

National Tuberculosis Programme

A CLINICAL MANUAL FOR NEPAL

First edition October, 1998
Reprint February, 2002
Second edition January, 2005
Reprint February, 2006
Third edition April, 2009
Published by the National Tuberculosis Centre
with assistance from Global Fund

CONTENTS

Foreword	1
Introduction	3
Glossary	5
Ch.1. Background information on tuberculosis	11
1.1 Tuberculosis	11
1.1.1 Basic facts about TB (<i>M. tuberculosis</i> , transmission, risk of progression to disease, natural history of untreated TB, epidemiology)	11
1.1.2 Pathogenesis of TB	13
Ch.2. Diagnosis of tuberculosis in adults	17
2.1 Pulmonary TB.....	17
2.1.1 Diagnostic approach	17
2.1.2 Clinical features	18
2.1.3 Flow Chart for the diagnosis of pulmonary TB in people with chronic respiratory symptoms.....	19
2.1.4 Diagnostic sputum smear microscopy	20
2.1.5 Differential diagnosis of pulmonary TB.....	23
2.1.6 Chest X-rays in diagnosis	24
2.1.7 Patterns of disease in pulmonary TB	25
2.1.8 Differential diagnosis of chest X-ray findings	25
2.2 Extrapulmonary TB	26
2.2.1 Diagnostic approach	27
2.2.2 TB lymphadenopathy	27
2.2.3 Miliary TB	28
2.2.4 Tuberculous serous effusions	29
2.2.5 Tuberculous meningitis	35
2.2.6 Bone tuberculosis	38
2.2.7 Renal and urinary tract tuberculosis	40
2.2.8 Gastrointestinal tuberculosis	41

2.2.9	Tuberculosis of the female genital tract.....	45
2.2.10	Tuberculosis of the male genital tract.....	46
Ch.3. Diagnosis of tuberculosis in children.....		47
3.1	How does TB in children differ from TB in adults?	47
3.2	Approach to diagnosis	48
3.3	Score system for the diagnosis of TB in children	50
3.4	Tubercular meningitis	52
3.5	Tuberculoma	52
3.6	TB nephritis	53
3.7	Tuberculin skin test	53
3.8	Management of child contacts of infectious adults	54
Ch.4. Standardised TB case definitions and treatment categories		57
4.1	Standardised case definitions	57
4.1.1	Introduction	57
4.1.2	Questions and answers about case definitions	57
4.1.3	Case definitions by site and result of sputum smear	59
4.1.4	Case definitions by previous treatment	60
4.2	Standardised treatment categories	61
Ch.5. Treatment of TB patients		63
5.1	Introduction	63
5.2	Modes of action of anti-TB drugs	64
5.3	TB treatment regimens	65

5.3.1	New cases	66
5.3.2	Retreatment cases	66
5.3.3	Standard code for TB treatment regimens	66
5.3.4	Recommended treatment regimens	67
5.3.5	Use of streptomycin and thiacetazone in areas of high HIV prevalence	68
5.4	TB treatment regimens: questions and answers	69
5.5	Use of anti-TB drugs in special situations: pregnancy, renal failure, liver disease	70
5.6	The role of steroid treatment: questions and answers	71
5.7	Monitoring of TB patients during treatment	72
5.7.1	Monitoring of patients	73
5.7.1.1	Monitoring of patients with sputum smear-positive PTB	73
5.7.1.2	Monitoring of patients with sputum smear-negative PTB	74
5.7.1.3	Monitoring of patients with extra-pulmonary TB	74
5.7.2	Recording treatment outcome in TB patients	74
Ch.6. Side effects of anti-TB drugs		77
6.1	Introduction	77
6.2	Prevention of side effects	77
6.3	Where to manage drug reactions	77
6.4	When to stop anti-TB drugs	78
6.5	Side effects of anti-TB drugs	79
6.6	Symptom-based approach to management of drug side-effects	80
6.7	Management of skin itching/rash	80
6.7.1	Treatment regimen includes thiacetazone	81

6.7.2	Treatment regimen does not include thiacetazone	81
6.8	Desensitisation	83
6.9	Management of hepatitis	83
Ch.7. Framework for effective tuberculosis control		85
7.1	Introduction	85
7.2	Components of TB control framework	85
7.2.1	Overall objectives of TB Control	86
7.2.2	Strategy for TB control	86
7.2.3	Targets for TB control	86
7.2.4	TB control policy package	87
7.2.5	Key features of a national TB Programme (NTP)	87
7.2.6	Indicators of NTP progress in TB control	87
7.2.7	Cohort analysis: questions and answers	88
7.3	Directly observed therapy	89
Ch.8. HIV-related TB		91
8.1	Basic Information	91
8.1.1	Epidemiology of co-infection of HIV and <i>M. tuberculosis</i>	91
8.1.2	HIV infection and risk of TB	91
8.1.3	Consequence of HIV/ <i>M. Tuberculosis</i> co-infection	91
8.1.4	Impact of HIV on TB control	92
8.1.5	Impact of TB on HIV	92
8.2	Patterns of HIV-related TB	92
8.2.1	Pulmonary TB	93
8.2.2	Extra-pulmonary TB	96
8.3	HIV-related TB in children	97
8.3.1	The impact of HIV on the diagnosis of TB in children	97
8.3.2	Differential diagnosis of PTB in HIV-infected children	98
8.3.3	Child contacts who may be HIV-infected	98

8.4	Response of HIV-positive TB patients to anti-TB treatment...	98
8.4.1	Side-effects of anti-TB drugs in TB/HIV patients	100
Ch.9. Diagnosis of HIV infection in adults with tuberculosis		101
9.1	Clinical recognition of HIV infection in TB patients	101
9.2	HIV testing	102
9.2.1	HIV tests	102
9.2.2	Objectives of HIV antibody testing in TB patients	103
9.2.3	Strategy for HIV antibody testing in TB patients	103
9.2.4	Diagnosis of HIV infection in individual TB patients	104
9.3	HIV counselling	105
Ch.10. Diagnosis of HIV infection in children with tuberculosis..		109
10.1	Clinical recognition of HIV infection in children	109
10.2	HIV testing	110
10.3	Counselling	110
Ch.11. Prevention of TB		113
11.1	Introduction	113
11.2	Protection against exposure to TB	113
11.2.1	Environmental control	114
11.2.2	Face-masks	114
11.2.3	Patient education	114
11.2.4	PTB suspects	115
11.2.5	Patients with sputum smear-positive PTB	115
11.3	Role of BCG in preventing TB	115
11.3.1	General	115
11.3.2	BCG protection against TB in HIV-infected children	116
11.3.3	BCG safety in HIV-infected children	116
11.3.4	WHO recommended policy on BCG and HIV	116

11.4	The role of the Expanded Programme on Immunisation (EPI)	116
11.5	Preventive treatment	117
11.5.1	Target groups for preventive treatment	117
11.5.2	Role of isoniazid preventive treatment in HIV-positive individuals	118

**ANNEX
DRUG-RESISTANT TUBERCULOSIS**

Based on guidelines for the management of drug-resitant tuberculosis (WHO)

Ch. 1. Introduction	121
1.1 Definitions	121
1.2 How is MDR Tuberculosis produced ?	122
1.3 How to prevent MDR Tuberculosis ?	123
Ch. 2. Basic Principles for management of MDR Tuberculosis ...	127
2.1 Specialised unit	127
2.2 Designing an appropriate regimen	127
2.3 Reliable susceptibility testing	127
2.4 Reliable drug supplies	128
2.5 Priority is prevention	128
2.6 Using WHO standard regimens for new cases and retreatment	128
2.7 MDR Tuberculosis as a consequence of poor treatment	129

2.8	Long-term involvement of staff and financial resources	129
Ch. 3. Assessing the individual case of apparent MDR Tuberculosis 131		
Ch. 4. Available drugs for MDR Tuberculosis 133		
4.1	Essential antituberculosis drugs	133
4.2	Second-line antituberculosis drugs	134
4.3	Cross-resistance	137
4.3.1	Thiamide and thiacetazone	137
4.3.2	Aminoglycosides	137
4.3.3	Fluoroquinolones	138
4.3.4	Cycloserline and terizidone	138
Ch. 5. Choosing a chemotherapy regimen for a patient with apparent MDR Tuberculosis 139		
5.1	Basic principles	139
5.2	Examples of acceptable regimens in programme conditions	140
5.2.1	Situation A : Susceptibility test results are not available before starting the new treatment	140
5.2.2	Situation B : Susceptibility test results are available	141
5.2.2.1	Resistance to isoniazid, but rifampicin still active	141
5.2.2.2	Resistance to at least isoniazid and rifampicin	142
Ch. 6. The place of surgery 145		
6.1	Indication for surgery	145
6.2	Timing of surgery	145
6.3	Anti-tuberculosis chemotherapy after surgery	145

C O N T E N T S

FOREWORD

This clinical manual is designed for clinicians dealing with diagnosis, treatment and management of tuberculosis. It focuses mainly on issues of diagnosis and management of tuberculosis, both in adults and children. We hope this manual will provide useful reference for all clinician involved in management of tuberculosis.

As we are aware that the epidemic of HIV infection has dramatically affected the tuberculosis situation in many parts of the world and also in Nepal to certain extent. This book also summarises the characteristics of tuberculosis and its interactions with HIV/AIDS. It provides guidance for the management for drug resistant tuberculosis which is on the increase in Nepal.

This manual is based on the WHO TB guidelines and international recommendations.

We are grateful to The Global Fund for their support for printing this manual

If you have any suggestions for improving this manual, please write to:

The Director,
National Tuberculosis Centre
Thimi
Bhaktapur.

INTRODUCTION

Tuberculosis remains a major public health problem in Nepal and one of the leading causes of death from communicable diseases among adults. Over 80,000 people in Nepal have the disease. Nearly 20,000 people develop infectious sputum positive TB every year and about 45,000 new cases of all forms of TB occur in the same period. It is estimated that about 5,000-7,000 people die from TB every year.

Objectives of the National Tuberculosis Control Programme (NTP) are to decrease morbidity, mortality and transmission of tuberculosis and to ensure avoiding the emergence of drug resistance. Directly Observed Treatment Short-course (DOTS) is the national strategy of the NTP programme which recommends provision of short-course chemotherapy with direct observation of treatment intake for all TB patients, especially smear positive cases. NTP targets are; 85% cure rate and 70% case detection rate among infectious tuberculosis cases.

This manual is mainly for doctors and health professionals in both public and private health care systems.

This pocket manual is designed so that it can be used while working in the ward, clinic and at home. There is not enough room in a pocket manual for all the possible information you may wish to know about TB and TB/HIV therefore at the end of each chapter there are suggestions for further reading. These suggestions include relevant books, background material, reviews and recent articles in journals.

We are extremely grateful to Dr. Madhu Ghimire, for his contribution to the section on gastrointestinal tuberculosis; Dr. Dibya S. Malla, for her contribution to the section on female genital tuberculosis; Dr. Ashok Banskota, for his contribution to the section on bone tuberculosis; Dr. Sudha Khakurel, for her contribution to the section on renal tuberculosis; Dr Ranendra Shrestha, for his valuable sugges-

tions on childhood tuberculosis and Dr. Ramesh Chokhani and Dr. Pushpa Malla for their valuable suggestions in lung tuberculosis. Finally we are grateful to Dr. M. Akhtar for his overall advise, revision and re-writing of this manual.

You are welcome to send any comments on the manual to the Director, National Tuberculosis Centre, Thimi, Bhaktapur.

GLOSSARY

This glossary explains abbreviations and some of the words used in this book.

<i>acquired resistance</i>	<i>..... resistance of Mycobacterium tuberculosis to anti-TB drugs in a TB patient who has previously received anti-TB treatment</i>
<i>adherence to treatment</i>	<i>..... the patient taking the medicines</i>
<i>adjuvant treatment</i>	<i>..... as an addition to other treatment</i>
<i>AFBs</i>	<i>..... Acid-Fast Bacilli</i>
<i>agranulocytosis</i>	<i>..... absence of polymorph white blood cells</i>
<i>AIDS</i>	<i>..... Acquired Immuno Deficiency Syndrome</i>
<i>anorexia</i>	<i>..... loss of appetite for food</i>
<i>ARC</i>	<i>..... AIDS-Related Complex</i>
<i>atypical mycobacteria</i>	<i>..... non-tuberculous mycobacteria</i>
<i>bactericidal</i>	<i>..... kills bacteria</i>
<i>bacteriostatic</i>	<i>..... stops bacteria from growing</i>
<i>BCG</i>	<i>..... Bacille Calmette-Guerin</i>
<i>bubo</i>	<i>..... swollen, pus-containing lymph node</i>
<i>caseation</i>	<i>..... tissue breakdown by TB bacilli, forming yellow-white, cheese-like material</i>
<i>chemotherapy</i>	<i>..... treatment with chemical drugs, e.g. anti-TB chemotherapy means treatment with anti-TB drugs</i>
<i>CD4 cells</i>	<i>..... sub-group of T-lymphocytes carrying CD4 antigens</i>
<i>CMV</i>	<i>..... CytoMegaloVirus</i>
<i>CNS</i>	<i>..... Central Nervous System</i>
<i>co-infection</i>	<i>..... infection with different pathogens at the same time, e.g. Mycobacterium tuberculosis and HIV.</i>
<i>contacts</i>	<i>..... people (often family members) close to a TB patient and at risk of infection</i>
<i>counselling</i>	<i>..... face-to-face communication in which one person (counsellor) helps another (patient/client) to make decisions and act on them</i>

<i>CSF</i>	CerebroSpinal Fluid
<i>dactylitis</i>	<i>inflammation of the fingers</i>
<i>default</i>	<i>patient stopping treatment before completion</i>
<i>desensitisation</i>	<i>spread throughout the body to may different organs</i>
<i>dormant</i>	<i>sleeping or inactive</i>
<i>DOT</i>	Directly Observed Therapy (supervisor watches patient to ensure the patient takes the tablets)
<i>erythema nodosum</i>	<i>painful, tender, red nodules over the front of the legs</i>
<i>Empirical treatment</i>	<i>treatment for a certain condition without exact diagnostic confirmation by test</i>
<i>EPI</i>	Expanded Programme on Immunisation
<i>extrapulmonary tuberculosis</i>	<i>tuberculosis outside the lungs</i>
<i>exudates</i>	<i>fluid with a high protein content and inflammatory cells in an area of disease</i>
<i>false negative test result</i> ..	<i>a test result which shows negative, when the true result is in fact positive</i>
<i>FBC</i>	Full Blood Count
<i>fluorochrome stain</i>	<i>shines brightly under ultraviolet light</i>
<i>gibbus</i>	<i>an acute angle in the spine due to vertebral collapse from TB</i>
<i>hilar</i>	<i>at the root of the lung</i>
<i>hilum</i>	<i>the root of the lung</i>
<i>HIV</i>	Human Immunodeficiency Virus
<i>HIV-negative</i>	<i>blood test shows absence of antibodies against HIV</i>
<i>HIV-positive</i>	<i>blood test shows presence of antibodies against HIV</i>
<i>HIV-related TB</i>	<i>TB occuring in somebody infected with HIV</i>
<i>HIV status</i>	<i>whether a person is known to be HIV-positive or HIV-negative</i>
<i>HIV test</i>	<i>blood test for antibodies against HIV</i>

home care providing care for a patient in his home rather than in hospital
hypersensitivity reaction.. type of immunological reaction to even a small amount of a drug or other antigen, e.g. tuberculin
i.m. injection intramuscular injection
immunosuppressant drugs drugs which suppress normal immunity
incidence the number of new cases of a disease in a population in a given time (usually one year)
induration..... thickening e.g. of the skin in a tuberculin test
initial resistance resistance of *Mycobacterium tuberculosis* to anti-TB drugs in a TB patient who has never before received anti-TB drugs
IUATLD..... **I**nternational **U**nion **A**gainst **T**B and **L**ung **D**isease
JVP..... **J**ugular **V**enous **P**ressure
KS..... **K**aposi's **S**arcoma
latent something that is there but not obvious (it can become obvious later)
lesion..... an area of disease in the body
LFTs **L**iver **F**unction **T**ests
MAC **M**ycobacterium **A**vium **i**ntra**C**ellular (one of the atypical mycobacteria)
MCV..... **M**ean **C**orpuscular **V**olume
meningism..... presence of clinical features suggestive of meningitis, e.g. headache, neck-stiffness, positive Kernig's sign
mutant bacilli..... bacilli which suddenly change genetically and become different from the rest of the population
mutation a sudden genetic change, e.g. which results in a bacillus becoming drug-resistant
NGO **N**on-**G**overnmental **O**rganisation
NSAID **N**on-**S**teroidal **A**nti-**I**nflammatory **D**rug

NTP *National Tuberculosis Programme*
opportunistic infection..... *an infection which “takes the opportunity” to cause disease when a person’s immune defense is weak*
“passive” case finding *detection of TB cases by active testing (sputum smear) of TB suspects attending health services*
pathogenesis..... *how a disease arises.*
PCP *Pneumocystis Carinii Pneumonia*
phlyctenular conjunctivitis *painful hypersensitivity reaction of the conjunctiva to primary tuberculosis infection, with inflammation and small red spots where the cornea meets the sclera*
PGL..... *Persistent Generalised Lymphadenopathy*
PPD..... *Purified Protein Derivative (tuberculin)*
preventive treatment *treatment aimed at preventing disease, e.g. isoniazid for the prevention of TB in certain circumstances*
PTB *Pulmonary TuBerculosis*
PTB suspect *patient presenting with features which make the health worker think the patient may have PTB, most importantly cough of more than 3 weeks’ duration*
regimen *a drug, or several drugs, given in certain doses for a stated duration*
relapse..... *disease starting again after a patient was declared cured*
SCC *Short–Course Chemotherapy*
scrofula *tuberculous lymph nodes in the neck*
sensitivity tests..... *tests of TB bacilli for sensitivity or resistance to anti-TB drugs*
seroconversion *when a blood test first shows that a person is HIV seropositive, usually about 3 months after HIV infection*
seroprevalence *the proportion of people testing seropositive (e.g. for HIV) in a population at any one time.*
slim disease..... *HIV-related chronic diarrhoea and weight*

loss
 spinal block..... obstruction to normal flow of CSF around
 the spinal cord
 sputum smear negative.... absence of AFBs on sputum microscopy
 sputum smear positive..... presence of AFBs on sputum microscopy
 STD Sexually Transmitted Disease
 Stevens–Johnson syndrome a characteristic rash with “target lesions”
 and inflammation of the mucous membranes
 syndrome a group of symptoms and signs
 TB..... TuBerculosis
 TB/HIV TB and HIV co-infection
 TB/HIV patient..... HIV-infected TB patient
 TEN Toxic Epidermal Necrolysis
 thrombocytopenia low platelet count
 T-lymphocytes type of lymphocyte providing cellular immu-
 nity
 TMP-SMX TriMethoPrim-SulfaMethoXazole
 tubercles..... small rounded areas of TB disease
 tuberculin protein extracted from TB bacilli (PPD)
 tuberculoma rounded area of TB disease, usually 1cm or
 more wide
 UNICEF United Nations Children’s Fund
 WHO World Health Organization
 window period the gap of about 3 months between the time
 when a person becomes infected with HIV
 and the time when the blood test for HIV
 first shows positive
 ZN Stain..... Ziehl-Neelsen stain

CHAPTER 1 BACKGROUND INFORMATION ON TUBERCULOSIS

1 1 TUBERCULOSIS (TB)

1 1 1 Basic facts about TB

Mycobacterium tuberculosis

TB is a bacterial disease caused by *Mycobacterium tuberculosis* (and occasionally by *Mycobacterium bovis* and *Mycobacterium africanum*). These organisms are also known as tubercle bacilli (because they cause lesions called tubercles) or as acid-fast bacilli (AFB). When examining sputum containing tubercle bacilli stained with certain dyes under the microscope, the bacilli look red. This is because they are acid-fast (they have kept the dye even after washing with acid and alcohol). Tubercle bacilli can remain dormant in tissues and persist for many years.

Transmission of infection

Transmission occurs through airborne spread of infectious droplets. Source of infection is a person with TB of the lung who expectorating bacilli. Coughing produces tiny infectious droplets (droplet nuclei). One cough can produce 3,000 droplet nuclei. Transmission generally occurs indoors, where droplet nuclei can stay in the air for a long time. Ventilation removes droplet nuclei. Direct sunlight quickly kills tubercle bacilli, but they can survive in the dark for several hours. Two factors determine an individual's risk of exposure: the concentration of droplet nuclei in contaminated air and the length of time breathing that air.

Risk of infection

An individual's risk of infection depends on the intensity and duration of exposure to droplet nuclei and susceptibility to infection. The risk of infection of a susceptible individual is therefore high with close, prolonged, indoor exposure to a person with sputum smear-positive pulmonary tuberculosis (PTB). The risk of transmission of infection from a person with sputum smear-negative PTB is low, and with extra-pulmonary TB is even lower.

Risk of progression of infection to disease.

Once infected with *M. tuberculosis*, a person stays infected for many years, probably for life. The vast majority (90%) of people without HIV infection who are infected with *M. tuberculosis* do not develop tuberculosis disease. In these healthy, asymptomatic, but infected individuals, the only evidence of infection may be a positive tuberculin skin test. Infected persons can develop tuberculosis disease at any time. The chance of developing disease is greatest shortly after infection and then steadily lessens with passage of time. Various physical or emotional stresses may trigger progression of infection to disease. The most important trigger is weakening of immune resistance, especially by HIV infection. Disease can affect most tissues and organs, but especially the lungs.

Natural history of untreated TB

Without treatment, after 5 years, 50% of pulmonary TB patients will die, 25% will be cured (self-cured by strong immune defence) and 25% will remain ill and continue to spread TB.

Epidemiology

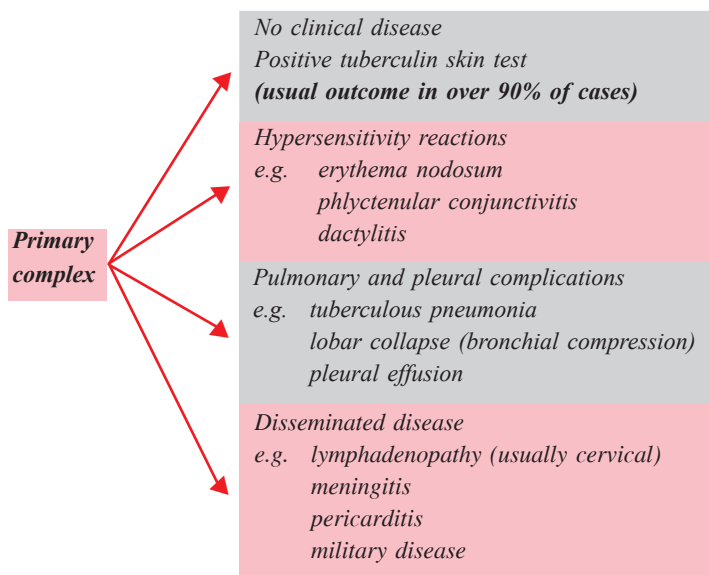
M. tuberculosis infects a third of the world's populations. World Health Organization estimates 13.7 million prevalent TB cases globally during 2007. There were approximately 9.27 million new TB cases during 2007. Among these an estimated 44% (4.1 million) were new smear positive cases. Asia (the South East Asia and Western Pacific regions) accounts for 55% of the global TB cases. Among 9.27 million incident cases reported during 2007 about 1.37 million (14.8%) were HIV positive. Similarly, during 2007 an estimated 1.776 million deaths were due to TB among these 456,000 were among HIV positive people.

In Nepal over 80,000 people have tuberculosis. Every year about 40,000 people develop tuberculosis, nearly half of these have infectious tuberculosis. It is estimated that about 6,000 to 7,000 people die from tuberculosis every year in Nepal. That is nearly 125 deaths every week or about 18 deaths each day.

