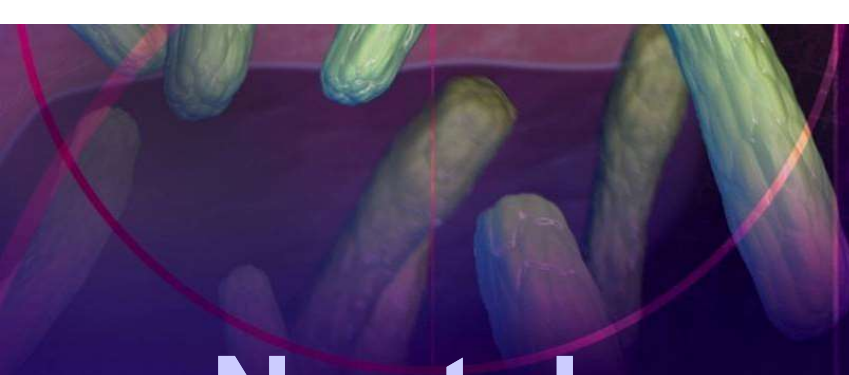


Nontuberculous Mycobacteria in the Immunocompromised Host

Kevin L. Winthrop, MD, MPH
Professor, School of Public Health
Division of Infectious Diseases
Oregon Health & Science University

Disclosures

- NTM Research funding
  - Insmed
  - PCORI
  - American Lung Association
  - NTMir

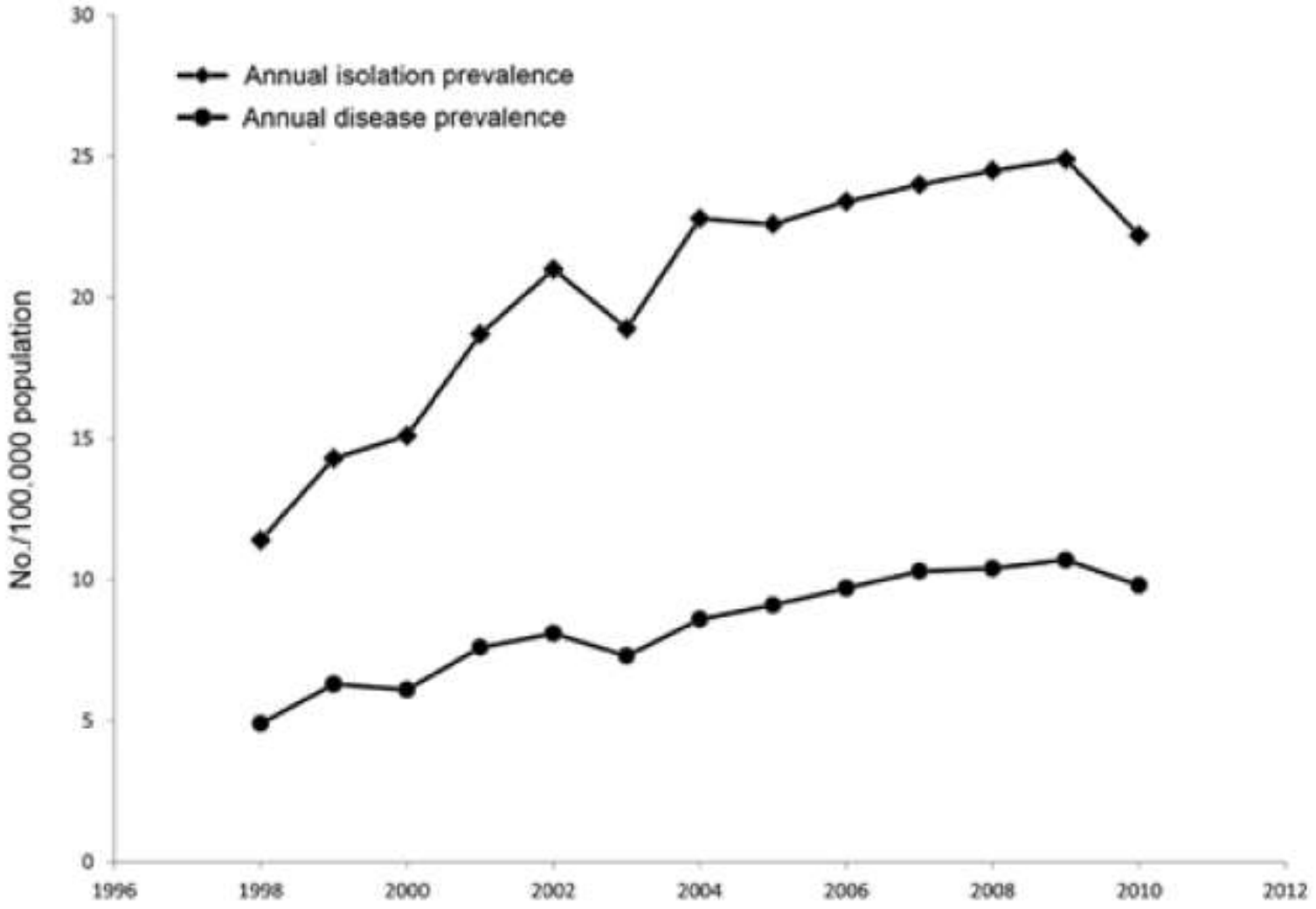


Figure. Annual isolation prevalence and disease prevalence per 100,000 persons of pulmonary nontuberculous mycobacteria, Ontario, Canada, 1998–2010.

Marras T, et al. EID 2013

NTM Disease Manifestations

Table 2. Nontuberculous mycobacterium (NTM) cases by species and disease site, Oregon 2007-2012

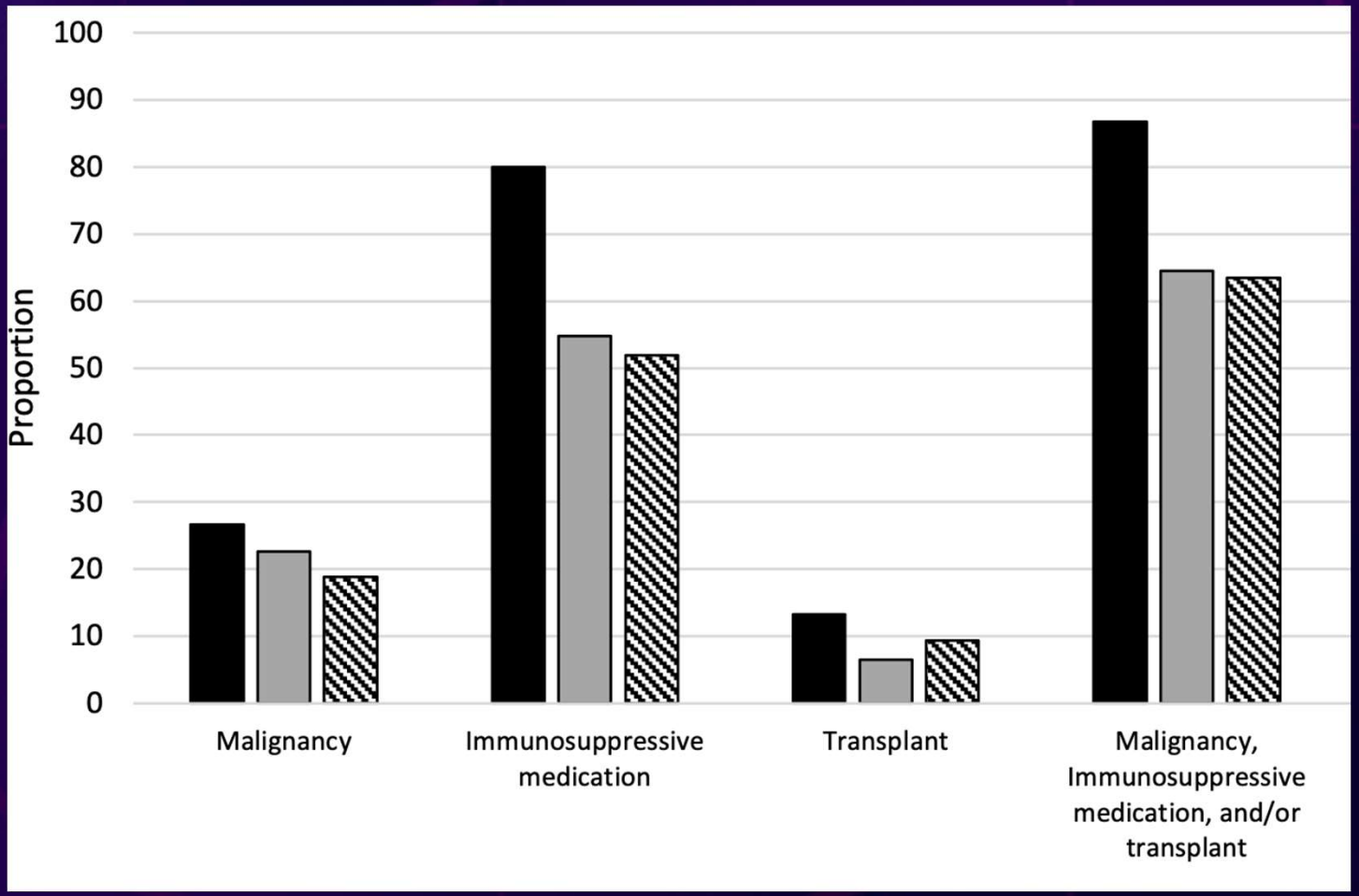
Mycobacterium species	Pulmonary	Skin/ soft tissue	Disseminated	Lymph	Other	Total
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
M. avium/intracellulare complex	1005 (92.8%)	68 (37.8%)	35 (79.5%)	21 (87.5%)	42 (60%)	1171 (83.6%)
M. abscessus/chelonae complex	46 (4.2%)	51 (28.3%)	1 (2.3%)	1 (4.2%)	9 (12.9%)	108 (7.7%)
M. fortuitum/ mucogenicum	5 (0.5%)	21 (11.7%)	2 (4.5%)	1 (4.2%)	3 (4.3%)	32 (2.3%)
M. marinum	-	17 (9.4%)	-	-	2 (2.9%)	19 (1.4%)
M. lentiflavum	6 (0.6%)	1 (0.6%)	-	-	-	7 (0.5%)
M. kansasii	5 (0.5%)	-	-	-	1 (1.4%)	6 (0.4%)
M. bovis	-	1 (0.6%)	-	-	3 (4.3%)	4 (0.3%)
M. goodii	-	4 (2.2%)	-	-	-	4 (0.3%)
M. xenopi	2 (0.2%)	1 (0.6%)	-	-	1 (1.4%)	4 (0.3%)
M. aubagnense	-	1 (0.6%)	1 (2.3%)	-	1 (1.4%)	3 (0.2%)
M. alvei	-	2 (1.1%)	-	-	-	2 (0.1%)
M. immunogenum	1 (0.1%)	-	-	-	1 (1.4%)	2 (0.1%)
Other (unspeciated and 13 species with a single case)	13 (1.2%)	12 (6.7%)	5 (11.4%)	1 (4.2%)	7 (10%)	38 (2.7%)
TOTAL	1083	180	44	24	70	1401

77% of NTM disease is pulmonary

Henkle E, et al. (abstract) ATS 2014

CDC Active Surveillance

- **Annualized prevalence was 7.5/100 000 (PNTM: 6.1/100 000; ENTM: 1.4/100 000)**



Jackson K et al. CID 2023

Nontuberculous *Mycobacterium* species and common sites of infection in immunosuppressed hosts

	Pulmonary	Disseminated	Skin/Soft Tissue/Catheter
Slow growers	MAC *M kansasii* *M xenopi* *M malmoense*	MAC *M kansasii* *M haemophilum* *M marinum* *M genavense* (R)	MAC *M marinum* *M haemophilum* (R)
Rapid growers	*M abscessus*	*M chelonae* *M abscessus* (R) *M fortuitum* (R)	*M abscessus* *M chelonae* *M fortuitum* *M mucogenicum* (R)

Abbreviations: MAC, *M avium/intracellulare* complex; (R), rare

Adapted from Griffith DE, Aksamit T, Brown-Elliot BA, et al. An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial disease. Am J Respir Crit Care Med 2007; 175(4): 367-416.

Immunosuppressive use common in Pulmonary NTM

TABLE 2. COMPARISON OF PULMONARY NTM DISEASE CHARACTERISTICS BETWEEN MALE AND FEMALE CASE SUBJECTS

	Female (*n* = 109)	Male (*n* = 75)
Age (median)	68 yr*	62 yr*
Cavitation†	22 (20%)	22 (31%)
Effusion	13 (12%)*	18 (24%)*
COPD	24 (22%)*	28 (37%)*
Bronchiectasis	22 (20%)	8 (11%)
Immunosuppressive Tx	32 (29%)	15 (20%)
Previous TB‡	8 (7%)	9 (12%)

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; TB = tuberculosis; Tx = treatment.

* Denotes $P < 0.05$ for comparison between columns designated male and female.

† Cavitation noted on either chest radiograph or computed tomography.

‡ Previous TB included history of latent TB infection (n = 11), prior active TB disease (n = 3), and history of unknown active versus latent TB (n = 3).

Winthrop et al. *AJRCCM* 2010

Steroids and Pulmonary NTM

- Case-control study in Oregon and Washington
  - OR = 8.0 for prednisone use
- Denmark COPD cohort
  - Inhaled corticosteroids (ICS) RR 1.24
- Japanese case-control study
  - ICS duration and dose associated with NTM among asthmatic
- In all three studies
  - Higher risk of NTM with oral prednisone doses >15 mg and >800 mg fluticasone equivalent.

Dirac MA et al. AJRCCM 2012; Hojo M et al. Respir 2012; Andrejak C et al Thorax 2013

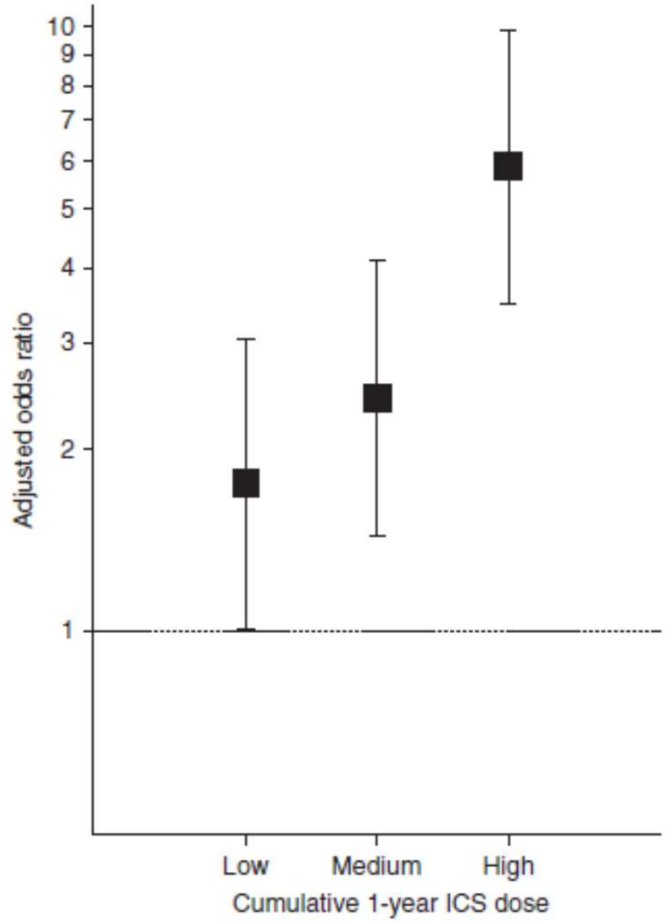


Figure 2. Adjusted odds ratios and 95% confidence intervals for nontuberculous mycobacterial pulmonary infection based on tertiles of cumulative dosage of beclomethasone-equivalent inhaled corticosteroid (ICS) use in the 1 year before cohort entry. The reference group is patients without ICS use in the year before cohort entry.

