

Mycobacteria/Tuberculosis

Outline

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II. Nontuberculous *Mycobacteria* (NTM), or *Mycobacteria* Other Than *tuberculosis* (MOTT)

- A. Distinguishing features from *M. tuberculosis*
- B. Classification by Clinical Syndrome

Reference: Am J Resp Crit Care Med 2000. Diagnostic Standards and Classification of Tuberculosis in Adults and Children. 161:1376-1395.

I. Tuberculosis/*Mycobacterium tuberculosis*

A. BACKGROUND

1. History

- a. Described in ancient civilizations
- b. 1882—MTB identified by Koch
 - Provides basis for Koch's postulates—bacterial pathogenesis
- c. Dreaded disease with high mortality until 1946
 - Historical impact—responsible for 30% all adult deaths in Europe during 19th century
 - 4–6% decrease/yr in morbidity & mortality 2° improved living conditions and development of immunity in population
- d. 1946—streptomycin
- e. 1952—isoniazid
 - Doubled annual rate of decrease in morbidity & mortality

2. Current significance/economic impact

- a. Worldwide
 - $\frac{1}{3}$ to $\frac{1}{2}$ world population infected
 - Leading cause of death 2° single microorganism – now ? surpassed by HIV
 - 8–10 million new cases active disease/year
 - 2 million deaths/year = 4–5% all deaths (significant HIV and TB co-infection globally and deaths in such cases generally not attributed to or counted as TB)
- b. U. S.
 - 1882–1985 decline in incidence
 - 1985–1992 - steady increase in incidence
 - 1992 peak - 26,480 cases
 - Contributing factors: HIV(15–50% TB and HIV co-infected)
/homelessness/poverty/substance abuse/ drug resistance/immigration/erosion of public health infrastructure/lack of sustained research effort and understanding of the basic biology of the organism
 - 1992 - 2002 - 5% decrease/year; 2002–2003 - only 1.5% decrease - leveling off
 - increased proportion occurring in foreign-born - 53% in 2003 vs. 25% in 1980's and early 1990's – (rate in foreign born 5–7 times that in U.S. born)
 - decrease in incidence in U.S. born while incidence in foreign born relatively stable
 - decreased community transmission in U.S. especially in areas of high incidence of HIV;
 - foreign born cases acquired in country of origin

B. MICROBIOLOGY

1. Morphology

- a. Size—slender, rod-shaped organism, 0.2–0.4 x 2– 10 μm
- b. Not motile, not spore forming

