Atypical Mycobacterium-a new front in the battle

CHP (Infection Control Branch)

Dr. Wu Tak Chiu
Consultant and Head
Division of Infectious Diseases
Department of Medicine
Queen Elizabeth Hospital

14 December 2016

NTM Definition

- Non tuberculous mycobacteria (NTM)
- A heterogenous group composed of more than 169 species.
- Also called atypical mycobacteria or mycobacteria other than M. tuberculosis (MOTT)
- Categorised based on characteristic colony morphology, **growth rate**, and pigmentation (the Runyon System of classification)

Time to detection of mycobacterial growth in culture

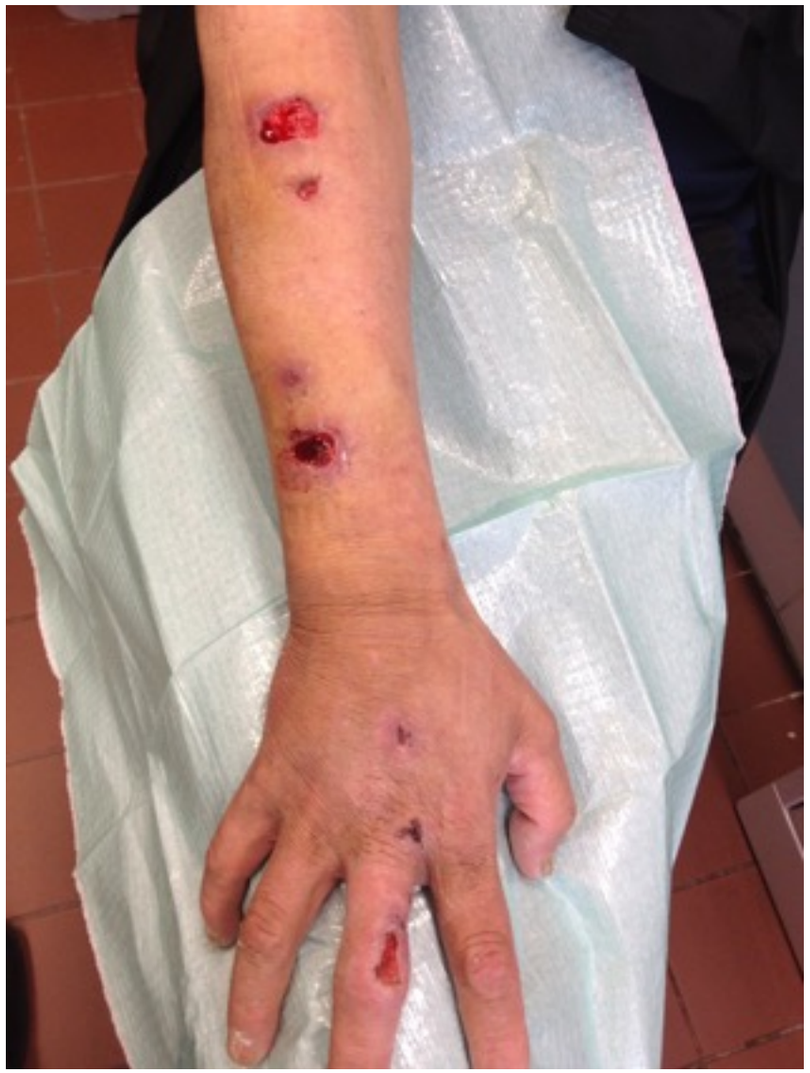
- Most NTM grow within 2-3 weeks on subculture
- **Rapid growing mycobacteria (RGM)**: colonies formation on subculture in 7 days or fewer
    - e.g. *M. abscessus, M. chelonae, M. fortuitum*
- **Slowly growing mycobacteria**: colonies formation on subculture in more than 7 days
    - e.g. M. avium complex, *M. Kansasii, M. marinum*
- Guided us empirical antibiotic choice

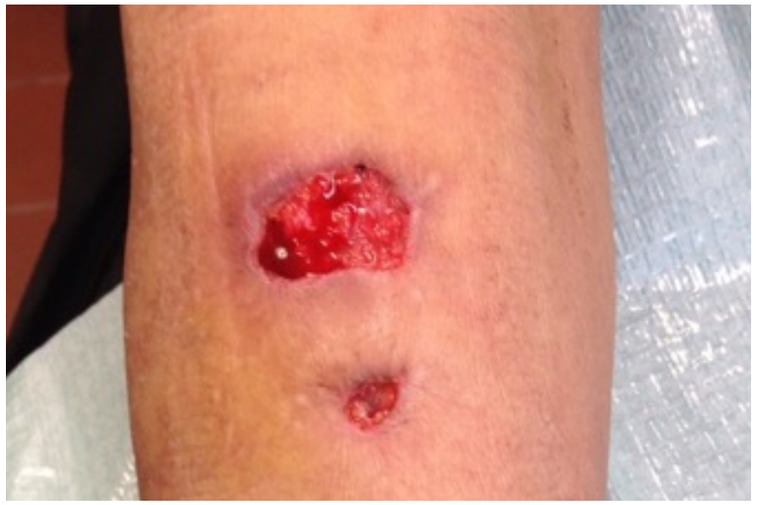
Taxonomy and new microbiology techniques

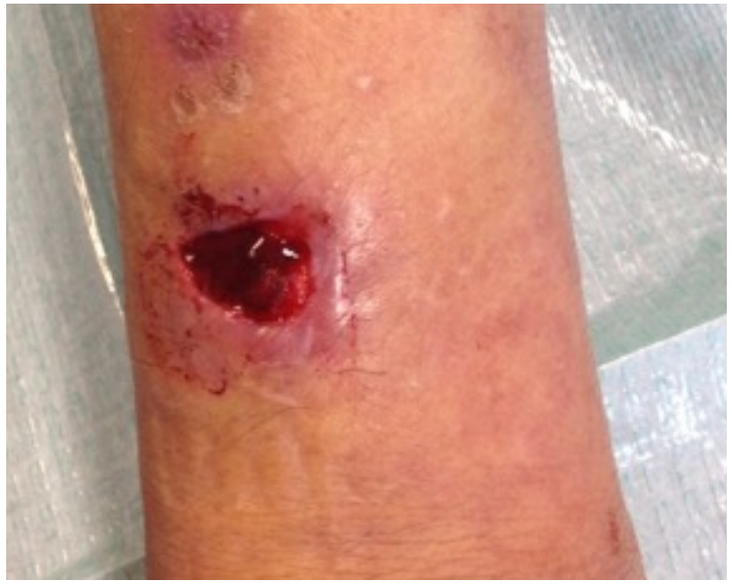
- 16S RNA gene was highly conserved
- Differences in the sequence of >1% defined as a new app.
- Expansion of new NTM

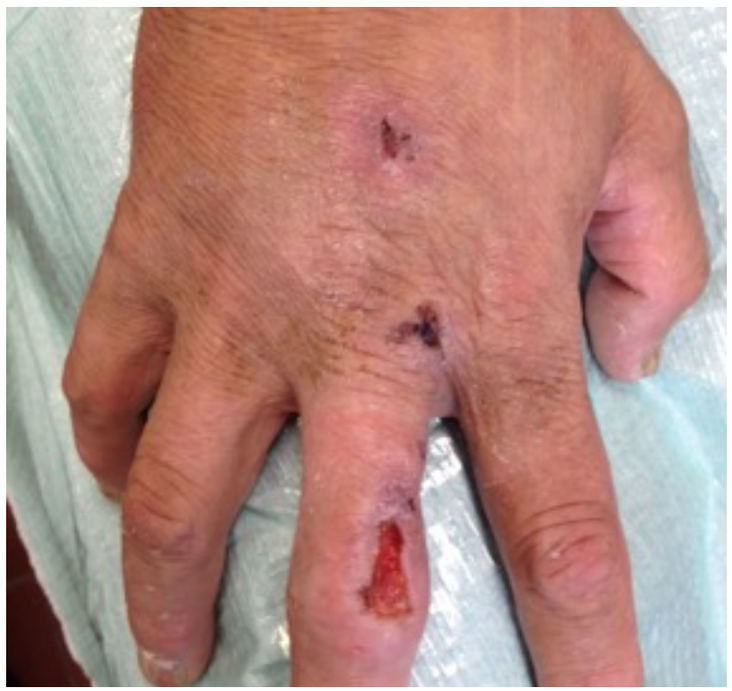
Case 1

- M/50
- Hx of post MI mural thrombus, ITP and DVT
- On long term warfarin therapy
- Injury to R M/F and wound exposed to **sea water** during work
- Debridement of the wound done
- Wound worsening despite debridement and Augmentin therapy for one month









What is the likely NTM?
What empirical antibiotic therapy?

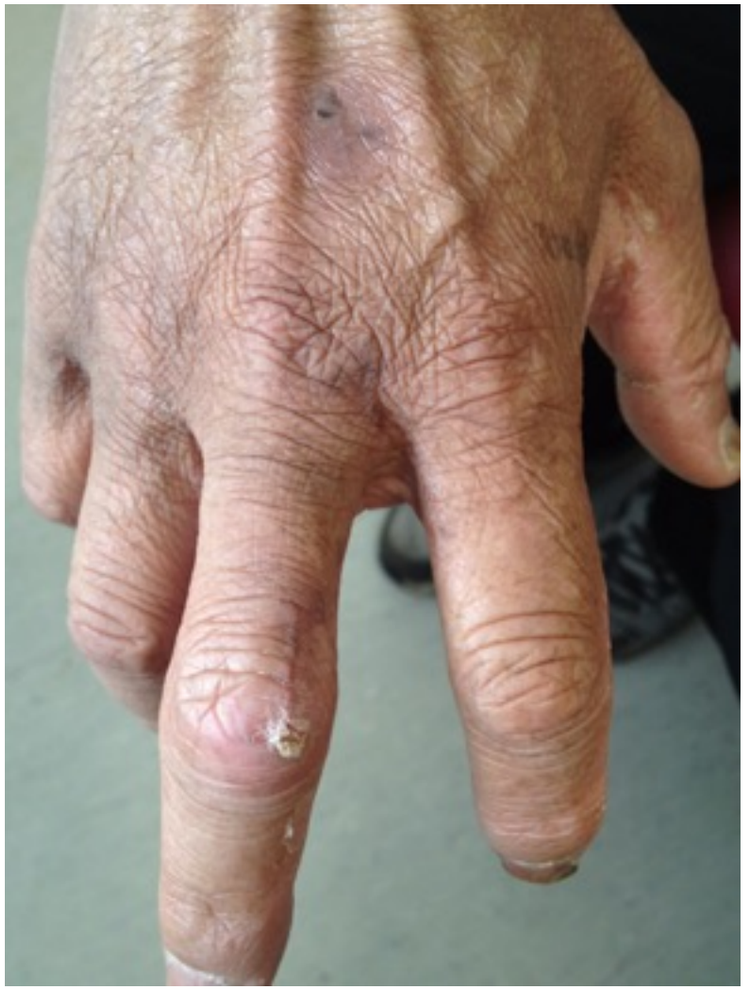
Source: Wound swab

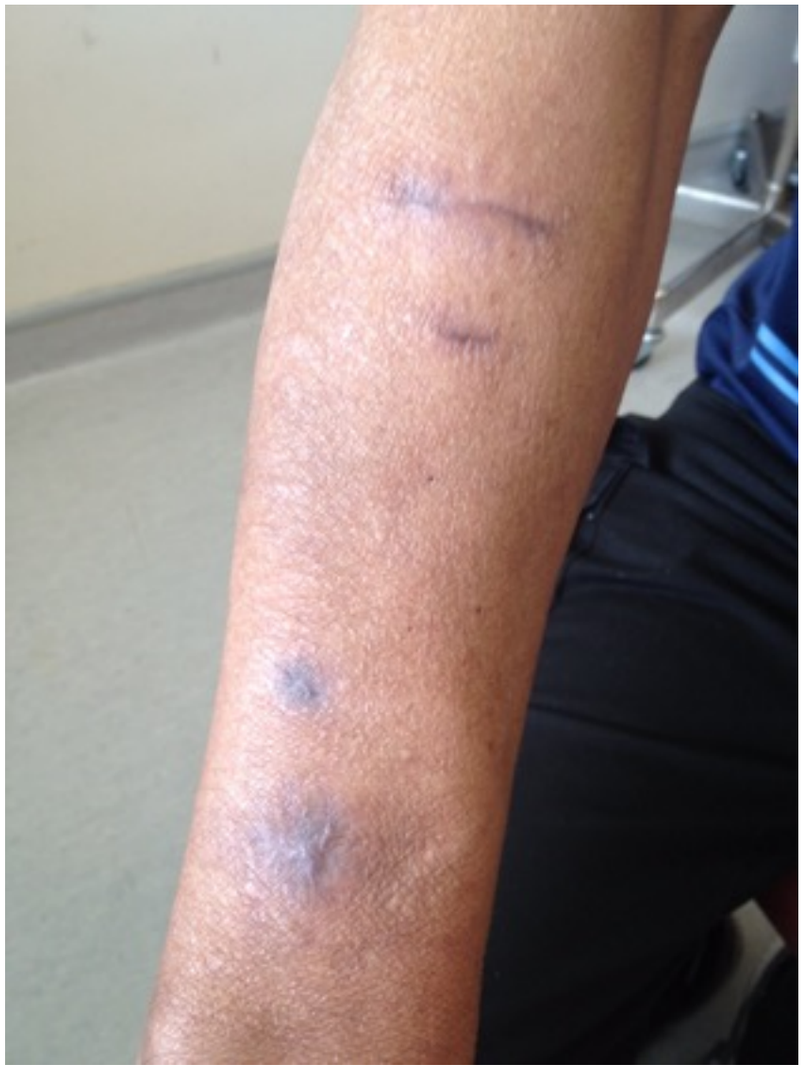
Culture:
Org 1: Mycobacterium marinum

Susceptibility results for Org 1:

	MIC(mg/L)	Interpretation
Amikacin(Agar pro)	8	S
Ethambutol(Agar pro)	2.5	S
Rifampicin(Agar pro)	0.5	S

After 3 months treatment





M. Marinum

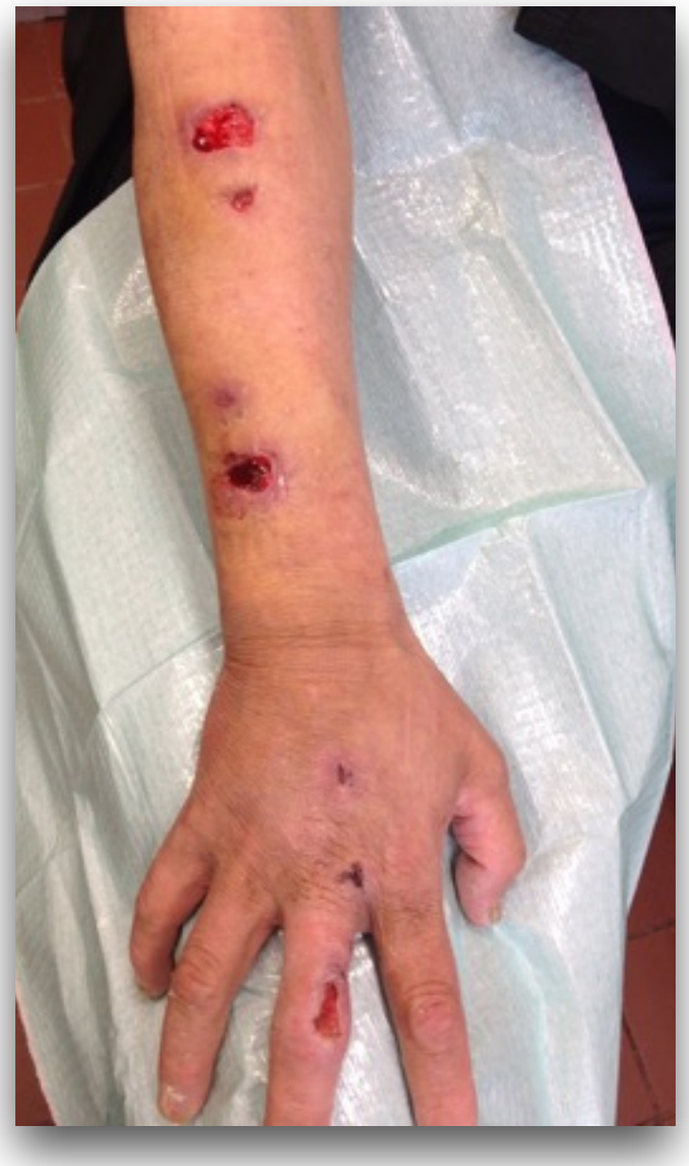
- Also called “swimming pool” or “fish tank” granuloma

- puncture wounds from saltwater fish, shrimp, fins or contacted with contaminated water source

- Small violet papules on hands and arms

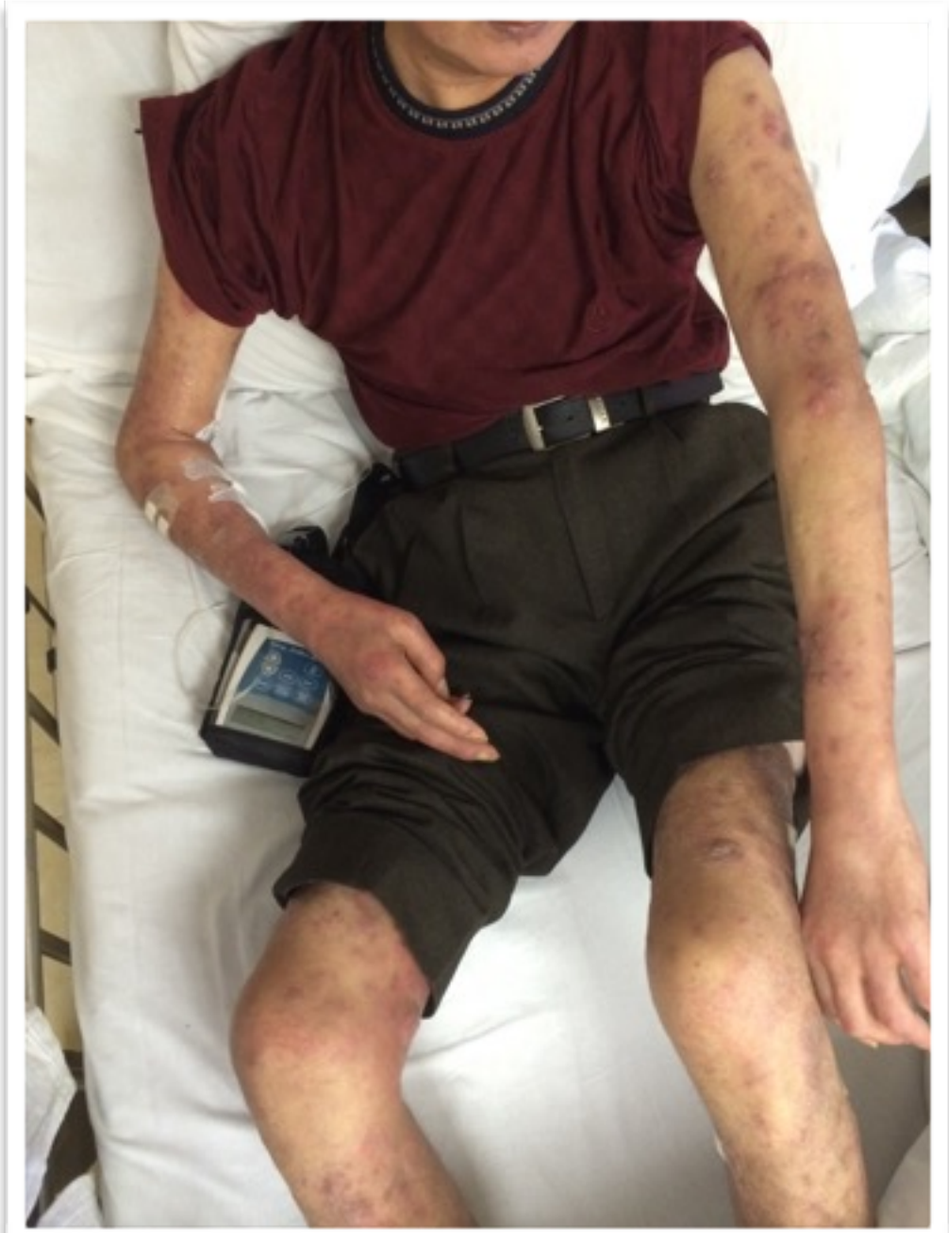
- May progress to shallow, crusty ulcerations

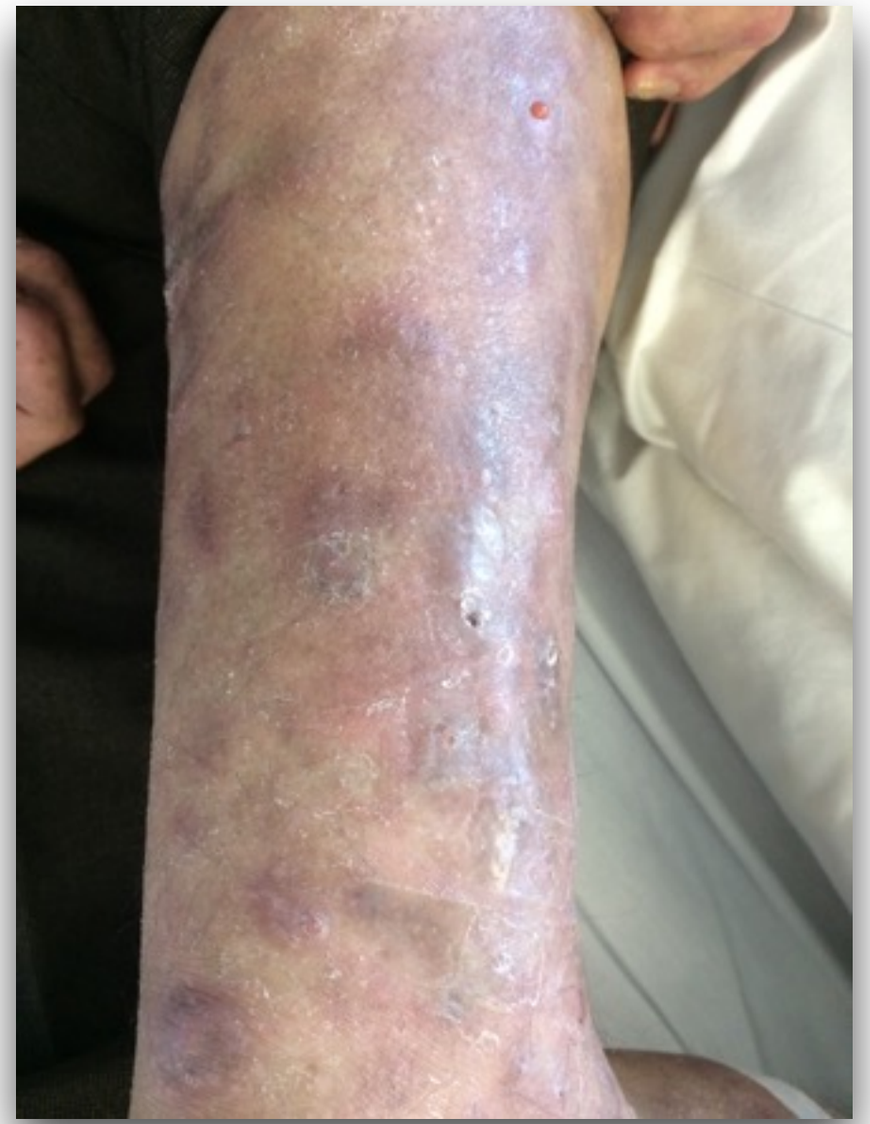
- **Multiple ascending lesions** resembling sporotrichosis

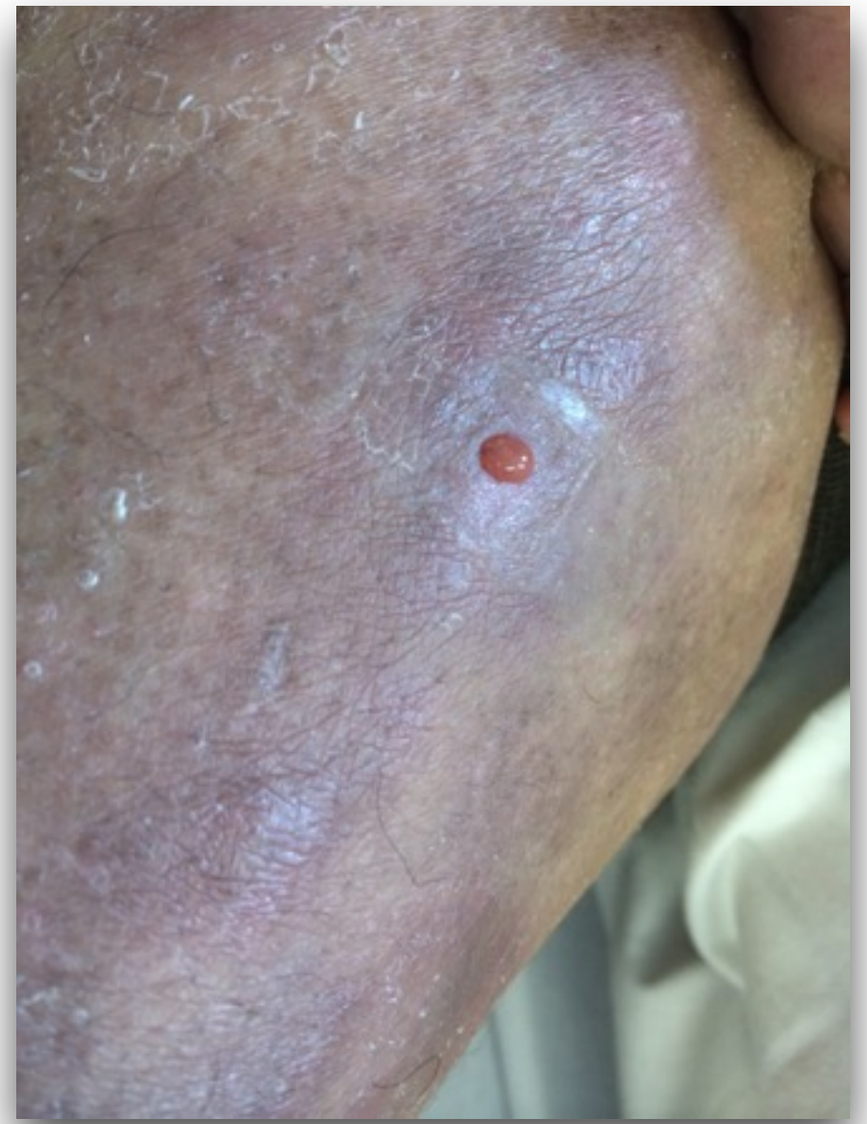


Case Two

- M/47
- DM HT
- Diagnosed of autoimmune disease, idiopathic fibrosing mediastinitis
- **steroid dependent** since 1991, currently on P20
- Pulmonary vein, SVC, axillary and brchicephalic vein thrombosis, on long term anticoagulation therapy
- c/o **multiple nodular skin lesions** for few months
- Skin biopsy (punch) done: **mild superficial perivascular inflammation**
- **Prednisolone** dose was increased