Primary infection

Primary infection occurs on first exposure to tubercle bacilli. Inhaled droplet nuclei are so small that they avoid the muco-ciliary defences of the bronchi and lodge in the terminal alveoli of the lungs. Infection begins with multiplication of tubercle bacilli in the lungs. This is called the Ghon focus. Lymphatics system drains the bacilli to the hilar lymph nodes. The Ghon focus and related hilar lymphadenopathy form the 'primary complex'. Bacilli may spread in the blood from the primary complex throughout the body. The immune response (delayed hypersensitivity and cellular immunity) develops about 4-6 weeks after the primary infection. The size of the infecting dose of bacilli and the strength of the immune response determine what happens next. In most cases, the immune response stops the multiplication of bacilli. However, a few dormant bacilli may persist. A positive tuberculin skin test would be the only evidence of infection. The immune response in a few cases is not strong enough to prevent multiplication of bacilli, and disease occurs within a few months.

Outcome of primary infection



PRACTICAL POINT

Following primary infection, rapid progression to intra-thoracic disease is more common in children than in adults. Hest X-ray may show intrathoracic lymphadenopathy and lung infiltrates.

Post-primary TB

Post-primary TB occurs after a latent period of months or years after primary infection. It may occur either by reactivation or by reinfection. Reactivation means that dormant bacilli persisting in tissues for after primary infection start to multiply. This may be in response to a trigger, such as weakening of the immune system by HIV infection. Reinfection means a repeat infection in a person who has previously had a primary infection.

Post-primary TB usually affects the lungs but can involve any part of the body. The characteristic features of post-primary PTB are: extensive lung destruction with cavitation; positive sputum smear; upper lobe involvement; usually no intrathoracic lymphadenopathy.

POST-PRIMARY TB

PULMONARY TB

*e.g. cavities
upper lobe infiltrates
fibrosis
progressive pneumonia
endobronchial*

EXTRA-PULMONARY TB

COMMON

Pleural effusion

Lymphadenopathy (usually cervical)

*Central nervous system
(meningitis, cerebral tuberculoma)*

*Pericarditis
(effusion/constrictive)*

*Gastro-intestinal
(ileocaecal, peritoneal)*

Spine, other bone and joint

LESS COMMON

Empyema

*Male genital tract
(epididymitis, orchitis)*

*Female genital tract
(tubo-ovarian, endometrium)*

Kidney

Adrenal gland

*Skin
(lupus vulgaris, tuberculids,
military)*

PRACTICAL POINT

Post-primary infection with pulmonary disease usually occurs in adults, with positive sputum smears.

SUGGESTIONS FOR FURTHER READING

Crofton J, Horne N and Miller F. Clinical Tuberculosis. The Macmillan Press Limited. 1992.

Davies PDO. Clinical Tuberculosis. Champan and Hall Medical 1994.

International Union Against Tuberculosis and Lung Disease. Tuberculosis Guide For Low Income Countries. pmi Verlagsgruppe. 3rd edition. Frankfurt, 1994.

Raviglione MC, Snider D, Kochi A. Global epidemiology of tuberculosis. Morbidity and mortality of a worldwide epidemic. JAMA 1995; 273: 220-226.

Dolin P.J., Raviglione M.C, Kochi A. Global tuberculosis incidence and mortality during 1990-2000. Bull. World Health Organization, 1994; 72(2): 213-220.

CHAPTER 2 DIAGNOSIS OF TUBERCULOSIS IN ADULTS

2 1 PULMONARY TB

2 1 1 Diagnostic approach

The highest priority for TB control is the identification and cure of the infectious cases, i.e. patients with sputum smear-positive PTB. Therefore all patients with clinical features suggesting PTB must submit sputum for diagnostic sputum smear microscopy.

Most TB suspects are ambulatory. The diagnosis of PTB is therefore usually on an out-patient basis. A few TB suspects are severely ill and/or bed-bound and therefore need investigation as in-patients.

Clinical screening by assessment of symptoms identifies PTB suspects among patients attending health facilities. The most cost-effective method of screening PTB suspects in high-prevalence countries is by sputum smear microscopy. When a suspect has a positive sputum smear, the person has sputum smear-positive PTB. Register this person with the appropriate health authority and start treatment. In most cases, a chest X-ray is unnecessary.

In populations with a high TB prevalence, the tuberculin skin test is of little value in the diagnosis of TB in adults. A positive tuberculin skin test does not by itself distinguish *M. tuberculosis* infection from tuberculosis disease. Previous exposure to environmental mycobacteria may also result in a false-positive test result. Conversely, the tuberculin skin test result may be negative, even when the patient does have TB. Conditions often associated with a false-negative tuberculin skin test include HIV infection, severe malnutrition and military TB.

2 1 2 Clinical features

Symptoms

The most important symptoms in the diagnosis of PTB are the following:

cough > 2 weeks

sputum production

weight loss

Over 90% of patients with sputum smear-positive PTB develop a cough soon after disease onset. However, cough is not specific to PTB. Cough is common in smokers and in patients with acute upper or lower respiratory tract infection. Most acute respiratory infections resolve within 3 weeks. Therefore a patient with a cough for more than 3 weeks is a PTB suspect and must submit sputums for diagnostic microscopy.

Patients with PTB may also have other symptoms. These may be respiratory or constitutional (general or systemic).

Respiratory: haemoptysis, chest pain, breathlessness

Constitutional: fever/night sweats, tiredness, loss of appetite

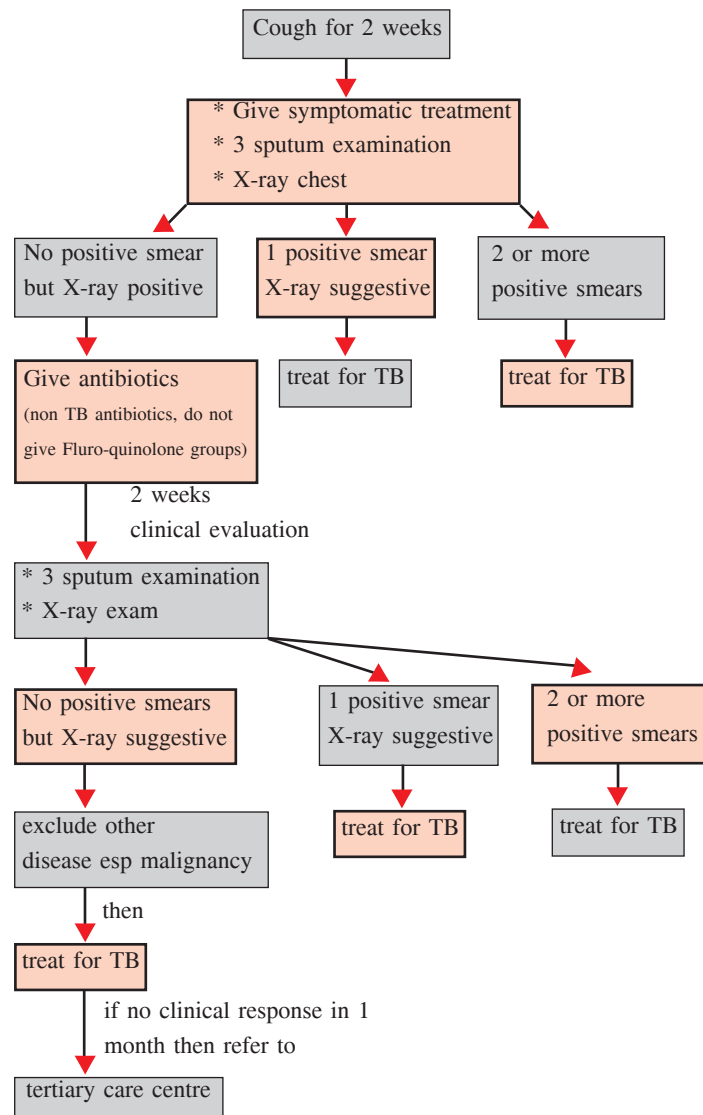
Physical signs

The physical signs in patients with PTB are non-specific. They do not

PRACTICAL POINT

PTB suspects (patients with suggestive symptoms) must submit sputums for sputum smear microscopy.

2 1 3 Flow Chart for the diagnosis of Pulmonary TB in people with chronic respiratory symptoms



NB. If only 1 smear is positive and the X-ray is negative always re-evaluate the case.

2 1 4 Diagnostic sputum smear microscopy

help to distinguish PTB from other chest diseases.

Collection of sputum samples

A PTB suspect should submit 3 sputum samples for microscopy. The chances of finding tubercle bacilli are greater with 3 sputum samples than with 2 samples or 1 sample. As secretions build up in the airways overnight therefore an early morning sputum sample is more likely than a sample later in the day to contain tubercle bacilli. It may be difficult for an out-patient to provide 3 early morning sputum samples.

Therefore in practice an out-patient usually provides sputum samples as follows:

day 1...sample 1... Patient provides an “on the spot” sample under supervision at the time of presenting to the healthy facility.

Give the patient a sputum container to take home for an early morning sample the following morning.

day 2 ...sample 2... Patient brings an early morning sample

sample 3... Patient provides another “on the spot” sample under supervision.

If a patient can't produce a sputum sample, a nurse or physiotherapist may help the patient to give a good cough and bring up some sputum. An in-patient can provide 3 early morning sputum samples under supervision in hospital.

Terminology

Mycobacteria are “acid- and alcohol-fast bacilli” (AAFB), often shortened to “acid-fast bacilli” (AFB). The waxy coat of mycobacteria retains an aniline dye (e.g. carbol fuchsin) even after decolourisation with acid and alcohol.

Ziehl-Neelsen (Z-N) stain

This simple stain detects AFB. This is how to perform the Z-N stain:

- **fix the smear on the slide**
▼
- **cover the fixed smear with carbol fuchsin for 3 minutes**
▼
- **heat, rinse with tap water, and decolourise with acid-alcohol for 3-5 seconds**
▼
- **counter-stain with methylene blue for 30 seconds**
▼
- **rinse again with tap water**
▼
- **Observe under the microscope**
(use the oil immersion lens (x100) and x6 or x8 eye-piece lens)
The bacilli appear as red, beaded rods, 2-4 mm long and 0.2-0.5 mm wide.

Fluorochrome stain

This is a different stain for tubercle bacilli. A special fluorescent microscope is necessary. The fluorochrome stain is phenolic auramine or auramine-rhodamine. After acid-alcohol decolourisation and a methylene blue counterstain, the bacilli fluoresce bright yellow against a dark background. The advantage of this method is that it is possible to scan smears quickly under low magnification.

Slide Reporting

The number of bacilli seen in a smear reflects disease severity and patient infectivity. Therefore it is important to record the number of bacilli seen on each smear. The table below shows the standard method of reporting.

NUMBER OF BACILLI SEEN IN A SMEAR		RESULT	REPORTED
no.	AFB found per 300 oil immersion fields	Negative	Negative
1-9	AFB found per 100 oil immersion fields	Record exact no. of AFB/100VF	
10-99	AFB found per 100 oil immersion fields	+	(1+)
1-10	AFB found per 50 oil immersion field	++	(2+)
>10	AFB found per 20 oil immersion field	+++	(3+)

The laboratory technician must examine all 3 sputum samples from each TB suspect. The technician must record the result of each sputum sample with the laboratory reference number in the laboratory register and on the sputum request form.

Sensitivity of sputum smear microscopy

Sputum smear microscopy for tubercle bacilli is positive when there are at least 10,000 organisms present per 1 ml of sputum.

False positive results of sputum smear microscopy

A false positive result means that the sputum smear result is positive even though the patient does not really have sputum smear-positive PTB. This may arise because of the following: red stain retained by scratches on the slide; accidental transfer of AFBs from a positive slide to a negative one; contamination of the slide or smear by environmental mycobacteria; various particles that are acid-fast (e.g. food particles, precipitates, other micro-organisms).

False negative results of sputum smear microscopy

A false negative result means that the sputum smear result is negative even though the patient really does have sputum smear-positive PTB. This may arise because of problems in collecting, processing, or interpreting sputum smear, or because of administrative errors.

PRACTICAL POINT

If a sputum smear result is unexpectedly negative (e.g. in a patient with upper lobe cavities on chest X-ray), think of the possibility of a false negative result and repeat the sputum microscopy.

Causes of false negative results of smear microscopy

TYPE OF PROBLEM	EXAMPLE
<i>sputum collection.....</i>	<i>patient provides inadequate sample inappropriate sputum container used sputum stored too long before smear microscopy</i>
<i>sputum processing.....</i>	<i>faulty sampling of sample for smear faulty smear preparation and staining</i>
<i>sputum smear interpretation...</i>	<i>inadequate time spent examining smear inadequate attention to smear (poor motivation)</i>
<i>administrative errors.....</i>	<i>mis-identification of patient incorrect labeling of sample mistakes in documentation</i>

2 1 5 Differential diagnosis of pulmonary TB

PRACTICAL POINT
A PTB suspect with 3 negative sputum smears may not have PTB at all. Reassess the patient in case he has a condition mistaken for PTB.

The table shows the differential diagnosis of PTB.

DIFFERENTIAL DIAGNOSIS	POINTERS TO THE CORRECT DIAGNOSIS
<i>Congestive cardiac failure left ventricular failure</i>	<i>symptoms of heart failure (dyspnoea, orthopnoea, paroxysmal nocturnal dyspnoea, haemoptysis, oedema, epigastric discomfort from hepatic congestion) signs of heart failure</i>
<i>asthma</i>	<i>intermittent symptoms, generalized expiratory wheezes</i>
<i>chronic obstructive airways disease</i>	<i>risk factor (smoking), chronic symptoms, prominent dyspnoea, generalized wheezes</i>
<i>bronchiectasis</i>	<i>large amounts of purulent sputum</i>
<i>bronchial carcinoma</i>	<i>risk factor (smoking)</i>
<i>other infections e.g. bacterial pneumonia lung abscess pneumocystis carinii</i>	<i>response to antibiotic abscess with fluid level on chest X-ray dyspnoea prominent</i>

PRACTICAL POINT

If a patient is breathless, has continuing haemoptyses, and has negative sputum smears, listen carefully for a low-pitched, rumbling, mid-diastolic murmur in case the diagnosis is mitral stenosis with pulmonary oedema.

2 1 6 Chest X-rays in diagnosis

INDICATIONS FOR CHEST X-RAY

Positive sputum smear

The first screening test for PTB suspects is sputum smear microscopy. In most cases of sputum smear-positive PTB a chest X-ray is unnecessary. In those few cases of sputum smear-positive PTB when a chest X-ray is necessary, the indications are as follows:

- a) suspected complications in the breathless patient, needing specific treatment, e. g. pneumothorax, (pericardial effusion or pleural effusion-positive sputum smear is rare);
- b) frequent or severe haemoptysis (to exclude bronchiectasis or aspergilloma);
- c) only 1 sputum smear positive out of 3 (in this case, an abnormal chest X-ray is a necessary additional criterion for the diagnosis of sputum smear-positive PTB).

Negative sputum smears

Re-assess the patient who continues to cough despite a course of broad-spectrum antibiotic, and who has had 3 negative sputum smears. It is often worthwhile repeating the sputum smears after 2 weeks. If you still suspect TB despite negative sputum smears, the patient needs a chest X-ray.

2 1 7 Patterns of disease in PTB

PRACTICAL POINT
No chest X-ray pattern is absolutely typical of PTB.

The table shows the so-called “classical” and “atypical” patterns. (The atypical pattern is more common in HIV positive patients).

CLASSICAL PATTERN	ATYPICAL PATTERN
<i>upper lobe infiltrates</i>	<i>interstitial infiltrates</i>
<i>bilateral infiltrates</i>	<i>(especially lower zones)</i>
<i>cavitation</i>	<i>no cavitation</i>
<i>pulmonary fibrosis and shrinkage</i>	<i>no abnormalities</i>

2 1 8 Differential diagnosis of chest X-ray findings

The chest X-ray findings associated with PTB are non-specific. Diseases other than PTB can cause both the “classical” and the “atypical” chest X-ray findings.

PRACTICAL POINT

The vast majority of patients (over 90%) with cavitary PTB are sputum smears-positive. Therefore, a patient with cavities on chest X-ray and repeated negative sputum smears probably has a disease other than PTB.

The table shows the differential diagnosis of chest X-ray findings often associated with PTB.

CHEST X-RAY FINDING	DIFFERENTIAL DIAGNOSIS
cavitation.....	infections <i>some bacterial pneumonias</i> <i>lung abscess</i> <i>some fungal infections</i> non-infectious disease <i>bronchial carcinoma</i> <i>connective tissue disease occupational lung disease</i>
unilateral infiltration.....	<i>pneumonia</i> <i>bronchial carcinoma</i>
bilateral infiltration.....	<i>pneumonia</i> <i>connective tissue disease</i> <i>occupational lung disease</i> <i>sarcoidosis</i>
mediastinal lymphadenopathy	<i>lymphoma</i> <i>bronchial carcinoma</i> <i>sarcoidosis</i>

2 2 EXTRAPULMONARY TB

Common forms of extrapulmonary TB include the following: lymphadenopathy, pleural effusion, pericardial disease, military, meningitis. Patients usually present with constitutional features (fever, night sweats, weight loss) and local features related to the site of disease. The local features related to the site of disease are similar in adults and children.

2 2 1 Diagnostic approach

Many patients with extrapulmonary TB also have co-existent pulmonary TB.

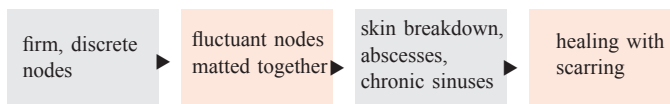
PRACTICAL POINT

If a patient has extrapulmonary TB, look for pulmonary TB. Send sputum samples for AFBs and, if sputum AFBs are negative, do a chest X-ray.

Definitive diagnosis of extrapulmonary TB is often difficult. Diagnosis may be presumptive, provided you can exclude other conditions. The degree of certainty of diagnosis depends on the availability of diagnostic tools, e.g. specialized X-rays, biopsy procedures.

2 2 2 Tuberculous lymphadenopathy

The lymph nodes most commonly involved are the cervical nodes. The usual course of lymph node disease is as follows:



PRACTICAL POINT

In severe immunocompromise, tuberculous lymphadenopathy may be acute and resemble acute pyogenic lymphadenitis.

The differential diagnosis of tuberculous lymphadenopathy includes the following: persistent generalised lymphadenopathy (PGL), lymphoma, Kaposi's sarcoma, carcinomatous metastases, sarcoid, drug reactions (e.g. phenytoin).

Practical approach to investigation of lymphadenopathy

PROCEDURE	TEST	RESULT	DIAGNOSIS
needle aspirate of lymph node	Look at material		
	aspirated.....	caseation	TB
	smear for AFBs.....	AFBs present.....	TB
	smear for cytology ...	malignant cells seen ...	malignancy e.g. KS, lymphoma, carcinoma
if no diagnosis after aspirate			
lymph node biopsy	look at cut surface ...	caseation	TB
	smear from cut		
	surface for AFBs.....	AFB seen	TB
	fresh node sent		
	for TB culture.....	positive TB culture.....	TB
	node in formalin		
	for histology	granuloma and AFBs..	TB
		malignant cells.....	malignancy

Diagnosis of tuberculous lymphadenopathy is possible even without laboratory facilities for histology or TB culture. Diagnostic sensitivity of tuberculous lymphadenopathy by aspirate and smear for AFBs is 70%. Diagnostic sensitivity increases to 80% if you excise a lymph node, look at the cut surface, and do a smear for AFBs.

2 2 3 Miliary TB

Miliary TB results from widespread blood-borne dissemination of TB bacilli. This is either the consequence of a recent primary infection or the erosion of a tuberculosis lesion into a blood vessel.

Clinical features

The patient presents with constitutional features. Hepatosplenomegaly and choroidal tubercles (fundoscopy) may be present.

Diagnosis

Chest X-ray shows diffuse, uniformly distributed, small miliary shadows. "Miliary" means "like small millet seeds". Full blood count may show pancytopenia. Liver function tests may be abnormal. Bacteriological confirmation is sometimes possible from sputum, C.S.F., or bone marrow.

Differential diagnosis

The differential diagnosis includes the following: slim disease, bacteraemia (including typhoid fever), disseminated carcinoma, disseminated infection with "atypical" mycobacteria.

2 2 4 Tuberculous serous effusions

Inflammatory tuberculous effusions may occur in any of the serous cavities of the body, i.e. pleural, pericardial or peritoneal cavities.

Approach to diagnosis

The presentation is usually with constitutional and local features. Microscopy of the aspirate from tuberculous serous effusions rarely shows AFBs because the fluid forms as an inflammatory reaction to TB lesions in the serous membrane. TB culture, even if available, is of no immediate help. A culture result usually takes 4-6 weeks. The white cell content is variable, usually with predominant lymphocytes and monocytes. The aspirate is an exudate (i.e. protein content is more than 30 g/l).

PRACTICAL POINT

A biochemistry laboratory is not essential to diagnose an exudate. Simply leave the aspirate standing: if it clots, it is an exudate.

TB is a common cause of an exudative serous effusion. The diagnosis is usually presumptive (i.e. without microbiological or histological confirmation). It is important to exclude other causes of an exudate.

PRACTICAL POINT

Interpret with caution the laboratory result of protein concentration in any aspirated fluid. If there has been a delay in laboratory analysis, a protein clot may have formed in the sample. The laboratory result may be falsely low.

TUBERCULOUS PLEURAL EFFUSION

The clinical and chest X-ray diagnosis of a pleural effusion is straightforward. The typical clinical features are constitutional and local (chest pain, breathlessness; tracheal and mediastinal shift away from the side of the effusion; decreased chest movement, percussion note and breath sounds on the side of the effusion). Chest X-ray shows unilateral, uniform white opacity, often with a concave upper border. If available, ultrasound confirms the presence of fluid in the pleural space in case of doubt.

Always perform diagnostic pleural aspiration if patient has a pleural effusion. The fluid is usually straw-coloured. The white cell count is usually high (about 1000-2,500 per mm³) with predominant lymphocytes. Occasionally the fluid is blood-stained. The presence of pus on aspiration indicates an empyema (purulent effusion).

PRACTICAL POINT

In a high TB prevalence population, if there are no facilities for aspiration, you should treat a patient with a unilateral exudative pleural effusion with anti-TB drugs.

If facilities are available, closed pleural biopsy using an Abrams needle is useful for histological diagnosis. Since distribution of TB lesions in the pleura is patchy, the diagnostic yield of closed pleural biopsy is about 75%. Multiple biopsies increases the diagnostic yield. A small open pleural biopsy increases the yield even further but is not usually necessary.

Differential diagnosis

The differential diagnosis of an exudative pleural effusion includes malignancy, post-pneumoic effusion, pulmonary embolism and amoebic liver abscess (extending on the right).

Tuberculous empyema

This usually arises when a tuberculous cavity in the lung ruptures into the pleural space. The physical signs are those of a pleural effusion, but aspiration reveals thick white/yellow pus. If the pus is too thick to remove using a needle and syringe, use an intercostals drain. Send the pus to the laboratory for examination for TB and also for Gram stain and bacterial culture. If facilities are available, closed pleural biopsy is useful for histological diagnosis.

The main differential diagnosis is bacterial empyema, when the patient is usually more acutely ill and toxic. It may be possible to confirm bacterial empyema by Gram stain and/or culture of the aspirated pus.

A succession splash is a splashing sound heard with the stethoscope while shaking the patient's chest. A succession splash indicates a pyopneumothorax (pus and air in the pleural space). After chest X-ray confirmation, insert a chest drain with underwater seal.

PRACTICAL POINT

Always test a patient with signs of a pleural effusion for a succession splash.

TUBERCULOUS PERICARDIAL EFFUSION

Diagnosis

The diagnosis usually rests on suggestive constitutional and cardiovascular features and investigation findings (ECG, chest X-ray and echocardiography). It is important to exclude uraemia and Kaposi's sarcoma.