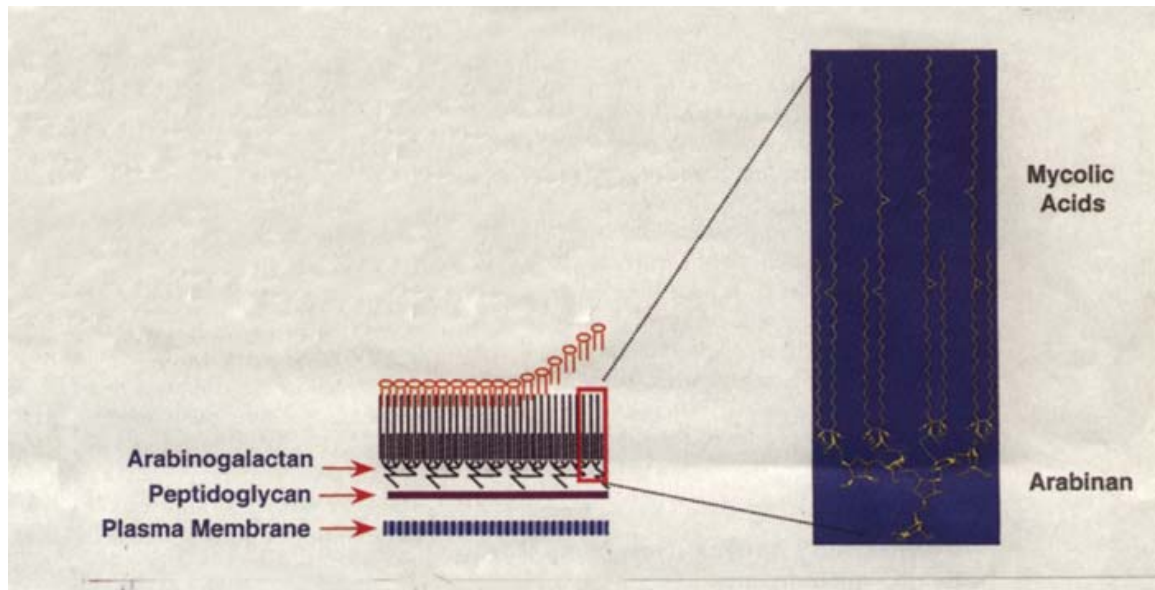


Fig. 1 *M. tuberculosis* cell wall structure

2. Unique cell wall (Fig. 1)—high lipid content
 - a. Mycolic acid (70–80 carbon fatty acids)
 - b. Arabinogalactan
3. Acid fast stain—to identify *Mycobacteria*
 - Relatively specific for *Mycobacteria* but doesn't differentiate MTB from other *Mycobacteria*; *Nocardia* weakly acid fast
 - a. High lipid content
 - Resistant to conventional staining procedures
 - ”Acid fast” = resistant to decolorization by acid alcohol/sulfuric acid
 - b. Types of stains used to identify *Mycobacteria*
 - Ziehl-Neelsen
 - Kinyoun
 - Rhodamine-auramine
 - c. Procedure
 - Heated and stained with a red dye such as carbol-fuchsin
 - Decolorization with acid alcohol
 - Counterstained with methylene blue
 - d. *Mycobacteria* appear red—resist decolorization = Acid-fast Bacilli (AFB)
 - Other bacteria appear blue—decolorized by acid alcohol
4. In vitro growth requirements
 - a. Complex medium containing eggs, vitamins, various sugars, among other components
 - b. Species traditionally differentiated by colonial morphology, nutritional requirements, and biochemical testing; now also done molecularly using DNA probes

5. Molecular level

- a. genetically homogeneous by polymorphism studies of structural genes → organism relatively young in evolutionary terms compared with more conventional bacteria
- b. Entire genome sequenced and found to consist of 4.4 million base pairs and contain about 4000 genes.
 - 40% proteins encoded for have known function by comparison with sequences of proteins of known function
 - 44% proteins encoded for similar to previously identified proteins
 - 16% proteins novel or resembled no known proteins
- c. General characteristics:
 - 1) relatively few (11) two-component sensor/response regulatory systems compared with ≥ 30 in *E. coli*
 - 2) eukaryotic-like systems - cytochrome p450 systems as in fungal organisms and serine/threonine protein kinases - also supports relative recent origins compared with conventional bacteria
 - 3) Drug resistance - sequences encoding β -lactamases, acetyl transferases, and drug efflux systems present - should facilitate effective drug development
 - 4) A very large portion of its genome (250 genes encoding 250 distinct enzymes) is devoted to the production of enzymes involved in lipogenesis and lipolysis which is consistent with the high lipid content of the MTB organism cell wall. Based on the identity of many of these enzymes, it is hypothesized that MTB uses mammalian host cells as a source of the lipids in its own cell wall. All of these enzymes represent potentially effective drug targets.
 - 5) Two unrelated families of proteins (400 genes) with a common repetitive sequence which resemble gene families responsible for high levels of antigenic variation in other micro-organisms

C. HOST DEFENSE MECHANISMS

—Same as those against respiratory-tract infections in general

**—Cellular immunity involving T-cells and macrophages

D. VIRULENCE FACTORS

1. High lipid content of cell wall—resistant to drying, acid, alkali conditions
—Killed by UV light, heating to 60°C for 30 min (pasteurization)
2. Growth requirements: strict aerobe/ \uparrow CO₂ (5–10%)/ pH 6.5–6.8/37°C not RT
—Favors growth within intracellular environment and in cavities to very high concentrations
3. Slow growth rate—doubling time 15–24 hr vs. 30 min of conventional bacteria
—Implications for clinical manifestations and treatment
 - a. Favors transmission and survival of microorganism;
 - Indolent process which allows infected host ample opportunity to transmit disease before diagnosis and treatment initiated
 - Prolonged use of antibiotics required to eradicate organism again allowing host to spread disease
 - b. Prolongs time to identify and determine drug susceptibility of organism
4. Latency/dormancy

