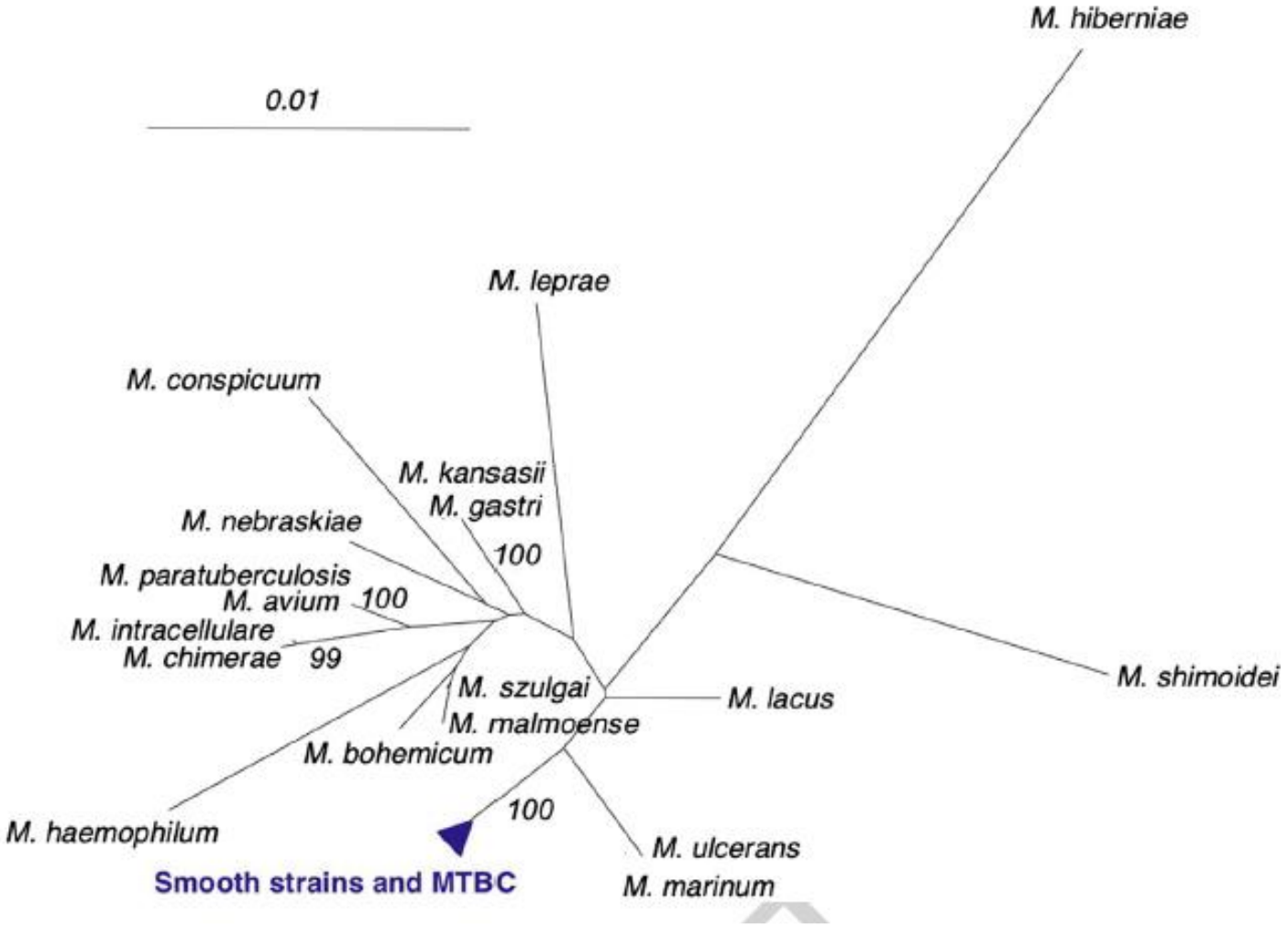
Mycobacteriosisok

Somosközi Ákos

Phylogenetic position of the MTBC and NTM within the genus *Mycobacteria*



Gutierrez and Somoskovi 2014 Encyclopedia of Human Biology

Increased identification of NTMs

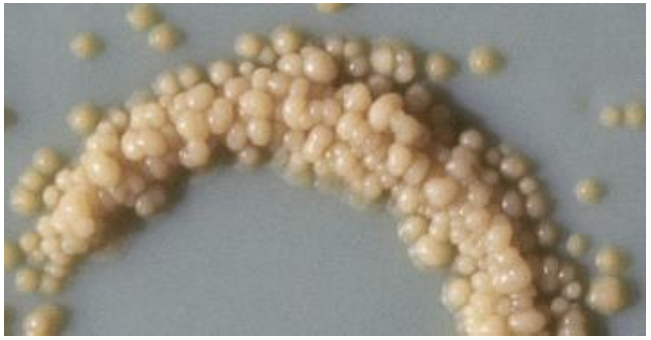
- Plethora of novel diagnostic (liquid culture) and identification methods (DNA sequencing)
- Nomenclature:
  - Atypical mycobacterium, MOTT, NTM
- Slow growers and rapid growers (</> 7 days)
- Scotochromogenic (in dark) or non-chromogenic (after light exposure)
- In 1980 41 valid species, currently 159

Saprophytic, opportunistic, pathogenic?

- Colonization vs. infection and disease manifestation
  - Presence or absence of host immune reaction (skin test, antibody) without disease manifestation
  - Transient, intermittent, prolonged
- Human to human transmission
  - Inhalation, GI ingestion, skin lesions
- Natural or manmade reservoir,
  - Natural and treated water systems, hot tub, foot bath, shower, tattoo ink, surgical ink, surgical ice, fish tanks, surgical equipment and endoscopes, piercing, implants
- Biofilms
  - plastic, rubber, glass, metal, metallic fluid
- Pseudo-infection

Determining clinical significance or pathogenic potential is crucial

- Almost all NTM are ubiquitous in the environment
- Obligatory pathogens
  - *M. tuberculosis complex, M. leprae, M. ulcerans*
- Human to human transmission?
- Opportunistic
  - *M. kansasii, M. szulgai*
  - *M. mucogenicum, M. terrae* from respiratory
- Saprophytes
  - *M. gordonae, M. vaccae, M. phlei*



What do we need to consider?

- Underlying/ associated diseases
  - Immunocompromised/ autoimmune (Rheumatoid arthritis or similar systemic inflammatory diseases)
  - Cystic fibrosis
  - Ciliary dyskinesia
  - COPD
  - Pneumoconiosis
  - Alveolar proteinosis
  - Esophageal disorders
- Clinical signs and symptoms
  - inflammation, granuloma etc.
  - Recidive acute exacerbations (fever, cough, sputum, hemoptysis, weight loss etc.)
- Radiologic appearance
  - (Nodular) bronchiectasis (limited, advanced)
  - Reticulonodular lung infiltration
  - “tree in buds” appearance
  - Apical fibrocavitary

What do we need to consider?

