DM SEMINAR
JULY 29, 2005

MDR TB AT EXTRAPULMONARY SITES – Current Concepts & Literature Review

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HEADINGS

- Salient features of EPTB
- Salient features of MDR TB
- Prevalence & Epidemiology of MDR EPTB
- Diagnosis of MDR in EPTB
- MDR at specific sites in EPTB
- Treatment of MDR EPTB

Overview of EPTB

EPTB - Overview

- From the initial phase of invasion of human lung, *M. tuberculosis* can disseminate through lymph vessels or bloodstream to any organ or tissue in the body
- Extrapul inv can occur in isolation or along with a pul focus (latter classified as PTB under NTP conditions)
- Term EPTB used to describe isolated occurrence of TB at sites other than lung

EPTB - Overview

- EPTB constitutes about:
  - 15-20 % of all TB cases in immunocompetent pts
  - >50 % of TB cases in immunosupressed pts
- M.C. sites of involvement :
  - LN > PI eff > Others
- S/S depend on area inv – often nonspecific
- Dx often delayed:
  - Atypical clinical presentation
  - No pathognomonic radiographic signs for any site
  - Poor diagnostic yield of conventional methods
  - Tissue samples for Dx often difficult to obtain

EPTB - Overview

TYPE OF LESION	APPROX BACTERIAL LOAD
Smear-positive TB	10^7-10^9 bacilli
Cavitary	10^7-10^9 bacilli
Infiltrating	10^4 -10^7 bacilli
Nodules	10^4 -10^6 bacilli
Adenopathies	10^4 -10^6 bacilli
Renal TB	10^7-10^9 bacilli
Extrapulmonary TB	10^4 -10^6 bacilli

EPTB - Overview

EPTB usually responds to std ATT

Site	Length of Therapy (*mo*)	Rating (Duration)	Corticosteroids‡
Lymph node	6	AI	Not recommended
Bone and joint	6–9	AI	Not recommended
Pleural disease	6	AII	Not recommended
Pericarditis	6	AII	Strongly recommended
CNS tuberculosis including meningitis	9–12	BII	Strongly recommended
Disseminated disease	6	AII	Not recommended
Genitourinary	6	AII	Not recommended
Peritoneal	6	AII	Not recommended

ATS/CDC/IDSA: Treatment of Tuberculosis
Am J Respir Crit Care Med 2003; 167: 603–662.

EPTB - Overview

- Some authors & scientific societies recommend extending duration of Rx to 9 m in meningeal, osteoarticular, and lymphatic TB BUT there is no firm evidence supporting this recommendation
- Treatment trials conducted for EPTB have not been as thorough as those for PTB
- Under NTP conditions, there should be no diff in Rx of EPTB and PTB

Overview of MDR TB

MDR TB - Overview

- MDR-TB caused by *MTB* resistant to both H & R ± resistance to other drugs
- Normally resistance to anti- TB drugs occur due to spon chromosomally borne mutations in *MTB*
- Mutations occur at predictable rates & unlinked
- Spon mutations causing resistance to INH & RIF occur in ~ $1/10^6$ & ~ $1/10^8$ replications → bacilli reqd for resistance to both INH & RIF

$$\sim 1/(10^6 \times 10^8) = 1/10^{14}$$

MDR TB - Overview

- Bacilli in extensive cavitatory PTB ~ 10^{7}-10^{9} → negligible chances of spontaneous occurrence of dual resistance to INH & RIF (i.e. spontaneous occurrence of MDR)
- 1° mechanism of MDR due to accumulation of altered target genes of individual drugs by:
  - Mutation of target genes
  - Overproduction of target genes

MDR TB - Overview

DRUG	GENE(s) FOR DRUG RESISTANCE
Isoniazid	Catalase-peroxidase (katG)
	Enoyl acp reductase (inhA)
	Alkyl hydroperoxide reductase (ahpC)
	Oxidative stress regulator (oxyR)
Rifampicin	RNA polymerase subunit B (rpoB)
Pyrazinamide	Pyrazinamidase (pncA)
Streptomycin	Ribosomal protein subunit 12 (rpsL)
	16s ribosomal RNA (rrs)
	Aminoglycoside phosphotransferase gene (strA)
Ethambutol	Arabinosyl transferase (emb A,B and C)
Fluoroquinolones	DNA gyrase (gyr A and B)

MDR TB - Overview

- Resistance of *M tuberculosis* to anti-TB drugs is man-made. Wild isolates that have never been exposed to anti-TB drugs are virtually never clinically resistant.