- persistence of viable organisms resulting in reactivation years later
- 5. Intracellular pathogen
 - a. Not killed or incapacitated by being phagocytosed
 - b. Escape antibody or complement mediated mechanisms of host defense
 - c. Tropism for macrophages which are antigen- presenting cells (APC) allows manipulation of immune system
 - Evidence for two consecutive genetic loci which confers ability of bacteria to invade (850 base fragment) and survive (685 base fragment) in mammalian cells
 - Encodes 52kD protein whose distribution/ function not yet known (not yet demonstrated directly in MTB itself)
- 6. Prevention of acidification of intracellular vacuole, phagosome-lysosome fusion, and resistance to oxidative and nitrosative injury
 - a. Problem: major function of macrophages is to kill bacteria, other invaders; macrophages possess an arsenal of antimicrobial weapons including defensins, toxic oxygen/nitrogen radicals, acid pH, and enzymes—MTB must find a way to thrive in this environment
 - b. Following phagocytosis, MTB is enclosed in a compartment called a phagosome → proton-ATPase is incorporated into the phagosomes membrane → decreases pH → acidified phagosomes fuse with lysosomes which contain toxic enzymes that are activated upon exposure to acidic pH
 - c. MTB prevents insertion of proton-ATPase into phagosomes and thus activation of potentially toxic enzymes—mechanism not yet clear; prevents the fusion of phagosomes with lysosomes, and are resistant to reactive nitrogen intermediates
- 7. Phagocytosis by macrophages does not result in TNF α production which is highly effective in containing MTB
- 8. MTB within macrophages do not activate CD4(+) T-cells which have been sensitized to MTB—
 - ? by blocking antigen presentation—either processing of MTB antigens themselves or appropriate MHC product, ? role of lack of acidification on Ag processing
 - Allows persistence of organism even in the presence of cell mediated immunity to MTB
- 9. Persistence – 2 recently reported bacterial genes prevent MTB's ability to persist in mice
 - a. isocitrate lyase (*icl*) – enables MTB to use fatty acids as a carbon source
 - b. cyclopropane synthetase (*pcaA*) – required for mycolic acid synthesis

E. TRANSMISSION/RISK OF INFECTION

- Humans are only significant reservoir
- 1. Inhalation of droplet nuclei—aerosolized particles of respiratory secretions 2° coughing, sneezing, talking—predominant mechanism
 - Remain suspended for ≥ 30 min and are small enough in size to bypass physical barriers in respiratory tract and reach alveoli
 - a. GI tract—ingestion of contaminated milk— unusual
 - b. Skin exposure—unusual
- 2. Risk of infection
 - a. Likelihood of infection directly proportional to exposure to organisms and generally requires prolonged exposure—AFB (+) > culture (+) > extrapulmonary

- b. 50% children who were household contacts of AFB(+) patients were PPD(+) vs. >90% with varicella or close to 100% with pertussis
- 3. Infection vs. active disease
 - a. Time—risk of disease highest in first year following infection ~ 3%
 - 54% of those who develop active disease do so within 1 yr of infection and 80% within 2 years—implications for treatment to prevent active disease
 - b. Age—risk of disease varies with age—greatest in infants < 6 mo
 - Lowest in adults 25–60 y/o
 - c. Nutritional status, underlying disease, immunosuppression affect risk
 - ~ 10-15% risk of active disease over lifetime in immunocompetent host vs. ~ 80% in HIV(+) host

E. PATHOGENESIS/PATHOPHYSIOLOGY

1. 1° infection—Unimpeded replication and dissemination
 - After reaching alveoli, replicate both extracellularly and intracellularly unimpeded for several weeks 2° lack of host immune response
 - Potential mechanisms described above
 - Also no known exo- or endotoxins
 - Disseminate through lymphatics and then hematogenously through entire body
2. Development of immune response—6–14 weeks after initial infection
 - ? 2° critical mass of organisms
 - Cellular events—eventually CD4(+) T lymphocytes become activated → replicate and production of cytokines → recruit and activate macrophages at sites of infection
 - Activated macrophages kill MTB and can cause host tissue damage
 - Activated macrophages encircle MTB foci to contain infection
 - Fuse to form multinucleated giant cells called Langhans cells
 - Form tubercles or granulomas histologically
 - Lesions become fibrosed
3. Clinical events—1° infection
 - a. Patients asymptomatic or have mild viral-like syndrome during this process
 - Accompanied by enlargement of hilar and peribronchial lymph nodes and pulmonary infiltrates
 - b. Resolution of infection—most common
 - Older children and immunocompetent adults
 - Ghon complex—fibrosis and calcification of a peripheral lung focus and hilar lymph nodes—Correlates with the development of a (+) PPD and usually no evidence of active disease
4. Progressive 1° disease
 - In very young children and/or immunocompromised, the initial infection often does not resolve but progresses to active disease
 - Differs from reactivation disease (see below) in that miliary or disseminated disease, central nervous system (CNS) involvement, and pleural disease in the absence of pulmonary parenchymal involvement are more common
5. Persistence of viable organisms—usual scenario

