Dr. Lauren Sullivan received her medical degree at NYU School of Medicine, followed by internal medicine residency and a chief resident year at UCLA. She completed pulmonary critical care fellowship at UCSD. Currently, she is an Assistant Clinical Professor of Medicine at both UCSD and the San Diego VA. Her clinical interests include bronchiectasis and nontuberculous mycobacterial infection.
Dr. Niaz Banaei received his medical education from Stanford University. After medical school he completed residency training in Clinical Pathology at the University of California, San Francisco. He then completed a postdoctoral fellowship in microbial pathogenesis at the New York University. He then moved back to Stanford University to join the department of Pathology and serve as Medical Director of the Clinical Microbiology Laboratory at Stanford Health Care. He is currently a Professor of Pathology and Medicine (Division of Infectious Diseases & Geographic Medicine) at Stanford University.
Management of Exacerbations

Wael ElMaraachli, MD
Associate Professor
UC San Diego

Dr. Wael ElMaraachli received his medical degree from the American University of Beirut. He then completed and internal medicine residency at the University of Iowa Hospitals and Clinics followed by a pulmonary and Critical Care Medicine Fellowship at the University of California San Diego (UCSD). He is currently an Associate Clinical Professor and Director of the Non CF Bronchiectasis and NTM Lung Infection Program at UCSD Medical Center.
Airway Clearance

Jeff Tarnow, RCP, RRT
Respiratory Therapist
UC San Francisco

Jeff is a Respiratory Care Practitioner with over 35 years experience practicing at UCSF Health in San Francisco, CA. In his role as a Clinical Coordinator, he practiced in critical care and all clinical areas of the hospital. Jeff was one of the founding members of UCSF’s Rapid Response Team. In 2021 Jeff transitioned to UCSF’s ambulatory care setting where he is the Clinical Specialist for the CF, bronchiectasis and NTM clinics.

Jeff has contributed to researched and co-authored several peer reviewed articles.
Cystic Fibrosis: Screening and Heterozygous Patients

Alyssa Perez, MD
Assistant Professor
UC San Francisco

Dr. Alyssa Perez received her medical degree from Sidney Kimmel Medical College. She then went to Brigham and Women’s Hospital for her internal medicine training and received a Master of Education from the Harvard Graduate School of Education. After residency, she came to UCSF for her pulmonary and critical care fellowship, including a year of advanced training in Advanced Lung Disease and lung transplantation. Dr Perez is now an assistant professor of medicine at UCSF and specializes in lung transplant and cystic fibrosis. She is also a medical educator. Dr Perez is a coach for the UCSF pulmonary and critical care fellowship program and is an associate program director for the UCSF internal medicine residency program.

Vicki Jue, PharmD, BCGP
Pharmacist
UC San Francisco

Vicki Jue received her pharmacy degree from the University of Michigan. She did her pharmacy residency at UCSF. Currently, she is the System-wide Transitions of Care (TOC) pharmacy supervisor at UCSF managing 13 TOC pharmacy technicians and 1 TOC pharmacist. She is also the Cystic Fibrosis and Bronchiectasis clinic pharmacist managing a pulmonary pharmacy technician. In addition, Vicki serves as an Associate Clinical Professor at UCSF School of Pharmacy.
Carlos Milla is Professor of Pediatrics and (by courtesy) of Medicine at Stanford University School of Medicine, where he is Associate Director for Translational Research at the Center for Excellence in Pulmonary Biology at Stanford. Dr Milla is also the Director of the Stanford Cystic Fibrosis Center, the Stanford Primary Ciliary Dyskinesia Center, and the Stanford CF Translational Therapeutics Development research program. He has actively participated in multiple clinical research studies and has accumulated substantial experience on the diagnosis and development of novel outcomes for pediatric pulmonary disorders. This includes participation in a large number of clinical trials, from early phase to pivotal trials, as well as participating in multiple advisory boards for drug development focused on CF, PCD and other airway disorders. Dr Milla has published and lectured extensively on the topics of cystic fibrosis and PCD, and the genetics of rare lung diseases. Current areas of research include early lung disease development and the pathophysiologic mechanisms involved in the defective mucociliary clearance characteristic of CF, PCD and bronchiectasis. Additional research interests include active programs for remote monitoring and biomarker discovery for chronic pulmonary conditions.
Case 2: Nodular Bronchiectatic, Macrolide Sensitive MAC Lung Disease

Alicia Mirza, MD
Assistant Professor
Stanford University

Dr. Alicia Mirza trained in Internal Medicine and Pediatrics at UCLA, and subsequently completed her PCCM fellowship at Stanford University. She has a subspecialty interest in cystic fibrosis and non-CF bronchiectasis. She is the Associate Program Director of the Adult Stanford CF program and a national committee member of the CHEST Bronchiectasis Section.
Bronchial Artery Embolization
from the IR Perspective

David Hovsepian, MD
Professor
Stanford University

Dr. David Hovsepian received his BA from Columbia University in 1982 and his MD from Columbia College of Physicians and Surgeons in 1986. He completed his residency in Radiology at Presbyterian Hospital in New York City, followed by a two-year fellowship in Interventional Radiology at Thomas Jefferson University. He joined the faculty at Washington University in St. Louis in 1993, where he later achieved the rank of Professor of Radiology and Surgery. He has been at Stanford University since 2007 and was awarded the Department of Radiology Clinician of the Year in 2022. He has served on the editorial boards of Radiology and the Journal of Vascular and Interventional Radiology, and has been an examiner for the American Board of Radiology since 1998. At Stanford, he is a member of the multidisciplinary HHT Center of Excellence and his interventional practice includes the treatment of pulmonary AVM's. His clinical expertise also extends to Vascular Malformations in children and adults.
Connective Tissue-Related Bronchiectasis

Jonathan Graf, MD
Professor
UC San Francisco

Dr. Jonathan Graf received his medical degree from The University of Pennsylvania. He completed his internal medicine residency and rheumatology fellowship at UCSF. Currently, he is the director of the UCSF Rheumatoid Arthritis Observational Cohort and c-STAIR, the center for the Study of Advanced Immunotherapeutics in Rheumatology.
Case 3: Mycobacterium Abscessus

Mohamed Fayed MD, Associate Clinical Professor of Medicine, UCSF, completed his residency in Internal Medicine at Wright State University and completed fellowship in Pulmonary Critical Care at University of California, San Francisco, Fresno.

Dr. Fayed has earned many awards including, quality improvement symposium for ECMO team establishment community regional hospital and UCSF Fresno 2017, Outstanding chief resident 2013 Wright State University, the Malcolm Block Award for Teaching Excellence Wright State University 2012, Best teaching resident of the year Wright State University 2011.

