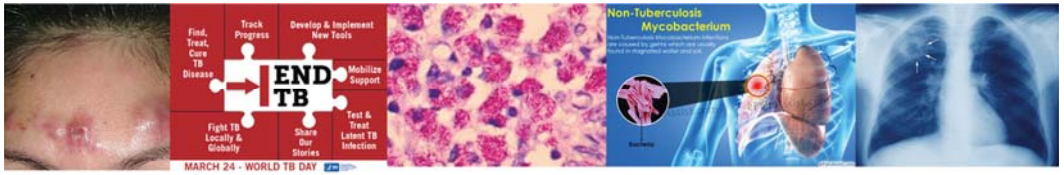

Pitfall in management of TB and NTM

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Thai Red Cross Society

Case 1

Underlying diseases: HBV cirrhosis child C S/P Orthotopic ***liver transplantation*** (17/11/57), **BW 52 kgs**

Lab baseline: TB 1.03, DB 0.54, ALP 98, SGOT 20, SGPT 14, Alb 3
BUN 34, Cr 1.92

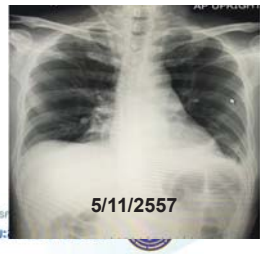
Medication: prograf (1) 4-0-4, prednisolone (5) 1x1, lamivudine (150) 1x1

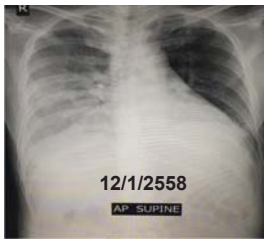
Admit 9/1/58 → ***fever with cough for 3 wks.***

สมาคมโรคติดเชื้อแห่งประเทศไทย
การอบรมระยะสั้นประจำปี 2562

Case 1: Orthotopic liver transplantation (17/11/57)

Date	Clinical	Medication	Remark
9/1/2558	Fever with cough for 3 wks Sputum smear positive 2+	INH(100) 3 tab, Rifam (300) 2 tab, PZA (500) 2.5 tab, etham (400) 2.5 tab, B5	Pleural fluid AFB neg, PCR-TB ***+ Mutation associated with INH resistant*** only were detected





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Case 1 continues

Date	Clinical	Medication	Remark
9/1/2558	Fever with cough for 3 wks Sputum smear positive 2+	INH(100) 3 tab, Rifam (300) 2 tab, PZA (500) 2.5 tab, etham (400) 2.5 tab, B5	Pleural fluid AFB neg, PCR-TB + Mutation associated with INH resistant only were detected
25/2/2558	Fever had gone, cough and dyspnea improved Sputum smear negative	Continuous IRZE	C/S TB: INH, Strep: resistant rifam, etham: sensitive PZA: sensitive
25/4/2558	No fever, BW ↑ 3 kgs	Off INH, Continues RZE	Plan RZE 6-9 mo.

สมาคมโรคติดเชื้อแห่งประเทศไทย
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What is the cause of this event?

1. TB involve brain
2. INH induce optic neuritis
3. Ethambutol toxicity
4. Side effect of prograft
5. All incorrect

Drug induce retrobulbar neuritis

- Ethambutol most common: risk factor (old age, ***renal impairment***)
- INH less common

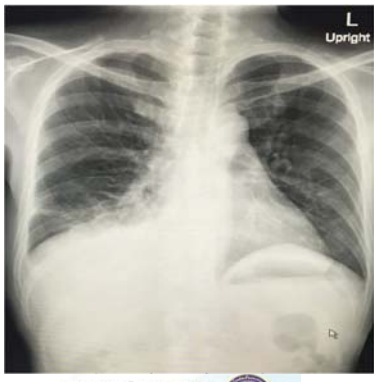
- Central fibers of optic nerve
  - First manifestation: dyschromatopsia (red-green or blue-yellow)
  - Central scotoma: ภาพตรงกลางดำมืด
- Peripheral fiber: visual field defect
- > 50% recovery (early stop)