Limitation of Antibiotic Therapy

- Amikacin, Azithromycin & septrin started

Culture:
Org 1: Mycobacterium chelonae

Susceptibility results for Org 1:

	MIC(mg/L)	Interpretation
Amikacin(Std Dil)		S
Cefoxitin(Std Dil)		R
Ciprofloxacin(Std Dil)		R
Clarithromycin(Std Dil)		S
Doxycycline(Std Dil)		R
Moxifloxacin(Std Dil)		R
Linezolid(Std Dil)		I
Trimethoprim/sulfamethoxazole(Std Dil)		S
Imipenem(Std Dil)		I

Limitation of Antibiotic Therapy

- Amikacin, Azithromycin & septrin started
- Amikacin stopped because of renal function deteriorating

Culture:
Org 1: Mycobacterium chelonae

Susceptibility results for Org 1:

	MIC(mg/L)	Interpretation
Amikacin(Std Dil)		S
Cefoxitin(Std Dil)		R
Ciprofloxacin(Std Dil)		R
Clarithromycin(Std Dil)		S
Doxycycline(Std Dil)		R
Moxifloxacin(Std Dil)		R
Linezolid(Std Dil)		I
Trimethoprim/sulfamethoxazole(Std Dil)		S
Imipenem(Std Dil)		I

Limitation of Antibiotic Therapy

- Amikacin, Azithromycin & septrin started

- Amikacin stopped because of renal function deteriorating

- Azithromycin stopped because of hearing loss

Culture:
Org 1: Mycobacterium chelonae

Susceptibility results for Org 1:

	MIC(mg/L)	Interpretation
Amikacin(Std Dil)		S
Cefoxitin(Std Dil)		R
Ciprofloxacin(Std Dil)		R
Clarithromycin(Std Dil)		S
Doxycycline(Std Dil)		R
Moxifloxacin(Std Dil)		R
Linezolid(Std Dil)		I
Trimethoprim/sulfamethoxazole(Std Dil)		S
Imipenem(Std Dil)		I

Limitation of Antibiotic Therapy

- Amikacin, Azithromycin & septrin started
- Amikacin stopped because of renal function deteriorating
- Azithromycin stopped because of hearing loss
- Septrin alone not strong enough for disseminated infection

Culture:
Org 1: Mycobacterium chelonae

Susceptibility results for Org 1:

	MIC(mg/L)	Interpretation
Amikacin(Std Dil)		S
Cefoxitin(Std Dil)		R
Ciprofloxacin(Std Dil)		R
Clarithromycin(Std Dil)		S
Doxycycline(Std Dil)		R
Moxifloxacin(Std Dil)		R
Linezolid(Std Dil)		I
Trimethoprim/sulfamethoxazole(Std Dil)		S
Imipenem(Std Dil)		I

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Oct. 2002, p. 3164–3167 Vol. 46, No. 10
0066-4804/02/$04.00+0 DOI: 10.1128/AAC.46.10.3164–3167.2002

Comparison of the In Vitro Activity of the Glycylcycline Tigecycline (Formerly GAR-936) with Those of Tetracycline, Minocycline, and Doxycycline against Isolates of Nontuberculous Mycobacteria

Richard J. Wallace, Jr.,* Barbara A. Brown-Elliott, Christopher J. Crist, Linda Mann, and Rebecca W. Wilson

Department of Microbiology, University of Texas Health Center, Tyler, Texas

Received 14 March 2002/Returned for modification 11 April 2002/Accepted 24 June 2002

We compared the in vitro activity of the glycylcycline tigecycline (formerly GAR-936) with those of tetracycline, doxycycline, and minocycline by broth microdilution against 76 isolates belonging to seven species of rapidly growing mycobacteria (RGM) and 45 isolates belonging to five species of slowly growing nontuberculous mycobacteria (NTM). By using a resistance breakpoint of >4 μg/ml for tigecycline and >8 μg/ml for tetracycline, all RGM were highly susceptible to tigecycline, with inhibition of 50% of isolates at ≤0.12 μg/ml and inhibition of 90% of isolates at 0.25 μg/ml for *Mycobacterium abscessus* and inhibition of both 50 and 90% of isolates at ≤0.12 μg/ml for *M. chelonae* and the *M. fortuitum* group. The MICs of tigecycline were the same for tetracycline-resistant and -susceptible strains, and RGM isolates were 4- to 11-fold more susceptible to tigecycline than to the tetracyclines. In contrast, no slowly growing NTM were susceptible to tigecycline, and isolates of *M. marinum* and *M. kansasii* were less susceptible to this agent than to minocycline. This new antimicrobial offers exciting therapeutic potential for the RGM, especially for isolates of the *M. chelonae-M. abscessus* group, against which the activities of the currently available drugs are limited.

Rapid Growing Mycobacteria

TABLE 2. MIC ranges and concentrations of tetracycline, minocycline, and doxycycline and the new glycylcycline tigecycline (GAR-936) that inhibit 50 and 90% of 50 clinical tetracycline-resistant[a] isolates of RGM

Species	MIC (μg/ml)		
	Range	50%	90%
M. fortuitum group (10)[b]			
Tigecycline	≤0.06–≤0.12	≤0.06	≤0.12
Tetracycline	16–64	16	32
Minocycline	2–>64	32	32
Doxycycline	32–>128	64	128
M. abscessus (18)			
Tigecycline	≤0.06–1	≤0.12	0.25
Tetracycline	32–>128	128	>128
Minocycline	64–>64	>64	>64
Doxycycline	128–>128	>128	>128
M. chelonae (22)			
Tigecycline	≤0.06–≤0.12	≤0.06	≤0.12
Tetracycline	16–>128	32	>128
Minocycline	2–>64	16	>64
Doxycycline	16–>128	>64	>128

[a] Tetracycline resistance was defined as an MIC ≥16 μg/ml.
[b] The values in parentheses are the number of isolates tested.

Slowly Growing Mycobacteria

TABLE 4. MIC ranges, concentrations that inhibits 50 and 90% of strains tested, and percentage of strains susceptible for tigecycline (GAR-936) and three tetracyclines against 43 isolates of three species of slowing growing mycobacteria[a]

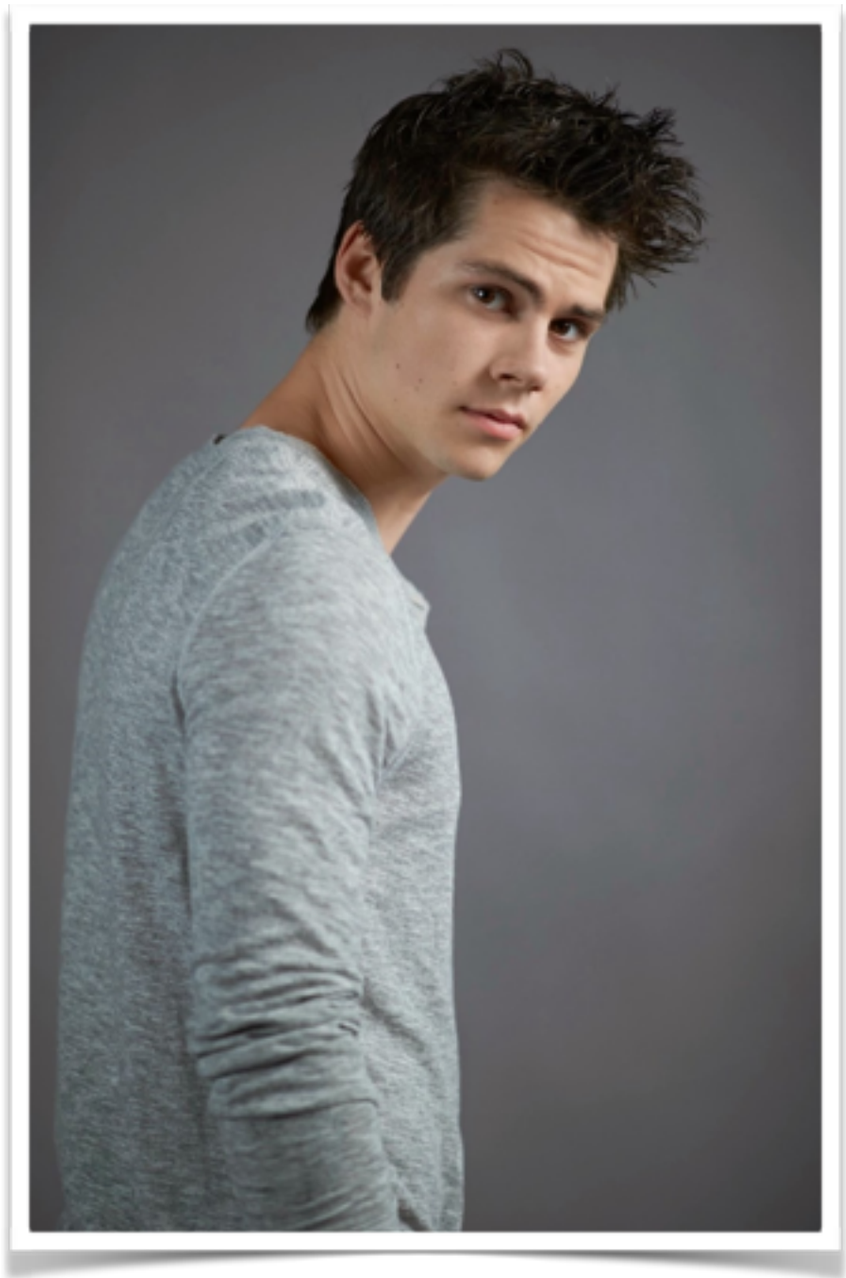
Species	MIC (μg/ml)			% Susceptible
	Range	50%	90%	
M. avium complex (11)[b]				
Tigecycline	32–>32	>32	>32	0
Tetracycline	64–>128	>128	>128	0
Minocycline	8–>64	64	>64	9
Doxycycline	8–>128	32	>128	9
M. lentiflavum (10)				
Tigecycline	32–>32	>32	>32	0
Tetracycline	16–>128	128	>128	0
Minocycline	16–>64	>64	>64	0
Doxycycline	2–>128	128	>128	0
M. marinum (11)				
Tigecycline	16	16	16	0
Tetracycline	4–16	16	16	45
Minocycline	2–8	4	4	100
Doxycycline	2–16	4	16	82
M. kansasii (11)				
Tigecycline	8–32	16	32	0
Tetracycline	16–128	32	128	0
Minocycline	2–8	8	8	100
Doxycycline	4–32	16	16	36

[a] The resistance breakpoints used were (≥8 μg/ml) for tigecycline and ≥16 μg/ml for the three older tetracyclines.
[b] The values in parentheses are the number of isolates tested.

- **Tigecycline plus Septrin** for ONE YEAR then
- Septrin alone as **long term suppressive therapy** in view of underlying steroid dependent medical condition

Case Three

- M/30
- GPH, Single
- PUO and weight loss for 20 lb in 6 months
- Oral thrush +
- CBP: lymphopenia
- HIV +ve with CD4 count 5 only
- BC +ve for AFB smear



What is the likely NTM?
What empirical antibiotic therapy?

Patient Category:	1. Diagnosis / Pretreatment
Specimen Type:	Blood
Anatomical Site:	PERIPHERAL
Nature of Specimen:	Culture isolate

Culture:
Organism 1: Mycobacterium avium complex

Susceptibility test proceeding.

MAC in HIV

- MAC disease typically occurs in HIV-infected patients with CD4 T lymphocyte **(CD4) cell counts <50 cells/mm^3**

- The incidence of disseminated MAC disease is **20% to 40%** in patients **with severe AIDS**, in the absence of effective antiretroviral therapy (ART) or chemoprophylaxis

- **Disseminated disease**: LNs enlargement, Hepatosplenomegaly, pneumonia, bacteraemia, anaemia

- Primary and secondary **prophylaxis** reduce MAC disease

- Immunreconstitution or **immune recover** after starting antiretroviral therapy

Case Four

- F52
- Hx of **cervical TB** with CT thorax findings compatible with pulmonary TB x 2 years ago, treated for one year in chest clinic
- **Cervical lymphadenopathy** and persistent fever for months
- **FNAC of cervical LN**: AFB smear +ve, grew *M. abscessus* in 5 days

Source: Tissue (Lymph node)

Culture:
Org 1: Mycobacterium abscessus

Susceptibility results for Org 1:

	MIC(mg/L)	Interpretation
Clarithromycin		R
Amikacin		S
Cefoxitin		I
Ciprofloxacin		R
Doxycycline		R

Susceptibility results interpretation: S = Susceptible, I = Intermediate, R = Resistant.

Inducible macrolide resistance is detected. It is associated with delayed treatment response and possible treatment failure in patients with lung disease on macrolide-containing regimens. However, including a macrolide (clarithromycin and azithromycin) in the multidrug regimen may still be considered in such situations as the choice of oral alternatives is limited.

Will you treat the patient?
What will you do next ?

NTM associated LN Enlargement

- Localised cervical LN enlargement is the most common NTM disease in children

- Localised NTM LN enlargement in adult is very uncommon

Further Ix

- HIV ab -ve
- CD4 count 628 (normal)
- CT thorax/abdomen/pelvic: para-aortic LNs enlargement

BC and sputum culture grew M. avium complex (MAC)

Specimen Type:	Blood
Anatomical Site:	PERIPHERAL
Nature of Specimen:	Culture isolate

Culture:
Organism 1: Mycobacterium avium complex

Susceptibility result:

Antimicrobial	Organism 1
Clarithromycin	S

S= Susceptible, I = Intermediate, R= Resistant

Disseminated dual NTM infections *M. abscessus* and MAC

Why did the patient have disseminated NTM?

