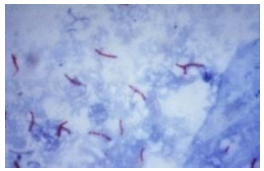
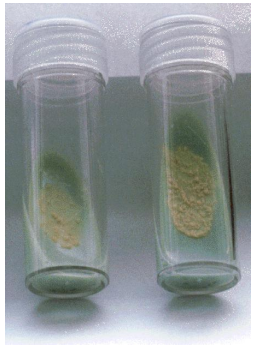
Tuberculosis / NTM

단국대학교 의과대학
박재석

Diagnosis of M.TB

- Conventional
  - AFB smear, culture
  - Drug susceptibility test





- Molecular
  - TB-PCR
  - 신속내성 검사
    - rpo-B gene (RIF 내성)
    - katG, Inh-A (INH 내성)

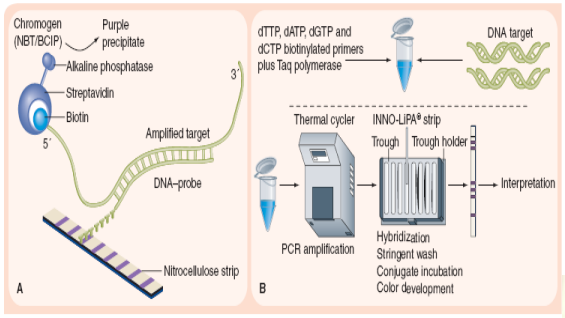


Figure 4. Line-probe assays for detection of drug resistance. (A) Principle of reverse hybridization. (B) INNO-LiPA® assay. The INNO-LiPA test contains ten

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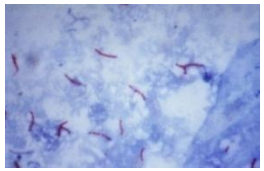

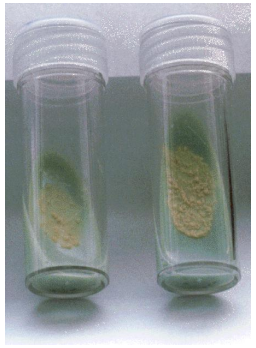

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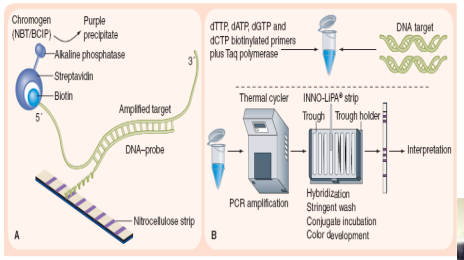


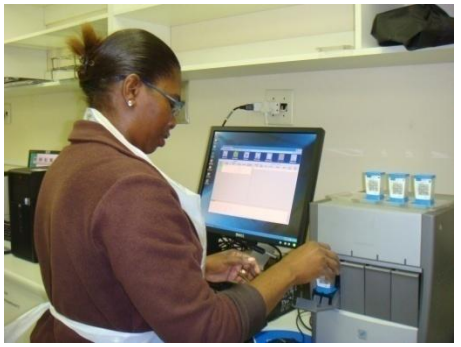
Figure 4. Line-probe assays for detection of drug resistance. (A) Principle of reverse hybridization. (B) INNO-LiPA® assay. The INNO-LiPA test contains ten

- 결과를 빨리 알 수 있고 민감도가 높지만
- 검사 과정이 복잡하고 잘 갖추어진 검사실과 숙련된 기사가 필요함.

Molecular Diagnosis of M.TB

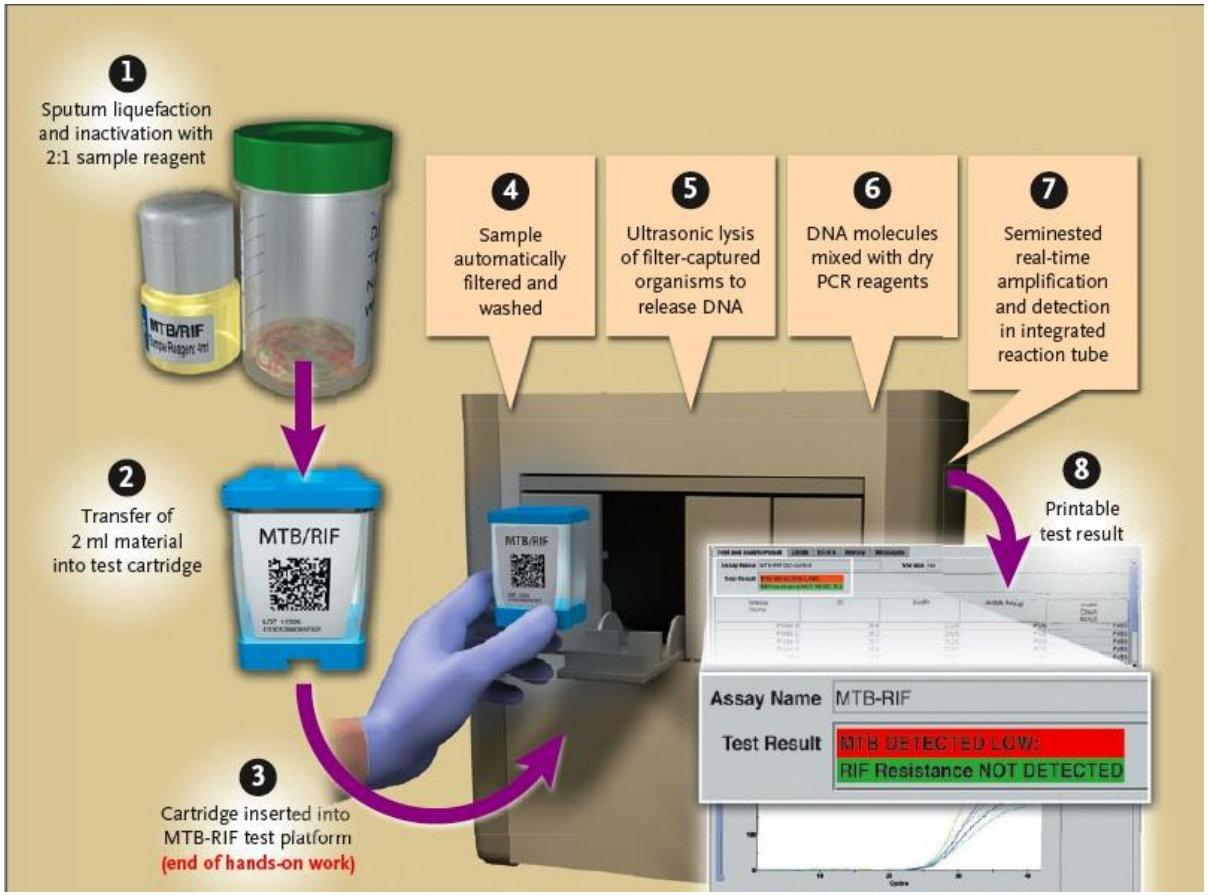
- TB-PCR
- 신속내성 검사
  - rpo-B gene (RIF 내성)
  - katG, Inh-A (INH 내성)

Xpert MTB/RIF

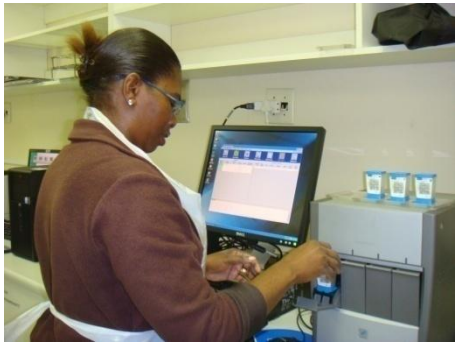


- Closed automated system
  - no technical skill or equipment required
  - Biosafe

Xpert MTB/RIF



- Detect MTB, and rpo-B gene
- Closed automated system
  - no special equipment and technical skill required
  - Biosafety
- Result in 2 hr