Liu, Winthrop, Lu, *et al.*: Inhaled Steroids and Pulmonary NTM Infection

Liu V et al. Ann Am Thor Soc 2018

Immunosuppression and NTM

- More frequently disseminated
  - Local inoculation versus GI route

Risk factors and conditions

- ESRD, prednisone, biologic immunosuppressives
- HIV
- Cancer, transplant, leukemia (hairy cell)
- Auto-antibody and cytokine/receptor deficiency states
  - INF-gamma, IL12-23 pathway, STAT-1

- Disease split between RGM and slow growers
  - RGM more common here than in pulmonary disease

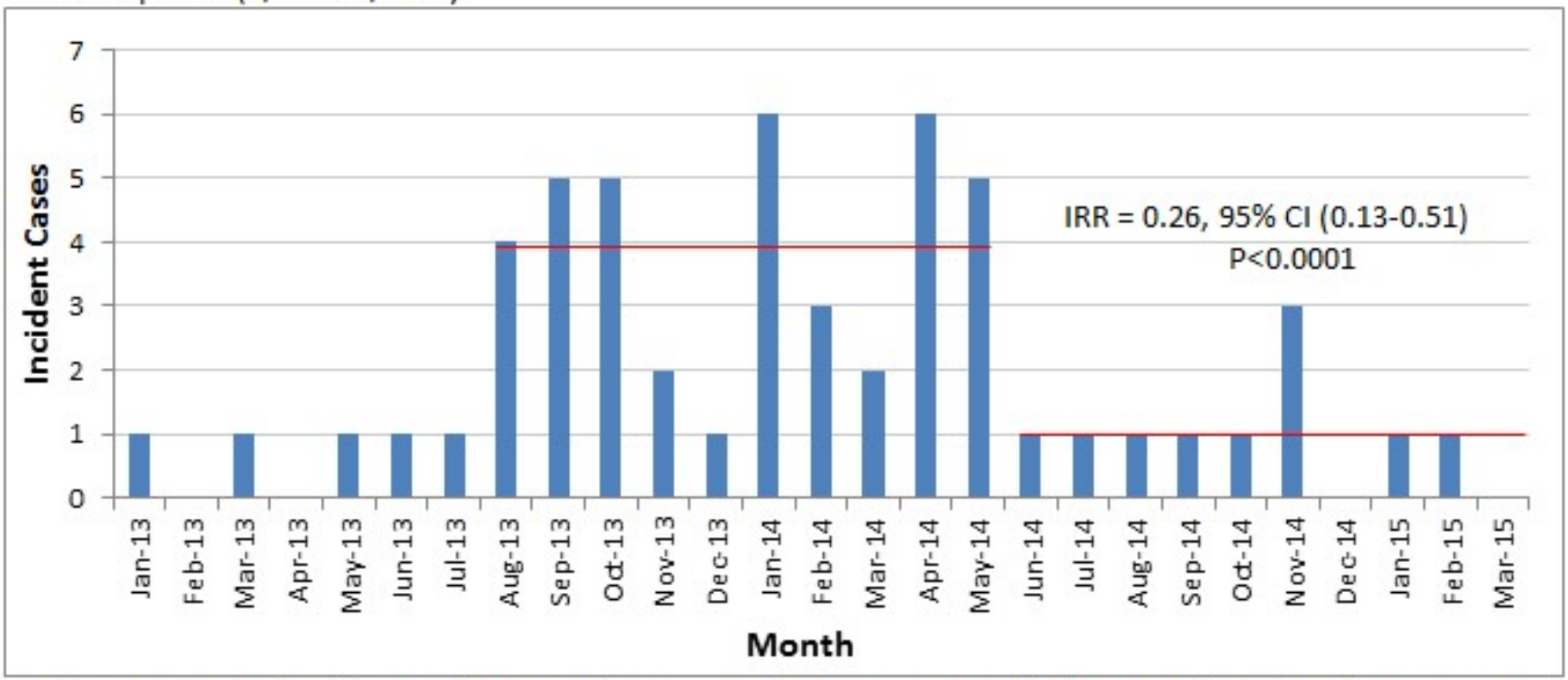
Table 1
Immunosuppressive conditions and risks for nontuberculous mycobacteria (NTM)

Underlying Disease or Treatment	No. of NTM Cases in Included References	Pulmonary (%)	Disseminated (%)	Skin/Soft Tissue/ Catheter (%)	Overall Risk/ Relative Risk (RR)	References
AIDS	972		(100)		24%	2
Hairy cell leukemia	9		(100)		5%	56
Hematopoietic stem cell transplant	97	18	9	70	0.4–4.9	48,53,62
Hematologic malignancies	34	76	24		1.2%	55
Solid organ transplant	40	50	15	35	0.02 (various organs) 1.1 (lung) per 100 person-years	49,51
Biological therapy for immune-mediated inflammatory diseases	123	56–67	8	35	74/100,000	15,25
Corticosteroid therapy for chronic respiratory disease	182	(100)			RR Oral: 8 Inhaled: 24.3	13,34

Henkle E et al. Clin Chest Med 2015

Lung Transplant

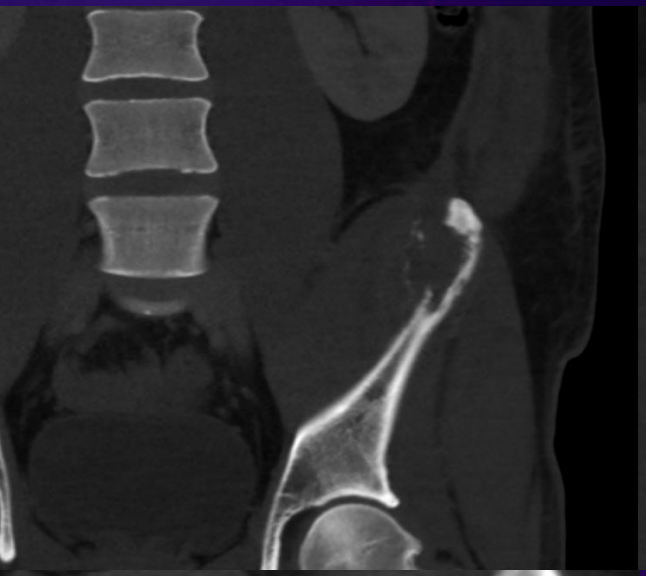
Figure. Incident cases of *Mycobacterium abscessus* by month from January 2013 through March 2015 among recently hospitalized lung transplant patients. The intervention period (6/2014-3/2015) was compared to the outbreak period (8/2013-5/2014).

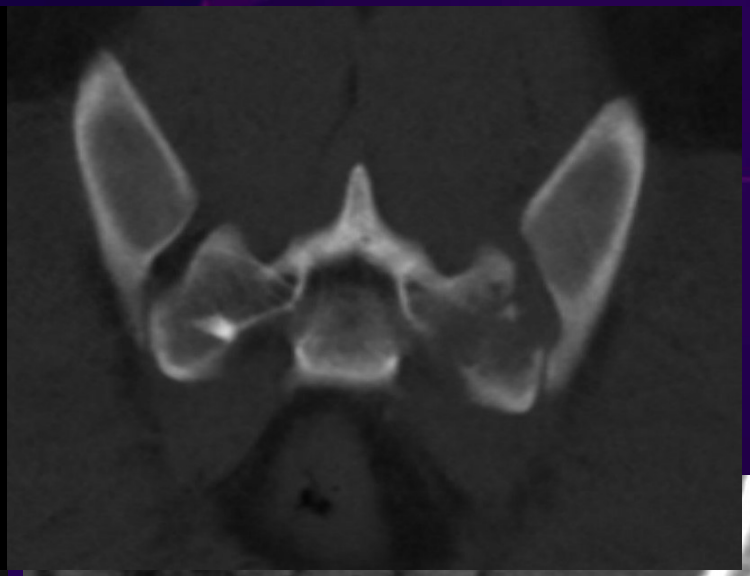


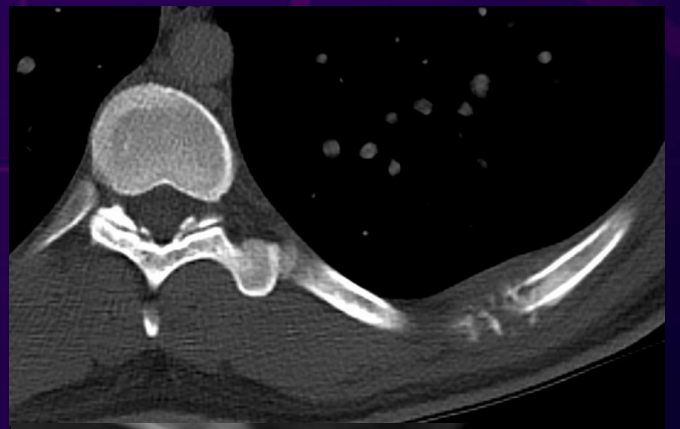
Note. Horizontal red lines indicate incidence rate (cases per month) during outbreak and intervention periods, respectively. IRR, incidence rate ratio; CI, confidence interval.

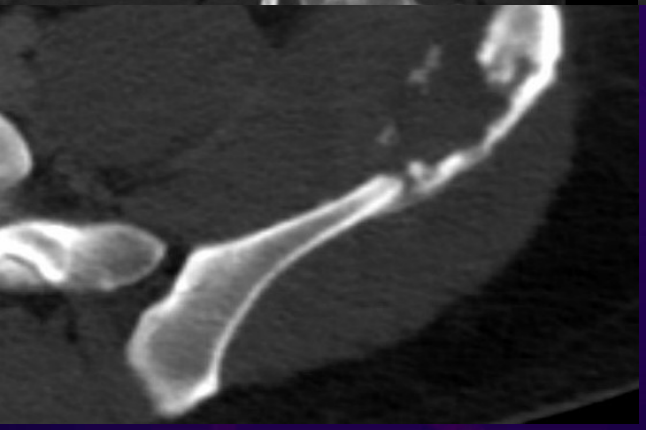
Baker et al. abstract ID Week 2015

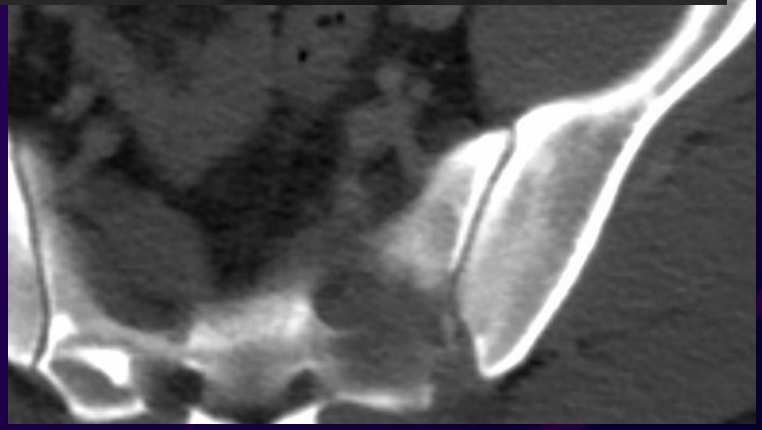
Interferon-γ receptor 1 (IFN-γR1)

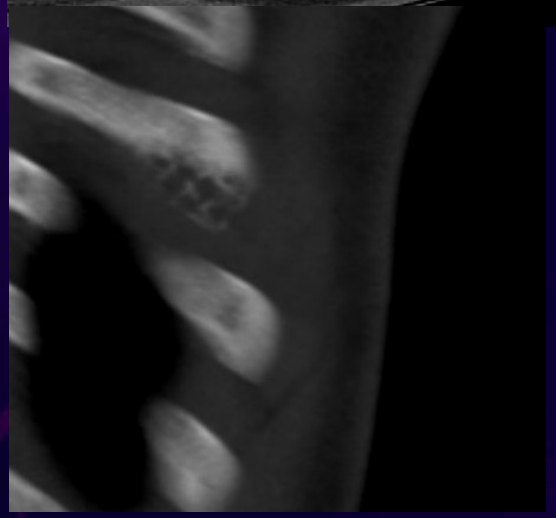












INF-gamma Auto-antibody

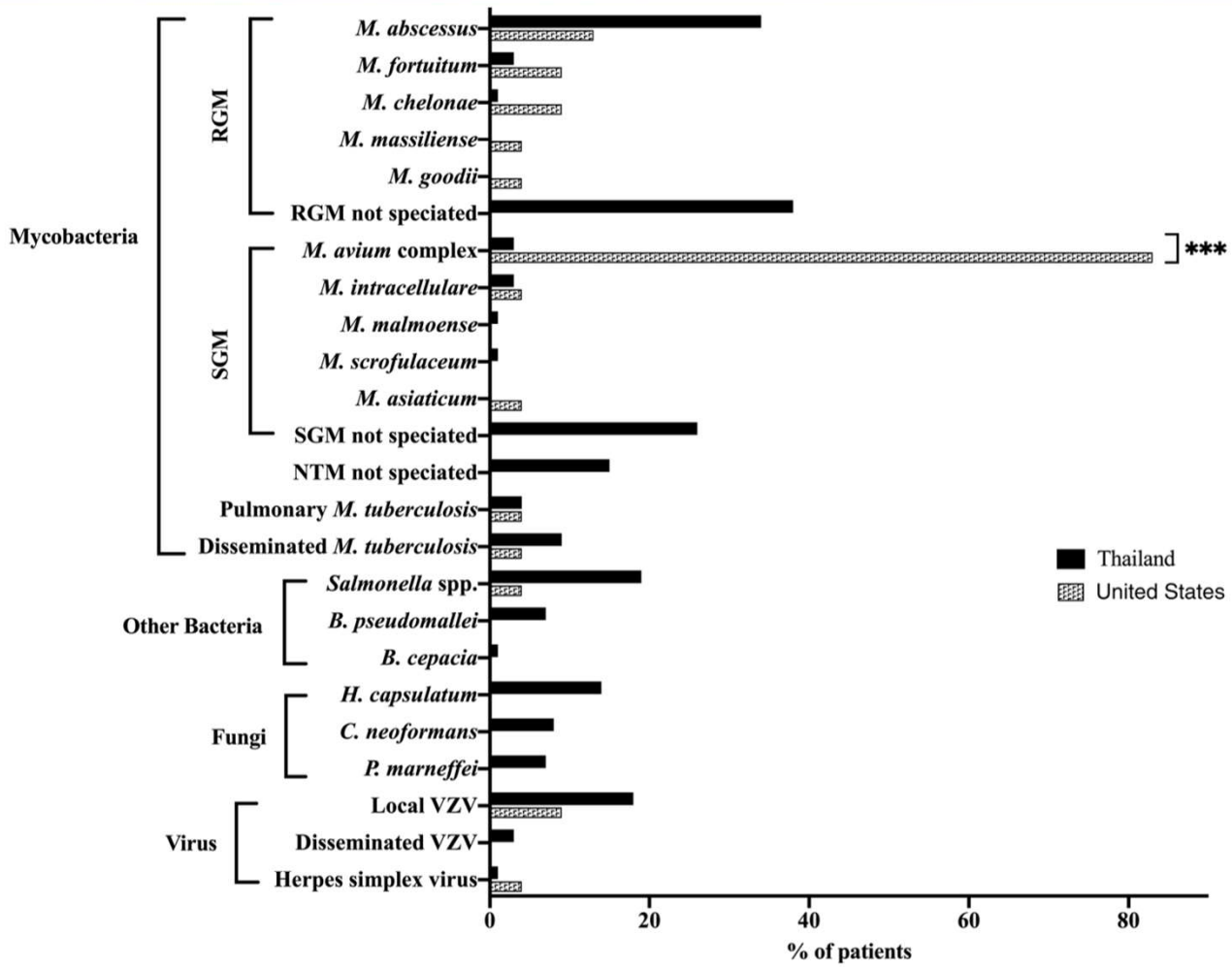
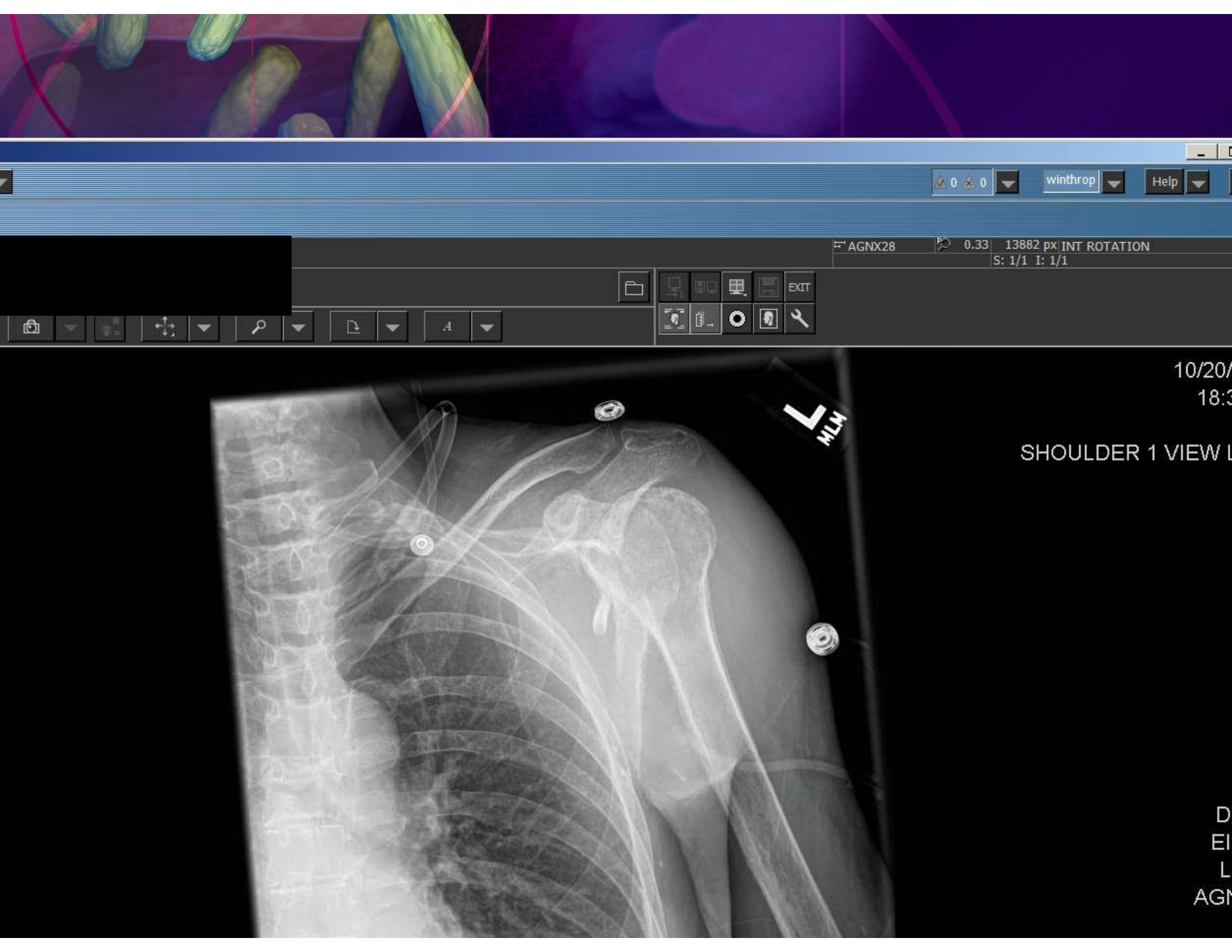