Pathogenesis

- CD4 count, IL-12, TNF-α and **IFN-ɣ** play a key role in controlling mycobacteria infection

- MAC disease typically occurs in HIV-infected patients with CD4 T lymphocyte **(CD4) cell counts <50 cells/mm^3**

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Adult-Onset Immunodeficiency in Thailand and Taiwan

Sarah K. Browne, M.D., Peter D. Burbelo, Ph.D., Ploenchan Chetchotisakd, M.D., Yupin Suputtamongkol, M.D., Sasisopin Kiertiburanakul, M.D., Pamela A. Shaw, Ph.D., Jennifer L. Kirk, B.A., Kamonwan Jutivorakool, M.D., Rifat Zaman, B.S., Li Ding, M.D., Amy P. Hsu, B.A., Smita Y. Patel, M.D., Kenneth N. Olivier, M.D., Viraphong Lulitanond, Ph.D., Piroon Mootsikapun, M.D., Siriluck Anunnatsiri, M.D., Nasikarn Angkasekwinai, M.D., Boonmee Sathapatayavongs, M.D., Po-Ren Hsueh, M.D., Chi-Chang Shieh, M.D., Ph.D., Margaret R. Brown, B.S., Wanna Thongnoppakhun, Ph.D., Reginald Claypool, R.N., Elizabeth P. Sampaio, M.D., Ph.D., Charin Thepthai, M.Sc., Duangdao Waywa, M.Sc., Camilla Dacombe, R.N., Yona Reizes, R.N., Adrian M. Zelazny, Ph.D., Paul Saleeb, M.D., Lindsey B. Rosen, B.S., Allen Mo, B.S., Michael Iadarola, Ph.D., and Steven M. Holland, M.D.

AUGUST 23, 2012

Neutralising anti-interferon-**ϒ** autoantibodies

- Disseminated NTM infections in patients with **Neutralising anti-interferon-ϒ autoantibodies (INF-ϒ).**
- All were **Asian-born Asian**
- Host genetic factors or environmental exposure
- Most NTM infection were **RGM** +/- other infections

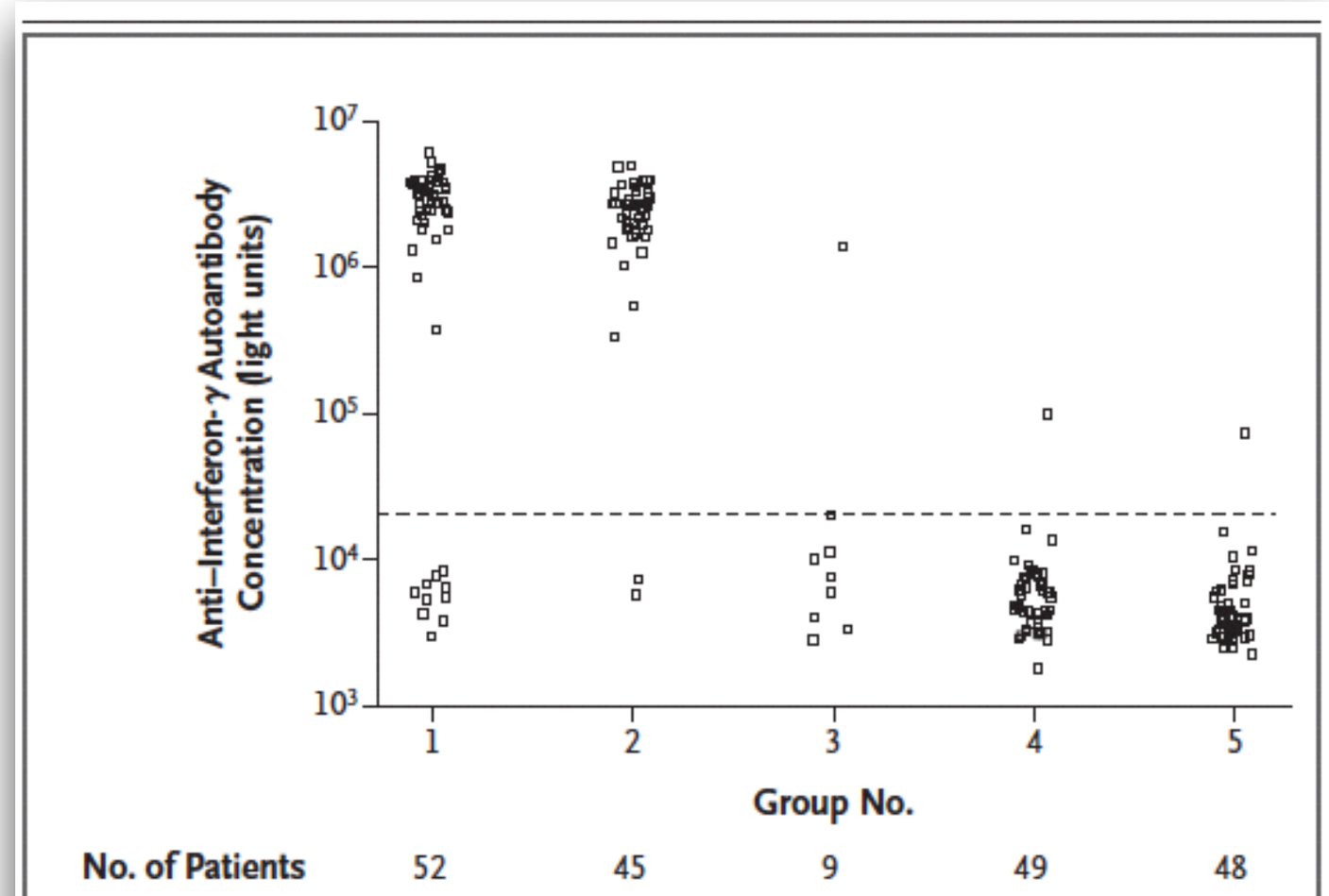


Figure 2. Anti–Interferon-γ Autoantibody Concentrations in 203 Participants, According to Study Group.

Interferon-γ autoantibodies were measured with the use of Luciferase Immunoprecipitation Systems. The dashed line is the estimated 99th percentile for the combined control groups of patients with pulmonary tuberculosis (group 4) and healthy controls (group 5), estimated with the use of the log-normal distribution. Participants with concentrations exceeding the 99th percentile were classified as autoantibody-positive.

Table 2. Isolated Organisms in 97 Patients with Opportunistic Infections.

Variable	Group 1 (N=52)	Group 2 (N=45)
Organisms isolated (no./patient)		
Median	1	2
Range	1–4	1–5
Mycobacteria (no. of patients)		
Rapidly growing	36	39
Slowly growing	15	8
Nontuberculous mycobacteria, not specified	5	2
Mycobacterium tuberculosis	4*	10†
Total	60	59
Bacteria (no. of patients)		
Salmonella species		25
Burkholderia pseudomallei		4
Other		9
Fungi (no. of patients)		
Cryptococcus neoformans		10
Histoplasma capsulatum		7
Penicillium marneffei		7
Varicella–zoster virus (no. of patients)		
Disseminated		3
Local	5	10
Parasites (no. of patients)		
Strongyloides stercoralis		1

How to treat?

Specimen Type: Blood

Anatomical Site: PERIPHERAL

Nature of Specimen: Culture isolate

Culture:
Organism 1: Mycobacterium avium complex

Susceptibility result:

Antimicrobial	Organism 1
Clarithromycin	S

Source: Tissue (Lymph node)

Culture:
Org 1: Mycobacterium abscessus

Susceptibility results for Org 1:

	MIC(mg/L)	Interpretation
Clarithromycin		R
Amikacin		S
Cefoxitin		I
Ciprofloxacin		R
Doxycycline		R

How to treat?

- Amikacin + EMB + Rifampicin + Klacid

Specimen Type: Blood

Anatomical Site: PERIPHERAL

Nature of Specimen: Culture isolate

Culture:
Organism 1: Mycobacterium avium complex

Susceptibility result:

Antimicrobial	Organism 1
Clarithromycin	S

Source: Tissue (Lymph node)

Culture:
Org 1: Mycobacterium abscessus

Susceptibility results for Org 1:

	MIC(mg/L)	Interpretation
Clarithromycin		R
Amikacin		S
Cefoxitin		I
Ciprofloxacin		R
Doxycycline		R

How to treat?

- Amikacin + EMB + Rifampicin + Klacid
- Amikacin stopped (ototoxicity)
- Rifampicin stopped (allergy reaction)
- Tigecycline + Rituximab

Specimen Type: Blood

Anatomical Site: PERIPHERAL

Nature of Specimen: Culture isolate

Culture:
Organism 1: Mycobacterium avium complex

Susceptibility result:

Antimicrobial	Organism 1
Clarithromycin	S

Source: Tissue (Lymph node)

Culture:
Org 1: Mycobacterium abscessus

Susceptibility results for Org 1:

	MIC(mg/L)	Interpretation
Clarithromycin		R
Amikacin		S
Cefoxitin		I
Ciprofloxacin		R
Doxycycline		R

How to treat?

- Amikacin + EMB + Rifampicin + Klacid
- Amikacin stopped (ototoxicity)
- Rifampicin stopped (allergy reaction)

Specimen Type: Blood

Anatomical Site: PERIPHERAL

Nature of Specimen: Culture isolate

Culture:
Organism 1: Mycobacterium avium complex

Susceptibility result:

Antimicrobial	Organism 1
Clarithromycin	S

Source: Tissue (Lymph node)

Culture:
Org 1: Mycobacterium abscessus

Susceptibility results for Org 1:

	MIC(mg/L)	Interpretation
Clarithromycin		R
Amikacin		S
Cefoxitin		I
Ciprofloxacin		R
Doxycycline		R

How to treat?

- Amikacin + EMB + Rifampicin + Klacid
- Amikacin stopped (ototoxicity)
- Rifampicin stopped (allergy reaction)
- Tigecycline + EMB + Klacid

Specimen Type: Blood

Anatomical Site: PERIPHERAL

Nature of Specimen: Culture isolate

Culture:
Organism 1: Mycobacterium avium complex

Susceptibility result:

Antimicrobial	Organism 1
Clarithromycin	S

Source: Tissue (Lymph node)

Culture:
Org 1: Mycobacterium abscessus

Susceptibility results for Org 1:

	MIC(mg/L)	Interpretation
Clarithromycin		R
Amikacin		S
Cefoxitin		I
Ciprofloxacin		R
Doxycycline		R

- We started **Rituximab** as well

- Rituximab is commonly used in patient with B-cell NHL and autoimmune disease such as RA

- Rituximab rapidly depletes $CD20^+$ B-lymphocytes, resulting in the interruption of autoantibody production

Rituximab Therapy

Anti-CD20 (rituximab) therapy for anti–IFN-γ autoantibody–associated nontuberculous mycobacterial infection

Sarah K. Browne,[1] Rifat Zaman,[1] Elizabeth P. Sampaio,[1,2] Kamonwan Jutivorakool,[1,3] Lindsey B. Rosen,[1] Li Ding,[1] Minjal J. Pancholi,[1] Lauren M. Yang,[1,4] Debra Long Priel,[5] Gulbu Uzel,[1] Alexandra F. Freeman,[1] Carlton E. Hayes,[6] Roger Baxter,[7] Stuart H. Cohen,[8] and Steven M. Holland[1]

[1]Laboratory of Clinical Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD; [2]Leprosy Laboratory, Oswaldo Cruz Institute, FIOCRUZ, Rio de Janeiro, Brazil; [3]Department of Medicine, Faculty of Medicine, Chulalongkorn University and King Chulalongkorn Memorial Hospital, Thai Red Cross Society, Bangkok, Thailand; [4]Washington University School of Medicine, St Louis, MO; [5]Clinical Services Program, SAIC-Frederick Inc, National Cancer Institute Frederick, Frederick, MD; [6]The Jackson Clinic, Jackson, TN; [7]The Permanente Medical Group, Oakland, CA; and [8]Department of Epidemiology and Infection Control, University of California, Davis, Davis, CA

BLOOD, 26 APRIL 2012 • VOLUME 119, NUMBER 17

Case Five

- F63
- hx of CA lung
- Admitted for fever and chills
- DIC and septic shock

Source: Blood culture

Culture:
Mycobacterium abscessus

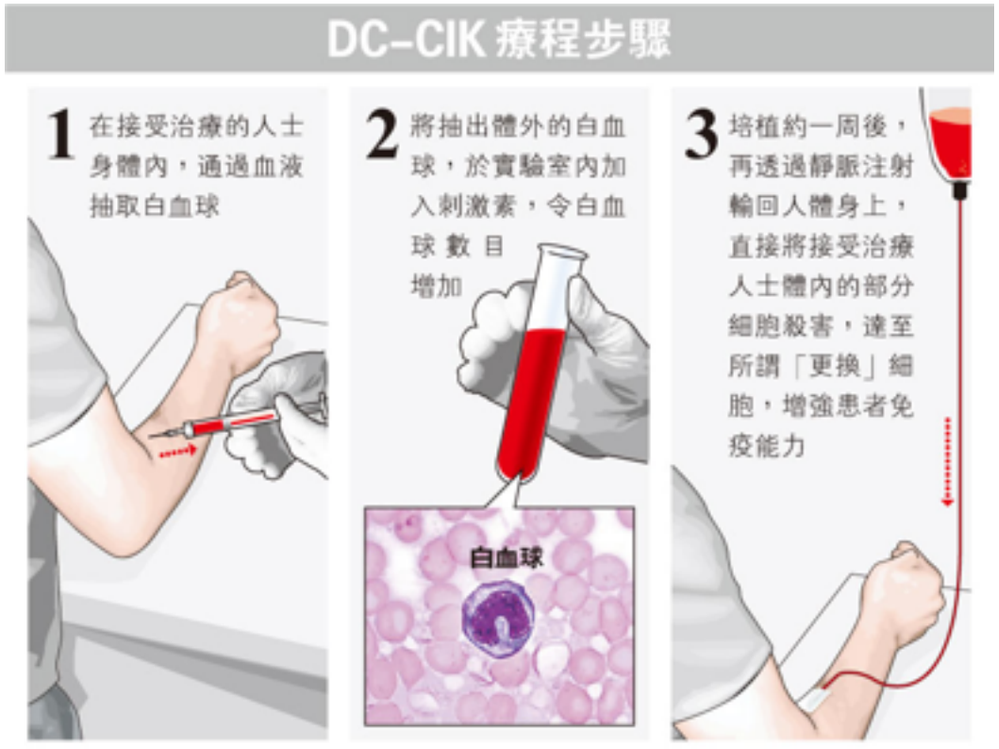
Antimicrobial Susceptibility Test(Etest)

Amikacin MIC: 8ug/mL
Imipenem MIC: >32ug/mL
Clarithromycin MIC: 4ug/mL
Linezolid MIC: >256ug/mL
Tigecycline MIC: 16ug/mL
Levofloxacin MIC: >32ug/mL

Susceptibility results for reference only, as guidelines for testing not generally available for this organism.
Clinical correlation is required.