- Drug resistance & MDR expected to occur with inappropriate application of ATT
→Incomplete or inadequate Rx most imp factor leading to development of MDR-TB

MDR TB - Overview

- Rx of drug resistant cases → Usage of 2nd line drugs → Rx more costly & complex → more frequent failures & deaths
- Implications of drug resistance for NTPs:
  1. Level of prevalence of MDR – even if moderate, presence of large no of total TB cases leads to high total burden of resistant cases
  2. Distinguishing b/w resistance among new cases & cases Rx previously
  - Planning TB control req assessment of no & distribution of MDR cases

Epidemiology of MDR TB

MDR TB - Epidemiology

- About 3% of all newly Dx pts have MDR-TB

  Dye et al. J Infect Dis 2002; 185 : 1197-1202

- 3 rounds of surveys (WHO/IUATLD b/w 1996-2002) → data on AT drug resistance among new & previously Rx cases (3rd round → data from 77 settings 1999-2002):

New (75 settings, n=55,779) – Median Prev:

- ≥ 1 AT drug (any resistance): 10.2%

  (Range 0% W Europe → 57.1% Kazakhstan)

- S = 6.3%, H = 5.9%, R = 1.4%, E = 0.8%
- MDR: 1.1%

  (Range 0% → 14.2% Kazakhstan, Israel)

MDR TB - Epidemiology

Prev Rx (66 settings, n=8405)–Median Prev:

- ≥ 1 AT drug (any resistance): 18.4%
  (Highest – 82.1% Kazakhstan)
- H = 14.4%, S = 11.4%, R = 8.7%, E = 3.5%
- MDR: 7.0%
  (Highest – 58.3% Oman, 56.4% Kazakhstan)

India

- (3 settings, no of strains tested = 757) – data on new cases only

Anti-TB drug resistance in the world. Report number 3. The WHO/IUATLD Global project on anti-TB drug resistance surveillance 1999– 2002. Geneva (Switzerland) World Health Organization; 2004.

MDR TB - Epidemiology

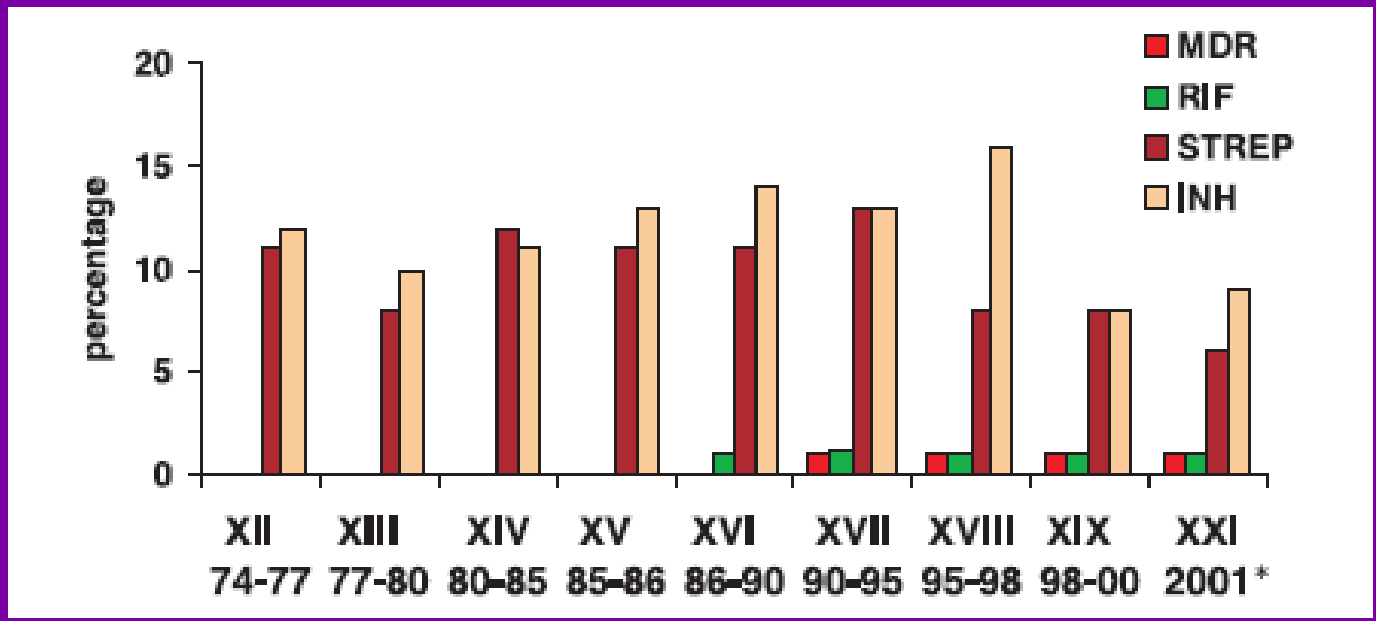
Location	Period	No. of isolates	Any resistance (%) to				
			S	H	R	SH	HR
9 Centres-ICMR I[13]	1964-65	1838	14.7	12.5	ND	6.5	ND
9 Centres-ICMR II[14]	1965-67	851	13.8	15.5		NA	ND
GCI-SH, Chennai[20]	1976	254	14.2	15.4	ND	4.7	ND
Bangalore[18]	1980's	436	5.7	17.4	3.0	3.9	1.1
Wardha[21]	1982-89	323	14.9	21.4	8.0	8.0	5.3
Gujarat[22]	1983-86	570	7.4	13.8	0.0	4.2	0.0
Bangalore[19]	1985-86	588	4.8	17.3	2.9	3.0	1.4
North Arcot[15]	1985-89	2779	11.6	21.3	1.7	8.0	1.6
Pondicherry[15]	1985-91	1841	8.1	10.8	1.0	3.7	0.8
Kolar[19]	1987-89	292	5.1	32.9	4.4	4.1	3.4
Raichur[15]	1988-89	244	11.4	19.3	3.3	6.6	3.3
North Arcot*	1989-90	241		12.9	2.5		1.7
North Arcot*	1989-98	747		19.0	11.8		4.4
Jaipur[23]	1989-91	1009	7.6	10.1	3.0	1.7	0.9
New Delhi[25]	1990-91	324	ND	18.5	0.6	ND	0.6
Military Hosp, Pune[26]	1992-93	473	8.2	3.2	4.0	2.1	1.0
Tamil Nadu state[11]	1997	384	6.8	15.4	4.4	4.4	3.4
North Arcot[12]	1999	282	12.4	23.4	2.8	8.5	2.8
Raichur[12]	1999	278	7.2	18.7	2.5	4.0	2.5
Wardha**	2000	197	7.6	15.0	0.5	3.0	0.5
Jabalpur**	2002	273	7.0	16.5	1.8	2.6	1.1