Figure 2. Isolated organisms at presentation in Thailand and the United States. Abbreviations: B, Burkholderia; C, Cryptococcus; H, Histoplasma; M, mycobacterium; NTM, nontuberculous mycobacteria; P, penicillium; RGM, rapid-growing mycobacteria; SGM, slow-growing mycobacteria; VZV, varicella-zoster virus.

Hong G et al. CID 2020

Case

- 52 year old female
  - Dermatomyositis
  - 7 mg prednisone for 15 years
- Left shoulder swelling, redness, pain X 3 months
  - Biopsy negative
  - Re-biopsy with AFB
- Which AFB?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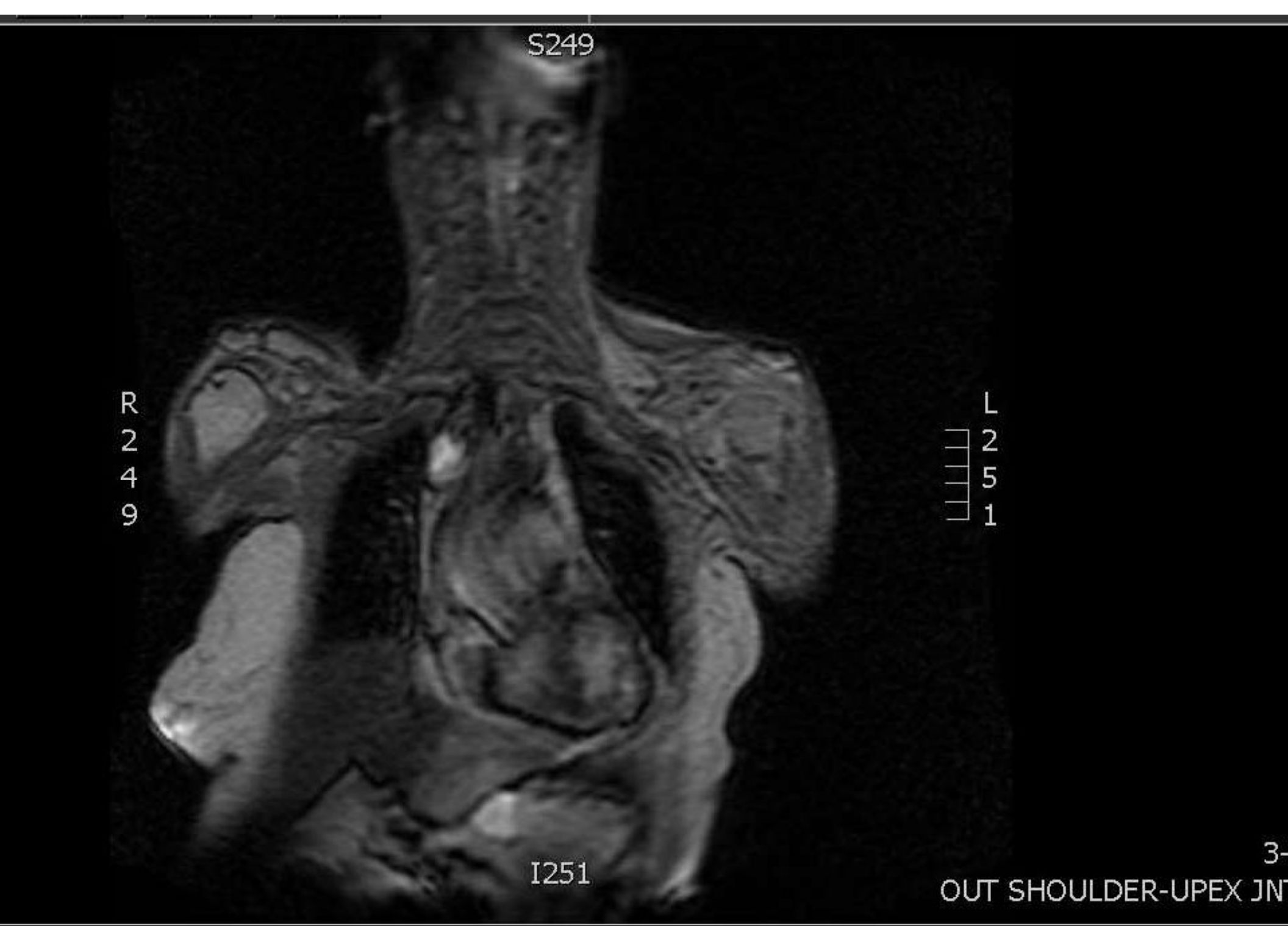
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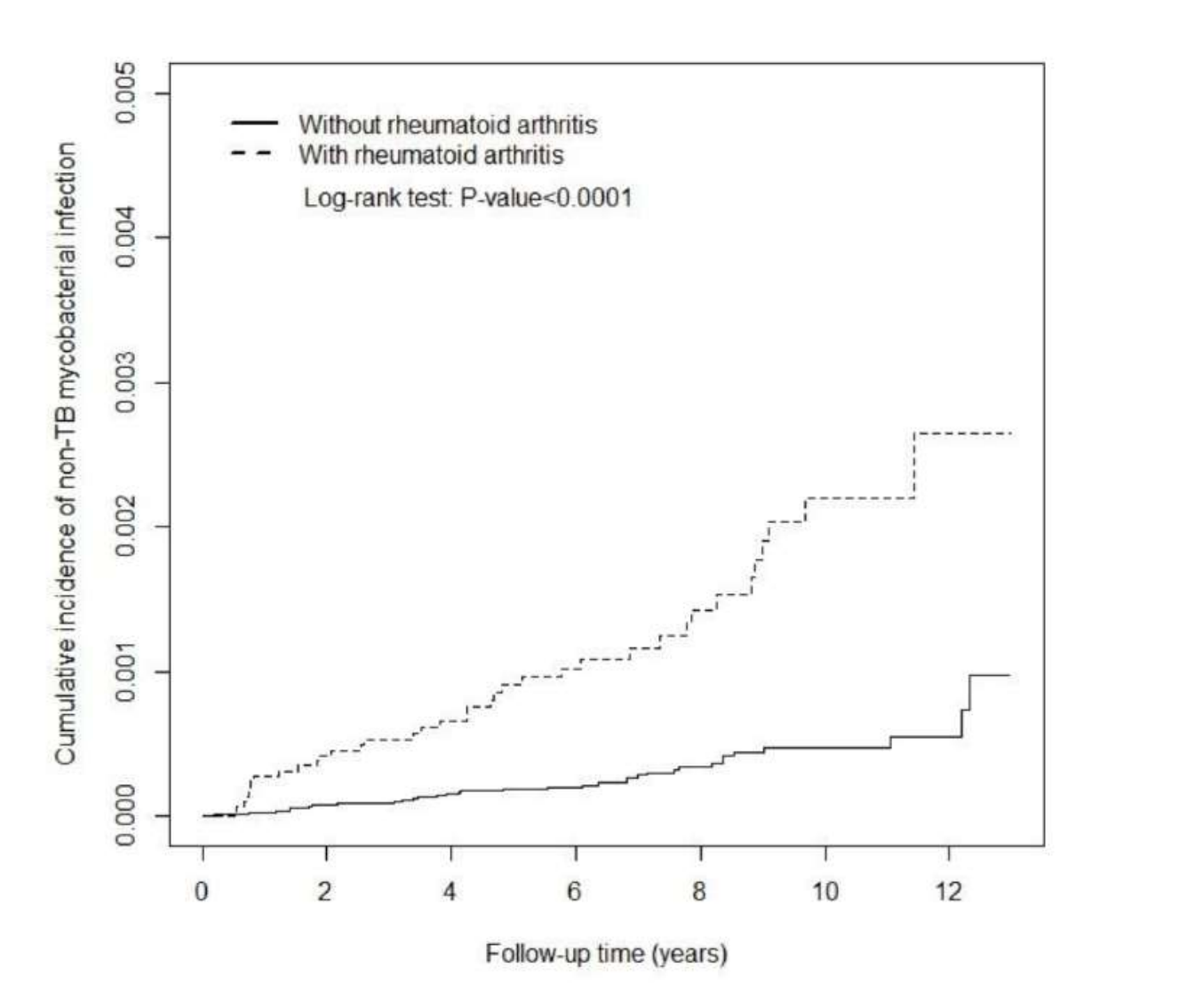
OUT SHOULDER-UPEX JNT

IMID Biologic Therapies

- TNF-α inhibition
  - Infliximab, adalimumab, golimumab, certolizumab (monoclonal antibodies)
  - Etanercept (soluble p75 receptor)
- Other Biologics
  - CD4 co-stimulation modulator: abatacept
  - B-cell (CD20+) antibody: rituximab
  - Anti-IL-6: tocilizumab, sarilumab
  - Anti- IL12/IL23 antibody: ustekinumab
  - Anti-IL-17A: secukinumab, Ixekizumab
- Small molecules (non-biologic)
  - JAK inhibitor: tofacitinib, baricitinib, upadicitinib, deucravicitinib

RA is risk factor for NTM



NTM risk among RA 4.1 X higher (Taiwan)