Payam Nahid. ATS/CDC/IDSA. Treatment of Drug-Susceptible Tuberculosis. CID 2016

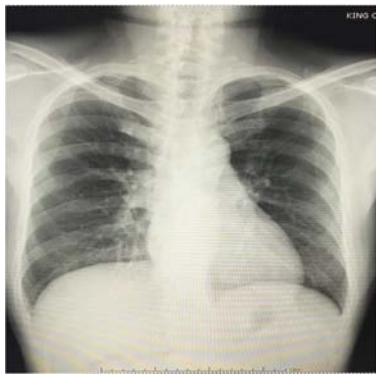
4/10/2558
Stop anti-TB (Total 9 mo)

18/3/2559
Much improve VF and VA 20/80, 20/60

25/2/2558



24/6/58

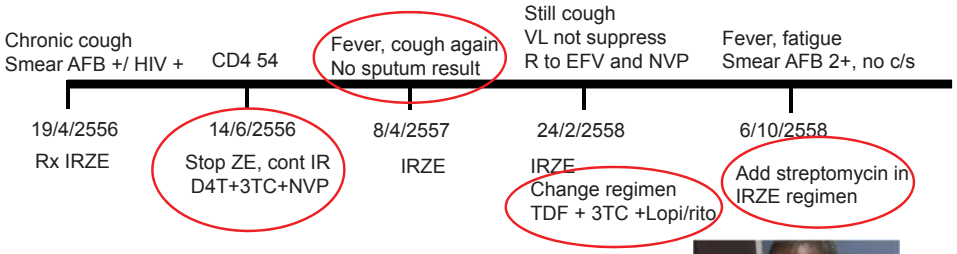


Recommendation doses of anti-TB in renal impairment patient

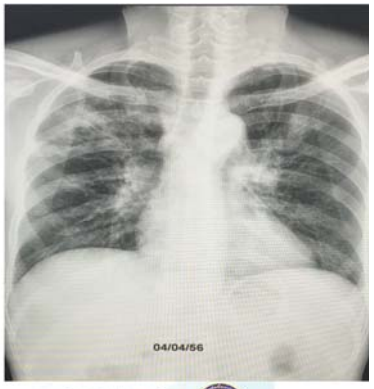
Anti-TB drugs	Frequency	Recommendation dose (CrCl < 30 ml/min)
Isoniazid	No change	Regular dose
Rifampicin	No change	Regular dose
Pyrazinamide	**Change**	**20-30 mg/kg, 3 times/wk**
Ethambutol	**Change**	**15-20 mg/kg, 3 times/wk**
Ofloxacin	**Change**	**600-800 mg/day, 3 times/wk**
Levofloxacin	**Change**	**750-1000 mg/day, 3 times/wk**
Moxifloxacin	No change	Regular dose
Cycloserine	**Change**	**250 mg/day (1 tab OD)**
Ethionamide	No change	Regular dose
PAS	No change	Regular dose
Aminoglycoside	**Change**	**15 mg/kg/day, 2-3 times/wk**

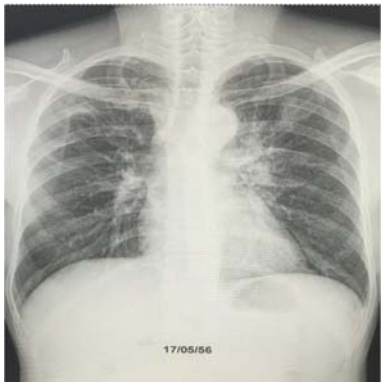
World Health Organization. Guideline for the programmatic management of drug-resistant tuberculosis