He is interested in pulmonary infection, lung cancer and ECMO.
Pseudomonas and MRSA Colonization in Non-CF Bronchiectasis

Lauren Sullivan, MD  
Assistant Clinical Professor of Medicine  
Division of Pulmonary, Critical Care, Sleep Medicine, and Physiology  
UC San Diego Health | VA San Diego Healthcare System
Relevant Disclosures

• Site Co-investigator for ENCORE (Insmed) + MACrO2 (AN2 therapeutics)
The vicious, ‘viscous’ cycle...

Initial insult

Chronic bronchial infection

Structural lung disease

Inflammation

Impaired mucociliary clearance

- Normal lung
- Bronchiectasis
Meet Ms. H

67 yo retired teacher with history of bronchiectasis, MAC lung infection (treatment ended 2 years ago), here for routine follow up.
Ms. H

F/F = 64%
FEV1 = 1.67 (70%)
FVC = 2.62 (85%)

Sputum cultures grow *Pseudomonas aeruginosa* and *Mycobacterium gordonae*
Question #1

*Pseudomonas* colonization in non-CF bronchiectasis is associated with:

A. Increased frequency of exacerbations
B. Higher mortality
C. Faster decline in lung function
D. Increased frequency of hospitalizations
E. All of the above
Question #1

*Pseudomonas* colonization in non-CF bronchiectasis is associated with:

A. Increased frequency of exacerbations
B. Higher mortality
C. Faster decline in lung function
D. Increased frequency of hospitalizations
E. All of the above
Pseudomonas aeruginosa

- Opportunistic gram-negative aerobic bacillus
- Ubiquitous – found in soil/water
- First described in 1882 by a French pharmacist who noted blue-green discoloration of soldier’s bandages
- In bronchiectasis, can cause both acute and chronic infection

Carle Gessard
Pseudomonas aeruginosa
Predicting factors for chronic colonization of *Pseudomonas aeruginosa* in bronchiectasis

A. Pieters¹ · M. Bakker¹ · R. A. S. Hoek¹ · J. Altenburg¹ · M. van Westreenen¹ · J. G. J. V. Aerts¹ · M. M. van der Eerden¹

Table 2  Factors associated with *Pseudomonas aeruginosa* colonization (in the multivariate model)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Multivariable analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% C.I.)</td>
</tr>
<tr>
<td>Age &gt; 55 years</td>
<td>0.150 (0.042–0.540)</td>
</tr>
<tr>
<td>HRCT (&gt; 3 lobes affected)</td>
<td>0.516 (0.188–1.418)</td>
</tr>
<tr>
<td>PCD</td>
<td>0.040 (0.007–0.288)</td>
</tr>
<tr>
<td>Post-infectious cause</td>
<td>0.048 (0.013–0.186)</td>
</tr>
<tr>
<td>Macrolide maintenance</td>
<td>0.950 (0.321–2.901)</td>
</tr>
<tr>
<td>Hypertonic saline inhalation</td>
<td>0.309 (0.100–0.959)</td>
</tr>
<tr>
<td>Inhalation antibiotics</td>
<td>0.059 (0.016–0.220)</td>
</tr>
</tbody>
</table>

~25% of patients with non-CF bronchiectasis
A Comprehensive Analysis of the Impact of *Pseudomonas aeruginosa* Colonization on Prognosis in Adult Bronchiectasis

Simon Finch¹, Melissa J. McDonnell², Hani Abo-Leyah¹, Stefano Aliberti³, and James D. Chalmers¹

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Pseudomonas</th>
<th>Non-Pseudomonas</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Weight</td>
</tr>
<tr>
<td>Aliberti 2014</td>
<td>3</td>
<td>39</td>
<td></td>
</tr>
<tr>
<td>Chalmers 2014</td>
<td>15</td>
<td>70</td>
<td>47</td>
</tr>
<tr>
<td>Chalmers 2015</td>
<td>6</td>
<td>44</td>
<td>17</td>
</tr>
<tr>
<td>Goeminne 2014</td>
<td>10</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Loebinger 2009</td>
<td>8</td>
<td>20</td>
<td>19</td>
</tr>
<tr>
<td>Martinez-Garcia 2014</td>
<td>38</td>
<td>126</td>
<td>41</td>
</tr>
<tr>
<td>McDonnell 2014</td>
<td>9</td>
<td>47</td>
<td>13</td>
</tr>
<tr>
<td>McDonnell 2015</td>
<td>13</td>
<td>34</td>
<td>27</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>400</td>
<td>1795</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

Total events: 184
Heterogeneity: Tau² = 0.13; Chi² = 11.72, df = 7 (P = 0.11); I² = 40%
Test for overall effect: Z = 5.29 (P < 0.00001)

Figure 2. Association between *Pseudomonas aeruginosa* colonization and mortality in bronchiectasis. CI = confidence interval; M-H = Mantel-Haenszel.

3x increase in mortality
Increased risk of hospital admission (almost 7x)

Average of 1 additional exacerbation per patient per year
The independent contribution of *Pseudomonas aeruginosa* infection to long-term clinical outcomes in bronchiectasis

The hazard ratio for death with chronic PsA infection = 2.02
(95% CI 1.53-2.66, p<0.001)
FEV1 declines more over time when PsA is present

No PsA present

PsA present
In bronchiectasis, PsA colonization is problematic & is associated with:

- Mortality
- Decline in FEV1
- Hospitalization
- Exacerbations
Question #2: Ms. H has isolated Pseudomonas in her sputum for the first time. How would you eradicate it?

A. Levofloxacin 750 mg daily for 14 days
B. IV ceftazidime + gentamicin via PICC line for 14 days
C. Inhaled tobramycin for 28 days
D. No eradication is indicated given her symptoms have not changed
Question #2: Ms. H has isolated Pseudomonas in her sputum for the first time. How would you eradicate it?