Initial drug resistance among *MTB i*solates in India

Venkataraman P et al. Drug resistant TB in India. Indian J Med Res 2004; 120: 377-386

MDR TB - Epidemiology

Data on prevalence of 1° drug resistance in India (TRC Chennai)



Venkataraman P et al. Drug resistant TB in India. Indian J Med Res 2004; 120: 377-386

MDR TB - Epidemiology

Location	Period	No. of isolates	Any resistance (%) to		
			H	R	HR
Gujarat[22]	1980-86	1574	47.7	28.3	—
Gujarat[22]	1983-86	1259	81.1	33.0	30.2
Wardha[21]	1982-89	302	47.0	12.6	9.6
North Arcot[16]	1988-89	560	67.0	12.0	10.9
Raichur[17]	1988-89	111	52.3	17.1	17.1
New Delhi[25]	1990-91	81	60.5	33.3	33.3
Tamil Nadu (4 districts)[27]	1996	162	—	—	20.3
Tamil Nadu State[11]	1997	16	(50.0)	(25.0)	(25.0)
North Arcot[12]	1999	16	(81.0)	(69.0)	(69.0)
Raichur[12]	1999	11	(100.0)	(100.0)	(100.0)
Wardha*	2000	9	(78.0)	(78.0)	(78.0)
Jabalpur*	2002	31	87.1	80.6	80.6

Acquired drug resistance among *MTB* isolates in India

Venkataraman P et al. Drug resistant TB in India.
Indian J Med Res 2004; 120: 377-386

Epidemiology of MDR EPTB

MDR EPTB - Epidemiology

- Australian Myco. Ref. Lab. Network:
  - 2003: 784 cases identified (43% EPTB, n=336)
  - Resistance to ≥ 1 AT drug: 10.2%
  - Mono-resistance:
    - Highest to H (5.7%)
    - R, E & Z < 0.4%
  - MDR: 7 (0.9%)
    - 6 – PTB, 1 – LN

	n*	Smear positive (%)†
Sputum	351	186 (53.0)
Bronchoscopy	97	31 (32.0)
Lymph node	176	41 (23.3)
Pleural	35	2 (5.7)
Genito-urinary	18	9 (50.0)
Bone/Joint	25	9 (36.0)
Peritoneal	24	2 (8.3)
Skin	11	ND†
CSF	6	ND†

96.3% initial resistance

93.8% immigrants

Lumb et al Commun Dis Intell. 2004; 28: 474-480.

MDR EPTB - Epidemiology

- Calgary (Canada):
  - Retrospective analysis for examination of
    - Distribution of TB by site
    - Prevalence & pattern of drug-resistance
  - All TB cases Dx from 1995-2002 (n = 435)
  - Exclusive EPTB = 49%
    - LN (usually cervical) 44% of all EPTB
  - Resistance to ≥ 1 AT drug: 16%
  - All resistant strains in immigrants
  - Higher prev of drug resistance in Asians (19%) & prev Rx pts (26%)

Yang H et al. Int J Tuberc Lung Dis. 2005; 9: 288-293.

MDR EPTB - Epidemiology

- Saudi Arabia:
  - Review of microbiological & clinical data of all pts with +ve isolates of MTB 1995-2000:
    - 320 isolates
    - EPTB = 183 (57%), PTB = 33%, & both = 10%
    - 76.9% isolates sensitive to all 5 1st drugs
    - Resistance to ≥ 1 drug = 11.3% (17.6% for Y2K)
    - H = 9.1%, S = 5%, R = 2.8%, E = 1.6%, Z = 3.6%
    - MDR: 2.8%
    - 78% 1° resistance
    - H/o ATT assoc with drug resistant MTB (OR =19.9)
    - Mean age of pts with resistant isolates = 42 yrs (~ 49 yrs for susceptible isolates)