Yeh JJ et al. Plos One 2014

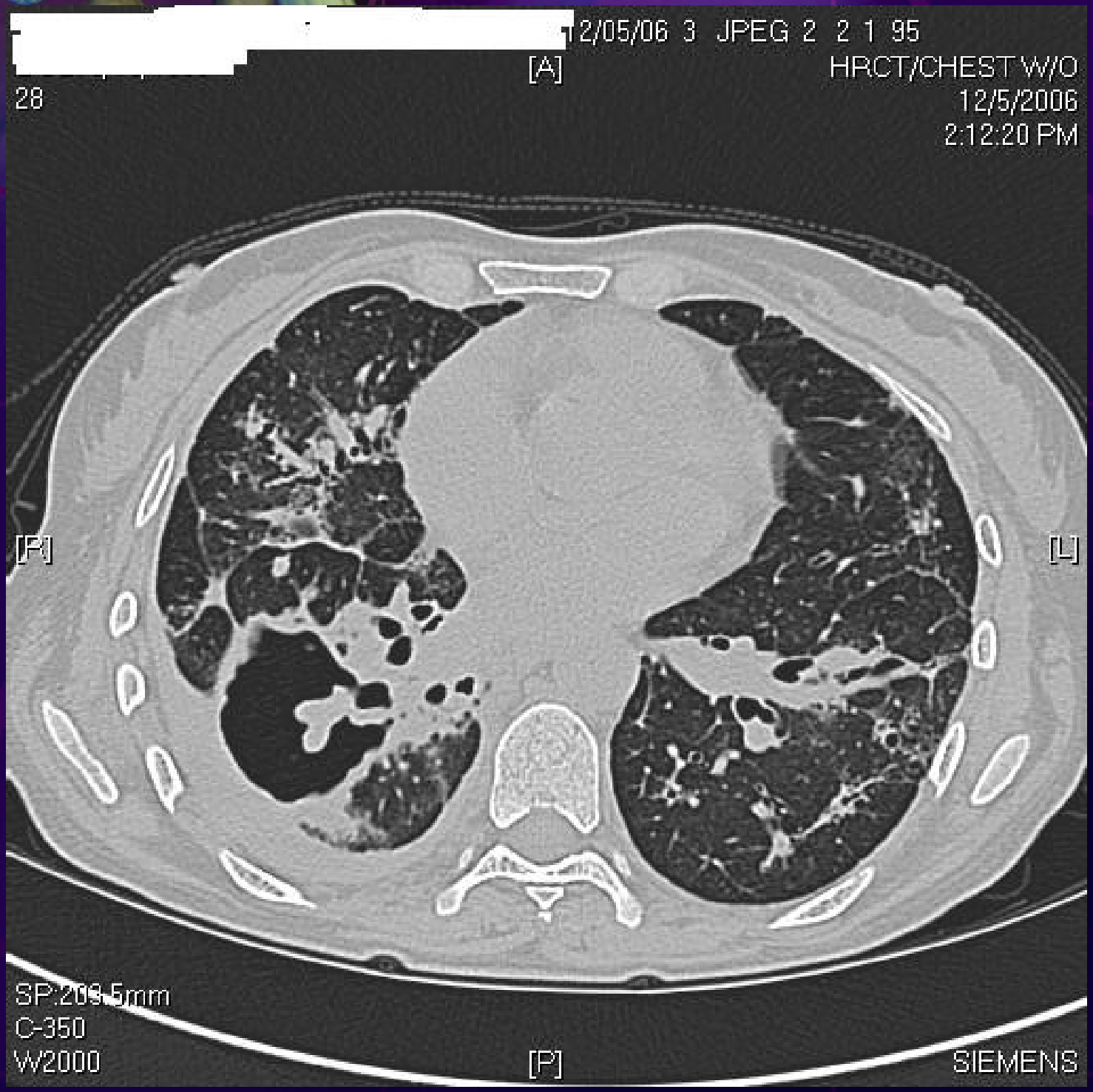

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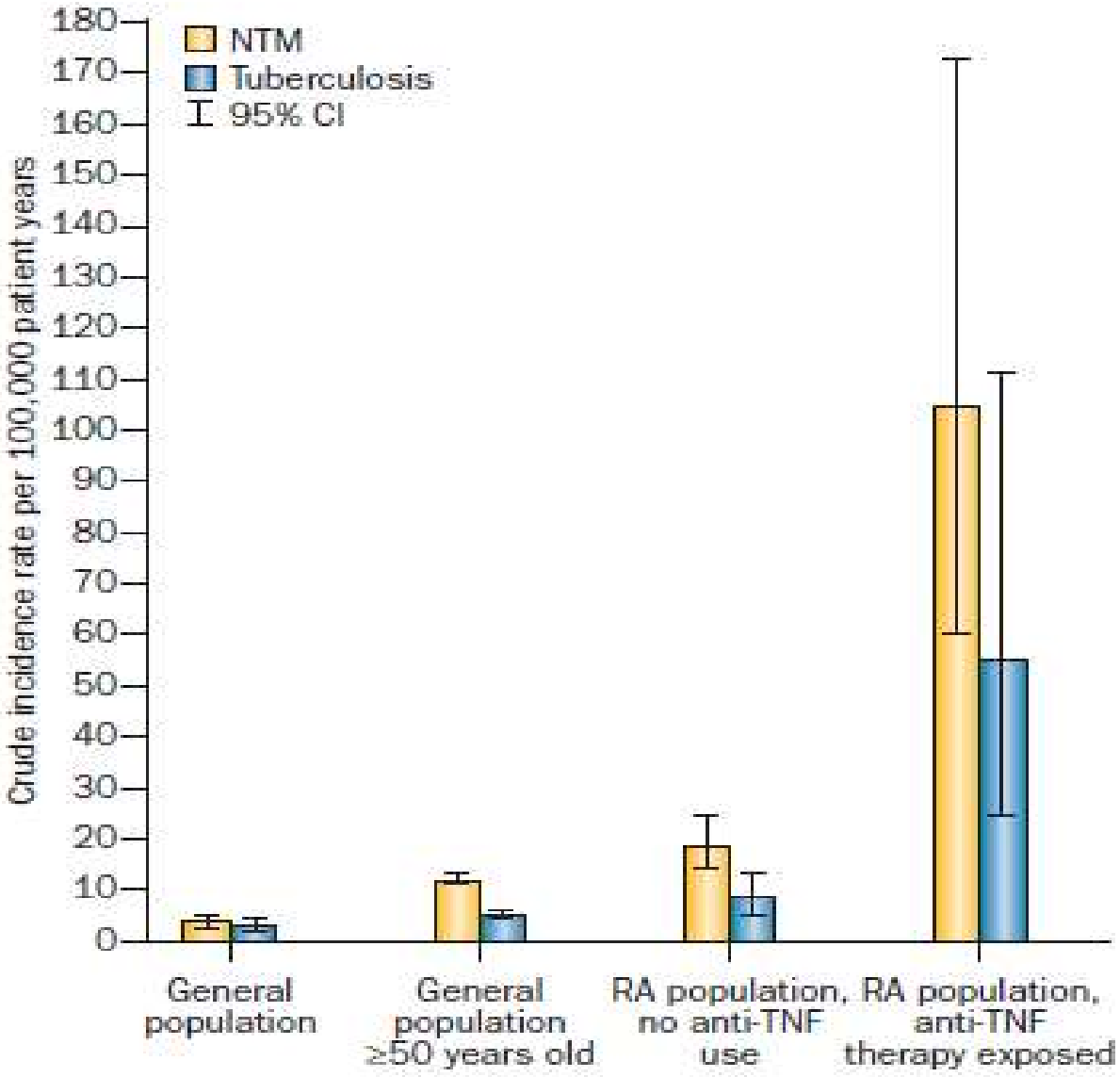
Figure 2



Winthrop KL et al. Ann Rheum Dis 2013; Winthrop KL Nat Rheum Rev 2013

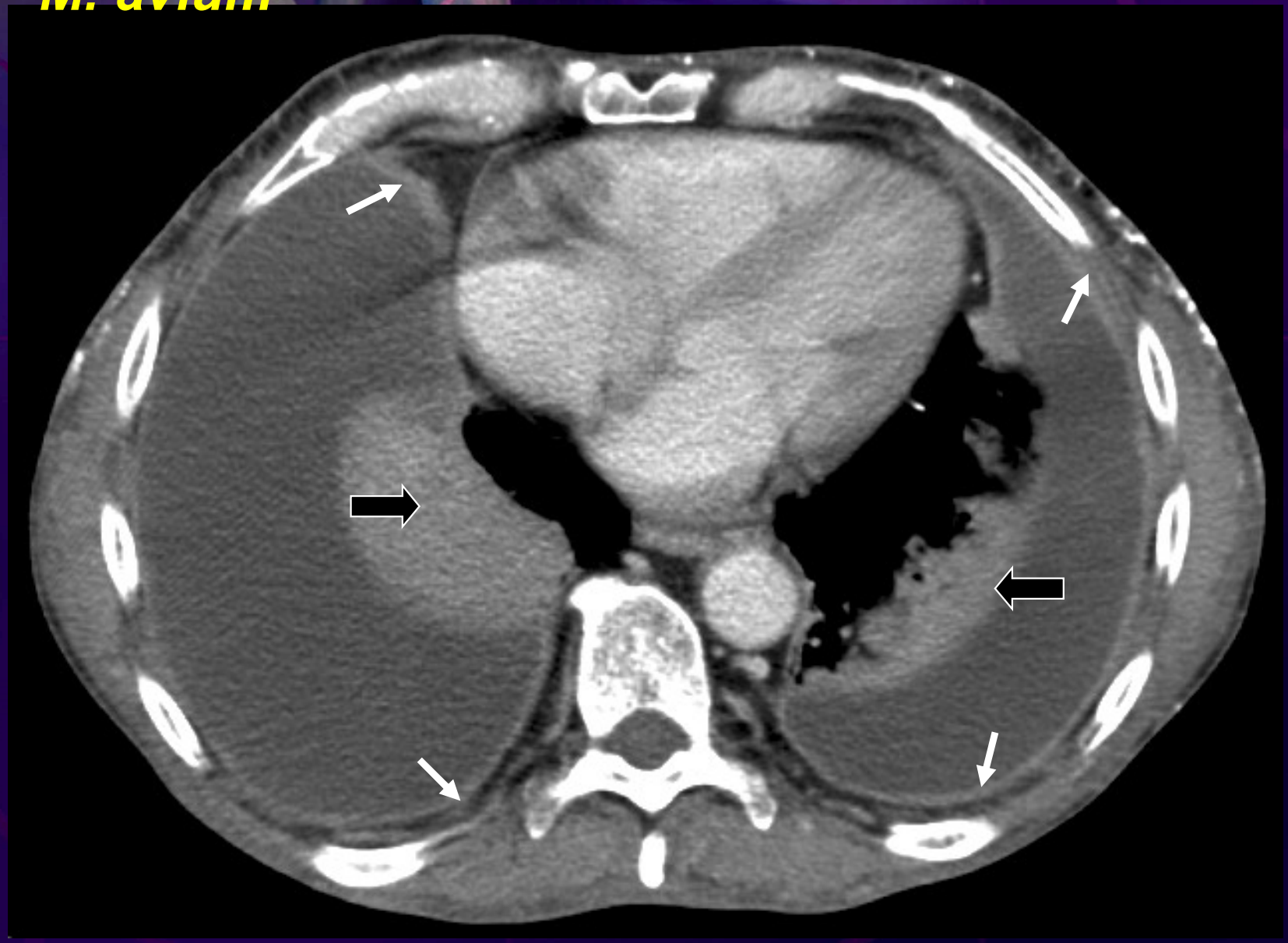
FDA MedWatch Anti-TNF therapy NTM Cases

	Pulmonary (n=59)	Extrapulmonary (n=46)
M. avium	43 (73%)	9 (20%)[+]
RGM*	6 (10%)	15 (33%)[+]
Age (years)	61	63
Sex (female)	41 (73%)	25 (54%)[+]
RA[±]	48 (81%)	25 (54%)[+]
Infliximab	40 (68%)	33 (72%)
Etanercept	13 (22%)	12 (26)%

[+]p value < 0.05 for comparison between pulmonary and extrapulmonary disease
*Rapidly growing mycobacteria (RGM)
[±]Rheumatoid arthritis (RA)

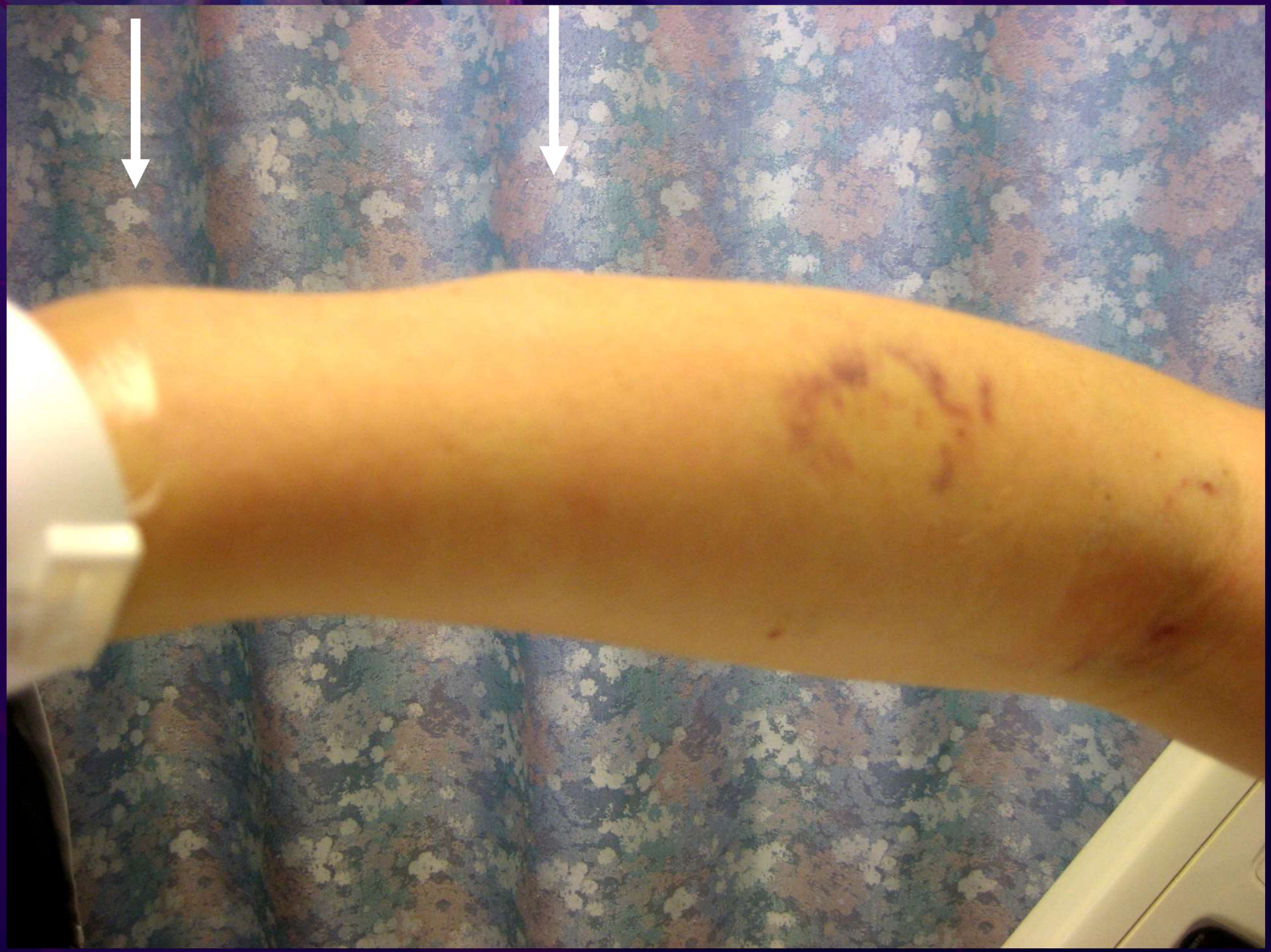
Winthrop KL Emerg Infect Dis 2009

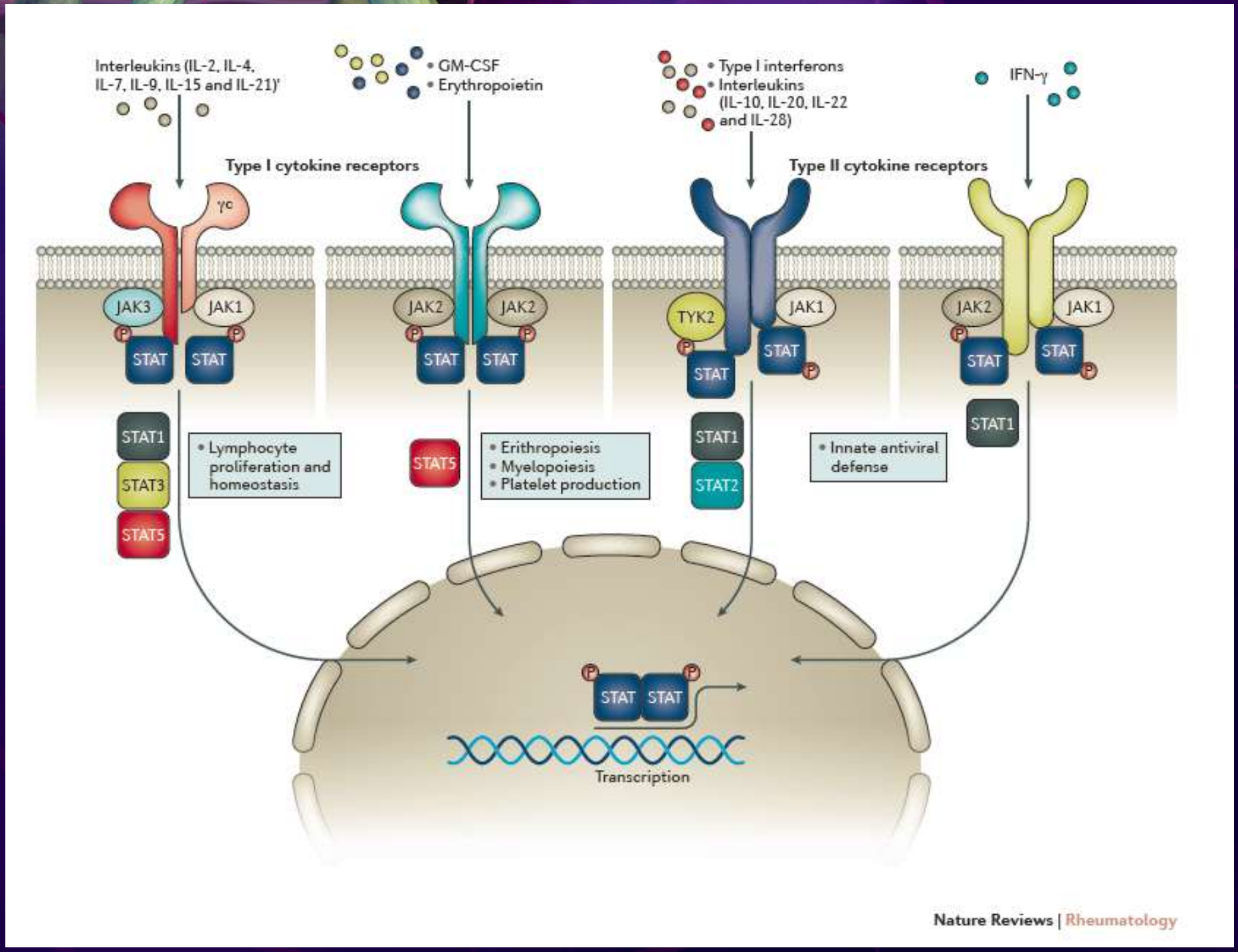
55 year old male, dermatomyositis, rituximab, *M. avium*