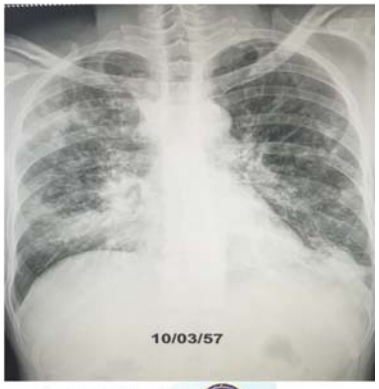
Case 2

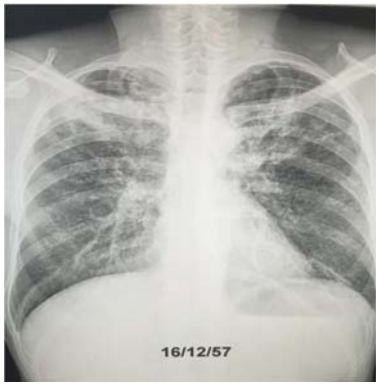


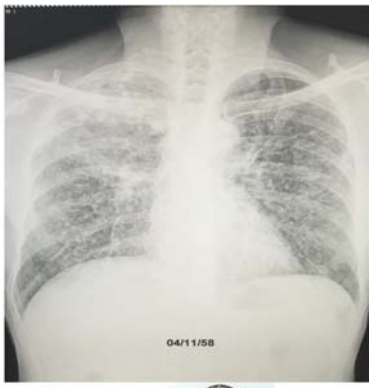
Clinical not improve, AFB persistent positive → refer to CU Dec 2558

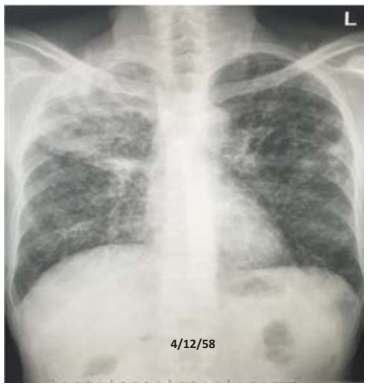












Clinically significant drug-drug interaction involving in *rifampicin and ARV*

ARV agent	Effect on Primary and/or Concomitant Drug Concentrations	Recommendations
Efavirenz	Efavirenz AUC ↓ 22%, Cmin ↓ 25%;	Maintain efavirenz dose at 600 mg once daily and monitor for virologic response
Nevirapine	Nevirapine AUC ↓ by >50%, Cmin ↓ 21-37%	**should be avoided if possible**. If necessary, initiate nevirapine no lead-in period)
Rilpivirine	Rilpivirine AUC ↓ 80%	**should be avoided**
Protease Inhibitors	Significantly ↓ PI exposure (>75%)	**should be avoided**
Raltegravir	Raltegravir AUC ↓ 40%, Cmin ↓ 60% Dolutegravir AUC ↓ 54%	Increase raltegravir dose to 800 mg PO twice daily, although clinical trial data show similar efficacy regular dose, Dolutegravir should be increased to 50 mg every 12 hr.

Rifabutin vs PI: PI level ok but higher level of rifabutin
Increase risk of uveitis (decrease dose from 300 mg/d→ 150 mg/d

Rifam reduces TAF plasma (not recommend)

Payam Nahid. ATS/CDC/IDSA. Treatment of Drug-Susceptible Tuberculosis. *CID* 2016

การให้ยาต้านเอชไอวีร่วมกับยาต้านวัณโรค

หลีกเลี่ยงการให้ Rifampin ร่วมกับ PI พิจารณายา efavirenz ก่อน nevirapine หรือ integrase inhibitor (ได้แก่ raltegravir/dolutegravir) เป็นส่วนประกอบแทน และให้สูตรยาวัณโรคตามปกติ

ถ้าไม่สามารถใช้ NNRTIs และ integrase inhibitor ได้ ให้พิจารณาปรับสูตร ยาวัณโรคเป็น 2 IEZ + quinolone/10-16IE + quinolone อาจพิจารณาเพิ่ม streptomycin ในช่วง 2 เดือนแรก ให้ระวังการดื้อกลุ่มยา quinolone ควร ส่งตรวจดื้อยาหากสงสัยมีการดื้อยา

การให้ยาต้านเอชไอวีร่วมกับยาต้านวัณโรค

กรณีที่มี rifampicin ในสูตรยารักษาวัณโรคให้พิจารณาดังนี้

1. Efavirenz ขนาด 600 มก./วัน
2. Nevirapine 200 มก. วันละ 2 ครั้ง โดยไม่ต้อง lead-in
3. Raltegravir ขนาด 400 มก. วันละ 2 ครั้ง
4. Dolutegravir (DTG) 50 มก. วันละ 2 ครั้ง

