived the sensitive part of the bacterial population. Transient resistance does not need any change of treatment, since it does not result in treatment failure.

**Q.** Write short essay on multidrug-resistant (MDR) tuberculosis, its diagnosis and management.

- Multiple drug resistance or multidrug resistant TB
  - Multidrug resistant tuberculosis (MDR-TB) is a form of TB that is resistance to at least both of INH and rifampicin, with or without other drug resistance. Hence, a patient should not be classified as multidrug resistant disease if the patient has an infection with a bacterium susceptible to rifampicin but resistant to many other drugs.
  - MDR-TB can rarely be observed in new cases. It is more common in individuals in re-treatment cases (prior history of TB, particularly if treatment has been inadequate, and those with HIV infection). It is a man-made phenomenon.
  - Chronic cases and MDR-TB cases are not synonymous. Chronic patients probably have MDR-TB because they have previously received at least two full courses of treatment with essential antituberculous drugs.
- Extensive drug resistance TB (XDR-TB)
  - Extensively drug resistance TB is a form of TB that is resistant to at least four of the core anti-TB drugs. These drugs include most important (core) anti-TB drugs, (1) isoniazid and (2) rifampicin and (3) injectable second-line aminoglycoside drugs (amikacin, capreomycin or kanamycin) + (4) fluoroquinolone (such as ofloxacin or moxifloxacin).
- Totally drug resistant TB or (Extremely XXDR, TDR)
  - Totally drug resistant tuberculosis (TDR-TB) is a form of TB strains that shows in-vitro resistance to all first and second line drugs tested (isoniazid, rifampicin, streptomycin, ethambutol, pyrazinamide, ethionamide, para-aminosalicylic acid, cycloserine, ofloxacin, amikacin, ciprofloxacin, capreomycin, kanamycin).
  - First reported in 2003 from Italy. In early January 2012, twelve cases had been diagnosed in Mumbai and all cases the strain of TB was resistant to all first and second line antitubercular drugs.

Factors contributing to the emergence of drug-resistant TB are listed in Table 6.45.

**Table 6.45:** Factors contributing to the emergence of drug-resistant TB.

- Drug shortages
- Use of poor-quality drugs
- Inadequate treatment regimen
- Inadequate supervision of therapy
- Poor absorption of drugs
- Development of adverse drug reactions
- Inadequate duration of treatment
- Infection due to organisms with primary resistance
- Transmission of drug-resistant strains
- Prior antituberculosis treatment
- Treatment failure (smear-positive at 5 months)
- Lack of good laboratory facilities to monitor drug susceptibility
- Genetic factors

**Q.** Write short essay/note on common causes of drug resistance.

**Suspicion of Drug Resistant TB**
- A close contact of drug resistant TB case
- All retreatment cases
- Extensive disease at start of treatment
- Extrapulmonary TB not responding to standard ATT regime.
- Treatment failures
- No sputum conversion after initial 2 months of ATT
- All HIV patients with TB
The overlying skin is frequently indurated or there can be sinus tract formation with draining caseous material but characteristically there is no erythema (cold abscess formation). The diagnosis is established by fine-needle aspiration biopsy. TB lymphadenitis is seen in nearly 35% of extrapulmonary TB cases.

Antituberculous drugs are highly effective for lymph node tuberculosis. Scrofuloderma is a mycobacterial infection of the skin caused by direct extension of tuberculosis into the skin from underlying structures or by contact exposure to tuberculosis.

**Tuberculous Osteomyelitis**

Tuberculous osteomyelitis is usually solitary but in patients with acquired immunodeficiency syndrome, it is frequently multifocal. It tends to be more destructive and resistant to control than pyogenic osteomyelitis.