Why did the patient get this NTM?

Contaminated Intravenous Infusate of Cytokine-Induced Killer Cell Therapy for Body Beautification and Health Boosting



Case Six

- F26
- hx of Tissue AVR due to severe AS in 2012
- Re-do mechanical AVR done in **Dec 2014**
- Excised AV tissue valve grew *Staphylococcus lugdunesis*
- BC x 3 -ve
- IV antibiotic given

PUO

- Admission in June 2016 for PUO and deranged LFT and RFT
- USG showed splenomegaly
- HIV ab -ve
- TEE no evidence of vegetation
- BC x 3 -ve
- PET: FDG uptake at the wall of the ascending aortic stent graft. This could represent post-OP change or inflammation
- BMA: active marrow

BM AFB culture positive **1 month after discharge**

Specimen Type: Bone marrow

Nature of Specimen: Culture isolate

Culture:
Organism 1: Mycobacterium avium complex

Susceptibility result:

Antimicrobial	Organism 1
Clarithromycin	S

S= Susceptible, I = Intermediate, R= Resistant

Is it a genuine pathogen?

Story continue…

- Called back for workup
- not septic looking and has returned to work
- repeat HIV ab -ve

Story continue…

- Called back for workup
- not septic looking and has returned to work
- repeat HIV ab -ve
- repeat BMA AFB culture: MAC
- BC for AFB: MAC

How and where did she get this NTM?

Prolonged Outbreak of *Mycobacterium chimaera* Infection After Open-Chest Heart Surgery

Hugo Sax,[1,a] Guido Bloemberg,[2,a] Barbara Hasse,[1,a] Rami Sommerstein,[1] Philipp Kohler,[1] Yvonne Achermann,[1] Matthias Rössle,[3] Volkmar Falk,[4] Stefan P. Kuster,[1] Erik C. Böttger,[2,b] and Rainer Weber[1,b]

[1]Division of Infectious Diseases and Hospital Epidemiology, University Hospital Zurich, [2]Institute of Medical Microbiology, National Centre for Mycobacteria, University of Zurich, [3]Institute of Surgical Pathology, and [4]Division of Cardiac Surgery, University Hospital Zurich, Switzerland

Background. Invasive *Mycobacterium chimaera* infections were diagnosed in 2012 in 2 heart surgery patients on extracorporeal circulation. We launched an outbreak investigation to identify the source and extent of the potential outbreak and to implement preventive measures.

Methods. We collected water samples from operating theaters, intensive care units, and wards, including air samples from operating theaters. *Mycobacterium chimaera* strains were characterized by randomly amplified polymorphic DNA polymerase chain reaction (RAPD-PCR). Case detection was performed based on archived histopathology samples and *M. chimaera* isolates since 2006, and the patient population at risk was prospectively surveyed.

Results. We identified 6 male patients aged between 49 and 64 years with prosthetic valve endocarditis or vascular graft infection due to *M. chimaera*, which became clinically manifest with a latency of between 1.5 and 3.6 years after surgery. *Mycobacterium chimaera* was isolated from cardiac tissue specimens, blood cultures, or other biopsy specimens. We were able also to culture *M. chimaera* from water circuits of heater-cooler units connected to the cardiopulmonary bypass, and air samples collected when the units were in use. RAPD-PCR demonstrated identical patterns among *M. chimaera* strains from heater-cooler unit water circuits and air samples, and strains in 2 patient clusters.

Conclusions. The epidemiological and microbiological features of this prolonged outbreak provided evidence for the airborne transmission of *M. chimaera* from contaminated heater-cooler unit water tanks to patients during open-heart surgery.

Medical Devices

Safety Communications

Information About Heparin

Reducing Risks Associated with Medical Device Misconnections

Mycobacterium chimaera Infections Associated with Sorin Group Deutschland GmbH Stöckert 3T Heater-Cooler System: FDA Safety Communication

FDA issued an **updated safety communication** on October 13, 2016.

But our patient had…

- AVR done in Dec in 2014
- MAC not *M. chimaera*
- Is it really related?

Long latency period

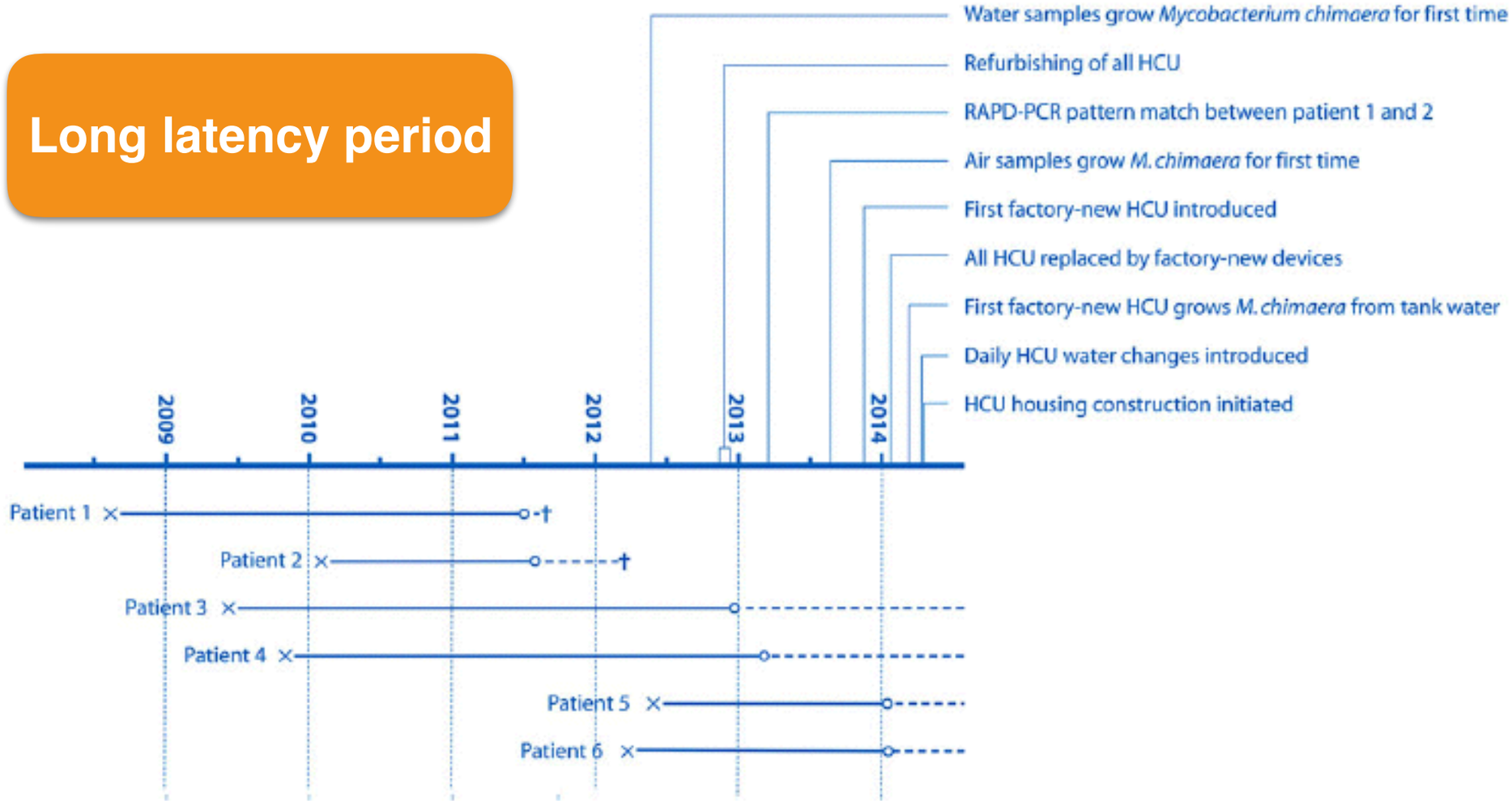


Figure 1. Evolution of the 6 cases of *Mycobacterium chimaera* infection and investigational activity. Abbreviations: x, open-chest heart surgery; ○, *M. chimaera* diagnosis; - - -, antibiotic and, in some cases surgical, treatment; +, fatality; HCU, heater-cooler unit; RAPD-PCR, randomly amplified polymorphic DNA polymerase chain reaction.

M. chimaera

- *M. chimaera* is a novel species within the *Mycobacterium avium complex* (MAC)

- Identification requires 16S rRNA gene sequencing

- MAC will not be routinely identified to spp. by PHLC

- Our isolate was confirmed to be *M. chimaera* by PHLC later

NTM and Environment

- NTM are **free-living mycobacteria** normally found in the soil, nature water
- Forming **biofilm** at the pipe and water interface in almost all collection and piping systems
- **Resistance** to being **washed away** in high flow rate
- Able to **survive** for weeks to months on inanimate surfaces
- **More resistant** to standard chemical disinfectants (e.g. chlorine and alkaline glutaraldehydes) than other non-spore forming bacteria

NTM and Outbreaks

- Important implications in epidemiology of infection **related to water** (health-care associated disease, outbreaks and pseudo-outbreaks)
- Tap water-major reservoir
- No evidence of person-to-person transmission

RESEARCH

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

Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 22, No. 6, June 2016

- *M. chimaera* found in the **water tanks** of Heat-cooler devices (HCD)
- Manufacture found *M. chimaera* contamination on the production line and water supply **at the HCD manufacturing facility.**
- **No direct contact** between the water circuit of HCD and the patient