Contrast enhanced chest CT showing bilateral pleural effusions with extensive pleural enhancement (white arrows) and passive atelectasis (black arrows)

32 year old, myositis, rituximab, disseminated M. Kansasii forearm nodules





Winthrop KL Nature Rheum Rev 2017

Clark JD et al. J Med Chem 2014

Tofacitinib and "Opportunistic" Infections (P2P3LTE)

- 60 OIs reported (IR 0.46/100 pys [0.36-0.59])
  - TB (n=26)
  - PCP (n=4)
  - CMV (n=6)
  - Candida Esophagitis (n=9)
  - Cryptococcus (n=3)
  - Pulmonary NTM (n=2)
  - HZ, multi-dermatomal (n=8)
  - BK encephalopathy (n=1)
  - Toxoplasmosis (n=1)

Winthrop K et al. ARD 2015

Tofa Diminishes NK Cell Activation

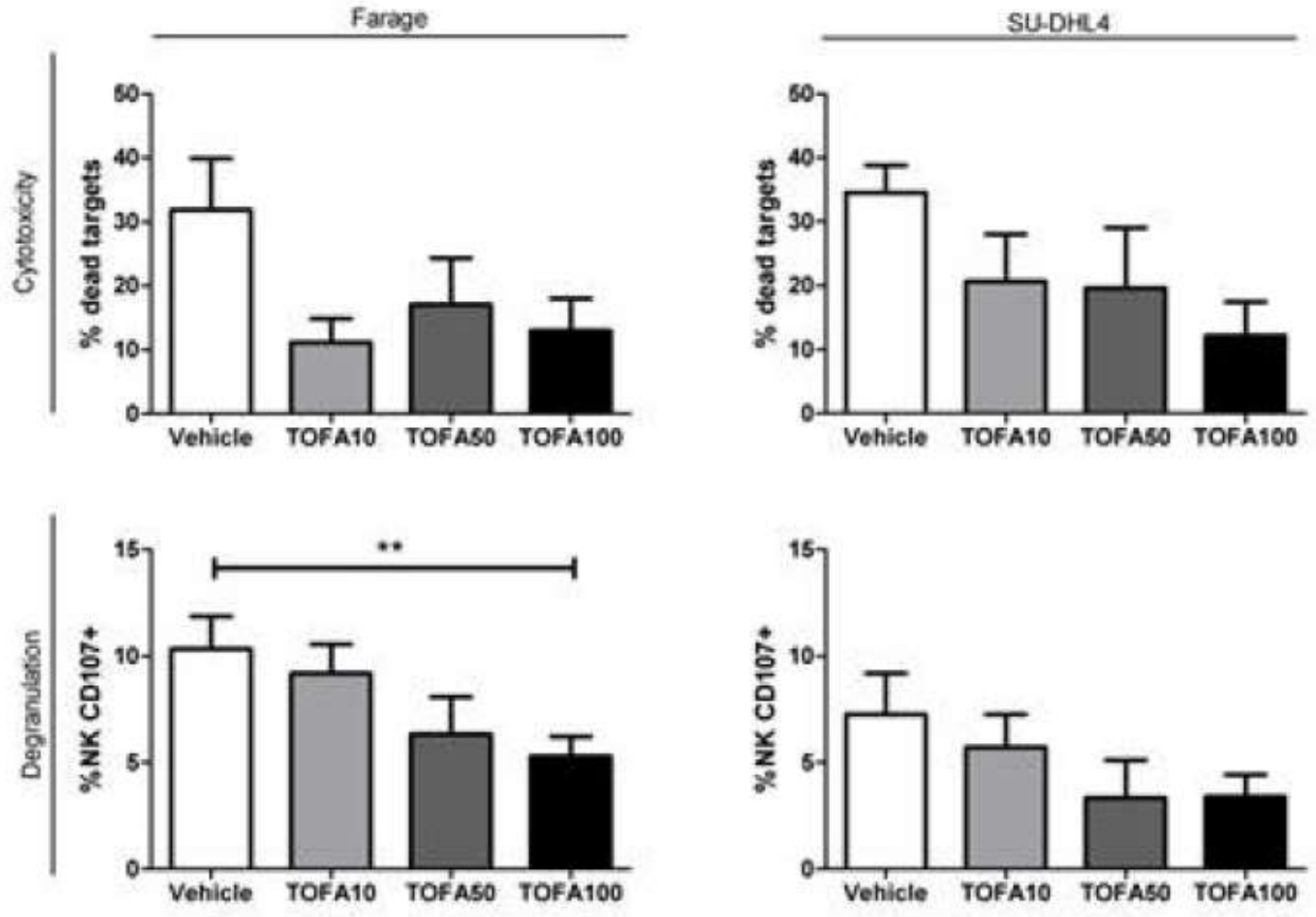


Figure 2: Anti lymphoma activity of tofacitinib exposed NK cells (**: p<0.01).

Nocturne G et al. ACR abstract 2016

Tofa Inhibits CD4 Proliferation in RA Patients

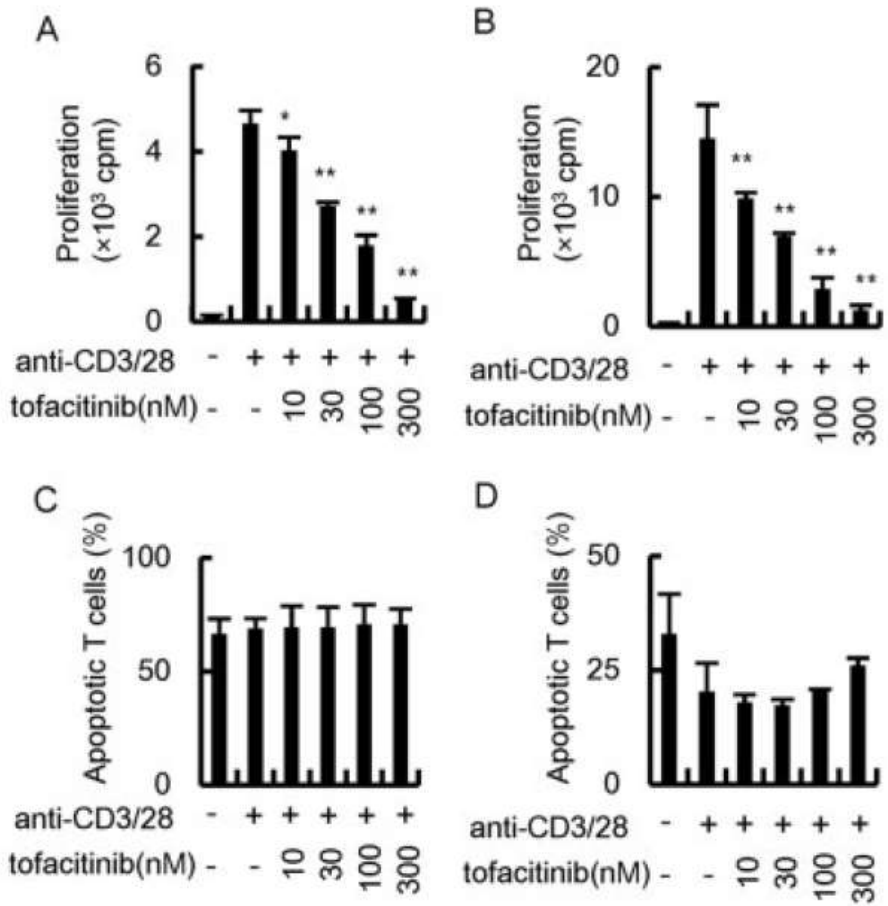


Figure 1. Tofacitinib inhibits proliferation of CD4+ T cells derived from the synovium and peripheral blood of patients with rheumatoid arthritis (RA), without cell toxicity. Synovial (**A** and **C**) and peripheral blood (**B** and **D**) CD4+ T cells were stimulated with anti-CD3/anti-CD28 antibodies in the presence of increasing doses of tofacitinib. **A** and **B**, To analyze cell proliferation, cells were pulsed with ^{3}H-

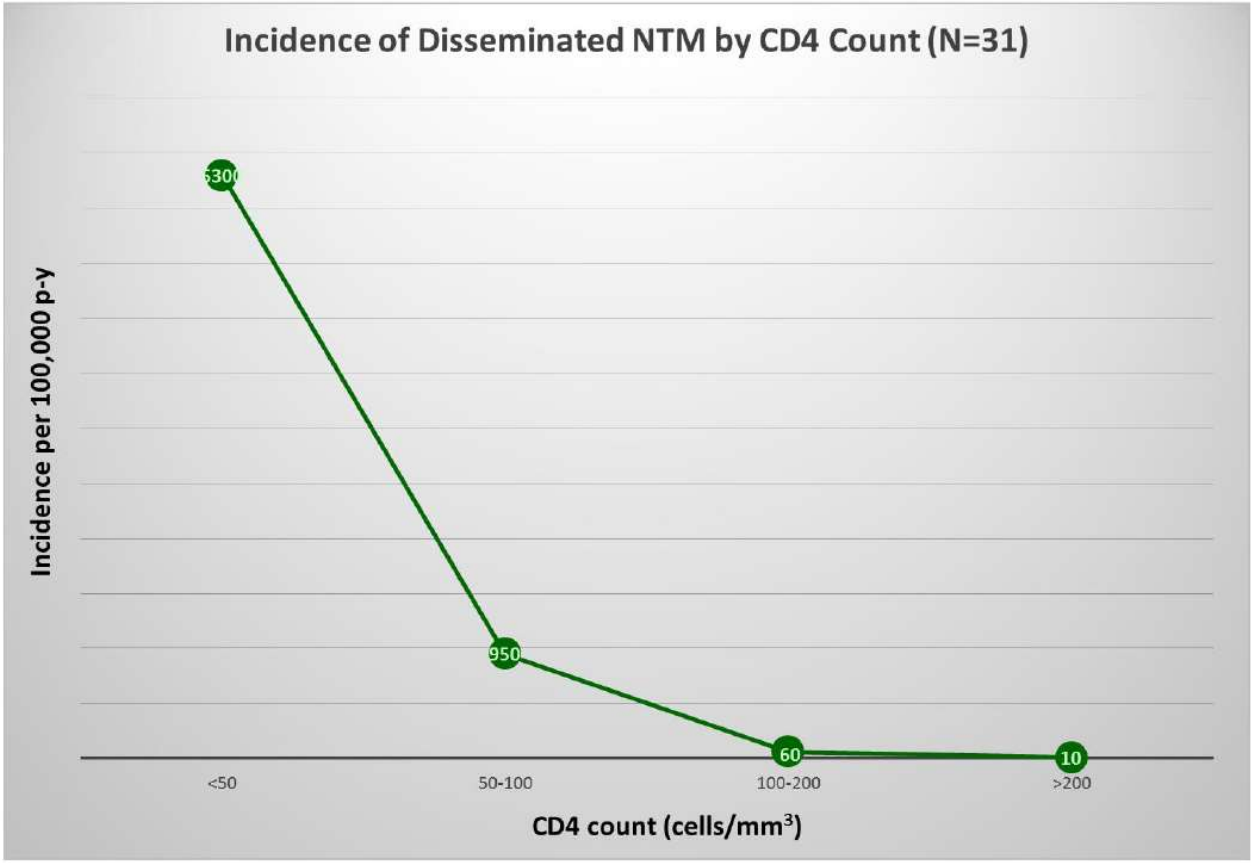
Maeshima et al
Arth Rheum 2012

Disseminated NTM in HIV

Annual Incidence of Disseminated NTM (N=37)					
Incidence per 100,000 person-years (95% Poisson Confidence Interval)					
2007	2008	2009	2010	2011	2012
110 (40-250)	200 (100-370)	50 (10-160)	130 (50-260)	70 (20-180)	110 (40-230)

Varley C et al. IDSA abstract 2015

Disseminated MAC in HIV



Incidence by CD4 Count Closest to Disseminated NTM Diagnosis Date (cells/mm^3) per 100,000 p-y (95% Poisson Confidence Interval)

< 50	50-100	100-200	> 200
5300 (3360-7950)	950 (310-2210)	60 (0-310)	10 (0-30)

Varley C et al. IDSA abstract 2015

MAC Therapeutic Options

- In immunosuppressed host
  - Treatment almost always (over observation)
  - Macrolide, rifampin, ethambutol
  - Amikacin (IV or inhaled), clofazimine
  - Length of therapy variable (dictated by disease type and immune system)
  - No macrolide monotherapy
  - Daily (not TIW. My opinion)

Griffith DG, et al. AJRCCM 2007

NTM in HIV

- Disseminated MAC
- GI route of infection
- Less frequent in HAART era
- Related issues
  - Clofazimine = might increase mortality (do not use!)
  - Rifabutin dose adjustment with PI
  - Immune reconstitution inflammatory syndrome (IRIS)

TABLE 7. REGIMENS FOR TREATMENT AND PREVENTION OF DISEASE DISSEMINATED *MYCOBACTERIUM AVIUM* IN HIV-INFECTED PATIENTS

Preferred (A, I)*	Alternative (B, I)*
Treatment	
Clarithromycin 500 mg orally twice daily + Ethambutol 15 mg/kg orally daily ± Rifabutin† 300 mg orally daily	Azithromycin 500 mg daily Ethambutol 15 mg/kg daily Rifabutin† 300–450 mg orally daily
Prevention‡	
Azithromycin 1,200 mg orally weekly	Clarithromycin 500 mg orally twice daily or Rifabutin† 300 mg orally daily

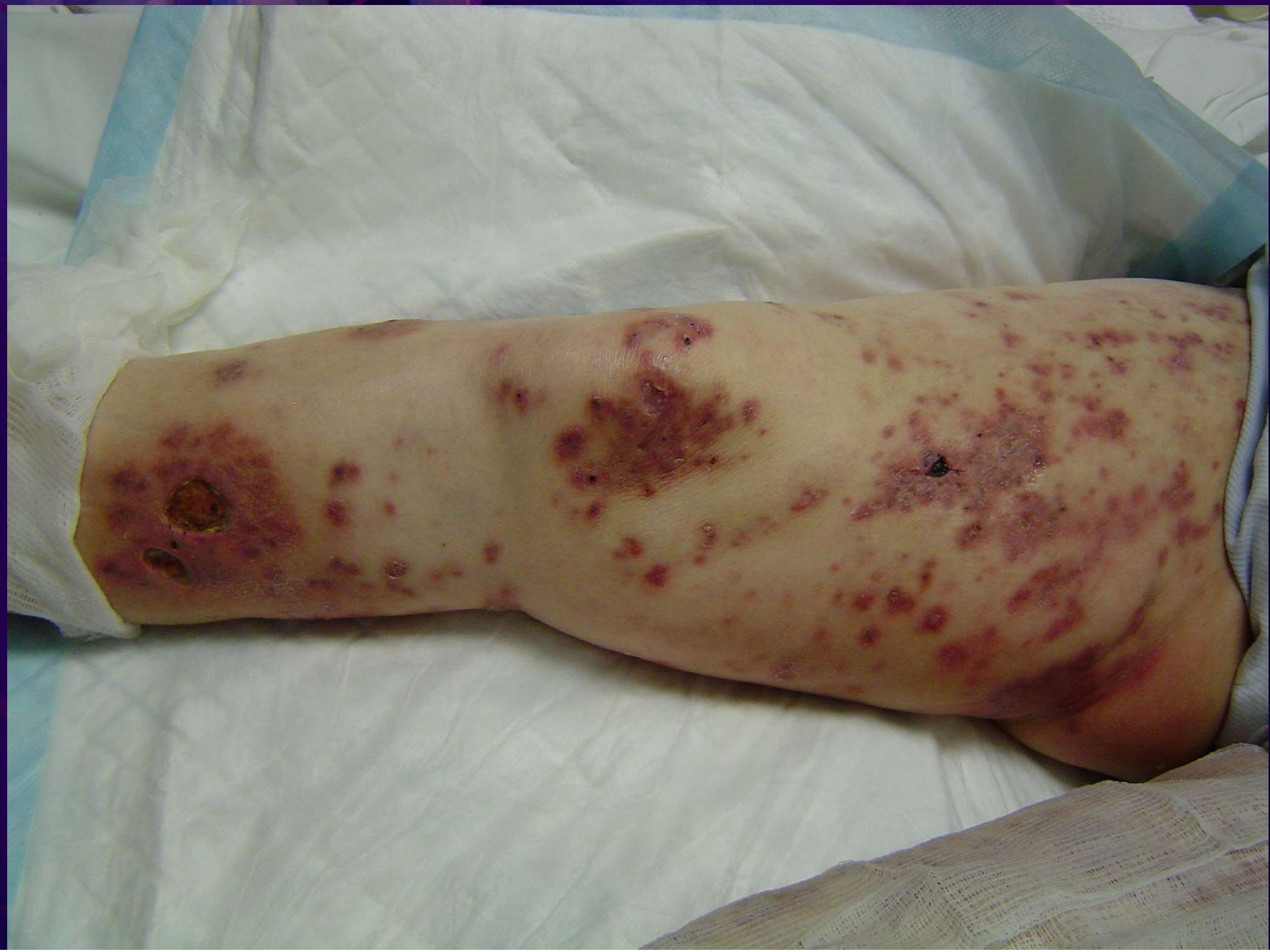
* For evidence quality, *see* Table 1.