- **Age:** Usually adolescents or young adults in developing countries.
- **Source of infection:** Pulmonary or extrapulmonary tuberculosis.
- **Predisposing factors:** Diabetes, elderly, immune compromised states and general debility.
- **Route of infection:**
  - **Blood-borne:** Usually blood-borne infection, which is from a focus of active pulmonary or extrapulmonary disease.
  - **Direct extension:** From lung into a rib and tracheobronchial nodes into adjacent vertebrae.
- **Sites:**
  - Spine (thoracic and lumbar vertebrae) commonly known as Pott’s disease. The infection breaks through intervertebral discs to involve multiple vertebrae and extends down into the soft tissues forming abscesses (cold abscess–psoas abscess).
  - Knees and hips.
- **Clinical course:**
  - Low-grade fever with evening rise of temperature
  - Pain on motion, localized tenderness
  - Weight loss.
- **Complications:**
  - **Spine:**
    - Destruction of vertebrae: Causes severe scoliosis or kyphosis and neurologic deficits due to spinal cord and nerve compression.
    - Psoas abscess: Infection from spine may rupture into the soft tissue anteriorly and pus and necrotic debris may drain along the spinal ligaments and form a cold abscess, i.e. an abscess lacking acute inflammation. Psoas abscess is the condition in which infection from lower lumbar vertebrae dissects along the pelvis, and appears as a draining sinus of the skin in the inguinal region. It may be the first manifestation of tuberculous spondylitis.
      - Tuberculous arthritis
      - Sinus tract formation
      - Amyloidosis.

**Tuberculous Meningitis (refer pages 980-2)**

**Gastrointestinal Tuberculosis**

- TB can affect any part of the bowel.
- Upper gastrointestinal tract involvement is rare.

**Intestinal Tuberculosis**

Discussed on pages 759-62.

Extrapulmonary sites of tuberculosis and their presentation are summarized in Table 6.47 and Figure 6.20.

<table>
<thead>
<tr>
<th>Extrapulmonary site</th>
<th>Presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pleural</td>
<td>Pleural effusion, pleuritis</td>
</tr>
<tr>
<td>Lymph nodes</td>
<td>Tuberculous lymphadenopathy (including mediastinal) nonhealing sinuses</td>
</tr>
<tr>
<td>Skeletal system</td>
<td>Tuberculous osteomyelitis, cold abscess, vertebral tuberculosis, pyarthrosis</td>
</tr>
<tr>
<td>Nervous system</td>
<td>Tuberculous meningitis tuberculous arteritis, cerebral tuberculosis</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Ulcerations of the tongue, intestinal tuberculosis, tuberculous peritonitis</td>
</tr>
<tr>
<td>Pericardium</td>
<td>Pericardial effusion and tamponade, constrictive pericarditis</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>Renal tuberculosis, salpingitis, tubal abscess, tuberculous epididymitis</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>Addison's disease (tuberculous adrenalitis), skin tuberculosis (Scrofuloderma, Lupus vulgaris, tuberculids), phylacteural keratoconjunctivitis, choroiditis, iritis, erythema nodosum</td>
</tr>
</tbody>
</table>
Miliary or Disseminated TB

Q Discuss the pathogenesis, types, clinical features, diagnosis and management of miliary tuberculosis in adults.

Miliary TB is the disseminated form of tuberculosis. The lesions are usually yellowish granulomas 1–2 mm in diameter. These lesions resemble millet seeds (hence termed miliary).

Route of Spread

Miliary tuberculosis results from widespread hematogenous dissemination of tubercle bacilli. The tubercle bacilli may enter the bloodstream either hematogenous or lymphatic route.

Types

Q Write short essay/note on miliary tuberculosis/non-reactive miliary tuberculosis/ disseminated non-reactive tuberculosis.

Clinically, the miliary TB patients may be divided into three different types: (1) Classical (acute) miliary tuberculosis, (2) cryptic (obscure) miliary tuberculosis and (3) non-reactive miliary tuberculosis.

1. Classical (acute) miliary tuberculosis
   - Age: Can occur at any age, but more commonly affects children and young adults.
   - Onset: Sudden or gradual. Usually present with insidious onset of fever, malaise and weight loss over weeks.
   - Other symptoms:
     - Systemic symptoms include high-grade fever, drenching night sweats and progressive pallor.
     - Cough and breathlessness are occasionally present.
   - Signs:
     - There may not be any abnormal physical signs in the lungs. Widespread crepitations may be heard late in the disease.
     - Hepatosplenomegaly may be seen.
     - Choroidal tubercles on ophthalmoscopy—diagnostic.