- Immunologic status of patient
  - HIV, TNF alpha blocker, corticosteroid or cancer therapy
- Site of disease or specimen was taken
  - Sterile body site, skin-soft tissue or respiratory specimen
- Respiratory tract
  - Number of positive cultures
  - CFU
  - Smear status
  - Multiple specimens (from same site)

ATS Criteria for Clinical Significance in Respiratory Tract

Clinical (both required)

1. Pulmonary symptoms, nodular or cavitary opacities on chest radiograph, or a high-resolution computed tomography scan that shows multifocal bronchiectasis with multiple small nodules (A, I)*

and

2. Appropriate exclusion of other diagnoses (A, I)

Microbiologic

1. Positive culture results from at least two separate expectorated sputum samples (A, II). If the results from (1) are nondiagnostic, consider repeat sputum AFB smears and cultures (C, III).

or

2. Positive culture result from at least one bronchial wash or lavage (C, III)

or

3. Transbronchial or other lung biopsy with mycobacterial histopathologic features (granulomatous inflammation or AFB) and positive culture for NTM or biopsy showing mycobacterial histopathologic features (granulomatous inflammation or AFB) and one or more sputum or bronchial washings that are culture positive for NTM (A, II)
4. Expert consultation should be obtained when NTM are recovered that are either infrequently encountered or that usually represent environmental contamination (C, III)
5. Patients who are suspected of having NTM lung disease but do not meet the diagnostic criteria should be followed until the diagnosis is firmly established or excluded (C, III)
6. Making the diagnosis of NTM lung disease does not, *per se*, necessitate the institution of therapy, which is a decision based on potential risks and benefits of therapy for individual patients (C, III)

* For evidence quality, *see* Table 1.

ATS 2007

Clinically significant NTMs with pulmonary disease

Common	Page	Comment	Uncommon	Page	Comment
		Pulmonary Disease			
M. abscessus	396	Worldwide; may be found concomitant with MAC	*M. asiaticum**		Rarely isolated
M. avium complex	386	Worldwide; most common NTM pathogen in U.S.	*M. celatum**		Cross-reactivity with TB-DNA probe
M. kansasii	395	U.S., Europe, South Africa, coal-mining regions	*M. chelonae*	398	
M. malmoense	399	U.K., northern Europe; uncommon in U.S.	*M. fortuitum*	398	Associated with aspiration
			M. haemophilum	399	Rarely isolated
M. xenopi	402	Europe, Canada; uncommon in U.S.; associated with pseudoinfection	*M. scrofulaceum*	400	South Africa; uncommon in U.S.
			*M. shimoidei**		Rarely isolated
			M. simiae	401	Southwest U.S., associated with pseudo-outbreaks
			M. smegmatis	401	Rarely isolated
			M. szulgai	401	Rarely isolated, not an environmental contaminant

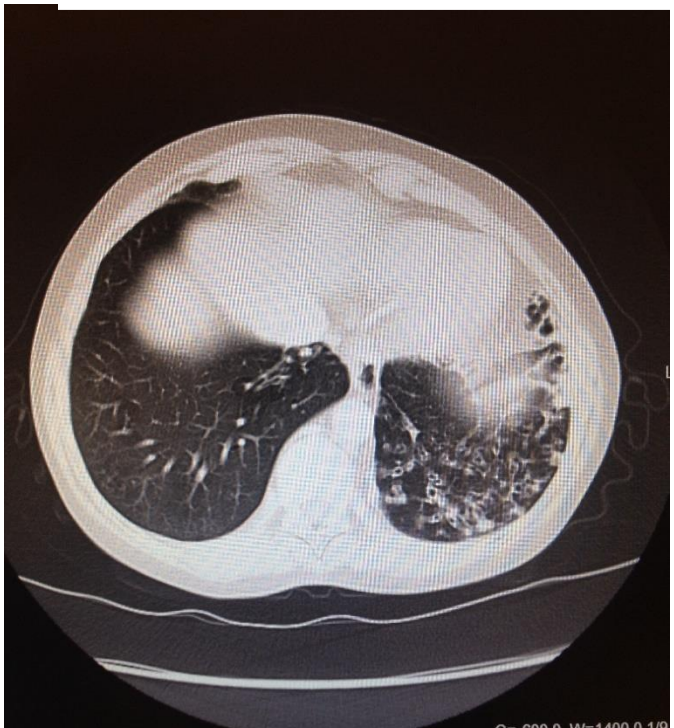
ATS 2007

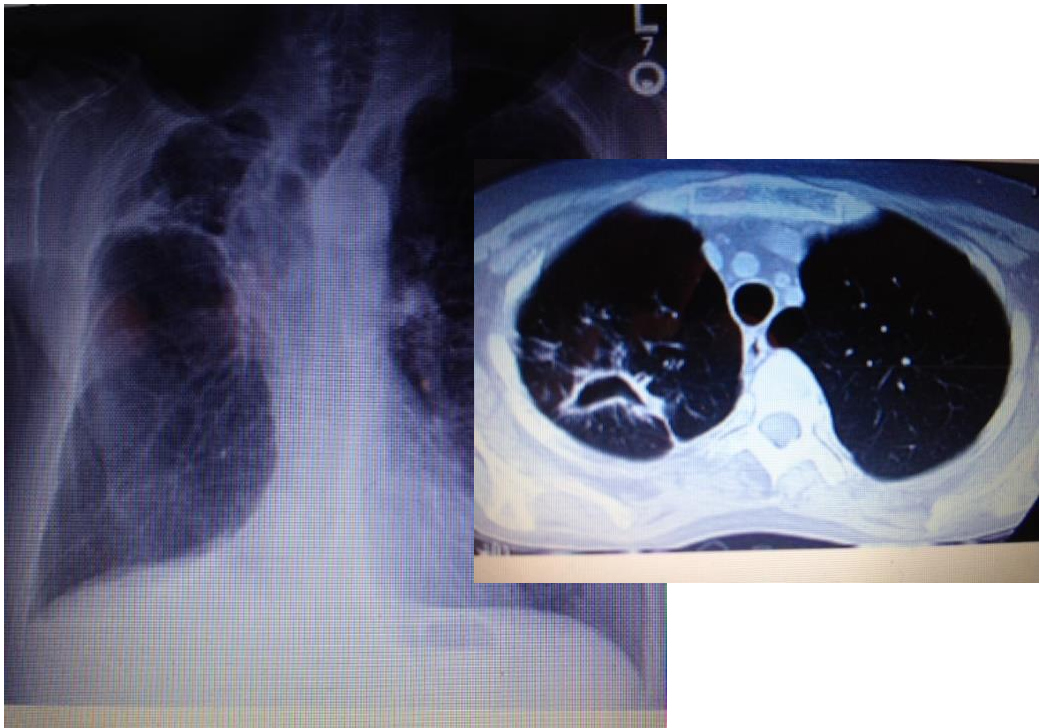
Clinical and radiological presentation of most common NTM with pulmonary manifestation

Table 2
Clinical and radiologic findings in pulmonary nontuberculous mycobacteria infections

Signs and Symptoms	Radiology
Cough (chronic)	Fibrocavitary: *M avium* complex
Fatigue	Nodular and interstitial nodular infiltrates: *M avium* complex
Weight loss	Fibrocavitary: *M kansasii*
Hemoptysis	Multilobar, reticulonodular, or mixed reticulonodular-alveolar
Dyspnea	Opacities: *M abscessus* complex

Data from Daley CL. Nontuberculous mycobacterial infections. Eur Respir Mon 2011;52:115–29.





NTM pulmonary infections
Who to treat?