† Rifabutin dose may need to be modified based on drug–drug interactions (*see* text).

‡ Preventive therapy indicated for persons with < 50 $CD4^+$ cells/μl; may stop if > 100 cells/μl.

Griffith D et al. AJRCCM 2007

M. chelonae in cancer patient



RGM Therapy

- *M. chelonae*
  - Macrolides, FQ, linezolid
  - IV drugs include aminoglycosides, imipenem, cefoxitin, tigecycline
  - Note: tobramycin is best for *M. chelonae*
- *M. fortuitum*
  - Macrolides,FQ, linezolid, bactrim, doxy (50%)
  - IV drugs include aminoglycosides, imipenem, cefoxitin, tigecycline

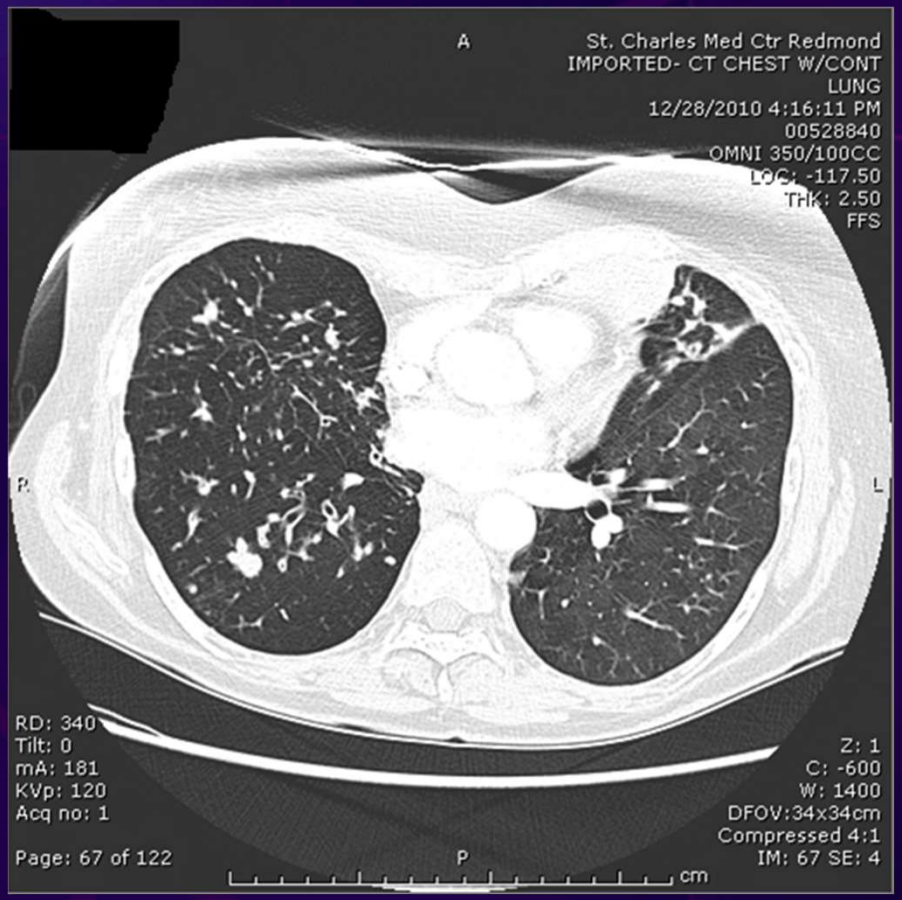
<u>Length of treatment for disseminated infection</u>

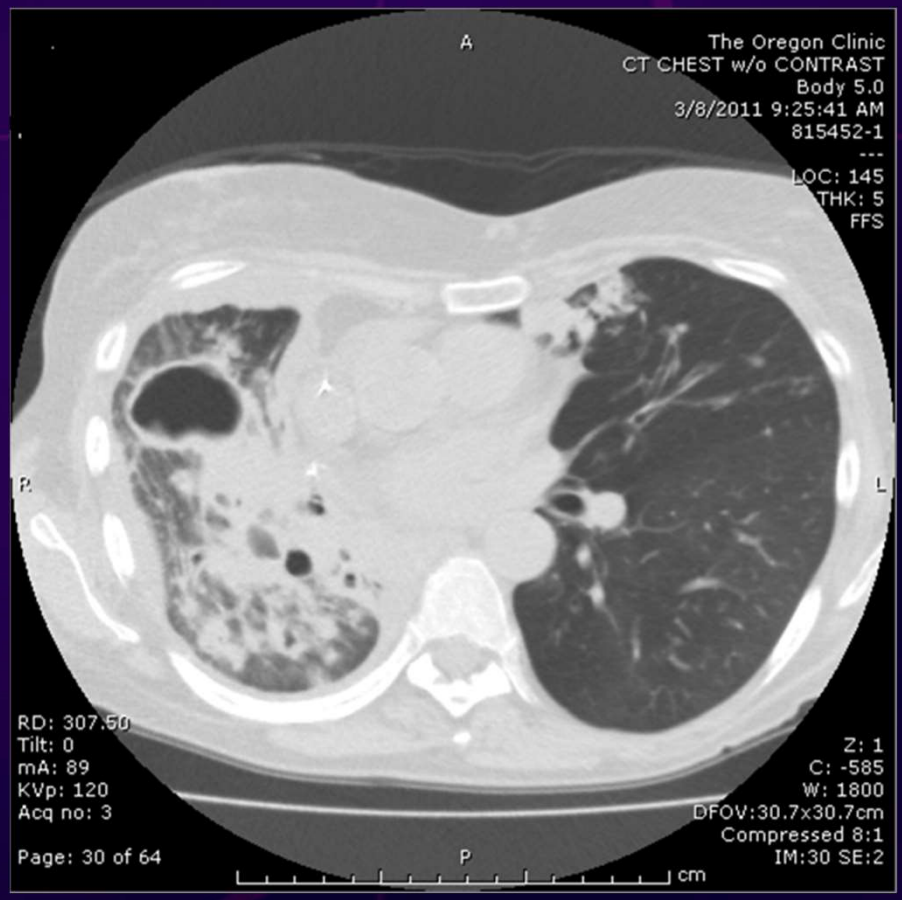
3 drugs (including 1 IV) X 4-6 months

Depends on immunosuppression reversal

Rapidly Progressive Disease

10 weeks while on therapy





IRIS

- Similar phenomenon as seen with TB (or other opportunistic infection)
- Incidence is variable
  - 5% of TNF-associated NTM cases
- Diagnosis of exclusion
- Can be clinically devastating
- Management with high dose prednisone
  - Anti-TNF therapy if needed

Winthrop K et al. CID 2008; Wallis R et al CID 2009

M. abscessus Therapy

- "Cure" = more difficult
- Limited antibiotic options based upon susceptibility testing
- Parenteral agents
  - Tigecycline 50mg daily
  - Cefoxitin 2gm TID,
  - Imipenam 1000mg BID
  - Amikacin 10mg/kg TIW

Omadacycline, in Phase 2

MUSC Medical University of South Carolina

One Center's Experience with Omadacycline for the Treatment of *Mycobacterium Abscessus* Infections

Christina M Mingora MD, Wendy Bullington PharmD, Susan E Dorman MD, Patrick A Flume MD
Medical University of South Carolina, Charleston, SC

RATIONALE

- *Mycobacterium abscessus* complex organisms are difficult to treat human pathogens that cause pulmonary and systemic disease
- Unfortunately, oral treat options are limited
- Omadacycline, an oral tetracycline analog, has been shown to demonstrate in vitro activity against *M. abscessus*
- This study sought to report efficacy, safety, and tolerability of this drug in the treatment of *M. abscessus* infections at our center

METHODS

- Retrospective chart review of all adult patients in our non-tuberculous mycobacterial disease clinic were screened
- Patients with confirmed diagnosis of *M. abscessus* infection and prescription of Omadacycline as part of directed antimicrobial regimen through December 31, 2021 were included (n = 36)
- Demographic data, relevant medical history, NTM history, and radiographic and microbiologic data (including organism subspecies and drug susceptibility testing to key antimicrobials) were recorded at time of Omadacycline initiation (baseline)
- Therapeutic drug monitoring parameters were recorded and baseline and monthly thereafter
- Descriptive statistics were performed

RESULTS

Table 1. Baseline Demographics at time of Omadacycline Initiation	
Age (years), mean ± SD	61.4 ± 15.9
Sex: Female, n (%)	23 (64%)
Race, n (%) • White/Caucasian • African American • Non-white Hispanic	 31 (86%) 4 (11%) 1 (3%)
Insurance Coverage, n (%) • Private • Medicare • Medicaid	
Body Mass Index (kg/m²)	22.8 ± 5.7
Pertinent Medical History at Time of NTM Diagnosis	
Pulmonary Disease, n (%)	21 (58%)
Other Key Diagnoses • Chronic Kidney Disease, n (%) • Connective Tissue Disease, n (%) • Immune Deficiency, n (%) • Transplant Recipient, n (%)	 7 (19%) 5 (14%) 2 (6%) 6 (17%)

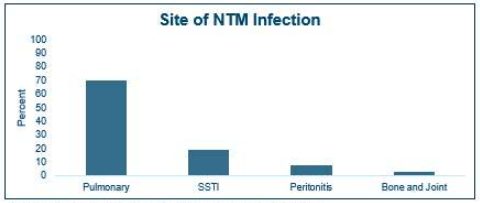


Figure X. Distribution of site of *M. abscessus* infection

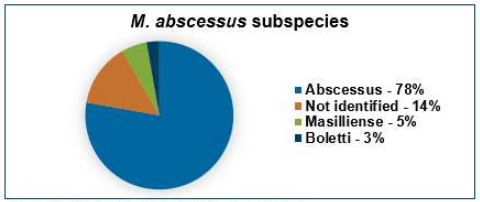


Figure X. Distribution of *M. abscessus subspecies*

Table X. Adverse Events	
Any Adverse Event During Treatment Period, n (%)	15 (42%)
Adverse Events Attributed to Omadacycline	• Gastrointestinal Issue: Nausea, vomiting, diarrhea, esophagitis • Abnormal hepatic function: Transaminitis, hyperbilirubinemia • Anemia • Eosinophilia • Rash
Action Taken Related to Adverse Event	
Omadacycline Drug Cessation	8 (22%)
Prescription of Other Therapies to Mitigate AE	6 (17%)

Table X. Omadacycline History (All patients received dose 300 mg by mouth daily)	
Duration of Treatment (months), mean ± SD	6.08 ± 5.29
Rationale for Use • Initial Therapy, n (%) • Transition from IV Tigecycline, n (%) • Treatment Refractory Disease, n (%) • Intolerance to Other NTM Therapy, n (%)	 3 (8%) 22 (61%) 7 (19%) 10 (28%)
Treatment Discontinued, n (%)	22 (61%)
Rationale for Therapy Discontinuation	
Microbiologic Cure, n (%)	9 (25%)
Adverse Event or Intolerance, n (%)	9 (25%)
Treatment Cost Prohibitive, n (%)	1 (3%)
Death, n (%)	3 (8%)

Table X. Microbiologic Data – *M abscessus* isolate	
Susceptibility to amikacin (average MIC)	12.8
Susceptibility to tigecycline (average MIC)	1.0
Inducible macrolide resistance present, n (%)	19 (53%)

Table X. Radiographic Features – Pulmonary Disease Only	
Bronchiectasis, n (%)	22 (61%)
Nodules, n (%)	25 (69%)
Cavitary Disease, n (%)	8 (22%)

CONCLUSIONS

- Omadacycline was generally well tolerated and demonstrated therapeutic efficacy with microbiologic cure in 25% of subjects and ongoing therapy in 56% of subjects
- This drug shows promise, particularly in isolates with macrolide resistance and in hosts with contraindication to other standard systemic therapies
- We are currently analyzing multi-center data collected in collaboration with NTM centers at NIH, NJH, NYU, and OHSU

Mingora C et al. ATS abstract 2022

Erythromycin Methylase Gene *erm*(41)

TABLE 3. TREATMENT RESPONSES FOR PATIENTS WITH *MYCOBACTERIUM ABSCESSUS* AND *MYCOBACTERIUM MASSILIENSE* LUNG DISEASE

	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%)	

Definition of abbreviation: HRCT = high-resolution computed tomography.