2. Cryptic (obscure) miliary tuberculosis

Q Write short essay/note on cryptic miliary tuberculosis.

- Age: Usually in the elderly.
- Symptoms:
  - Prolonged low-grade pyrexia common presenting manifestation
  - Lassitude, weight loss and general debility.
- Signs:
  - Hepatosplenomegaly may occur.
  - Chest is usually normal
  - Choroidal tubercles are rare.
3. **Non-reactive miliary tuberculosis**
   - Rare usually develops in elderly with disease re-activation
   - Acute severe form of tuberculous septicemia, resulting in necrotic lesions without granulomatous reaction containing numerous bacilli.
   - Patients are extremely ill and die rapidly.

**Diagnosis**

- **Chest radiograph (Fig. 6.21)**: If it shows the characteristic miliary shadows (miliary mottling), it is virtually diagnostic. Miliary mottling appears as diffuse small shadows of 1–2 mm diameter and evenly distributed throughout both lung fields. Upper zones are always involved. The early lesions may be difficult to appreciate. These lesions are better visualized by (1) an over penetrated (dark) radiograph and a bright light behind the outer rib spaces, (2) lateral chest film, (3) underpenetrated anteroposterior radiograph or (4) high resolution CT of chest.
- **Positron emission tomography CT (PET-CT)**: Using radiopharmaceutical 18F labeled 2-deoxy-D-glucose (FDG) may show ‘hot’ spots. It can determine the activity of lesion, guide biopsy and detect occult foci.
- **Sputum** smear is usually negative but bronchoalveolar lavage and bronchial biopsy are likely to be positive.
- **Culture**: Confirmation of diagnosis should be done by culture of sputum, urine or bone marrow.
- **Hematological abnormalities**: These include anemia, leukopenia, neutrophilic leukocytosis and leukemoid reaction. Rarely DIC can develop.
- **Elevation of alkaline phosphatase and other liver enzymes may be observed in patient with severe liver involvement.**
- **Hyponatremia may develop in about 50% cases.**
- **Bone marrow biopsy**: May show miliary tubercles/bacilli on histology. Part of the specimen should be sent for culture for tubercle bacilli.
- **Liver biopsy**: May show miliary tubercles.
- **Tuberculin test**: Only of limited value in miliary tuberculosis.

![Fig. 6.21: Chest X-ray showing miliary mottling.](image)

**Write short essay/note on management of miliary tuberculosis.**

**Management**

- **Acute and cryptic miliary tuberculosis**: Standard antituberculous chemotherapy. In severely ill patients prednisolone is given along with chemotherapy. It reduces the life-threatening toxicity and gives the time for antituberculous drugs to act.
- **If the diagnosis is not proved** (e.g. cryptic miliary tuberculosis): Therapeutic trial of antituberculous chemotherapy.

**Tuberculous Pleural Effusion**

- **Discuss the etiology, pathogenesis, clinical features, investigations, complications and management of tuberculous pleural effusion.**
- **Write short note on tuberculous pleural effusion and its laboratory diagnosis.**
- **Age group**: Tuberculous pleural effusion usually occurs in younger individuals.
- **Underlying pulmonary tuberculosis**: Only one-third of patients show simultaneous pulmonary tuberculosis and in the majority remaining it is not found.

**Pathogenesis**

Involvement of pleura by *M.tuberculosis* may occur by various routes namely via lymphatics, blood-stream or by direct extension.

- **Isolated pleural effusion** usually due to recent primary infection. The collection of fluid in the pleural space represents a hypersensitivity response to mycobacterial antigens.
- Pleural disease may also develop from contiguous parenchymal spread form post-primary/secondary tuberculosis of lung.
- **Rupture of subpleural caseous focus** into the pleural cavity. This produces delayed hypersensitivity reaction to tuberculous protein. It causes increased permeability of pleural capillaries, mild lymphatic block by fibrosis. Cultures of the pleural fluid from most these patients with tuberculous pleural effusions are negative (because it is a hypersensitivity response).
• **Sequelae:** Left untreated, the pleura may become thick and fibrotic (pleural fibrosis) and pleural adhesions may develop. Pleural adhesion causes restrictive ventilator dysfunction. Early treatment is necessary to prevent these sequelae.

**Clinical Features, Investigations and Management**

Refer pages 313-4.

**Pleural fluid analysis**

**Q. Write a note on pleural fluid findings in tuberculous pleural effusion.**

- **Color:** Fluid is usually straw/amber colored, but sometimes hemorrhagic.
- **Exudative in nature:** Characteristically fluid is an exudate, with a high protein content (>3 g/dL) >50% of that in serum (usually 4–6 g/dL) a normal to low glucose concentration, a pH of –7.3 (occasionally <7.2) and raised white blood cells (usually 500–6000/µL).
- **Cells:** Predominant lymphocytosis. Neutrophils may predominate in the early stage (less than 2 weeks), but lymphocytosis is the typical finding later. Mesothelial cells are usually rare or absent. If the pleural fluid shows more than 10% eosinophils, diagnosis of tuberculous effusion is unlikely unless the patient has a pneumothorax or had previously undergone thoracocentesis.
- **Smear for AFB:** Smears prepared from the centrifuged deposit may rarely show the tubercle bacilli (<10% of immunocompetent cases).
- **Culture for M tuberculosis:** Positive in approximately 25–50% of patients and are more common among postprimary/secondary cases.
- **Determination of the pleural concentration of adenosine deaminase (ADA):** It is a useful screening test, and TB can be excluded if the value is very low.

**Q. Write short note on adenosine deaminase.**

- It is a T-lymphocyte enzyme.
- In majority of cases, the levels of **ADA in the pleural fluid are elevated** (>40 IU/L) and is probably due to increased activity of T lymphocytes (CD4+) in the pleural fluid.
- Other causes with high ADA, e.g. rheumatoid arthritis, lymphoma, chronic lymphatic leukemia, empyema, and mesothelioma. However, because the incidence of tuberculosis far exceeds than any other cause of a lymphocytic pleural effusion (like in India), high ADA level has a predictive value.
- Specificity of raised levels of ADA in diagnosing tuberculous effusion is nearly 0.83 and the reported sensitivity 77–100%. Specificity increased if combined with pleural fluid lymphocytes/polymorph ratio greater than 3.
- ADA not useful in HIV patients with TB.
- There are two isoenzymes of ADA namely ADA1 and ADA2. ADA1 isoenzyme is found in all cells and they are high in lymphocytes and monocytes. ADA2 isoenzyme is present only in monocytes. In **tuberculous pleural effusion, ADA2 isoenzyme** is mainly responsible for high ADA concentration.

- **Interferon-gamma** (**INF-γ**): Produced by lymphocytes specifically sensitized to PPD. Its level above 140 pg/mL is very suggestive of TB and is elevated irrespective of immune status. More expensive than ADA.
- **Other tests** on pleural fluid: Includes raised LDH, raised lysozymes, marked elevation in the levels of soluble interleukin-2 (IL-2) receptors, and PCR for DNA of *M. tuberculosis*. Nucleic acid amplification technology has low sensitivity.
- **Pleural biopsy:** Closed pleural biopsy shows non-caseating granulomas in 80% of patients. It should be stained with Z-N stain and cultured for mycobacteria. Diagnostic yield increases to 90% with pleural biopsy and biopsy cultures for AFB.

**Management**

- **Therapeutic aspiration of pleural fluid:** May be required in patients with severe symptoms.
- **Antituberculous chemotherapy**
- **Corticosteroid:** May reduce the symptoms of toxemia. However, they do not reduce the incidence of pleural fibrosis. Prednisolone is administered in the dose of 0.75 mg/kg/day for up to 4 weeks with gradual reduction over an additional 2–4 weeks.

**BCG Vaccination**

**Q. Write short essay/note on BCG vaccination (Bacillus Calmette-Guerin vaccine).**

BCG (Bacille Calmette-Guerin) is a freeze-dried, live attenuated (lost its virulence) vaccine derived from *M. bovis*. In India, Danish strain 1331 is being used for BCG vaccine production.
**APPENDIX 1: LABORATORY VALUES OF CLINICAL IMPORTANCE**

In this appendix, tables of reference values of some important common laboratory investigations are provided which will help in interpreting the results during examinations as well as during clinician practice. The term ‘reference values’ has replaced older terminology ‘normal values/ranges’. A variety of factors can influence reference values and it varies between laboratories depending on the laboratory methods, mode of standardization and other factors. This is especially the case with enzyme assays. The reference or ‘normal’ ranges given in this appendix may, therefore, not be appropriate for all laboratories and they should only be used as general guidelines. Hence, reference values provided by the laboratory performing the test should be used in the interpretation of laboratory results. Most clinical laboratories and all medical and scientific journals use SI system. Since, conventional units are still used in many laboratories of developing countries, in this section, laboratory values are given in both conventional and international units. Many analytes are measured in either serum (the supernatant of clotted blood) or plasma (the supernatant of anticoagulated blood).

The laboratory reference values in this appendix is divided into different section namely: (1) hematology and coagulation (Table A 1.1), (2) clinical chemistry of blood (Table A 1.2), (3) lipid profile (Table A 1.3), (4) urea and electrolytes (Table A 1.4), (5) thyroid function tests (Table A 1.5), (6) urine (Table A 1.6), and (7) cerebrospinal fluid (Table A 1.7), short list of routinely used formulas in medicine (Table A 1.8).

**Hematology and Coagulation (Table A 1.1)**

<table>
<thead>
<tr>
<th>Component (specimen)</th>
<th>Reference value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Conventional</td>
</tr>
<tr>
<td><strong>RBCs and hemoglobin</strong></td>
<td></td>
</tr>
<tr>
<td>RBC count</td>
<td>4.5–5.5 × 10^{12}/L (mean 5.0 × 10^{12}/L)</td>
</tr>
<tr>
<td>• Males</td>
<td>3.8–4.8 × 10^{12}/L (mean 4.3 × 10^{12}/L)</td>
</tr>
<tr>
<td>• Females</td>
<td>6.7–7.7 µm (mean 7.2 µm)</td>
</tr>
<tr>
<td>RBC indices (absolute values)</td>
<td>82–100 fl</td>
</tr>
<tr>
<td>• Mean corpuscular volume (MCV)</td>
<td>27–32 pg</td>
</tr>
<tr>
<td>• Mean corpuscular hemoglobin (MCH)</td>
<td>31–35 g/dL</td>
</tr>
<tr>
<td>• Mean corpuscular hemoglobin concentration (MCHC)</td>
<td>11.5–14.0%</td>
</tr>
<tr>
<td>• Red cell distribution width (RDW)</td>
<td>1.20 days</td>
</tr>
<tr>
<td>RBC lifespan</td>
<td></td>
</tr>
<tr>
<td>• Westergren, 1st hour</td>
<td>0–15 mm 1st hour</td>
</tr>
<tr>
<td>• Wintrobe, 1st hour</td>
<td>0–9 mm 1st hour</td>
</tr>
<tr>
<td>• Ferritin (serum)</td>
<td>20–300 µg/L</td>
</tr>
<tr>
<td>• Hematocrit (PCV)</td>
<td>38–47%</td>
</tr>
<tr>
<td>• Haptoglobin (serum)</td>
<td>40–240 mg/dL</td>
</tr>
</tbody>
</table>

*Contd...*
### Component (specimen) Reference value

**Component (specimen)** | **Conventional** | **SI units**
--- | --- | ---
Hemoglobin (Hb)  
- Adult hemoglobin (HbA)  
- Males  
- Females  
- Hemoglobin A2 (HbA2)  
- Hemoglobin, fetal (HbF) in adults  
- HbF, children under 6 months | 95–98%  
13.0–17.0 g/dL  
12.0–15.0 g/dL  
1.5–3.5%  
<0–2%  
<5% |
Iron, total (serum)  
- Total iron binding capacity (TIBC)  
- Iron saturation | 50–150 µg/dL  
310–340 µg/dL  
20–45% | 7–25 µmol/L  
45–73 µmol/L  
0.20–0.45 |
Osmotic fragility  
- Slight hemolysis  
- Complete hemolysis  
- Mean corpuscular fragility | at 0.45 to 0.39 g/dL NaCl  
at 0.33 to 0.36 g/dL NaCl  
0.4–0.45 g/dL NaCl |
Reticulocytes  
- Adults  
- Infants  
- Newborn (cord blood) | 0.5–2.5%  
2–6%  
1–7% |
Transferrin saturation  
- Male  
- Female | 25–56%  
14–51% |
Vitamin B₁₂ (serum)  
- Body stores  
- Daily requirement  
- Serum level | 10–12 mg  
2–3 µg  
280–1000 pg/mL |
Autohemolysis test (whole blood) | 0.4–4.50% | 0.004–0.045 |
Autohemolysis test with glucose (whole blood) | 0.3–0.7% | 0.003–0.007 |
### Leukocytes

#### Differential leukocyte count (DLC)
- P (polymorphs or neutrophils)  
- L (lymphocytes)  
- M (monocytes)  
- E (eosinophils)  
- B (basophils) | 40–70% (2,000–7,500/µL)  
20–40% (1,500–4,000/µL)  
2–10% (200–800/µL)  
1–6% (40–450/µL)  
<1% (10–100/µL) |
Total leukocyte count (TLC)  
- Adults  
- Infants (full term, at birth)  
- Infants (1 year) | 4,000–11,000/µL  
10,000–25,000/µL  
6,000–16,000/µL |
### Platelets and coagulation

#### Bleeding time (BT)
- Ivy's method  
- Template method | 2–7 min  
2–9 min |
#### Clot retraction time (clotted blood)
- Qualitative  
- Quantitative | Visible in 60 min (complete in <24 hours)  
48–64% (55%) |
#### Clotting time (CT)
- Lee and White method | 4–11 minutes |
### Bibliography

Index

Page numbers followed by b refer to box, f refer to figure, fc refer to flow chart, and t refer to table.

A
- α-antitrypsin deficiency 844
- α-fetoprotein 1066
- α-thalassemia 571, 578
- β-adrenoceptor antagonists 438
- β-blocker therapy 489
- β-hemolytic streptococci 1178
- β-lactam antibiotics 1185
- β-thalassemia 578
- intermedia 580
- major 578
- minor 580
- syndromes 578
- Abacavir 236, 238
- Abaloparatide 711
- Abscess 113, 478, 855
- Abdominal distension, causes of 776, 776b
- Abdominal pain
  - recurrent episodes of 741
  - severe 1189
- Abdominal paracentesis
  - complications of 830
  - indication of 830
  - procedure of 830
- Abdominal tuberculosis
  - complications of 759
  - differential diagnosis of 759
  - etiology of 759
  - investigations of 759
  - treatment of 759
- Abelallopaproteinemia 571
- ABO blood group compatibility 912
- Abortus fever 135
- Abscess 113, 478, 855
  - aspiration 310
  - crypt 763, 768
  - drainage of 840f
  - epidermal 987
  - intra-abdominal 313
  - intracardiac 479
  - metastatic 304
  - myocardial 478
  - pancreatic 855
  - psosas 297
  - pyogenic 839
  - rupture of 840
  - therapeutic aspiration of 841
- Absorption atelectasis 306
- Acanthocytosis 571, 812
- Acanthosis nigricans 353, 1068, 1158
- skin lesions of 1158f
- Acebrophylline 272
- Acetabular dysplasia 698
- Acetaminophen 1041, 1050
  - metabolism 1051f
- Acetazolamide 22
- Acetic acid test 155
- Acetoacetic acid 97
- Acetylsalicylic acid 1052
- Acetylation 1183
- Achalasia cardia 737
- Achilles tendinitis 685
- Achilles tendon 685
- Achondroplasia 1106
- Acid load test 889
- Acid peptic disease
  - etiology of 738
  - investigations of 738
  - management of 738
- Acid regurgitation 735
  - Acid-base balance 864, 877, 928
  - maintenance of 929
  - physiology of 928
  - regulation of 929
- Acid-base disorders
  - chronic 934
  - classification of 929, 929f
  - Acid-base disturbances 934
- Acid-base imbalance 802
- Acid-base status 728
- Acid-base tests 381, 389
- Acid-fast organisms and structures 281f
- Acid-fast bacilli 281, 309
- Acetate 1183
- Acetyl salicylic acid 1052
- Acetic acid test 155
- Actinomyces israelii
  - Actinomycosis 336, 376
  - abdominal 336
  - pulmonary 336
- Activated partial thromboplastin time 633, 639, 682
- Active anti-retroviral therapy 238
- Active ischemic colitis, left-sided 755
- Active kidney injury
  - causes of 873, 874f
  - 875f, 876f
  - classification of 873f
  - complications of 876, 876f
  - etiology of 876
  - network classification 873f
  - types of 875, 876, 876f
- Acute leukemia
  - Acute nonlymphoblastic leukemia, WHO classification of 594f
  - Acute lymphoblastic leukemia, classification of 594f
  - management of 596
  - Acute leukemia of childhood
  - classification of 596
  - management of 596
  - Acute myeloblastic leukemia, WHO classification of 594f
  - Acute myeloid leukemia
  - classification of 595
  - management of 597
  - Acute myelogenous leukemia
  - WHO classification of 593f
  - Acute myelomlastic infarction
  - complications of 424f
  - emergency management of 1200
  - management of 426
- Acute onset dyspnea, differential diagnosis of 379
- Acute pancreatitis
  - causes of 850f
  - classification of 850
  - complications of 855, 855f
  - diagnosis of 852
  - etiology of 850
  - interstitial edematous 850
  - management of 850, 856f
  - severe 850
  - treatment of 852, 855, 855f
  - Acute pneumothorax, management of 325
- Acute post-streptococcal glomerulonephritis, complications of 881
- Acute pulmonary edema
  - diagnosis of 492
  - management of 492, 1190
  - treatment of 493
  - Acute pyelonephritis
  - diagnosis of 905
  - etiology of 905
  - investigations of 905
  - management of 905
  - Acute radiation sickness, mild 21
  - Acute renal failure
  - causes of 871, 873
  - classification of 871
  - diagnosis of 871
  - investigations of 871
  - management of 871
  - Acute respiratory syndrome, severe 341
  - Acute rheumatic carditis, features of 446
  - Acute rheumatic fever
  - diagnosis of 447
  - management of 448
  - Acute serum sickness, treatment of 1131b
  - Acute severe
  - aortic regurgitation, management of 470
  - asthma, management of 257, 264, 1202
  - mitral regurgitation, management of 458
  - Acute stroke
  - complications of 955
  - Acute tubulointerstitial nephropathy, etiology of 888b
  - Acute upper gastrointestinal hemorrhage, causes of 722f
  - Acute urinary infection
  - diagnosis of 902
  - symptoms of 902
  - treatment of 902
  - Acute varicell bleeding, management of 417
  - Acute viral hepatitis
  - complications of 795, 795f
  - diagnosis of 788
  - management of 788
  - prevention of 788
- Acute myocardial infarction
  - diagnosis of 470
  - management of 470
  - Acute parasitic infections
  - causes of 590f
  - classification of 850
  - complications of 855, 855f
  - diagnosis of 852
  - etiology of 850
  - interstitial edematous 850
  - management of 850, 856f
  - severe 850
  - treatment of 852, 855, 855f
  - Acute pneu