- Patient
  - Increased susceptibility?
  - Clinical symptoms and overall condition of patient
  - Extent of radiograph abnormalities and if there is evidence of progression
- Organism
  - Species has been isolated
  - Bacteriologic load (smear +/-)
- Overall goal of therapy
  - Cure, bacteriologic conversion, symptom relief, prevention of progression

Treatment of MAC diseases

	Initial Therapy for Nodular/Bronchiectatic Disease*	Evidence Quality†	Initial Therapy for Cavitary Disease	Evidence Quality†	Advanced (Severe) or Previously Treated Disease	Evidence Quality†
Macrolide	Clarithromycin 1,000 mg TIW or azithromycin 500–600 mg TIW	B, II	Clarithromycin 500‡–1,000 mg/d or azithromycin 250–300 mg/d	A, II	Clarithromycin 500‡–1,000 mg/d or azithromycin 250–300 mg/d	B, II
Ethambutol	25 mg/kg TIW		15 mg/kg/d		15 mg/kg/d	
Rifamycin	Rifampin 600 mg TIW		Rifampin 450‡–600 mg/d		Rifabutin 150‡–300 mg/d or rifampin 450‡–600 mg/d	
IV aminoglycoside	None		Streptomycin or amikacin§ or none		Streptomycin or amikacin§	

Definition of abbreviations: IV = intravenous; TIW = three times weekly.

* Not recommended for severe or previously treated disease.

† Rating for entire multidrug regimen, not necessarily for individual agents. For evidence quality, *see* Table 1.

‡ Lower dose for weight < 50 kg.

§ *See* text for dosing recommendation.

ATS 2007

Treatment outcome of SGM

- *M. kansasii* > 95%
  - INH (macrolid), RMP, EMB
- MAC 60-85%
  - Macrolid, RMP, EMB

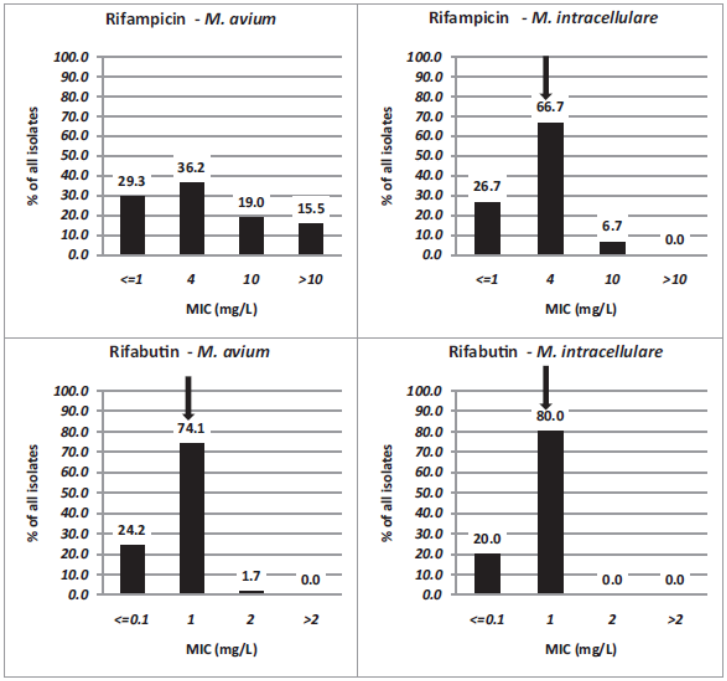
ATS 2007

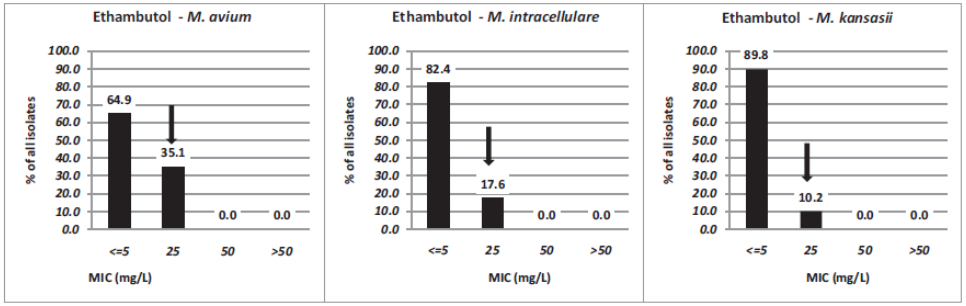
Drug susceptibility distributions in slowly growing non-tuberculous mycobacteria using MGIT 960 TB eXiST

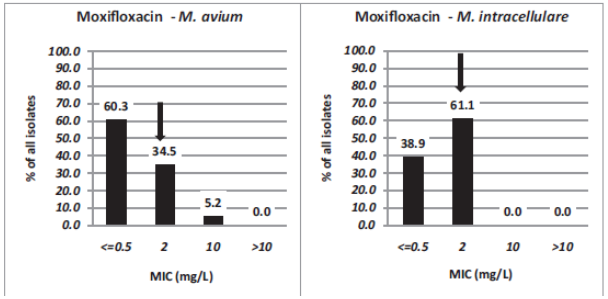
Michael Hombach*, Akos Somosközi, Rico Hömke, Claudia Ritter, Erik C. Böttger

Institut für Medizinische Mikrobiologie, Universität Zürich, Nationales Zentrum für Mykobakterien, Zürich, Switzerland

- Importance of ECOFF (epidemiological cut off) vs. clinically sensitive breakpoint







Hombach et al. 2013 Int J Med Microbiol

Antimicrobial agent	MIC (mg/L) of susceptible *Mycobacterium tuberculosis*[a]	Concentration (mg/L) in serum[b]	Concentration (mg/L) used for testing[c]	
			Low	High
Isoniazid	0.05–0.2	5–10	0.1	0.4
Rifampin	0.5	10	2	–
Pyrazinamide	20	40–50	100	–
Ethambutol	1–5	2–5	2.5	7.5
Ofloxacin	0.25–0.5	2–10	2	–
Ethionamide	0.5–2.5	2–20	1.25	–
Streptomycin	0.5–1.0	25–50	2	6
Amikacin	0.5–1.0	20–40	1	–
Capreomycin	2–5	10–30	5	–

[a]MIC of wild-type *M. tuberculosis*.
[b]Concentrations 1–4 h after usual dosage.
[c]Drug concentration ('critical concentration') used for testing in the diagnostic laboratory; these concentrations may differ slightly for different media, e.g. BACTEC broth, 7H10 medium, and 7H11 medium.

Clinically significant newly recognized slow growers

Prosthetic Valve Endocarditis and Bloodstream Infection Due to *Mycobacterium chimaera*

Yvonne Achermann,[a] Matthias Rössle,[b] Matthias Hoffmann,[c] Vanessa Deggim,[d] Stefan Kuster,[a] Dieter R. Zimmermann,[b] Guido Bloemberg,[d] Michael Hombach,[d] Barbara Hasse[a]

Division of Infectious Diseases and Hospital Epidemiology, University and University Hospital Zurich, Zurich, Switzerland[a]; Institute of Clinical Pathology, University and University Hospital Zurich, Zurich, Switzerland[b]; Division of Infectious Diseases and Hospital Epidemiology, Cantonal Hospital St. Gallen, St. Gallen, Switzerland[c]; Institute of Medical Microbiology, University of Zurich, Zurich, Switzerland[d]

Prosthetic valve endocarditis (PVE) due to fast-growing nontuberculous mycobacteria (NTM) has been reported anecdotally. Reports of PVE with slowly growing NTM, however, are lacking. We present here one case of PVE and one case of bloodstream infection caused by *Mycobacterium chimaera*. Randomly amplified polymorphic DNA (RAPD)-PCR indicated a relatedness of the two *M. chimaera* strains. Both patients had heart surgery 2 years apart from each other. A nosocomial link was not detected.

