Mycobacterium chimaera Disseminated Infections

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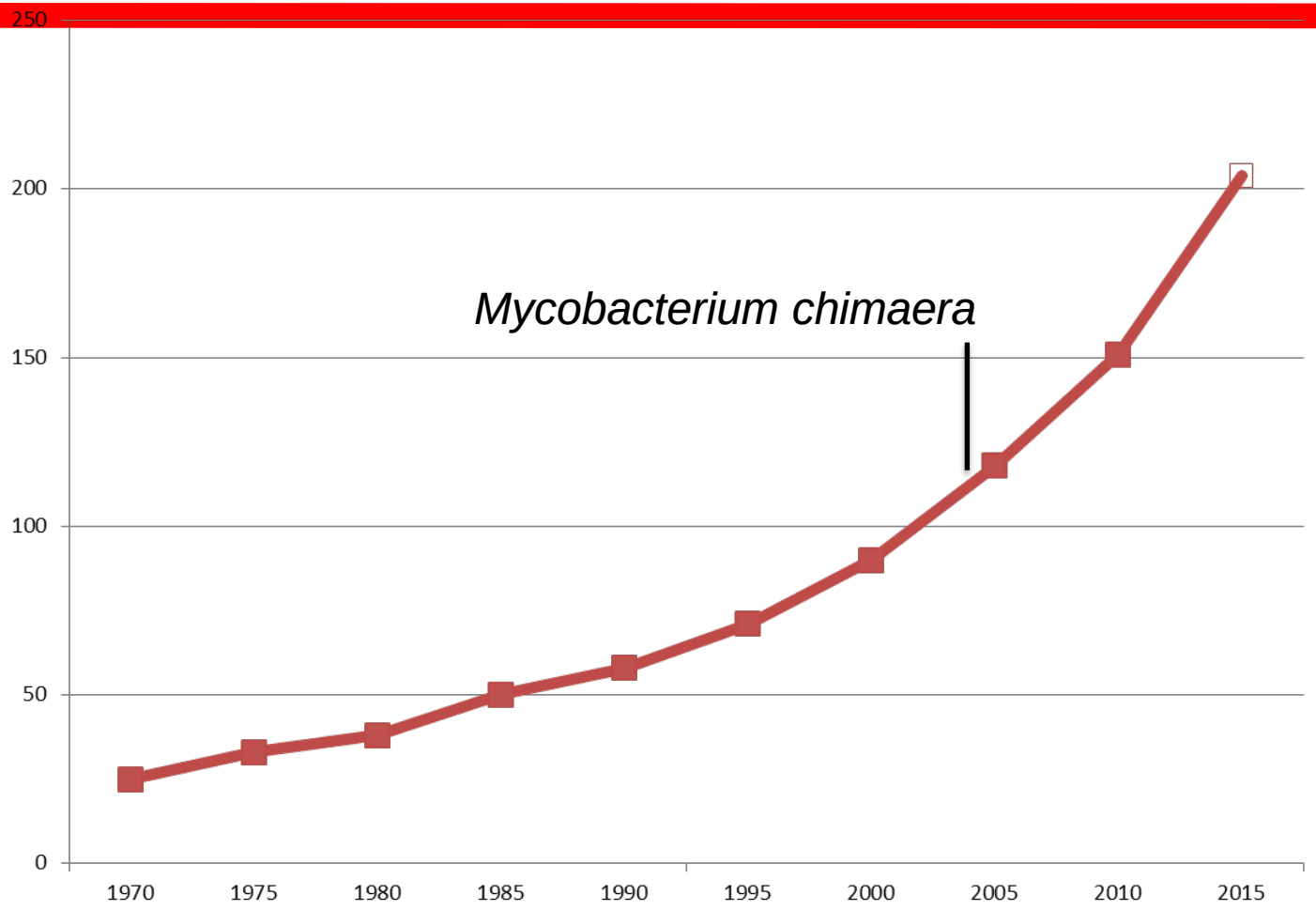
Outline