Alrajhi AA et al. Saudi Med J. 2002; 23: 305-310

MDR EPTB - Epidemiology

- Rawalpindi (Pakistan):
  - 2 yr study (Sep 2000 - Aug 2002) on pts with suspected TB → 899 pul & 460 EP specimens (291 pul & 98 EP +ve)
  - Radiometric BACTEC 460 TB system used for culture & antimicrobial susceptibility testing
  - Frequency of EPTB = 25.2%
    - Pus = 11.3% (44.9% of EPTB)
    - LN = 3.3% (13.3% of EPTB)
    - Pl fluid = 3.3% (13.3% of EPTB)
  - Res (1 drug = 13.3%, MDR = 21.4%, all drugs = 9.2%)

Butt T et al. J Pak Med Assoc. 2003; 53: 328-332

MDR EPTB - Epidemiology

- NICD (Delhi):
  - 1000 suspected cases of TB (Jan 2001 – Aug 2002)
  - 234 isolates of *M. tuberculosis* on LJ medium
  - Drug testing by Proportion method
  - No diff in drug resistance patterns b/w PTB & EPTB

	UnRx (Initial Res)	**Prev Rx (Acq Res)**
n =	142	92
H	21.8%	62.0%
S	9.9%	35.9%
R	15.5%	53.4%
E	4.2%	20.7%
MDR	**12.0%**	**42.4%**
All	2.8%	26%

Negi SS et al. J Commun Dis. 2003; 35: 74-81

MDR EPTB – When to suspect ?

MDR EPTB – Diagnosis

- RISK FOR DRUG RESISTANT TB
  - Pts at ↑ risk of drug resistant disease:
    - S/S of TB with H/o Rx failure or relapse
    - Failure to show at least a partial clinical response & persistence of fever after several weeks of std 4 drug regimen
    - Worsening radiographic disease after several weeks of therapy (PTB)
    - Failure to convert culture to negative within 2 months

Seaworth BJ. MDR TB Infect Dis Clin North Am 2002; 16:73-105

MDR EPTB – Diagnosis

- Pts at ↑ risk of drug resistant disease:
  - Recent exposure to pt with proven MDR PTB
  - H/o residence in areas with high incidence of drug-resistant TB
  - Disease acquired in hospitals/health care institutions (esp those lacking adequate infection control measures & serving populations harboring drug-resistant TB)
  - TB occuring in health care workers and staffs of health care facilities (often identical strains of drug-resistant TB as pts)

Seaworth BJ. MDR TB Infect Dis Clin North Am 2002; 16:73-105

MDR EPTB – Diagnosis

- Pts at ↑ risk of drug resistant disease:
  - Not on Rx with DOTS/combination drug regimen
  - Rx in areas where drug supplies are inadequate and TB programs are weak
  - Review of Rx records → inadequate regimen, serious errors in Rx, e/o noncompliance or intermittent medication ingestion
  - Not able to provide Rx details (names of drugs, duration of Rx, or even color/no of diff tablets) → poor adherence to Rx
  - HIV infection/immunosupressed states

Seaworth BJ. MDR TB Infect Dis Clin North Am 2002; 16:73-105

MDR EPTB – Diagnosis

- PHENOTYPIC:
  1) Absolute Conc Method
  2) Relative Resistance Method
  3) Proportion Method
  4) Microscopic observation of broth cultures
  5) Micro colony detection
  6) Dye reduction test
  7) Luciferase reporter phage assay

MDR EPTB – Diagnosis

- GENOTYPIC:
  1. Automated DNA sequencing
     - DNA sequencing after PCR amplification most widely used genotypic method (?'gold standard')
  2. PCR SSCP
     - Based on property of SS DNA to fold into 3° structure
     - SS DNA differing by ≥ 1 bases fold into diff conformations → diff mobilities on gel electrophoresis (SSCP)
  - Both 1 & 2 used for detection & characterization of resistance to RIF, INH, STM, Cipro

MDR EPTB – Diagnosis

3. PCR HDF
   - Amplified DNA from test organisms mixed with DNA of susceptible control strains → hybrid DNA
   - Presence & absence of resistant strain → Heteroduplex & Homoduplex hybrid DNAs resp.→ diff electrophoretic mobility
   - Heteroduplex used to detect all RIF resistant strains having mutation within *rpo* B gene
4. Ligase chain reaction (LCR)
   - Use of DNA ligase → links 2 SS DNA → DS DNA
   - Occurs only when ends are complementary & match exactly → detects mismatch of even 1 nucleotide

MDR EPTB – Diagnosis

5. LiPA (Line probe assay)
   - Based on **HYBRIDIZATION** of amplified DNA from cultured strains/clinical specimens **WITH** 10 sequence specific probes representing core region of *rpo* B gene of *MTB*
   - **Absence** of hybridization to any probe → absence of any of known mutations that encode resistance
   - **Presence** of hybridization → mutation represented by specific probe to which hybridization occured
   - Used for rapid detection of *MTB* & RIF resistance

MDR EPTB – Diagnosis

6. DNA strain typing using RFLP
   - Based on principle that if 2 apparently identical strands of DS DNA diff by ≥1base → cleavage by restriction endonuclease + electrophoresis → diff banding patterns (RFLPs)
   - RFLP = 'genomic or DNA fingerprinting' → no change even after development of drug resistance → Useful for:
     - Epidemiological investigations for determining spread of MDR strains
     - Relapse after successful Rx → Diff endogenous reactivation or exogenous reinfection