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 9, 2010 VOL. 363 NO. 11

Rapid Molecular Detection of Tuberculosis and Rifampin Resistance

1. MTB detection

Culture (+)

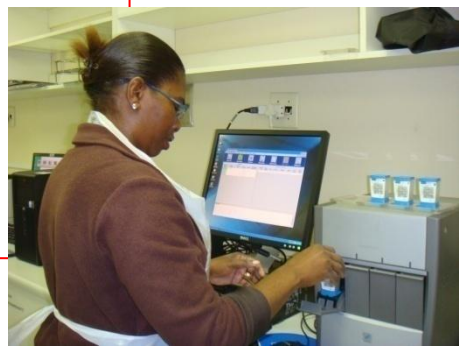
- Xpert MTB/RIF sensitivity AFB S(+) : 98.2%
- Xpert MTB/RIF sensitivity AFB S(-) : 72.5%

Xpert MTB/RIF specificity : 99.2%

2. RIF resistance

PPV : 97.6%

NPV : 98.1%



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   Xpert MTB/RIF test specificity : 99.2%

2. RIF resistance

   PPV : 97.6%

   NPV : 98.1%

- Xpert MTB/RIF is highly sensitive and specific in controlled studies
- but no data from district health facilities in TB-endemic area.

Feasibility, diagnostic accuracy, and effectiveness of

decentralised use of the Xpert MTB/RIF test

for diagnosis of TB and MDR

: a multicenter implementation study.

Lancet 2011;377:1495–505

6648 adults, suspected TB or MDR-TB

- urban health centers (South Africa, Peru, and India)
- drug-resistance screening facilities (Azerbaijan and the Philippines)
- emergency room (Uganda)

- compared XpertMTB/RIF with sputum S/C, and drug-susceptibility test.

Feasibility, diagnostic accuracy, and effectiveness of decentralised use of the Xpert MTB/RIF test for diagnosis of tuberculosis and multidrug resistance : a multicenter implementation study.

Lancet 2011;377:1495–505

- MTB, Culture (+)
  - Xpert MTB/RIF sensitivity : 90.3%
    - Xpert MTB/RIF sensitivity AFB S(-)/C(+) :76.9%

- Xpert MTB/RIF test specificity : 99·0% (2846 of 2876 non-TB samples).

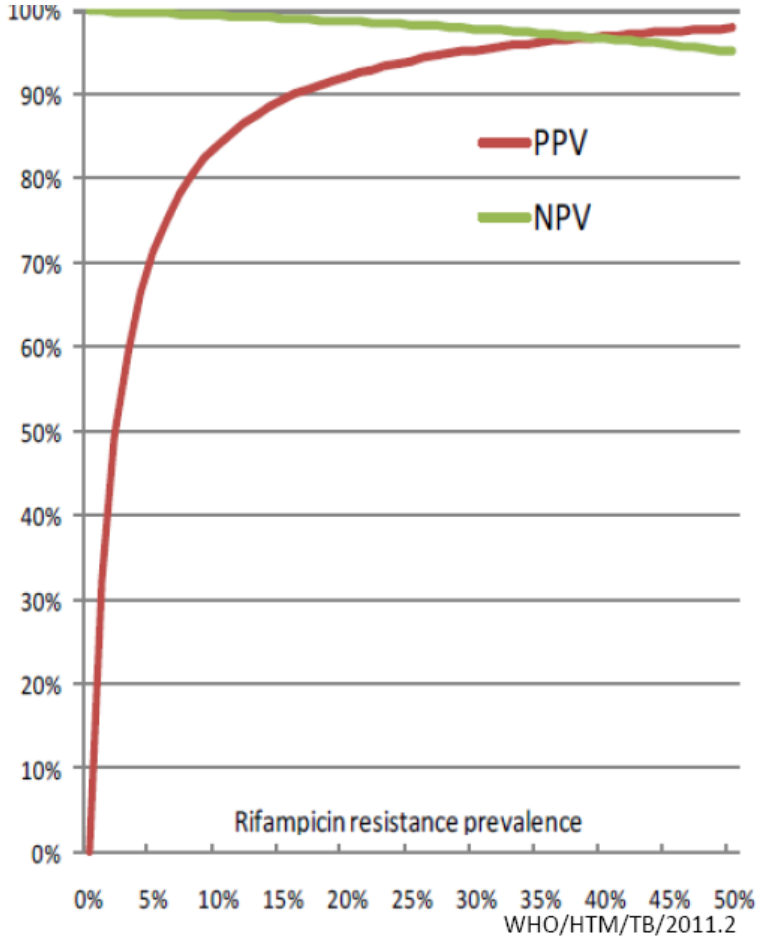
- Xpert MTB/RIF test for rifampin resistance(rpo-B gene)
  - sensitivity : 94.4%
  - specificity : 98.3%

PPV of RIF resistance with Xpert MTB/RIF

According to RIF resistance prevalence

Rifampicin resistance prevalence	PPV	NPV	True positive*	False negative*	False positive*	True negative*
1%	32.4%	99.9%	9.5	0.5	19.8	970.2
2%	49.2%	99.9%	19	1	19.6	960.4
3%	59.5%	99.8%	28.5	1.5	19.4	950.6
4%	66.4%	99.8%	38	2	19.2	940.8
5%	71.4%	99.7%	47.5	2.5	19	931
6%	75.2%	99.7%	57	3	18.8	921.2
7%	78.1%	99.6%	66.5	3.5	18.6	911.4
8%	80.5%	99.6%	76	4	18.4	901.6
9%	82.4%	99.5%	85.5	4.5	18.2	891.8
10%	84.1%	99.4%	95	5	18	882
11%	85.4%	99.4%	104.5	5.5	17.8	872.2
12%	86.6%	99.3%	114	6	17.6	862.4
13%	87.7%	99.2%	123.5	6.5	17.4	852.6
14%	88.5%	99.2%	133	7	17.2	842.8
15%	89.3%	99.1%	142.5	7.5	17	833
20%	92.2%	98.7%	190	10	16	784
25%	94.1%	98.3%	237.5	12.5	15	735

* Sensitivity (95%) and specificity (98%) for Xpert MTB/RIF rifampicin resistance, compared with reference method (culture)



우리나라 초회 다제내성율 : 2.4% (2003) CDMR 2005;16:101-7

Potential limits of Xpert MTB/RIF

- Unknown performance at a district level.
- **In a low level MDR-TB prevalence (< 10%)-setting, the assay needs to be confirmed**
- Need AFB S/C and DST
  - Monitoring to response
  - DST for other drugs
- Cost

Sensitivity of Xpert MTB/RIF

According to HIV status

	HIV positive	HIV negative
Sensitivity in culture-positive samples		
Smear microscopy	86/193 (44·6%, 37·7–51·6)	234/341 (68·6%, 63·5–73·3)
MTB/RIF test	173/210 (82·4%, 76·7–86·9)	304/335 (90·7%, 87·2–93·4)
Sputum positive	84/86 (97·7%, 91·9–99·4)	204/206 (99·0%, 96·5–99·7)
Sputum negative	89/124 (71·8%, 63·3–78·9)	100/129 (77·5%, 69·6–83·9)

Xpert MTB/RIF

WHO policies

- Reference test for MDR suspects and for TB/HIV
- Approved for smear (-) cases
- District lab.

HIV와 다제내성결핵이 많고

검사시설을 갖추기 어려운

후진국의 지방 의료기관에서 유용...

Xpert MTB/RIF

WHO policies

- Reference test for MDR suspects and for TB/HIV
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- District lab.

Korean policies ?

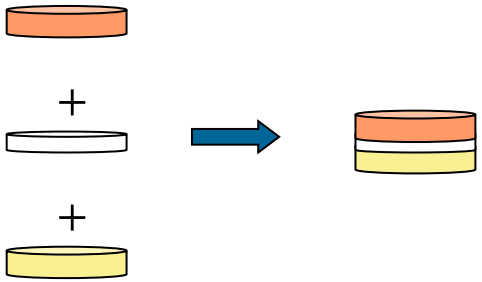
다제내성 결핵이 의심되거나

검사 결과를 빨리 알고 싶을 때 ...