Cardiovascular symptoms

- chest pain
- shortness of breath
- cough
- dizziness and weakness (low cardiac output)
- leg swelling
- right hypochondrial pain (liver congestion)
- abdominal swelling (ascites)

Cardiovascular signs

- tachycardia
- low blood pressure
- pulsus paradoxus
- raised jugular venous pressure (JVP) with small amplitude “a” and “v” waves
- impalpable apex beat
- quiet heart sounds
- pericardial friction rub
- signs of right-sided heart failure (e.g. hepatomegaly, ascites, oedema)

PRACTICAL POINT

The signs may be subtle. Assess carefully any patient with oedema and/or ascites with the possibility of pericardial effusion in mind.

Chest X-ray

- large globular heart
- clear lung fields
- pleural fluid

ECG

- tachycardia
- ST and T wave changes
- low voltage QRS complexes

Echocardiography

- pericardial fluid
- strands crossing between visceral and parietal pericardium

Pitfalls in diagnosis of pericardial effusion

Clinicians have mis-diagnosed pericardial effusion as the following:

- congestive cardiac failure;
- hepatoma or amoebic liver abscess (enlarged liver);
- bilateral pleural effusions.

Pericardiocentesis

This is only safe under the following conditions:

- a) echocardiography has confirmed a moderate to large pericardial effusion;
- b) the operator is experienced.

Therapeutic pericardiocentesis is necessary if there is cardiac tamponade (acute life-threatening cardiac impairment).

PRACTICAL POINT

In high TB prevalence populations, TB is the most likely treatable cause of pericardial effusion. It may be safer for the patient to start presumptive anti-TB treatment rather than undergo diagnostic pericardiocentesis.

Treatment with steroids and anti-TB drugs, without pericardiocentesis, usually results in satisfactory resolution of tuberculous pericardial effusion.

Outcome

A possible complication despite TB cure is the development of pericardial constriction. Medical management of heart failure due to pericardial constriction helps in some cases. A surgeon may weigh up the possible benefit to the patient of pericardiectomy, set against the operative risks.

Differential diagnosis

Apart from TB, the differential diagnosis of pericardial effusion includes the following:

TRANSUDATESuraemia, heart failure, liver failure

EXUDATES.....malignancy, bacterial pericardial empyema, inflammatory diseases, hypothyroidism.

TUBERCULOUS ASCITES

Ascites results from peritoneal TB. Routes of spread of TB to the peritoneum include the following:

- a) from tuberculous mesenteric lymph nodes;
- b) from intestinal TB (pulmonary TB patients may develop intestinal ulcers and fistulae as a result of swallowing infected sputum);
- c) blood-borne.

Clinical features

Patients present with constitutional features and ascites. There may be palpable abdominal masses (mesenteric lymph nodes). Adhesion of nodes to bowel may cause bowel obstruction. Fistulae may develop between bowel, bladder and abdominal wall.

Investigations

Do a chest X-ray to look for associated PTB. Always do a diagnostic ascetic tap. The aspirated fluid is usually straw-coloured, but occasionally turbid or blood-stained. The fluid is an exudate, usually with more than 300 white cells per mm³ and predominantly lymphocytes. Ultrasound, if available, may show features consistent with TB, including enlarged mesenteric or retroperitoneal lymph nodes.

PRACTICAL POINT

An ill, wasted patient with TB ascites may have a low serum albumin concentration. In this case, the usual threshold of 30 g/l albumin concentration for diagnosing an exudates is too high. Instead, calculate the difference between the albumin concentrations in serum and ascites. A serum-ascites albumin difference of less than 11 g/l means that the ascites is an exudates.

Diagnosis

The diagnosis is usually presumptive. Definitive diagnosis rests on a peritoneal biopsy, available in some hospitals. Blind percutaneous needle biopsy of the peritoneum has a low pick-up rate and a high complication rate. In experienced hands, laparoscopy under local anaesthetic has a high pick-up rate. Laparoscopy enables direct visualisation and biopsy of peritoneal TB lesions. Laparotomy will confirm the diagnosis in nearly every case but is too invasive for routine use.

Differential diagnosis

Apart from tuberculosis, the differential diagnosis of ascites includes the following:

TRANSUDATESheart failure, renal failure, nephrotic syndrome, liver failure, hypoproteinaemia;

EXUDATESmalignancy, other infections causing peritonitis.

2 2 5 Tuberculous meningitis

Routes of spread of TB to the meninges include the following:

- a) from rupture of a cerebral tuberculoma into the subarachnoid space;
- b) blood-borne.

Clinical features

The patient may present with constitutional features and a chronic meningitis. There is gradual onset and progression of headache and decreased consciousness. Examination often reveals neck stiffness and a positive Kernig's sign. Cranial nerve palsies result from exudates around the base of the brain. Tuberculomas and venous occlusion may cause focal neurological deficits and seizures. Obstructive hydrocephalus may develop. Spinal meningeal involvement causes paraplegia (spastic or flaccid).

Diagnosis

The diagnosis usually rests on clinical grounds and cerebrospinal fluid (C.S.F.) examination. In most cases of clinically suspected TB meningitis, lumbar puncture is safe.

PRACTICAL POINT

Lumbar puncture is hazardous if the patient has a focal neurological deficit (cerebral space-occupying lesion) or if fundoscopy shows papilloedema (raised intra-cranial pressure). In these circumstances, a C.A.T. brain scan is helpful, if available. Otherwise, it may be safer to start presumptive treatment with anti-TB drugs rather than risk lumbar puncture.

The C.S.F. opening pressure is high. The C.S.F. may look clear or cloudy. The white cell count is usually about 500 per mm³ with predominantly lymphocytes (or early in the course of infection, predominantly polymorphs). Usually the protein level is high and the glucose low. C.S.F. microscopy shows AFBs in a minority of cases. It is possible to increase the diagnostic pick-up rate by the following:

- a) examine the deposit on centrifugation of a 10 ml C.S.F. sample;
- b) examine the deposit for at least half an hour before reporting it as negative;
- c) examine several C.S.F. samples obtained over a few days.

PRACTICAL POINT

Always exclude cryptococcal meningitis by C.S.F. microscopy (India ink stain) and, if available, fungal culture.

Differential diagnosis

The table below shows the differential diagnosis of TB meningitis, with typical C.S.F. abnormal findings.

Differential diagnosis of tuberculous meningitis

DISEASE	CSF WHITE CELLS	PROTEIN	GLUCOSE	MICROSCOPY
<i>tuberculous..... meningitis</i>	<i>Elevated..... L > PMN</i>	<i>Increased...</i>	<i>Decreased.....</i>	<i>AFB (in some cases)</i>
<i>partially *..... treated bacterial meningitis</i>	<i>Elevated.....</i>	<i>Increased...</i>	<i>Decreased.....</i>	<i>Bacteria on Gram stain (rarely)</i>
<i>viral..... meningitis</i>	<i>Elevated..... L > PMN</i>	<i>Increased....</i>	<i>Normal (low in mumps or H.Simlplex)</i>	
<i>acute..... syphilis</i>	<i>Elevated..... L > PMN</i>	<i>Increased.....</i>	<i>Normal</i>	
<i>tumour..... (carchinoma/ lymphoma)</i>	<i>Elevated..... L > PMN</i>	<i>Increased.....</i>	<i>Decreased.....</i>	<i>Cytology shows malignant cells</i>
<i>leptospirosis.....</i>	<i>Elevated..... L > PMN</i>	<i>Increased.....</i>	<i>Decreased.....</i>	<i>Leptospire</i>
<i>amoebic..... meningitis</i>	<i>Elevated..... L > PMN</i>	<i>Increased.....</i>	<i>Decreased.....</i>	<i>Amoebae</i>
<i>cryptococcal..... meningitis</i>	<i>Elevated..... L > PMN</i>	<i>Increased....</i>	<i>Decreased.....</i>	<i>Positive India ink staining</i>

PMN = polymorphonuclear leucocytes; L= lymphocytes

*common differential diagnosis

Tuberculosis can spread from primary complex to any bone or joint. Tuberculosis can affect any bone but the weight bearing bones are more likely to be affected. The spine is more frequently affected, then the hip joint, then knee and the bones of the foot. Arms and hands are less affected. The slow onset of swelling either over the bone or joint should make one think of tuberculosis.

SPINE

Tuberculosis of the spine is the commonest manifestation of bone tuberculosis.

Clinical Features

The common presentation is back pain of variable duration, fever and weight loss. Examination may reveal local tenderness or muscular spasm and mild kyphosis. In advanced cases there may be gross kyphosis and gibbus formation. There may be cold abscess formation and paraparesis.

Diagnosis

Plain X-ray of the spine shows erosion of the anterior edges of the superior and inferior borders of adjacent vertebral bodies with narrowing of the disc space. The lower thoracic, lumbar and lumbosacral vertebrae are the sites most commonly involved. Paravertebral abscess formation is a common complication of spinal tuberculosis.

Invasive procedures either by needle biopsy or by open exploration may be undertaken to establish a diagnosis. It is important that specimens are collected not only for histology, but also for culture for both pyogenic organism and *M. Tuberculosis*.

CT scanning is valuable in demonstrating and assessing the extent of tuberculous skeletal involvement.

HIP

Clinical features

The common presentation is pain in the hip and limping – “irritable hip”. In children the child may refuse to walk. There is gradual loss of the range of motion and flexion deformity of the hip may occur. There may be unexplained wasting of the thigh muscles.

Diagnosis

Plain X-ray of both hip joints to compare.

Early changes: rarefaction of the bone and widening of the joint space.

Late changes: the joint may be destroyed with abscess formation or at times there may even be dislocation. Synovial biopsy is very useful. Bacterial examination of all aspirated material should be done.

KNEE

Clinical features

Usual presentation is insidious synovial swelling and pain of the knee with wasting of the quadriceps. Chronic suprapatellar synovitis and bursitis may be observed. Knee contracture is often found.

Diagnosis

Plain X-ray of the knee joint. Synovial biopsy

ANKLE

Clinical presentation

There is painful and gradual restriction of the range of motion of the joint. There may be synovial swelling and formation of draining sinuses.

Diagnosis

Plain X-ray of the ankle and synovial biopsy.

Other manifestations of bone tuberculosis are:

TB of the dactyl, presenting with drumstick swelling. Calcaneal TB, presenting with draining sinuses. Elbow TB, presenting with swelling and range of movement loss.

Diagnosis is based on X-ray and synovial biopsy.

2 2 7 Renal and urinary tract tuberculosis

Most tuberculosis infections of the urinary tract are due to secondary blood-borne spread from the primary pulmonary lesion and remain silent for many years. Tuberculous granulomata develop at the glomerular capillaries which subsequently rupture involving the tubules and the medulla. Medullary granulomata enlarge with caseation and rupture into the renal pelvis spreading to the ureter, urinary bladder and the genital tract. Subsequent healing of the infection by fibrosis leads to renal parenchymal atrophy, obstruction of the urinary tract and calcification. Diffuse parenchymal involvement may lead to small contracted kidneys and chronic renal failure.

Clinical features

Dysuria, frequency of micturation, macroscopic haematuria (painless), loin pain, fever, loss of weight, features of chronic renal impairment e.g. polyuria and salt wasting can be present in renal tuberculosis. Bladder tuberculosis can present with cystitis, nocturia, haematuria, pyuria and dysuria.

Diagnosis

In 90% of patients with renal tuberculosis the urine is abnormal. The main findings are pyuria and/or haematuria. The finding of pus in acid urine with no organism isolated from a routine urine should prompt an evaluation for tuberculosis. Urine culture for *M. tuberculosis* is a definitive test. Three to five early morning specimens should be examined because of intermittent excretion of tuberculosis bacilli, and positive results are obtained in 80%-90% of cases. Ziehl Neelsen stain for AFB in concentrated urine sediment may reveal the organism, however the yield is low when compared with positive cultures. Intravenous urography is abnormal in 90% of cases. In early renal tuberculosis, calyceal irregularities may be demonstrated. With

progression, the pelvis size is reduced and may be obliterated. Up to 24% of patients with tuberculosis kidneys may be associated with renal calcification. CT scan findings show calyectasis, low parenchymal density, parenchymal retraction and calcification. Cystoscopy may reveal cystitis, granulomata and small contracted bladder.

Always look for pulmonary tuberculosis by doing 3 sputum examinations and a X-ray and also monitor renal function test. Corticosteroids should be given in conjunction with anti TB treatment for interstitial nephritis. Surgery is indicated in non-functioning kidney with extensive disease and severe secondary infection. Reconstructive surgery is done for obstruction of the urinary tract and small contracted bladder with severe symptoms.

2 2 8 Gastrointestinal Tuberculosis

Tuberculosis of the oesophagus, stomach, duodenum, jejunum, ileum, ileo-caecal valve, caecum, ascending, transverse and descending colon, sigmoid colon and rectum accounts for 50% of all gastrointestinal tuberculosis. Tuberculosis of the peritoneum accounts for about 30-35% of cases. Tuberculosis of the mesenteric or retro-peritoneal lymph nodes accounts to 15-20% and tuberculosis of the liver, pancreas and spleen to 1% or less. (Dr. M. Ghimire's experience in Nepal). The commonest site is the distal ileum and the caecum. Diffuse disease in the small or the large bowel is not uncommon.

Pathogenesis: Primary complex (silent bacillema) spread to the submucosa of the bowel and the regional lymph nodes (immune response) with healing but few bacilli may remain alive in a dormant state (subsequent reactivation). Primary focus in the bowel infected by *M. bovis* or the secondary spread via swallowed sputum from active disease in the lung may occur but are probably much rarer than haematological spread and reactivation.

Clinical Features

TB can occur in any age (more common between 2nd and 4th decades), both sexes (slightly higher incidence among females)
Presentation - non-specific, varied and at times quite deceptive.

Weight loss, abdominal pain, diarrhoea, malabsorption and /or intermittent constipation associated with worsening of the pain appear to be the most common presenting features in Nepal. Fever is absent in majority of the cases or may be slight. Abdominal mass is now a relatively rare finding among urban population but is still seen in about 20-25% of the patients from the rural areas with less frequent visits to qualified health facilities. Presentation with dysenteric syndrome (loose stools mixed with blood and mucus and associated with lower abdominal cramps) is becoming more common in recent years. Non-healing ano-rectal fissures, painful nodular peri-anal lesion or fistulas occasionally turn out to be tuberculous in aetiology, Rarely, tuberculosis may underlie peptic ulcer like symptom, gastric or duodenal outlet obstruction, dysphagia or odynophagia.

Diagnosis in relation to the presenting symptoms

In order not to miss tuberculosis in patients presenting with clinical features outlined above, a high index of suspicion is mandatory among medical care providers in Nepal. A strongly positive Mantoux test, in the range of 15 to 30 mm induration, may make the diagnosis more probable but a negative Mantoux does not rule out the diagnosis. A healed focus in the chest X-ray from a patient with significant bowel symptoms may indicate the possibility of active disease in the bowel. In a patient with proven active TB elsewhere, symptoms suggestive of bowel disease can be monitored under chemotherapy without further investigation. In others a sequential and logical approach to providing the diagnosis should be made. Ever so often, however, decision regarding treatment may have to be based on inferential evidence. Routine haematological and biochemical screening may reveal mild to moderate normochromic anaemia, raised sedimentation rate and hypoalbuminaemia but do not contribute much to the diagnostic process. The main presenting symptoms in individual cases would dictate the appropriate diagnostic procedure.

Dysphagia: Chest X-ray (always with PA and lateral views) for mediastinal glands, CT scan for demonstrating matting and necrosis in the enlarged glands, upper g.i endoscopy to visualise stricture, fistulae or ulceration of the involved area. Endoscopic biopsy may not always be

helpful in identifying the suggestive histology or in demonstrating the bacillus.

Epigastric pain, vomiting and weight loss: Upper g.i endoscopy and biopsy (a) to look for ulcerative or infiltrative lesions in the stomach and for histology and identification of the bacillus (direct smear, histology and/or culture): (b) to look for gastric or duodenal obstruction by chronic ulceration and stricture formation or due to extrinsic compression by a mass of enlarged nodes.

Malabsorption: Malabsorption occurs from extensive mucosal involvement associated with villous atrophy, bacterial overgrowth in stagnant loops proximal to the partially obstructed segment of the bowel, fistula formation or from lymphatic obstruction. Abdominal echogram can sometimes demonstrate enlarged nodes or thickened bowel wall. CT scan can provide the same information in greater detail. Barium studies can demonstrate non-specific malabsorption pattern or a localised stricture or both. Endoscopic duodenal biopsies will often demonstrate partial villous atrophy or inflammatory infiltrates. Clinching histological evidence of TB or identifying bacilli in this group of patients can be very difficult indeed. Colonoscopic, ileoscopy and multiple biopsies from the ileum may provide the diagnostic material in certain cases. It is possible to demonstrate AFB in the aspirate from the ileum in occasional patients.

Right Iliac Fossa pain, mass or subacute small bowel obstructive symptoms: plain film of the abdomen in erect position may give a helpful clue by showing a localized air-fluid level. Echogram of the abdomen may reveal a complex bowel mass with or without localised fluid collection in the area. It may also demonstrate a thickening of the bowel wall to suggest chronic inflammatory bowel disease. Barium study of the distal small bowel may reveal contracted rigid and deformed caecum that is pulled high. There is usually loss of the normal ileo-caecal angle. The terminal ileum may appear stiff and straight and the ileo-caecal valve gaping and/or incompetent. Colonoscopy usually reveals friable and inflamed mucosa that appear nodular and ulcerate most commonly in the caecum and terminal ileum and less commonly

in the ascending and transverse colon. Biopsies from these lesions can demonstrate the tubercular histology and/or the bacilli.

Dysentery syndrome: A diligent study of the direct stool smear for AFB may prove fruitful. Colonoscopy may reveal patchy or diffuse ulceration. Intervening mucosa may also look inflamed or friable. Pseudo-polyps and/or strictures are not infrequent. In fact the disease can easily be confused with non-specific bacterial or amoebic colitis or with ulcerative colitis or Crohn's disease. Multiple biopsies usually yields the diagnosis by providing suggestive histological appearance or by showing the bacilli.

Ano-rectal lesion: Procto-sigmoidoscopy may also reveal associated diffuse proctitis, ulceration or nodular hyperplastic lesions in the rectum. Definitive diagnosis can usually be established by taking biopsy from such lesions.

Ascites: Diagnostic tap usually reveals straw coloured fluid. Occasionally it may be blood stained or chylous. Protein and LDH concentrations are high and cellular infiltration is usually lymphocytic. AFBs can be rarely demonstrated in the direct smear of the centrifuged deposit. Peritonscopic biopsy from suspect lesion is said to yield the diagnosis in more than 90% of cases. In occasional cases open peritoneal biopsy has to be performed in order to prove the diagnosis.

Intra-abdominal lymph node enlargement: In case where intra abdominal lymph node enlargement is suspected, confirmation of this finding with ultrasound or CT scanning is necessary. Diagnosis of tuberculosis may be established by performing thin needle aspiration under ultrasound or CT guide. Failing this, laparotomy and biopsy of the lymph node, or the peritoneum may be necessary. In one patient with POU of 6 weeks duration and several hypo-echoic nodules in the spleen, laparotomy was done with a view to confirm the diagnosis of lymphoma. Diagnosis of splenic TB was established. Recovery with anti-TB treatment was complete.

Almost always secondary to a primary infection elsewhere in the body, genital tuberculosis, spreading usually by bloodstream or the lymphatic channel affects the female genital organs; mostly the fallopian tubes. The uterus, cervix, vulva, vagina and the ovaries do not get spared either.

Clinical features

The infection, usually seen in the young reproductive period with or without a past or family history of tuberculosis may remain silent or manifest in forms such as:

- Infertility due to tubal pathology, disturbed ovarian or endometrial function.
- Menstrual abnormalities like menorrhagia, amenorrhoea, oligomenorrhoea.
- Chronic pelvic pain
- Tubo ovarian mass unresponsive to standard antimicrobial therapy.
- Constitutional symptoms: malaise, weight loss, anorexia, anaemia.
- Non-healing wounds, painful tender vulval ulcers.
- Mucopurulent vaginal discharge, post-coital bleeding.

Diagnosis

Study the patients profile, examination findings and investigations. Pelvic findings may be totally negative and misleading or may show up as thickened tubes, nodules felt through the fornices on bi-manual examination; the findings confirmed by a simple per rectal examination. Investigations aim to identify the primary lesion and confirm the genital one. Diagnostic dilatation and curettage is done in the pre-menstrual period when the tubercles rise to the surface of the endometrium for histopathology, culture, Ziehl Neelsen staining. Hystero-salpingogram shows 'tobacco pouch tubes', rigid tubes with nodulations or calcified shadows. Ultrasound of the pelvis reveals only a mass. Tissue biopsy of cervical, vaginal or vulval lesions is essential. Diagnostic laparoscopy for infertility workup or chronic pelvic pain may help diagnose genital tuberculosis.

The most common genital sites of tuberculosis infection are the epididymis and the prostate; the testicle is infected less commonly. The usual mode of infection are by antegrade infection from the kidneys, or direct extension from neighbouring foci in the genital tract, and haematogenous seeding.

Clinical features

Local symptoms are usually insidious and progressive, and can be confused with other bacterial infections, fungal disease, tumours and cysts as well as with a number of less common illness. Epididymitis commonly manifests as scrotal swelling, with or without pain, developing over several years. Prostatic involvement manifests as urinary frequency, urgency, haematuria or haemospermia.

Diagnosis

Often evidence of renal/urinary tract tuberculosis. Histopathologic findings are cultures of appropriate biopsy material are needed to produce an accurate diagnosis.

SUGGESTIONS FOR FURTHER READING

Toman K. Tuberculosis. Case finding and chemotherapy. Geneva: WHO, 1979.

Crofton J, Horne N and Miller F. Clinical Tuberculosis. The MacMillan Press Limited. 1992.

Davies PDO. Clinical Tuberculosis. Chapman and Hall Medical. 1994.

CHAPTER 3 DIAGNOSIS OF TUBERCULOSIS IN CHILDREN

3 1 HOW DOES TB IN CHILDREN DIFFER FROM TB IN ADULTS?

Transmission of TB to children

The source of transmission of TB to a child is usually an adult (usually a family member) with sputum smear-positive PTB.

Public health importance

Cases of TB in children usually represent between 5-15% of all TB cases. The frequency of childhood TB in a given population depends on the following: the number of infectious cases, the intensity of transmission, and the age structure of the population. Children rarely have sputum smear-positive TB. So they are rarely infectious. TB in children is therefore due to failure of TB control in adults. Failure of TB control in adults means failure to cure the infectious cases (patients with sputum smear-positive PTB.)

PRACTICAL POINT

A good TB control programme is the best way to prevent TB in children.

The highest priority in TB control is to cure the infectious cases. Children are rarely infectious. However, it is still important to cure them! Good treatment of TB in childhood will result in the following: a) decreased morbidity and mortality; b) improved NTP credibility and reputation.

Risk of infection

Risk of infection depends on 2 factors: a) extent of exposure to infectious droplet nuclei, and b) susceptibility to infection. Consider an infant whose mother has sputum smear-positive PTB. The infant has a high risk of acquiring infection: mother and infant are in very close contact; immune defences are poor. An infant with HIV infection has an even greater susceptibility to infection with tubercle bacilli.



Risk of progression of infection to disease.

The vast majority of HIV-negative children infected with *M. tuberculosis* do not develop TB disease. In these healthy, asymptomatic, but TB-infected children, the only evidence of infection may be a positive tuberculin skin test. However, an infected child can develop TB disease at any time. The chance of developing disease is greatest shortly after infection and then steadily decreases as time goes by. Various physical or emotional stresses may trigger progression of infection to disease. The most important trigger is weakening of immune resistance, especially by HIV infection. Other important triggers include the following: other infections (especially measles and whooping cough) and malnutrition.