---

Transmission of *M. chimaera* from Heater–Cooler Units

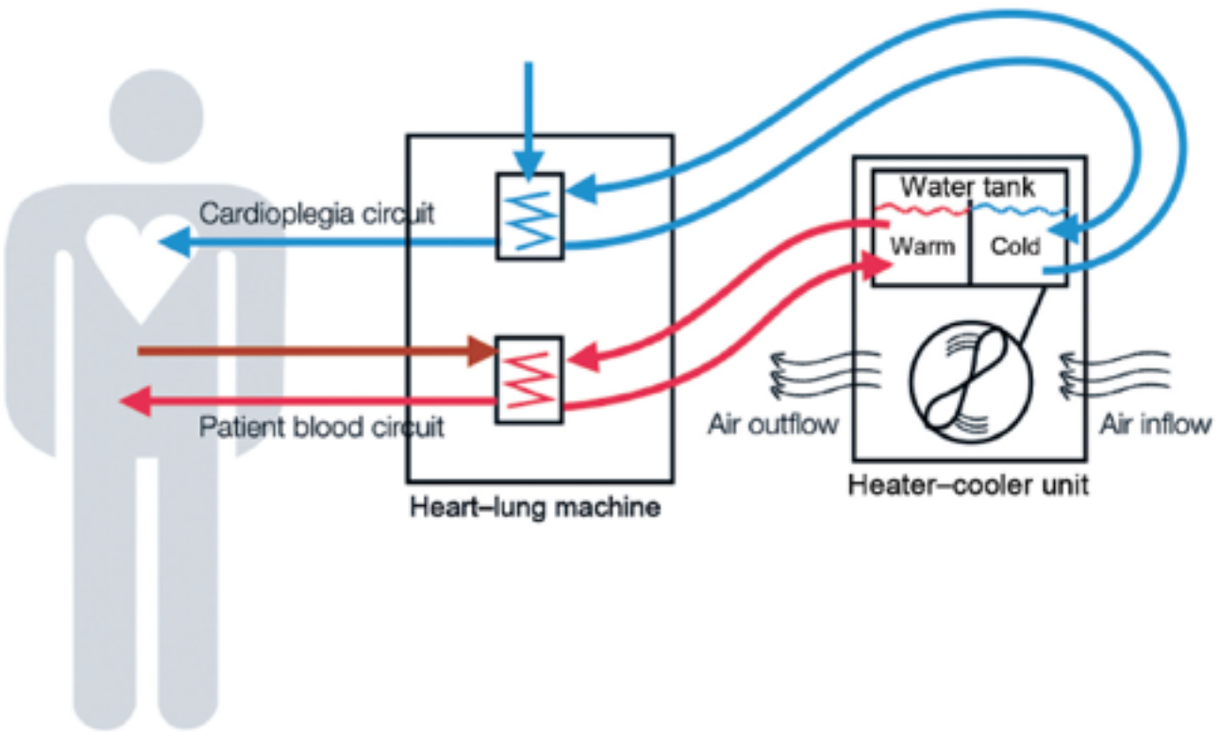
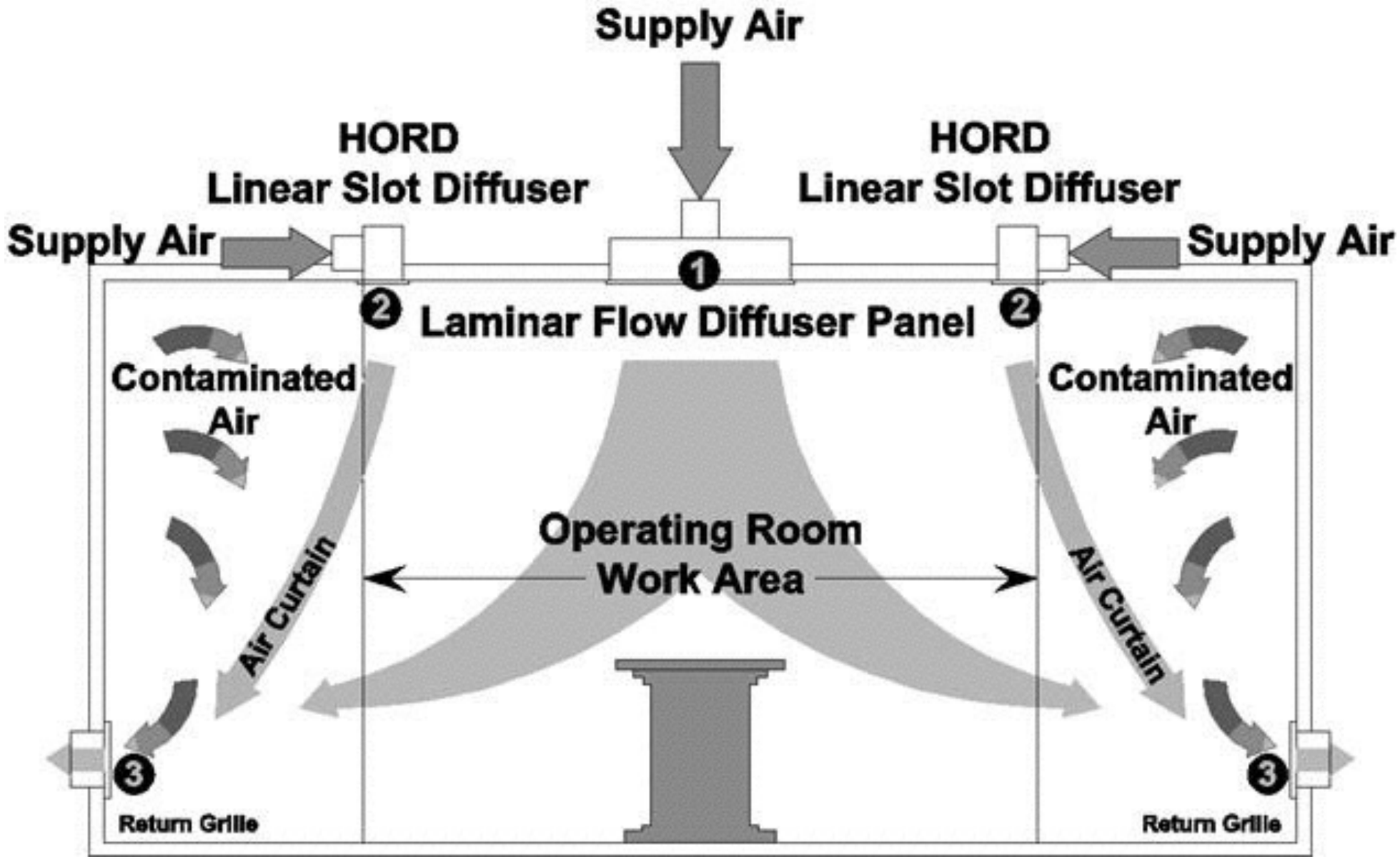
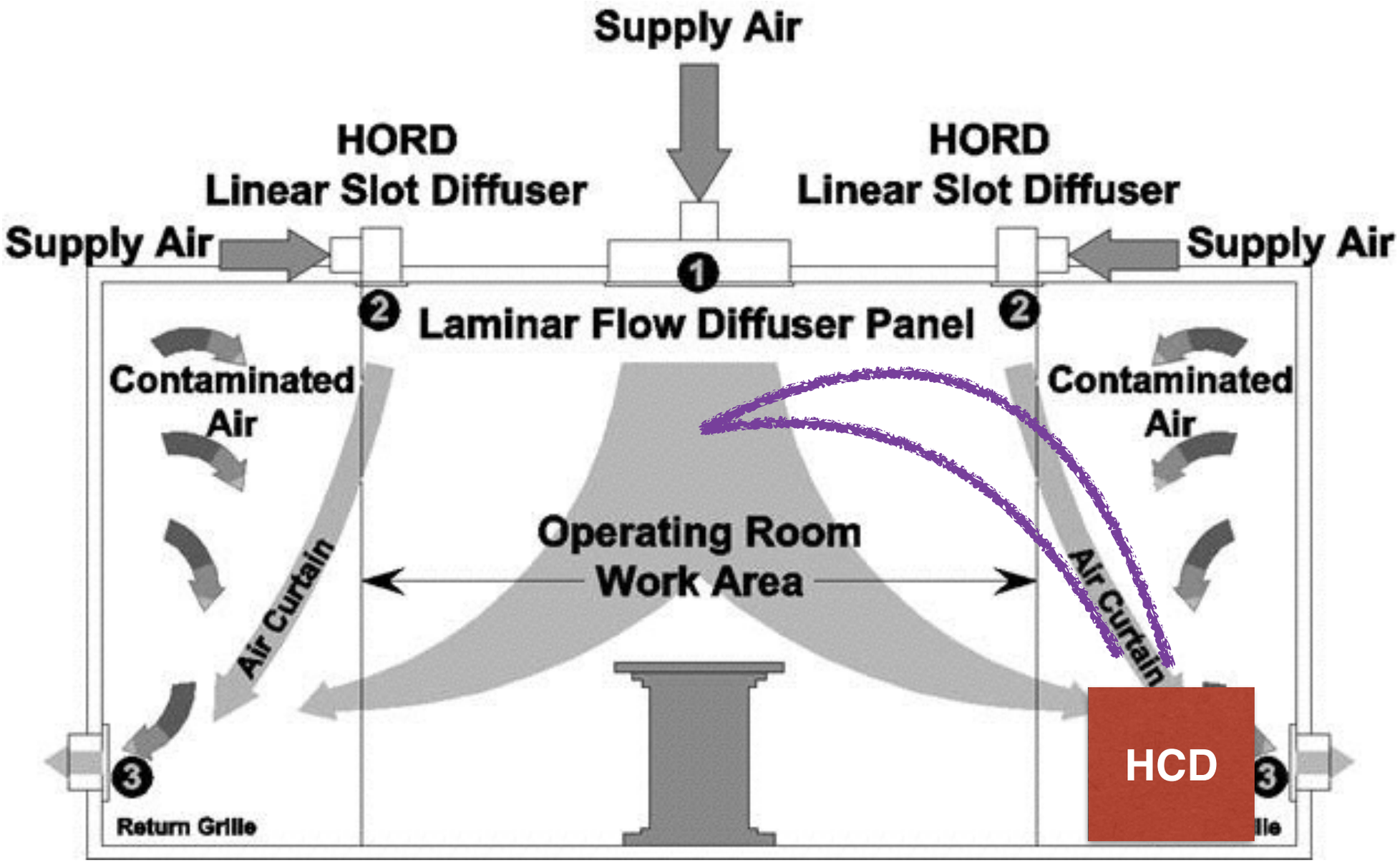


Figure 1. Schematic representation of heater–cooler circuits tested for transmission of *Mycobacterium chimaera* during cardiac surgery despite an ultraclean air ventilation system. Blue arrows indicate cold water flow, and red arrows indicate hot water flow and patient blood flow.



http://www.acmv.org/lecture/view.php?id=136

Aerosolisation of the contaminated water in the water tank of HCD



http://www.acmv.org/lecture/view.php?id=136

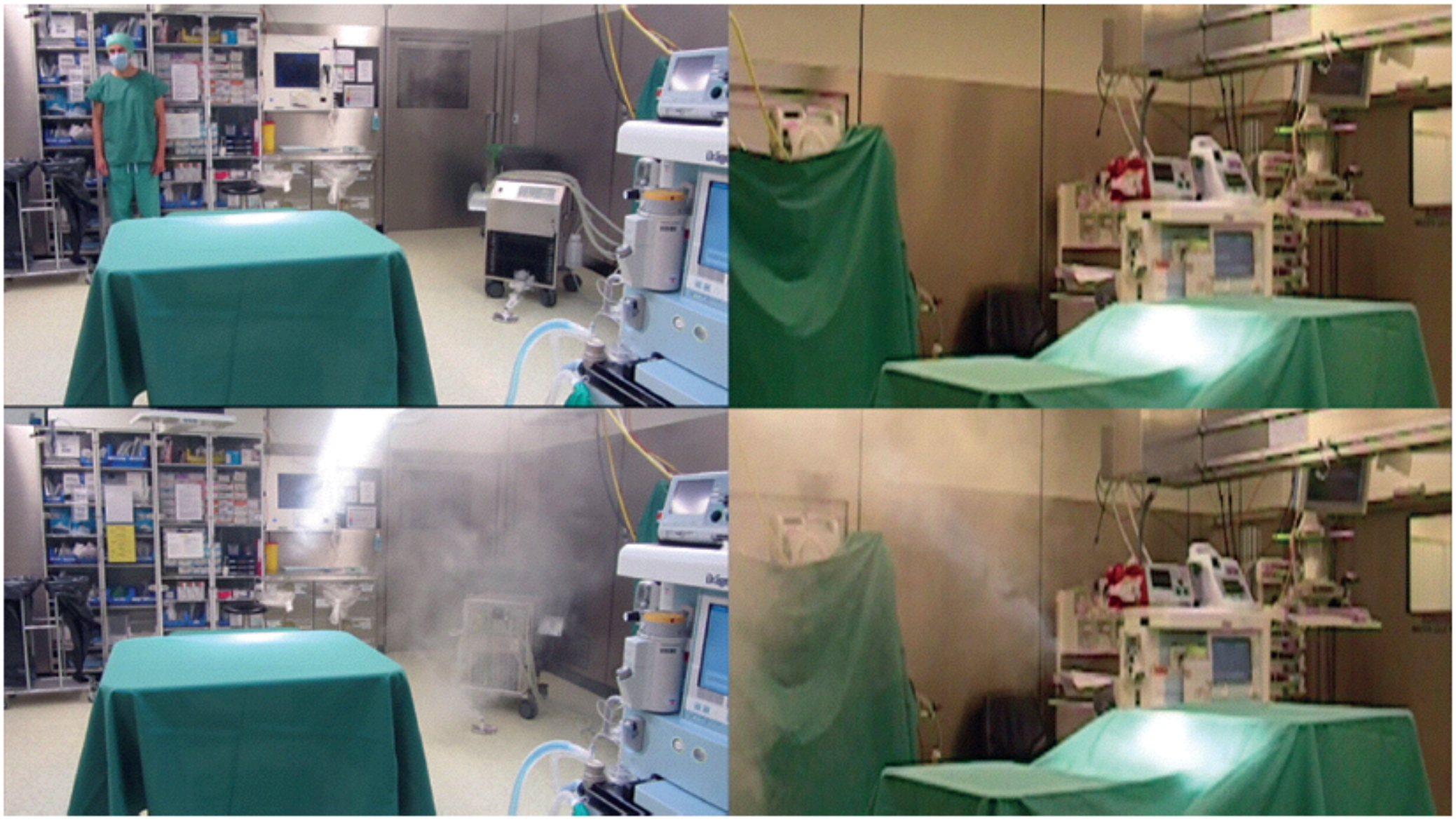


Figure 2. Video image captures showing effect of heater–cooler unit orientation on smoke dispersal in a cardiac surgery room and transmission of *Mycobacterium chimaera* during cardiac surgery despite an ultraclean air ventilation system (Video, http://wwwnc.cdc.gov/EID/article/22/6/16-0045-V1.htm). The device was switched on and began to ventilate 10 s after the start of the video. Frames on the left show an overview including unit placement. Frames on the right provide a lateral view of the operating field under the laminar airflow. Simultaneously recorded videos in the upper 2 frames show the first scenario, in which the main ventilation exhaust was directed *away* from the operating field. Simultaneously recorded videos in the lower 2 frames show the second scenario, in which the main ventilation exhaust was directed toward the operating field.