Group	Medicine	Abbreviation
Group A: Include all three medicines (unless they cannot be used)	Levefloxacin OR Moxifloxacin	Lfx, Mfx
	Bedaquiline	Bdq
	Linezolid	Lzd
Group B: Add both medicines (unless they cannot be used)	Clofazimine	Cfz
	Cycloserine OR Terizidone	Cs, Trd
Group C: Add to complete the regimen and when medicines from Groups A and B cannot be used	Ethambutol	E
	Delamanid	Dlm
	Pyrazinamide	Z
	Imipenem-cilastatin OR Meropenem	Ipm, Cln Mpm
	Amikacin (OR Streptomycin)	Am (S)
	Ethionamide OR Prothionamide	Eto, Pto
	p-aminosalicylic acid	PAS

WHO 2018

ART and drugs used to treat DR-TB

- Bedaquiline (metabolized by CYP3A4)
  - Model predicts EFV ***reduces steady-state concentration by 52%***
  - Nevirapine dose not affect concentrations
  - Lopinavir/ritonavir ***increase AUC at ~ 3 months by 62% (monitor QT)***
  - No interaction with integrase inhibitors or rilpivirine
- Effect of efavirenz-based ART on moxifloxacin
  - Clearance increased by 42%
  - ***AUC reduced by 30%***
  - Clinical implications: requires further study

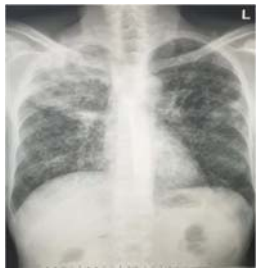
Svensson, Antimicrob Agents Chemother 2013
Pandie, J Antimicrob Chemother 2016

Recommendation of ATS/CDC/IDSA and WHO 2017

- A single new drug ***is never to be added to a failing regimen*** as it can lead to amplification of drug resistance, including acquired resistance to the newly added drug
- Recommendation in patients who require TB retreatment, ***the category II regimen should no longer be prescribed*** and drug-susceptibility testing should be conducted to inform the choice of treatment regimen (Good practice statement).

Payam Nahid. ATS/CDC/IDSA. Treatment of Drug-Susceptible Tuberculosis. CID 2016

WHO update 2017

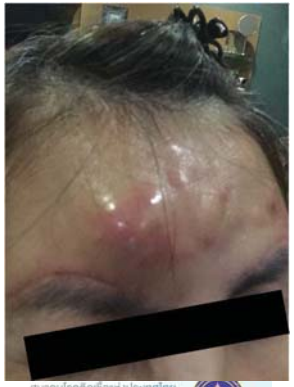


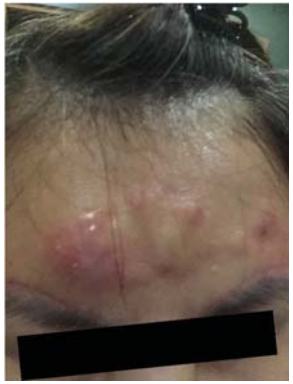
4/12/2558

Sputum AFB+, PCR-TB positive: Mutation associated with INH and Rif resistant were detected
Culture TB: pending

Lab baseline: TB 2.61, DB 2.01, ALP 172, SGOT 29, SGPT 12, Alb 2.6, BUN 10, Cr 0.96, Hct 24%

Case 3: 45 years old female, present with skin lesions after cosmetic surgery
(ร้อยไหม และ ฉีดฟิลเลอร์)