Pathogenesis

The usual route of infection and early sequence of events in primary pulmonary infection are similar in adults and children. TB disease in children is usually primary TB. A child may have asymptomatic *M. tuberculosis* infection: the tubercle bacilli can lie dormant for many years. If the tubercle bacilli reactivate some years later, causing post-primary TB, the child has usually grown into an adult by then. The age when a child is infected determines the pattern of primary disease. Up to puberty, blood-borne spread is common. This results in disseminated (miliary and extrapulmonary) disease. After puberty, pulmonary spread is more common.

PRACTICAL POINT

Malnourished children may develop severe PTB at any age.

3 2 APPROACH TO DIAGNOSIS

If you find the diagnosis of TB in children easy, you are probably over-diagnosing TB. If you find the diagnosis of TB in children difficult, you are not alone. It is easy to over-diagnose TB in children. It is also easy to miss TB in children. Carefully assess all the evidence before making the diagnosis.

Adults with PTB usually present with cough and sputum. Although sputum culture is the definitive test, in practice the readily available usual “gold standard” test for adults with PTB is sputum smear microscopy. However, there is no such “gold standard” test in children. TB in children is a general disease which may appear in any part of body. Also, under the age of 10 years, children with PTB rarely cough up sputum. They usually swallow their sputum. Gastric suction and laryngeal swabs are generally not useful unless facilities are available for *M. tuberculosis* culture. The diagnosis of TB in children is therefore nearly always presumptive. This means that bacteriological confirmation is usually not possible. This situation in children is similar to that in adults with sputum smear-negative PTB or extrapulmonary TB.

The clinical features are constitutional and local (depending on the part of the body affected). The local clinical features related to the site of disease are similar in children and adults (see Chapter 2 for details). The diagnosis rests on consistent clinical features and investigation findings. If available, a tuberculin skin test may be helpful. In most cases of suspected PTB, the child has usually received treatment with a broad-spectrum antibiotic, with no clinical response. In some hospitals, helpful special diagnostic investigations may be available. These may include specialised X-rays, biopsy and histology, and TB culture.

Always look for the following 2 important clues to TB in children:

- 1) it is usually possible to identify the adult source of infection;
- 2) failure to thrive or weight loss (growth falterings).

In the absence of these 2 clues, TB is less likely.

PRACTICAL POINT

Ask the mother of a child with suspected TB for the child’s “road to health” card (growth card). Look at the card for growth faltering or weight loss.

3 3 SCORE SYSTEM FOR THE DIAGNOSIS OF TB IN CHILDREN

A source system is one way to trying to improve the diagnosis of childhood TB. The basis of a score system is the careful and systematic collection of diagnostic information. A score system helps guide your clinical judgement. A score above a certain threshold indicates a high likelihood of TB. The table shows a score chart (adapted from Crofton, Horne and Miller) for helping to diagnose childhood TB. A score of 7 or more indicates a high likelihood of TB.

Score chart for the diagnosis of TB in children						
SCORE IF FEATURE PRESENT						
Feature	0	1	2	3	4	Score
General						
duration of illness (weeks)	<2	2-4		>4		
nutrition (% weight for age)	>80	60 - 80		<60		
family history of TB	none	reported by family		proved sputum positive		
tuberculin test				positive		
malnutrition				not improving after 4 weeks		
unexplained fever and night sweats			no response to malaria treatment			
local						
				lymph nodes		
				joint or bone swelling		
				abdominal mass or ascites		
				C.N.S. signs, and usually abnormal C.S.F. findings.		
					angle deformity of spine	
TOTAL SCORE						

3 4 TUBERCULAR MENINGITIS

Tubercular meningitis is the most serious form of childhood tuberculosis. The highest incidence is recorded in the preschoolers. It is always the result to hematogenous spread from the primary lesion elsewhere.

Clinical features

Prodromal stage: Symptoms are vague and include drowsiness, mild fever, convulsion, vomiting and headache.

Transitional stage: During this stage, the manifestations of raised intracranial tension and meningeal irritation appear.

Terminal stage: This is the stage of paralysis and coma.

Diagnosis

Lumbar puncture: CSF pressure is raised. Clear or occasionally turbid, when kept in a test tube for 12 hours, a cobweb is formed. Increase in cell count (10-500/cmm with predominance of lymphocyte). Increase in protein, decrease in sugar and chlorides. Absolute confirmation is by demonstrating the bacilli in the CSF smear.

Differential Diagnosis

Viral meningitis, brain tumour, partially treated bacterial meningitis, status epilepticus, tuberculoma, amoebic meningitis.

3 5 TUBERCULOMA

About one half of the intracranial space occupying lesions are accounted in tropical infants and children. It is always secondary to a primary tuberculosis lesion elsewhere in the body. Since the host resistance is good enough, the bacilli which spread to the brain fail to cause meningitis. But they keep forming granulomatous tissue which is infratentorial in majority of the cases.

Clinical features

The onset is usually gradual with vomiting, headache, cerebellar ataxia and diminished vision. Most of the patients have fever as well.

Diagnosis

Good history, X-ray may demonstrate calcification. CT scan may reveal a hypodense mass with a ring enhancement and associated with oedema.

Differential diagnosis

Tuberculoma needs to be differentiated from brain abscess, subdural haematoma, brain tumour and cysticercosis.

3 6 TB NEPHRITIS

The presentation is similar to acute nephritis. When there is no response to penicillin and diuretics consider the possibility of TB. Diagnosis require bacteriological confirmation which can be obtained in most patients by culturing urine specimens.

3 7 TUBERCULIN SKIN TEST

Tuberculin is a purified protein derived from tubercle bacilli. Thus, another name for tuberculin is PPD (Purified Protein Derivative). Following infection with *M. tuberculosis*, a person develops hypersensitivity to tuberculin. Tuberculin injected into skin of an infected person produces a delayed local reaction after 24-48 hours. We quantify this reaction by measuring the diameter of skin induration (thickening) at the site of the reaction. Various conditions may suppress this reaction. The reaction indicates hypersensitivity. In other words, the reaction only shows that the person has at some time had infection with *M. tuberculosis*.

PRACTICAL POINT

A tuberculin test does not measure immunity. By itself it does not indicate the presence or extent of tuberculosis disease; it only indicates infection.

The technical details about tuberculins and how to administer and read a tuberculin test are beyond the scope of this book. "Clinical tuberculosis" (Crofton, Horne and Miller) gives a good account.

Value of a negative tuberculin test

A tuberculin test is negative when the diameter of skin induration is less than 10 mm. This is regardless of whether or not the person has had BCG. A negative tuberculin skin test does not exclude TB. In other words, a negative test is of no help in deciding that someone does not have TB. The table shows the conditions which may suppress a tuberculin skin test in a person with active TB.

CONDITIONS WHICH MAY SUPPRESS THE TUBERCULIN SKIN TEST

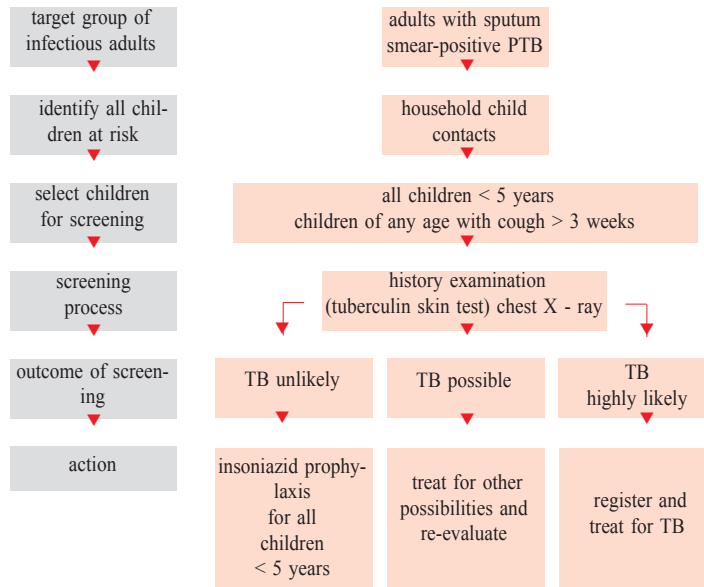
<i>HIV infection</i>
<i>malnutrition</i>
<i>severe bacterial infections, including TB itself</i>
<i>viral infections, e.g. measles, chickenpox, glandular fever</i>
<i>cancer</i>
<i>immunosuppressive drugs, e.g. steroids</i>

3 8 MANAGEMENT OF CHILD CONTACTS OF INFECTIOUS ADULTS

Children with TB may present to health units when they are ill. However, most National TB Control Programmes also recommend active contact tracing of children who are household contacts of infectious adults. In order to be effective, this screening must be systematic. If you don't have a systematic, organised process for child contact screening where you work, could you start one?

The scheme in next page shows how to manage child contacts of infectious adults (with sputum smear-positive PTB).

How to identify and manage the child contacts of infectious adults



In new born children, if a baby is born to a women with active tuberculosis and if the baby is sick with fever and failure to thrive, give a full course of treatment for tuberculosis. If the baby is well give isoniazid chemoprophylaxis for 3 months and then do a tuberculin testing. If the tuberculin test is negative, stop the isoniazid, and give BCG. If the tuberculin test is positive, continue the isoniazid up to 6 months.

Consider a child under 5 years of age living with a sputum smear-positive PTB patient. This child household contact is at high risk of TB infection and developing TB disease, especially if HIV-positive. Tuberculin skin testing is often not available. Also, tuberculin skin testing is not a reliable way of distinguishing TB-infected from non-

TB-infected children. The IUATLD therefore recommends isoniazid preventive treatment for all child household contacts (under 5 years of age) of sputum smear-positive PTB patients. Compliance with isoniazid preventive therapy should be strictly monitored by the treating physician.

SUGGESTIONS FOR FURTHER READING

Miller FHW. Tuberculosis in children. New Delhi: Churchill-Livingstone, 1986.

Chaulet P and collaborators. Children in the tropics. Childhood tuberculosis, still with us. International Children's Centre, Paris, 1992.

Crofton J, Horne N and Miller F. Clinical Tuberculosis. The Macmillan press limited. 1992.

International Union Against Tuberculosis and Lung Disease. Tuberculosis guide for low income countries. pmi Verlagsgruppe. 3rd edition. Frankfurt, 1994.

Topley JM, Maher D, Mbewe LN. Transmission of Tuberculosis to contacts of sputum positive adults in Malawi. Arch Dis Child 1996; 74: 140-143.

CHAPTER 4 STANDARDISED TB CASE DEFINITIONS AND TREATMENT CATEGORIES

4 1 STANDARDISED CASE DEFINITIONS

4 1 1 Introduction

The diagnosis of TB means that a patient has TB. But what type of TB? It is important to answer this question before starting treatment. A case definition tells us the type of TB. We define TB cases in a standardised way. This means that when we talk about a certain type of TB, we are all talking about the same thing.

PRACTICAL POINT

On making the diagnosis of TB, you must also decide on the TB case definition.

4 1 2 Questions and answers about case definitions

Why make case definitions? There are 2 purposes:

- a) to determine treatment;
- b) for recording and reporting (see Chapter 7).

Why do case definitions determine treatment? There are 3 reasons:

- a) to identify priority cases;
- b) to make the most cost-effective use of resources (by targeting resources on priority cases);
- c) to minimize side-effects for patients (by using the most intensive regimens only for certain cases).

What determines a case definition? There are 4 determinants:

- a) site of TB
- b) result of sputum smear
- c) previous TB treatment
- d) severity of TB

PRACTICAL POINT

Always ask a “new” TB patient if he or she has ever had TB treatment before.

The table below shows the determinants of case definition and their importance.

DETERMINANT OF CASE DEFINITION	IMPORTANCE
<i>site of TB</i>	<i>recording and reporting (in a good NTP, at least 50% of total cases will be pulmonary)</i>
<i>result of sputum smear for AFBs</i>	<i>priority is to identify sputum smear-positive cases (since these are infectious cases) recording and reporting (monitoring of bacteriological cure is readily available only in this group)</i>
<i>previous TB treatment</i>	<i>the previously treated patient who is still sputum smear-positive has a high risk of drug-resistant TB and so needs a different and more powerful regimen</i>
<i>severity of TB</i>	<i>most authorities recommend a more intensive regimen for smear-negative PTB patients with extensive disease rather than limited disease</i>

4 1 3 Case definitions by site and result of sputum smear

Pulmonary TB

Smear positive case:

Patient with at least two sputum smears positive for acid-fast bacilli by microscopy

OR

a patient with at least one sputum specimen positive for acid fast bacilli, and X-ray abnormalities consistent with TB

OR

a patient with at least one sputum specimen positive for acid fast bacilli, which is culture positive for *M. tuberculosis*

Smear negative case:

A patient with three sputum smears negative for AFB on microscopy, but X-ray evidence consistent with active tuberculosis, which does not clear with non-tuberculous antibiotics

OR

a patient whose sputum smears are all negative for AFB on microscopy, but culture positive for *M. tuberculosis*

Extrapulmonary TB

A patient with at least one positive culture for *M. tuberculosis* from an extra-pulmonary site.

OR

A patient with X-ray or histological or clinical evidence consistent with active tuberculosis at an extra-pulmonary site (that is, at a site other than the lungs).

Pulmonary tuberculosis refers to disease involving the lung parenchyma. Therefore TB of the lymph nodes in the chest and TB of the pleura are classified as extra-pulmonary TB.

There are many types of extra-pulmonary TB. These include pleurisy, gland, intestinal, miliary, meningitis, bone, urogenital, skin and eye TB. They are not infectious.

Diagnosis of the extra-pulmonary TB is difficult. It must be confirmed by an experienced medical doctor.

If a patient has TB affecting several different extra-pulmonary sites, classify him according to the most severe form of the disease. For example, if a patient has gland TB and abdominal TB, classify him as abdominal TB.

PRACTICAL POINT

The following are forms of extrapulmonary TB: pleural effusion (pleura are outside the lungs); hilar lymphadenopathy (hilar lymph nodes are outside the lungs); miliary (TB is widespread throughout the body and not limited to the lungs).

4 1 4 Case definitions by previous treatment

New

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

Relapse

A patient previously treated for tuberculosis who has been declared cured or treatment completed, and is diagnosed with bacteriologically positive (at least one smear or culture) tuberculosis.

Treatment failure

A patient who remains, or becomes, sputum smear-positive 5 months or more after starting treatment.

Treatment after default

A patient who returns to treatment with positive bacteriology, following interruption of treatment for two months or more.

Transfer in

A patient who has been transferred from another tuberculosis register to continue treatment in a different register area.

Other

All cases who do not fit the above definitions. This group 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 TB drugs.

4 2 STANDARDISED TREATMENT CATEGORIES

Based on case definition, a TB patient falls into 1 of 2 categories for treatment. The table below shows the patients belonging to each category.

TB TREATMENT CATEGORY	PATIENT
<i>Category 1</i>	<i>new sputum smear-positive PTB, sputum negative PTB and extra pulmonary TB</i>
<i>Category 2</i>	<i>relapse treatment failure treatment after default (interrupted treatment)</i>

The table below shows the severe and less severe forms of extrapulmonary TB.

SEVERE EXTRAPULMONARY TB	LESS SEVERE EXTRAPULMONARY TB
<ul style="list-style-type: none"> • meningitis • miliary • pericarditis • peritonitis • bilateral or extensive pleural effusion • spinal • intestinal • genitor-urinary 	<ul style="list-style-type: none"> • lymph node • pleural effusion (unilateral) • bone (excluding spine) • peripheral joint • adrenal gland

Children

Children and adolescents often fall into Category I. PTB in children is almost always “smear-negative” (actually smear not done, since children rarely cough up sputum). Young people infected during adolescence may develop primary TB. This usually presents as pleural effusion or small parenchymal lesions in the lungs. In one series of adolescents with pleural effusion, without treatment about 25% went on to develop PTB.

SUGGESTED FURTHER READING

WHO. Treatment of tuberculosis. Guidelines for national programmes. Geneva, 1993.

Aims of anti-TB drug treatment

- To cure the patient of TB.
- To prevent death from active TB or its late effects.
- To prevent TB relapse.
- To decrease TB transmission to others.

PRACTICAL POINT

Properly applied anti-TB drug treatment will achieve these aims and prevent the emergence of drug resistant *M. tuberculosis*.

Effective anti-TB drug treatment = properly applied Short-Course Chemotherapy

We have known for over 100 years that *M. tuberculosis* causes TB. We have had effective anti-TB drugs for nearly 50 years. Yet the world's TB problem is now bigger than ever. Why? The problem is not the lack of an effective treatment. Properly applied short-course chemotherapy (SCC) fulfills the above aims of anti-TB drug treatment. The problem is an organisational problem: how to apply SCC properly? The answer is a properly managed TB control programme. Chapter 7 describes the organisational framework of an effective TB control programme.

Standardised TB treatment regimens

There are many different possible anti-TB treatment regimens. The World Health Organization (WHO) and the International Union Against Tuberculosis and Lung Disease (IUATLD) recommend standardised TB treatment regimens. The national TB control programme (NTP) in your country recommends which regimens to use. When properly applied, these standardised regimens fulfill the above aims of anti-TB drug treatment. The regimens are affordable.

The World Bank recognizes short-course chemotherapy (SCC) as one of the most cost-effective of all health interventions.

The essential anti-TB drugs

The table shows the essential anti-TB drugs and their mode of action, potency, and recommended dose.

ESSENTIAL ANTI-TB DRUG (ABBREVIATION)	MODE OF ACTION	POTENCY	RECOMMENDED DOSE(MG/KG)		
			DAILY	INTERMITTENT	
				3x/WK	2x/WK
isoniazid (H)	bactericidal	high	5	10	15
rifampicin (R)	bactericidal	high	10	10	10
pyrazinamide (Z)	bactericidal	low	25	35	50
ethambutol (E)	bactericidal	low	15	(30)	(45)
streptomycin (E)	bactericidal	low	15	15	15

The available formulations and combinations of the marketed drugs vary from brand to brand. Check them before you prescribe.

Below mentioned medicines are available in fixed dose combination forms such as:

- 1: Isoniazide [75 mg] + Rifampicin [150 mg] + Pyrazinamide [400mg] + Ethambutol [275mg] (HRZE)
2. Isoniazide (150mg) + Rifampicin [150mg] (HR)
3. Isoniazide [75 mg] + Rifampicin [150 mg] + Ethambutol [275mg] (HRE)

5 2 MODES OF ACTION OF ANTI-TB DRUGS

Consider a population of TB bacilli in a TB patient. This population of bacilli consists of the following groups:

- a) metabolically active, continuously growing bacilli inside cavities;
- b) bacilli inside cells, e.g. macrophages;
- c) semi-dormant bacilli (persisters) which undergo occasional spurts of metabolism.
- d) dormant bacilli which fade away and die on their own.

Different anti-TB drugs act against different groups of bacilli.

PRACTICAL POINT

Anti-TB drug treatment is so long because it is difficult to kill the semi-dormant TB bacilli.

Bactericidal drugs

Isoniazid kills 90% of the total population of bacilli during the first few days of treatment. It is most effective against the metabolically active, continuously growing bacilli.

RIFAMPICIN can kill the semi-dormant bacilli which isoniazid cannot.

PYRAZINAMIDE kills bacilli in an acid environment inside cells, e.g. macrophages.

Sterilising action

This means killing all the bacilli. The persisters are hardest to kill. The aim of killing all the bacilli is to prevent relapse. Rifampicin is the most effective sterilising drug. Its effectiveness makes short-course chemotherapy possible. Pyrazinamide is also a good sterilising drug, since it kills the bacilli protected inside cells.

Preventing drug resistance

Consider a population of TB bacilli never previously exposed to anti-TB drugs. There will be a few naturally-occurring drug-resistant mutant bacilli. Faced with anti-TB drugs, these drug-resistant mutant bacilli will grow and replace the drug-sensitive bacilli under the following circumstances:

- a) inadequate anti-TB drug combinations;
- b) anti-TB drug treatment not properly applied.

Isoniazid and rifampicin are most effective in preventing resistance to other drugs. Streptomycin and ethambutol are slightly less effective.

5 3 TB TREATMENT REGIMENS

Treatment regimens have an initial (intensive) phase and a continuation phase.

5 3 1 New cases

Initial phase (2 months)

During the initial phase, there is rapid killing of TB bacilli. Infectious patients become non-infectious within about 2 weeks. Symptoms improve. The vast majority of patients with sputum smear-positive TB become sputum smear-negative within 2 months. Directly observed therapy (DOT) is essential in the initial phase to ensure that the patient takes every single dose. This protects rifampicin against the development of drug resistance. The risk of drug resistance is higher during the early stages of anti-TB drug treatment when there are more TB bacilli.

Continuation phase (4-5 months)

Fewer drugs are necessary, but for a longer time, in the continuation phase. The drugs eliminate the remaining TB bacilli. Killing the persisters prevents relapse after completion of treatment. Directly observed therapy is the ideal when the patient receives rifampicin in the continuation phase. If local conditions do not allow directly observed therapy, the next best is a close supervision as possible, for example weekly supervision. The risk of drug resistance is less during the continuation phase when there are fewer TB bacilli.

The patient usually receives monthly drug supplies for self-administered treatment during a continuation phase which does not include rifampicin.

5 3 2 Retreatment cases

The initial phase lasts 3 months, with directly observed therapy. The continuation phase lasts 5 months, with close supervision.

5 3 3 Standard code for TB treatment regimens

There is a standard code for TB treatment regimens. Each anti-TB drug has an abbreviation (shown above). A regimen consists of 2 phases. The number before a phase is the duration of that phase in

months. A number in subscript (e.g. 3) after a letter is the number of doses of that drug per week. If there is no number in subscript after a letter, then treatment with that drug is daily. An alternative drug (or drugs) appears as a letter (or letters) in brackets.

Examples

2 SHRZ/6 HE. This is a common regimen.

The **initial phase** is **2SHRZ**. The duration of the phase is 2 months. Drug treatment is daily (no subscript number, e.g. 3 after the letters.), with streptomycin (S), isoniazid (H), rifampicin (R) and pyrazinamide (Z).

The **continuation phase** is **6 HE**. The duration of the phase is 6 months. Drug treatment is daily, with isoniazid (H) and ethambutol (E).

2 SHRZ/4 H₃R₃. In some countries, resources are available to provide rifampicin in the continuation phase as well as in the initial phase.

The intensive phase (**2 SHRZ**) is the same as before.

The continuation phase is **4 H₃R₃**. The duration is 4 months, with isoniazid and rifampicin three times per week (subscript number 3 after the letters).

NTP Nepal used fixed dose combination regimen such as in all new TB patients used in intensive phase 2 month HRZE and 4 month HR in continuation phase.

For retreatment cases (relapse, failure, RAD positive)

2-S-HRZE + 1-HRZE + 5- HRE

5 3 4 Recommended treatment regimens

There are several different possible regimens. The regimen recommended depends on the patient treatment category (see Chapter 4). The table shows possible alternative regimens for each treatment category. Follow the regimens recommended by the NTP in your country. Look in the NTP Manual.

ALTERNATIVE TREATMENT REGIMENS FOR EACH PATIENT TREATMENT CATEGORY

TB TREATMENT CATEGORY	TB PATIENTS	ALTERNATIVE TB TREATMENT REGIMENS	
		INITIAL PHASE	CONTINUATION PHASE
1	New smear-positive PTB, Smear-negative PTB and extrapulmonary TB	2 HRZE	4 HR
2	Sputum smear-positive: relapse, treatment failure, and return after default	2 SHRZE / 1HRZE 2 SHRZE / 1 HRZE 2 S ₃ H ₃ R ₃ Z ₃ E ₃ /1H ₃ R ₃ Z ₃ E ₃	5 HRE

However, NTP Nepal is providing fixed dose combination drug treatment regimen as recommended by WHO and international experts. (See Chapter-4, Regimen Table)

*Note: The National Regimen of Fixed Dose Combination (Combined)

SHORT COURSE REGIMEN FOR CHILDREN (0-8 YEARS OLD)

PATIENT BODY WEIGHT (KG)	INTENSIVE PHASE (2 MONTHS)	CONTINUATION PHASE (4 MONTHS)	* SM (1.0mg)
	HRZE (H=30mg, R=60mg, Z=150mg)	HR (H=30mg, R=60mg)	2 MONTH (IP) ONLY
3 - 7 Kg	1	1	As per Body weight
8 - 9 Kg	1.5	1.5	0.120 gm
10 - 14 Kg	2	2	0.180 gm
15 - 19 Kg	3	3	0.250 gm
20 - 24 Kg	4	4	0.350 gm
25 - 29 Kg	5	5	0.400 gm

Note :

Drugs composition: H(30 mg) + R(60 mg) + z(150 mg): HRZ

* Inj. Streptomycin is only for child with TB Meningitis, TB Miliary and Spinal TB with Neurological complication

Nepal NTP use daily Regimen, if recommended for 7 month continuation phase patient with TB Meningitis, Miliary TB and Spinal TB with Neurological complication.