- What's in a name – *Mycobacterium chimaera*
- Clinical Presentation - When to suspect disseminated disease
- Diagnosis – A Clinical Laboratory Perspective
- Treatment – Challenging under any circumstance

Conflict of Interest Disclosures

- Investigator in multicenter randomized placebo controlled clinical trial of inhaled liposomal amikacin in pulmonary NTM infections (Insmed)
- Investigator in Bronchiectasis and NTM Research Registry (COPD Foundation)
- Investigator, Colorado CF/NTM Research Development Program (Cystic Fibrosis Foundation)

174 Species and 13 Subspecies in genus *Mycobacterium* as of March 29, 2016



Source: http://www.bacterio.net/mycobacterium.html

Mycobacterium avium Complex

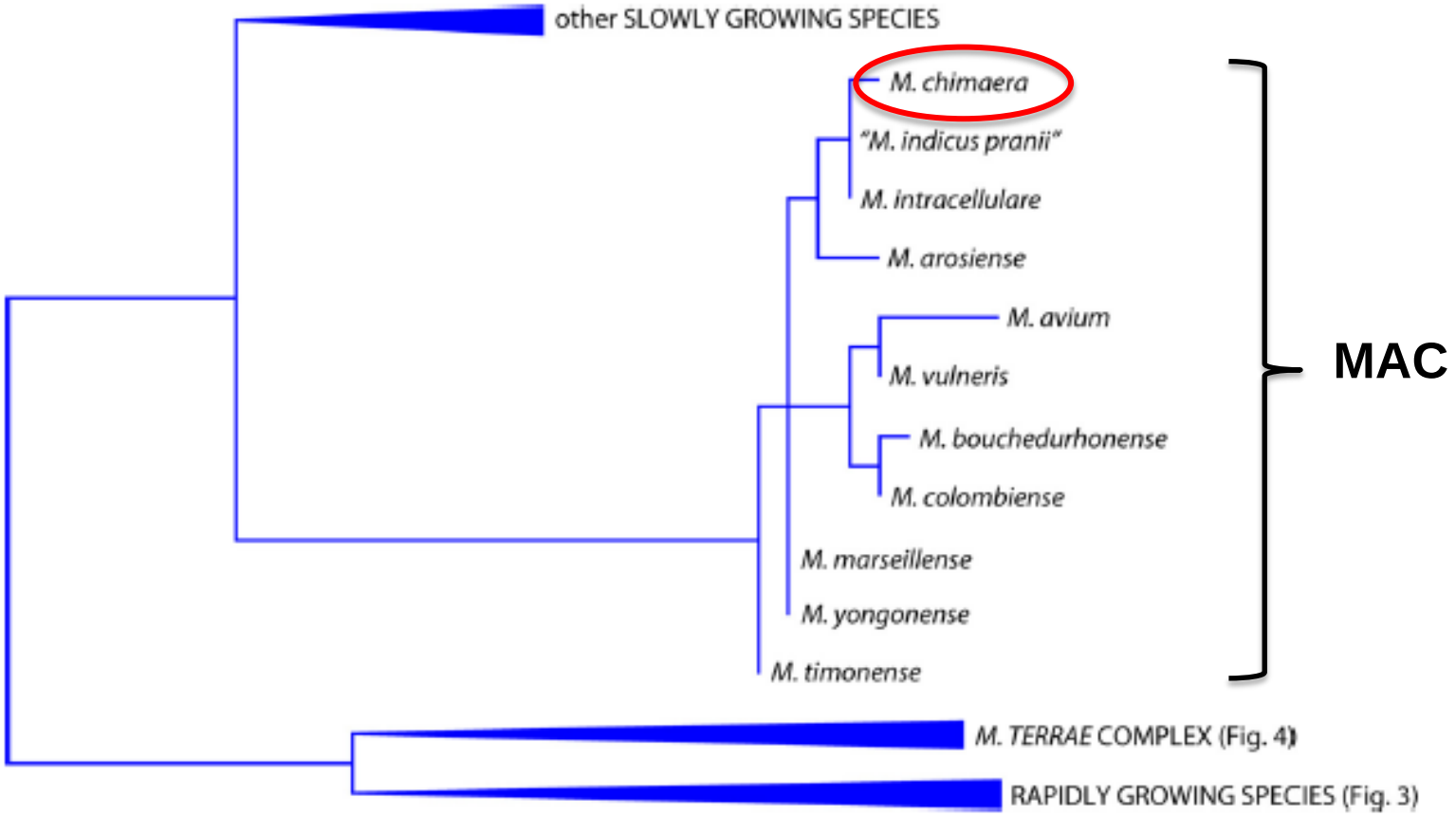


FIG 5 Phylogenetic tree, based on the 16S rRNA gene, for the species belonging to the *M. avium* complex.

Tortoli E, et al. J System Evol Micro 2004;54:1277-1285
Tortoli E. Clin Micro Rev 2014;27:727-752

Occurrence and Clinical Relevance of *M. chimaera*, Germany

- 97 patients from Charité University Hospital between 2002-2006 *and*
- 69 isolated provided by National Reference Laboratory (Borstel, Germany)
  - 166 *Mycobacterium intracellulare* strains identified by 16s rRNA-based methods