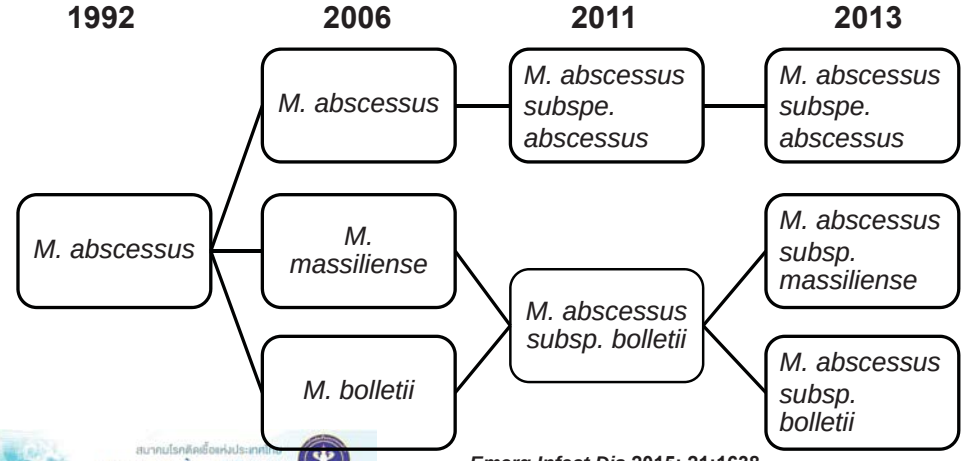
AFB smear positive/
PCR negative

Culture: *Mycobacterium abscessus*

What is the best appropriate management?

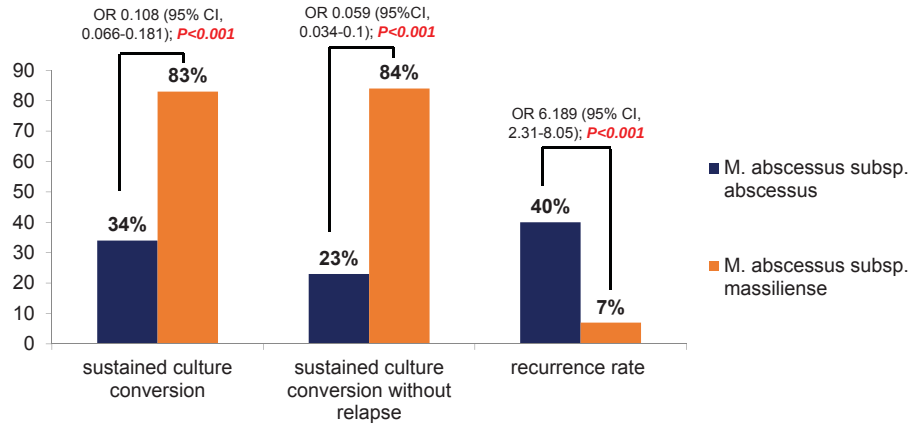
1. Clarithromycin at least 3-4 mo
2. Clarithromycin + levofloxacin + doxycycline at least 3-4 mo
3. Amikacin IV/M only first 2 wk + Clarithromycin + levofloxacin at least 3-4 mo
4. Clarithromycin + levofloxacin + Amikacin IV/M 3-4 mo
5. Clarithromycin + Amikacin IV/M + Cefoxitin + Imipenem 3-4 months

Evolution of taxonomy



Emerg Infect Dis 2015; 21:1638

Treatment of Pulmonary *M.abscessus* : systematic review 19 studies



M.abscessus: total N = 233
M.massiliense: total N =144

Antimicrob Agents Chemother 2017; Oct 24;61(11).

RGM characteristics: macrolide resistance

MAB subspecies	CLR susceptibility days 3-5	CLR susceptibility days 14	Macrolide susceptibility phenotype	Genetic implication	Macrolide effect
M. massiliense (M. abscessus)*	Susceptible	Susceptible	Macrolide susceptible	Dysfunctional erm**(41) gene	Anti-mycobacterial
M. abscessus M. bolletii	**Susceptible**	**Resistant**	**Inducible macrolide resistance**	**Functional erm(41) gene**	**Immuno-modulatory**
Any	Resistant	Resistant	High-level constitutive macrolide resistance	23S ribosomal RNA point mutation	Immuno-modulatory

*15-20% of M.abscessus have a dysfunctional erm41
**erm: erythromycin resistance methylase

***Thorax* 2017;72(Suppl 2):ii1**

M. abscessus

MIC	Interpretation
MIC ≤ 2µg/ml on day 3 and 14	Susceptible
Susceptible on day 3 but resistant on day 14 of DST	Inducible macrolide resistance
MIC ≥ 8µg/ml on day 3	Resistance

***Thorax* 2017;72(Suppl 2):ii1**

The erm gene: dominant in ***M.abscessus* subsp. *abscessus*, *M.abscessus* subsp. *bolloltii*, and *M.fortitum*** strains but not in *M. chelonae*

↓

promotes methylation of the 23S rRNA

↓

bacteria resistant against macrolides → Use of monotherapy of macrolide for infections caused by RGM ***is not recommended***

***PLOS Neglected Tropical Diseases* Feb 14, 2019**

Percent of inducible macrolide resistance among *M. abscessus* subspecies.