A. Levofloxacin 750 mg daily for 14 days
B. IV ceftazidime + gentamicin via PICC line for 14 days
C. Inhaled tobramycin for 28 days
D. No eradication is indicated given her symptoms have not changed
First Isolation - Attempt eradication

European Respiratory Society guidelines for the management of adult bronchiectasis

BRITISH THORACIC SOCIETY
GUIDELINE FOR BRONCHIECTASIS IN ADULTS
First/new isolation of Pseudomonas

- Oral fluoroquinolone
  - 2 weeks
  - IV antibiotics (B-lactam + aminoglycoside)
  - Inhaled antibiotics
  - Total duration = 3 months

- IV antibiotics (B-lactam + aminoglycoside)
  - 2 weeks
  - Inhaled antibiotics
  - Total duration = 3 months

- Oral fluoroquinolone OR IV antibiotics + inhaled antibiotics
  - 2 weeks
  - Continue inhaled antibiotics
  - Total duration = 3 months
First/new isolation of Pseudomonas

1st line: Ciprofloxacin 500-750 mg BID x 2w

2nd line: anti-PsA B-Lactam + IV aminoglycoside

3 months inhaled colistin, gentamicin, or tobramycin
You treat Ms. H with 2 weeks of levofloxacin, with initial clearance of her cultures. Unfortunately, over the course of the subsequent year, she has 3 separate exacerbations requiring antibiotics, and her respiratory cultures now consistently grow *Pseudomonas*.

**Question #3:**

*What treatment would you prescribe?*

A. Inhaled tobramycin  
B. Inhaled ciprofloxacin  
C. Daily azithromycin  
D. None – continue to treat exacerbations as they occur
You treat Ms. H with 2 weeks of levofloxacin, with initial clearance of her cultures. Unfortunately, over the course of the subsequent year, she has 3 separate exacerbations requiring antibiotics, and her respiratory cultures now consistently grow *Pseudomonas*.

**Question #3:**

What treatment would you prescribe?

A. Inhaled tobramycin (per the guidelines...)
B. Inhaled ciprofloxacin
C. Daily azithromycin
D. None – continue to treat exacerbations as they occur
≥3 exacerbations/year

PsA present

Long-term inhaled antibiotics

No PsA present

Long-term macrolide

Lack of response, intolerance

Inadequate response

Combined oral + inhaled antibiotics
Inhaled antibiotics – what are the options?

- Tobramycin
- Gentamicin
- Aztreamonam
- Colistin
The efficacy and safety of inhaled antibiotics for the treatment of bronchiectasis in adults: a systematic review and meta-analysis

Irena F Laska, Megan L Crichton, Amelia Shoemark, James D Chalmers

- Systematic review / meta-analysis of all RTCs of inhaled-antibiotic use in adults with non-CF bronchiectasis and chronic respiratory tract infections

- Main findings:
  - ↓ bacterial load in sputum
  - ↑ rates of bacterial eradication
  - ↓ exacerbations
  - ↓ frequency of severe exacerbations
Inhaled antibiotics – what are the downsides?

Efficacy and safety of long-term inhaled antibiotic for patients with noncystic fibrosis bronchiectasis: a meta-analysis

Jia-Wei Yang¹,²*, Li-Chao Fan¹*, Hai-Wen Lu¹, Xia-Yi Miao¹, Bei Mao¹,² and Jin-Fu Xu¹,²

Table 3. Subgroup analysis of the common adverse events

<table>
<thead>
<tr>
<th>AEs†</th>
<th>Number of studies</th>
<th>Events/total</th>
<th>Effect size</th>
<th>Heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Macrolide</td>
<td>Control</td>
<td>OR (95%CI)</td>
</tr>
<tr>
<td>Any†</td>
<td>5</td>
<td>165/216</td>
<td>169/221</td>
<td>1.02 (0.65, 1.61)</td>
</tr>
<tr>
<td>Cough</td>
<td>3</td>
<td>26/123</td>
<td>24/28</td>
<td>1.11 (0.33, 3.69)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>3</td>
<td>20/83</td>
<td>13/84</td>
<td>1.96 (0.38, 10.20)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3</td>
<td>12/83</td>
<td>12/86</td>
<td>1.03 (0.44, 2.44)</td>
</tr>
<tr>
<td>Headache</td>
<td>3</td>
<td>11/106</td>
<td>12/113</td>
<td>0.97 (0.41, 2.31)</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>3</td>
<td>7/117</td>
<td>6/121</td>
<td>1.20 (0.39, 3.74)</td>
</tr>
<tr>
<td>Nausea</td>
<td>2</td>
<td>8/46</td>
<td>2/49</td>
<td>4.12 (0.95, 17.78)</td>
</tr>
<tr>
<td>Wheeze</td>
<td>3</td>
<td>20/83</td>
<td>4/84</td>
<td>6.74 (2.22, 20.52)</td>
</tr>
<tr>
<td>Bronchospasm</td>
<td>4</td>
<td>16/173</td>
<td>6/177</td>
<td>2.84 (1.11, 7.25)</td>
</tr>
<tr>
<td>Abnormal taste</td>
<td>3</td>
<td>15/107</td>
<td>7/116</td>
<td>2.34 (0.96, 5.69)</td>
</tr>
<tr>
<td>Overall§</td>
<td>5</td>
<td>135/921</td>
<td>86/958</td>
<td>1.77 (1.32, 2.36)</td>
</tr>
</tbody>
</table>

*Significant difference compared with control.
†The number of patients with adverse events.
‡Patients with any adverse events reported in the included studies.
§The overall adverse events represented in this meta-analysis.
AEs, adverse events.
Inhaled antibiotics – what are the downsides?

- Variable reports of antibiotic resistance
- No benefits / differences seen in terms of quality of life
Macrolides in *Pseudomonas* colonization

Long-term macrolide antibiotics for the treatment of bronchiectasis in adults: an individual participant data meta-analysis


---

**Table 2: Subgroup analysis of bronchiectasis exacerbation frequency**

<table>
<thead>
<tr>
<th></th>
<th>Number of participants (intervention vs placebo)</th>
<th>Incident rate ratio (95% CI)</th>
<th>p value</th>
<th>pInteraction value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pseudomonas aeruginosa infection</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.45</td>
</tr>
<tr>
<td>Yes</td>
<td>61 (31 vs 30)</td>
<td>0.36 (0.18-0.72)</td>
<td>0.0044</td>
<td>-</td>
</tr>
<tr>
<td>No</td>
<td>280 (142 vs 138)</td>
<td>0.53 (0.38-0.74)</td>
<td>&lt;0.0001</td>
<td>-</td>
</tr>
</tbody>
</table>

IRR=incident rate ratio. NE=not estimable. NA=not applicable. BMI=body-mass index. SGRQ=St George’s Respiratory Questionnaire.