  - 143 (86%) were *Mycobacterium chimaera* by sequencing 16S-23S ITS region

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Schweickert B, et al. Emerg Infect Dis 2008;14:1443-1446

Nontuberculous Mycobacteria at National Jewish Health

> 8,800 isolates were analyzed using *rpoB* gene sequencing

Seven *Mycobacterium* species accounted for ~80% of all isolates tested

24.4%	*M. abscessus* group	
19.9%	*M. avium*	42.3%
16.4%	*M. intracellulare*	
6.0%	*M. chimaera*	
5.1%	*M. fortuitum*	
3.8%	*M. gordonae*	
3.7%	*M. chelonae*	

Source: Max Salfinger, MD

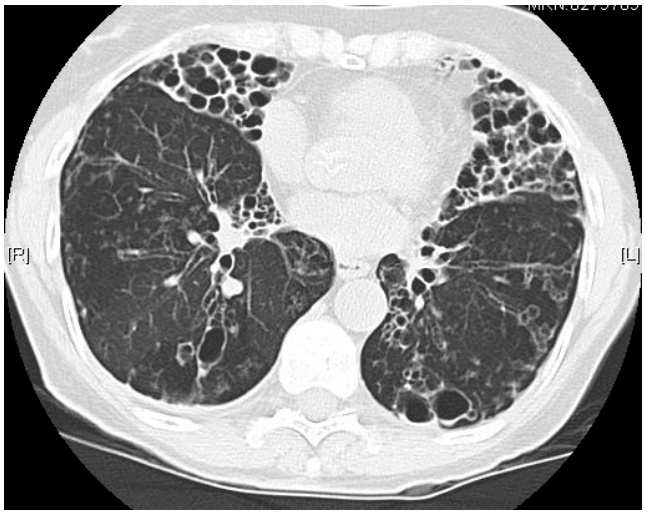
Mycobacterium avium Complex What's in a Name?

- **Acquisition of infection**
  - *M. avium* and *M. chimaera* are found in water. *M. intracellulare?*
- **Pathogenicity**
  - *M. intracellulare* ≥ *M. avium* > *M. chimaera*
- **Clinical Presentation**
  - *M. intracellulare* presents with more advanced disease
- **Treatment outcomes**
  - *M. chimaera* and *M. avium* may have a higher rate of clinical recurrence than *M. intracellulare*

Schweickert B, et al. Emerg Infect Dis 2008;14:1443-1446.
Wallace RJ, et al. J Clin Micro 2013;51:1747-1752
Koh WJ, et al. Chest 2012:142:1482-1488
Boyles DP, et al. AJRRCM 2015:191:1310-1317