- 2 hr ?
- District lab. ?
- Cost vs benefit

Fixed Dose Combination (FDC, 복합제)

- A combination of two or more drugs in a fixed ratio of doses



Rationale for FDC (결핵 치료)

- INH : 75 mg
- RIF : 150 mg
- EMB : 275 mg
- PZA : 400 mg

Body weight	Tablet number
30-37	2
38-54	3
55-70	4
>70	5

- Reduce pill burden
  - Patient convenience
  - Patient adherence
- Inadequate regimen or dosage prevented
  - Prevention of drug resistance

WHO recommend FDC for TB

Uncertainties regarding the quality of FDC formulations.

- the transition from single drug formulations to FDC formulations.
- Need good quality and proven rifampin bioavailability.

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Efficacy and safety of a 4-Drug fixed-dose combination(FDC) regimen compared with separate drugs for treatment of pulmonary tuberculosis : the study C randomized controlled trial.

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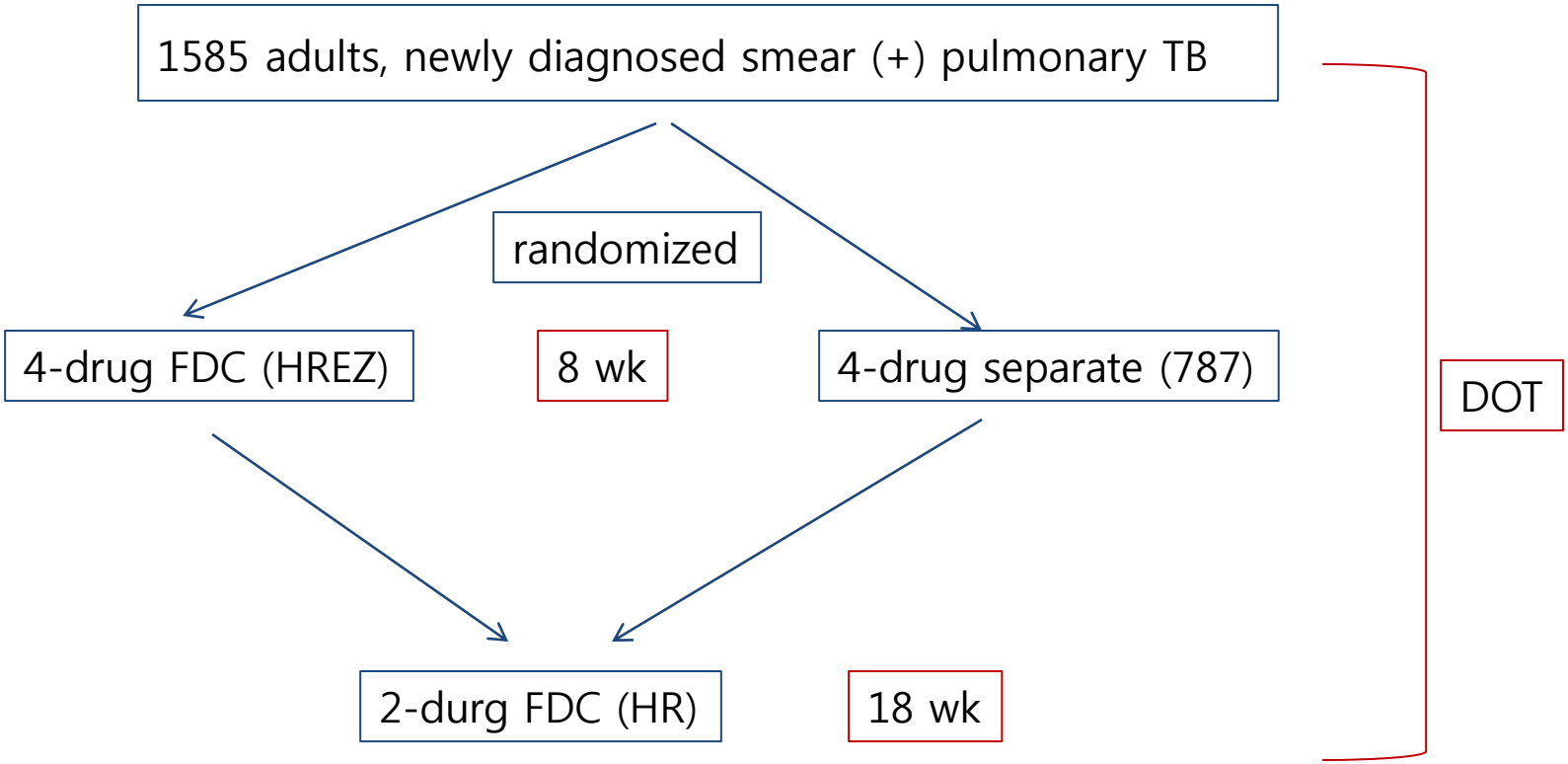

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Response	No. FDC (n = 591)	No. Separate Drugs (n = 579)
Favorable response		
Culture-negative		
At 18 mo	534	528
At 24 mo	22	20
Total, No. (%)[a]	555 (93.9)	548 (94.6)

DOT

Adverse events

	FDC (n = 797)[a]	Separate Drugs (n = 784)[a]
Patients with adverse events in months 1 or 2 (probably or possibly drug-related)	31	36
Action taken		
None	15	27
Interruption	6	6
Stopped study drugs	10	3
Adverse events by type		
Rheumatological	7	11
Stopped study drug	0	0
Dermatological	16	15
Stopped study drug	7	2
Hepatic	5	1
Stopped study drug	2	0
Gastrointestinal	6	11
Stopped study drug	1	1

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제품명	**튜비스정**
복지부분류	613 [주로 항산성균에 작용하는 것]
보험약가	259 원/정
제품성상	타원형의 양쪽이 볼록한 오렌지색의 필름코팅정
성분/함량	1정 중 --- Isoniazid 75 mg Rifampicin 150 mg Pyrazinamide 400 mg Ethambutol 275 mg
효능/효과	성인 및 8세 이상 소아의 결핵 치료
용법/용량	1일 1회 식전 1시간에 아래와 같은 용량으로 투여한다.

필름정 수량	환자체중(kg)
2 필름정	30 – 37*
3 필름정	38 – 54
4 필름정	55 – 70
5 필름정	≥ 71**

2012. 11 한국에서 처음 출시

튜비스정은 체중 30 kg 이하의 환자들에게는 부적합하다.
일반적으로, 고정된 용량의 배합제제로서 리팜피신이 함유된 필름정을 복용하는 대부분의 환자들은 1일 3정 또는 4정을 복용한다. 성인 결핵환자의 소수만이 체중 70 kg 이상의 그룹으로 분류된다. 이들은 리팜피신과 이소니아지드의 일반적인 1일 용량, 즉 600 mg 및 300 mg을 초과하는 용량이 필요할 수 도 있다.