---

**Table 3: Subgroup analysis of time to first bronchiectasis exacerbation**

<table>
<thead>
<tr>
<th></th>
<th>HR (95% CI)</th>
<th>p value</th>
<th>pInteraction value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pseudomonas aeruginosa infection</td>
<td>-</td>
<td>-</td>
<td>0.47</td>
</tr>
<tr>
<td>Yes</td>
<td>0.36 (0.19-0.69)</td>
<td>0.0017</td>
<td>-</td>
</tr>
<tr>
<td>No</td>
<td>0.47 (0.34-0.65)</td>
<td>&lt;0.0001</td>
<td>-</td>
</tr>
</tbody>
</table>

HR=hazard ratio. BMI=body-mass index. SGRQ=St George’s Respiratory Questionnaire.
Macrolides in *Pseudomonas* colonization

Long-term macrolide antibiotics for the treatment of bronchiectasis in adults: an individual participant data meta-analysis

*James D Chalmers*, Wim Boersma, Mike Lonergan, Lata Jayaram, Megan L Crichton, Noel Karalus, Steven L Taylor, Megan L Martin, Lucy D Burr, Conroy Wong, Josje Altenburg

No significant difference in FEV1 or quality of life measures

Highest level of benefit for macrolides was actually patients with *Pseudomonas*!
Meet Ms. A 🧔

42yo woman with SLE, APLS, untreated MAC lung infection.
Ms. A

F/F = 80%
FEV1 = 2.04 (71%)
FVC = 2.53 (75%)

Sputum cultures (4 over the past year) growing MRSA
Impact of MRSA colonization

- *Staph aureus* is a gram-positive bacteria. It is a commensal organism and major human pathogen with the ability to form biofilms and persist within the airways
- MRSA prevalence has been increasing
- In cystic fibrosis, associated with more severe disease and poorer outcomes
- Impact in non-CF bronchiectasis is less well understood
The Bronchiectasis Severity Index
An International Derivation and Validation Study

James D. Chalmers¹, Pieter Goeminne², Stefano Aliberti³, Melissa J. McDonnell⁴,⁵, Sara Lonni³, John Davidson⁴, Lucy Poppelwell¹, Waleed Salih¹, Alberto Pesci³, Lieven J. Dupont², Thomas C. Fardon¹, Anthony De Soyza⁴,⁵, and Adam T. Hill⁶

Table 2: Spirometry, Previous Hospital Admissions, Exacerbations, and Baseline Medical Research Council Dyspnea Score as Predictors of Future Morbidity and Mortality

<table>
<thead>
<tr>
<th>Specific organisms</th>
<th>N</th>
<th>4-yr Mortality</th>
<th>Hospitalizations</th>
<th>Exacerbations</th>
<th>SGRQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemophilus influenzae</td>
<td>177</td>
<td>10 (5.6%)</td>
<td>61 (34.5%)</td>
<td>2.03 (1.5)</td>
<td>45.1 (22.0)</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>70</td>
<td>15 (21.2%)†</td>
<td>62 (88.6%)†</td>
<td>2.85 (1.5)†</td>
<td>60.7 (21.7)†</td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
<td>35</td>
<td>2 (5.7%)</td>
<td>11 (31.4%)†</td>
<td>2.13 (1.5)</td>
<td>49.3 (21.6)</td>
</tr>
<tr>
<td>Moraxella catarrhalis</td>
<td>63</td>
<td>5 (7.9%)</td>
<td>26 (41.3%)†</td>
<td>2.08 (1.3)†</td>
<td>48.4 (22.1)†</td>
</tr>
<tr>
<td>Staphylococcus aureus (excluding MRSA)</td>
<td>43</td>
<td>5 (11.6%)</td>
<td>14 (32.6%)†</td>
<td>2.04 (1.7)</td>
<td>43.7 (21.6)†</td>
</tr>
<tr>
<td>MRSA</td>
<td>8</td>
<td>5 (62.5%)†</td>
<td>5 (62.5%)†</td>
<td>3.10 (2.4)†</td>
<td>50.7 (33.3)†</td>
</tr>
<tr>
<td>Gram-negative Enterobacteriaceae</td>
<td>40</td>
<td>6 (15.0%)</td>
<td>21 (52.5%)†</td>
<td>2.29 (1.5)†</td>
<td>55.2 (21.2)</td>
</tr>
</tbody>
</table>

†Significant difference from baseline.
The Prevalence and Significance of *Staphylococcus aureus* in Patients with Non–Cystic Fibrosis Bronchiectasis

Mark L. Metersky¹, Timothy R. Aksamit², Alan Barker³, Radmila Choate⁴, Charles L. Daley⁵, Leigh A. Daniels⁶, Angela DiMango⁷, Edward Eden⁸, David Griffith⁹, Margaret Johnson¹⁰, Michael Knowles¹¹, Anne E. O'Donnell¹², Kenneth Olivier¹³, Matthias Salathe¹⁴, Byron Thomashow¹⁵, Gregory Tino¹⁶, Gerard Turino⁸, Kevin L. Winthrop³, and David Mannino⁴

- Retrospective cohort study of the Bronchiectasis Research Registry
- Looked at 3 cohorts:
  - Positive for *S. aureus* (~11%), with 33% MRSA
  - Negative for *S. aureus* and NF-GNB
  - Negative for *S. aureus* but positive for at least one of the other NF-GNB
- >1/3 of patients in *S. aureus* group also had NF-GNB
- In multivariate analysis, there were no significant differences between the *S. aureus* and the other two groups
- No difference between MSSA and MRSA

*Staphylococcus aureus* was not an independent risk factor for disease in the Bronchiectasis Research Registry
Epidemiology and outcomes of multidrug-resistant bacterial infection in non-cystic fibrosis bronchiectasis

Chih-Hao Chang¹,²,³, Chiung-Hsin Chang²,³, Shih-Hao Huang¹,²,³, Chung-Shu Lee¹,²,³, Po-Chuan Ko⁴, Chun-Yu Lin²,³, Meng-Heng Hsieh²,³, Yu-Tung Huang⁴, Horng-Chyuan Lin²,³, Li-Fu Li²,³,⁵, Fu-Tsai Chung¹,²,³, Chun-Hua Wang²,³ and Hung-Yu Huang¹,²,³∗

• Retrospective cohort study a Taiwanese research database looking at bronchiectasis patients with and without MDR organisms

• MDR organisms were:
  • MRSA (18.4%)
  • Acinetobacter baumannii
  • PsA aeruginosa
  • Klebsiella pneumoniae
  • E. coli

• Looked at in-hospital and 3 year mortality
Epidemiology and outcomes of multidrug-resistant bacterial infection in non-cystic fibrosis bronchiectasis

Chih-Hao Chang¹,²,³, Chiung-Hsin Chang²,³, Shih-Hao Huang¹,²,³, Chung-Shu Lee¹,²,³, Po-Chuan Ko⁴, Chun-Yu Lin²,³, Meng-Heng Hsieh²,³, Yu-Tung Huang⁴, Horng-Chyuan Lin²,³, Li-Fu Li²,³,⁵, Fu-Tsai Chung¹,²,³, Chun-Hua Wang²,³ and