MDR EPTB – Diagnosis

- RIF Resistance:
  - RIF resistance-determining region (RRDR) of *rpoB* gene – main site for mutations
    - 50 MTB clinical isolates (44 res & 6 sen) analyzed by DNA sequencing
    - 53 mutations of 18 types detected (17 point mutations)
    - Mutations detected in 43 of 44 resistant isolates.
    - 3 new mutations & 2 new mutations outisde RRDR

Mani C et al, J. Clin. Microbiol. 2001; 39: 2987–2990

MDR EPTB – Diagnosis

- RIF Resistance:
  - 'Surrogate marker for MDR'
    - 116 isolates (Bactec 460TB system)
    - Loci for drug resistance (*rpo beta, gyr A, kat G)* studied for mutations by PCR – SSCP
    - RIF reistance found in 53.5% → 93% of RIF resistant isolates resistant to ≥ 1 other AT drug

    Siddiqi N et al. Mem Inst Oswaldo Cruz. 1998; 93: 589-594
  - Detection of mutations in *rpoB* gene used for rapid Dx of MDR PTB (? Application for MDR EPTB)

MDR EPTB – When not to suspect ?

Apparent worsening while on Rx does not always translate into drug resistance!

MDR EPTB – Mimickers

- Paradoxical response
  - Enlargement of old lesions or appearance of new lesions during apparently adequate ATT:
    - TB LNE → Appearance of new LN or ↑ in size of original LN
    - EPTB → Development of new pul infiltrates
    - PTB → Development of PE & progression of pul infiltrates
    - 1° TB (children) → ↑ in size of LN & pul infiltration
    - PE → Development of C/L PE & ↑ in amount of I/L PE & even appearance of new pul lesions

Chol YW et al. Radiology 2002; 224: 493–502

MDR EPTB – Mimickers

- Usually occurs 3–12 wks after initiation of ATT
- Mechanism – not fully clear :
  - Active TB → altered CMI → Immunosuppression → appropriate ATT → ↑ focal immune response (immunologic rebound) → Recruitment of Ly. & Macr. at site of lesions → enlargement of lesions (radiologically inapparent → visible)
  - Hypersensitivity to tuberculoproteins released from dying mycobacteria
- Usually regresses without change of initial drug regimen

Chol YW et al. Radiology 2002; 224: 493–502

Site Specific MDR EPTB

MDR EPTB – Site Specific

- MDR TBM
  - Timely confirmation of Dx is challenging because pts of MDR TBM Rx with1st line drugs are likely to be dead before results of conventional susceptibility tests are available!
  - Case Report:
    - 21 m/F → Dx of TBM →Initial std ATT → no response →CSF Culture → MDR-TBM
    - Rx with cipro + cyclo + E + ethio + rifabutin x 2 yrs
    - 'Pt survived long enough for clinicians to adjust ATT to 2nd line drugs'

DeVincenzo et al. Ann Pharmacother. 1999; 33: 1184-1188

MDR EPTB – Site Specific

MDR TBM

- Even now Rx with std ATT prevents death or disability in <50% → MDR TBM threatens resurgence of prechemotherapeutic era in which all pts with TBM died
- KwaZulu-Natal (South Africa)
  - 1999–2002 → 350 pts identified by CSF C/S
  - MDR 8.6% (n = 30)
  - 17 died & rest had significant morbidity
  - 18 HIV +ve
  - 22 pts Rx & 3 pts not Rx prev for TB in past

Patel et al. MDR TBM in South Africa. Clin Infect Dis 2004; 38: 851–56

MDR EPTB – Site Specific

- MDR TBM
  - Drugs:
    - Greatest CSF penetration is of PZA & INH (80% & 50% of plasma conc). STM & RFM cross BBB →provide therapeutic levels in presence of meningeal infl only
    - Data on CSF penetration & pharmacokinetics of 2nd line drugs scanty
    - Ethionamide, prothionamide & cycloserine all reported to cross BBB well (? effective)
    - ? Aminoglycosides and other drugs that penetrate BBB less well may be given by intrathecal route

Thwaites GE et al. TBM: many Q, too few A. Lancet Neurol 2005; 4: 160–70

MDR EPTB – Site Specific

- MDR TBM
  - Outcome of MDR TBM worse ~ TBM by susceptible organisms → Rx by 2nd line drugs
  - Effect of resistance to INH and/or STM on outcome controversial:
    - INH has potent early bactericidal activity & free passage into CSF → Resistance to INH assoc with longer times to CSF sterility. However no reliable data to support or reject an effect of INH resistance on outcome from TBM
    - Until larger studies are done, current evidence suggests that for TBM caused by INH resistant organisms → duration of Rx to be extended + inclusion of PZA throughout duration of Rx