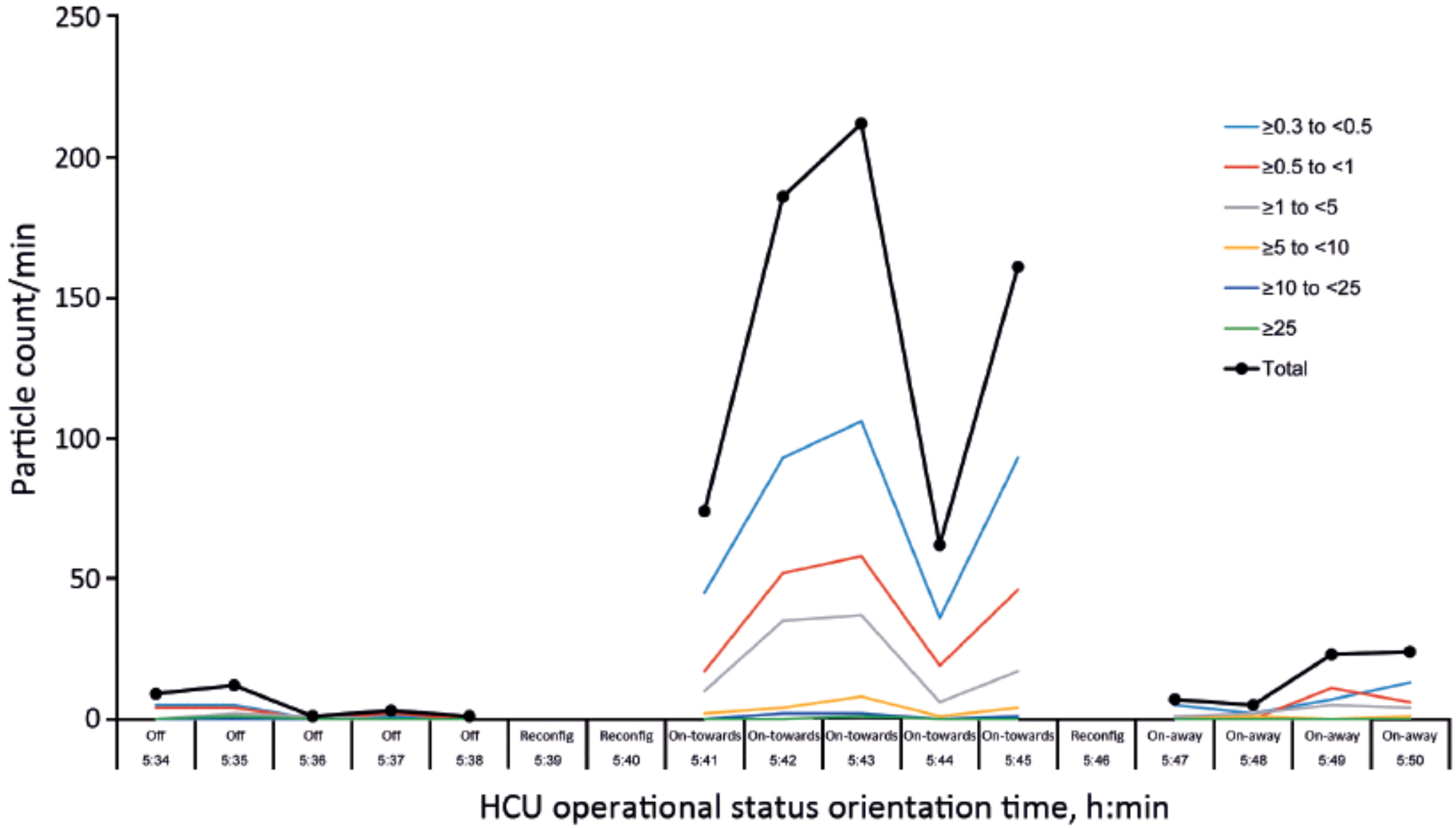
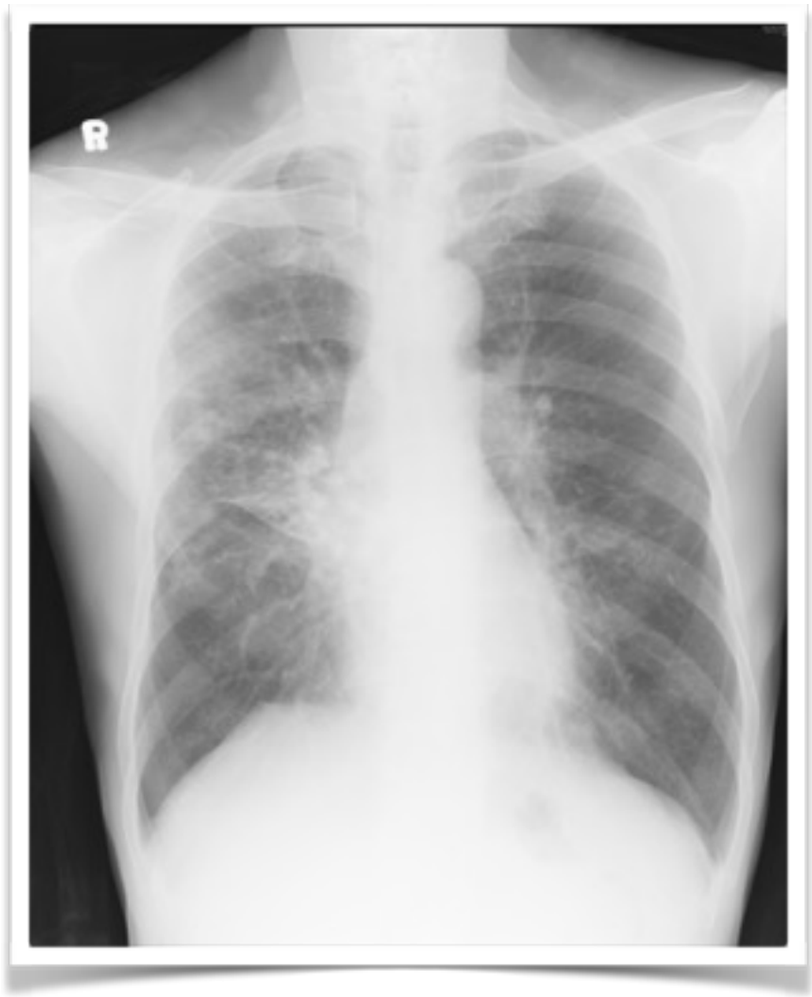


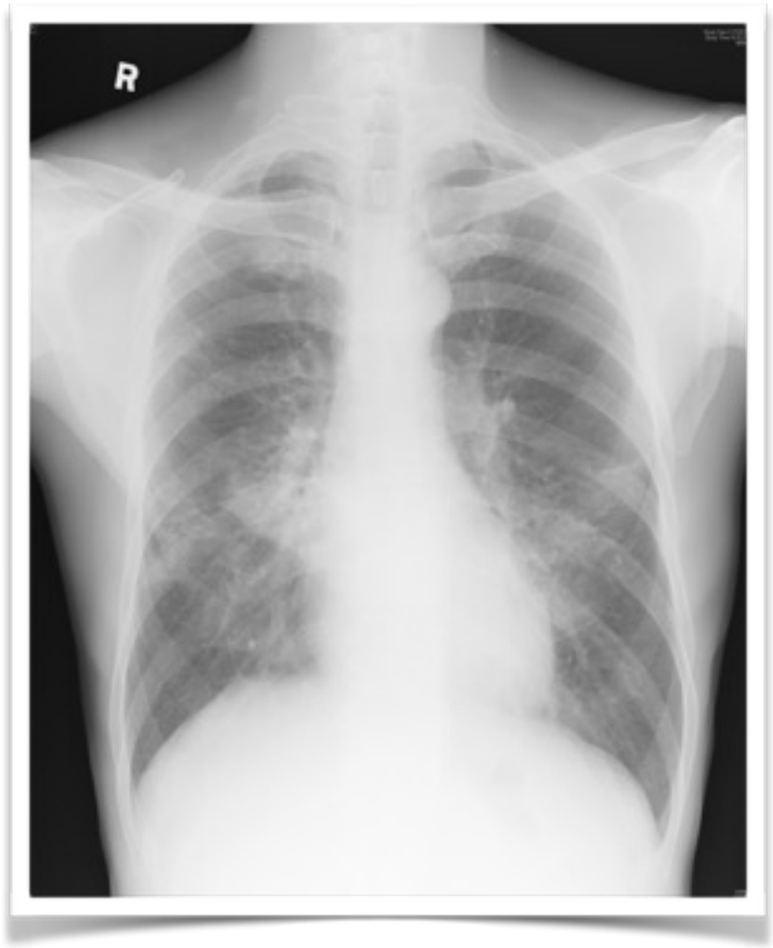
Figure 3. Laser particle measurements in cardiac operating room tested for transmission of *Mycobacterium chimaera* during surgery despite an ultraclean air ventilation system. Shown are measurements over time regarding heater–cooler unit (HCU) operational status (Off/On) and orientation (toward/away) with respect to the operating table. Lines indicate particle size ranges (in micrograms) captured by 6 gates and total particle count of the laser particle counter. Reconfig, time to reconfigure HCU status.

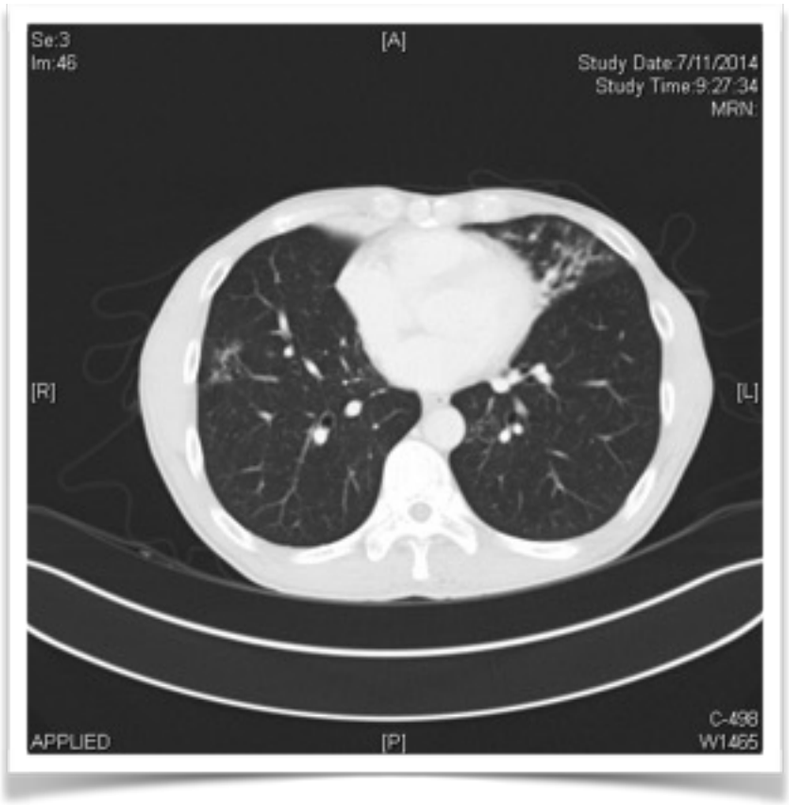
Case Seven

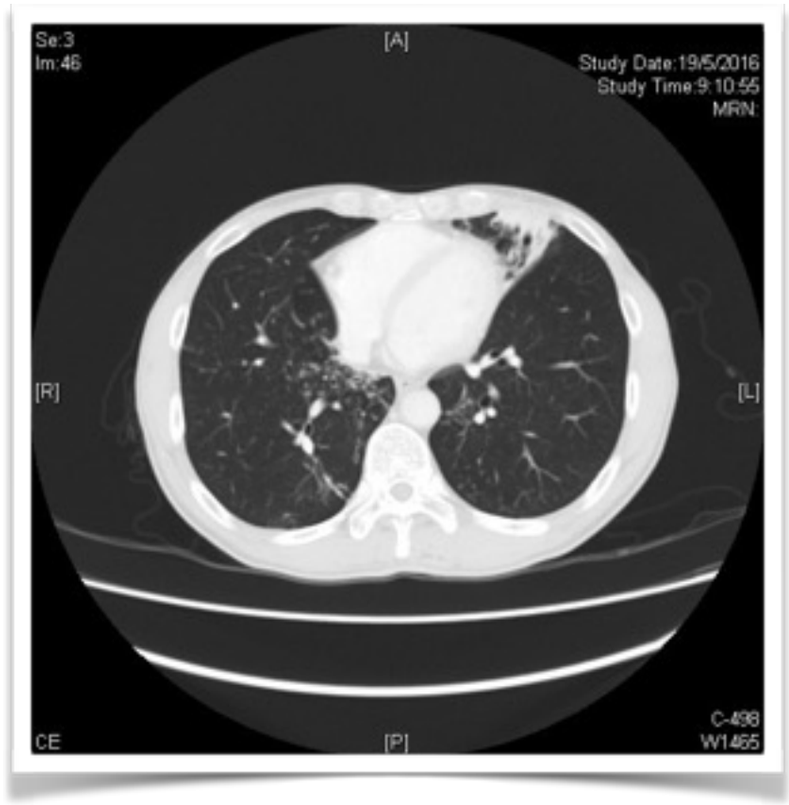
- M61
- Left ear deafness
- Bronchiectasis for 20 yrs
- HRCT in 2005 showed mild bronchiectasis in RML and lingula
- c/o chest condition deteriorating recently
- repeated sputum culture grew *M. abscessus*
- Transbronchial biopsy: granulomatous inflammation