Fig. 2 Kaplan–Meier survival curves for (A) 3-year mortality of the cohort (Control and MDR groups); (B) 3-year mortality of the cohort (Control and MDR subgroups) MDR, multidrug-resistant
Epidemiology and outcomes of multidrug-resistant bacterial infection in non-cystic fibrosis bronchiectasis

Chih-Hao Chang\textsuperscript{1,2,3}, Chiung-Hsin Chang\textsuperscript{2,3}, Shih-Hao Huang\textsuperscript{1,2,3}, Chung-Shu Lee\textsuperscript{1,2,3}, Po-Chuan Ko\textsuperscript{4}, Chun-Yu Lin\textsuperscript{2,3}, Meng-Heng Hsieh\textsuperscript{2,3}, Yu-Tung Huang\textsuperscript{4}, Horng-Chyuan Lin\textsuperscript{2,3}, Li-Fu Li\textsuperscript{2,3,5}, Fu-Tsai Chung\textsuperscript{1,2,3}, Chun-Hua Wang\textsuperscript{2,3} and Hung-Yu Huang\textsuperscript{1,2,3*}

\textbf{Table 6} Adjusted hazard ratio of in-hospital and 3-year mortality in MDR subgroups

<table>
<thead>
<tr>
<th>MDR subgroups</th>
<th>In-hospital mortality</th>
<th>3-year mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDR-AB</td>
<td>2.865 (2.024-4.055)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>2.376 (1.971-2.864)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ESBL-E coli</td>
<td>1.816 (0.898-3.672)</td>
<td>0.097</td>
</tr>
<tr>
<td></td>
<td>1.204 (0.833-1.741)</td>
<td>0.324</td>
</tr>
<tr>
<td>ESBL-KP</td>
<td>2.184 (1.371-3.480)</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>2.190 (1.715-2.796)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MDR-Pseudomonas</td>
<td>1.856 (1.055-3.265)</td>
<td>0.032</td>
</tr>
<tr>
<td></td>
<td>1.525 (1.125-2.066)</td>
<td>0.007</td>
</tr>
<tr>
<td>MRSA</td>
<td>2.551 (1.594-4.082)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>1.611 (1.248-2.080)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

\textit{Note}: AB, Acinetobacter baumannii; ESBL, extended-spectrum-beta-lactamases; KP, Klebsiella pneumoniae; MDR: multidrug-resistant; MRSA, methicillin-resistant Staphylococcus aureus
First isolation - Attempt eradication?

European Respiratory Society guidelines for the management of adult bronchiectasis

We suggest **not offering** eradication antibiotic treatment to adults with bronchiectasis following new isolation of pathogens other than *P. aeruginosa* (conditional recommendation, very low quality of evidence)

BRITISH THORACIC SOCIETY GUIDELINE FOR BRONCHIECTASIS IN ADULTS

**Offer** patients with bronchiectasis associated with clinical deterioration and **a new growth of methicillin-resistant S. aureus (MRSA)** (1st isolation or regrowth in the context of intermittently positive cultures) eradication. This should be attempted especially in view of infection control issues. (D)
Oral preparation

1st line:
- Doxycycline 100 mg BID
- Rifampicin BID*
- Trimethoprim 200 mg BID

2nd line:
- Linezolid 600 mg BID

IV preparation

1st line: IV vancomycin

2nd line:
- Linezolid 600 mg BID
Summary & Top points

- Pseudomonas colonization is associated with poor outcomes in non-CF bronchiectasis, including mortality.
- Attempted eradication of newly-isolated PsA is recommended in both ERS and BTS guidelines.
- Consider inhaled antibiotics or chronic macrolide therapy for patients with PsA and frequent exacerbations.
  - Use of the macrolides is likely superior based on available data, but may be limited by co-morbid NTM infection.
- The impact of MRSA colonization is less well understood, with low quality evidence to support eradication.
References


References


MAKING THE MOST OF RESPIRATORY CULTURES: BACTERIAL AND AFB

Niaz Banaei, MD
Professor of Pathology and Medicine, Stanford University
Medical Director of Clinical Microbiology Laboratory, Stanford Health Care
RELEVANT FINANCIAL DISCLOSURES

- I have no relationship with ACCME defined ineligible companies.
Laboratory Diagnosis of CF Respiratory Infection: Major Challenges

- Contamination of sputum with oral bacteria

10^{10-12} bacteria/mL

PMID: 36069902
Flow of Specimens for CF Cultures

- Hospital and Clinics
  - Accessioning
    - Processing/
      Setup (micro lab)
      - Aerobic bacteriology
      - Mycobacteriology
      - Mycology
    - Respiratory
    - AST
Preanalytical Factors Impacting CF Respiratory Cultures

- **Sputum Quality**
  - Deep cough or induced sputum $\rightarrow$ lower respiratory secretions
  - Ask patient to rinse mouth with water immediately prior to specimen collection

- **Sputum Volume**
  - Should exceed 5 ml based on AFB studies
    (PMID: 10806154)

- **Sputum timing**
  - Either am or pm based on AFB studies
    (PMID: 23099183)
Testing Criteria for non-CF Respiratory Cultures

Respiratory culture rejected if:

1. Gram stain performed on sputum shows $\geq 10$ epithelial cells per low power (10x) per field
### Patterns to look for in Gram stains from respiratory specimens

<table>
<thead>
<tr>
<th>Pneumonia - acceptable</th>
<th>Indicate poor sample collection</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very few squamous epithelial cells</td>
<td>Many squamous epithelial cells</td>
<td>Many squamous epithelial cells seen on slide, indicates that upper</td>
</tr>
<tr>
<td>&lt;10 per low power (10x) field</td>
<td>≥10 per low power (10x) field</td>
<td>respiratory secretions and saliva are present in the sample. Unable to</td>
</tr>
<tr>
<td></td>
<td></td>
<td>interpret culture. Sample should be rejected and a new</td>
</tr>
<tr>
<td></td>
<td></td>
<td>sample collected.</td>
</tr>
</tbody>
</table>
Sputum, Gram stain, 100x
Testing Criteria for non-CF Respiratory Cultures

Respiratory culture rejected if:

1. Gram stain performed on sputum shows ≥10 epithelial cells per low power (10x) per field
   
   Exception: Cystic fibrosis culture (PMID:12149331), AFB and fungal culture
Utility of Gram Staining for Evaluation of the Quality of Cystic Fibrosis Sputum Samples