Clinical Presentation
Pulmonary Infection

Symptoms	**Chronic cough** **Fatigue**, Fever, Weight loss, Shortness of breath
Signs	Thin in stature Adventitious breath sounds
Laboratory Values	Lymphocytopenia, Elevated CRP Normal immunological tests (immunoglobulins, lymphocyte phenotyping)



Dissemination outside of the lung does not occur unless severely immunocompromised

Clinical Presentation
Disseminated Infection

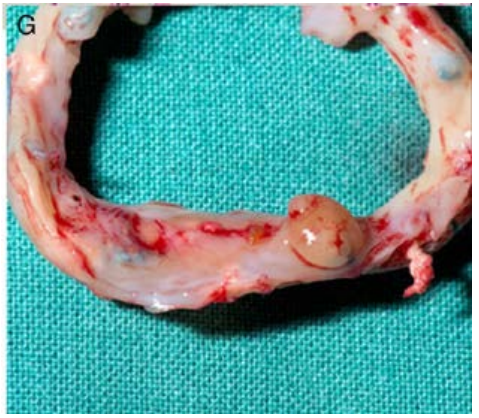
Time to Presentation – median 21 months (5-40)

Symptoms	Fever, Fatigue, Weight loss, Shortness of breath
Signs	Splenomegaly Chorioretinitis
Laboratory Values	Anemia, Lymphocytopenia, Thrombocytopenia, Elevated CRP Elevated transaminases Elevated creatinine

Achermann Y, et al. J Clin Microbiol 2013;51:1769
Sax H, et al. Clin Infect Dis 2015;61:67 Kohler P, et al. Eur Heart J 2015;36:2745

Manifestation of Infections

- Prosthetic valve endocarditis
- Vascular graft infection
- Manifestations of disseminated disease:
  - Emboli
  - Bone marrow involvement
  - Splenomegaly
  - Nephritis
  - Myocarditis
  - Osteomyelitis



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Delays in Diagnosis

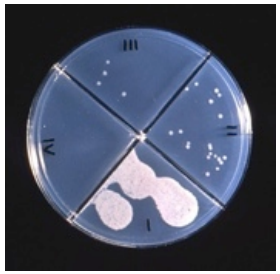
- Long period from index surgery to clinical presentation
- Various clinical manifestations
- Lack of appropriate cultures at presentation
- Slow growth of *M. chimaera*
- Disbelief on behalf of provider

Diagnosis of NTM Infections

Routine Methods Take a Long Time!

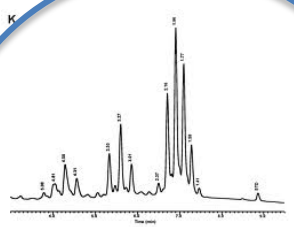
Think about it!