Koh et al. *AJRCCM* 2011

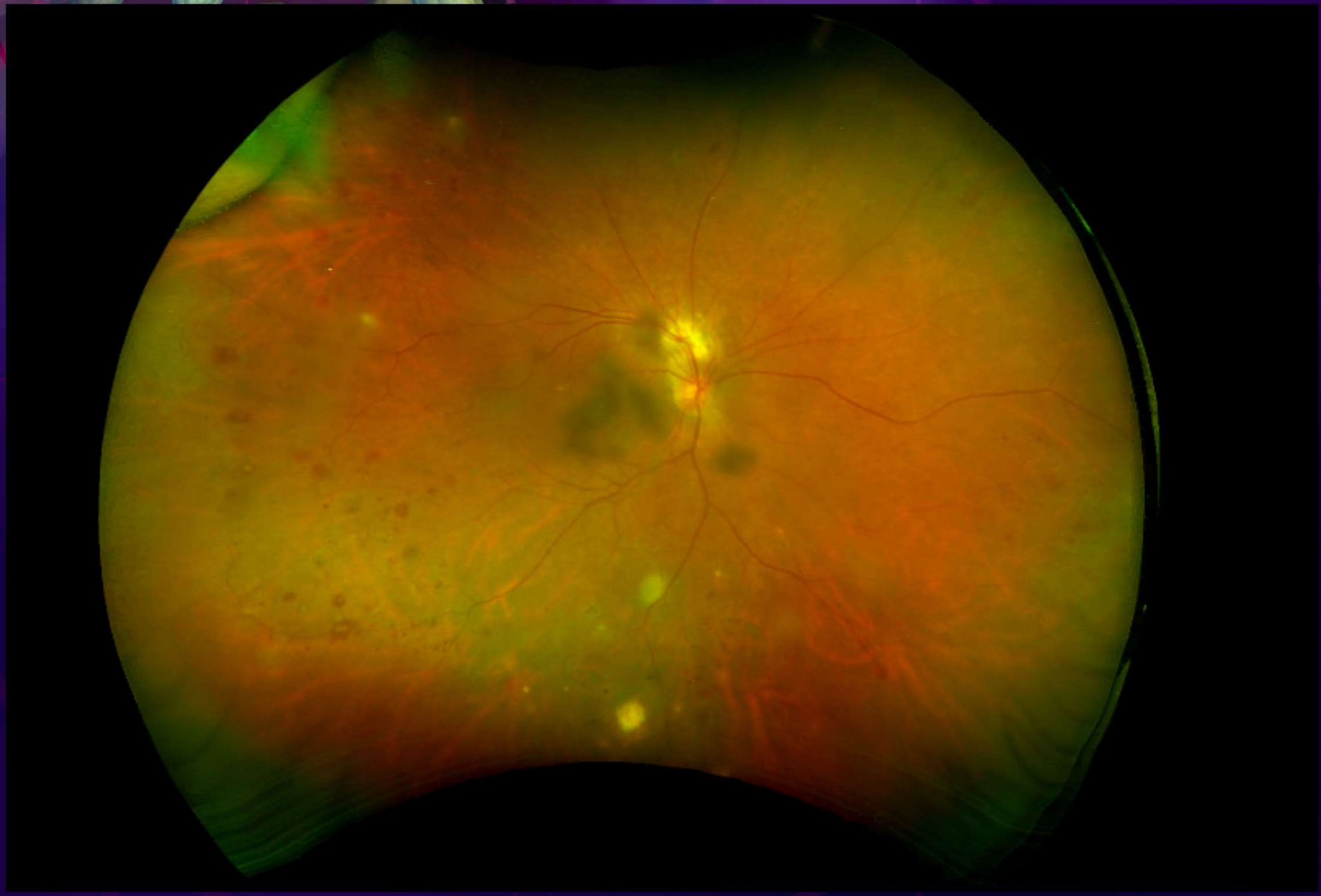
Amikacin Resistance (MAI)

Initial amikacin MIC (µg/ml)	No. of isolates	Cumulative % of isolates
<1	7	1.5
2	18	5.4
4	57	17.7
8	144	48.9
16	171	85.9
32	46	95.9
64	9	97.8
>64	10	100

16S RNA gene A1408G mutation

[a] These data were determined with the CLSI-approved broth microdilution method (4).
[b] MIC mode, 16 µg/ml; MIC_{50}, 16 µg/ml; MIC_{90}, 32 µg/ml.

Brown-Elliott B, et al *J Clin Microbiology* 2013



M. chimaera

Transmission of *Mycobacterium chimaera* from Heater–Cooler Units during Cardiac Surgery despite an Ultraclean Air Ventilation System

Rami Sommerstein, Christian Rüegg, Philipp Kohler, Guido Bloemberg, Stefan P. Kuster, Hugo Sax

Sommerstein R et al, EID 2016

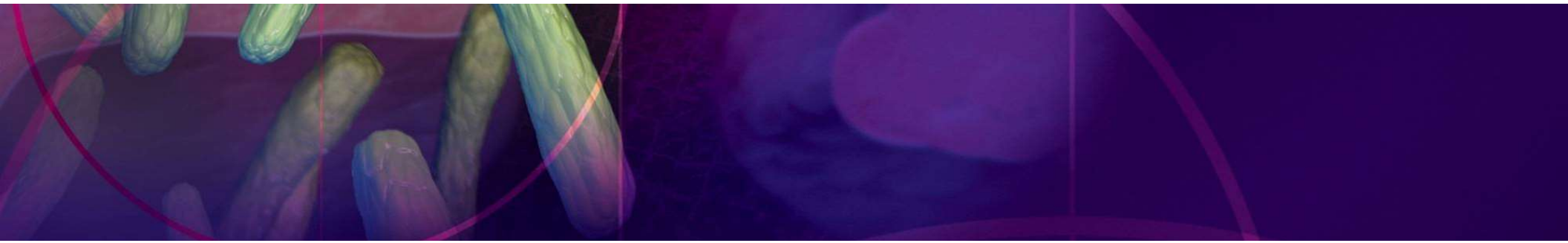


Table 1. Published Cases of *Mycobacterium chimaera* Infection Related to the Heater–Cooler Unit

	Latency		
Outbreak Location/N/Citation	Surgery to Symptoms	Symptoms to Diagnosis	Mortality (%)
Europe/10/[7]	Median, 18 months	Median, 21 (5–40 months)	5/10 (50)
United Kingdom/30/[28]	Median, 14.5 months (range, 1.5–60 months)	Median, 7 weeks	18/30 (60)
Germany/5/[17]	Range, 5–60 months	NR	1/5 (20)
Pennsylvania/8/[26]	NR	Median, 1.2 years (1–27 months)	5/8 (63)
United States/24/[25]	NR	Mean, 1.6 years (range, 0.1–6.3 years)	11/24 (46)
New York/2/[31]	NR	Mean, 14.5 months (range, 12–17 months)	0
Montreal, Canada/2/[21]	Range, 13–16 months	Additional 2–3 months from presentation	0
Florida/1/[24]	72 months	NR	0
Minnesota/3/[22]	Range, 16–26 months	NR	2/3 (67)
Italy/1/[27]	14 months	12 months	0

Abbreviation: NR, not reported.

Up to 6 years

Up to 3.3 years

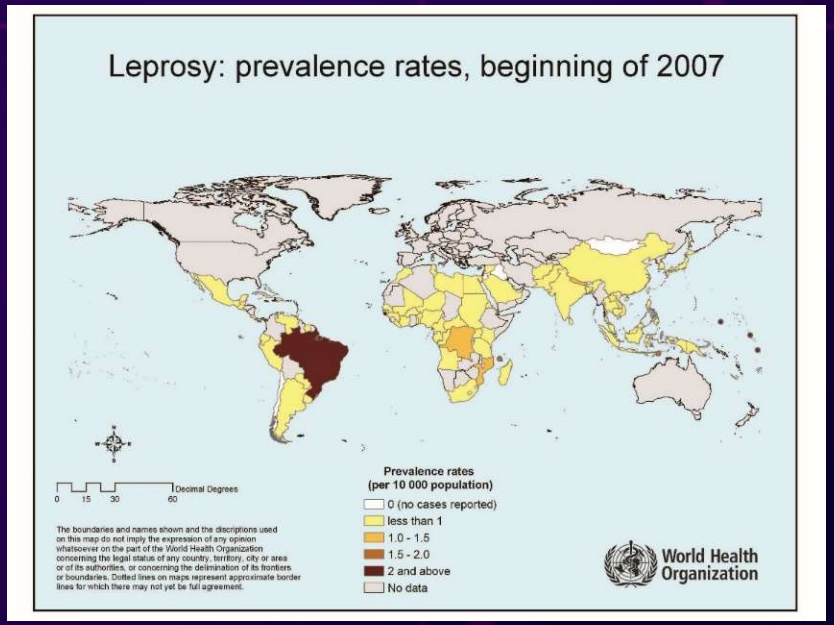
Up to 67%

Disseminated Chimaera

- Remove implanted material if possible
- AZI/EMB/RIF plus Amikacin/Clofaz
- Outcomes are poor
  - 50% mortality or higher

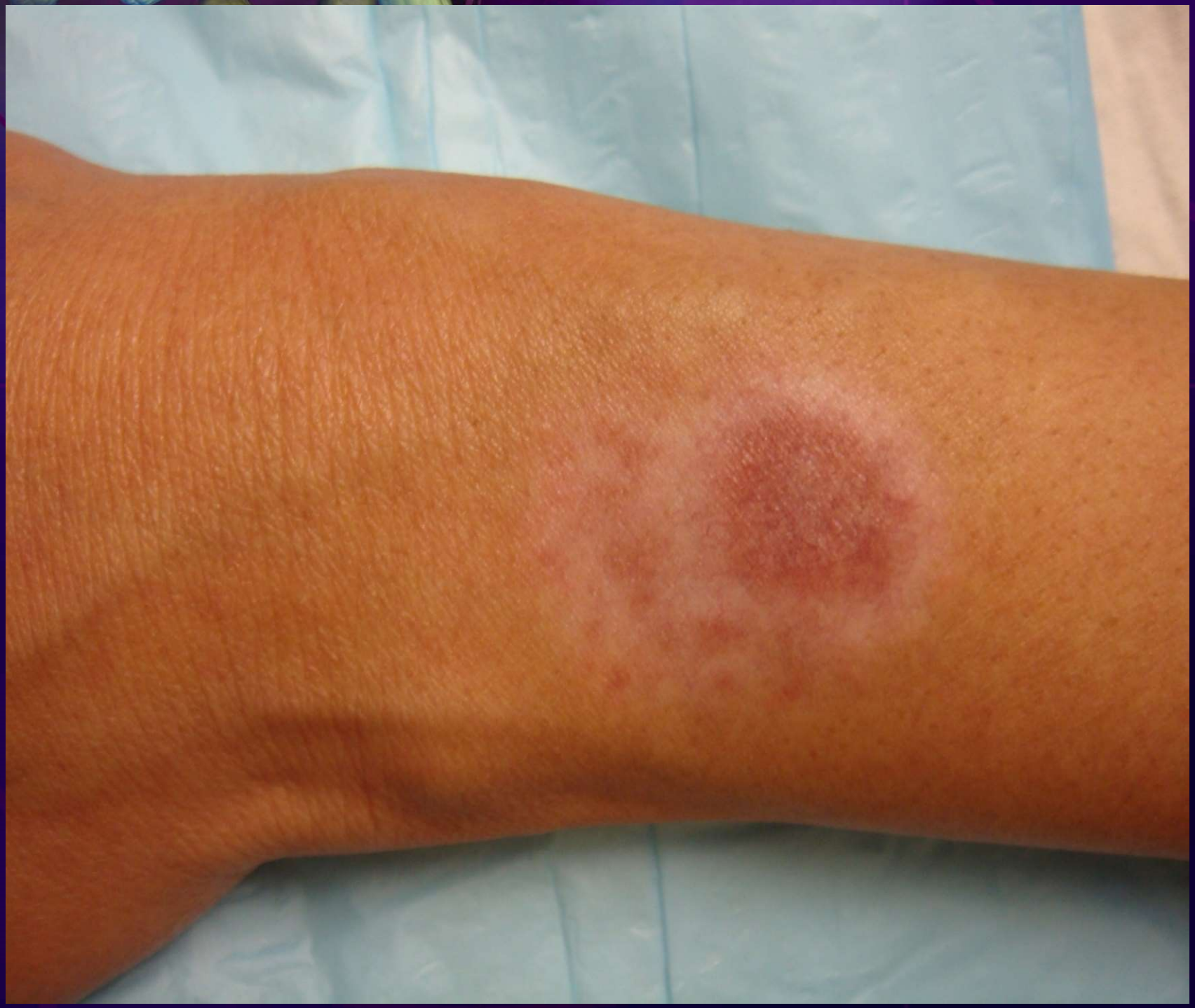
Hansen's Disease (Leprosy)

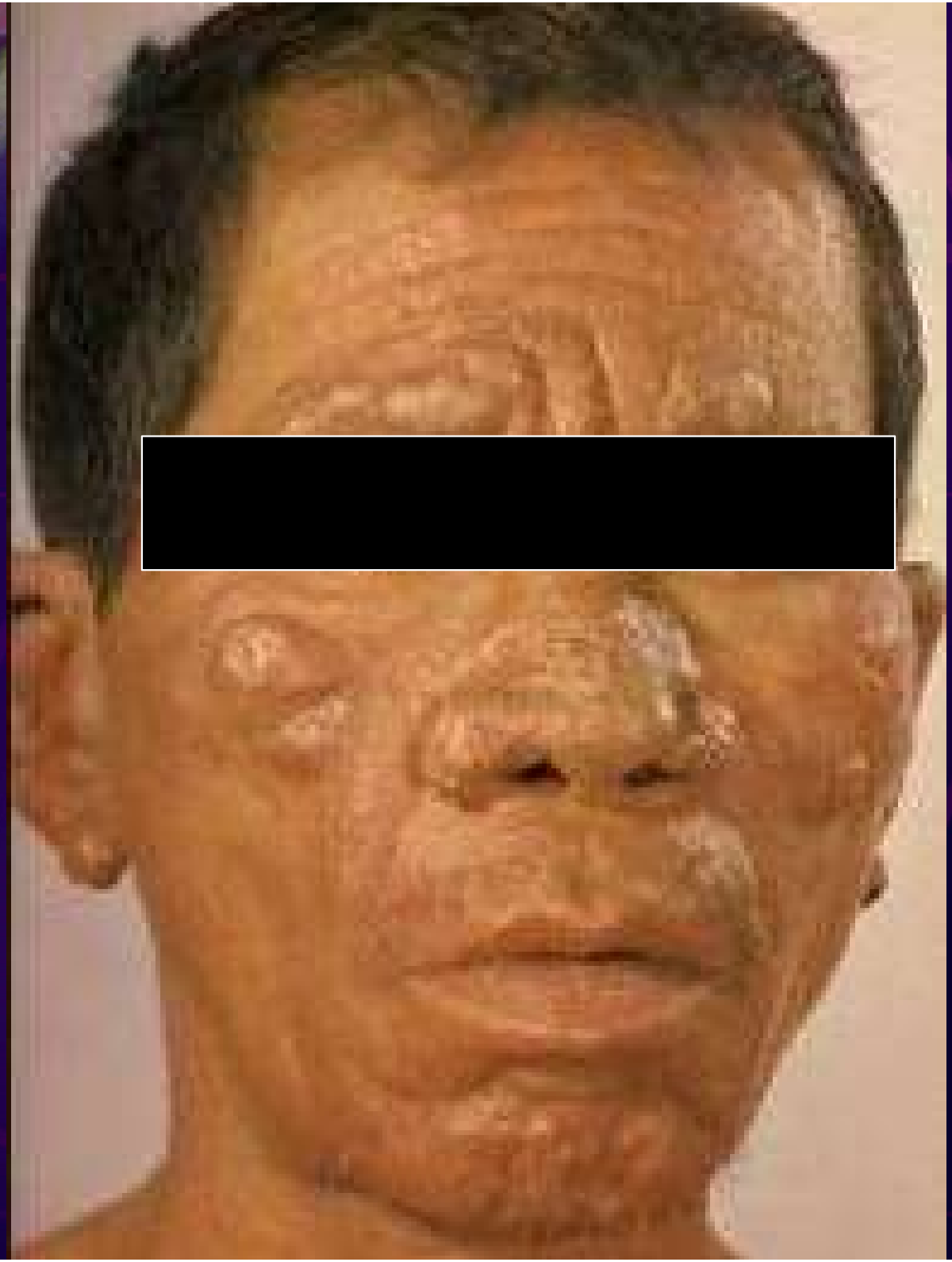
- Rare in US (40-50 cases per year)
  - Armadillos and gulf region
  - Rest imported
- Most humans resistant
  - Household contacts at risk (low risk)
  - Nasopharyngeal transmission?
- *M. leprae* does not grow in culture



Leprosy Disease Classification

- **Paucibacillary (PB)**
  - Most common form
    - *"Tuberculoid"*
    - Bacillary load < 1 million
    - Skin biopsy: AFB negative
    - ≤5 skin lesions
- **Multibacillary (MB)**
  - *"Lepromatous"*
  - Massive bacillary load
  - Skin biopsy: Floridly positive for AFB
  - >5 skin lesions.