Bindu Nair,1 Jenny Stapp,2 Lynn Stapp,2 Linda Bugni,2 Jill Van Dalfsen,3 and Jane L. Burns1,2,∗

Division of Infectious Disease, Department of Pediatrics, University of Washington1, Cystic Fibrosis Foundation Therapeutic Development Network Core Microbiology Laboratory,2 and Chiron Corporation,3 Seattle, Washington

Received 28 December 2001/Returned for modification 18 March 2002/Accepted 12 May 2002

The microscopic examination of Gram-stained sputum specimens is very helpful in the evaluation of patients with community-acquired pneumonia and has also been recommended for use in cystic fibrosis (CF) patients. This study was undertaken to evaluate that recommendation. One hundred one sputum samples from CF patients were cultured for gram-negative bacilli and examined by Gram staining for both sputum adequacy (using the quality [Q] score) and bacterial morphology. Subjective evaluation of adequacy was also performed and categorized. Based on Q score evaluation, 41% of the samples would have been rejected despite a subjective appearance of purulence. Only three of these rejected samples were culture negative for gram-negative CF pathogens. Correlation between culture results and quantitative Gram stain examination was also poor. These data suggest that subjective evaluation combined with comprehensive bacteriology is superior to Gram staining in identifying pathogens in CF sputum.
Proposing a standardized 5-point color scale (from 0=lighter to 5=darker) for objective macroscopic description of sputum.
Preanalytical Factors Impacting CF Respiratory Cultures

Transport
- Respiratory specimens should be processed <2 hrs
- Respiratory specimens that can't be process rapidly should be refrigerated up to 24-48 hrs
Preanalytical Factors Impacting CF Respiratory Cultures

Transport
- Respiratory specimens should be processed <2 hrs
- Respiratory specimens that can’t be process rapidly should be refrigerated up to 24-48 hrs

Time between Collection and Storage Significantly Influences Bacterial Sequence Composition in Sputum Samples from Cystic Fibrosis Respiratory Infections

Spontaneously expectorated sputum is traditionally used as the sampling method for the investigation of lower airway infections. While guidelines exist for the handling of these samples for culture-based diagnostic microbiology, there is no comparable consensus on their handling prior to culture-independent analysis. The increasing incorporation of culture-independent approaches in diagnostic microbiology means that it is of critical importance to assess potential biases. The aim of this study was to assess the impact of delayed freezing on culture-independent microbiological analyses and to identify acceptable parameters for sample handling. Sputum samples from eight adult cystic fibrosis (CF) patients were collected and aliquoted into sterile Bijou bottles. Aliquots were stored at room temperature before being frozen at −80°C for increasing intervals, up to a 72-h period. Samples were treated with propidium monoazide to distinguish live from dead cells prior to DNA extraction, and 16S rRNA gene pyrosequencing was used to characterize their bacterial compositions. Substantial variation was observed in samples with high-diversity bacterial communities over time, whereas little variation was observed in low-diversity communities dominated by recognized CF pathogens, regardless of time to freezing. Partitioning into common and rare species demonstrated that the rare species drove changes in similarity. The percentage abundance of anaerobes over the study significantly decreased after 12 h at room temperature \((P = 0.006)\). Failure to stabilize samples at −80°C within 12 h of collection results in significant changes in the detected community composition.

PMID: 24920767
Flow of Specimens for CF Cultures

- Hospital and Clinics
  - Accessioning
    - Processing/Setup (micro lab)
      - Aerobic bacteriology
      - Mycobacteriology
      - Mycology
      - Respiratory
      - AST
Plate Streaking
Processing “Contaminated” Specimens

1. Decontaminate specimen with NaOH (oxalic acid for CF)

2. Liquify with a mucolytic agent, e.g. N-acetyl-L-cysteine

3. Neutralize and dilute with buffer.

4. Centrifuge at 3000 x g.
Processing “Contaminated” Specimens in BSL3
Processing “Contaminated” Specimens
Media Used to Culture Pathogens
# Media Used to Culture Respiratory Pathogens

<table>
<thead>
<tr>
<th>Non-selective Agars</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood Agar</td>
</tr>
<tr>
<td>Chocolate Agar</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Selective Agars</th>
</tr>
</thead>
<tbody>
<tr>
<td>Columbia Agar</td>
</tr>
<tr>
<td>MacConkey Agar</td>
</tr>
</tbody>
</table>
Media Used to Culture CF Respiratory Pathogens

Non-selective Agars

- Blood Agar
- Chocolate Agar

Selective Agars

- Columbia Agar
- MacConkey Agar
- Burkholderia cepacia selective agar
- Staphylococcus aureus chromagar
Canonical CF Pathogens

Blood Agar with Pseudomonas aeruginosa
Canonical CF Pathogens

Staphylococcus aureus chrom agar
Staphylococcus aureus

Blood agar
Wild-type Staph. aureus
Small colony variant
Canonical CF Pathogens

Burkholderia Cepacia Selective agar
Burkholderia cepacia complex
Canonical CF Pathogens

Enterobacterales: E. coli, Klebsiella spp., others
Non-fermenting GNR: Acinetobacter spp., Stenotrophomonas maltophilia, and Achromobacter spp.

Blood Agar

MacConkey Agar
Bacterial Identification with MALDI-TOF Mass Spectrometry
**Burkholderia cepacia** complex has 17 defined species

<table>
<thead>
<tr>
<th>Species</th>
<th>Former genomovar designation</th>
<th>Yr identified and/or named</th>
<th>Reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>B. cepacia</em></td>
<td>I</td>
<td>1950, 1997</td>
<td>34, 322</td>
</tr>
<tr>
<td><em>B. multivorans</em></td>
<td>II</td>
<td>1997</td>
<td>322</td>
</tr>
<tr>
<td><em>B. cenocepacia</em></td>
<td>III</td>
<td>1997, 2003</td>
<td>321, 322</td>
</tr>
<tr>
<td><em>B. stabilis</em></td>
<td>IV</td>
<td>1997, 2000</td>
<td>322, 323</td>
</tr>
<tr>
<td><em>B. vietnamiensis</em></td>
<td>V</td>
<td>1995, 1997</td>
<td>107, 322</td>
</tr>
<tr>
<td><em>B. dolosa</em></td>
<td>VI</td>
<td>2001, 2004</td>
<td>58, 335</td>
</tr>
<tr>
<td><em>B. ambifaria</em></td>
<td>VII</td>
<td>2001</td>
<td>63</td>
</tr>
<tr>
<td><em>B. anthina</em></td>
<td>VIII</td>
<td>2002</td>
<td>319</td>
</tr>
<tr>
<td><em>B. pyrocinia</em></td>
<td>IX</td>
<td>2002</td>
<td>319</td>
</tr>
<tr>
<td><em>B. ubonensis</em></td>
<td></td>
<td>2000, 2008</td>
<td>333, 355</td>
</tr>
<tr>
<td><em>B. latens</em></td>
<td></td>
<td>2008</td>
<td>333</td>
</tr>
<tr>
<td><em>B. diffusa</em></td>
<td></td>
<td>2008</td>
<td>333</td>
</tr>
<tr>
<td><em>B. arboris</em></td>
<td></td>
<td>2008</td>
<td>333</td>
</tr>
<tr>
<td><em>B. seminalis</em></td>
<td></td>
<td>2008</td>
<td>333</td>
</tr>
<tr>
<td><em>B. metallica</em></td>
<td></td>
<td>2008</td>
<td>333</td>
</tr>
<tr>
<td><em>B. contaminans</em></td>
<td></td>
<td>2009</td>
<td>332</td>
</tr>
<tr>
<td><em>B. lata</em></td>
<td></td>
<td>2009</td>
<td>332</td>
</tr>
</tbody>
</table>
CF Pathogens