Diagnosis
8 weeks

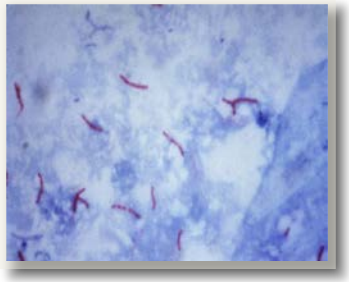


Drug susceptibility

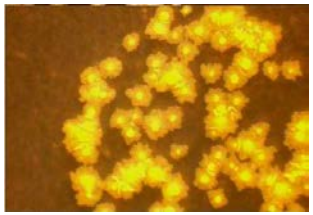
Collect a specimen



Identification



Microscopic examination



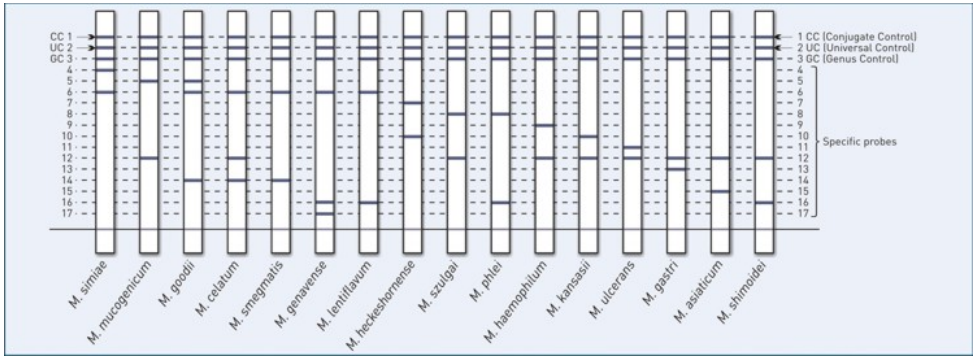
Culture (liquid and solid media)

Molecular Methods of Identification/Speciation

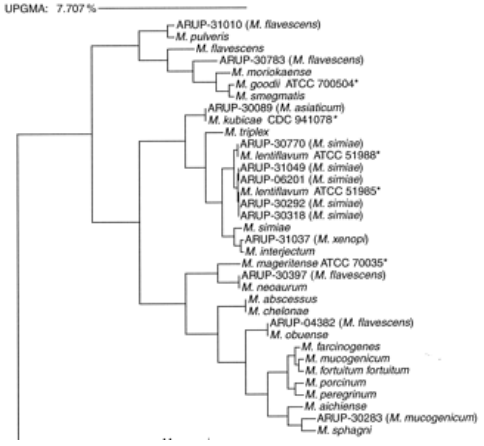
In-solution hybridization probes

(MAC, *M. avium, M. intracellulare, M. gordonae, M. kansasii*, Mtb)

Line Probe



Sequencing



rpoB
hsp65

Sequencing For Identification

- Many clinical laboratories nationwide do not use sequencing nor provide final identification for NTM species: expertise in NTM identification is not common in the US
- Using rpoB sequencing NJH is able to produce final identification for the vast majority of NTM species (methods are validated by CLIA standards)
  - Once a positive culture is received, turn-around time is typically between 3-5 days for identification to species level: *M. abscessus* may require an additional 2-3 days to identify subspecies and erm41 mutations
- Testing is routinely performed at NJH 7 days a week to improve turn around times and capacity can be increased by addition of staff in order to meet turn-around time expectations

Antimicrobial Susceptibility Testing

Slowly growing NTM

- NTM10: 10-Drug MIC(CLF, CIP, MXF, AMK, STR, RFB, LZD, CLR, RIF, EMB, RIF/EMB)

- Singe Drug MIC: (CLF, CIP, MXF, AMK, STR, RFB, LZD, CLR, RIF, EMB, ETH, LVX, AZM, OFX, CS)