보험코드	653102670	Approval	EU Approval
보관방법	기밀용기, 실온보관, 제조일로부터 24개월		
포장단위	120 T (PTP 12T X 10)		

결핵치료에서 복합제 사용

- INH : 75 mg
- RIF : 150 mg
- EMB : 275 mg
- PZA : 400 mg

Body weight	Tablet number
30-37	2
38-54	3
55-70	4
>70	5

- Reduce pill burden
  - Patient convenience
  - Patient adherence
- Inadequate regimen or dosage prevented
  - Prevention of drug resistance

→ FDC for TB tx

(질병관리본부 권고)

Extensively drug resistant (XDR) TB

TABLE 7.1 **Alternative method of grouping antituberculosis agents**

GROUPING	DRUGS
Group 1 – First-line oral agents	isoniazid (H); rifampicin (R); ethambutol (E); pyrazinamide (Z); rifabutin (Rfb)[a]
Group 2 – Injectable agents	kanamycin (Km); amikacin (Am); capreomycin (Cm); streptomycin (S)
Group 3 Fluoroquinolones	moxifloxacin (Mfx); levofloxacin (Lfx); ofloxacin (Ofx)
Group 4 – Oral bacteriostatic second-line agents	ethionamide (Eto); protionamide (Pto); cycloserine (Cs); terizidone (Trd); *p*-aminosalicylic acid (PAS)
Group 5 – Agents with unclear efficacy (not recom mended by WHO for routine use in MDR-TB patients)	clofazimine (Cfz); linezolid (Lzd); amoxicillin/clavulanate (Amx/Clv); thioacetazone (Thz); imipenem/cilastatin (Ipm/Cln); high-dose isoniazid (high-dose H);[b] clarithromycin (Clr)

Linezolid (Zyvox)

- New family of antibiotics (oxazolidinone)
- active against G(+) cocci like vancomycin resistant enterococcus (VRE).
    - 1200 mg /d
    - 2-3 wk

- Limited data of long term (> 1yr) treatment for XDR-TB
    - Efficacy
    - Adverse effect : neuropathy, myelosuppression
        - Dosage (600 mg vs 300 mg / day)

To evaluate the efficacy and adverse effect of long term linezolid tx for XDR-TB

- 마산 국제결핵연구소
- 2008-2012
- Randomized prospective study
- linezolid for XDR-TB (> 18 mo)
- Evaluate
  - Efficacy
  - Adverse effect
    - 600 mg /d
    - 300 mg /d

Linezolid for treatment of chronic XDR-tuberculosis.

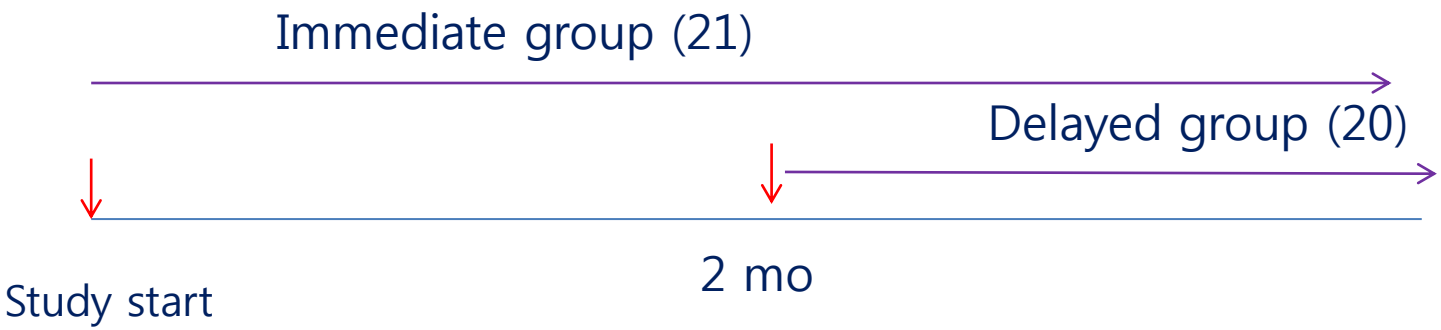
N Engl J Med. 2012;367:1508-18

대상

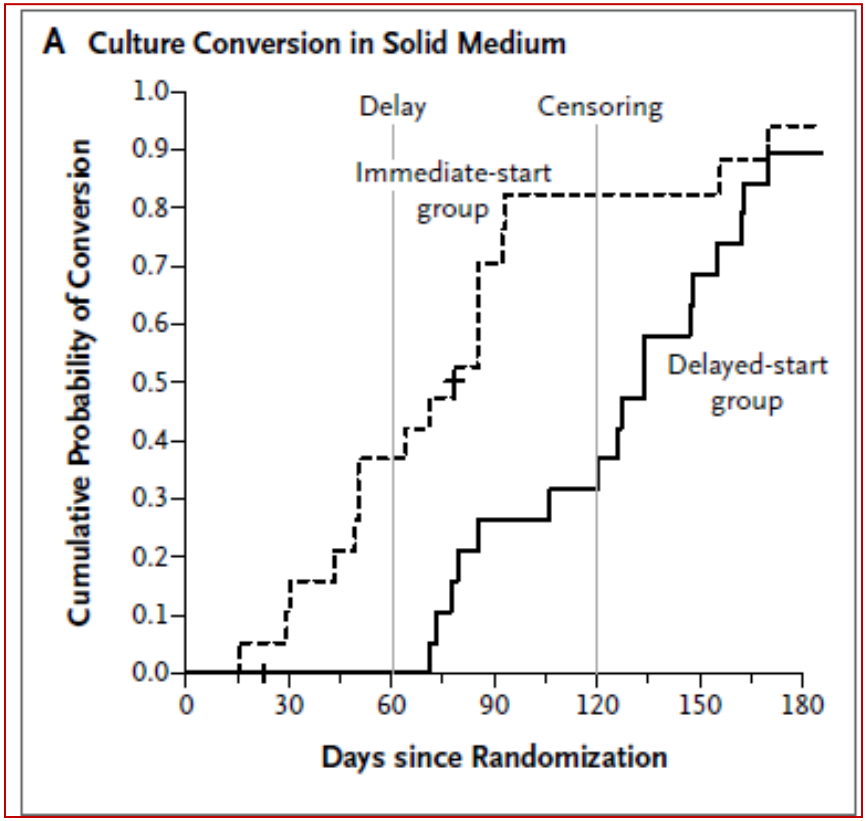
- 41 adult XDR-TB pt, 최근 6개월간 치료에도 균음전 실패
  - 5 prev. tx episodes (median)
  - Resistant to 11 drugs (mean)