NTP also recommends the use use of fixed dose combination drugs to prevent monotherapy and improve compliance. Direct Observation of treatment which includes Refampicin is strongly recommended.

5 3 5 Use of streptomycin in areas of high HIV prevalence

Streptomycin

- In high TB/HIV prevalence population, overcrowding is common in TB wards. The high staff workload may result in inadequate sterilisation of needles and syringes used for streptomycin injectri- ons. There is a risk of transmission of HIV and other blood-born pathogens between patients.
- Streptomycin injections are very painful in wasted HIV-infected TB patients
- Many NTPs now recommend the use of ethambutol in place of streptomycin.

5 4 TB TREATMENT REGIMENS: QUESTIONSAND ANSWERS

Why use 4 drugs in the initial phase?

- There is a high degree of initial resistance in some populations.

- Use of a 3-drug regimen runs the risk of selecting out drug-resistant mutants. This may happen especially in patients with high bacillary loads, e.g. cavitary pulmonary TB.
- A 4-drug regimen decreases the risks of drug resistance, treatment failure, and relapse.

Why use pyrazinamide only in the initial phase?

- Pyrazinamide has its maximum sterilising effect within the first 2 months. There is less benefit from longer use.

Is a 4 month continuation phase possible?

- A 4 month continuation phase is possible with rifampicin throughout (e.g. 2 EHRZ/ 4HR). This is because isoniazid and rifampicin are both potent bactericidal drugs. In the usual 6 month continuation phase (6 HE or 6 HT), the only potent bactericidal drug is isoniazid. Although NTP Nepal used 2 month HRZE and 4 month HR for New Smear +ve, -ve PTB and EP cases.

Why not always use regimens containing rifampicin throughout?

- Rifampicin is too expensive for many countries to afford these regimens. If rifampicin is used in the continuation phase without supervision, there is a risk of creating rifampicin resistance. But Rifampicin use, through the treatment under DOT.

Why is it so important to prevent rifampicin resistance?

- Rifampicin is the most effective anti-TB drug. It is unlikely that a new anti-TB drug will become widely available in the near future. If rifampicin resistance becomes widespread, TB will be effectively untreatable.

How do we prevent rifampicin resistance?

- Bad TB control programmes, lack of supervision of anti-TB treatment, bad prescribing by clinicians, and the use of rifampicin alone generate acquired drug resistance. The best way to prevent rifampicin resistance is to strengthen NTPs and ensure directly observed therapy when and where possible. It is important to use methods of drug administration which avoid the danger of the use of rifampicin alone. These include the use whenever possible of fixed-dose combination tablets and of anti-TB drugs supplied in blister packs.

What is the treatment for multi-drug resistant TB?

- Multi-drug resistant TB arises from failure to deliver anti-TB drug treatment properly. Multi-drug resistance represents NTP failure. In many high TB prevalence countries, second-line drugs are prohibitively expensive and unavailable, e.g. ethionamide, cycloserine, kanamycin, capreomycin. Multi-drug resistant TB is therefore often untreatable. [See Annex 5]

What should we do when faced with multi-drug resistant TB?

- The cause of the problem is NTP failure. The answer is to devote time, effort and resources to improving the NTP. In some countries, one or two specialist centres may have the specialist expertise and second-line drug available to treat patients with **multi-drug resistant TB**.

5 5 USE OF ANTI-TB DRUGS IN SPECIAL SITUATIONS

Pregnancy

- Streptomycin during pregnancy can cause permanent deafness in the baby.
- **Do not give streptomycin in pregnancy.** Use ethambutol instead.

Renal failure

- Rifampicin, isoniazid and pyrazinamide are safe.
- The excretion of streptomycin is renal. The excretion of ethambutol and thiacetazone is partly renal.
- Avoid streptomycin and ethambutol if there are alternatives. Otherwise give in reduced doses at less frequent intervals.
- **Do not give thiacetazone.** The margin is too narrow between the therapeutic and toxic dose.

Liver disease

- Most anti-TB drugs can cause liver damage. Jaundiced patients who develop TB should receive treatment with the following regimen: 2 SHE / 10 HE.
- **Do not give pyrazinamide to patients with liver disease.**

5 6 THE ROLE OF STEROID TREATMENT: QUESTIONS AND ANSWERS

What are the indications for treatment with steroids?

- TB meningitis (decreased consciousness, neurological defects, or

spinal block).

- TB pericarditis (with effusion or constriction).
- TB pleural effusion (when large with severe symptoms).
- Hypo-adrenalism (TB of adrenal glands).
- TB laryngitis (with life-threatening airway obstruction).
- Severe hypersensitivity reactions to anti-TB drugs.
- Renal tract TB (to prevent ureteric scarring).
- Massive lymph node enlargement with pressure effects.

What is adjuvant steroid treatment?

Adjuvant steroid treatment is steroid treatment given in addition to anti-TB drug treatment. Prospective controlled clinical trials have confirmed the benefit of steroids in TB meningitis and pleural and pericardial TB.

What are the recommended treatment doses of prednisolone?

Rifampicin is a potent inducer of hepatic enzymes which metabolise steroids. The effective dose of prednisolone is therefore half the prescribed treatment dose given to the patient. The table below shows suggested treatment doses of prednisolone.

INDICATION	PREDNISOLONE TREATMENT
TB meningitis	60mg daily for weeks 1-4, then decrease over several weeks
TB pericarditis	60mg daily for weeks 1-4 30mg daily for weeks 5-8 then decrease over several weeks
TB pleural effusion	40mg daily for 1-2 weeks

Is steroid treatment safe in TB/HIV patients?

Steroids are immunosuppressant. The worry is that steroids may further depress immunity and increase risk of opportunistic infections in HIV-positive patients. However, on balance, TB/HIV patients are still likely to benefit from the use of steroids for the above indications.

5 7 MONITORING OF TB PATIENTS DURING TREATMENT

Bacteriological monitoring is readily available only for patients with sputum smear-positive pulmonary TB. Routine monitoring of treatment response by chest X-rays is unnecessary and wasteful of resources. For other TB patients, clinical monitoring is the usual guide to treatment response.

PRACTICAL POINT

Recording treatment results in sputum smear-positive pulmonary TB patients is vital to monitor patient cure and NTP effectiveness (see Chapter 7).

5 7 1 Monitoring of patients

5 7 1 1 Monitoring of patients with sputum smear-positive PTB

WHEN TO MONITOR	8 MONTH TREATMENT REGIMEN	6 MONTH TREATMENT
At time of diagnosis	SPUTUM SMEAR	SPUTUM SMEAR
At end of initial phase	SPUTUM SMEAR	SPUTUM SMEAR
In continuation phase	SPUTUM SMEAR (Month 5)	SPUTUM SMEAR (Month 5)
On completion of treatment	SPUTUM SMEAR (Month 8)	SPUTUM SMEAR (Month 6)

Sputum smear at end of initial phase

The vast majority of patients have a negative sputum smear at the end of the initial phase. If the sputum smear is still positive at the end of the initial phase, continue initial phase treatment with the same 4 drugs for 4 more weeks. If you check the sputum smear again at this point, it is unlikely still to be positive. Go on to the continuation phase (even if the sputum smear after the extra 4 weeks of initial phase treatment is still positive).

Sputum smear in continuation phase

In 8 month regimens, a positive sputum smear at 5 months (or any time after 5 months) means treatment failure. In 6 month regimens, a positive sputum smear at 5 months (or any time after 5 months) means treatment failure. A common cause of treatment failure is the failure of the programme to ensure patient adherence to treatment. The patient changes treatment category to Category 2 and starts the retreatment regimen.

Sputum smear on completion of treatment

In 8 month regimens, negative sputum smears at 5 and at 7 or 8 months mean bacteriological cure. In 6 month regimens, negative sputum smears at 5 and 6 months mean bacteriological cure. (Do not use anti-tuberculosis treatment for more than the recommended period).

5 7 1 2 Monitoring of patients with sputum smear-negative PTB

Do a X-ray at the end of the 1st month especially in smokers and patients more than 40 years of age to rule out the possibility of malignancy. If there is no clinical improvement and the X-ray findings support the clinical findings at month 1, then refer the patient to a tertiary centre for further investigations. Do a sputum examination at the end of 2 months for all smear-negative PTB patients.

5 7 1 3 Monitoring of patients with extra-pulmonary TB

Do a sputum examination at the end of the second month if earlier chest X-ray has not already been done to rule out pulmonary tuberculosis.

5 7 2 Recording treatment outcome in PTB patients

At the end of the treatment course in each individual patient, the recordings of treatment outcomes should be as follows:

Cured	<i>A patient who was initially sputum or culture positive at the beginning of the treatment but converted to negative smear or culture status in the last month of treatment and on at least one previous occasion.</i>
Treatment completed	<i>A patient who completed treatment but who did not meet the criteria to be classified as a cure or a failure. This definition applies to pulmonary smear positive and smear negative and extra pulmonary TB patients.</i>
Treatment failure	<i>(1) A new patient who is smear or culture positive at five months or later during treatment, or who is switched to Category IV treatment because sputum culture revealed MDR TB> (ii) A previously treated patient who is sputum or culture positive at the end of the re-treatment regimen or who is switched to Category IV treatment because sputum culture revealed MDR TB.</i>
Died	<i>A patient who died from any cause during the course of TB treatment</i>

Defaulted (treatment interrupted) *A patient whose treatment was interrupted for two consecutive months or more.*

Transferred out *A patient who was transferred to a health facility in another basic management unit and for whom the treatment outcome is not known.*

SUGGESTIONS FOR FURTHER READING

WHO. Treatment of tuberculosis. Guidelines for national programmes. Geneva, 1993.

Horne NW. Modern drug treatment of tuberculosis. Chest, Heart and Stroke Association. 7th edition. London, 1990.

Dean P, Ebrahim GJ. The practical care of sick children. A manual for use in small tropical hospitals. London: Macillan. 1986.

WHO Guidelines on the management of drug-resistant tuberculosis. WHO/TB/96.210, Geneva, 1996.

CHAPTER 6 SIDE EFFECTS OF ANTI-TB DRUGS

6 1 INTRODUCTION

Most TB patients complete their treatment without any signification during side effects. However, a few patients do develop side effects. So clinical monitoring of all TB patients for side effects is important during TB treatment. Routine laboratory monitoring is not necessary.

How do health personnel monitor patients for drug side effects?

- a) by teaching patients how to recognise symptoms of common side effects and to report if they develop such symptoms.
- b) by asking specifically about these symptoms when they see all patients at least monthly during treatment.

6 2 PREVENTION OF SIDE EFFECTS

Health personnel should be aware of the special situation which influence the choice and close of anti-TB drugs (see Chapter 5).

It is possible to prevent the peripheral neuropathy caused by isoniazid. This neuropathy usually shows a burning sensation of the feet. It occurs more commonly in HIV-positive individuals, in drinkers (alcohol), and in patients with diabetes. These patients should receive preventive treatment with pyridoxine 10 mg daily. Ideally, where possible pyridoxine 10 mg daily should routinely accompany isoniazid.

6 3 WHERE TO MANAGE DRUG REACTIONS

REACTION	WHERE TO MANAGE REACTION
minor, e.g. gastro-intestinal joint pains	out-patient setting
major, e.g. jaundice severe rash	refer to district or central hospital

6 4 WHEN TO STOP ANTI-TB DRUGS

When a patient has minor drug side-effects, explain the situation, offer symptomatic treatment, and encourage him/her to continue treatment.

When a patient has a major reaction, stop the suspected drug(s) responsible at once. A patient who develops one of the following reactions must never receive that drug again:

REACTION	DRUG RESPONSIBLE
<i>hearing loss or disturbed balance.....</i>	<i>streptomycin</i>
<i>visual disturbance (poor vision and colour perception)....</i>	<i>ethambutol</i>
<i>renal failure, shock, or thrombocytopenia.....</i>	<i>rifampicin</i>

SIDE EFFECTS OF ANTI-TB DRUGS

DRUG	COMMON SIDE EFFECTS	RARE SIDE EFFECTS
<i>isoniazid</i>	<ul style="list-style-type: none"> • peripheral neuropathy • hepatitis 	<i>convulsions, pellagra, joint pains, agranulocytosis, lupoid reactions, skin rash</i>
<i>rifampicin</i>	<ul style="list-style-type: none"> • gastrointestinal: anorexia, nausea, vomiting, abdominal pain • hepatitis • reduced effectiveness of oral contraceptive pill 	<i>acute renal failure, shock, thrombocytopenia, skin rash, "flu syndrome" (intermittent doses), pseudomembranous colitis, pseudoadrenal crisis</i>
<i>pyrazinamide</i>	<ul style="list-style-type: none"> • joint pains • hepatitis 	<i>gastrointestinal symptoms, skin rash, sideroblastic anaemia</i>
<i>ethambutol</i>	<ul style="list-style-type: none"> • optic neuritis 	<i>skin rash, joint pains, peripheral neuropathy</i>
<i>streptomycin</i>	<ul style="list-style-type: none"> • auditory and vestibular nerve damage (also to foetus) • renal damage 	<i>skin rash</i>

PRACTICAL POINT

Rifampicin reduces the effectiveness of the oral contraceptive pill. Advise a woman to choose between the following two options. Following consultation with a physician, she could take an oral contraceptive pill containing a higher dose of oestrogen (50mcg). Alternatively, she could use another form of contraception.

6 6 SYMPTOM-BASED APPROACH TO MANAGEMENT OF DRUG SIDE EFFECTS

SIDE EFFECTS	DRUG(S) PROBABLY RESPONSIBLE	MANAGEMENT
minor		continue anti-TB drugs
<i>anorexia, nausea</i>	<i>rifampicin</i>	<i>give tablets last thing</i>
<i>abdominal pain</i>		<i>at night</i>
<i>joint pains</i>	<i>pyrazinamide</i>	<i>aspirin</i>
<i>burning sensation in feet</i>	<i>isoniazid</i>	<i>pyridoxine 100 mg daily</i>
<i>orange/red urine</i>	<i>rifampicin</i>	<i>reassurance</i>
major		stop drug(s) responsible
<i>skin itching/rash</i>	<i>thiacetazone</i> <i>(streptomycin)</i>	<i>stop anti-TB drugs (see below)</i>
<i>deafness</i> <i>(no wax on auroscopy)</i>	<i>streptomycin</i>	<i>stop streptomycin,</i> <i>ethambutol instead</i>
<i>dizziness</i> <i>(vertigo and nystagmus)</i>	<i>streptomycin</i>	<i>stop streptomycin, use</i> <i>ethambutol instead</i>
<i>jaundice</i> <i>(other causes excluded)</i>	<i>most anti-TB drugs</i>	<i>stop all anti-TB drugs until</i> <i>jaundice resolves (see below)</i>
<i>vomiting and confusion</i> <i>(suspected drug-induced</i> <i>pre-icteric hepatitis)</i>	<i>most anti-TB drugs</i>	<i>stop anti-TB drugs, urgent</i> <i>liver function tests</i>
<i>visual impairment</i>	<i>ethambutol</i>	<i>stop ethambutol</i>
<i>generalised, including</i>	<i>rifampicin</i>	<i>stop rifampicin</i>
<i>shock and purpura</i>		

MANAGEMENT OF SKIN ITCHING/RASH

The approach depends on whether or not the patients is receiving thiacetazone. In populations with a high TB/HIV prevalence, thiacetazone is the drug most likely to cause skin reactions.

6 7 1 Treatment regimen includes thiacetazone

If a patient starts to itch, and there is no other obvious cause (e.g. scabies), stop and the anti-TB drugs at once. The itching may be a warning sign of severe skin reaction. Stopping the thiacetazone at once may avert, or decrease the severity, of the skin reaction.

Give the patient intravenous fluids if skin reaction is severe:

- a) exfoliative dermatitis or toxic epidermal necrolysis
- b) mucous membrane involvement
- c) hypotension

Many physicians give steroid treatment although there is no firm evidence that this helps. A typical dose schedule consists of 60 mg daily of oral prednisolone until there is some improvement. A gradual reduction in dose over the next few days depends on the patient's response. Initially, if a patient is unable to swallow, give intravenous hydrocortisone 100-200 mg daily (instead of oral prednisolone). On recovery, restart anti-TB drugs, replacing thiacetazone with ethambutol.

PRACTICAL POINT

Never give a patient thiacetazone again after any thiacetazone reaction.

A severe reaction may mean stopping anti-TB treatment for 3-4 weeks. A severely ill TB patient may die without anti-TB treatment. In this case, give 2 or more previously unused drugs until the reaction has resolved. Then reintroduce the initial regimen (with ethambutol instead of thiacetazone).

Treatment regimen does not include thiacetazone

If a patient starts to itch, exclude other obvious causes. Try treatment with anti-histamines, continue anti-TB treatment and observe the patient closely. In some cases, the itching resolves. In other cases, a rash develops. In this case, stop the anti-TB drugs. Wait for the rash to resolve. If the reaction is severe, the patient may need supportive treatment as above.

The problem is now re-introducing TB treatment when we don't know which anti-TB drug was the drug responsible for the reaction. The table shows the standard approach to re-introducing anti-TB drugs one by one after a drug reaction.

RE-INTRODUCTION OF ANTI-TB DRUGS FOLLOWING DRUG REACTION

DRUG	LIKELIHOOD OF CAUSING A REACTION	CHALLENGE DOSES		
		DAY 1	DAY 2	DAY 3
Isoniazid	least likely	50mg	300mg	300 mg
Rifampicin	↓	75mg	300mg	Full dose
Pyrazinamide		250mg	1 gram	Full dose
Ethambutol		100mg	500mg	Full dose
Streptomycin		125mg	500mg	Full dose
		most likely		

If possible, while the patient undergoes drug challenging, give 2 anti- TB drugs which the patient has not had before. The idea of drug challenging is to identify the drug responsible for the reaction. Drug challenge starts with the anti-TB drug least likely to be responsible for the reaction (i.e. isoniazid). Start with a small challenge dose. If a reaction occurs to a small challenge dose, it will not be such a bad reaction as to a full dose. Gradually increase the dose over 3 days. Repeat the procedure, adding in one drug at time. A reaction after adding in a particular drug identifies that drug as the one responsible for the reaction.

If the drug responsible for the reaction is pyrazinamide, ethambutol, or streptomycin, resume anti-TB treatment without the offending drug. If possible, replace the offending drug with another drug. It may be necessary to extend the treatment regimen. Consider the start of the resumed regimen as a new start of treatment. This prolongs the total time of TB treatment, but decreases the risk of recurrence.

PRACTICAL POINT

Refer patients with severe drug reactions to specialist centres.

6 8 DESENSITISATION

Rarely, patients develop hypersensitivity reactions to the 2 most potent anti-TB drugs, isoniazid and rifampicin. These drugs form the corner-stone of SCC. If an HIV-negative patient has had a reaction (but not a severe reaction) to isoniazid or rifampicin, it may be possible to desensitise the patient to the drug. However, never attempt desensitisation in TB/HIV patients because of the high risk of serious toxicity. The following method for desensitisation therefore does not apply to TB/HIV patients.

Start desensitisation with a tenth of the normal dose. Then increase the dose by a tenth each day, until the patient has the full dose on the tenth day. Once drug sensitisation is over, give the drug as part of the usual treatment regimen. If possible, while carrying out desensitisation, give the patient 2 anti-TB drugs which the patient has not had before. This is to avoid the risk of drug resistance developing during desensitisation.

PRACTICAL POINT

Never attempt desensitisation in TB/HIV patients.

6 9 MANAGEMENT OF HEPATITIS

Most anti-TB drugs can damage the liver. Isoniazid and pyrazinamide are most commonly responsible. Ethambutol is rarely responsible. When a patient develops hepatitis during anti-TB treatment, the cause may be the anti-TB treatment or another cause. It is often difficult to find out. Try to rule out other possible causes before deciding that the hepatitis is drug-induced. Hepatitis presents with anorexia, jaundice and often liver enlargement.

If you diagnose drug-induced hepatitis, stop the anti-TB drugs. Wait until the jaundice resolves. It is strange, but fortunate, that in most cases the patient can re-start the same anti-TB drugs without hepatitis returning. A severely ill TB patient may die without anti-TB drugs. If jaundice returns, and the patient had not completed the intensive phase, give him 2 months of streptomycin, isoniazid and ethambutol followed by 10 months of isoniazid and ethambutol. If the patient has completed the intensive phase, give him isoniazid and ethambutol until he has a total 8 months treatment for SCC.

SUGGESTIONS FOR FURTHER READING

*Crofton J, Horne N and Miller F. Clinical Tuberculosis
The Macmillian Press Limited. 1992.*

*Horne NW. Modern Drug Treatment of Tuberculosis. The Chest, Heart
and Stroke Association. Seventh edition. London, 1990*

CHAPTER 7 FRAMEWORK FOR EFFECTIVE TUBERCULOSIS CONTROL

7 1 INTRODUCTION

WHO has declared that TB is a global emergency, because TB is out of control in many parts of the world. The following are the main reasons why TB is out of control:

- a) governments in many parts of the world have neglected the disease;
- b) inadequate TB control programmes have led to an increased burden of disease (inadequately treated TB patients live longer with chronic disease and infect other people) and the emergence of drug resistant TB;
- c) high rates of population growth have contributed to an increased number of TB cases;
- d) the HIV epidemic has led to an enormous increase in the number of TB cases, in places where HIV and TB are both common.

WHO has developed a new framework of strategy and policy for TB control in response to this global emergency. This strategy and policy is unchanged in the face of the epidemic of TB/HIV co-infection. It is vital for successful TB control for health care workers to treat TB patients within this framework in a National TB Programme (NTP).

7 2 COMPONENTS OF TB CONTROL FRAMEWORK

The framework consists of the following:

1. **Overall objectives of TB control.**
2. **Strategy for TB control.**
3. **Targets for TB control.**
4. **TB control policy package.**
5. **Key operations of a national TB programme.**
6. **Indicators to measure progress in TB control.**

7 2 1 Overall objectives of TB Control

To reduce mortality, morbidity and disease transmission (while avoiding the development of drug resistance).

7 2 2 Strategy for TB Control

To provide short-course chemotherapy under direct observation to, at least, all identified smear-positive TB cases (the sources of infection).

7 2 3 Targets for TB control

Add new STOP TB strategy

a) To cure 85% of new detected cases of sputum smear-positive PTB. A national TB programme which achieves at least an 85% cure rate in patients with sputum smear-positive PTB has the following impact on TB:

- i)* TB prevalence and the rate of TB transmission both decrease immediately;
- ii)* TB incidence decreases gradually;
- iii)* there is less acquired drug resistance (which makes future treatment of TB easier and more affordable).

b) To detect 70% of existing cases of sputum smear-positive PTB. It is important to expand case-finding only when a national TB programme has achieved a high cure rate. A national TB programme which has low cure rate makes the TB problem worse:

- i)* there are more cases of sputum smear-positive PTB treatment failure;
- ii)* transmission of acquired drug-resistance increases.

A treatable epidemic becomes an untreatable epidemic.

AN EFFECTIVE NTP HAS A HIGH CURE RATE AND A LOW LEVEL OF ACQUIRED DRUG RESISTANCE.

In the presence of a high cure rate, increased case detection of sputum smear-positive PTB cases will decrease TB transmission.

7 2 4 TB control policy package

The success of the WHO strategy depends on the implementation of a 5-point package:

- i)* government commitment to a national TB programme;
- ii)* case detection through “passive” case-finding (sputum smear microscopy for PTB suspect attending health services);
- iii)* short-course chemotherapy for all smear-positive PTB cases (under direct observation for, at least, the initial phase of treatment);
- iv)* regular, uninterrupted supply of all essential anti-TB drugs;
- v)* monitoring system for programme supervision and evaluation.

7 2 5 Key features of a national TB programme (NTP)

- i)* NTP has a central unit.
- ii)* NTP manual available in districts.
- iii)* A recording and reporting system using standardized registers.
- iv)* A training programme covering all aspects of the policy package.
- v)* Microscopy services nationwide.
- vi)* Treatment services integrated with existing health services, with priority for supervised short-course chemotherapy.
- vii)* Regular supply of drugs and diagnostic materials.
- viii)* Plan of supervision.
- ix)* A project development plan, with details of budget, sources of funding and responsibilities.

7 2 6 Indicators of NTP progress in TB Control.

- i)* NTP manual available in districts (reflects government commitment).
- ii)* The number of administrative areas in the country which are implementing the new TB control strategy.
- iii)* The cure rate.
- iv)* The case detection rate.

What is cohort analysis?

A cohort of TB patients consists of all those sputum smear-positive PTB patients registered during a certain time. The time period may be a quarter of a year or one year. New and previously treated patients form separate cohorts. For example, consider all those sputum smear-positive PTB patients registered from 1 Shrawan to 31 Kartik in any year. They form the cohort for that quarter-year. Cohort analysis refers to the statistical breakdown of that cohort according to certain indicators. These indicators are the standardised case definitions and treatment categories (see Chapter 4) and the 6 treatment outcomes described in Chapter 5.

Who performs cohort analysis and how often?

Cohort analysis is a continuous process. The District TB/Leprosy Assistant (DTLA) performs cohort analysis on TB patients registered in his district every four months. The Regional TB/Leprosy Assistant (RTLA) performs cohort analysis on all TB patients registered in the region every four months. Similarly, the NTP performs cohort analysis on all TB patients registered nationally.

What is cohort analysis for?

Cohort analysis is the key management tool used to evaluate the effectiveness of TB control programme delivery. It enables regional NTP staff and the NTP directorate to identify districts with problems. Examples of problems identified include the following: low cure rate, high default rate, higher than expected proportions of sputum smear-negative PTB or extrapulmonary TB, lower than expected case detection rate. Identification of problems enables the NTP to overcome them and improve programme delivery.

What is directly observed therapy?

To ensure the treatment cures the patient, we have to ensure patient adherence to the treatment. Patient adherence to short-course chemotherapy means the patient takes every dose of the recommended treatment regimen. It is difficult for a patient to adhere to anti-TB treatment for long duration such as 6 or more. It is difficult to predict which TB patients will adhere to self-administered treatment. Direct observation of therapy (DOT) means that a treatment supporter or supervisor watches the patient swallowing tablets. The NTP trains and monitors treatment supporters and supervisors.

Directly observed therapy as close to the patient's home as possible

A TB patient is unlikely to adhere to treatment if the distance from his/her place of residence/work and health institution where patient is enrolled for treatment is long. One of the aims of the NTP is to provide TB services as close to patient's home or work as possible. For those TB patients who live close to a health facility (e.g. health centre, district hospital) treatment should be supervised by any of the health staff in the health facility. TB patients who live far from a health facility treatment can be supervised by a trained local community care schemes and family member. The HIV/AIDS home care providers with suitable training and supervision can administer directly observed therapy.

Integration of TB treatment services with general health services

In the past, some TB programmes have relied only on TB hospitals and clinics, separate from the general health services. The big problem with that system is that many TB patients live far from such TB hospitals and clinics and patients had to leave their homes and jobs in order to get TB treatment. One reason why TB is out of control in many countries is because TB patients do not have easy access to TB diagnosis and treatment services. A successful NTP brings TB diagnosis and treatment services closer to the TB patients. The best option for TB diagnostic and treatment provision is that these should be provided through general health care/primary health care settings as close to patient as possible.

SUGGESTIONS FOR FURTHER READING

World Health Organization. TB - A Global Emergency. WHO report on the TB epidemic, 1994. Geneva: WHO, 1994

World Health Organization. Stop TB at the source. WHO report on the TB epidemic, 1995. Geneva: WHO, 1995.

World Health Organization. Groups at risk. WHO report on the TB epidemic, 1996, Geneva: WHO, 1996.

World Health Organization. Framework for effective tuberculosis control. WHO Tuberculosis Programme, 1994. Geneva: WHO, 1994.

World Health Organization. Treatment of Tuberculosis: Guidelines for national programmes. Geneva: WHO, 1993.

International Union Against Tuberculosis and Lung Disease. Tuberculosis guide for low income countries. pmi Verlagsgruppe. 3rd edition. Frankfurt, 1994.

CHAPTER 8 HIV-RELATED TB

8 1 BASIC INFORMATION

8 1 1 Epidemiology of co-infection of HIV and *M. Tuberculosis*

By the end of 2000, about 11.5 million HIV-infection people world wide were coinfectd with *M. tuberculosis*. 70% of coinfectd people were in sub-Saharan Africa, 20% in South-East Asia and 4% in Latin America and the Caribben.

Number of coinfectd adults (15-49 years) in WHO regions by end 2000

WHO REGION	NUMBER OF PEOPLE COINFETED WITH TB & HIV (THOUSAND)	% OF GLOBAL TOTAL
Africa	7979	70
America	468	4
Eastern Mediterranean	163	1
Europe	133	1
South-East Asia	2269	20
Western pacific	427	4
Total	11440	100

8 1 2 HIV infection and risk of TB

HIV probaby increases susceptibility to infection with *M. tuberculosis*. HIV increases the risk of progression of *M. tuberculosis* inection to TB disease. This risk increases with increasing immunosuppression. HIV increases not only the risk but aslo the rate of progression of recent or latent *M. tuberculosis* infection to disease. The table below shows the effect of HIV infection on the lifetime risk of *M. tuberculo-sis* infected individual developing TB.

HIV STATUS	LIFETIME RISK OF DEVELOPING TB
negative	5-10%
positive	50%

PRACTICAL POINT

HIV is the most powerful factor known to increase the risk of TB.

8 1 3 TB in the course of HIV Progression

TB can occur at any point in the course of progression of HIV infection. The risk of developing TB rises sharply with worsening immune status.

8 1 4 Consequence of HIV/M. tuberculosis co-infection

Compared to an individual who is not infected with HIV, an individual infected with HIV has a 10 times increased risk of developing TB. TB notifications have increased in populations where both HIV infection and *M. tuberculosis* infection are common e.g. some parts of sub-Saharan Africa have seen a tripling in the number of notifications over the past decade. HIV seroprevalence in these TB patients is up to 70%. In sub-Saharan Africa, one third or more of HIV-infected people may develop TB.

8 1 5 Impact of HIV on TB control

The principles of TB control are the same even when there are many HIV/TB patients. However, in populations where HIV/TB is common, health services struggle to cope with the large and rising numbers of TB patients.

The consequences include the following:

- **over-diagnosis of sputum smear-negative PTB**
- **under-diagnosis of sputum smear-positive PTB**
- **inadequate supervision of anti-TB chemotherapy**
- **low cure rates**
- **high mortality rates during treatment**
- **high default rates because of adverse drug reactions**
- **high rates of TB recurrence**
- **increased emergence of drug resistance**
- **increased transmission of drug resistance strains among HIV infected patients in congregate settings**

8 2 PATTERNS OF HIV-RELATED TB

As HIV infection progresses, CD4 +lymphocytes decline in number and function. These cell play an important role in the body’s defence against tubercle bacilli. Thus the immune system is less able to prevent the growth and local spread of *M. tuberculosis*. Disseminated and extra-pulmonary disease is more common.

8 2 1 Pulmonary TB

Even in HIV-infected patients, PTB is still the commonest form of TB. The presentation depends on the degree of immunosuppression. The table below shows how the clinical picture, sputum smear result and chest X-ray appearance often differ in early and late HIV infection.

<i>lymphoma)</i>		
<i>features of PTB</i>	<i>Stage of HIV infection</i>	
	<i>early</i>	<i>late</i>
<i>clinical picture</i>	<i>often resembles post-primary PTB</i>	<i>often resembles primary PTB</i>
<i>sputum smear result</i>	<i>often positive</i>	<i>often negative</i>
<i>chest X-ray appearance</i>	<i>often cavities</i>	<i>often infiltrates with no cavities.</i>

Weight loss and fever are more common in HIV-positive PTB patients than in those who are HIV-negative. Conversely, cough and haemoptysis are less common in HIV-positive PTB patients than in those who are HIV-negative. This is probably because there is less cavitation, inflammation and endobronchial irritation in HIV positive patients.

Sputum microscopy

Sputum smear positivity rates in TB/HIV patients also depend on the degree of immunocompromise, as shown below.

DEGREE OF IMMUNOCOMPROMISE	LIKELIHOOD OF POSITIVE SPUTUM SMEAR
<i>mild</i>	<i>similar to HIV-negative patient</i>
<i>severe</i>	<i>decreased (decreased inflammation in lungs)</i>

Chest X-ray appearance

The classical chest X-ray pattern is more common in HIV-negative patients. The atypical pattern is more common in HIV-positive patients.

PRACTICAL POINT

Chest X-ray changes in TB/HIV patients reflect the degree of immunocompromise. In mild immunocompromise, the appearance is often classical (with cavitation and upper lobe infiltrates.) In severe immunocompromise, the appearance is often atypical.

Distinguishing other HIV-related pulmonary diseases from PTB.

This is a common, and often difficult, diagnostic problem. Several diseases in HIV-positive individuals may present in a similar way with cough, fever, sometimes chest signs, and chest X-ray shadowing. In each case it is important to make a careful clinical assessment and send sputum samples for AFBs if the patient has had cough for 3 weeks or more.

Acute bacterial pneumonia

This is common in HIV-positive patients. The shorter history usually differentiates pneumonia from PTB. The most common pathogen is *Streptococcus pneumoniae*. Regardless of HIV status, acute bacterial pneumonia usually responds well to standard treatment with penicillin, co-trimoxazole and ampicillin.

PRACTICAL POINT

If pneumonia fails to respond to standard antibiotics, consider other pathogens, e.g. *M. tuberculosis*.

Kaposi's sarcoma (KS)

The clinical recognition of KS is straightforward when there are typical lesions on the skin and mucous membranes. The diagnosis of pulmonary or pleural KS is more difficult. The patient usually presents with cough, fever and dyspnoea, and usually has KS elsewhere. Chest X-ray shows a diffuse nodular infiltrate or pleural effusion. The pleural fluid is usually blood-stained. Cytology may provide the diagnosis. It can be difficult to rule out concurrent PTB.

Pneumocystis carinii pneumonia (PCP)

The incidence of PCP in HIV-infected individuals shows a wide geographic variation. The patient usually presents with dry cough and progressive dyspnoea. The table below shows the clinical and chest X-ray features which help to distinguish PCP from PTB.

Clinical and chest X-ray features of PCP in contrast with TB

	TYPICAL OF PCP	TYPICAL OF TB
SYMPTOMS	<i>dry cough sputum mucoid if any dyspnoea</i>	<i>productive cough purulent sputum pleuritic chest pain, haemoptysis</i>
SIGNS	<i>normal fine inspiratory crackles</i>	<i>signs of consolidation signs of pleural effusion</i>
CHEST X-RAY	<i>bilateral diffuse interstitial shadowing normal</i>	<i>lobar consolidation cavitation pleural effusion intrathoracic lymphadenopathy</i>

The definitive diagnosis of PCP rests on finding the cysts in induced sputum, broncho-alveolar lavage or biopsy specimens. These investigations are often unavailable in district hospitals. The diagnosis therefore depends on the clinical and chest X-ray features, exclusion of TB and response to a trial of high-dose cotrimoxazole.

Other conditions

Two other rare conditions are cryptococcosis and nocardiosis. They may present in a similar way to TB. The diagnosis of pulmonary cryptococcosis rests on finding the fungal spores in sputum smears. Nocardiosis may be particularly difficult to differentiate from TB. The chest X-ray often shows upper lobe, cavitory infiltrates. The organism may also stain weakly acid-fast. Associated soft-tissue and brain abscesses raise clinical suspicion. The diagnosis rest on finding beaded and branching Gram positive rods on sputum smear.

8 2 2 Extra-Pulmonary TB

The commonest forms of extra pulmonary TB are M pleural affusion, lymphadenopathy, pericardial disease, miliary disease, meningitis, disseminated TB (with mycobacteraemia)

Extrapulmonary TB is common in HIV-positive patients. The commonest forms are the following: lymphadenopathy, pleural effusion, pericardial disease, miliary disease, meningitis. Serous effusions are a more common form of TB in HIV-positive than in HIV-negative individuals. Miliary TB is an under-diagnosed cause of end-stage wasting in HIV-positive individuals.

PRACTICAL POINT

Some of the CSF findings may be normal in TB meningitis especially in HIV-positive patients. The percentages of HIV-positive TB meningitis patients with normal CSF findings are as follows: glucose 15%, protein 40%, white cell count 10%.

Persistent generalised lymphadenopathy (PGL)

PGL is a feature of HIV infection which develops in up to 50% of HIV-infected individuals. There is no specific treatment. The diagnostic criteria for PGL are as follows:

*lymph nodes larger than 1 cm in diameter
in 2 or more extra-inguinal sites
for 3 or more months duration.*

The nodes are non-tender, symmetrical, and often involve the posterior cervical and epitrochlear nodes. PGL may slowly regress during the course of HIV infection and may disappear before the onset of AIDS. In populations with a high HIV prevalence, PGL is the commonest cause of lymphadenopathy. In HIV - positive individuals PGL is a clinical diagnosis. Only investigate further if there are features of another disease. The table below shows the features of lymph nodes which indicate further investigation, including biopsy.

Features of lymph nodes which indicate further investigation

- large (> 4 cm diameter) or rapidly growing lymph nodes
- asymmetrical lymphadenopathy
- tender/painful lymph nodes not associated with local infection
- matted/fluctuant lymph nodes
- obvious constitutional features (e.g. fever, night sweats, weight loss)
- hilar or mediastinal lymphadenopathy or chest X-ray.

The histological appearance of tuberculous lymph nodes from HIV positive patients depends on the degree of immunocompromise, as shown below.

DEGREE OF IMMUNOCOMPROMISE.....	HISTOLOGICAL APPEARANCE OF LYMPH NODES
<i>mild</i>	<i>caseating lesions with few or no AFBs</i>
<i>severe</i>	<i>little cellular reaction with many AFBs</i>

Features of other forms of extrapulmonary TB are described in chapter 2.

8 3 HIV-RELATED TB IN CHILDREN

As in adults, the natural history of TB in a child infected with HIV depends on the stage of HIV disease. Early in HIV infection, when immunity is good, the signs of TB are similar to those in a child without HIV infection. As HIV infection progresses and immunity declines, dissemination of TB becomes more common. Tuberculous meningitis, miliary tuberculosis, and widespread tuberculous lymphadenopathy occur.

8 3 1 Impact of TB and HIV

In an individual infected with HIV the presence of other infection, including TB may allow HIV to multiply more quickly. This may result in fore rapid progression of HIV disease.

8 3 2 The impact of HIV on the diagnosis of TB in Children

HIV makes the diagnosis of TB in children even more difficult than usual, for the following reasons:

- a) Several HIV-related disease, including TB, may present in a similar way.
- b) The interpretation of tuberculin skin testing is even more unreliable than usual. An immunocompromised child may have a negative tuberculin skin test despite having TB.
- c) A child with HIV infection usually comes from a household where the parents have HIV infection. One or both parents may have died from AIDS. It may be difficult for the child to attend a health facility.

8 3 3 Differential diagnosis of PTB in HIV-infected children

- bacterial pneumonia
- viral pneumonia, e.g. cytomegalovirus
- fungal pneumonia, e.g. candida, cryptococcus
- *Pneumocystis carinii* pneumonia
- lymphocytic interstitial pneumonitis
- pulmonary lymphoma

8 3 4 Child contacts who may be HIV-infected

Refer to chapter 3 for the management of child contacts of infectious (sputum smear positive) adults.

Suspicion that a child contact is HIV-infected may arise because of the following: the child has clinical evidence of HIV infection; the parent (the infectious TB patient) is known, or suspected to be, HIV-positive. If you suspect a child contact is HIV-infected, it is important to counsel the parents before HIV-testing the child.

Case fatality

The case fatality of TB/HIV patients of 1 year after starting TB treatment is about 20%. This is greater than case fatality in HIV-negative TB patients. The excess deaths in TB/HIV patients during and after treatment are partly due to TB itself and partly due to other HIV-related problems. These other HIV-related problems include the following: septicæmia, diarrhoea, pneumonia, anaemia, Kaposi's sarcoma, cryptococcal meningitis.

Case fatality is less in TB/HIV patients treated with SCC than with the old standard regimen (2 SHT or SHE/ 10 HT or HE). This is partly because SCC is a more effective anti-TB treatment. Also, rifampicin has broad-spectrum antimicrobial activity as well as anti-TB activity. This may decrease case fatality due to HIV-related bacterial infections during anti-TB treatment.

Response in survivors

Several studies have assessed the clinical, radiological, and microbiological response to SCC in HIV-positive and HIV-negative TB patients. Excluding patients who died, response rates were similar in HIV-positive and HIV-negative TB patients. The only exception was that on average weight gain was less in HIV-positive than in HIV-negative TB patients.

RECURRENCE OF TB AFTER COMPLETING ANTI-TB TREATMENT***Old standard treatment***

The recurrence rate is higher in HIV-positive than in HIV-negative TB patients. In one study of TB/HIV patients there was an association between recurrence and cutaneous reaction to thiacetazone. A severe thiacetazone reaction necessitated interruption of treatment and a change to ethambutol. There are several possible explanations for link between increased risk of recurrence and thiacetazone reaction. These include treatment interruption, subsequent poor compliance, more advanced immunocompromise, and change to the combination of isoniazid and ethambutol in the 10 months continuation phase.

SCC

The recurrence rate is similar in HIV-positive and HIV-negative TB patients who complete treatment.

Recurrence: relapse or re-infection?

When TB recurs after previous cure, there are 2 possibilities:

- a) true relapse (reactivation of persisters not killed by anti-TB drugs);
- b) re-infection (due to re-exposure to another source of infection).

The proportions of recurrences due to these 2 possibilities are not known.

8 4 1 Side effects of anti-TB drugs in TB/HIV patients

Adverse drug reactions are more common in HIV-positive than in HIV-negative TB patients. Risk of drug reaction increases with increased immunocompromise.

Most reactions occur in the first 2 months of treatment.

Skin rash

This is the commonest reaction. Fever often precedes and accompanies the rash. Mucous membrane involvement is common. The usual drug responsible is thiacetazone. Streptomycin and rifampicin are sometimes to blame. Severe skin reactions, which may be fatal, include exfoliative dermatitis, Stevens-Johnson syndrome and toxic epidermal necrolysis.

Other reactions

The commonest reactions necessitating change in treatment include gastrointestinal disturbance and hepatitis. There may be an increased risk of rifampicin-associated anaphylactic shock and thrombocytopenia.

PRACTICAL POINT

Following a drug reaction, never attempt desensitisation in TB/HIV patients.

SUGGESTIONS FOR FURTHER READING

Narain JP, Raviglione MC, Kochi A. HIV-associated tuberculosis in developing countries: epidemiology and strategies for prevention. Tubercle and Lung Disease 1992; 73: 311-321.

Dolin PJ, Raviglione MC, Kochi A. Global tuberculosis incidence and mortality during 1990-2000. Bull. World Health Organization 1994; 72(2): 213-220.

WHO TB/HIV Clinical Manual - 2004

CHAPTER 9 DIAGNOSIS OF HIV IN ADULTS WITH TUBERCULOSIS

9 1 CLINICAL RECOGNITION OF HIV INFECTION IN TB PATIENTS

In areas where the prevalence of both TB and HIV are high, the only HIV-related illness present in many TB/HIV patients is TB. However, certain clinical features are more common in HIV-positive TB patients than in HIV-negative TB patients. The table below shows these clinical features suspicious of HIV infection.

CLINICAL FEATURES SUSPICIOUS OF HIV CO-INFECTION IN TB PATIENTS	
Past history	sexually transmitted disease (STD) herpes zoster (shingles) recurrent pneumonia bacteraemia (especially <i>Salmonella typhimurium</i>)
Symptoms	weight loss (> 10 kg or > 20% of original weight) diarrhoea (> 1 month) pain on swallowing (suggests oesophageal candida) burning sensation of feet (peripheral sensory neuropathy)
Signs	scar of herpes zoster pruritic papular rash Kaposi's sarcoma symmetrical generalised lymphadenopathy oral candidiasis oral hairy leukoplakia persistent painful genital ulceration

PRACTICAL POINT

Full blood count (FBC) findings suspicious of HIV infection are unexplained anaemia, leucopenia or thrombocytopenia.

The definitive diagnosis of HIV infection rests on a positive HIV test.

9 2 HIV TESTING

9 2 1 HIV tests

There are different ways of testing for HIV. The most widely available way of identifying HIV-infected individuals is the detection of HIV antibodies in serum or plasma samples. The table below shows the 3 main methods of HIV-testing. The technical details of these tests are beyond the scope of this manual, but there is a good account in “AIDS in Africa: a manual for physicians”.

HIV TESTING METHODS WITH ADVANTAGES AND DISADVANTAGES

HIV TESTING METHOD	ADVANTAGES	DISADVANTAGE
ELISA	less expensive than immunoblot large numbers of sera can be tested daily sensitive and specific	some specialised laboratory immunoblot equipment necessary
simple/rapid (e.g. rapid immuno-binding assay)	simple, rapid less expensive than immunoblot no specialised equipment necessary	older tests less sensitive and less specific but newer tests improved
Immunoblot	most sensitive and specific	expensive specialised laboratory equipment necessary

The usual type of test for HIV antibodies is the ELISA (Enzyme-Linked ImmunoSorbent Assay). (The cost per individual ELISA test is about US \$0.75-1.75). There are ELISA tests available which test for both HIV-1 and HIV-2.

9 2 2 Objectives of HIV antibody testing in TB patients

There are 3 main possible objectives in performing HIV antibody tests in TB patients:

- a) diagnosis of HIV infection in individual TB patients;
- b) surveillance (anonymous testing to monitor epidemiological trends);
- c) research (voluntary testing for epidemiological, clinical, or virological studies).

9 2 3 Strategy for HIV antibody testing in TB patients (Which tests to use and when to use them)

HIV testing methods vary in accuracy and cost. In general, WHO recommends different HIV-testing strategies, depending on the objective of testing. The aim is to maximise accuracy and minimise cost. The table below shows the strategy appropriate for the objective of testing.

OBJECTIVES, STRATEGIES AND INTERPRETATION OF HIV TESTS

OBJECTIVE	TESTING STRATEGY	INTERPRETATION OF RESULT
Diagnosis of HIV infection in individual TB patients (a group with usually a high HIV sero-prevalence)	Test sample with ELISA or simple/rapid assay If 1 st assay positive, re-test using ELISA or simple/rapid assay based on a different antigen preparation or test	1 st assay negative = patient HIV negative
		1 st assay positive + 2 nd assay positive = patient HIV positive
		1 st assay positive + 2 nd assay negative - > repeat both assays
Surveillance (in population with HIV prevalence >10%)	Test sample with ELISA or simple/rapid assay	Results remain discordant - > repeat sample and testing
		Assay negative = patient HIV negative
		Assay positive = patient HIV positive

PRACTICAL POINT

Many low-income countries cannot afford the cost of the strategy of 2 positive tests in order to diagnose HIV infection in an individual patient. In practice, a patient has 1 test only: test negative = patient HIV negative; test positive = patient HIV positive.

9 2 4 **Diagnosis of HIV infection in individual TB patients**

The link between HIV and TB is well known. TB in populations with high HIV prevalence is a leading cause of morbidity and mortality. It is important to offer counselling and voluntary HIV testing, if available, to TB patients on account of the following possible benefits:

- a) the patient may want to know his/her HIV status;
- b) better diagnosis and management of other HIV-related illnesses;
- c) avoidance of drugs associated with a high risk of side-effects;
- d) increased condom use and decreased HIV transmission.

PRACTICAL POINT

Anti-TB drug treatment is the same for HIV-positive and HIV-negative TB patients, with one exception: do not give thiacetazone to HIV-positive TB patients (increased risk of severe and sometimes fatal skin reactions).

A policy of compulsory HIV testing (even if this were legal) of TB patients would be counter-productive. This type of policy would have the following results:

- a) patients deterred from seeking care;
- b) decreased case-finding in at-risk groups;
- c) reduced credibility of health services.

9 3 HIV COUNSELLING

Confidential counselling is essential before and after HIV antibody testing. The patient gives explicit informed consent to have the test. The patient must understand what the test involves and the implications of testing. The counsellor provides support. Counselling is a dialogue between patient and counsellor.

Counsellors

With suitable training, anyone who works with patients and families can be a counsellor. Counsellors may be members of the community or health workers. Many health workers have had counselling training. In the course of their duties they have the opportunity to counsel patients for HIV testing. Doctors and other clinicians are often in a good position to counsel patients for HIV testing. This is because clinicians have already established a relationship with the patient, who usually trusts the clinician.

Pre-test counselling

The aim is to enable the patient to make an informed decision to have the test or not. The patient needs to know what the test involves and what are the implications of the result. The main issues for discussion are assessments of the following: a) the patient's likelihood of having acquired HIV infection, b) knowledge about HIV, and c) ability to cope with a positive result.

POINTS TO CONSIDER BEFORE A HIV TEST

a) Assessment of risk of having acquired HIV infection	<ul style="list-style-type: none">• multiple sex partners• sex with commercial sex workers• for men, sex with other men• non-sterile skin piercing, e.g. scarification, tattooing• previous blood transfusion• intravenous drug use• sexual partner/spouse of person at risk
b) Assessment of knowledge about HIV	<ul style="list-style-type: none">• what does the test involve and mean?• how does HIV transmission occur?• what is high risk behaviour?
c) Assessment of ability to cope with result	<ul style="list-style-type: none">• patient's expected reaction to result• who will provide emotional support?• impact of a positive result on<ul style="list-style-type: none">- relationships- social issues, e.g. employment- future health

PRACTICAL POINT

The HIV test does not become positive until usually 6 weeks, and up to about 3 months, after infection (the “window period”).

Post-test counselling

The content of post-test counselling depends on the HIV test result. The aims are to discuss the result, share information, provide support, and encourage future, safe sexual behaviour. Always ensure confidentiality. Break the news openly and sympathetically. When someone has a positive HIV test result, common reactions at different times may include shock, anger, guilt, grief and depression. Patients will need continuing support.

Issues for discussion when the HIV test result is negative.

- A negative result does not mean that the patient definitely does not have HIV infection (the test could be in the seroconversion “window period”).
- Avoidance of unsafe sexual behaviour.
- Promotion of healthy behaviour.

Issues for discussion when the HIV test result is positive.

- General health (good diet, balance of rest and exercise, avoiding infections, when to seek advice about symptoms of other HIV-related illnesses).
- Awareness of possible anti-TB drug side-effects.
- Safe sexual behaviour.
- Avoidance of blood or organ donation.
- The patient’s reaction to the result.
- Emotional and psychological support for the patient.
- How to tell friends, family and lovers.
- Counselling partner(s) if possible.
- Referral to local community services and support groups, if available.
- Social implications, e.g. employment, life insurance.

SUGGESTIONS FOR FURTHER READING

WHO. AIDS in Africa: a manual for physicians. Geneva 1992.

WHO. Weekly Epidemiological Record. 1992; 67: 145-149.

WHO. Guidelines for HIV Surveillance Among Tuberculosis Patients. Geneva 1994.

WHO. AIDS Series 8. Guidelines for Counselling About HIV Infection And Disease. Geneva 1990.

WHO Global Programme on AIDS. Counselling for HIV/AIDS: a key to caring. Geneva 1995

WHO Global Programme on AIDS. Living with AIDS in the community. Geneva 1992.

CHAPTER 10 DIAGNOSIS OF HIV IN CHILDREN WITH TUBERCULOSIS

10 1 CLINICAL RECOGNITION OF HIV INFECTION IN CHILDREN

HIV infection in children may show in many ways. The clinical signs are often not specific for HIV infection. For example, weight loss, fever and cough are common in TB, with or without HIV infection. The clinical definition of HIV infection is therefore difficult.

PRACTICAL POINT

Parents provide important clues to possible HIV infection in their children. Ask the parents about their health. Sometimes parents may reveal their own HIV status.

The table below shows clinical signs suspicious of HIV infection in children.

CLINICAL SIGNS SUSPICIOUS OF HIV INFECTION IN CHILDREN

weight loss or abnormally slow growth
chronic diarrhoea (>1 month)
prolonged fever (>1 month)

generalised lymph node enlargement
oropharyngeal candidiasis
recurrent common infections, e.g. ear infections, pharyngitis
persistent cough
generalised rash

neurological problems
delay in development
bilateral parotid gland enlargement
enlarged spleen
enlarged liver
recurrent abscesses
meningitis
recurrent herpes simplex

10 2 HIV TESTING

Positive and negative HIV tests are not always reliable. Rarerly, a baby with HIV infection has a negative HIV antibody test. The reason for this is not known.

The definitive diagnosis of HIV infection rests on a positive HIV test. However, a positive HIV antibody test is not a reliable indicator of HIV infection in early childhood (up to 18 months of age). During the pregnancy of a mother with HIV infection, the mother's antibodies to HIV cross the placenta. Therefore almost all children born to HIV-positive mothers have HIV antibodies in their blood at birth. However, only about one third of children born to HIV-infected mothers are infected. Initially, HIV antibody testing cannot therefore distinguish uninfected from infected children. In **uninfected** children, these maternal antibodies usually become undetectable by 9 months of age. Occasionally maternal antibodies remain detectable until 18 months. Most **infected** children make their own antibodies, so the HIV antibody test will still be positive after 18 months.

PRACTICAL POINT

In children under 18 months, the diagnosis of HIV infection rests on clinical features in the baby and a positive HIV test in the mother.

10 3 COUNSELLING

A child with suspected HIV generally means a family with suspected HIV. Counselling therefore has to take into consideration the mother and, if possible, the father. See Chapter 9 for the issues for discussion with adults with suspected HIV.

Pre-test counselling

It is important to counsel the mother and obtain her consent before testing her blood (if the child is under 18 months) or the child's blood (if the child is over 18 months) for HIV. If her child tests HIV positive, then it is extremely likely that she is the source of infection and is HIV positive.

Consider the bad news for the mother when she hears that her child may have HIV infection:

- her child may have an incurable and fatal disease;
- she herself may have HIV;
- her husband may have HIV;
- any future children may have HIV.

Her decision to have a test or not is difficult. She will need time and support while she considers the advantages and disadvantages of a test. If she knows she is HIV-positive, the main advantage is that she can plan for the future. The main disadvantage is the fear that her husband may beat her or leave her if she tells him that she is HIV-positive.

PRACTICAL POINT

The mother may like to bring her husband for joint pre-test counselling. It is usually easier for a woman to tell her husband she may be HIV-positive than to tell him afterwards that she is HIV-positive.

Post-test counselling

Consider a mother whose child has TB and suspected or known HIV infection. See Chapter 9 for the issues for discussion relevant to anyone who tests HIV-positive. There are other issues specific to a mother who tests HIV-positive. These include the poor outlook for the child and the risk for future babies of HIV infection. About one third of children born to HIV-positive women are also HIV-infected.

When counselling women who are breast-feeding or who have delivered recently it is important to discuss breast-feeding. There may be a small risk of HIV transmission by breast-feeding. However, in many low-income countries, breast-feeding is still a safer alternative to bottle-feeding. For example, consider a child whose mother is HIV-positive and who lives in an environment where there is no clean water. The child is probably at higher risk of dying from diarrhoea if bottle-fed than from AIDS if breast-fed.

SUGGESTIONS FOR FURTHER READING

Chintu C, Bhat G, Luo C, et al. Seroprevalence of human immunodeficiency virus type 1 in Zambian children with tuberculosis.

Pedr Infect Dis J 1993; 12: 499-504

Sassan-Morokro M, De Cock KM, Ackah A, et al. Tuberculosis and HIV infection in children in Abidjan, Cote d'Ivoire.

Trans Royal Soc Tr Med And Hygiene 1994; 88: 178-181.

WHO AIDS Series 8. Guidelines for counselling about HIV infection and disease. Geneva, 1990.

WHO Global Programme on AIDS. Counselling for HIV/AIDS: a key to caring. Geneva 1995.

CHAPTER 11 PREVENTION OF TB

11 1 INTRODUCTION

From the public health point of view, the best way to prevent TB is to provide effective treatment to the infectious TB cases. This interrupts the chain of transmission. Good treatment programmes are the best prevention programmes. HIV-infected individuals are particularly susceptible to infection with *M. tuberculosis* and the development of TB. What are the ways of protecting people from exposure to TB in health care settings? What is the role of BCG? What is the role of preventive treatment? Can we do anything about those HIV-infected individuals who are already infected with *M. tuberculosis* and have a high risk of developing active TB? This chapter addresses these questions.

11 2 PROTECTION AGAINST EXPOSURE TO TB

Patients and staff in health units face daily exposure to TB. The risk of exposure is greatest in adult medical wards and TB wards where there are many PTB cases. Often the wards are crowded and badly ventilated. We do not yet know the size of this risk.

Prompt diagnosis and treatment of patients with sputum smear-positive PTB helps to reduce exposure to TB. Out-patient diagnosis and treatment of PTB patients avoids hospital admission. This is an advantage in decreasing exposure to TB in hospital wards. In some NTPs there is a move away from an in-patient intensive phase towards out-patient management.

Known HIV-positive health workers should not work with PTB patients. They should therefore not work in TB wards or adult medical wards.

11 2 1 Environmental Control

Good ventilation helps reduce TB transmission indoors. Sunlight is a source of ultraviolet light which can kill TB bacilli. So ideally, wards should have large windows.

PRACTICAL POINT

In wards, out-patient clinics, sputum collection rooms, and microbiology laboratories, keep the doors closed and the windows open.

11 2 2 Face-masks

A face-mask decreases the risk that the person wearing the mask can infect other people. So a TB suspect or a TB patient, if possible, should wear a mask if moving from one part of a hospital to another.

Often a health worker wears a mask for protection against TB, e.g. when working on the TB ward. In fact, a mask is generally not very good at protecting the person wearing the mask from inhaling other people's infectious droplets. The exception is when the health worker is supervising a cough-inducing procedure, e.g. bronchoscopy, or sputum induction using nebulised hypertonic saline.

11 2 3 Patient education

Health workers should teach TB suspects and TB patients simple measures how to decrease the risk of transmitting TB. These include covering the mouth with the hand when coughing, and using sputum pots with lids. When examining TB patients or suspects, ask them to turn their head to one side. This is to avoid the patient coughing directly at the health worker.

11 2 4 PTB suspects

In the majority of cases, PTB suspects attend as out-patients for the diagnosis of TB. In some cases it is necessary to admit PTB suspects to hospital. If possible admit them to a separate ward from other patients. There are often no facilities to separate PTB suspects from other patients. At least try to keep PTB suspects in a part of the ward away from other patients.

11 2 5 Patients with sputum smear-positive PTB

In many NTPs, sputum smear-positive PTB patients spend at least part, and often all, of the intensive phase of anti-TB treatment in hospital. Isolation of these patients in TB wards helps reduce the risk of TB exposure to other patients. Do not admit a patient to the TB ward until you have made the diagnosis of TB. In particular, a TB suspect with HIV infection and high susceptibility to TB should avoid exposure to TB. A TB suspect may not turn out to have TB.

11 3 THE ROLE OF BCG IN PREVENTING TB

11 3 1 General

BCG (Bacille Calmette-Guerin) is a live attenuated vaccine derived originally from *M. bovis*. The route of injection is intra-dermal. The usual dose is 0.05 ml in neonates and infants under the age of 3 months, and 0.1 ml in older children. In high TB prevalence countries, WHO recommends a policy of routine BCG immunisation for all neonates shortly after birth.

The benefit of BCG is in protecting young children against disseminated and severe TB, e.g. TB meningitis and miliary TB. BCG has little or no effect in reducing the number of adult cases of PTB.

11 3 2 BCG protection against TB in HIV-infected children

It is not known if HIV infection reduces the protection of BCG against TB in children. There is some evidence that conversion to a positive tuberculin test after BCG is less frequent in HIV-infected children. The significance of this finding for protection against TB is not clear.

11 3 3 BCG safety in HIV-infected children

There have been a few case reports of local complications and disseminated BCG infection after BCG immunisation of HIV-infected children. However, prospective studies comparing BCG immunisation in HIV-infected and uninfected infants showed no difference in risk of complications. So, in the vast majority of cases, BCG immunisation is safe.

11 3 4 WHO recommended policy on BCG and HIV

WHO recommended policy depends on the TB prevalence in a country, as shown below. In a high TB prevalence country, the possible benefits of BCG immunisation outweigh the possible disadvantages.

COUNTRY TB PREVALENCE	WHO RECOMMENDED POLICY
<i>high</i>	<i>BCG for all children (according to standard programme) except children with symptoms of HIV disease/AIDS</i>
<i>low</i>	<i>Do not give BCG immunisation to HIV-infected children.</i>

11 4 THE ROLE OF THE EXPANDED PROGRAMME ON IMMUNISATION (EPI)

BCG is not the only immunisation in the EPI which may help to protect a child against TB. Measles and whooping cough lower a child's resistance to TB. So whenever you treat a child for TB, check the child's immunisation record. If a child has not received scheduled immunisations, encourage the mother to bring him/her for immunisations, once symptoms of TB have resolved. WHO has collaborated

with UNICEF in establishing guidelines for immunisation. The recommendation for individuals with known or suspected asymptomatic HIV infection **is that they should** receive all EPI vaccines, according to national schedules.

11 5 PREVENTIVE TREATMENT

The aim of preventive treatment is to prevent progression of *M. tuberculosis* infection to disease. A 6 month course of preventive treatment with daily isoniazid (5 mg/kg) is effective. However, preventive treatment for all individuals infected with *M. tuberculosis* is not a recommended TB control strategy. It is not feasible to try to identify all individuals infected with *M. tuberculosis*. TB disease develops in only 10% of all individuals infected with *M. tuberculosis*. So it is not cost-effective to identify and treat all infected individuals in order to prevent disease in 10%.

However, it is possible to identify certain groups at high risk of progressing from *M. tuberculosis* infection to TB disease. It may be cost-effective to target preventive treatment at these high-risk groups.

11 5 1 Target groups for prevention treatment

Young children are at special risk, especially if they are HIV-infected. HIV infection, in children and in adults, is a potent cause of progression of *M. tuberculosis* infection to TB disease.

Infants of mothers with PTB

A breast-feeding infant has a high risk of infection from a mother with PTB, and a high risk of developing TB. The infant should receive 6 months' isoniazid treatment, followed by BCG immunisation. An alternative policy is to give 3 months' isoniazid, then perform a tuberculin skin test. If the skin test is negative, stop the isoniazid and give BCG. If the skin test is positive, continue another 3 months' isoniazid, then stop isoniazid and give BCG.

Children under 5 years of age

It is important to screen child house-hold contacts of adults with sputum smear-positive PTB (see Chapter 3). Screening identifies those children under 5 years of age without symptoms. Give these children 6 months' isoniazid preventive treatment. Children under 5 years of age with symptoms need investigation for TB. If investigations show TB, the child receives anti-TB treatment. If investigations do not show TB, the child should receive isoniazid preventive treatment.

HIV-infected individuals

Controlled clinical studies have shown that isoniazid preventive treatment reduces the risk of TB disease in HIV-positive individuals also infected with *M. tuberculosis*. The evidence of *M. tuberculosis* infection is a positive tuberculin skin test. In HIV-positive individuals, the extra benefit of a reduced risk of TB may also be a reduced rate of progression of HIV infection.

11 5 1 Role of isoniazid preventive treatment in HIV-positive individuals

The theoretical benefits of isoniazid preventive treatment are attractive. The table shows the potential disadvantages and necessary precautions.

POTENTIAL DISADVANTAGE	NECESSARY PRECAUTION
<i>risk of drug toxicity (especially liver damage)</i>	<i>do not give to people with chronic disease or who drink alcohol regularly</i>
<i>emergence of drug-resistance (if the patient has undetected TB disease and not just <i>M. tuberculosis</i> infection)</i>	<i>in all cases</i> <i>exclude TB disease by chest X-ray,</i> <i>in cases with cough</i> <i>of 3 weeks' duration or more by sputum microscopy</i>
<i>diversion of resources from NTP activities</i>	<i>funding must be from sources other than NTP (e.g. AIDS control programme, voluntary sector)</i>

There are limitations in the feasibility of isoniazid preventive treatment on a wide scale in developing countries like Nepal and India.

- a) Voluntary HIV testing is not widely available, so the number of suitable known HIV-positive persons is a small proportion of all HIV-positive persons.
- b) Resources are often inadequate to ensure satisfactory exclusion of TB disease, treatment compliance and patient monitoring for drug toxicity.
- c) When HIV-positive persons develop TB, we do not know how many are due to reactivation of old infection and how many to new infection. Isoniazid preventive treatment will protect against new infection only during the 6 months of treatment. So the effectiveness of a course of isoniazid preventive treatment will be limited if TB is often due to new infections.
- d) Many HIV-positive persons infected with *M. tuberculosis* have a negative tuberculin skin test. So screening for *M. tuberculosis* by tuberculin skin testing will not identify all persons infected with *M. tuberculosis*.
- e) HIV-positive persons who feel well may be reluctant to accept TB screening and consideration of isoniazid preventive treatment.

Isoniazid preventive treatment programmes need evaluation. We need to know their cost, sustainability, potential impact, and effect on drug resistance.

WHO does not at present recommend widespread isoniazid preventive treatment for HIV-positive persons in high TB prevalence countries. Isoniazid preventive treatment may have a role in selected groups (e.g. workers in a factory, health workers, soldiers) and in selected individuals.

SUGGESTIONS FOR FURTHER READING

WHO. Expanded Programme on Immunisation. Childhood tuberculosis and BCG vaccination. BCG - gateway to EPI. Geneva: WHO, 1989.

WHO. Global Programme for Vaccines and Immunisation. Immunisation Policy. Geneva, 1995.

WHO/IUATLD. Tuberculosis preventive therapy in HIV-infected individuals. A joint statement of the WHO Tuberculosis Programme and the Global Programme on AIDS, and the International Union Against Tuberculosis and Lung Disease (IUATLD). Weekly Epidemiological Record 1993; 68: 361-364.

O'Brien RJ, Perriens JH. Preventive therapy for tuberculosis in HIV infection: the promise and the reality. AIDS 1995; 9: 665-673.

CHAPTER 1 INTRODUCTION

At present the National Tuberculosis programme (NTP) in Nepal is not in a position to supply treatment to MDR TB patients. The focus of the programme is to prevent the emergence of MDR TB by implementing an effective NTP. All patients being treated for MDR tuberculosis must be supervised for the complete duration of treatment by a specialist with experience and skill in managing MDR TB. The patient and family must be told about the situation and the costs involved (about Rs 500,000) to treat a case of MDR TB with about 50% chance of cure. The total drug requirement must be bought before starting treatment and kept with the patient's supervisor. Ideally all NTPs should have a SPECIALISED UNIT to deal with the MDR TB cases. This section on MDR TB has been added to this manual because there is a lack of information about the correct use of the second-line drugs and many doctors have asked for information on treating MDR TB cases.

1 1 DEFINITIONS***Drug resistant tuberculosis***

This is a case of tuberculosis (usually pulmonary) excreting bacilli resistant to one or more antituberculosis drug.

In patients who have not had prior treatment with antituberculosis drugs, the bacterial resistance is called primary resistance (if it is certain that the patient has not had previous treatment). After the clinical assessment, if it is doubtful that the patient really has not received prior treatment, this is called initial resistance. Initial resistance is a mixture of primary resistance and undisclosed acquired resistance.

In patient with some record of previous treatment, the bacterial resistance is called acquired resistance.

In new patients, the WHO standard first-line regimens (6 months or 8 months) overcome the risk of failure due to primary resistance.

In the majority of the previously treated patients (more than one month), the WHO standard retreatment regimen (8 months) reduces the risk due to failure due to acquired resistance.

Failure of retreatment

The definition of failure of the WHO retreatment regimen is tuberculosis patient excreting bacilli after 5 months of chemotherapy given under direct observation by a health worker or after completion of the fully supervised 8-months retreatment regimen.

Chronic case

A chronic case is now defined by the failure of a **fully supervised** WHO retreatment regimen. A chronic case has received at least 2 courses of chemotherapy, and some times more than two courses (complete or incomplete). Chronic cases are usually, but not always, excretors of resistant bacilli (the rate of acquired resistance is high in this category of patients) and often excretors of MDR bacilli.

MDR bacilli and MDR tuberculosis

MDR bacilli are resistant to at least isoniazid and rifampicin, the main antituberculosis drugs. MDR is the most severe form of bacterial resistance today. It is why MDR tuberculosis is an important concern in many countries. [See Chapter 5 MDR TB]

1 2 HOW IS MDR TUBERCULOSIS PRODUCED?

As with other forms of drug resistance, the phenomenon of MDR is entirely man made.

Drug resistant bacilli are the consequence of human error in any of the following:

- prescription of chemotherapy
- management of the drug supply
- case management
- process of drug delivery to the patient

The most common medical error leading to the selection of resistant bacilli are the following:

the prescription of inadequate chemotherapy to the multibacillary pulmonary tuberculosis cases (e.g. only 2 or 3 drugs during the initial phase of treatment in a new smear-positive patient with bacilli initially resistant to isoniazid):

the addition of one extra drug in the case of failure, and repeating the addition of a further drug when the patient relapses after what amounts to monotherapy.

The most common errors observed in the management of drug supply are the following:

the difficulty experienced by poor patients in obtaining all the drugs that they need (due to lack of resources or social insurance); frequent or prolonged shortage of antituberculosis drugs (due to poor management and/or financial constraints in developing countries); use of drugs (or drug combinations) of unproven bio-availability.

The following also have effect of multiplying the risk of successive monotherapies and selection of resistant bacilli:

the patient's lack of knowledge (due to a lack of information or due to inadequate explanation before starting treatment)

poor case-management (when the treatment is not directly observed, especially during the initial phase).

1 3 HOW TO PREVENT MDR TUBERCULOSIS?

In new cases

The best prevention is to give each new case of sputum-positive pulmonary tuberculosis an effective regimen of short course chemo-

therapy (6 or 8 months course) with four drugs (isoniazid, rifampicin, pyrazinamide and ethambutol or streptomycin) during the least the first two months, given under direct observation.

WHO recommended regimen are as effective in patients with bacilli initially resistant to isoniazid and /or streptomycin as in patients with susceptible bacilli. The cumulative resistant rate of failure and relapse after 3 years is from 0%-4% in new cases, and 0%-3% in patients with initially susceptible bacilli and 0%-13% in patients with primary resistance.

Theoretically, infection with MDR bacilli will be the cause of failure of the very few individuals to respond to the initial regimen. Failure to respond because of infection with MDR bacilli represents an exceptional situation. Even when transmission of MDR bacilli from an 'old' patient to a new is clearly demonstrated, it has still not been documented that primary MDR contributes significantly to the treatment failure rate of WHO standard regimens for cases in programme conditions.

In old cases

In the group of tuberculosis patients previously treated with one or several courses of chemotherapy and who remain positive (by smear or culture), three subpopulations can be observed:

- patients excreting bacilli still susceptible to all antituberculosis drugs;
- patients excreting bacilli resistant to at least isoniazid, but still susceptible to rifampicin;
- patients excreting resistant to at least isoniazid, and rifampicin.

The respective proportion of the three subpopulations varies according to the chemotherapy applied in the community during the past years.

It varies also with the number of courses of chemotherapy received by the patients.

- a) In patients who have failed after the **first course of chemotherapy** (WHO recommended regimen or any other), the proportion of

patients excreting bacilli still susceptible to all drugs is higher than the proportion of the two other subpopulations. For this reason, the standard WHO retreatment regimen of 8 months (using 5 drugs for the first 2 months, then 4 drugs for the third month, then 3 drugs for the remaining 5 months of treatment i.e. 2 SHRZE/1 HRZE/5 HRE) given under direct observation, can cure the majority of patients: those having still susceptible bacilli, and those having bacilli resistant to isoniazid and/or streptomycin, but still susceptible to rifampicin.

- b) In patients who have failed after two courses of chemotherapy (the second being the fully supervised WHO retreatment regimen), the proportion of patients excreting resistant bacilli is the majority (up to 80%). The proportion of patients with MDR tuberculosis can be as much as 50% of this group of patients with bacterial resistance. For this reason, a second application of the standard WHO retreatment regimen is likely to fail.

ANNEX

CHAPTER 2 BASIC PRINCIPLES FOR MANAGEMENT OF MDR TUBERCULOSIS

2 1 SPECIALISED UNIT

Treatment of patients with MDR tuberculosis (especially those with resistance to rifampicin and isoniazid) may have to involve 'second line' reserve drugs. These are drugs other than the standard essential antituberculosis drugs, i.e. rifampicin, isoniazid, streptomycin, ethambutol, pyrazinamide and thioacetazone. These reserve drugs are much more expensive, less effective and have many more side effects than standard drugs. They should only be made available to a specialised unit and not in the free market. It is the responsibility of national health authorities to establish strong pharmaceutical regulations to limit the use of second-line reserve drugs in order to prevent the emergence of incurable tuberculosis.

2 2 DESIGNING AN APPROPRIATE REGIMEN

Designing an appropriate regimen for the individual patient needs experience and skill. It includes allocating the time and patience to define precisely the following.

- a) which regimen(s) the patient had received;
 - b) whether the patient took all the drugs in each regimen prescribed and for how long;
 - c) to find out what happened bacteriologically, in terms of sputum positivity during and after the administration of each regimen.
- Clinical and radiological progress or deterioration is much less reliable but may be used as a check on the bacteriological results.

2 3 RELIABLE SUSCEPTIBILITY TESTING

The specialised unit must have the services of a laboratory able to carry out culture and reliable tests for drug resistance (to the essential drugs and also to second-line drugs). The quality of the susceptibility tests carried out in this laboratory should be regularly checked by another reference laboratory at national or supranational level.

2 4 RELIABLE DRUG SUPPLIES

The unit must also be guaranteed reliable supplies of expensive 'second line' reserve drugs, so as to ensure that any treatment undertaken for the individual can be successfully completed.

2 5 PRIORITY PREVENTION

A country with limited resources may reasonably decide that its resources should be concentrated on ensuring that all patients complete the standard national treatment and are thereby cured. With good standard treatment meticulously administered, multi-drug resistance should not occur.

The proper assumption is that the emergence of **MDR tuberculosis is always due to medical error**: prescribing an unavailable regimen, using unreliable regimen, using unreliable drugs, or failing to ensure (by directly observed treatment and education of the patients and the family) that the patient takes the drug as prescribed and for the full period prescribed. **MDR tuberculosis should always be regarded as a result of failure of effective implementation of the national programme.** Top priority should be given to preventing such failure.

2 6 USING WHO STANDARD REGIMENS FOR NEW CASES AND RETREATMENT

The following patients should be given the WHO retreatment regimen: Patients with treatment failure after the standard national regimen; relapse; patients returning after premature interruption of treatment. The vast majority will be cured with this retreatment regimen. Most failures are due to the use of an incorrect regimen and/or failure to ensure that the regimen is fully administered and directly observed.

Very rarely may failure be due to initial resistance to three or more of the five drugs used in the retreatment regimen.

2 7 MDR TUBERCULOSIS AS A CONSEQUENCE OF POOR TREATMENT

In some countries MDR tuberculosis has arisen from poor treatment before the introduction of the National Programme or because some patients received poor treatment outside the National Programme. As a wide variety of different poor regimens may have been used for such patients, the MDR tuberculosis cases which arise will require detailed assessment by the specialised unit.

2 8 LONG-TERM INVOLVEMENT OF STAFF AND FINANCIAL RESOURCES

With these considerations in mind, **a specialised unit for dealing with MDR tuberculosis may reasonably be regarded as an expensive luxury which is only affordable where national resources are moderate or good.** If such a unit is set up a gross waste of resources will occur unless it is run by skilled and experienced specialist who are given ongoing long-term responsibility for it, and who work closely with a reference laboratory able to carry out reliable tests for drug resistance. It must be provided with the resources outlined above. An inadequately resourced unit can do more harm than good. It may perpetuate and spread MDR tuberculosis, with the result that tuberculosis patients and health workers lose confidence in the treatment.

The suspicion of MDR tuberculosis occurs in two situations:

- a) when you receive a report from a laboratory indicating at least “strains resistant to isoniazid and rifampicin”;
- b) when you observe in a smear-positive patient no response to the standard WHO retreatment regimen.

CONSIDERING THE CRITERIA OF FAILURE OF THE RE-TREATMENT REGIMEN

- **Persistently positive sputum** at 5-6 months of treatment
- **Fall and rise phenomenon:** Sputum smear initially becomes negative, and later becomes persistently positive.
- **Report of drug resistance:** Do not accept reports uncritically, labs may vary in reliability and errors may occur. Look at the clinical evidence, especially trends in sputum positivity.
- **Radiological deterioration?** Deterioration in a chest X-ray may be a sign of failure but deterioration may be due to one of the following:
 - a) intercurrent pneumonia
 - b) pulmonary embolism
 - c) supervening carcinoma
- **Clinical deterioration?** This is the least reliable evidence of failure. It may be due to many conditions other than tuberculosis. If there is no accompanying bacteriological or radiological deterioration, clinical deterioration is unlikely to be due to tuberculosis.

ANNEX

CHAPTER 4 AVAILABLE DRUGS FOR MDR TUBERCULOSIS

In general, in cases of failure or relapse following the WHO retreatment regimen, acquired resistance to isoniazid and rifampicin is highly likely. While waiting for the results of the susceptibility test, the physician must prescribe a regimen which initially does not contain isoniazid and rifampicin.

The chosen regimens will consist of a mix of essential drugs, and second-line drugs.

The choice of drugs depends on the interpretation of data collected from each individual patient.

4 1 ESSENTIAL ANTITUBERCULOSIS DRUGS

Streptomycin

Resistance to streptomycin has become less common since the wider use of ethambutol as a fourth drug in the WHO standard regimen for new cases, and the use of streptomycin only during the first 2 months in the WHO standard retreatment regimen.

Pyrazinamide

Resistance to pyrazinamide is neither easy to acquire nor to prove by susceptibility testing. As pyrazinamide has a bactericidal effect in an acid medium (bacilli inside macrophages), it would be wise to use pyrazinamide in combination with streptomycin or another aminoglycoside (active against actively multiplying bacilli, outside macrophages) to obtain a maximal bactericidal effect against all population (inside and outside macrophages).

Ethambutol

Ethambutol when they are used during the continuation phase of WHO standard regimens (all new cases and retreatment cases), are probably useless for the treatment of apparent MDR tuberculosis. If a reliable susceptibility test shows that ethambutol is still active, this bacteriostatic agent might be valuable as a companion drug for preventing the emergence of resistance to other active drugs.

Thiacetazone, a very poor bacteriostatic agent, has no place (except as a last resort) in the treatment of MDR tuberculosis. There is a risk of cross-resistance with thioamides and additional toxicity when thioacetazone is associated with thioamide. The risk of severe adverse reactions prohibit the use of this drug in HIV-positive patients.

4 2 SECOND-LINE ANTITUBERCULOSIS DRUGS

Second line antituberculosis drugs are applicable in the treatment of apparent or proved MDR tuberculosis.

Classes of second-line antituberculosis drugs

AMINOGLYCOSIDES

When resistance to streptomycin is proven or highly suspected, one of the other aminoglycoside can be used as a bactericidal agent against actively multiplying organism:

- kanamycin, the least expensive, but largely used for indications other than tuberculosis in some countries.
- amikacin, as active as kanamycin and better tolerated, but much more expensive.
- capreomycin, very expensive but very useful in cases with tubercle bacilli resistant to streptomycin, kanamycin and amikacin.

These are bactericidal agents of the aminoglycoside class. Cross resistance between kanamycin and amikacin is usual. The average daily dose is 15mg/kg body weight.

Adverse reactions:

These are similar to the side-effects associated with streptomycin and capreomycin. Ototoxicity, deafness or vertigo may occur. Reversible nephrotoxicity may occur.

Precautions:

In patients with impaired renal function. This drug should not be used in pregnant women except as a last resort.

ETHIONAMIDE

Ethionamide or prothionamide are 2 different presentations of the same active substance, with bactericidal activity. Prothionamide may be better tolerated than ethionamide in some population. These are bactericidal agents from the class thioamides. The optimal daily dose is 10-20 mg/kg.

Adverse reactions:

Prothionamide is generally considered to be less unpleasant and better tolerated than ethionamide. But adverse reactions are essentially similar. The main troubles are epigastric discomfort, anorexia, nausea, metallic taste and sulphurous belching. Psychotic reactions including hallucinations and depression may occur. Hepatitis may occur in about 10% of cases, but is rarely serious.

Precautions:

This drug should not be administered in pregnancy as it has been shown to be teratogenic in animals. It should be carefully monitored if given to patients with diabetes, liver disease, alcoholism or mental instability.

FLUOROQUINOLONES

Ofloxacin and ciprofloxacin are two different drugs, but with complete cross-resistance within the group. These drugs have a low bactericidal activity, and are useful in association with other drugs. The pharmacokinetics of ofloxacin are better than the pharmacokinetics of ciprofloxacin. Sparfloxacin should be avoided because of severe cutaneous side effects (photo-sensitisation). Norfloxacin should not be used, because it does not give adequate serum levels. Daily dose is 600-800 mg of ofloxacin (7.5-15 mg/kg) or 1000-1500 mg of ciprofloxacin during the initial phase. If the daily dose of ofloxacin (800mg) is poorly tolerated, the daily dose can be reduced to 400 mg during the continuation phase.

Adverse reaction:

Adverse reactions are uncommon but consist of gastrointestinal disturbance or central nervous system (such as dizziness, headache, mood changes).

Precautions:

These drugs should not be used in pregnant women and growing children. Because of drug interaction, the following drugs should be avoided: antacids, iron, zinc and sucralfate.

CYCLOSERINE (OR TRIZIDONE)

This is a bacteriostatic agent. It has no cross-resistance with other antituberculosis agents. It might be valuable to prevent resistance to other active drugs, but its use is limited by its high toxicity. The maximum daily dose is 15-20 mg/kg; the usual dose is 500-750 mg of cycloserine. The daily dose can be given in two intakes.

Adverse reactions

These include dizziness, slurred speech, convulsions, headache, tremor, insomnia, confusion, depression and altered behaviour. The most dangerous risk is that of suicide so mood should be carefully watched. Very rarely there may be generalised hypersensitivity reaction or hepatitis.

Precautions

Cycloserine should be avoided in patients with a history of epilepsy, mental illness or alcoholism. It should also be used very carefully in patients with renal failure.

PARA-AMINOSALICYCLIC ACID (PAS)

This is a bacteriostatic agent, valuable for preventing resistance to isoniazid and streptomycin in the past and to other bactericidal drugs today. PAS is bulky and unpleasant to take because of gastrointestinal discomfort. The daily dosage is 150 mg/kg or 10-12 gms daily in two divided doses.

Adverse reactions

The main adverse reactions are gastrointestinal disturbance and general skin or other hypersensitivity including hepatic dysfunction. Hypokalaemia may occur. Prolonged administration in large doses may produce hypothyroidism

and goitre as PAS has an antithyroid effect. These will reverse when the drug is withdrawn.

Precautions

PAS is best avoided in renal failure as it may make acidosis worse.

Others

Other drugs, sometimes mentioned as second line antituberculosis drugs, have no place in the treatment of MDR tuberculosis. These include rifabutin, which shows almost complete cross resistance with rifampicin, and clofazimine, which has no anti tuberculosis activity.

4 3 CROSS-RESISTANCE

Consideration of cross-resistance is important for selecting the drugs for treatment of apparent or proven MDR tuberculosis. As usual in the treatment of infectious diseases when the combination of several drugs is required, it is ineffective to combine two drugs of the same group or to combine in the prescribed chemotherapy regimen a drug potentially ineffective because of cross-resistance.

4 3 1 Thionamide and thioacetazone

Ethionamide, in the group of thionamides, induces complete cross-resistance with prothionamide. They should be considered as the same drug. Frequently there is also cross-resistance between thioamides and thioacetazone: strains naturally resistant to thioacetazone are usually still susceptible to ethionamide-prothionamide: strains resistant to ethionamide-prothionamide are usually resistant also to thioacetazone, in more than 70% of cases.

4 3 2 Amnioglycosides

- Strains resistant to streptomycin are susceptible to kanamycin-amikacin.

- Resistance to kanamycin induces a complete cross-resistance with amikacin: they should be considered as the same drug. Resistance to kanamycin-amikacin induces also resistance to streptomycin.
- Strains resistant to streptomycin, kanamycin, amikacin are still susceptible to capreomycin.

4 3 3 Fluoroquinolones

Ofloxacin, ciprofloxacin and sparfloxacin induce complete cross resistance for all fluoroquinolones. It is why the use of ofloxacin must be carefully considered, since some new more active quinolones (e.g. levofloxacin) could replace ofloxacin in the future.

There is no cross-resistance with other classes of drugs.

4 3 4 Cycloserine and terizidone

There is complete cross-resistance between these two drugs: They should be considered as the same drug. There is no cross-resistance with other classes of drugs.

5 1 BASIC PRINCIPLES

We assume that all patients **with apparent drug-resistance tuberculosis will have bacilli resistant to isoniazid.**

Patient with **additional resistance**, or suspected resistance, to streptomycin and/or thioacetazone (but not to rifampicin) should respond well to the WHO standard retreatment regimen (2HRZES/1 HRZE) in the initial phase.

The following therefore applies to MDR patients with **resistance to isoniazid and rifampicin**, patients considered to have **failed on the WHO standard retreatment regimen**, and other patients who have received a variety of bad regimens outside national programmes.

Such patients will often require the use of at least some **second-line drugs**. These drugs are less effective and have more side effects than the present standard essential drugs. It must be made clear to the patient and the staff that meticulously taking the prescribed reserve regimen is all that stands between the patients and death. The patients must try to tolerate any unpleasant side effects in order to achieve survival. He/she must agree to remain under direct observation, with each dose supervised, at least until the sputum is negative. The patient must receive clear and complete explanation before treatment, and permanent psychological support and attention.

In designing a regimen **do not aim to keep drugs in reserve**. That is the way to lose one battle after another. The patient has already lost several battles. This last battle must be won. As outlined above, decide to what drugs the patient's bacilli are, or likely to be, still sensitive. Then prescribe what is likely to be the most effective regimen available to him/her.

In the first place **prescribe drugs which the patient has not had previously**. The bacilli are fairly certain to be sensitive to these. The

practice of adding isoniazid to these drugs confers no advantage. The initial regimen should consist of at least three drugs, preferably four or five, to which the bacilli are likely to be fully sensitive, i.e. drugs not previously used for that patient.

Among these drugs, it is desirable to use in combination an injectable aminoglycoside (according to the rank of choice) and pyrazinamide (even if previously used, because resistance is usually unlikely). This combination has a good bactericidal activity. When the patient's sputum has converted to negative, you can withdraw one or more drugs, preferably a weaker drug which is causing side effects.

The treatment with these weaker drugs should be continued for at least 18 months after the sputum conversion to prevent relapse.

In any regimen, especially when weaker drugs are used, the treatment should be given daily and should be directly observed. It is also mandatory to monitor bacteriologically results (smear and culture) monthly from the second month until the sixth month, and then quarterly until the end of treatment.

5 **2** DOTS - PLUS

High levels of multidrug resistant TB (MDR-TB) in some areas threaten TB control efforts. MDR TB is TB that is resistant to at least isoniazide and rifampicin, DOTS-TB is a comprehensive management initiative, built upon the five elements of the DOTS strategy. However, DOTS-PLUS also takes into account specific issues, such as the use of second-line anti-TB drugs. The goal of DOTS plus is to prevent further development and spread of MDR-TB DOTS plus is not intended for universal application and is not required in all settings. The aim of implementation of DOTS-plus in selected areas with significant levels of MDR-TB is to combat an emerging epidemic. The underlying principle is that the first step in controlling MDR-TB is prevention by full implementation of DOTS. An effective DOTS-based TB control programme is a prerequisite for implementation of DOTS Plus.

5 3 EXAMPLES OF ACCEPTABLE REGIMENS IN PROGRAMME CONDITIONS

In programme conditions, even in specialised units in connection with reliable laboratory susceptibility test results are not obtainable immediately: a delay of 2-4 months is usual. Sometimes, the result cannot be obtained for various reasons: initial cultures negative or contaminated: failure in logistics (transport of specimens, temporary shortage of reagents etc.). In practice, two situations should be considered depending on the availability of susceptible test results.

5 3 1 Situation A : Susceptibility test results are not available before starting the new treatment

5 2 2 1 Principles of Treatment

The treatment regimen should include at least 4 drugs including an injectable agent and fluoroquinolone in initial phase, and at least 3 of the most active and best-tolerated drugs in the continuation phase. An initial phase of at least 6-8 months should be followed by a continuation phase of 12-18 months.

While drug susceptibility testing may not be available in some resource-limited settings, all efforts should be made to obtain an accurate essential drug susceptibility testing profile of patients failing short-course chemotherapy and chronic disease in order to confirm the presence of MDR. Programmes planning to implement the use of reserve drugs in a standardized regimen but unable to perform susceptibility testing should set up relationship with supranational laboratories until such facilities can be established locally.

Standardized regimens are the choice in settings where susceptibility testing of reserve drugs is not available. However, drug susceptibility testing is recommended in patients who fail the standardized regimen and, when possible, these cases should be referred to specialized centres for individualized treatment.

Use of regimens tailored to the susceptibility patterns of reserve drugs requires highly specialized laboratory and microbiological follow-up facilities that are not yet available in most resource-limited countries.

In Nepal, the NTP is using a 3rd line treatment regimen with 5 drugs in the intensive phase and 4 drugs in the continuation phase (see table below)

- In this situation, after a failure of the WHO standard retreatment regimen, a “third line” regimen should be prescribed containing:
 - at least **3 drugs never used:** kanamycin, ethionamide, ofloxacin.
 - and **pyrazinamide.**
- After bacteriological conversion (usually after three to four months), if the initial susceptibility test results cannot be obtained, the continuation phase during the 18 months should employ the two drugs best tolerated and more usually more active: ethionamide and ofloxacin. (table below)

Acceptable “third-line” regimen before (or without) susceptibility test results

Initial phase		Continuation phase	
<i>Drugs</i>	<i>Minimum duration in months</i>	<i>Drugs</i>	<i>Duration in months</i>
1 Kanamycin	8	1 Ethionamide	16
2 Ethionamide	8	2 Ofloxacin #	16
3 Pyrazinamide	8	3 Pyrazinamide	16
4 Ofloxacin #	8	4 Cycloserine	16
5 Cycloserine	8		

The daily dose of 800 mg can be reduced to 400 mg if poorly tolerated already using cycloserine

5 3 2 Situation B: susceptibility test results are available

Either before prescribing a new treatment, or during the initial phase of the regimen prescribed in situation A. Several regimens are acceptable, depending on the result of the susceptibility test.

5 3 2 1 Resistance to at least isoniazid and rifampicin

- Resistance to **isoniazid alone** or in **combination with resistance to streptomycin**

When the two most important antituberculosis drugs are not active, a five drug regimen is mandatory.

During the initial phase, use ethionamide plus ofloxacin plus another bacteriostatic drug (ethambutol if possible) with pyrazinamide and aminoglycoside available for a minimum of 3 months of until smear conversion.

During the continuation phase, use ethionamide plus ofloxacin plus another bacteriostatic drug for at least 18 months after smear conversion.

- **Resistance to isoniazid and ethambutol** (with or without resistance to **streptomycin**)

During the initial phase, use ethionamide plus ofloxacin plus another bacteriostatic drug (cycloserine or PAS) with pyrazinamide and an aminoglycoside available for a minimum of 3 months or until smear conversion. During the continuation phase, use ethionamide plus ofloxacin plus cycloserine (or PAS) for at least 18 months after smear conversion.

Acceptable "third line" regimen for the treatment of MDR Tuberculosis

<i>Resistance to</i>	<i>Initial phase</i>		<i>Continuation phase</i>	
	<i>Drugs</i>	<i>Minimum duration in months</i>	<i>Drugs</i>	<i>Duration in months</i>
• Isoniazid, rifampicin, streptomycin	1 aminoglycoside*	8	1 ethionamide	16
	2 ethionamide	8	2 ofloxacin #	16
	3 pyrazinamide	8	3 ethambutol	16
	4 ofloxacin #	8		
	5 ethambutol	8		
• Isoniazid, rifampicin, streptomycin, ethambutol	1 aminoglycoside*	8	1 ethionamide	16
	2 ethionamide	8	2 ofloxacin #	16
	3 pyrazinamide	8	3 cycloserine +	16
	4 ofloxacin #	8		
	5 cycloserine +	8		

* Kanamycin or amikacin or capreomycin

The Daily dose of 800 mg can be reduced to 400 mg if poorly tolerated

+ PAS if cycloserine is not available or too toxic.

Usually, reliable information on susceptibility of *M. Tuberculosis* to pyrazinamide is not available. But of the resistance to pyrazinamide is duly proven and compatible with clinical data, pyrazinamide should be stopped and cycloserine or PAS may be included in the regimen.

SUGGESTIONS FOR FURTHER READING

Regimen used by DOTS-Plus Pilot Project in Nepal (2005)

Standardized Regimen for Multi Drug Resistance TB Management Protocol

WHO. Guidelines for establishing DOTS-Plus Pilot Projects for the management of MDR-TB. Geneva 2000 (Who/CDS/TB2000.279)

DOTS-Plus Manual of NTP Nepal

ANNEX

CHAPTER 6 THE ROLE OF SURGERY

6 1 INDICATION FOR SURGERY

Surgery should be considered for a patient with bacilli resistant, or probably resistant, to all except two or three relatively weak drugs. Unfortunately many such patients will have too extensive disease and/or too poor lung function for surgery to be possible. If the patient has a large localised cavity with little other disease, reasonable lung function and only two or three (weak) drugs available, surgery should be seriously considered.

6 2 TIMING OF SURGERY

To avoid serious, and potentially fatal tuberculosis complication of surgery, operate when the bacillary population is likely to be at its lowest. If only a very weak regimen is available, experience has shown that the most favourable time is after two months' treatment.

6 3 ANTI-TUBERCULOSIS CHEMOTHERAPY AFTER SURGERY

After surgery, the same regimen should be continued for at least 18 months.

SUGGESTIONS FOR FURTHER READING

WHO. Guidelines for the management of drug-resistant tuberculosis. Geneva, 1997.