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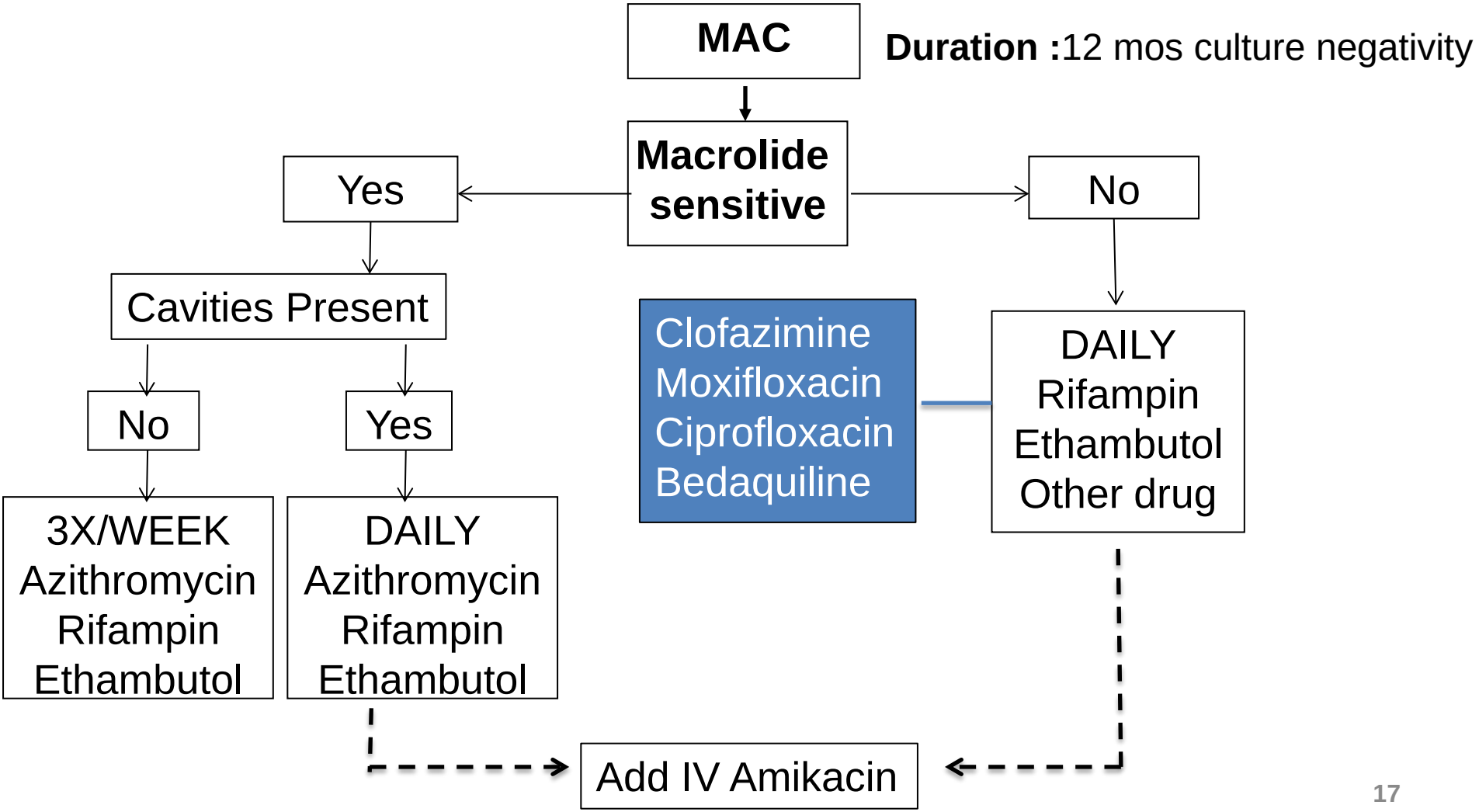
Treatment

M. avium complex Pulmonary Infection



Treatment Outcomes for Pulmonary MAC

	Culture Conversion
Macrolide susceptible	
Non cavitary	80%
Cavitary	<50%
Macrolide resistant	
No surgery/aminoglycoside	5%
Surgery + aminoglycoside*	80%