- *M. avium* complex
  - *M. avium subsp. avium/ hominissuis/ paratub.*
  - *M. intracellulare*
  - *M. chimaera*

Achermann et al. J Clin Microbiol, 2013

Clinically significant rapid growers

- *M. abscessus complex*
  - *M. abscessus senso lato*
  - *M. bolletii*
  - *M. massiliense*
- *M. chelonae*
  - Skin, soft tissue, bone
  - Tattoo ink, piercing, esthetic surgery
  - Liposuction
  - LASIK, contact lens related keratitis
- *M. fortuitum*
  - Skin, soft tissue, bone
  - Mammoplasty,
  - Nail salon footbaths (man made new reservoirs)

M. abscessus complex

- Rapid grower, non-chromogenic
- Water (drinking), soil
- White, female, > 60 years, no predisposing factors
- Bronchiectasis
- Reticulonodular lung infiltration
- CF
- achalasia (vomiting)
- Chemotherapy resistant

- *M. abscessus* subsp. *abscessus*
- *M. abscessus* subsp. *bolletii*
- *M. abscessus* subsp. *massiliense*

Postsurgical wound infections due to rapidly growing mycobacteria in Swiss medical tourists following cosmetic surgery in Latin America between 2012 and 2014

F P Maurer (florian.maurer@imm.uzh.ch)[1,2], C Castelberg[1], A von Braun[3], A Wolfensberger[3], G V Bloemberg[1], E C Böttger[1,2], A Somoskovi[1,2]

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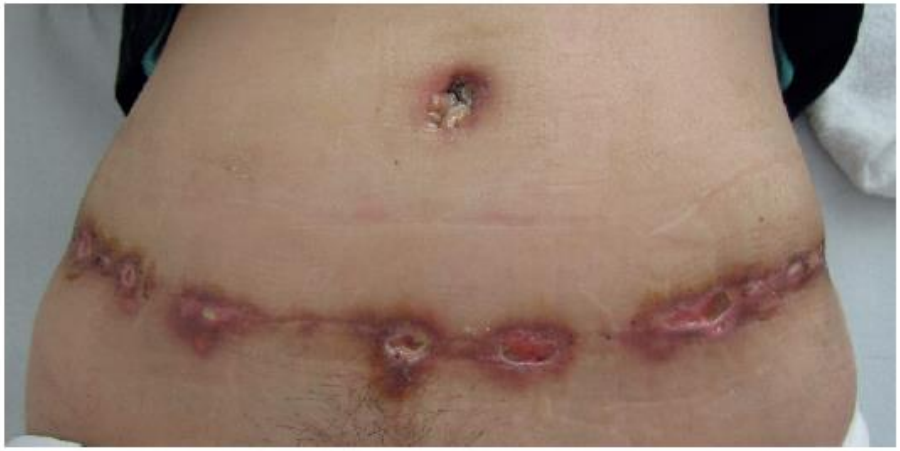
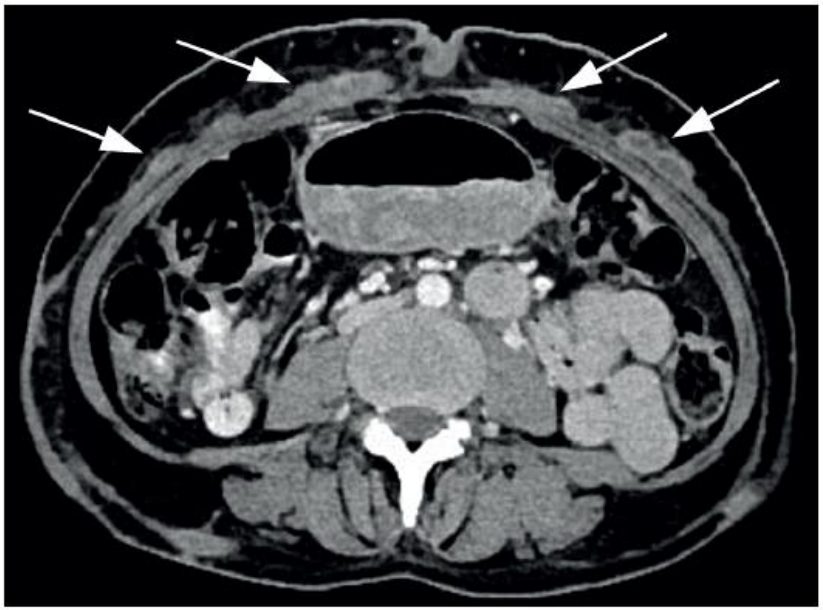


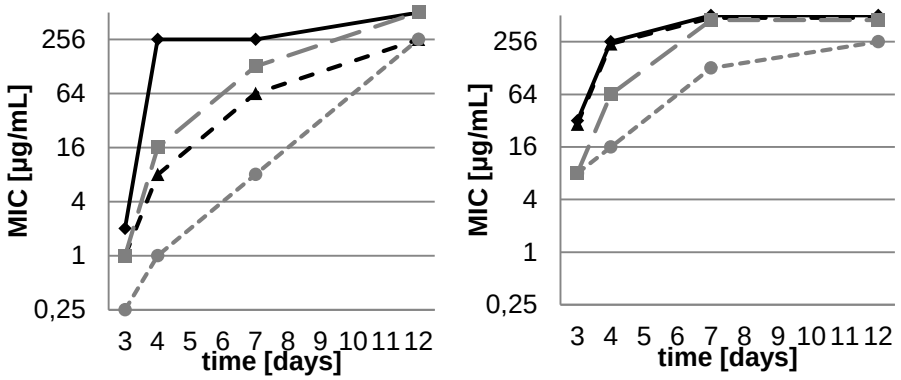


Maurer et al. 2014 Eurosurveillance

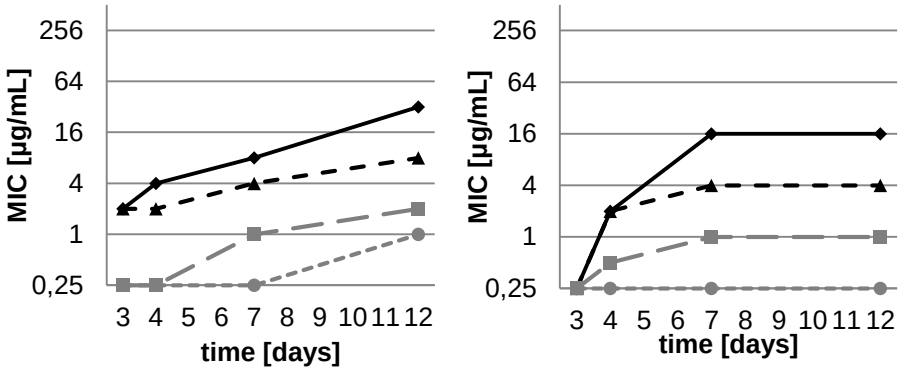
Typical DST panel of *M. abscessus* supsp. *abscessus*