- a. Despite containment of infection and lack of active disease, organisms remain viable but dormant for years, perhaps by being sequestered from CD4(+) T-cells which have been sensitized to MTB
- b. Can persist at disseminated foci 2° dissemination of organism throughout entire body during initial phases of infection
 - Certain sites favorable for persistence of organism—lung apices, lymph nodes, meninges, bones, kidneys—correlates with common sites for reactivation disease
 - Accounts for subsequent development of active disease at both pulmonary and extra-pulmonary sites
 - Patients clinically asymptomatic
 - 85-90% of immunocompetent patients infected will **never** develop active disease! → the end of the TB infection
- 6. Reactivation disease—remaining 10-15% infected individuals
 - a. Occurs following period of weeks–months but may be decades
 - Frequently in setting of underlying illness, particularly those which result in immuno-compromise or in the case of the elderly, waning immunity against MTB
 - e.g. HIV, steroid use, transplantation, malignancy
 - b. Balance between host defense mechanisms and virulence of MTB tips in favor of MTB organism
 - Due to mechanisms not yet clear, cellular immune response no longer able to contain MTB organisms → proliferation and spread of organism, tissue destruction resulting in clinically evident disease
 - c. Location of disease
 - 1. Pulmonary (parenchymal)—~85%, most frequently apical-posterior
 - 2. Extrapulmonary—~15%
 - Lymph node, pleural*, bone/joint, miliary, GU, CNS (meningeal)
 - Can have both
 - d. Pulmonary cavity formation
 - 1. Replication of MTB induces inflammatory response consisting of an alveolar exudate containing inflammatory cells → caseating necrosis, which liquefies and drains into bronchial tree → cavity formation
 - 2. Allows concentration of organisms to reach enormous titers (10^9 – 10^{11} organisms/gram tissue) 5–6 LOG fold greater than noncavitary lesions—implications for spread and treatment of disease
 - e. Localized spread of disease predominates e.g. via bronchial tree vs. lymphatic, hematogenous spread with 1° infection
- 7. Exogenous reinfection
 - a. Previous infection/immunity ([+] PPD) confers some protection
 - b. Occurs in high-risk settings
 - 1. High level of exposure—developing countries, homeless shelters,
 - 2. Waning immunity—underlying illness, elderly

F. CLINICAL MANIFESTATIONS

- 1. Pulmonary disease
 - a. Early reactivation—generally asymptomatic

- b. Systemic symptoms predominate and precede pulmonary symptoms in onset—fever, fatigue, weight loss, anorexia, chills, night sweats
- c. Pulmonary symptoms—nonspecific
 - Productive cough—usually 2° bronchial irritation from inflammatory secretions
 - hemoptysis—erosion of bronchial wall
 - Pleuritic chest pain—extension of inflammation to pleura
- d. Physical Exam
 - Fever, cachexia, often otherwise unremarkable
 - With extensive pulmonary cavity formation, parenchymal involvement, may find signs of consolidation
- e. Laboratory findings
 - Mild anemia
 - Normal WBC, normal differential
 - Elevated ESR
 - (+) direct exam of sputum for AFB
 - (+) sputum culture for MTB
- f. X-ray—nonspecific
 - Suggestive—apical infiltrates or cavities, hilar adenopathy
- 2. Extrapulmonary Disease
 - Due to dissemination of MTB during initial stages of infection
 - All characterized by systemic symptoms (same as pulmonary disease)
 - Diagnosis best made by biopsy and culture of involved tissues
 - Lymph node, pleural*, bone/joint, miliary, GU, CNS (meningeal)
 - a. Lymph node—seen in progressive 1° or reactivation disease
 - Involves cervical nodes
 - Diagnosis—biopsy of node
 - b. Miliary—diffusely disseminated disease vs. localized disease
 - Progressive 1° or hematogenous dissemination from a localized site of disease, particularly in the setting of significant immune compromise
 - Huge number of granulomas in tissues resemble millet seeds, hence “miliary”
 - Often no grossly evident or localizing lesions
 - c. CNS—meningitis most common
 - Progressive 1° or reactivation disease
 - 75% have evidence of disease elsewhere
 - Headache, altered mental status
 - Cerebrospinal fluid (CSF) profile
 - Glucose normal or ↓
 - Protein ↑
 - Pleocytosis with lymphocytic predominance
 - *Direct exam for AFB and culture often negative!
- 3. Distinguishing characteristics of TB in patients infected with HIV
 - a. ↑↑ risk of active disease following infection
 - ≥ 80% risk over lifetime vs. ≤ 15% for immunocompetent hosts
 - b. ↑ risk of progressive 1° disease but reactivation still more common