* ≥ 6 months IV aminoglycoside

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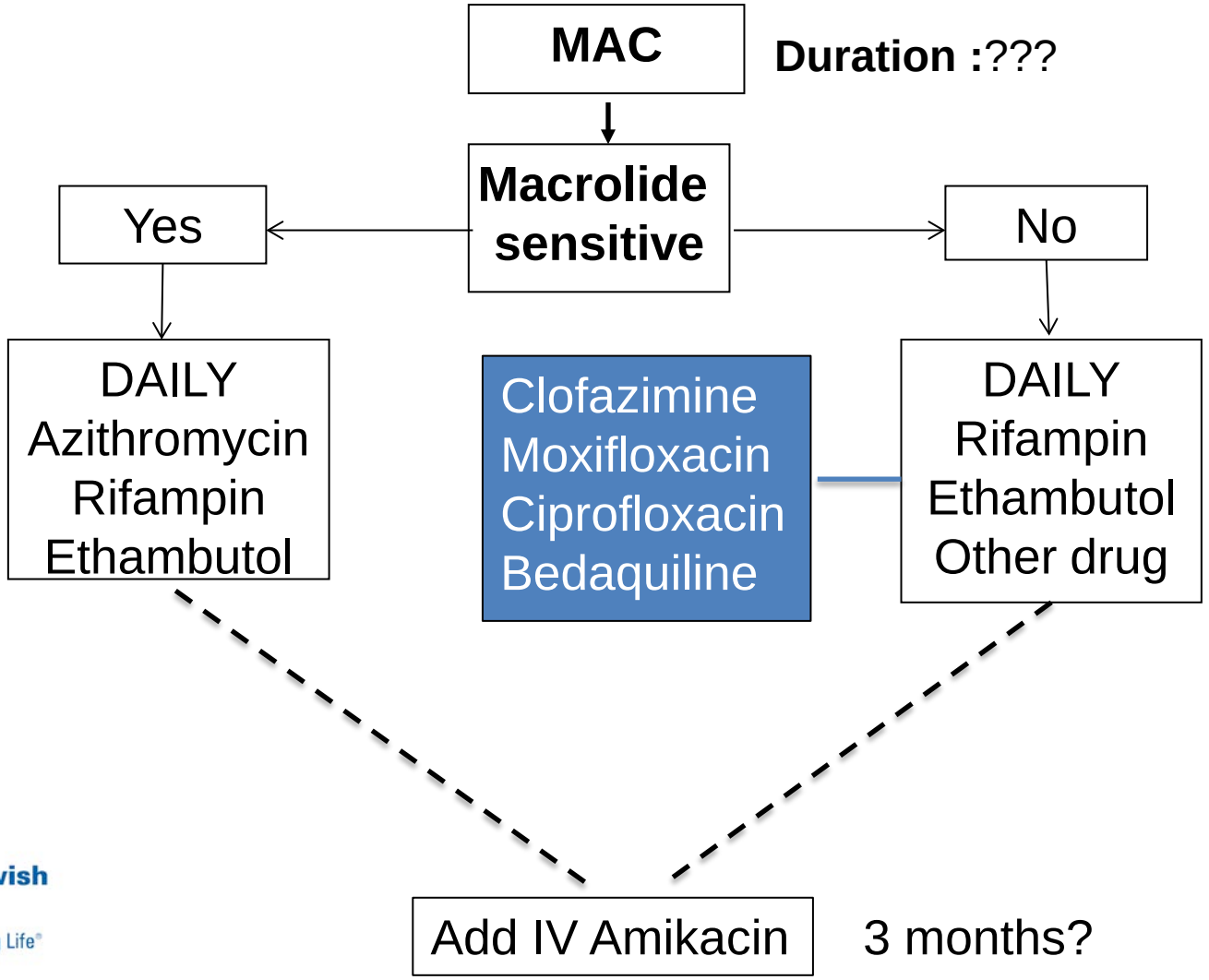
Griffith DE, et al. AJRCCM 2006;174:928
Wallace R, et al. Chest 2014:146:276-282
Jeong BH, et al. AJRCCM 2015:191:96-103