Blood Agar
Rapidly growing mycobacteria
Mycobacterium abscessus
Media Used to Culture Mycobacteria

- MGIT liquid medium
- 7H11/7H11S agar
- Specimen concentrate
- Growth supplement
- PANTA
MGIT Culture System

MGIT 960

320 tubes per unit

Positive
### Incubation of Mycobacterial Cultures

<table>
<thead>
<tr>
<th>Media</th>
<th>Incubation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liquid</td>
<td>37°C 6 wks</td>
</tr>
<tr>
<td>Solid</td>
<td>CO₂, 37°C 6 wks</td>
</tr>
</tbody>
</table>
Multiplex, Real-time PCR Paradigm for Identification of Common AFB Isolates

AFB + Culture

Rxn 1
1. M. tb complex
2. M. avium complex
3. AFB genus

Rxn 2
1. M. chelonae/abscessus
2. M. fortuitum group
3. AFB genus

Rxn 3
1. M. gordonae

NTM

MALDI-TOF
Flow of Specimens for CF Cultures

- Hospital and Clinics
- Accessioning
- Processing/Setup (micro lab)
  - Aerobic bacteriology
  - Mycobacteriology
  - Mycology
  - Respiratory
  - AST

Pre analytical

Post analytical
Automated Phenotypic Antibiotic Susceptibility Testing Systems

bioMerieux Vitek 2

Siemens MicroScan
Manual Antibiotic Susceptibility Testing Systems on CF Isolates

Disk Diffusion

E-Test

Pseudomonas aeruginosa and Burkholderia cepacia Complex
Automated Phenotypic Antibiotic Susceptibility Testing Systems

bioMerieux Vitek 2

Siemens MicroScan

S. aureus and other non-fermenting Gram-negative Rods and Enterobacterales
Sensititre Plates for Phenotypic AST of Rapid and Slow Growing NTM

Genotypic Detection of Clarithromycin resistance in *M. abscessus* group

PMID: 25903572
The Sense and Nonsense of Antimicrobial Susceptibility Testing in Cystic Fibrosis

John J. LiPuma
Division of Pediatric Infectious Diseases, Department of Pediatrics, University of Michigan Medical School, Ann Arbor, Michigan, USA

Antimicrobial susceptibility testing (AST) has been used to guide therapy of airway infection in persons with cystic fibrosis (CF) for decades. However, evidence that AST adds benefit to treatment outcomes in CF is lacking. In fact, the routine use of AST has potential to exacerbate inappropriate antibiotic use. Several features of airway infection in CF contribute to the limitations of AST in predicting treatment outcomes, providing rationale for abandoning this practice altogether. Other features of CF infection suggest, however, that selective use of AST can provide worthwhile guidance to antibiotic selection.
Nonsense

- Antibiotic susceptibility testing not indicated when using topical (inhaled) therapy
  - Chronic suppressive therapy
  - Eradication therapy

- Antibiotic susceptibility testing not supported by systematic reviews of treatment response (PMID: 30709744) and features of CF
  - Episodic treatment of pulmonary exacerbation
In Vivo Features Impossible to Replicate in Standard AST

CF Airway Infection

Polymicrobial

Choice of Species

Roles of other species?

Microbial Interactions

Some protect others: β-lactamases, pyocyanin & HQNO

Chronic

Bacterial Diversification & Adaptation

Choice of Isolate

Metabolism and growth rate, biofilm formation, antibiotic resistance and tolerance

Many morphotypes and many distinct antibiograms per morphotype

PMID: 36069902
Decrease in the diversity of CF airway bacterial communities as lung disease progresses

Targeting the dominant pathogen based on AST Result?

PMID: 22451929
Summary

• There is a lot of limitations to using microbiological results to make treatment decisions in CF patients.

• Antibiotic susceptibility testing is not supported by treatment response and CF features.
Questions?
Identification and Susceptibility Per Expert Guidance and CLSI Breakpoints

- Any amount of S. aureus
- Pure or predominant β-hemolytic Streptococci
- Any amount of Pseudomonas aeruginosa, Burkholderia cepacia complex, and Acinetobacter spp., Stenotrophomas maltophilia, and Achromobacter xylosoxidans
- Pure or predominant other non-fermenters
- Pure or predominant Enterobacterales
- Any amount of H. influenza
- Mycobacteria depending on the species
# The Sense and Nonsense of Antimicrobial Susceptibility Testing in Cystic Fibrosis

John J. LiPuma

## Stanford Health Care Antibiogram Data for 2023

<table>
<thead>
<tr>
<th>Gram negative rods</th>
<th>PENICILLINS</th>
<th>CEPHEMS</th>
<th>LACTAMS</th>
<th>AMINOGLYC's</th>
<th>OTHERS</th>
<th>Urine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent Susceptible</td>
<td>No. Tested (n)</td>
<td>Ampicillin</td>
<td>Ampicillin</td>
<td>Penicillin G</td>
<td>Carbenicillin</td>
<td>Cefazolin (g)</td>
</tr>
<tr>
<td><strong>Pseudomonas aeruginosa</strong></td>
<td>7/17</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>63</td>
<td>82</td>
</tr>
<tr>
<td>Ps. aeruginosa CF-isolated (e)</td>
<td>115</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>86</td>
<td>87</td>
</tr>
<tr>
<td>Ps. aeruginosa CF non-isolated (e)</td>
<td>58</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>61</td>
<td>93</td>
</tr>
</tbody>
</table>
Multiplex, Real-time PCR for Detection of Clarithromycin resistance in *M. abscessus* group
Multiplex, Real-time PCR for Detection of Clarithromycin resistance in *M. abscessus* group
RELEVANT FINANCIAL DISCLOSURES