- c. ↑↑ incidence of extrapulmonary disease (50% vs. 15%)
- d. Lack of inflammatory response → cavitory pulmonary disease much less common
- e. concurrent initiation of HAART for HIV, and restoration of immunologic function, results in paradoxical “worsening” of TB following initiation of appropriate treatment – does not necessarily indicate drug resistant TB or ineffective Rx. Many symptoms of infectious diseases due to host defense or immune response; also likely decreases risk of active disease

G. TUBERCULIN SKIN TESTING

1. PPD = purified protein derivative
 - a. Protein extract derived from MTB—containing multiple antigens
—Standardized by biological activity
 - b. Types of skin tests—Mantoux,* Tine—not reliable
 - c. Mantoux = administer known amount of material intradermally on the volar aspect of the forearm and measure delayed hypersensitivity to MTB organism by the development of induration at the site
 - d. (+) reaction occurs if CD4(+) T-cells are sensitized to MTB and activated, and recruit and activate macrophages to site of antigenic challenge = induration
2. Interpretation of skin test—measured by mm of induration 48–72 hr after administering antigen
 - < 5 mm = nonreactive or negative
 - ≥ 5 mm = positive in patients at highest risk for TB
 - Close contact with recently documented cases of infectious TB
 - Infected with HIV or at high risk for infection with HIV
 - With chest x-rays highly suggestive of old TB
 - ≥ 10 mm = positive in patients with some risk for TB
 - including those who have received BCG
 - ≥ 15 mm = positive in patients without identifiable risk factors for TB
3. Only cause of reactivity to PPD other than infection with MTB is infection with nontuberculous *Mycobacteria*
4. BCG (see more under “Prevention”)
 - Conversion of TB skin test following BCG < 80%
 - Mean reaction to PPD is <10 mm
 - If PPD is reactive, reaction is markedly reduced or absent after 5-6 years
5. False negative—↓ ability to respond to tuberculin
 - Often reflects a decrease in cell-mediated immunity
 - Anergic = failure to respond to PPD or controls and invalidates test as measure of infection with TB
 - a. Improper administration or reading
 - b. Concurrent infection—viral, bacterial
 - c. Malnutrition
 - d. Immunosuppression—drug-induced, underlying disease
 - e. Age
 - f. Overwhelming infection with TB

6. Booster effect

- a. Phenomenon most common in patients >55 y/o, which reflects waning immunity or sensitivity to MTB over time that is boosted by skin testing
- b. Initial skin test following prolonged absence of exposure to MTB is nonreactive or <5 mm induration; this antigenic challenge of MTB “boosts” previously existent immune response to MTB and results in a positive result on subsequent testing and appears to be a “conversion” from a negative to a positive PPD
- c. **Cannot make a truly negative or noninfected patient have a positive or reactive skin test—no harm in repeat testing**

H. DIAGNOSIS

1. History/physical exam—risk factors, symptoms/ signs
2. Tuberculin skin testing
3. Interferon γ production by WBCs of infected patients when exposed to MTb antigens – recently FDA licensed test
4. Appropriate specimen for direct exam for AFB and histopathology
5. Culture
6. Nucleic acid based tests (PCR, DNA probes)