Thwaites GE et al. TBM: many Q, too few A. Lancet Neurol 2005; 4: 160–70

MDR EPTB – Site Specific

- MDR TB LNE
  - Systematic, retrospective review of all cases of TB Lymphadenitis (Jan 1990 - Dec 2000)
  - Manitoba (Canada)
  - n =147
  - Single cervical LNE (80%)
  - 77% culture +ve (No atypical mycobacteria)
  - 68% F
  - 59% immigrants
  - 13% drug resistance (all immigrants)

Cook VJ et al. Can Respir J. 2004; 11: 279-286

MDR EPTB – Site Specific

- MDR TB LNE
  - Prospective double blind 1 yr study
  - Mumbai
  - 250 pts with suspected TBL
  - n = 161
    - FNAC +ve = 82.1%
    - Culture +ve = 80.7% (n = 130 incl 5 NTM)

	UnRx (Initial Res)	**Prev Rx (Acq Res)**
n =	50	30
H	16 %	48 %
S	12 %	32 %
R	6 %	30 %
E	4 %	12 %
MDR	**1 %**	**16 %**
Any	61%	

Nataraj G et al. Postgrad Med 2002; 48: 113-116

MDR EPTB – Site Specific

- MDR TB Empyema
  - 5 pts with past h/o TB PE → ch loculated empyema → reactivation of TB → formation of BPF → drug-resistant *MTB* in sputum
  - 3 pts underwent Re Rx (2 underwent surgery) → culture –ve
  - 2 pts remained culture +ve
  - 'Thick, calcified pl walls limit penetration of drugs into the infected empyema space, resulting in suboptimal drug conc & drug resistance'

Iseman MD et al. Chest. 1991; 100: 124-127

MDR EPTB – Site Specific

- MDR TB Empyema
  - 5 yr retrospective study (1990 – 1995)
  - Taiwan n = 35
  - S/S → nonspecific
  - CXR → advanced parenchymal lesions
  - *MTB* culture +ve in 60% (20% MDR, n=7)
  - All received ATT (8 pts reqd surgical Mx)
  - 63% Rx successful, 34% died/defaulted
  - 'Rx outcome of TB empyema less satisfactory than PTB'

    Bai KJ et al. TB empyema Respirology. 1998; 3: 261-266

MDR EPTB – Site Specific

MDR-TB Breast:

- 28/F
- Lt breast abscess & Lt axillary LNE x 6 wks
- Investigated → Dx of TB Dx
- RHEZ → 3 m → no response
- Culture isolate →*M. tuberculosis* (resistant to H, R & S)
- Rx with H + Z + kanamycin + ofloxacin + PAS + ethionamide → recovered

Kumar P et al. Indian J Chest Dis Allied Sci. 2003 45: 63-65

MDR EPTB – Site Specific

MDR-TB Spleen:

- 25/M
- Hypodense lesions in spleen + LNE (B/L cervical & peripancreatic)
- Cold abscess neck → pus C/S → MTB Resistant to INH, RIF, Cipro & PAS
- Rx with E + Z + cycloserine + ofloxacin + ethionamide → DIH → (Z & ethionamide) replaced with clofazimine
- Recovered with 18 m of Rx

Sharma SK et al. Indian J Tuberc. 2004; 51: 43-46

MDR EPTB – How to treat?

MDR EPTB – Treatment

- MDR EPTB difficult to Dx:
  - Clinical features non-specific
  - Conventional bacteriology insensitive
  - Assessment of newer methods for Dx incomplete
- No published RCTs on Rx of MDR EPTB
- Best combination, dose & duration of drugs for Rx of MDR EPTB unknown
- Until more data are available Rx of MDR EPTB should abide by principles of Rx of MDR PTB

MDR EPTB – Treatment

Susceptibility testing to essential drugs	Initial phase		Continuation phase	
	Drugs	Duration	Drugs	Duration
Not available[a]	Km[b] + Et + Q[c] + Z +/- E	At least 6 months	Et + Q + Z +/- E	12–18 months
Available:				
Resistance to H + R	S[d] + Et + Q[c] + Z +/- E	At least 6 months	Et + Q + Z +/- E	12–18 months
Resistance to all essential drugs	1 injectable +1 fluoro-quinolone + 2 of these 3 oral drugs: PAS, Et, Cs	At least 6 months	The same drugs except injectable	18 months
Susceptibility testing to reserve drugs available	Tailor regimen according to susceptibility pattern[e]			