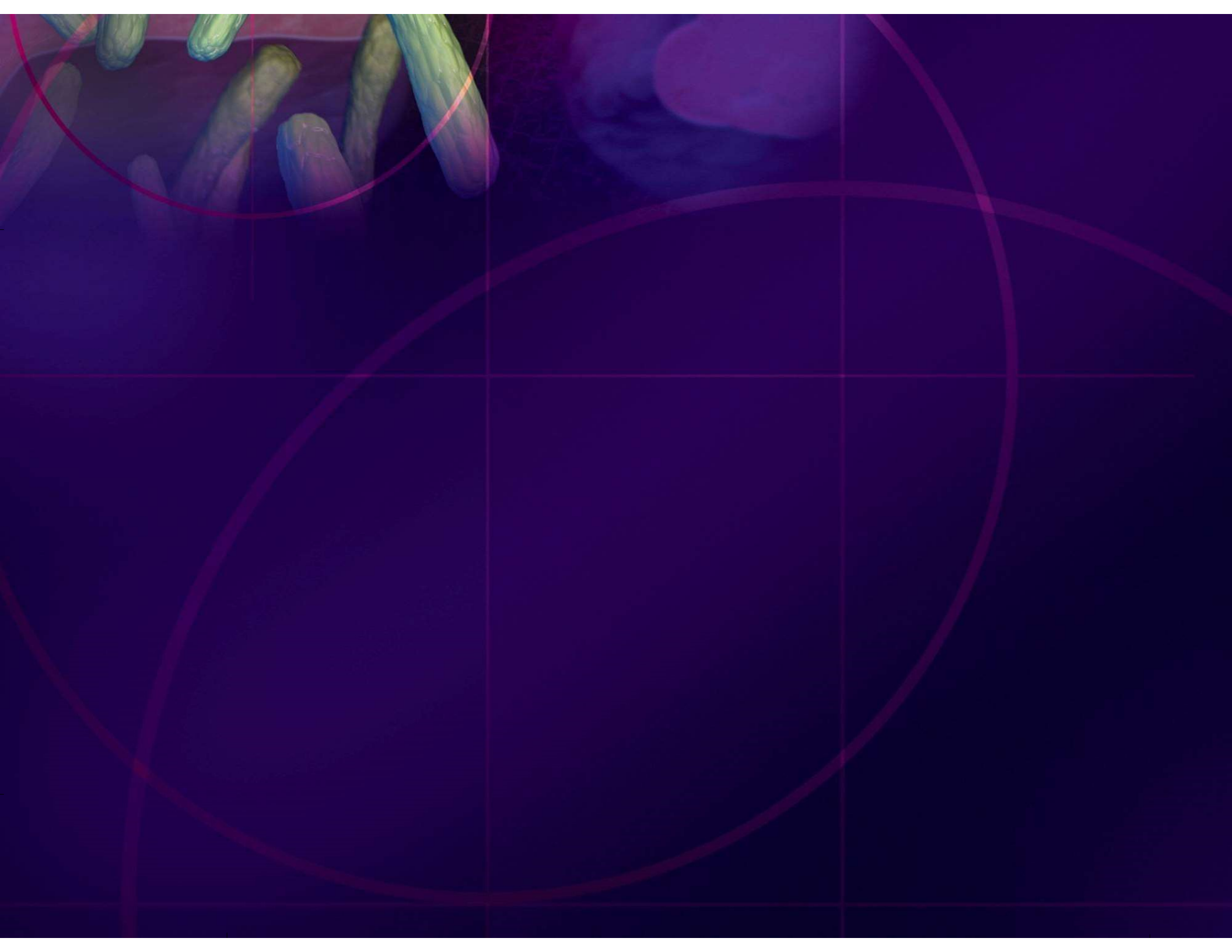
Leprosy Treatment

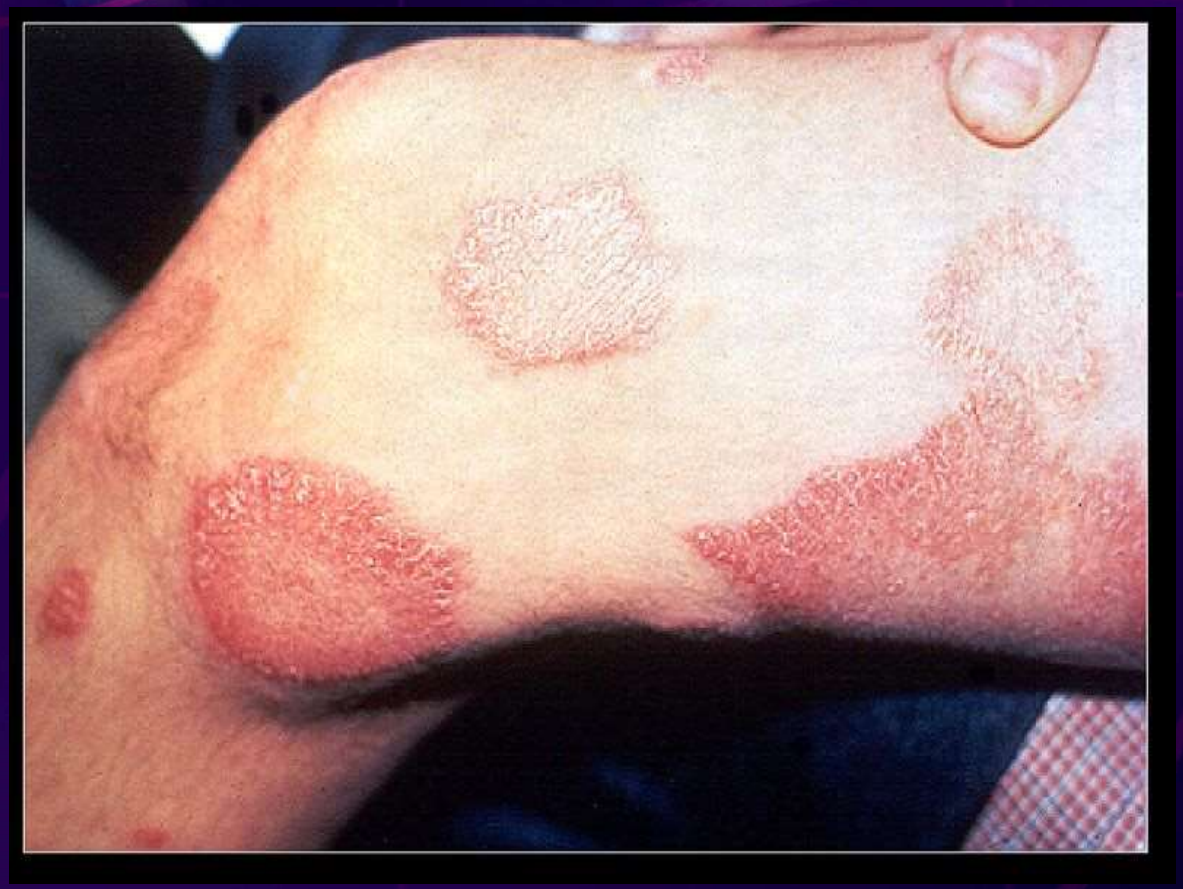
- PB (6-12 months)
  - Dapsone 100mg daily
  - Clofazimine 50mg daily
  - *Rifampin 600mg once monthly
  - (US guidelines are daily RIF and no Clofaz for 12 months)
- MB (12-24 months)
  - Dapsone 100mg daily
  - Clofazimine 50mg daily
  - Rifampin 600mg daily

Complications: reversal reactions, erythema nodosum
Treat with prednisone, thalidomide, other

Acknowledgements

- NTM Research Consortium
  - OHSU, NJC, UT Tyler, NIH
- Close colleagues and friends at variety of institutions including:
  - OHA, Univ. Ontario, U Florida, CDC, ATS/IDSA, NYU, Georgetown, others





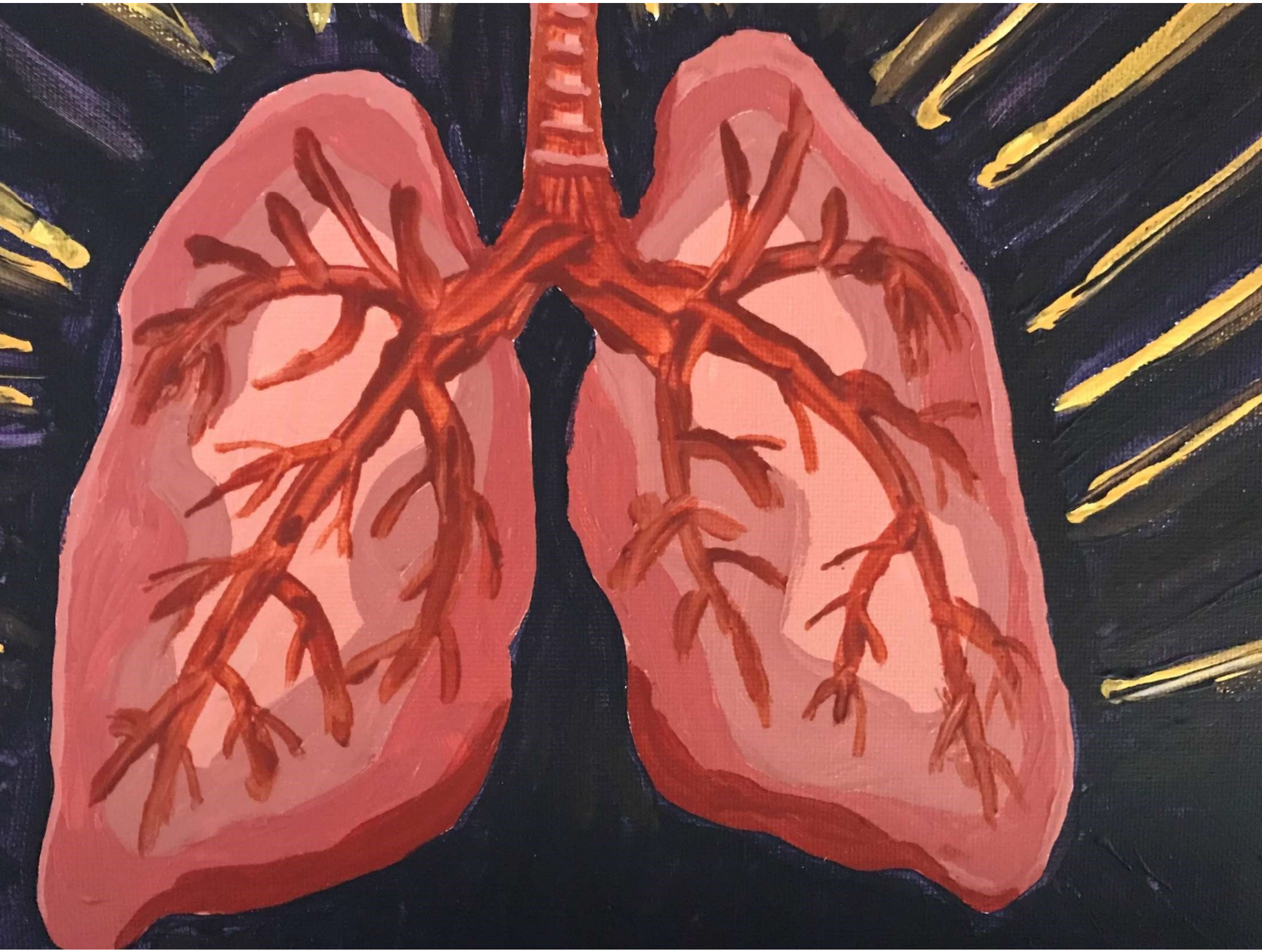
Tigecycline

- Efficacy unknown
  - Disease stabilization
- Use limited by severe nausea and vomiting
  - CF kids versus elderly
- 50mg once daily
  - Pre-treat zofran or other anti-emetic

Omadacycline

Drug-Drug Interactions

- Rifampin
  - Beta-blockers, Levothyroxine, CA2+ blockers, warfarin
  - Tacrolimus, steroids, cyclosporin
  - Azoles, Protease inhibitors, FQs
- Azithromycin
  - Digoxin, warfarin
- Clarithromycin has many of the above
- QT issue
  - Clari/azi, FQs, Bedaquiline, Clofaz, others



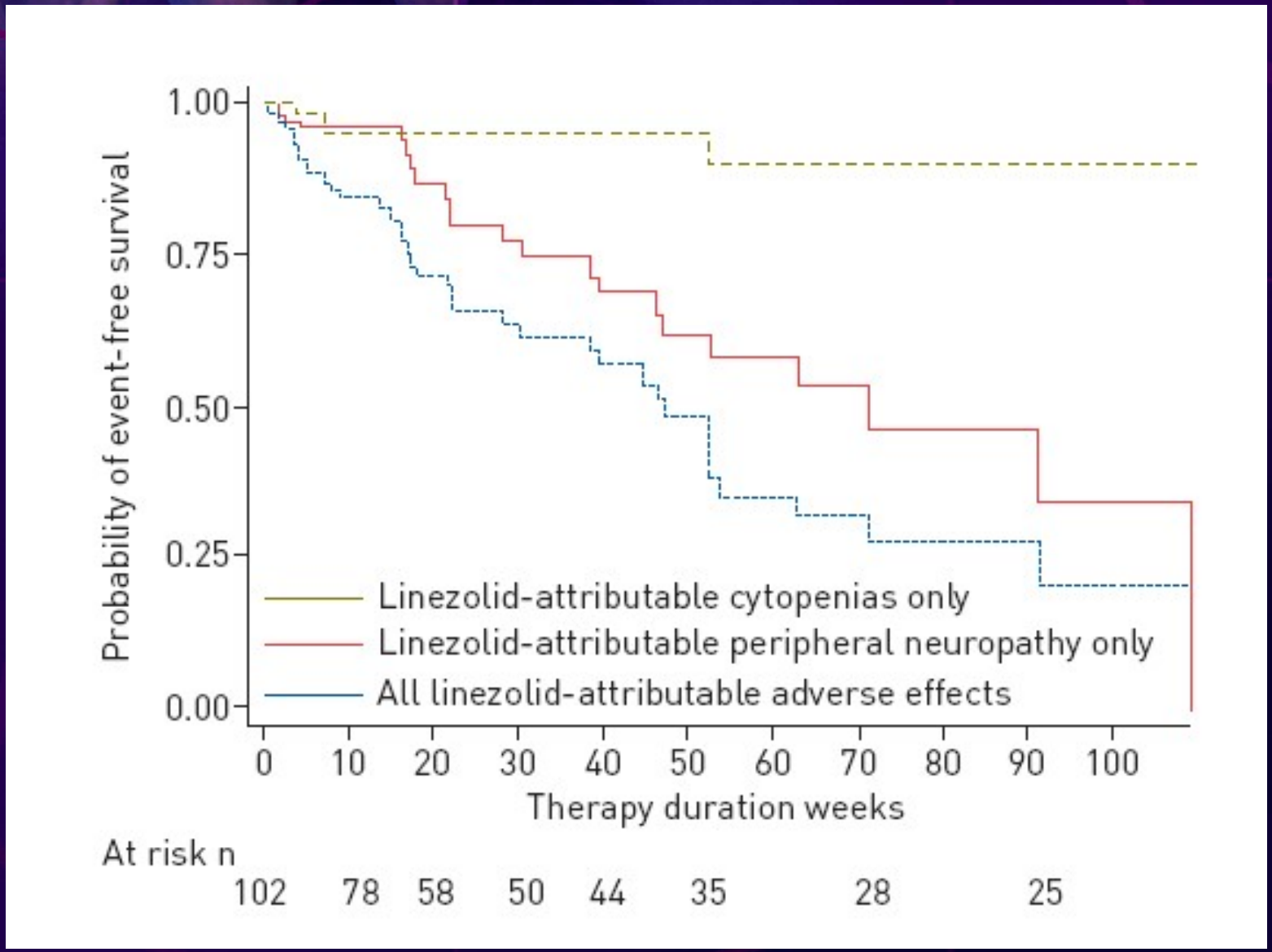
Clofazimine

- Must get from FDA
  - Investigational New Drug application
- Leprosy and MDR-TB
- NTM?
  - Experience in HIV patients with MAC
  - Immunosuppressive versus antimicrobial effects
  - Possible synergism with amikacin
  - GI intolerance and reversible tan

Linezolid

- Drug developed for Staph (MRSA) and other gram positives
  - Has anti-mycobacterial activity
  - NTM efficacy unknown
- 600mg once daily
- 100mg B6
  - Cytopenias
  - Peripheral neuropathy
  - Optic neuritis

Discontinuation Due to Linezolid-attributed Adverse Events



Winthrop KL et al. ERJ 2014