Getestete Antibiotika	Grenzwerte mg/l Tag 7		Mikrodilution	Mikrodilution	Mikrodilution	Mikrodilution	Mikrodilution	
	sensibel	resistent	201231135	201231135	201231135	201231135	201231135	
			2012181337	2012181337	2012181337	2012181337	2012181337	
			30.08.2013	30.08.2013	30.08.2013	30.08.2013	30.08.2013	
Ablesetag			Tag 3	Tag 5	Tag 7	Tag 9	Tag 12	
Amikacin	≤ 16.0	≥ 64.0	1-2	2	2	4-8	4-8	
Tobramycin	≤ 4.0 (2)	≥ 16.0 (8)	2-4	4-8	8	8	8-16	
Streptomycin	-	-	2-4	4-8	8-16	16-32	16-32	
Capreomycin	-	-	32-64	256	256	>256	>256	
Gentamycin	-	-	2-4	4-8	4	4-8	8	
Clarithromycin	≤ 16.0 (2)	≥ 64.0 (8)	<0.5	<0.5	'1-2	8-16	16-32	Induktion
Cefoxitin	≤ 16.0	≥128.0	64-128	128	128-256	>256	>256	
Ciprofloxacin	≤ 1.0	≥ 4.0	2-4	4-8	8-16	8-16	16-32	
Levofloxacin	≤ 1.0 (keine)	≥ 4.0 (keine)	4-8	4-8	8-16	16-32	16-32	
Moxifloxacin	≤ 0.5 (1)	≥ 2.0 (4)	2-4	2-4	4	4-8	4-8	
Linezolid	≤ 8.0	≥ 32.0	1-2	2-4	2-4	4-8	4-8	
Doxycyclin	≤ 1.0	≥ 16.0 (8)	128	256	>256	>256	>256	
Tigecyclin	-	-	0.25-0.5	4-8	8	8-16	16-32	
Minocyclin	-	-	128	256	256	256	256	
Ethambutol	-	-	128-256	256	>256	>256	>256	
Imipenem	≤ 4.0	≥ 16.0 (32)	128	128-256	>256	>256	>256	
Meropenem	-	-	256	>256	>256	>256	>256	
Azythromycin	-	-	0.5-1	8-16	64	128-256	256	
Tetracyclin	-	-	128-256	256	256	>256	>256	
Clofazimine	,-	,-	<0.5	<0.5	<0.5	<0.5	<0.5	
Polymixine B			256	>256	>256	>256	>256	
Polymixin E	-	-	256	>256	>256	>256	>256	
Thioridazin	-	-	32	32	32	32-64	32-64	
		rrl: WT, keine Mut.; erm41: T28			CFU=20			

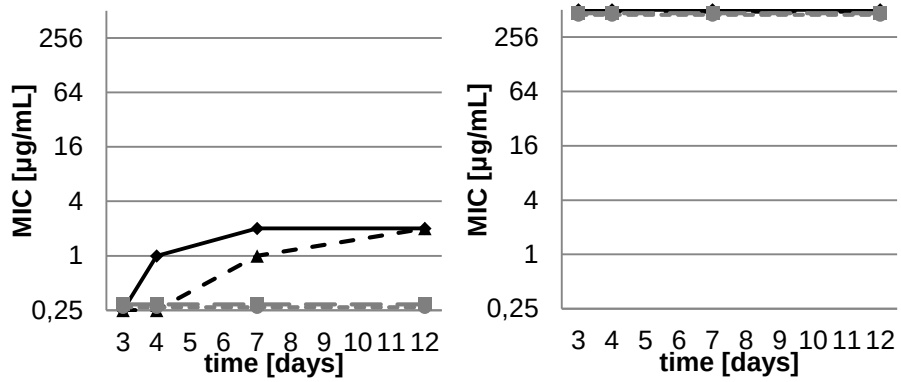
M. abscessus subsp. abscessus T28



M. abscessus subsp. abscessus C28

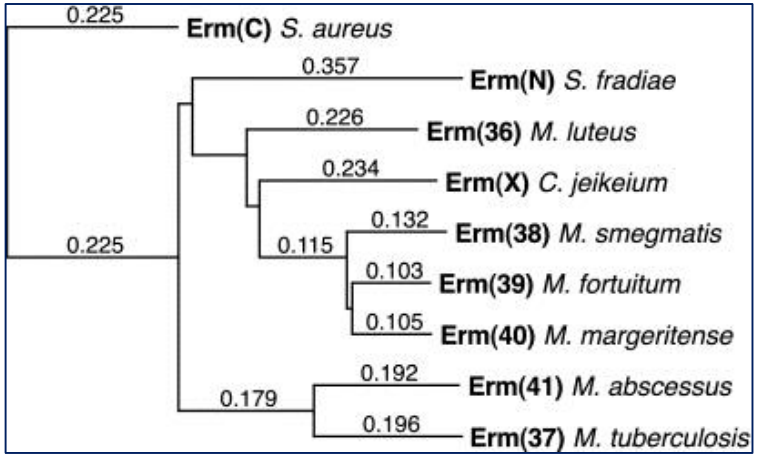


M. abscessus subsp. massiliense



Members of the *M. abscessus* complex differ in *erm*(41) and inducible macrolide resistance

erm(41) gene feature	*M. abscessus*	*M. bolletii*	*M. massiliense*
Size of PCR1 amplicon (bp)	892	892	616
Promoter sequence at position −35	TATCGA	TGTCGA	TGTCGA
Nucleotide at position 28	T or C	T	T
Deletion	No	No	Nucleotides 64 and 65; 276 bp after nucleotide 158[b]



Bastian et al. AAC 2011

Mauer and Somoskovi AAC 2014

Clinical relevance of isolation

- N=95
- *M. abscessus* (inducible or non-inducible phenotype?)
  - 50% (9/18) met ATS criteria
- *M. massiliense* (non-inducible deletion of erm41)
  - 29% (2/7) met ATS criteria
- *M. bolletii*
- 20% (1/5) met ATS criteria

van Ingen et al. 2009 J Infect

CF and MAB and lung transplant

Patient No.	Sex and Age (y)*	Age at LTx (y)	Mycobacteria	Other Infections	ABPA	Culture Positive at Time of LTx	Outcomes
1	M 39	39	*M abscessus*	*S maltophilia*	No	Yes	Sputum positive just prior to LTx. Received inadequate treatment initially. Still BAL-positive. Well 1 y post-LTx.
2	F 25	29	MAC	*P aeruginosa*	Yes	No	Well 13 y after LTx.
3	M 18	35	*M abscessus*	*P aeruginosa*	No	No	Poor lung function due to chronic rejection 8 mo after LTx.
4	F 7	19	MAC	*A xylosoxidans*	Yes	No	Deteriorating lung function 5 y after LTx.
5	M 13	22	*M abscessus*	*A xylosoxidans*	No	Yes	Well 2 y after LTx, but ongoing *M abscessus* in substernal abscess.
6	F 13	22	*M abscessus*	*P aeruginosa P apista*	Yes	Yes	Received continuous NTM treatment. Died 19 days post-LTx from ARDS/graft dysfunction.
7	M 20	30	*M abscessus*	*P aeruginosa*	No	Yes	Initial deep tissue *M abscessus* infection. Well and culture negative 4 y post-LTx.
8	F 10	26	*M abscessus*	*S maltophilia*	No	No	Died 3 y after LTx from chronic rejection.
9	M 20	29	*M abscessus*	*S maltophilia*	Yes	Yes	Died 2 mo after LTx from invasive *Aspergillus* infection. No NTM at autopsy.

Quist et al. 2013 Transpl Proc

Treatment of *M. abscesuss*

Macrolid p.o.

+

Amikacin i.v.

+

Cefoxitim or imipenem i.v.