	Korea (*IJID* 2017)	Taiwan (*JAC* 2017)	Thailand (*PloS Med* 2018)
M. abscessus subsp. *abscessus* (% inducible macrolide resistance)	8/10 (80%)	16/28 (57%)	**21/29 (72.4%)**
M. abscessus subsp. *massiliense* (% inducible macrolide resistance)	0/10 (0%)	0/38 (0%)	0/35 (0%)
M. abscessus subsp. bolletii	0	0/1	-

Treatment of *M. abscessus*

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Mycobacterium abscessus	Antibiotic regimen
Clarithromycin sensitive or inducible macrolide-resistant isolates	**Initial phase: ≥ 1 month**[a]

[a]due to poorer response rate in patients with inducible or constitutive macrolide resistant isolates, ***IV antibiotic should extend to 3-6 months*** as tolerate

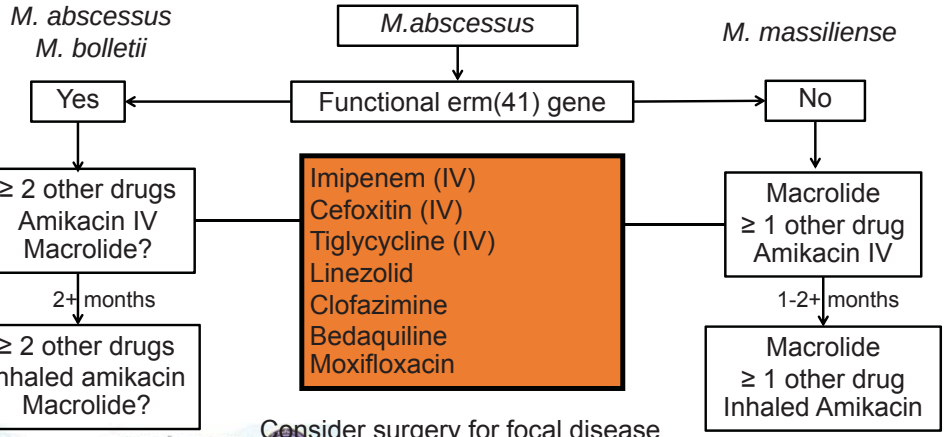
British Thoracic Society Guidelines 2017

Mycobacterium abscessus	Antibiotic regimen
Macrolide-resistant isolates	**Initial phase: ≥ 1 month**[a]

[a] due to poorer response rate in patients with inducible or constitutive macrolide resistant isolates, ***IV antibiotic should extend to 3-6 months*** as tolerate

British Thoracic Society Guidelines 2017

Treatment of *M.abscessus* group



Consider surgery for focal disease
Duration 12 mos culture negativity

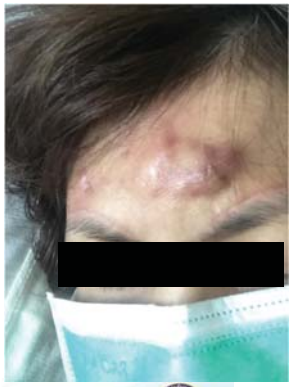
Shanon K; USA guideline

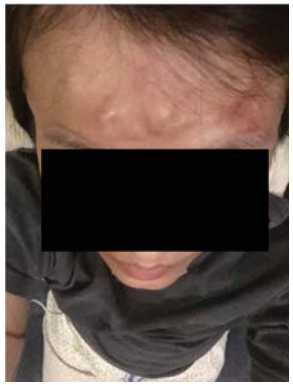
Summary of recommendations from previous studies for the treatment of *Mycobacterium abscessus* complex infections in humans

Type of disease	Recommended initial regimen	Recommended Rx duration
Pulmonary	macrolide-based Rx in combination of IV antimicrobial Rx	until sputum negative for 12 mo.
Skin and soft-tissue infection	macrolide in combination with Amikacin plus cefoxitin/imipenem plus surgical debridement	Minimum of 4 mo, including of 2 wk combined with IV agents
Central nervous system infection	clarithromycin-based combination with IV antimicrobial Rx	at least 12 mo

Meng-Rui Lee. *Emerging Infectious Diseases* 2015

1 months after treatment





M. abscessus subsp. *abscessus*

Susceptible on day 3 but resistant on day 14 of DST

inducible macrolide resistance

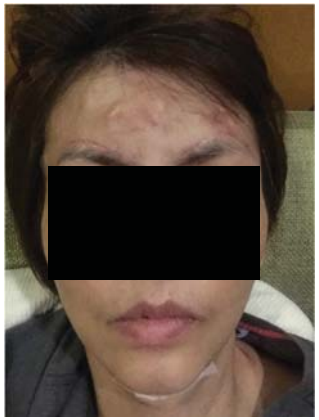
Extended Amikacin IM to 3 months

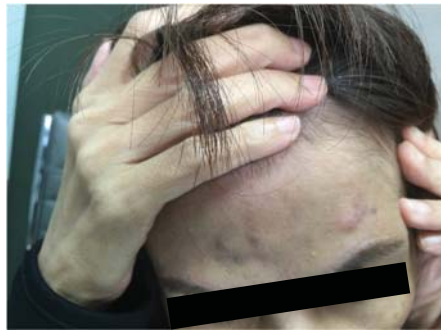
Summary the resistance of *M. abscessus* to different antimicrobial agents

Study	N	Percent resistant					
		CLR	DOX	MXF	FOX	AMK	IPM
Multicenter study	749	13.9%	85.1%	74.1%	15.1%	7.7%	55.6%
USA study	64	6.2%	87.7%	93.8%	4.7%	0%	65.6%
Chulalongkorn*	**30**	**0%**	**80%**	**90%**	**50% (I*=46.6%)**	**0%**	**96%**

***Linezolid: resistant 10/30 (33.3%), sensitive 13/30 (43.3%), Intermediate 7/30**

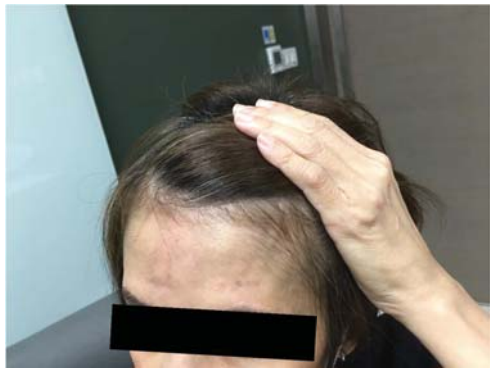
Meng-Rui Lee, *Emerging Infectious Diseases* 2015

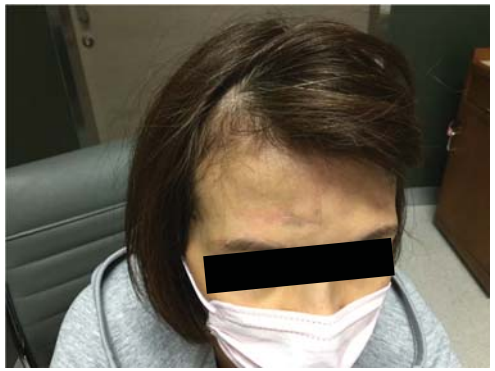




Aug 2018

4 months after treatment





Nov 2018

Take home messages

- Ethambutol can cause ***retrobulbar neuritis*** especially in elderly and impaired renal function patient
- A ***single new drug is never to be added*** to a failing regimen as it can lead to amplification of drug resistance
- Rifampicin ***should be avoided*** concomitant with protease inhibitor and rilpivirine

Take home messages

- **Identification of subsp. of *M.abscessus*** can help predict whether there is a higher propensity for recurrence or relapse and choice of oral antibiotics and duration of IV antibiotic

- **Extended-culture-based methods** have to do especially, *M. abscessus* subsp*. abscessus* in order to appropriate duration and choice of antimicrobial agents

Thank you very much for your attention!

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