WHO: Treatment of Tuberculosis – Guidelines for National Programmes 2003

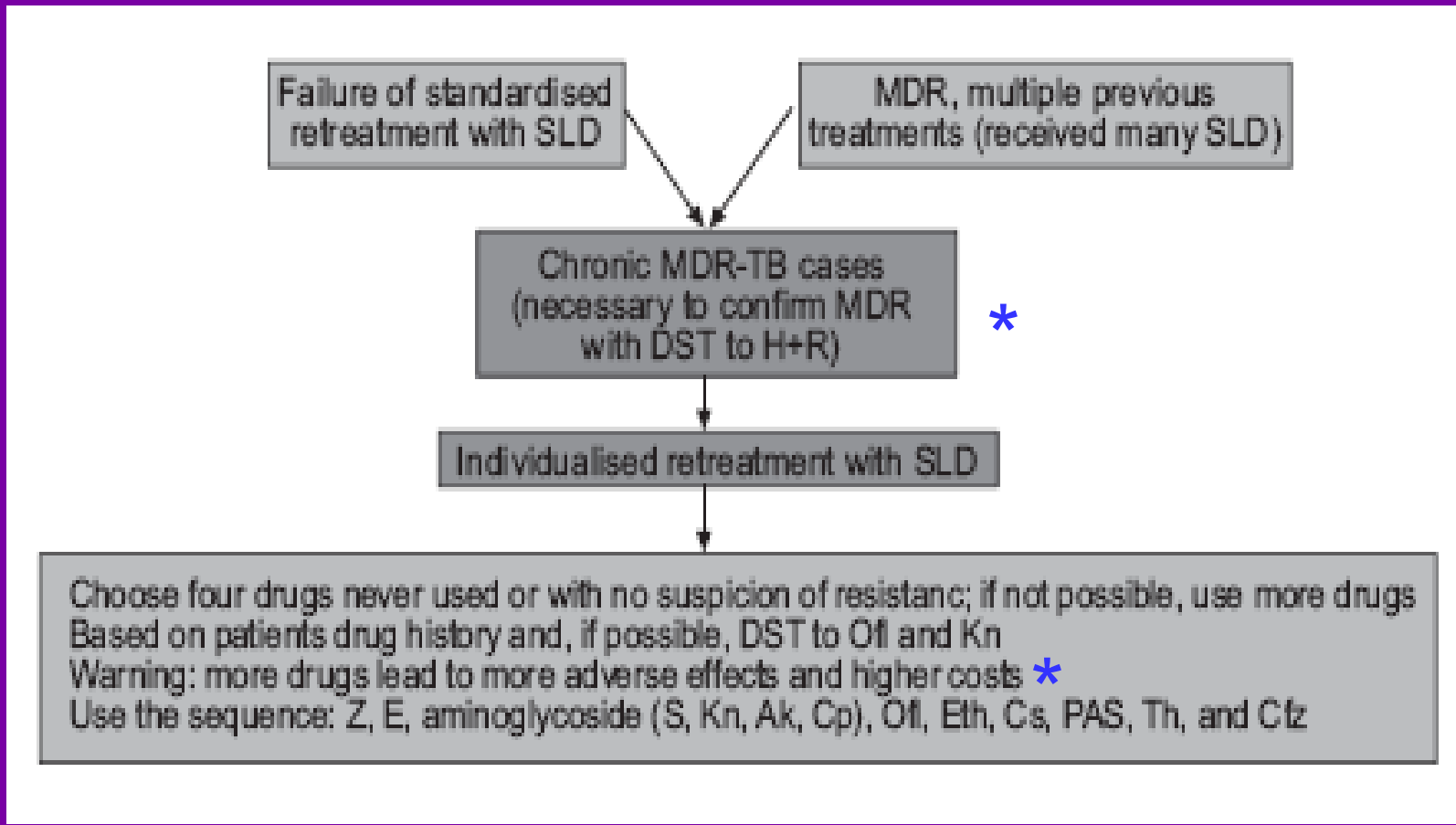
MDR EPTB – Treatment

Guidelines for formulating a reRx regimen

1. Initiate re-treatment in the ambulatory setting if there is adequate infrastructure and social environment for outpatient monitoring. Otherwise initiate re-treatment with the patient admitted to a reference centre.
2. The scheme should be designed by personnel with extensive experience in the handling of second-line drugs.
3. It is very important to establish a detailed history of the drugs used by the patient in the past.
4. Associate at least three drugs that have never been used by the patient or for which no drug resistance exists (i.e., well associated in earlier treatment regimens).
5. Use the maximum possible number of bactericidal drugs.
6. Always include an aminoglycoside or capreomycin.
7. Caution is required due to possible cross-resistance among drugs, especially:
   - Aminoglycosides*: streptomycin → kanamycin → amikacin
   - All quinolones
   - UNIDIRECTIONAL RESISTANCE
8. Minimum treatment time:
   - 18 months if isoniazid and rifampicin cannot be used
   - 12 months if isoniazid or rifampicin can be used
9. Strict supervision of treatment administration is required.
10. **Never** add a single drug to an ineffective or failing regimen.

Caminero JA. TB guide for specialist physicians. IUATLD 2004

MDR EPTB – Treatment



Caminero JA. Mx of MDR TB & pts in ReRx. Eur Respir J 2005; 25: 928-936

WHAT'S NEW ON THE HORIZON?