I. TREATMENT

—Clinical Classification of Infection with MTB— implications for treatment

1. (+) Exposure, no evidence of infection (PPD[-])
 - a. Generally requires no Rx
 - b. Recent ($\leq 2-3$ mo) requires repeat testing
 - c. High risk, e.g., young children may be initiated on Rx regardless
2. (+) infection (PPD[+]), no evidence of active disease = Latent TB infection (LTBI)
 - a. Critical to evaluate for presence of active disease \rightarrow implications for Rx
 - Symptoms, chest x-ray
 - b. Goal is to treat those at highest risk for developing active disease to prevent this from occurring
 - Risk and cost of Rx precludes treatment of all patients in this category
 - c. Most recent guidelines/recommendations for the management of latent tuberculosis infections released in 2000
 - treatment of latent TB infection (LTBI), no longer “preventive or prophylaxis”
 - emphasis on targeted testing
 - multiple treatment regimens
 - d. Indications for Treatment of (+) PPD - No Active Disease

Groups for whom benefits of treatment > risks/expense or adverse effects of Rx:

Two categories: 1) Those likely to have been recently infected

- 2) Those with increased risk of progression from latent TB infection (LTBI) to active disease

Those with likely recent infection:

- 1) recent development of reactive PPD (≤ 2 years)
- 2) close contacts of recent known cases of infectious TB
- 3) Persons who live or work in institutional settings where TB exposure likely (hospitals, prisons, homeless shelters, nursing homes)
- 4) Children < 5 y/o

Those with increased risk of progression to active TB:

- 1) previously untreated patients with history of prior TB or chest x-ray evidence of prior TB
 - fibrotic changes
 - apical scarring, calcified granuloma alone not indication for Rx (no demonstrable increased risk of progression to active TB)
- 2) immunosuppressed - HIV, drug-induced,
- 3) underlying disease associated with \uparrow risk of active disease
- 4) *Immigration within 5 years from areas with high rates of TB*
- 5) *Children, adolescents, and young adults** (formerly < 35 y/o)
- 6) *Underweight persons ($< 10\%$ under ideal body weight)*
- 7) *Injection drug users (increased risk independent of HIV e.g. HIV seronegative)*

e. Isoniazid (INH) x 9 months – preferred regimen

-regimen with which there is most experience in this situation;

f. Other drugs/regimens appear effective:

- 1) Rifampin x 4 mos
- 2) Rifampin/PZA x 2 mos - no longer recommended due to increased hepatotoxicity

g. Use of single agent effective - relatively low # organisms, \downarrow incidence of resistance

- not 100% effective (≈ 60 -80%)

3. (+) Infection, active disease

TREATMENT PRINCIPLES/REGIMENS FOR ACTIVE *M. TUBERCULOSIS* DISEASE

A. Principles

- *1. Multiple drugs - MUST ALWAYS use at least 2 effective drugs to eradicate disease.
- *2. Prolonged course of treatment - ≥ 6 months.
 - a. High incidence of spontaneous drug resistance ($1/10^6$ - $1/10^7$).
 - b. Unusually high organism load with cavitary disease 10^9 - 10^{11} organisms/gram of tissue.
 - c. Slow rate of replication - requires long time to eradicate - ample opportunity for resistance to develop.

3. All initial M. tuberculosis isolates should undergo antimicrobial susceptibility testing and therapy should be dictated by this information.
 - a. Drug resistance is a major problem and consideration.
 - b. From the early 1980's through the early 1990's there was a 6 fold increase in the incidence of resistant isolates which has been largely reversed due to the implementation of various measures such as directly observed therapy (DOT) or supervised treatment.

	<u>U.S.</u>	<u>NYC</u>
<u>1992</u>		
≥1 drug resistant	14%	33%
multi-drug resistant (MDR)*	2.8%	19%
<u>2002</u>		
≥1 drug resistant	14%**	16%**
multi-drug resistant (MDR)	1.3%	3.3%
*resistant to both isoniazid and rifampin		
** 1997 data		

- c. In 1991, only 13 U.S. states reported MDR TB. By 1997, 42 U.S. states reported MDR TB, only part of which may be explained by increased susceptibility testing of M. tuberculosis isolates.
 - d. No consistent susceptibilities.
 - e. A major challenge is the length of time required to determine susceptibilities; conventional procedures require weeks.
 - Susceptibility is not available at time of diagnosis, therefore, empiric treatment must be initiated.
4. Public health measures are an essential component of treatment.
 - a. Earlier identification of active cases.
 - b. Respiratory isolation until non-infectious.
 - c. Aggressive contact tracing, testing, and evaluation of all contacts.
 - d. Directly observed therapy (DOT).

B. Regimens

1. Initial treatment - 4 drugs (if rate of INH resistance $\geq 4\%$ or unknown - most of U.S.).
 - a. Given current prevalence of drug resistance, $\geq 95\%$ patients will be effectively treated on such an empiric regimen.
 - b. Results in more rapid sputum conversion even with susceptible organisms.
 - c. Can be given intermittently from beginning of therapy - practical implications for directly observed therapy (DOT).
 - d. Decreases the likelihood of emergence of drug resistance.

→ Isoniazid, rifampin, pyrazinamide, ethambutol

M. tuberculosis isolated from patients following 14 days of effective treatment appear to no longer be infectious and patient no longer requires isolation.

2. M. tuberculosis isolates susceptible to all drugs - requires minimum of 6 months treatment.
 - a. Pyrazinamide MUST be used for the first two months of treatment.
 - b. INH and rifampin MUST be used for the full 6 months.
 - c. Drug toxicity can prevent use of these drugs and necessitates longer course of treatment.
3. Extrapulmonary disease - controversial recommendations but treatment as for pulmonary disease probably effective (generally lower organism load).
 - a. Corticosteroids useful in TB pericarditis and meningitis.
4. Multi-drug resistant TB.
 - a. Often due to noncompliance with treatment and selection for resistant organisms.
 - b. Must ALWAYS start ≥ 2 new drugs to which organism is susceptible.
 - c. Requires prolonged respiratory isolation and duration of treatment (≥ 18 -24 months).
 - d. Must document and continuously monitor absence of organisms in sputum.
 - e. High mortality rate.
5. Compliance with treatment - major challenge.
 - a. Typical regimen consists of 12 pills for minimum of 6 months, frequently longer.
 - b. Treatment should be supervised whenever possible (DOT or directly observed therapy) - associated with higher success rates of treatment.
 - c. No correlation between socioeconomic status and likelihood of compliance.

J. PREVENTION—BACILLUS CALMETTE GUÉRIN (BCG) VACCINE

1. Live, attenuated or relatively avirulent strains derived by cultivating the organism in vitro for prolonged periods of time
 - originally produced at Pasteur Institute in France by Calmette and Guérin
2. Problems
 - a. Studies do not consistently demonstrate efficacy of BCG vaccine
 - Ranges from negative benefit to 80% protection
 - No standardized strain, procedure for making strain
 - Cellular/molecular components of organism which induce immunity not known
 - b. relatively short-lived protection
3. Studies highly suggestive that BCG vaccines protect infants and young children from more serious forms of TB such as meningitis
4. Usually given in early childhood or upon entry to school
5. Adults who have previously received BCG and are PPD(+) should generally be considered infected and managed accordingly
 - Reasons discussed above
 - Setting in which BCG would be given is also setting in which one is at significant risk for truly acquiring infection with MTB

II. Nontuberculous Mycobacteria (NTM) or Mycobacteria Other than Tuberculosis (MOTT)

"Atypical mycobacteria" – misnomer

- *Mycobacterium leprae* – cause of leprosy
 - *Mycobacterium avium complex* (MAC) or *mycobacterium avium intracellulare* (MAI) most common
 - Rapid growers becoming a more common problems with wound /cutaneous infections
- A. General distinguishing characteristics from MTB
1. Differentiated from MTB microbiologically/biochemically –
 - e.g. niacin negative
 2. Ubiquitous in soil, H₂O, food, etc.
 3. NO person-person transmission
- B. Classification by major clinical syndromes
1. Pulmonary Disease
 - *M. avium complex*
 - *M. kansasii*
 2. Lymphadenitis
 - *M. avium complex*, *M. scrofulaceum*
 3. Skin/Soft Tissue
 - *M. fortuitum*, *M. chelonae*, *M. abscessus*, *M. marinum*
 4. Disseminated Disease
 - *M. avium complex*, *M. haemophilum*