2-4 months

→

- Macrolid + inh. amikacin
- Intermittent i.v. regimen
- Macrolid + other oral

  - Linezolid
  - FQ
  - Clofazimine
  - cyclin

Treatment Outcomes for *M. abscessus* Lung Disease
National Jewish Denver

Culture conv.	n	Medical n	Surgical+Med n
Conv., no relapse	33 (48%)	18 (39%)	15 (65%)
Never. Conv.	36 (52%)	28 (61%)	8 (35%)

25% MASS vs 75% MAB

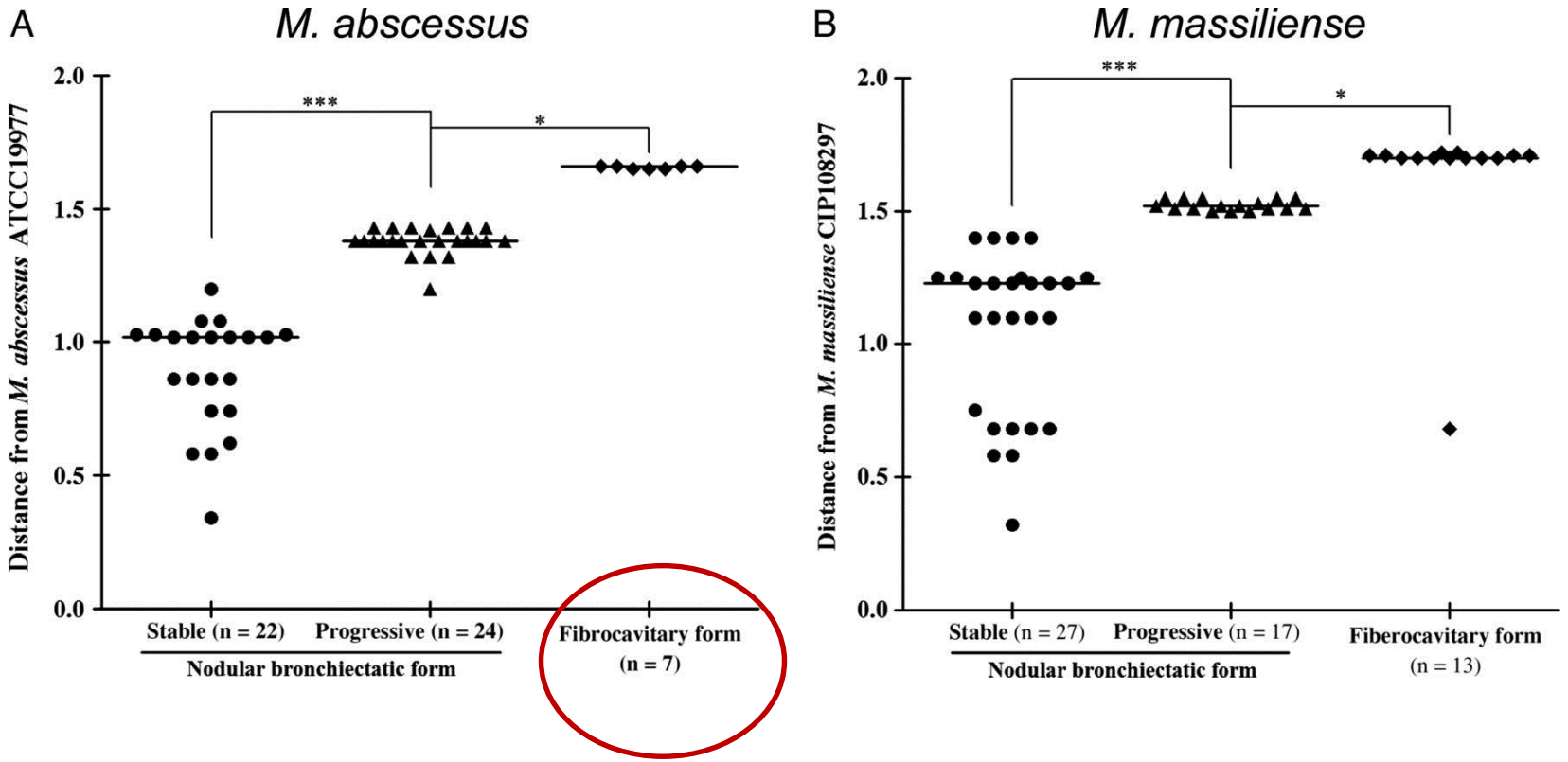
CID 2011

Acquired macrolide resistance: *rrl* gene associated point mutations

Patient	Isolate	Source	Date of isolation: month/year	months since first isolate	Clarithromycin MIC (mg/L) by method: microdilution day 3	microdilution day 7	microdilution day 14	Etest day 7	Genotype: *erm*(41)[a]	23S peptidyltransferase region	*rpoB*
Control	MAZ01.1	left forearm	08/08	0	0.5	1	1	0.064	C28	wild-type	*M. abscessus* subsp. *abscessus*
MAZ02	MAZ02.1	respiratory tract	06/08	0	1	>128	>128	0.5	T28	wild-type	*M. abscessus* subsp. *abscessus*
	MAZ02.2	respiratory tract	10/08	4	2	>128	>128	0.125	T28	wild-type	
	MAZ02.3	respiratory tract	02/09	8	2	>128	>128	0.25	T28	wild-type	
	MAZ02.4	respiratory tract	10/09	16	1	>128	>128	1	T28	wild-type	
	MAZ02.5	respiratory tract	08/11	38	0.5	128	>128	4–256	T28	wild-type	
MAZ03	MAZ03.1	respiratory tract	01/09	0	0.5–8	64	128	0.25	T28	wild-type	*M. abscessus* subsp. *abscessus*
	MAZ03.2	respiratory tract	05/09	5	<0.25	4	128	0.5	ND	wild-type	
	MAZ03.3	respiratory tract	07/09	7	2	>128	>128	6–256	ND	wild-type	
	MAZ03.4	respiratory tract	09/09	9	<0.25	>128	>128	>256	T28	wild-type	
	MAZ03.5	respiratory tract	04/10	16	<0.25	>128	>128	8–256	ND	wild-type	
	MAZ03.6	respiratory tract	08/10	20	<0.25	>128	>128	>256	ND	wild-type	
	MAZ03.7	respiratory tract	12/10	23	<0.25	>128	>128	>256	ND	wild-type	
	MAZ03.8	respiratory tract	01/11	24	<0.25	>128	>128	>256	T28	wild-type	
	MAZ03.9	wound secretion	01/11	24	<0.25	>128	>128	>256	ND	wild-type	
MAZ04	MAZ04.1	sputum	04/07	0	<0.25	8	64	0.032–0.5	T28	wild-type	*M. abscessus* subsp. *abscessus*
	MAZ04.2	sputum	07/08	15	0.5	>128	>128	0.25–256	T28	wild-type/2058A→G[b]	
	MAZ04.3	sputum	08/09	28	32	>128	>128	>256	T28	2058A→G	
	MAZ04.4	sputum	10/11	54	128	>128	>128	>256	T28	2058A→G	
MAZ07	MAZ07.1	respiratory tract	06/08	0	0.5	16	>128	0.19	T28	wild-type	*M. abscessus* subsp. *abscessus*
	MAZ07.2	respiratory tract	02/09	8	0.5	>128	>128	0.125–256	T28	wild-type/2058A→G[b]	
	MAZ07.3	respiratory tract	04/09	10	1–128	>128	>128	1–256	T28	wild-type/2058A→C/2058A→G[b]	
	MAZ07.4	respiratory tract	09/09	15	2–128	>128	>128	1–256	T28	wild-type/2058A→C/2058A→G[b]	
	MAZ07.5	respiratory tract	12/09	18	>128	>128	>128	>256	T28	2058A→C/2058A→G[b]	
	MAZ07.6	respiratory tract	12/10	30	>128	>128	>128	>256	T28	2058A→C/2058A→G[b]	
	MAZ07.7	respiratory tract	01/11	31	>128	>128	>128	>256	T28	2058A→C/2058A→G[b]	
MAZ08	MAZ08.1	respiratory tract	08/08	0	<0.25	16	>128	1–256	T28	wild-type	*M. abscessus* subsp. *abscessus*
	MAZ08.2	respiratory tract	10/10	26	>128	>128	>128	>256	T28	wild-type/2058A→G[b]	
	MAZ08.3	respiratory tract	12/10	28	>128	>128	>128	>256	T28	wild-type/2058A→G[b]	
	MAZ08.4[c]	respiratory tract	08/11	36	1	>128	>128	1.5–256	T28	wild-type	
MC879[d]	850	sputum	06/91	0	0.5	4	32	ND	T28	wild-type	*M. abscessus* subsp. *abscessus*
	852	sputum	09/93	27	>128	>128	>128	ND	T28	2058A→C	
MC958[d]	855	BAL	11/91	0	0.5	16	>128	ND	T28	wild-type	*M. abscessus* subsp. *abscessus*
	858	BAL	09/92	10	>128	>128	>128	ND	T28	2059A→G	
MC1448[d]	868	sputum	08/94	0	>128	>128	>128	ND	T28	2058A→G	*M. abscessus* subsp. *abscessus*