MDR EPTB – Treatment

- 4th gen fluoroquinolone derivatives
  - Possibly sup to 2nd gen (& even 3rd gen)
  - Not as easily available
  - More expensive
  - No info on long-term tolerance & toxicity
  - Cross-resistance
  - Lack adequate clinical experience to be routinely used in reRx regimens (unlike 2nd & 3rd gen)
- Macrolides
  - Some drugs have *in vitro* antimycobacterial activity with good MICs → insufficient evidence to be recommended for use in Rx of MDR TB

MDR EPTB – Treatment

- Rifamycin derivatives
  - Rifabutin and Rifapentine have MOA & MICs ~ RIF
  - Cross resistance with RIF= 70% & 100% resp → cannot be used in MDR TB
- Oxazolidinone derivatives
  - Linezolid, U-100480 and esperezolid
  - Anti TB activity *in vitro*
  - Linezolid activity *in vivo* → used on experimental basis in MDR-TB
  - Very expensive
  - Scant data on long term toxicity
  - Cannot be recommended even as rescue medications

MDR EPTB – Treatment

- Nitroimidazole derivatives
  - PA-824 & other compounds ~ metronidazole
  - Bactericidal against *MTB* both *in vitro* and *in vivo*
  - Similar to INH:
    - Efficacy
    - Restricted spectrum of action (highly specific for TB)
    - MOA (bacterial cell wall lipid synthesis but at diff stage)
    - Acts on rapidly multiplying mycobacterial population
  - Adv over INH:
    - Inhibits protein synthesis as addl MOA
    - ? Effective against bacilli not actively replicating
    - Effective against *MTB* strains resistant to 1st line drugs
    - Less toxic
  - Holds promise as a good alt to 1st line drugs
  - Cannot be recommended for use (further studies)

MDR EPTB – Treatment

- Substances that inhibit mycobacterial growth:
  - Derivatives of vit K or CoEnzyme Q (gangamycin)
- Substances that interfere with biosynthesis of vital components of mycobacteria
  - Mycoside C synthesis inhibitors
  - Arabinogalactan synthesis inhibitors
  - Transmethylation inhibitors
  - Mg chelating agents
  - Membrane cation flow inducers
  - Substances interfering with mycobactin synthesis
  - Membrane receptor blockers
  - Trehalose phosphate synthetase inhibitors
  - Analogues of mesodiaminopimelic- D-alamine
  - Mycobactin analogues
  - Inhibitors of muramic acid enzymatic glycosylation

MDR EPTB – Treatment

- Re-sensitisation of prev resistant strains
  - Membrane permeators
  - Beta-lactamase inhibitors (amox/clavulanate)
  - Inhibitors of aminoglycoside-inactivating enzymes
- Immunotherapeutic agents/immunomodulators
  - Monoclonal antibodies
  - New vaccines
  - Substances that improve opsonisation
  - Cytokines
  - Immune-enhancing microbiological agents

MDR EPTB – Treatment

- Liposomes
  - Phospholipid vesicles with ≥ 2 layers
  - Can encapsulate drugs & macromolecules (size: 0.2 nm to 2-3 nm)
  - Phagocytosed by macrophages → preferential delivery of drugs to macrophages and RES
  - i/m → effect upto 5 wks → ↓no of injections → ↑ compliance

MDR EPTB – Treatment

Surgery for Mx of MDR EPTB

- Obtaining samples for Dx
- Rx of
  - Constrictive pericarditis
  - Vertebral abscesses causing cord compression
  - Superficial & accessible abscesses in osteoarticular TB
  - Peripheral LNE → not indicated except if mechanical complications & their sequelae

MDR EPTB – Treatment

Surgery for Mx of MDR EPTB

- Mediastinal LNE:
  - Compression of mediastinal structures and/or LNE mass perforating into tracheobronchial tree
  - Most important surgical manoeuvres are opening & curetting of LNE → insignificant morbidity & mortality of surgery
  - Attempts to dissect or extirpate LNE not justified if no imp adherences (risk of serious vascular accidents)

MDR EPTB – Treatment

- Surgery for Mx of MDR TB Empyema:
  - Indications:
    - Preventing gross endobronchial spillage of empyema fluid to uninvolved regions
    - Preventing Rx failure & acquired drug resistance (early initiation of ATT & use of optimal regimen)
  - Procedures include decortication (std or limited to parietal aspect), thoracoplasty, muscle flap, open drainage & resection of entire lung + pleura

Sahn SA & Iseman MD. TB empyema. Seminars in Respiratory Infections 1999; 14: 82-87

MDR EPTB – Treatment

- Surgery for Mx of MDR TB Empyema:
  - Experienced surgeons reqd in view of problems assoc with surgery:
    - Obscuration of anatomical landmarks by thickened & calcified pleura
    - Densely adherent pleura →Difficult Sx → Post op chronic air leak(s)
    - Respiratory insufficiency (Damage to I/L or C/L lung during surgery)

Sahn SA & Iseman MD. TB empyema. Seminars in Respiratory Infections 1999; 14: 82-87

MDR EPTB - Prevention

- New drugs for TB unlikely to be available in near future → PREVENTION is cornerstone for control of MDR TB (incl EPTB cases)
- A strong NTP (esp DOTS) is cost effective:
  - Detects majority of cases esp PTB
  - Ensures completion of Rx
  - ↓ incidence of drug resistance in community by preventing generation of resistant strains
- Greater role of DOTS PLUS & GLC to take care of existing MDR cases

Summary

MDR EPTB

- MDR:
  - Difficult to Rx
  - Rx often needs to be individualized
  - Rx limited success
- EPTB:
  - Difficult to Dx
  - Rx difficult to monitor

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- Difficult to Dx
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THANK YOU