I have the following relationships with ACCME defined ineligible companies:

- Site PI: ENCORE (Insmed), MACrO2 (AN2 Therapeutics)

I **WILL**/**WILL NOT** discuss off-label use and/or investigational use of any drugs or devices.
Learning Objectives

- Identify the clinical criteria for a bronchiectasis exacerbation as defined by international recommendations
- Determine efficient evaluation and initial therapy of a bronchiectasis exacerbation
- Describe complications of prolonged or recurrent exacerbations
- Identify when suppressive antibiotic or inhaled therapy is indicated
Bronchiectasis Exacerbation

DEFINITION
Results of the exacerbation definition. #: other potential causes of clinical deterioration have been discounted.

Definition of a bronchiectasis pulmonary exacerbation for clinical trials

A person with bronchiectasis with a deterioration in three or more of the following key symptoms for at least 48 h:

1) Cough
2) Sputum volume and/or consistency
3) Sputum purulence
4) Breathlessness and/or exercise tolerance
5) Fatigue and/or malaise
6) Haemoptysis

AND a clinician determines that a change in bronchiectasis treatment is required#
Case: Patient Description

80 year old lady with bronchiectasis, pseudomonas colonization of the airways with worsening productive cough and shortness of breath for several days.

- Non smoker.

November 2023
Past Medical History

- Bronchiectasis
  - S/P right middle lobectomy
  - S/P azithromycin Oct 2019 - Mar 2021
- Pseudomonas colonization of the airways
  - Pneumonitis with inhaled colistin.
  - S/P cyclic inhaled aztreonam 2020.
- Antibiotic courses for acute bronchiectasis exacerbations:
  - May 2021 Meropenem IV.
  - December 2021: Meropenem IV.
  - August 2023: doxycyline
Patient with Bronchiectasis

- **Microbiology**
  - Sputum Feb, March June, July, October 2023:
    - heavy *Pseudomonas aeruginosa*
    - Susceptible to ciprofloxacin. (but patient not tolerant)
  - Sputum July and August 2023:
    - *Moraxella catarrhalis*
  - All Acid fast bacillus cultures of the above samples
    - Negative
Bronchiectasis Exacerbation Evaluation

- Sputum culture
  - *Haemophilus influenzae*, *Moraxella catarrhalis*, *Staphylococcus aureus*, *Pseudomonas aeruginosa* (especially mucoid types), *Stenotrophomonas maltophilia*.
  - Previous sputum bacteriology results can be useful in deciding which antibiotic to use

- Respiratory viral panel

- Consider a CXR
  - If suspect pneumonia: fever, chills, night sweats, severe shortness of breath
Bronchiectasis Exacerbation Treatment

- Mostly outpatient
  - Oral antibiotic if possible
  - Based on prior sputum culture data

- Pseudomonas
  - Ciprofloxacin is the only oral antibiotic available

- Optimal duration of therapy unknown. (10-14 days)
  - Paucity of trials addressing this issue.
  - In mild disease without *P. aeruginosa*, shorter courses of antibiotics may be appropriate
<table>
<thead>
<tr>
<th>Organism</th>
<th>1st line treatment</th>
<th>Duration in days</th>
<th>2nd line</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strep pneumonia</td>
<td>Amoxicillin</td>
<td>14</td>
<td>Doxycycline</td>
</tr>
<tr>
<td>H. Influenza (b lactamase negative)</td>
<td>Amoxicillin</td>
<td>14</td>
<td>Doxycycline</td>
</tr>
<tr>
<td>H. Influenza (b lactamase negative)</td>
<td>Amoxicillin/clavulanic acid</td>
<td>14</td>
<td>Doxycycline or 3rd gen cephalosporin</td>
</tr>
<tr>
<td>Moraxella catarrhalis</td>
<td>Amoxicillin/clavulanic acid</td>
<td>14</td>
<td>Doxycycline or 3rd gen cephalosporin</td>
</tr>
<tr>
<td>Staph aureus (MSSA)</td>
<td>Amoxicillin</td>
<td>14</td>
<td>Doxycycline</td>
</tr>
<tr>
<td>Coliforms for example, Klebsiella, enterobacter</td>
<td>3rd gen cephalosporin</td>
<td>14</td>
<td>FLQ</td>
</tr>
</tbody>
</table>

**Bronchiectasis Exacerbation Treatment**
# Bronchiectasis Exacerbation Treatment

<table>
<thead>
<tr>
<th>Organism</th>
<th>1st line treatment</th>
<th>Duration</th>
<th>2nd line</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>ciprofloxacin</td>
<td>14</td>
<td>Intravenous ceftazidime, aztreonam, cefepime, meropenem, pip/tazo</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Consider combining with: inhaled aztreonam or tobramycin or Colistin</td>
</tr>
<tr>
<td>MRSA</td>
<td>Doxycycline, trimethoprim</td>
<td>14</td>
<td>Vancomycin, Linezolid</td>
</tr>
</tbody>
</table>
Bronchiectasis Exacerbation Treatment

- Treatment should be prompt
- Avoid FLQ if no evidence of pseudomonas
- No evidence for use steroids
- Inhaled antibiotics should not used as monotherapy for exacerbations
- In cases of limited culture data
  - What to do?
Bronchiectasis Exacerbation
Treatment- Negative cultures

- 84 yr old retired psychiatrist referred to my clinic for Bronchiectasis, chronic productive cough (>1 yr) and weight loss.

- Underwent extensive work up before presentation:
  - Bronch (negative cultures), CT abd/pelvis, fungal serologies.

- Next step?
Bronchiectasis Exacerbation Treatment- Negative cultures

- 84 yr old retired psychiatrist referred to my clinic for Bronchiectasis, chronic productive cough (>1 yr) and weight loss.

- Underwent extensive work up before presentation:
  - Bronch (negative cultures), CT abd/pelvis, fungal serologies.

- Next step?
  - Doxycycline 100mg BID x 10 days.
  - Resulted in complete resolution of cough.
  - 4 yrs later have not needed another course of antibiotics.
Bronchiectasis Exacerbation Treatment

- Treatment should be prompt
- Avoid FLQ if no evidence of pseudomonas
- No evidence for use steroids
- Inhaled antibiotics should not used as monotherapy for exacerbations
- In cases of limited culture data
  - What to do?
    - