ur website **www.jaypeebrothers.com,** for detailed information on medicine books, visit our website **www.jaypeebrothers.com**

JAYPEE

CLINICAL TUBERCULOSIS

Diagnosis & Treatment



RAJENDRA PRASAD

Co-author
Nikhil Gupta

Foreword
SP Agarwal

Contents

1. Landmarks in Tuberculosis Treatment **1**

2. Case Definitions in Tuberculosis **8**

- Case Definitions 8
- Disease Classification 9
- Types of Tuberculosis Patients 11
- Directly Observed Treatment 11
- Directly Observed Treatment Plus 12
- Treatment Outcomes of DOTS 12
- Drug Resistant Tuberculosis 13
- Treatment Outcomes in DOTS-Plus 14
- HIV Setting Case Definitions 16

3. Epidemiology of Tuberculosis **18**

- Epidemiological Indices 18
- Global Burden of Tuberculosis 22
- Tuberculosis Burden in India 24

4. Clinical Presentation of Tuberculosis **33**

- Congenital Tuberculosis 33
- Primary Tuberculosis 34
- Post-primary Tuberculosis 39

5. Miliary Tuberculosis **47**

- Pathogenesis 47
- Pathology 48
- Diagnosis 49
- Treatment 50
- Complications 50

6. Endobronchial Tuberculosis **52**

- Epidemiology 52
- Pathophysiology 53

- Natural History 54
- Diagnosis 55
- Differential Diagnosis 59
- Treatment 60
- Endobronchial Tuberculosis in Special Situations 61

7. Lower Lung Field Tuberculosis 69

- Definition 69
- Prevalence 70
- Pathogenesis 70
- Clinical Features 70
- Investigations 71
- Associated Medical Conditions 74
- Management 74

8. Hemoptysis 77

- Pseudo or Spurious Hemoptysis 78
- Grades of Hemoptysis 78
- Recurrent Hemoptysis 78
- Etiology of Hemoptysis 78
- Hemoptysis with Normal Chest X-ray 80
- Mechanism of Bleeding 80
- Pathogenesis of Hemoptysis in Tuberculosis 81
- Diagnosis of Hemoptysis 81
- Treatment of Hemoptysis 85

9. Diagnostic Techniques in Tuberculosis 90

9A: Diagnosis of Latent Tuberculosis Infection 90
- Tuberculin Skin Test 90
- Interferon-γ Assays 94

9B: Radiology 97
- Imaging Modalities 97
- Imaging in Pulmonary Tuberculosis 97
- Sequelae and Complications of Tuberculosis 106
- Radiographic Follow-up Schedule 107

9C: Bacteriology 109
- Direct Demonstration by Staining Technique 109
- Mycobacterial Culture in the Diagnosis of Tuberculosis 110
- Drug Susceptibility Testing 113
- Newer Tools Under Development 115

9D: Histopathology 119

9E: Polymerase Chain Reaction (PCR) 121

9F: Serology 124
- Antibody-based Tests 124
- Antigen-based Tests 128
- Serology in Diagnosing Pulmonary TB in Patients with HIV Infection 129

- Role of Serology in Diagnosing Tuberculosis in Children 130
- Role of Serology in Diagnosing Extrapulmonary TB 130

9G: Fiberoptic Bronchoscopy 134

- Indications 134
- Specimen Collected 134
- Result 135
- Precautions 136
- Drawback 136

9H: Others 138

- Fine Needle Aspiration Cytology 138
- Radioactive Bromide Particles Test 138
- Adenosine Deaminase Assay 138
- Tuberculostearic Acid Estimation 138

10. Differential Diagnosis of Pulmonary Tuberculosis 140

- Pneumonia 140
- Fungal Diseases 141
- Parasitic Disease 142
- Bronchiectasis 143
- Lung Abscess 144
- Allergic Bronchopulmonary Aspergillosis 145
- Pulmonary Edema 147
- Lung Cancer 147
- Sarcoidosis 152
- Occupational Lung Diseases 154
- Pulmonary Infarction 154
- Congenital Conditions 154
- Cardiovascular Diseases 154

11. Complications of Tuberculosis 156

- Hemoptysis 156
- Fungus Ball 157
- Bronchiectasis 159
- Tuberculosis Endobronchitis and Tracheitis 159
- Spontaneous Pneumothorax 160
- Calcification 160
- Tuberculous Laryngitis 160
- Tuberculous Enteritis 161
- Open Negative Syndrome 161
- Scar Carcinoma 162
- Physiological Changes 162
- Amyloidosis 163
- Chronic Respiratory Failure 164
- Chronic Cor Pulmonale 164

12. Post-tubercular Obstructive Airway Impairment 169
- Pathophysiology 169
- Diagnosis 171
- Treatment 172

13. Antitubercular Drugs Used in Newly Diagnosed Patients of Tuberculosis and their Adverse Effects 174
- Isoniazid 174
- Rifampicin 178
- Ethambutol 180
- Pyrazinamide 181
- Streptomycin 183
- Thioacetazone 184
- Management of Common Adverse Effect 185

14. Antitubercular Drug Used in Previously Treated Patients of Tuberculosis and their Adverse Effect 189
- Kanamycin 189
- Amikacin 194
- Capreomycin 200
- Ethionamide and Prothionamide 202
- Cycloserine 205
- Para-aminosalicylic Acid (PAS) 208
- Levofloxacin 210
- Moxifloxacin 212
- Ofloxacin 215
- Clofazimine 217
- Thiacetazone 218
- Clarithromycin 219
- Linezolid 221
- Imipenem/Cilastatin 222
- Amoxicillin Clavulanate 223

15. How Does Tuberculosis Treatment Work? 225
- Bacteriological Factors 225
- Environmental Factors 226
- Pharmacological Factors 227

16. Basic Concepts in Treatment of Tuberculosis 229
- Role of Special Diet and Rest 229
- Role of Hospitalization 230
- Single Drug Therapy versus Multiple Drugs 230
- Single versus Divided Doses 230
- Optimum Duration of Treatment 231
- Fixed Dose Combinations (FDCs) versus Separate Drugs 231

- Daily versus Intermittent Therapy 233
- Monitoring of Progress of Chemotherapy 234
- Causes of Failure of Chemotherapy 235
- Role of Surgery in Pulmonary Tuberculosis 236

17. Anti-tubercular Drug Doses and Regimens for Adults and Children 240

18. Duration of Treatment in Tuberculosis 245

- Sputum Positive Pulmonary Tuberculosis 245
- Sputum Smear-negative Pulmonary Tuberculosis 245
- Standard Conventional Long-term Nonrifampicin-containing Regimen 245

19. Treatment of Tuberculosis in Special Conditions—Pregnancy, Liver and Renal Disease 248

- Pharmacokinetics of Antitubercular Drugs 248
- Treatment of Tuberculosis in Pregnancy and Lactation 250
- Treatment of Tuberculosis in Renal Insufficiency 251
- Treatment of Tuberculosis in Liver Diseases 254

20. Treatment of Tuberculosis in Special Conditions—Pregnancy, Liver and Renal Diseases—Case-based Approach 259

- Treatment of Tuberculosis in Pregnancy and Lactation 259
- Treatment of Tuberculosis in Renal Insufficiency 260
- Treatment of Tuberculosis in Liver Disease 261

21. Treatment of Extrapulmonary Tuberculosis 263

- Tuberculous Lymphadenitis 264
- Pleural Effusion 265
- Tuberculous Meningitis (TBM) 266
- Bone and Joint Tuberculosis 267
- Miliary Tuberculosis 268
- Tuberculous Pericarditis 269
- Abdominal Tuberculosis 269
- Genitourinary Tuberculosis 270
- Ocular Tuberculosis 270
- Upper Respiratory Tract Tuberculosis 271
- Cutaneous Tuberculosis 271

22. Corticosteroids in Tuberculosis 276

- Indications of Corticosteroids in Tuberculosis 276
- Dose and Duration of Corticosteroids 281

23. Management of Retreatment Cases in Tuberculosis 284

- Relapse 284
- Defaulters or Treatment after Default 285
- Failure 286
- Poor Adherence to Treatment 286
- Drug Resistant Tuberculosis 287
- Prevention of Retreatment Cases 293

24. Drug Resistant and Multidrug Resistant Tuberculosis: Current Status 297

- Definition 297
- Types of Drug Resistance 298
- Prevalence of MDR-TB: Global 298
- Trends in MDR-TB: Global 302
- Prevalence of MDR-TB: India 303
- HIV Infection and Multidrug Resistant Tuberculosis 306
- Risk Factors of MDR-TB 308
- Sources and Causes of MDR-TB 308
- Control of MDR-TB 309

25. Drug Resistant and Multidrug Resistant Tuberculosis: Management 313

- Definition 313
- Mechanism of Drug Resistance 313
- Genetic Basis of Drug Resistance 314
- Virulence and Drug-resistant Strains 314
- Impact of Drug Resistance on the Outcome of Chemotherapy 315
- Diagnosis of Drug Resistant and Multidrug Resistant Tuberculosis 315
- Treatment of Drug Resistant and Multidrug Resistant Tuberculosis 319
- Outcome of Treatment 329

26. Multidrug Resistant Tuberculosis: Case-based Management 335

- Case I 335
- CASE II 337
- CASE III 337
- CASE IV 340
- CASE V 340
- CASE VI 343

27. Multidrug Resistant Tuberculosis—Monitoring of Treatment and Adverse Drug Reaction 345

- Pretreatment Screening and Evaluation 345
- Monitoring Progress of Treatment 345
- Monitoring for Adverse Effects During Treatment 347
- Management of Adverse Effects 348

28. Multidrug Resistant Tuberculosis—Management in Special Situation 354

- M/XDR-TB in Pregnancy 354
- M/XDR-TB in Breastfeeding 355
- M/XDR-TB in Contraception 356
- M/XDR-TB in Children 356
- M/XDR-TB in Diabetes Mellitus 358
- M/XDR-TB in Renal Insufficiency 358
- M/XDR-TB in Liver Disorders 358
- M/XDR-TB in Seizure Disorders 359
- M/XDR-TB in Substance Dependence 360
- M/XDR-TB in Patients with Psychosis 360

29. Multidrug Resistant Tuberculosis Contacts: Management 363

- Management of Symptomatic Adult 363
- Contacts of Patients with MDR-TB 363
- Management of Symptomatic Pediatric 364
- Contacts of Patients with MDR-TB 364
- Chemoprophylaxis of Contacts of DR-TB Index Cases 365

30. Multidrug Resistant and Extensively Drug Resistant Tuberculosis: Prevention 367

- General Guidelines for the Prevention of MDR- and XDR-TB 368

31. Extensively Drug Resistant Tuberculosis: Current Status and Management 374

- Definition 374
- Epidemiology 375
- Factors Responsible for XDR-TB 377
- Diagnosis 377
- Treatment 378
- Monitoring of Treatment 380
- Outcomes of Treatment 381
- Role of Surgery 382
- HIV and XDR-TB 382
- XDR-TB in Pediatric Patients 383
- XDR-TB in Pregnancy 384

- WHO Response Strategies for XDR-TB
  Control of XDR-TB 386

32. Bacillus Calmette-Guerin (BCG) 390

- Basis of Giving BCG 390
- Types of BCG Vaccine 391
- Dose and Site of Vaccination 391
- Routes of Vaccination 391
- Efficacy and Safety 391
- Contraindications to BCG Vaccination 392
- Normal Reaction after BCG Vaccination 392
- Complications 393
- Various Strategies for the Development of
  Newer Tuberculosis Vaccines 396

33. Chemoprophylaxis in Tuberculosis 402

- Chemoprophylaxis in Tuberculosis 402
- Treatment Regimens and Duration 404
- Chemoprophylaxis Under Revised National Tuberculosis
  Control Program 404
- Chemoprophylaxis for Drug Resistant Tuberculosis 405
- Limitations of Chemoprophylaxis 405
- Place of Secondary Chemoprophylaxis in
  Tuberculosis Control 405

34. Tuberculosis Control in India: DOTS 408

- Landmarks of Tuberculosis Control in India 409
- Revised National Tuberculosis Control Program Strategy 411
- Revised National Tuberculosis Control Program Structure 412
- Diagnosis Under Revised National Tuberculosis
  Control Program (RNTCP) 412
- Treatment Regimen Used in Revised National
  Tuberculosis Control Program (RNTCP) 415
- Achievements of Revised National Tuberculosis
  Control Program 420
- Others Priority Initiatives in Revised National
  Tuberculosis Control Program 421
- Impact of Revised National Tuberculosis Control Program 424
- Challenges for Revised National Tuberculosis
  Control Program 424
- Problems of Revised National Tuberculosis
  Control Program 425

35. Tuberculosis Control in India: DOTS Plus 427

- Framework 427
- Case Finding Strategy 428

- Enrolment into DOTS-Plus Program 429
- Confirmed MDR-TB Case 430
- Drug Resistant Tuberculosis Center 431
- Pre-treatment Evaluation 432
- Counseling 432
- Monitoring Progress During Treatment 433
- Category IV Regimen 434
- Drug Dosages and Administration 434
- Treatment Duration 435
- Regimen for XDR-TB 436
- Duration of Regimen for XDR-TB 436
- Treatment Interruption and Default 437
- Treatment Outcomes 438
- Providing Patient and Family Counseling 439
- Monitoring for Early Detection of Adverse Reactions 440
- Role of DR-TB Committee in the 440
- Management of Adverse Reactions 440
- Adherence 441
- Follow-up of the Non-adherent Patient 441
- DOTS-Plus Plan 442

36. Tuberculosis and HIV 444

- Epidemiology 444
- Impact of HIV on Tuberculosis 445
- Impact of Tuberculosis on HIV 446
- Diagnostic Difficulties in Persons with HIV/TB 446
- Coinfection 446
- Revised WHO Clinical Staging of HIV/AIDS for Adults and Adolescents with Confirmed HIV Infection 446
- Diagnosis of Pulmonary Tuberculosis 448
- Extrapulmonary Tuberculosis 450
- Investigations 452
- Treatment of Tuberculosis in HIV Positive Patients 454
- Adjuvant Corticosteroids in Extrapulmonary TB 455
- Highly Active Antiretroviral Therapy 455
- Interactions of Antituberculosis 456
- Therapy and Antiretroviral Therapy 456
- Immune Reconstitution Syndrome 458
- HIV and Drug Resistant TB Drug Interactions of Second Line Drugs and ART 459
- Recurrence of Tuberculosis after Completion of Tuberculosis Treatment 460
- Treatment of TB and HIV—WHO Recommended Collaborative TB/HIV Activities 460

37. Interaction between Antitubercular and Antiretroviral Drugs 465

- Antiretroviral Therapy for the Treatment of HIV Infection 465
- Pharmacokinetic Issues in the Treatment of HIV-related Tuberculosis 469
- Interaction between Antiretroviral and Antitubercular Drugs 469
- Drug-Drug Interactions in the Treatment of HIV and Drug Resistant-TB (DR-TB) 471

38. Tuberculosis and Diabetes 473

- Epidemiology 473
- Effect of Diabetes on Pulmonary Tuberculosis 474
- Effect of Pulmonary Tuberculosis on Diabetes 475
- Clinical Features and Course of Tuberculosis in Diabetics 475
- Roentgenographic Aspects of Tuberculosis in Diabetics 476
- Multidrug Resistant Tuberculosis (MDR-TB) and Diabetes 477
- Effect of Antituberculosis Drugs on Blood 477
- Glucose Level and OHA in Tubercular Diabetics 477
- Principles of Management 477

39. Tuberculosis and Pregnancy 480

- Effect of Pregnancy on Tuberculosis 480
- Effect of Tuberculosis on Pregnancy and Childbirth 481
- Diagnosis of Tuberculosis in Pregnant Woman 481
- Treatment of Pregnant Woman with Active Tuberculosis 482
- Treatment of Tuberculosis in Lactating Woman 483
- Isoniazid Prophylaxis in Pregnant Woman 484
- Isoniazid Prophylaxis for Infant Born to Woman with Active Tuberculosis 484

40. Tubercular Pleural Effusion 487

- Epidemiology 487
- Pathogenesis 487
- Clinical Manifestations 488
- Clinical Manifestations in HIV Positive Patients 489
- Diagnosis 489
- Natural History of Untreated Tuberculous Effusion 496
- Treatment 496
- Response to Treatment 498

41. Tubercular Empyema 504

- Etiopathogenesis 504
- Clinical Features 505

- Diagnosis 506
- Treatment 506

42. Tubercular Lymphadenitis 511

- Epidemiology 511
- Pathogenesis 512
- Clinical Features 512
- Diagnosis 513
- Treatment 515

43. Tuberculosis in Children 518

- Epidemiology 518
- Clinical Presentation of Tuberculosis 520
- Postprimary Extrapulmonary Tuberculosis 520
- Diagnosis of Childhood Tuberculosis 520
- Treatment of Tuberculosis in Children 522

44. Tuberculosis in Elderly 527

- Epidemiology 527
- Reasons for Reactivation 528
- Clinical Features 528
- Diagnosis 530
- Investigations in Tuberculosis in Elderly 530
- Treatment 531

45. Tuberculosis Abdomen 533

- Pathogenesis 533
- Clinical Features 534
- Investigations 538
- Treatment of Abdominal Tuberculosis 543

46. Tuberculosis of Kidney and Urinary Tract 547

- Epidemiology 547
- Pathophysiology 548
- Clinical Features 548
- Diagnosis of Tuberculosis of Kidney and Urinary Tract 551
- Treatment 556

47. Genitourinary Tuberculosis in Male 559

- Epidemiology 559
- Pathogenesis 559
- Clinical Features 560
- Investigations 561
- Treatment 563

48. Genitourinary Tuberculosis in Female 566

- Epidimiology 566

- Pathogenesis 567
- Clinical Presentation of Female Genital Tuberculoisis 568
- Diagnosis 568
- Treatment 571

49. Non-tubercular Mycobacteria 573

- Epidemiology 573
- Mode of Infections 574
- Classifications of NTM 575
- Distribution 576
- Clinical Presentations 576
- Diagnosis 577
- Features of NTM 580
- Treatment 582

50. Infection Control in Tuberculosis 587

- Mode of Infection in Tuberculosis 587
- The Difference between TB Infection and TB Disease 588
- Standard Precautions 589
- Hierarchy of Infection Control to Reduce Risk of Transmission of Respiratory Pathogens 589
- Managerial Activities for National, State, Hospital Administration, and Local Health Officials 590
- Administrative Control Strategies for Healthcare Facilities 591
- Environmental Control Measures 594
- Protection of Healthcare Workers and Staff 595
- Multidrug Resistant TB 596
- Drug Rehabilitation Centers and Corelations Institutions 597

Index 599

Chapter 2

Case Definitions in Tuberculosis

Aim of the present chapter is to define various definitions used in tuberculosis (TB).

CASE DEFINITIONS

Tuberculosis Suspect

Any person who presents with symptoms or signs suggestive of TB. The most common symptom of pulmonary TB is productive cough for more than 2 weeks, which may be accompanied by other respiratory symptom (shortness of breath, chest pains, hemoptysis) and/or constitutional symptoms (loss of appetite, weight loss, fever, night sweats, and fatigue).[1]

Case of Tuberculosis

A definite case of TB (defined below) or one in which a clinician or other medical practitioner has diagnosed TB and has decided to treat the patients with full course of TB treatment. Any person given treatment for tuberculosis should be recorded as a case. Incomplete trial tuberculosis treatment should not be given as a method for diagnosis.

Definite Case of Tuberculosis

A patient with *Mycobacterium tuberculosis* complex identified from a clinical specimen, either by culture or by a newer method such as molecular line probe assay. In countries that lack the laboratory capacity to routinely identify *M. tuberculosis*, a pulmonary case with one or more initial sputum smear examinations positive for acid-fast bacilli (AFB) is also considered to be a "definite" case, provided that there is a functional external quality assurance (EQA) system with blind rechecking.

JAYPEE BROTHERS

The four determinants of case definition are:

- Site of TB disease
- Bacteriology (result of sputum smear)
- Severity of TB disease
- History of previous treatment of TB
- HIV status of the patients.

DISEASE CLASSIFICATION

TB cases are classified as pulmonary and extrapulmonary.

Pulmonary Tuberculosis

Tuberculosis involving only the lung parenchyma.

Extrapulmonary Tuberculosis

Tuberculosis of organs other than the lungs, e.g. pleura, lymph nodes, abdomen, genitourinary tract, skin, joints and bones, meninges. Tuberculous intrathoracic lymphadenopathy (mediastinal and/or hilar) or tuberculous pleural effusion, without radiographic abnormalities in the lungs, therefore, constitutes a case of extrapulmonary TB (EPTB). The definition of an extrapulmonary case with several sites affected depends on the site representing the most severe form of disease. Patients with both pulmonary and extrapulmonary TB should be classified as a case of pulmonary TB.

Pulmonary TB is further classified as smear-positive and smear-negative.

Smear-positive Patient

A case of pulmonary TB is considered to be smear-positive if one or more sputum smear specimens at the start of treatment is positive for AFB [provided that there is a functional external quality assurance (EQA) system with blind rechecking].

A patient with a new sputum smear-positive pulmonary TB is at least one sputum sample in countries with a well functioning EQA system.

In countries without functional EQA, the definition of a smear-positive pulmonary TB case was defined as one with:

- Two or more initial sputum smear examinations (direct smear microscopy) positive for acid-fast bacilli (AFB);

OR

- A patient with one sputum examination positive for AFB and radiographic abnormalities consistent with active pulmonary TB as determined by the treating clinician and other medical practioner.

OR

- A patient with one sputum specimen positive for AFB and culture-positive for *M. tuberculosis*.

JAYPEE BROTHERS

Smear-negative Patient

A patient having symptoms suggestive of TB with at least 2 sputum examinations negative for AFB, and radiographic abnormalities consistent with active pulmonary TB as determined by the treating clinician and other medical practioner, followed by a decision to treat the patient with a full course of anti-TB therapy;

OR

A patient whose diagnosis is based on culture-positive for *M. tuberculosis* but sputum smear examinations negative for AFB.

The following forms of smear-negative pulmonary TB are classified as seriously ill:

Seriously ill smear-negative TB[2]

- Miliary TB
- Extensive parenchymal infiltration
- Co-infection with HIV
- Pulmonary disease with cavitations
- All forms of pediatric sputum smear-negative pulmonary TB except primary complex.

Diagnosis of extrapulmonary tuberculosis (EPTB) should be based on:

1. One culture-positive specimen from the site of disease, or
2. Histological evidence of TB, or
3. Strong clinical evidence, consistent with active extrapulmonary TB, followed by the diagnosing medical practitioner's decision to treat the patient with a full course of anti-TB treatment. Depending upon the site of the infection, various diagnostic tools may be used. For example, fine needle aspiration cytology (FNAC)/biopsy is used for diagnosing TB lymphadenitis.

Certain forms of EPTB are considered as seriously ill

Seriously ill EPTB[2]

- Meningitis
- Pericarditis
- Peritonitis
- Bilateral or extensive pleural effusion
- Spinal TB with neurological involvement
- Intestinal
- Genitourinary
- Co-infection with HIV
- All forms of pediatric extrapulmonary TB other than lymph node TB and unilateral pleural effusion are considered to be seriously ill.

Not seriously ill EPTB

- Lymph node
- Pleural effusion (unilateral)

JAYPEE BROTHERS

- Peripheral joints
- Skin
- Adrenal gland.

Any patient, with pulmonary or extrapulmonary TB, who is known to be HIV positive based on voluntary sharing of results and/or history of antiretroviral therapy, is considered as seriously ill. For the purpose of categorization, HIV testing should not be done.

TYPES OF TUBERCULOSIS PATIENTS

New

A TB patient who has never had treatment for TB or one who has taken anti-TB drugs for less than one month.

Relapse

Relapse is defined in a person previously treated for TB who has been declared cured or treatment completed, and is diagnosed with bacteriologically positive (smear or culture) tuberculosis.[1,3]

Treatment after Default

A TB patient who received anti-TB treatment for one month or more from any source and returns to treatment after having defaulted, i.e. not taken anti-TB drugs consecutively for two months or more, and who is found to be sputum smear-positive.

Failure

Any TB patient who is smear-positive at 5 months or more after starting treatment. Failure also includes a patient who was treated with Category III regimen but who becomes smear-positive during treatment.

Chronic

A TB patient who remains smear-positive after completing a re-treatment regimen.

Others

TB patients who do not fit into the above-mentioned types. Reasons for putting a patient in this type must be specified.

DIRECTLY OBSERVED TREATMENT

Directly observed treatment (DOT) means that an observer watches the patient swallowing their tablets, in a way that is sensitive and supportive to the patient's needs. This ensures that a TB patient takes the right antitubercular drugs, in the right doses, at the right intervals.[4]

JAYPEE BROTHERS

DIRECTLY OBSERVED TREATMENT PLUS

Directly observed treatment plus (DOT-Plus) is an integral component of RNTCP to manage MDR-TB which is to be implemented through program infrastructure of the DOTS program. The strategy is designed to manage MDR-TB using second-line anti-TB drugs within the DOTS strategy in low- and middle-income countries like India.

TREATMENT OUTCOMES OF DOTS

In RNTCP, every patient registered has one and only one of the following six outcomes. This needs to be reported in individual treatment cards. The possible treatment outcomes are as follows:

Cured

Initially sputum smear-positive patient who has completed treatment and had negative sputum smears, on at least two occasions, one of which was at the end of treatment.

Treatment Completed

A sputum smear-positive patient who has completed treatment, with negative smears at the end of IP but none at the end of treatment; or a sputum smear-negative patient who has received a full course of treatment and has not become smear-positive during or at the end of treatment; or an EPTB patient who has received a full course of treatment and has not become smear-positive during or at the end of treatment.

Died

Patient who died during the course of treatment, regardless of the cause of death.

Failure

Failure is defined on the basis of two aspects bacteriologically, i.e. on sputum smear and culture status. In low- and middle-income countries like India where cultures are less frequently used, sputum smears are used to define failures. Failure for initially smear-positive patients (CAT I and CAT II) is defined as sputum smear-positive at the end of the fifth month of treatment or later.[1] Failure for initially smear-negative patients (Category III) regimen is defined as who became smear-positive during treatment.[1]

Based on culture failure is defined as the reappearance, whilst the patient is receiving treatment and after the negative conversion of cultures, of bacteriological activity.[1,3] It is also considered treatment failure when cultures do not become negative during the course of treatment.

JAYPEE BROTHERS

Defaulted

A patient who has not taken anti-TB drugs for 2 months or more consecutively after starting treatment.

Transferred Out

A patient who has been transferred to another TB unit or district and for whom the treatment result (outcome) is not known.

DRUG RESISTANT TUBERCULOSIS

Drug resistant tuberculosis is defined as a case of tuberculosis excreting bacilli resistant to one or more antitubercular drugs. DR-TB is confirmed through laboratory tests that show that the infecting isolates of *M. tuberculosis* grow in vitro in the presence of one or more anti-tuberculosis drugs. Four different categories of drug resistance have been established:[4]

Mono-resistance

Resistance to one antituberculosis drug.

Poly-resistance

Resistance to more than one antituberculosis drug, other than both isoniazid and rifampicin.

Multidrug-resistant Tuberculosis (MDR-TB)

Resistant to isoniazid (H) and rifampicin (R) with or without resistance to other drugs.

MDR-TB Suspect

A TB patient who fails an RNTCP Category I or III treatment regimen and any RNTCP Category II patient who is sputum smear-positive at the end of the fourth month of treatment or later.[4] Recently criteria for defining a MDR TB Suspect has been divided into three groups under programmatic management of drug-resistant tuberculosis.[5] The program uses a strategy that screens patients with initially a very high risk of MDR-TB using DST. As laboratory and treatment capacity builds, the program will scale up to achieve universal access to quality assured DST. The MDR Suspects have been divided into three criteria based on the risk of MDR TB. Criteria A includes all failures of new TB cases, smear positive previously treated cases who remain smear positive at 4th month onwards, all pulmonary TB cases who are contacts of known MDR TB case. Criteria B includes in addition to Criteria A all smear positive previously treated pulmonary TB cases at diagnosis, any smear positive follow up result in new or previously treated cases. Criteria C includes in addition to Criteria B all smear negative previously treated pulmonary TB

JAYPEE BROTHERS

cases at diagnosis, HIV TB co-infected cases at diagnosis. Initially DST will be performed in those patients fulfilling Criteria A and as capacity builds up it will progress to Criteria B and then C.[5]

Confirmed MDR-TB Case

A TB patient whose sputum is culture positive for *Mycobacterium tuberculosis* and is resistant in vitro to isoniazid and rifampicin with or without other anti-tubercular drugs based on DST results from an RNTCP-certified Culture and DST Laboratory. An "MDR-TB suspect" confirmed by an RNTCP-certified Culture and DST laboratory to have MDRTB, or any rifampicin resistance, will be treated with the RNTCP Regimen for MDR TB.[5]

Extensively Drug-resistant Tuberculosis (XDR-TB)

The term extensively drug resistant TB (XDR-TB) is a new term which was provisionally defined as those persons with TB whose isolates were resistant to isoniazid and rifampicin and at least three of the six main classes of second line drugs[6] (SLDs) (Aminoglycosides, Polypeptides, Fluoroquinolones, Thioamides, Cycloserine, and Para-aminosalicylic Acid). But in October 2006, the World Health Organization revised the case definition of XDR-TB as TB with resistance to at least isoniazid and rifampicin as well as further resistance to a fluoroquinolone and a second-line injectable agent (Kanamycin, Amikacin or Capreomycin).[7,8]

XDR-TB Suspect

If the 6th month follow-up culture of MDR patients under DOTS-Plus treatment is found to be positive, then at this time culture isolate should to be sent for second-line DST.[4]

Extremely Drug-resistant Tuberculosis (XXDR-TB) or Total Drug-resistant Tuberculosis (TDR-TB)

The term XXDR-TB or TDR-TD has been proposed for cases resistant to all available first and second-line drugs.[8-11] The term "totally drug-resistant" tuberculosis is not yet recognised by the WHO. For now these cases are defined as extensively drug-resistant tuberculosis (XDR-TB), according to WHO definitions.[12]

TREATMENT OUTCOMES IN DOTS-PLUS[5]

Standardized treatment outcome definitions are to be used following treatment of an MDR-TB case and are as follows:

Cure

An MDR-TB patient who has completed treatment and has been consistently culture negative (with at least 5 consecutive negative results in the last 12 to

JAYPEE BROTHERS

15 months). If one follow-up positive culture is reported during the last three quarters, patient will still be considered cured provided this positive culture is followed by at least 3 consecutive negative cultures, taken at least 30 days apart, provided that there is clinical evidence of improvement.

Treatment Completed

A MDR-TB patient who has completed treatment according to guidelines but does not meet the definition for cure or treatment failure due to lack of bacteriological results.

Death

A MDR-TB patient who dies for any reason during the course of MDR-TB treatment.

Treatment Failure

Treatment will be considered to have failed if two or more of the five cultures recorded in the final 12–15 months are positive, or if any of the final three cultures are positive.

Treatment Default

A MDR-TB patient whose MDR-TB treatment was interrupted for two or more consecutive months for any reasons.

Transfer Out

A MDR-TB patient who has been transferred to another reporting unit and for whom the treatment outcome is not known.

Treatment Stopped Due to Adverse Drug Reactions

A patient on MDR-TB treatment who develops severe adverse reactions and could not continue the MDR-TB treatment in spite of the management of the adverse reactions as per the defined protocols and decision has been taken by the DOTS-Plus site committee to stop treatment.

Treatment Stopped Due to Other Reasons

A patient on MDR-TB treatment who could not continue the MDR-TB treatment for any other medical reason (than adverse drug reactions), and a decision has been taken by the DOTS-Plus site committee to stop treatment.

Still on Treatment

A MDR-TB patient who, for any reason, is still receiving their RNTCP CAT IV treatment at the time of the submission of the RNTCP DOTS-Plus Treatment Outcome Report.

JAYPEE BROTHERS

HIV SETTING CASE DEFINITIONS[10,13]

The following are suggested case definitions for use in HIV-prevalent settings:

Smear-positive Pulmonary Tuberculosis

- One sputum smear examination positive for acid-fast bacilli (AFB)
- Laboratory confirmation of HIV infection
- Strong clinical evidence of HIV infection.

Smear-negative Pulmonary Tuberculosis

- At least two sputum specimens negative for AFB
- Radiographical abnormalities consistent with active tuberculosis
- Laboratory confirmation of HIV infection
- Strong clinical evidence of HIV infection
- Decision by a clinician to treat with a full course of antituberculosis chemotherapy

OR

- A patient with AFB smear-negative sputum which is culture-positive for *M. tuberculosis*.

Extrapulmonary Tuberculosis

- One specimen from an extrapulmonary site culture-positive for *Mycobacterium tuberculosis* or smear-positive for AFB

OR

- Histological or strong clinical evidence consistent laboratory confirmation of HIV infection
- Strong clinical evidence of HIV infection and
- Decision by a clinician to treat with a full course of antituberculosis chemotherapy with active extrapulmonary tuberculosis.

REFERENCES

1. Training Module for Medical Practitioners 2010. Central TB Division, Directorate General of Health Services, Ministry of Health and Family Welfare, Nirman Bhawan, New Delhi.
2. WHO policy on TB infection control in health care facilities, congregate settings and households. Geneva, World Health Organization. 2009 (WHO/HTM/TB/2009.419).
3. Caminero JA. Guía de la Tuberculosis para Médicos Especialistas. [Tuberculosis Guide for Specialist Physicians]. Paris, International Union Against Tuberculosis and Lung Disease, 2003.
4. Guidlines for the programmatic management of drug resistant tuberculosis; emergency update 2008. Geneva. WHO 2008 (WHO/HTM/TB/2008.402), 2011 (WHO/HTM/TB/2011.6).
5. Guidelines on Programmatic Management of Drug Resistant TB (PMDT) in India 2012. Central TB Division, Directorate General of Health Services, Ministry of Health and Family Welfare, Nirman Bhavan, New Delhi.
6. Centers for Disease Control and Prevention (CDC) Emergence of *Mycobacterium tuberculosis* with extensive resistance to second-line drugs—Worldwide, 2000–2004. MMWR. 2006;55:301-5.

JAYPEE BROTHERS

7. Centers for Disease Control and Prevention (CDC) Notice to readers: Revised definition of extensively drug-resistant tuberculosis. MMWR. 2006;55:1176.
8. Migliori GB, Loddenkemper R, Blasi F, Raviglione MC. 125 years after Robert Koch's discovery of the tubercle bacillus: the new XDR-TB threat: is "science" enough to tackle the epidemic? Eur Respir J. 2007;29:423-7.
9. Joshi JM. Preventing Extremely Drug Resistant Tuberculosis: Directly Observed Treatment is the Only Answer. Editorial. Indian J Chest Dis Allied Sci. 2008;50:183-5.
10. Velayati AA, Masjedi MR, Farnia P, et al. Emergence of new forms of totally drugresistant tuberculosis bacilli: super extensively drug-resistant tuberculosis or totally drug-resistant strains in Iran. Chest 2009;136:420–5.
11. Udwadia ZF, Amale RA, Ajbani KK, Rodriguez C. Totally drug-resistant tuberculosis in India. Clin Infect Dis. 2012;54:579-81.
12. WHO Stop TB Department Drug-resistant tuberculosis Frequently Asked Questions. Updated 24 January 2012. Available at: http://www.who.int/tb/challenges/mdr/TDRFAQs160112.
13. Improving the diagnosis and treatment of smear-negative pulmonary and extrapulmonary tuberculosis among adults and adolescents. Recommendations for HIV-prevalent and resource-constrained settings. WHO/HTM/TB/2007.379.

JAYPEE BROTHERS

for detailed information on medicine books, visit our website **www.jaypeebrothers.com,** for detailed information on medicine b

CLINICAL TUBERCULOSIS
Diagnosis & Treatment

This book *Clinical Tuberculosis: Diagnosis and Treatment* is written with the aim of defining a practical approach to every aspect of tuberculosis. Chapters practically covers all the aspects of tuberculosis ranging from epidemiology, varying presentation of tuberculosis, diagnosis and practical approach to the treatment of pulmonary as well as common extrapulmonary tuberculosis including HIV and TB. It also covers practical approach to drug resistant including multidrug-resistant tuberculosis and extensively drug resistant tuberculosis. Chapters also include prevention of tuberculosis and TB control in India. Pharmacokinetics of antituberculosis used in new and retreatment cases of tuberculosis including their doses, regimens, adverse effects are highlighted. Special chapters on case-based approach to treatment of tuberculosis in special situation and MDR-TB have also been included. Chapters on TB in children, TB in elderly, nontuberculous mycobacteria and infection control in TB are also included. Chapters have been written in the background of current literature and practical experience gained from day-to-day dealing with different patients suffering from tuberculosis. Undergraduate, postgraduate medical students, practitioners and program manager in TB control will find this book as a practical guide.



Rajendra Prasad MD DTCD FAMS FCCP (USA) FNCCP FCAI FIAB FIMSA DSC (Honoris Causa) Director, Vallabhbhai Patel Chest Institute, University of Delhi, Delhi (India), Former Professor and Head, Department of Pulmonary Medicine, King George's Medical University, Lucknow, Uttar Pradesh, India and Former Director, UP Rural Institute of Medical Sciences and Research, Saifai, Etawah, Uttar Pradesh, did his MBBS in 1974 and MD in 1979 from King George's Medical College, Lucknow, Uttar Pradesh. He received advance training in pulmonary medicine including clinical tuberculosis and TB control from Japan. He is also Honorary Consultant to Armed Forces Medical Services, India in respiratory diseases. He has been International Governor of American College of Chest Physicians, USA. He has unique distinction of being President of all major scientific bodies in the field of pulmonary medicine in India like National College of Chest Physicians, Indian Chest Society, Indian College of Allergy, Asthma and Applied Immunology, Indian Association for Bronchology, and Chairman, Standing Technical Committee, Tuberculosis Association of India. Besides several prestigious fellowships of reputed national and international organizations, he was awarded Fellowship of the National Academy of Medical Sciences, India. He has supervised about 150 researches, and published 225 articles in reputed national and international journals and books. He has presented over 1,200 guest lectures and scientific papers at various national and international meetings.

Professor Rajendra Prasad is a nationally acclaimed chest physician and tuberculosis expert, possessing nearly 4 decades' illustrious teaching and research experience with proven excellence in quality patient care. Apart from being a clinician par excellence, he is also a very popular medical teacher in pulmonary medicine. His contribution in the field of tuberculosis and multidrug-resistant tuberculosis (MDR-TB) are widely acclaimed. His dynamic leadership in academic and administrative areas has earned him a large number of awards from various international and national scientific societies. He has been mentor of many students who are now assuming important positions in pulmonary medicine.

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

Shelving
Recommendation
MEDICINE

ISBN 978-93-5152-221-8

9 789351 522218