방법

- Maintain current anti-TB drug
- Add linezolid 600 mg/day



Addition of linezolid to background regimen

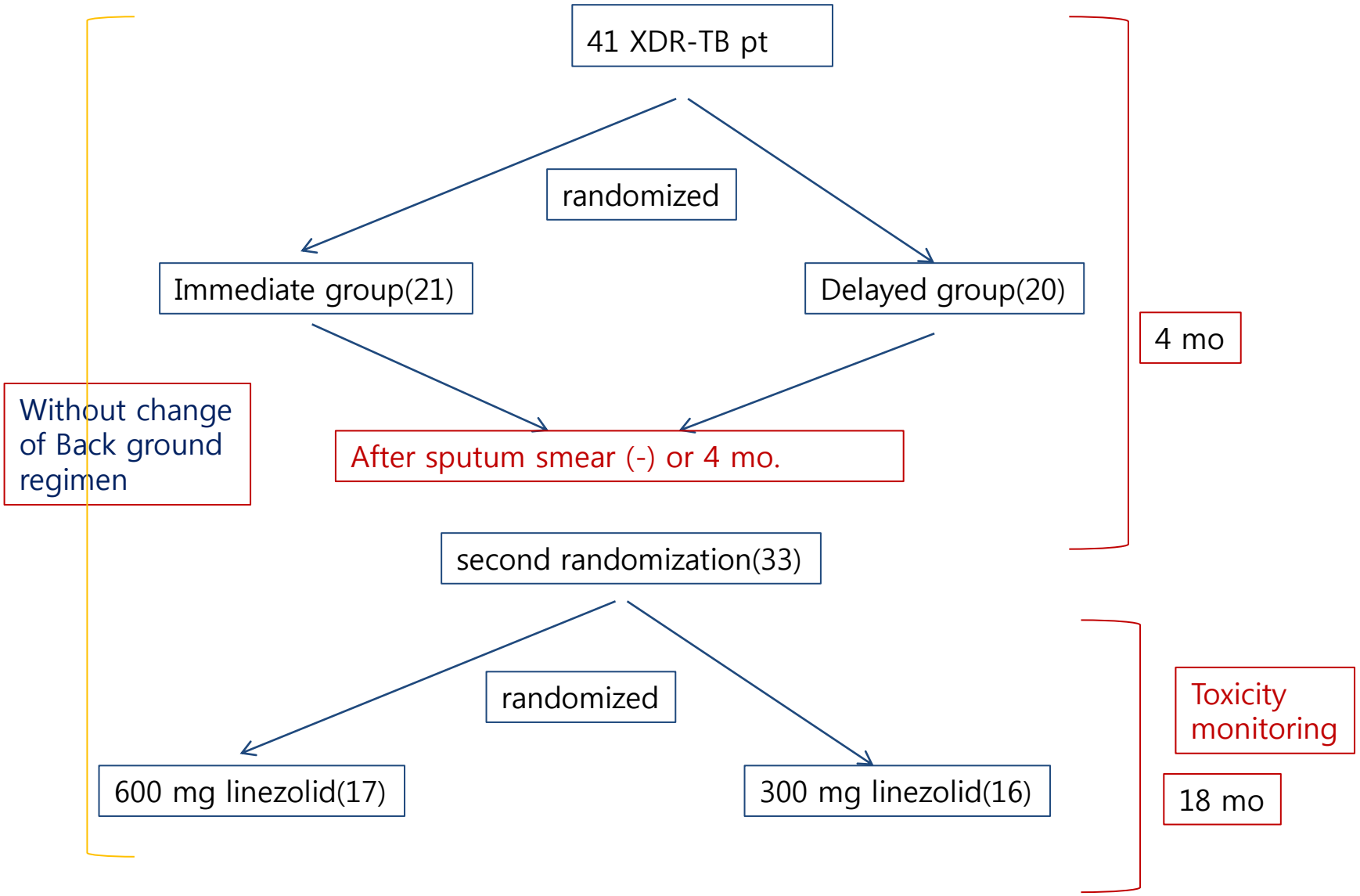


- Culture (-) conversion rate, (4 mo)

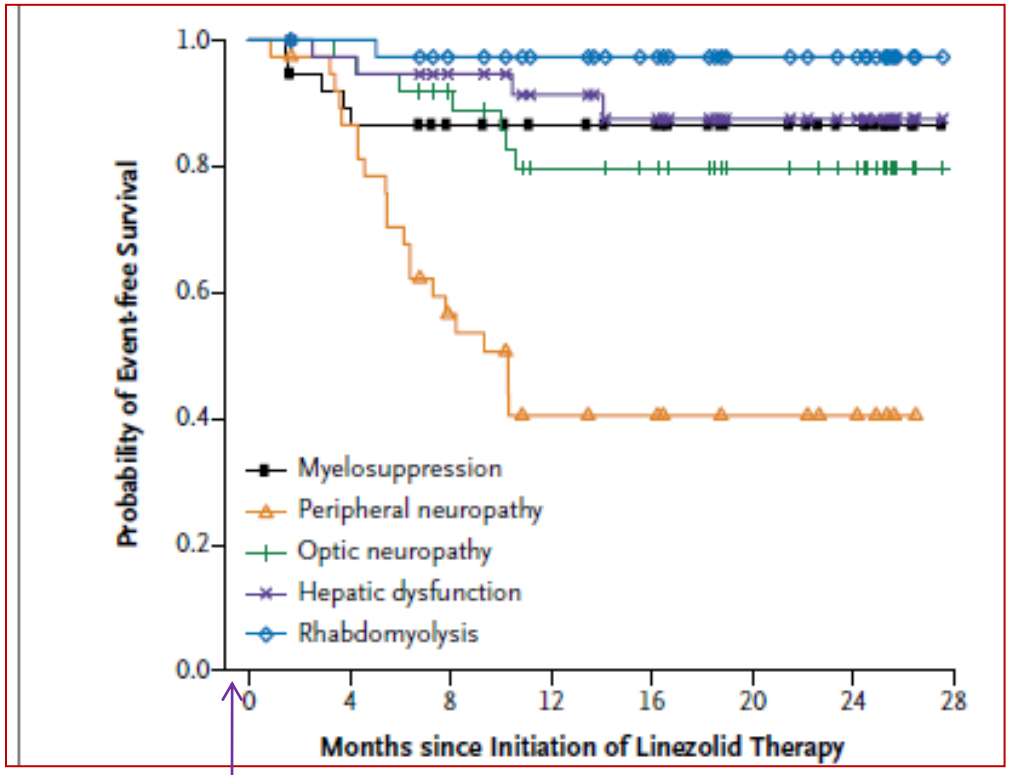
  immediate group(79%) > delay group(35%) (p=0.001)

- Most (87%) had sputum culture (-) within 6 mo after linezolid

Adverse event of linezolid



Adverse event of linezolid

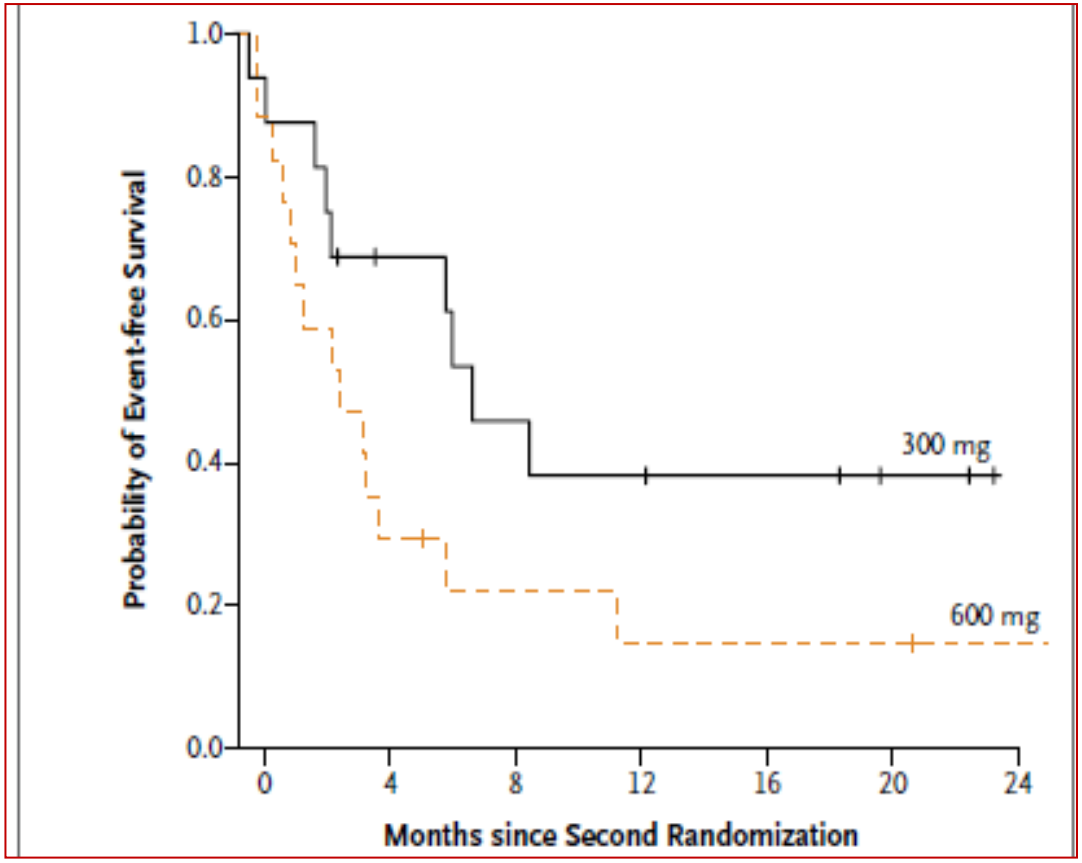


Linezolid 600mg/d or 300 mg/d

- Pph. Neuropathy : 55%
- Optic neuropahty : 18%

- 82% had adverse event
  - Most resolved quickly after discontinuation of linezolid
  - Only 3 permanently stopped due to drug toxicity (2 optic neuopathy, 1 anemia)

Adverse event of linezolid



- Adverse event : 300 mg group(69%) < 600 mg group(88%).
- 65% of 600 mg group reduced to 300 mg due to adverse event

Linezolid for treatment of chronic XDR-tuberculosis.

N Engl J Med. 2012;367:1508-18

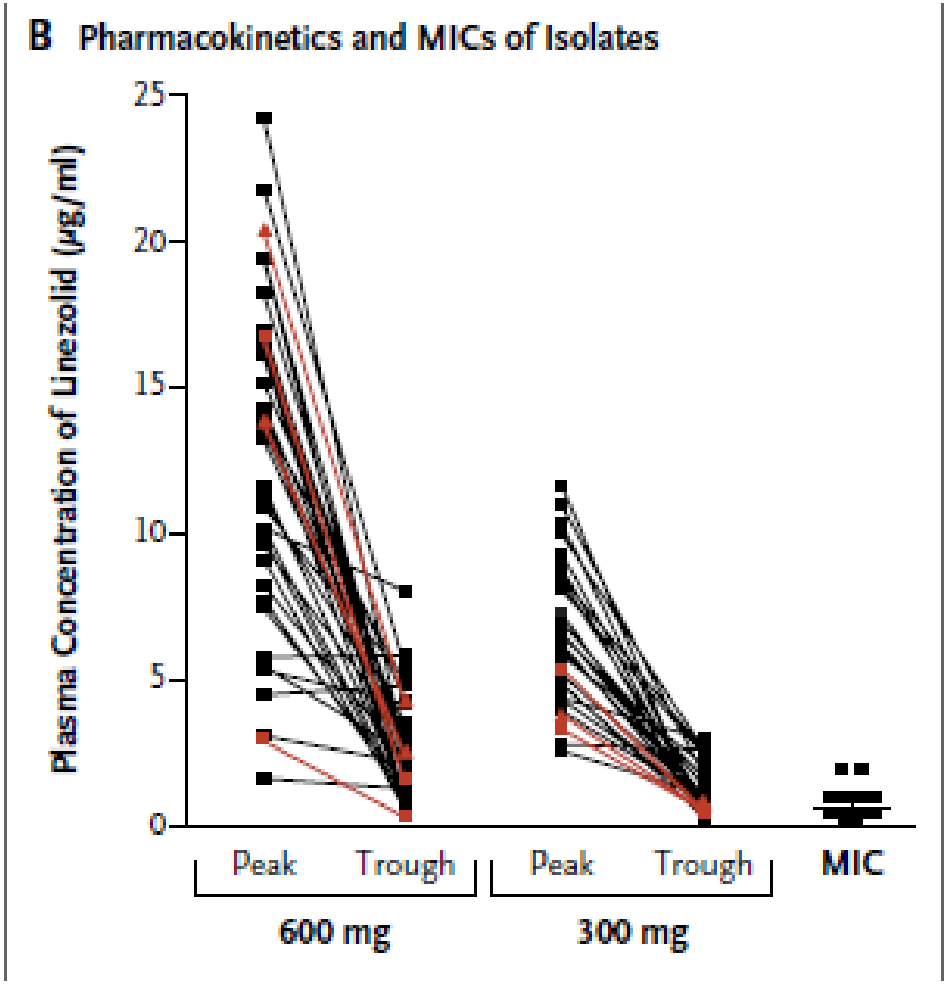
- Maintain linezolid 18 mo after culture conversion
  - f/u for 12 mo.
- Study end point (May 1, 2012, from 2008)
  - 17 : receiving tx
  - 13 : completed therapy
    - 6 : no relapse during tx period
    - 4 : no relapse at 6 mo f/u
    - 3 : no relapse at 12 mo f/u
  - 8 : withdrew early
    - 3 : tx failure
    - 1 : relapse after 1 yr
    - 3 : adverse event
    - 1 : personal reason

Linezolid for treatment of chronic XDR-tuberculosis.

N Engl J Med. 2012;367:1508-18

Linezolid 조기 중단 (8)

- 3 : tx failure
  - : 300mg (2), 600mg (1)
- 1 : relapse after 1 yr : 600mg
- 3 : adverse event
- 1 : personal reason

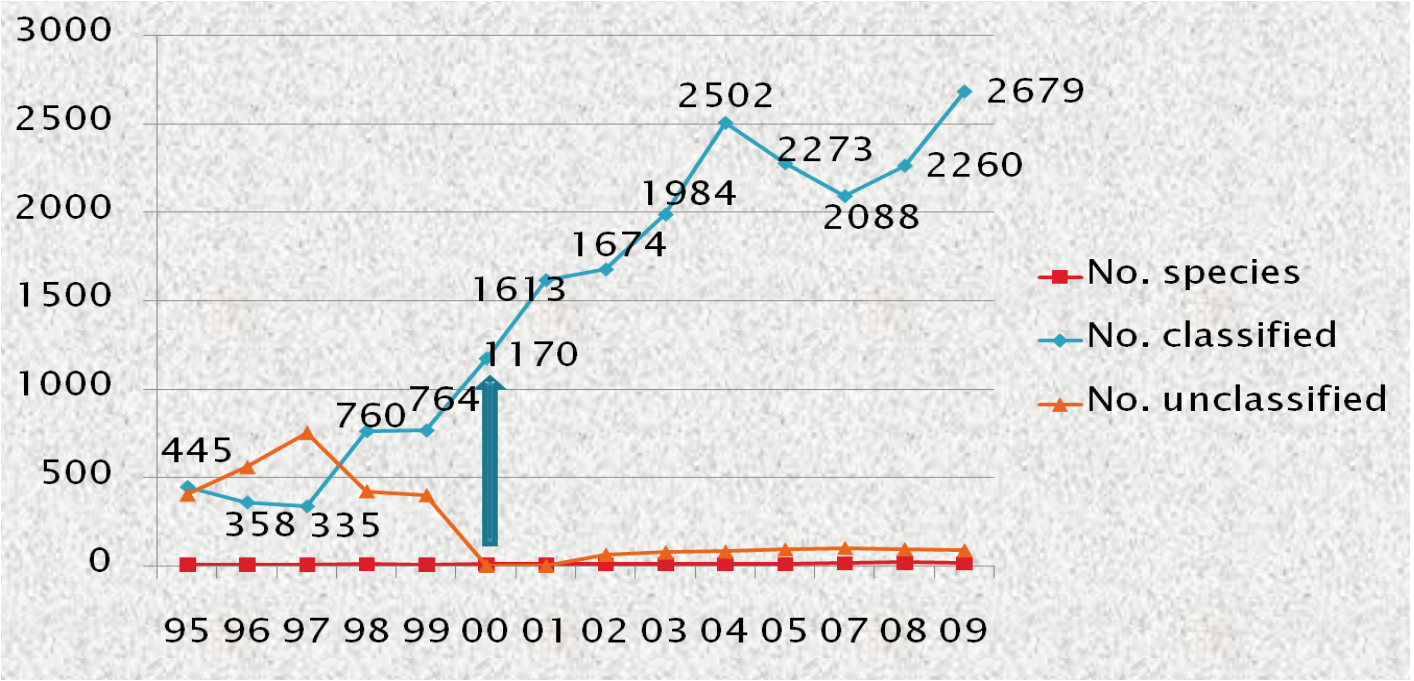


Linezolid for treatment of chronic XDR-tuberculosis.
N Engl J Med. 2012;367:1508-18

- Longterm linezolid for XDR-TB (> 18 mo)
  - Highly effective
  - Dosage
    - 300mg/d or
    - Start 600mg/d -> reduce to 300mg/d if toxicity develop
  - Close monitoring of adverse event

Need more evidence..

Non-tuberculous Mycobacteria (NTM)



NTM identification (결핵 연구원, annual report)

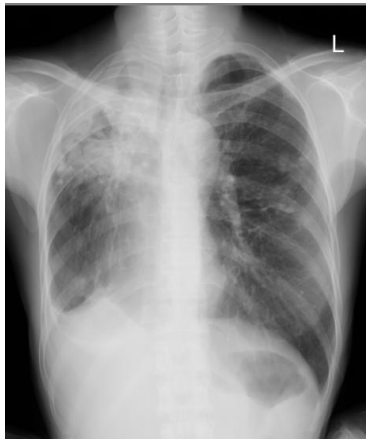
Species of NTMs isolated from sputum (Korea)

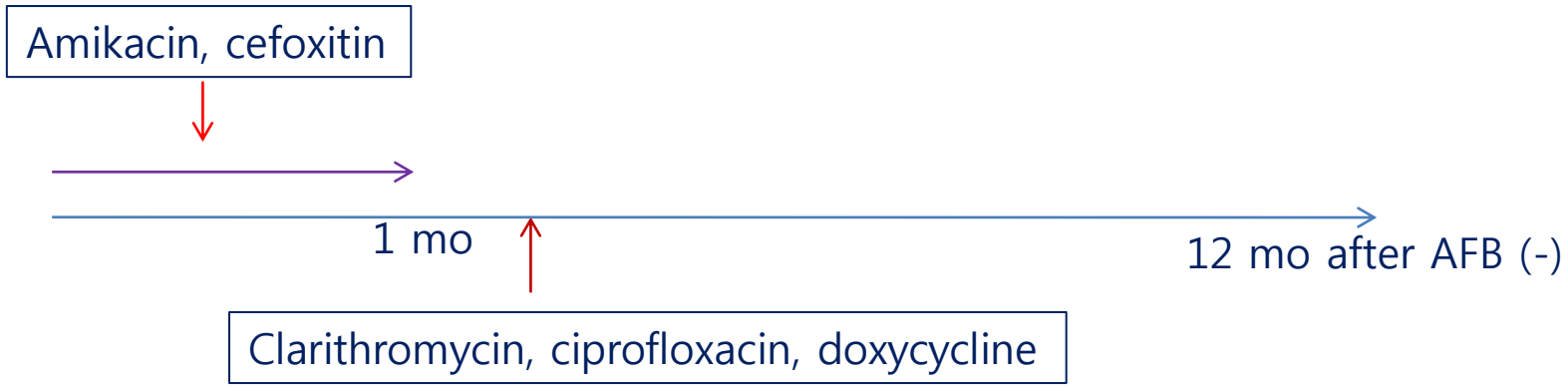
Organisms	NTM isolated pt. No	NTM lung ds pt, No(%)
M avium complex (MAC)	219	98 (44.7)
M. intracellulare	108	56 (51.9)
M avium	111	38 (34.2)
M abscessus	141	64 (45.4)
M fortuitum complex	217	21 (9.7)
M gordonae	84	0
Mycobacterium terrae complex	48	0
Mycobacterium kansasii	14	7 (50.0)
Mycobacterium szulgai	32	2 (6.3)
Mycobacterium chelonae	25	6 (24)
Mycobacterium celatum	11	1 (9.1)
Mycobacterium gastri	2	0
Mycobacterium xenopi	1	0

Chest 2006;129:341-8

M. abscessus lung ds

- **Difficult to tx**
- **Poor response to tx.**



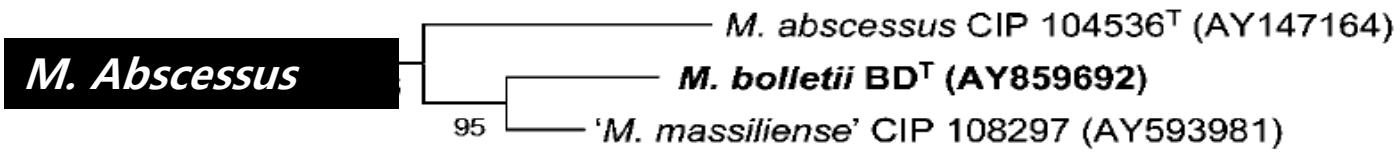


- Initial sputum conversion and maintenance of conversion rate : 61%

Am J Respir Crit Care Med 2011 ; 183: 405–410

M. massiliense

- identified at 2004



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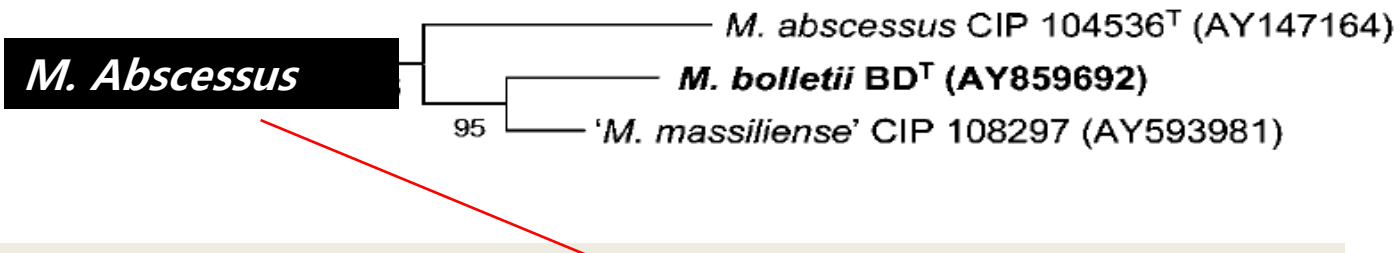
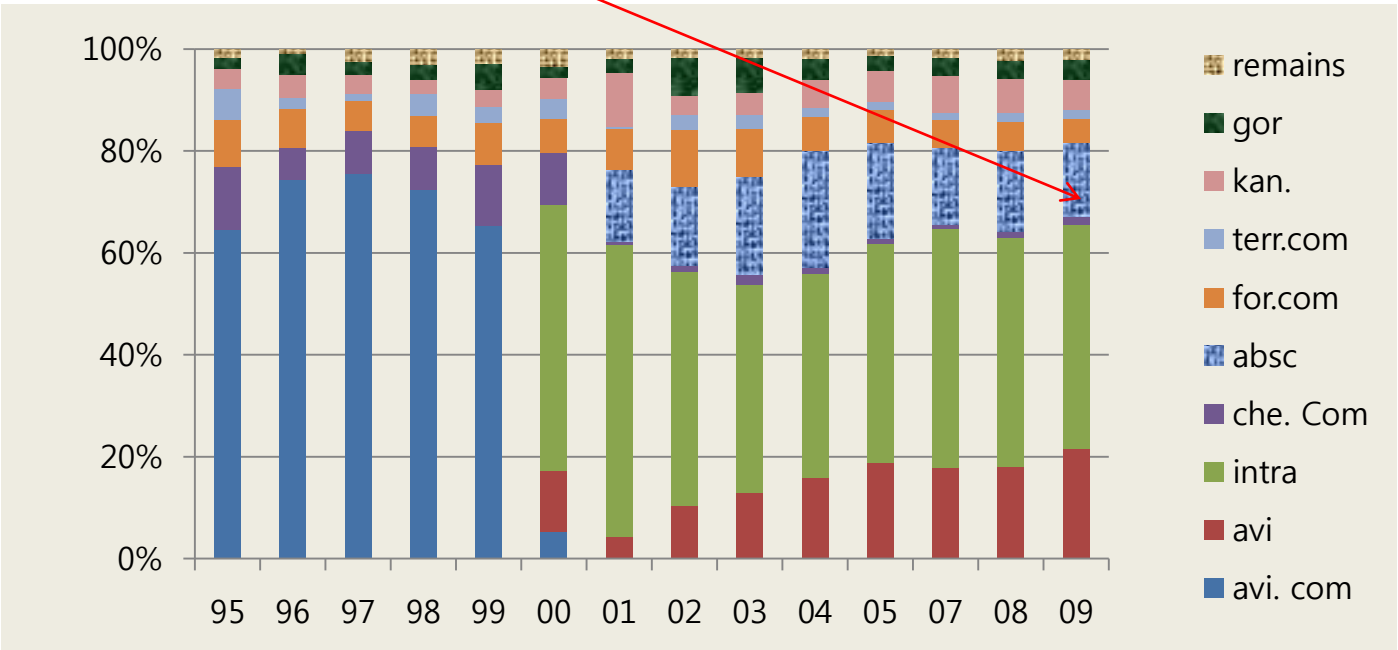
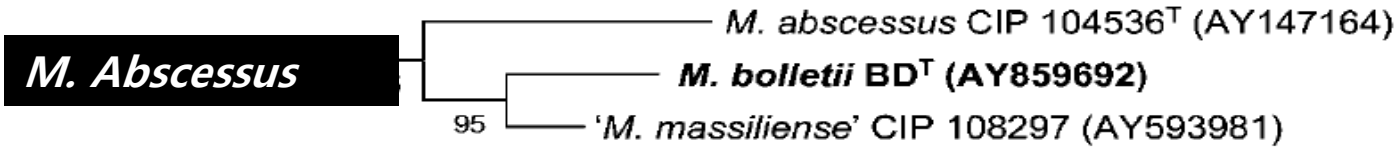