Maurer et al. 2012 JAC

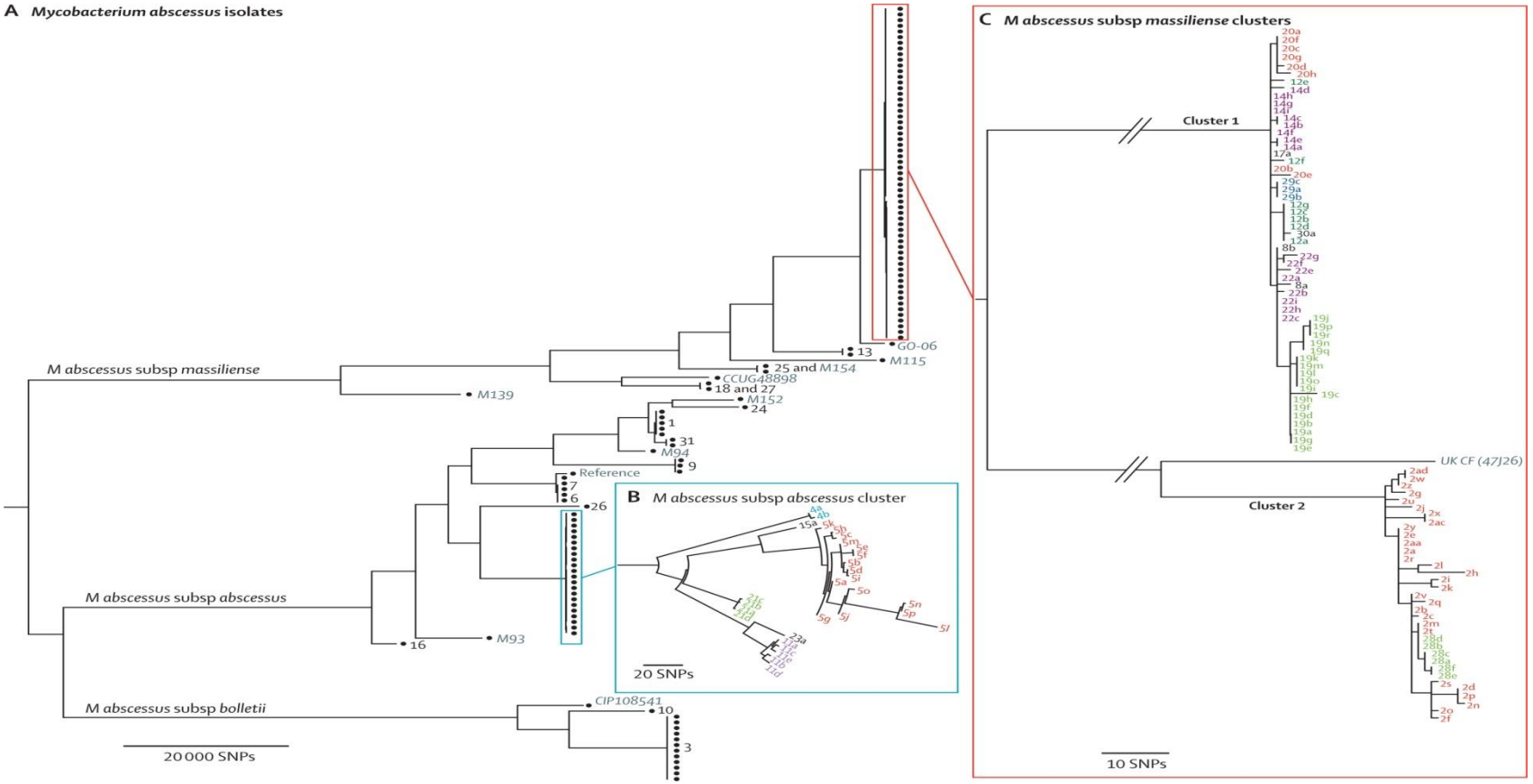
Different pheno- (radiographic and disease progression) and VNTR genotypes are associated with different disease manifestation



Shin S J et al. Clin Infect Dis. 2013;57:32-39

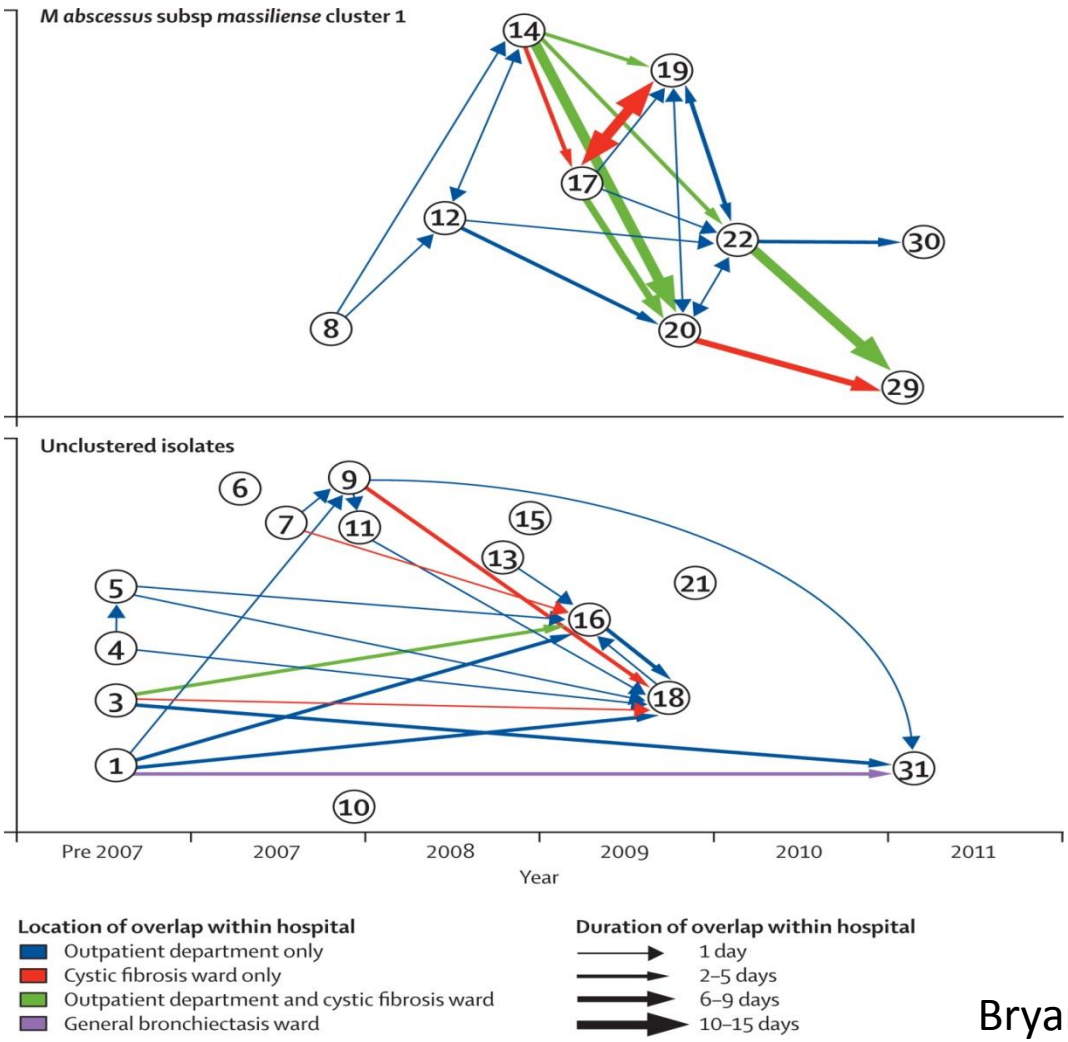
Human to human transmission?

Whole Genome Sequencing



Bryant et al. Lancet 2013

Network analysis of patients with clustered and non-clustered *M. abscessus* subsp. *massiliense*



Bryant et al. Lancet 2013

A mutation associated with clofazimine and bedaquiline cross-resistance in MDR-TB following bedaquiline treatment

TABLE 1. Quantitative phenotypic drug susceptibility testing results for first- and second-line antituberculous drugs[#], and DNA sequencing results of resistance-associated genes

	TB isolate[¶] 2011		TB relapse isolate[+] 2013	
	MGIT 960 phenotype	Resistance genotype	MGIT 960 phenotype	Resistance genotype
Clofazimine mg·L^{-1}		Rv0678 wild type		Rv0678 fMet1Ala
0.5	Resistant		Resistant	
1.0	Susceptible		Resistant	
4.0	Susceptible		Resistant	
Bedaquiline		*atpE* wild type		*atpE* wild type
Not available	Not available	Rv0678 wild type	Not applicable	Rv0678 fMet1Ala

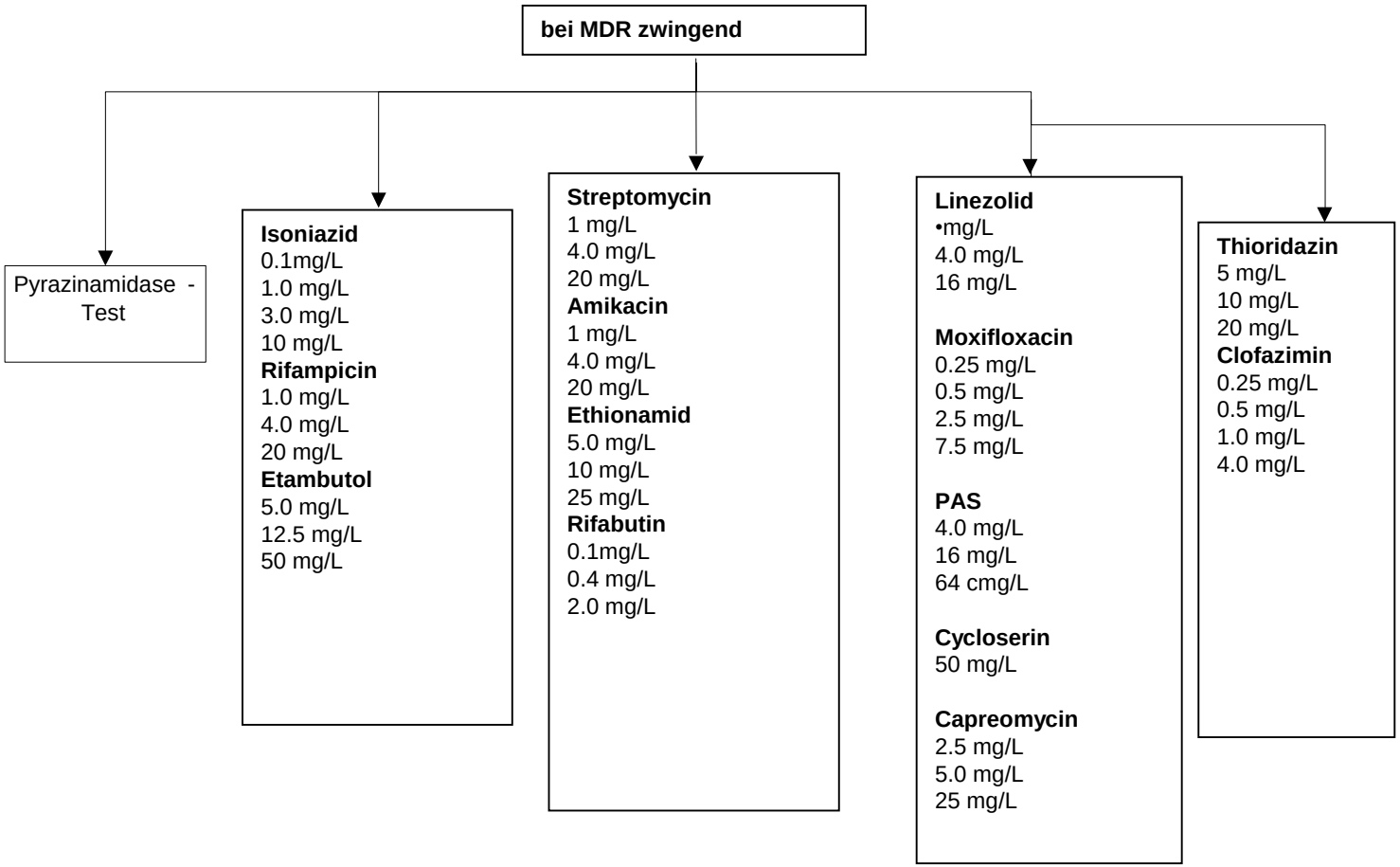
Somoskovi et al. 2014 Eur. Resp. J.

Salfinger and Somoskovi 2014 N Eng J Med

Conclusions

- NTM related disease are identified in increased numbers
- NTM related diseases are newly evolving (man made environment)
- Rapid and accurate identification of NTMs is indispensable
- Clinical significance has to be carefully evaluated in each patient to confirm relevance or to exclude pseudo infections
- *M. abscessus* complex related infections are especially troublesome due to complex drug resistance
- Standardized DST and breakpoints vs. clinical outcomes for clinically significant species
- Develop national guidelines in line with local needs

Quantitative drug susceptibility testing



- Screening concentration
- Concentration to separate low level resistant from intermediate resistance
- Concentration to separate high level resistant

Springer et al. JCM 2009