Treatment

Disseminated *M. chimaera*



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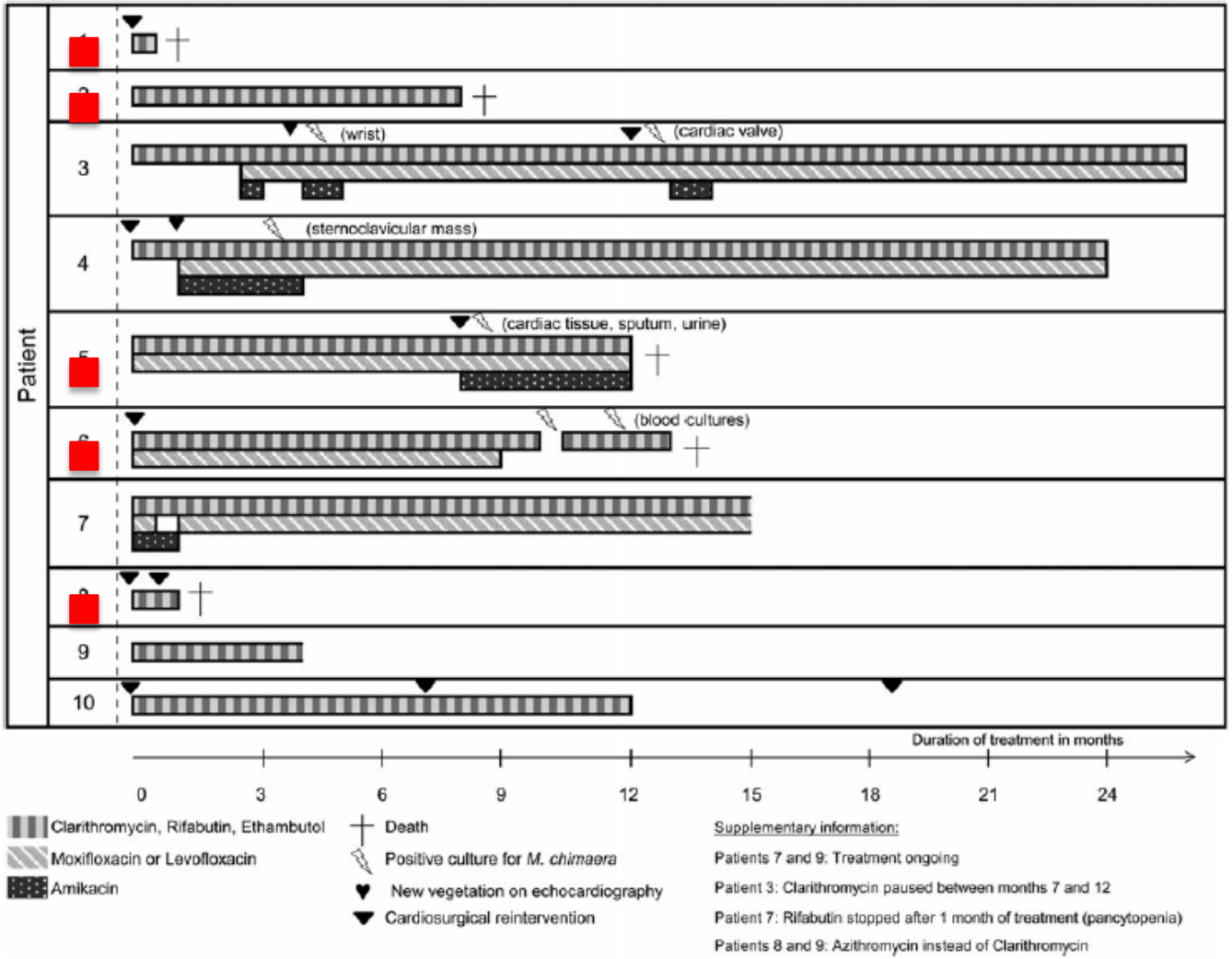
Clinical Outcomes of Disseminated *M. chimaera* Infections



Kohler P, et al. Eur Heart J 2015;36:2745

Why so Difficult to Treat?

- Delay in diagnosis resulting in widespread disseminated infection
- Endovascular infection involving foreign material (biofilm)
- Largely bacteriostatic drugs
- Low serum drug concentrations
- Co-morbidities

Summary

- Disseminated *M. chimaera* infections post-cardiac surgery presents with evidence of endovascular and disseminated disease
- Diagnosis should be considered when such a patient presents with the typical signs, symptoms, and laboratory values described to date
- Delays in diagnosis and treatment are multifactorial in nature
- Precise speciation should be performed and antimicrobial susceptibility testing performed to at least the macrolides and amikacin
- Treatment should include a macrolide-based regimen and addition of intravenous amikacin if possible
- Surgery to removed infected valves/grafts should be considered as mortality is high (we need additional data on impact of surgery)
- Hopefully earlier diagnosis and initiation of treatment will improve outcomes