

Drug Resistant Tuberculosis

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Introduction

- 1940s – introduction of anti-TB chemotherapy, turning point in the history of the disease
- Soon followed by resistance
- 1950s – combination chemotherapy, drug resistance became less important
- 1970s – introduction of rifampicin

Mechanisms of resistance

- Random single-step spontaneous mutations of mycobacterial house-keeping genes
- Low predictable frequency
 - 1 in every 10^8 cell divisions for rifampicin
 - 1 in every 10^6 for isoniazid
- Drug resistance due to sequential accumulation of such mutations

Mechanisms of resistance

- Wild isolates of MTB never exposed to anti-TB drugs not clinically resistant
- Few exceptions but thought not to contribute significantly to overall burden of resistance
- Exposure to single drug – permits multiplication of preexisting drug mutants

Mechanisms of drug resistance

- Acquired drug resistance - Resistance among previously treated cases
- Primary drug resistance – Resistance among new cases

TB drug resistance

A man-made consequence of

- inappropriate chemotherapy
- erratic drug supply
- poor patient management
- poor patient adherence
- misuse of TB drugs
- poor TB control

Definitions

- MDR-TB
 - In vitro resistance to isoniazid and rifampicin, with or without resistance to other drugs
- Rationale for strict definition
 - Isoniazid, the most powerful mycobactericidal drug, ensures early sputum conversion, thus helps decrease the transmission of TB
 - Rifampicin, mycobactericidal and sterilizing action, crucial for preventing relapses

Definitions

- **Definition**
 - “XDR TB” defined as MDR TB that also has resistance to ≥ 3 of 6 major classes of SLDs (tested) (*Shah et al*)
 - **Amikacin or Kanamycin (AG)**
 - **Capreomycin (CM)**
 - **Ciprofloxacin or Ofloxacin (FQ)**
 - **Ethio/prothionamide (TA)**
 - **Cycloserine (CYS)**
 - **PAS**

MDR-TB Challenges

- 2nd line drugs less effective, expensive, toxic
 - Drug costs SA
 - R 350 (Drug-susceptible TB, new)
 - R 800 (Drug-susceptible TB, reRx)
 - R20 000 - R30 000 (MDR-TB, standardised)
- Limited number of 2nd line drugs available
- 2nd-line drug susceptibility testing not standardised
- Prolonged treatment required (up to two years)
- Patients typically difficult, often with social problems
- Case-holding a major problem
- Ethical and legal dilemmas

Epidemiology of MDR-TB in S.A

- National survey by MRC 2001 – 2002
 - New: 1.6% (range 1.0% - 2.6%)
 - Retreatment: 6.6% (range 4.0% - 13.9%)
 - Treatment failures: 39.9% any drug resistance
25.5% MDR
- 6 000 MDR cases annually
- Risk factors identified
 - Previous TB treatment
 - Hospitalisation
- MDR-TB 'hot spots' in several provinces
 - 3% or higher among new patients or total cases >500

Diagnostic Principles-MDR-TB

- MDR-TB is ALWAYS a laboratory diagnosis
- Culture and DST required for
 - Retreatment patients
 - Patients failing to convert
 - Close contacts of MDR-TB cases
 - Risk groups (MDR-TB contacts, health care workers)
- MDR-TB ≠ Nontuberculous mycobacteria

Management Principles-MDR-TB

- **Patient identification**
 - Culture and DST (H, R, E) for all retreatment, failure and non-converting patients, and risk groups
- **Standardised regimen**
 - High MDR-TB burden, limited expertise
 - Limited use of 2nd line drugs
 - Background resistance levels low
- **Restricted use of 2nd line drugs**
 - Centralised procurement and availability
 - Restricted prescription

Management Principles-MDR-TB

- Hospitalisation until culture conversion / at least during intensive phase
- Dedicated MDR-TB wards/centres with MDR-TB management teams
 - Administrative measures, infection control, collective decisions on ethical/legal issues
- Dedicated discharge network (primary health care clinics), drugs by prescription only
- Electronic MDR-TB Register for monitoring & evaluation
 - Patient details, treatment, bacteriology, adherence, drug adverse effects, outcomes, management reports

Challenges with XDRTB

- Extent of the problem unknown
 - Sampling bias
 - No true denominator; not possible to determine case rates, only case counts
 - Differing indications for SLD testing (all patients, failures/retreatment cases, only MDR isolates)
- May be virtually untreatable
- Diagnosis – laboratory capacity, rapid diagnostic tests
- Infection control
- Resources – diagnosis, management, extent of contact tracing and infection control measures

Transmission of drug resistant TB

- Significant challenges facing those committed to controlling MDR-TB is understanding more about infectiousness of resistant strains
- What is the relative infectiousness of resistant strains of MTB compared to sensitive strains?
- Are drug resistant strains as virulent as drug susceptible strains?

Transmission of drug resistant TB

- **Conflicting epidemiological evidence**
 - Cases of MDRTB in some settings appear to cluster less than sensitive strains
 - Molecular fingerprinting in some studies suggested reduced propensity for clustering
 - Longitudinal and some molecular studies, however suggested higher cluster rates with MDRTB
- **Animal studies 1950s, invitro research on virulence**
- **Epidemiological evidence of clustering contradicts this notion , other research has also shown that resistance may not attenuate pathogenic behavior**

Diagnosis of drug resistant TB

- Detection of drug resistance in MTB remains a “bottleneck” in the management of cases of TB
- Currently – culture and susceptibility testing, TAT 30 days
- Research efforts are directed to finding ways to speed up process of susceptibility testing while limiting costs and complexity of methods

Diagnosis of drug resistant TB

- Phenotypic techniques
 - employ novel markers to indicate changes in mycobacteria physiology, can be utilized directly on clinical specimen, mycobacteriophage based methods
- Genotypic approaches
 - detect genetic determinants of drug resistance, potentially rapid results
- Rifampicin resistance is the most amenable to rapid genotypic diagnosis and research has focused on this aspect
- Rifampicin resistance is a surrogate marker for MDR-TB

Resistance genes

- INH – catalase peroxidase gene (katG), inhA gene, alkyl hydroperoxidase
- Rifampicin – RNA polymerase beta subunit (rpoB)
- Streptomycin – mutations in 16S RNA
- Pyrizinamide – nicotinamidase gene (pncA) gene
- Quinolone – DNA gyrase A subunit (gyrA) gene
- Ethambutol – embB gene

Challenges with new diagnostic tests

- Criteria to be considered when considering applicability in clinical microbiological settings include
 - High intralaboratory and inter-laboratory reproducibility in distinguishing resistant and susceptible strains
 - Applicability of biosafety measures
 - Minimal investment is special equipment and supplies
 - Minimal labor time
 - Ability to perform numerous tests simultaneously

Isoniazid Preventive Therapy

- Latent infection
- Advantages
 - IPT decreases the risk developing TB by 40% in those who take it
 - The screening before IPT is given helps to detect TB
 - Very low risk of resistance if effective screening for active TB is done
- Disadvantages
 - Risk of non adherence
 - Risk of resistance if poor screening for TB