❖ Sequence analysis of the *rpo B* and *hsp65* gene of 158 clinical isolates of *M. abscessus*

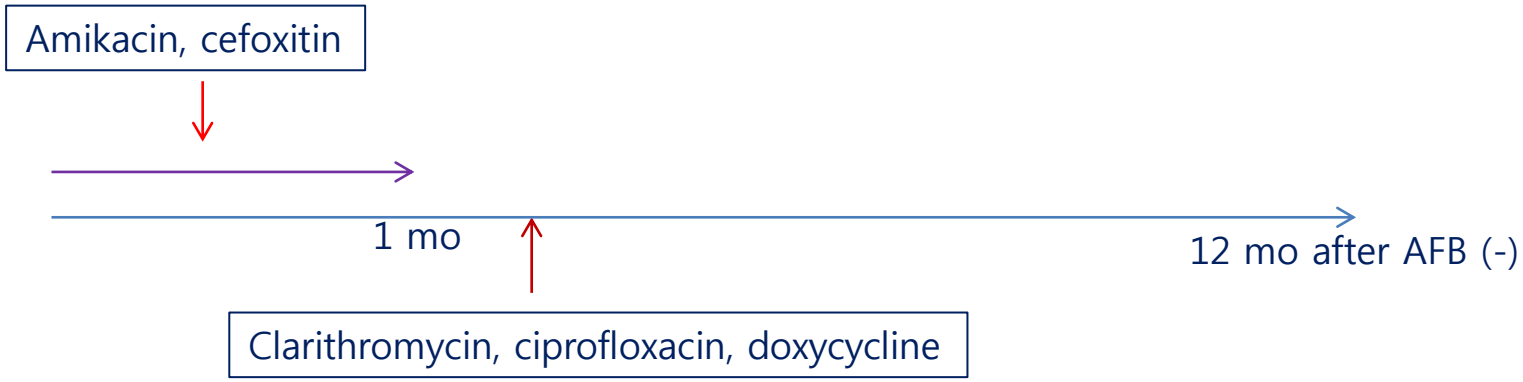
- *M. abscessus : 44%*
- *M. massiliense : 55%*
- M. bolletii : 1%

Am J Respir Crit Care Med 2011 ; 183: 405–410

Clinical significance of differentiation of *Mycobacterium massiliense* from *Mycobacterium abscessus*.

Am J Respir Crit Care Med 2010;183:405-10

- Retrospective
- 145 pt. who prev. treated as *M.abscessus* lung dis
  - *M. abscessus* lung ds (64)
  - *M. massiliense* lung ds (81)
- Compare clinical features, tx outcome



Clinical features between *M. abscessus* and *M. massilense* lung ds

	M. abscessus ($n = 64$)	*M. massiliense* ($n = 81$)	*P* Value
Age, yr	57.6 (13.0)	56.0 (12.9)	0.467
Sex, female	47 (71)	61 (75)	0.545
Body mass index, kg/m^2	20.5 (3.1)	20.8 (2.8)	0.566
Smoking			
Nonsmoker	56 (88)	69 (85)	0.923
Current or ex-smoker	8 (12)	12 (15)	
Underlying disease			
Previous tuberculosis	33 (52)	44 (54)	0.741
COPD	3 (5)	8 (10)	0.347
Diabetes mellitus	3 (5)	1 (1)	0.321
Lung cancer	6 (9)	5 (6)	0.537
Other malignancy	8 (13)	5 (6)	0.185
Symptoms			
Cough	55 (86)	73 (90)	0.437
Sputum	55 (86)	68 (84)	0.741
Hemoptysis	27 (42)	27 (33)	0.273
Positive AFB smear	44 (69)	47 (58)	0.185
Type of disease			
Nodular bronchiectatic form	53 (83)	56 (69)	
Upper lobe cavitary form	8 (12)	17 (21)	0.161
Unclassifiable form	3 (5)	8 (10)	

In vitro drug susceptibility of *M. abscessus* and *M. massilense* isolates

Etiology	Drug	Resistance Rate
M. abscessus	Amikacin	3 (5%)
	Cefoxitin	0
	Imipenem	27 (44%)
	Clarithromycin	3 (5%)
	Doxycycline	53 (83%)
	Ciprofloxacin	37 (58%)
	Moxifloxacin	30 (47%)
M. massiliense	Amikacin	6 (8%)
	Cefoxitin	1 (1%)
	Imipenem‡	50 (67%)
	Clarithromycin	3 (4%)
	Doxycycline	58 (73%)
	Ciprofloxacin	48 (61%)
	Moxifloxacin	42 (53%)

Treatment response between *M. abscessus* and *M. massilense* lung ds

	M. abscessus ($n = 24$)	*M. massiliense* ($n = 33$)	*P* Value
Symptomatic response			0.040
Improved	18 (75%)	32 (97%)	
Unchanged	4 (17%)	1 (3%)	
Worsened	2 (8%)	—	
Radiographic response on HRCT			0.003
Improved	10 (42%)	27 (82%)	
Unchanged	7 (29%)	5 (15%)	
Worsened	7 (29%)	1 (3%)	
Microbiologic response			<0.001
Initial sputum conversion and maintenance of conversion	6 (25%)	29 (88%)	
Initial sputum conversion, with sputum relapse	4 (17%)	3 (9%)	
Failure to sputum conversion	14 (58%)	1 (3%)	

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약제 감수성 검사에는 차이가 없는데

치료에 대한 반응에서 현격한 차이가 나는 이유 ?

Inducible resistance to clarithromycin of *M. abscessus* and *M. massilense*

Incubate bacteria in low conc. of clarithromycin

Isolate	Clarithromycin Resistance (*MIC*, μg/ml)	No. of Clinical Isolates		
		Day 3	Day 7	Day 14
M. abscessus (n = 19)	Susceptible			
	≤0.5	9 (47%)	—	—
	1	6 (32%)	—	—
	2	4 (21%)	—	—
	Intermediate			
	4	—	—	—
	Resistant			
	8	—	1 (5%)	—
	16	—	8 (42%)	—
	32	—	4 (21%)	3 (16%)
	≥64	—	6 (32%)	16 (84%)
M. massiliense (n = 28)	Susceptible	20 (71%)	20 (71%)	20 (71%)
	≤0.5			
	1		8 (29%)	8 (29%)
	2	—	—	—
	Intermediate			
	4	—	—	—
	Resistant			
	≥8	—	—	—

Clinical significance of differentiation of *Mycobacterium massiliense* from *Mycobacterium abscessus*.

Am J Respir Crit Care Med 2010;183:405-10

- *M. abscessus* shows poor response to tx.
  - Due to inducible resistance to clarithromycin

- NTM 균동정 검사 (rapid grower)
  - *M. abscessus* or *M. massiliense*

- NTM 폐질환의 치료
  - *M. abscessus* lung ds : 소극적 치료
  - *M. massiliense* lung ds : 적극적 치료

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경청해 주셔서 감사합니다 ^^