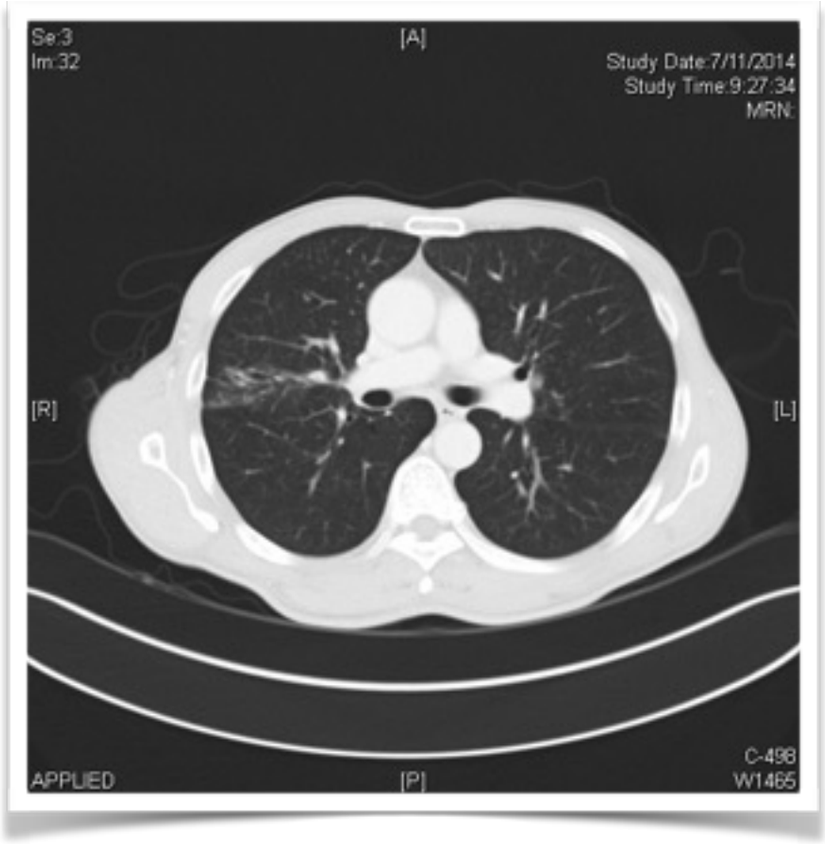
3 months later

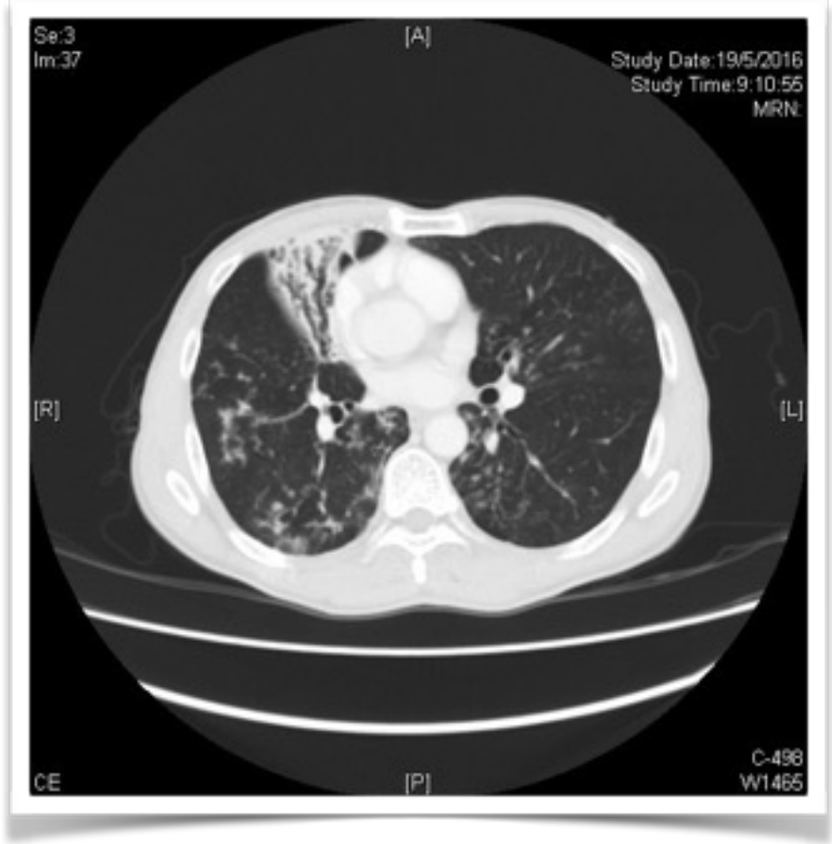






6 months later





Will you treat?
What antibiotics you will give?

Culture:
Organism 1: Mycobacterium abscessus

Susceptibility result:

Antimicrobial	Organism 1
Amikacin	S
Cefoxitin	I
Ciprofloxacin	R
Clarithromycin	R
Doxycycline	R
Imipenem	S

His left ear is deaf

Challenges in clinical management

- Imipenem and Amikacin started

Challenges in clinical management

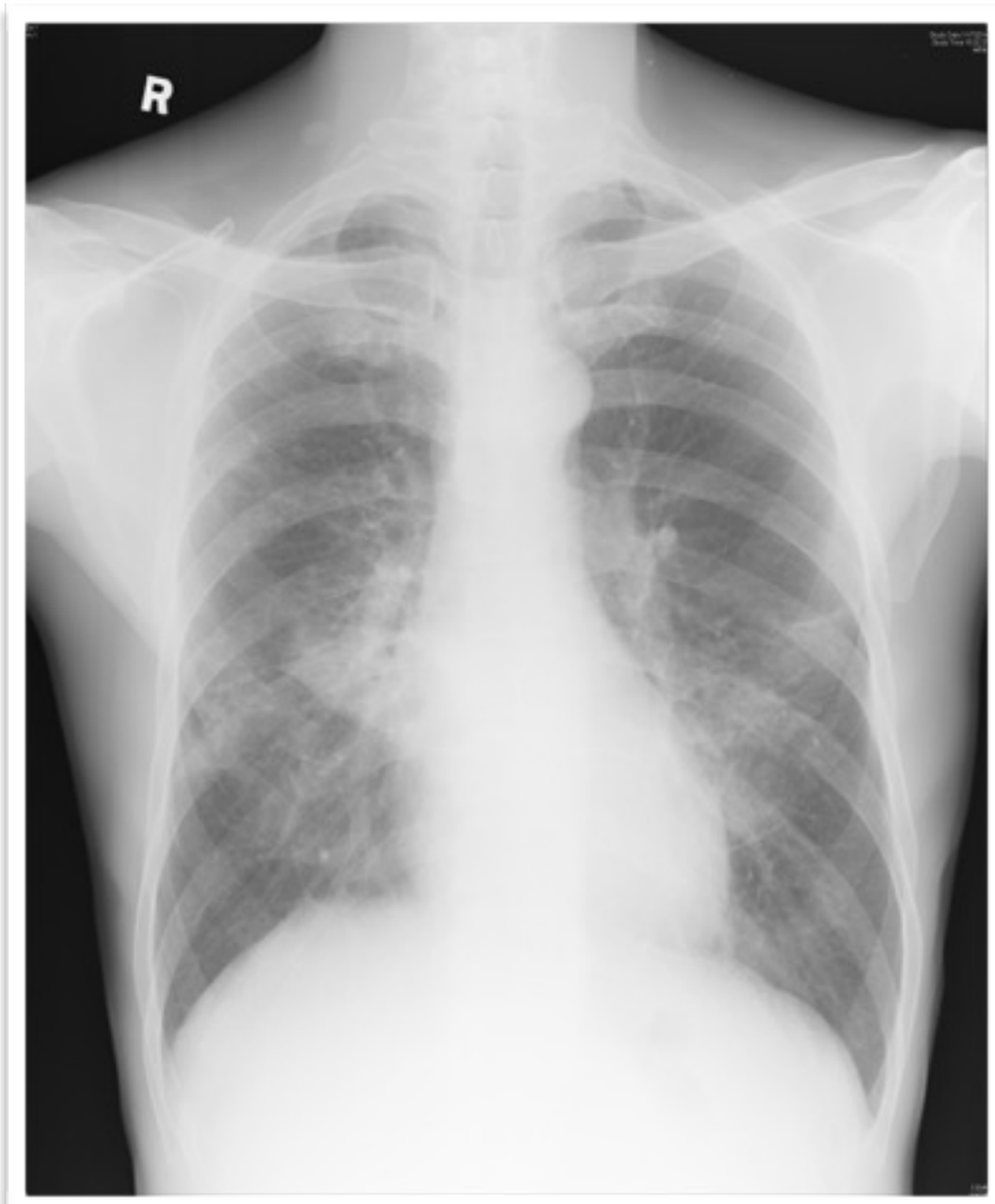
- Imipenem and Amikacin started
- Imipenem stopped after 4 weeks treatment because of prolonged beta lactam induced neutropenia

Challenges in clinical management

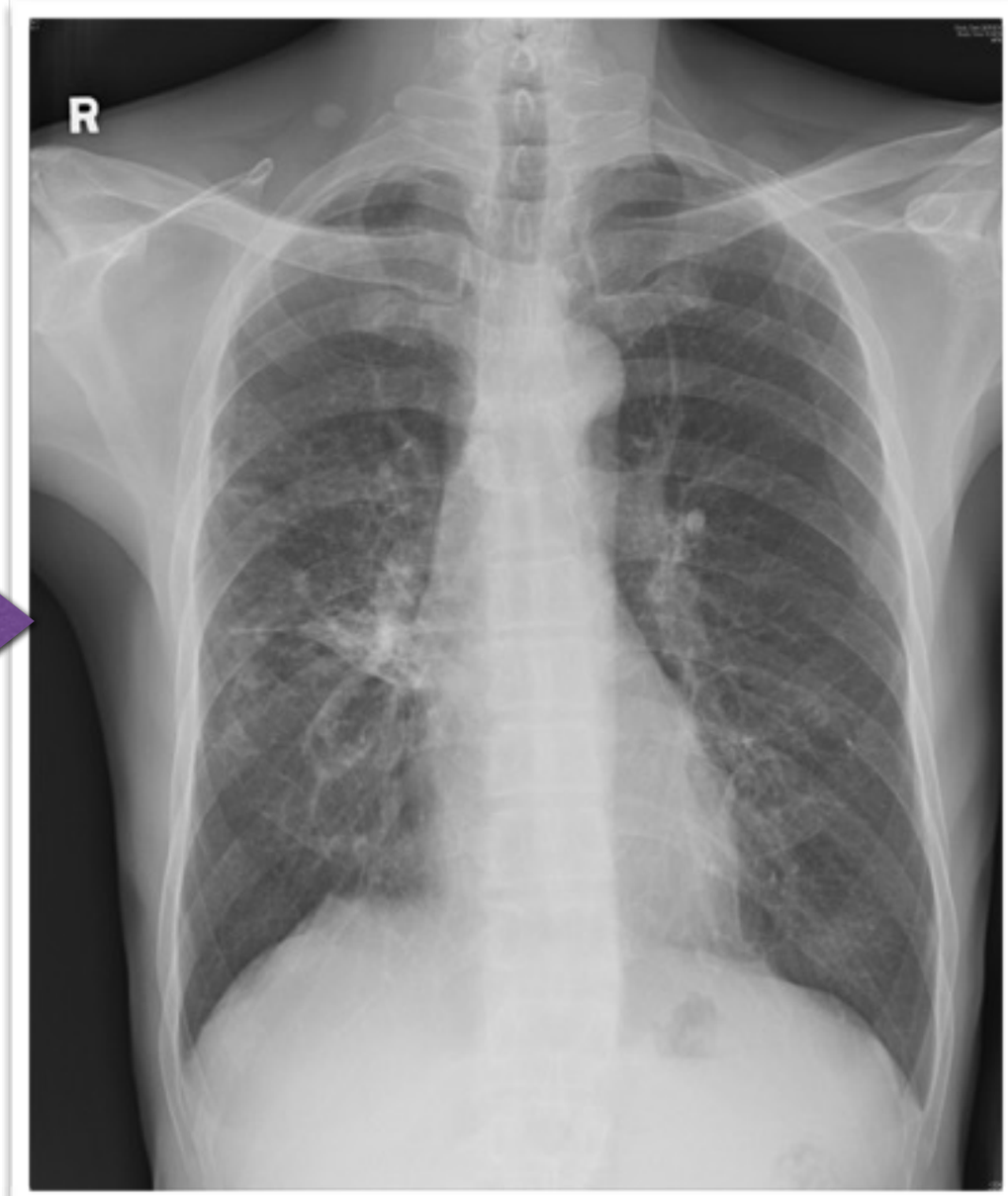
- Imipenem and Amikacin started
- Imipenem stopped after 4 weeks treatment because of prolonged beta lactam induced neutropenia
- Tigecycline started empirically but poorly tolerated because of severe GI upset

Challenges in clinical management

- Imipenem and Amikacin started
- Imipenem stopped after 4 weeks treatment because of prolonged beta lactam induced neutropenia
- Tigecycline started empirically but poorly tolerated because of severe GI upset
- Both Tigecycline and Amikacin stopped after 2 months treatment because of intolerance
- So now we don’t have alternative antibiotic choice



After 4 months treatment



Pulmonary NTM

- Commonly occurs in structural lung disease

- MAC, M. kanasii and M. abscessus were the most frequent pulmonary NTM

Diagnosis

American Thoracic Society Documents

An Official ATS/IDSA Statement: Diagnosis, Treatment, and Prevention of Nontuberculous Mycobacterial Diseases

- Contamination of respiratory specimens can occurs
- A single positive sputum culture is generally regarded as indeterminant for diagnosis

TABLE 3. CLINICAL AND MICROBIOLOGIC CRITERIA FOR DIAGNOSING NONTUBERCULOUS MYCOBACTERIAL LUNG DISEASE*

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.

Am J Respir Crit Care Med Vol 175. pp 367–416, 2007

Summary 1

- Commonly found in the environment e.g. water, pipe system

- Can **cause a variety of diseases depending on the host** e.g. localised LN enlargement, SSTI, pulmonary infection, bacteremia and disseminated infection

- Look for underlying **undiagnosed immunocompromised condition** such as HIV infection

- Sometimes associated with **healthcare associated outbreaks and new medical technology**

Summary 2

- **Challenges of clinical management**
  - Species specific ST profile
  - Long TAT of identification of isolates and culture results
  - Limited antibiotic choice because of high resistant profile in certain spp. such as *M. abscessus*
  - Requirement of prolonged course of antibiotics therapy but poor drug tolerance
  - Novel antibiotics as salvage therapy such as Tigecycline

Thank You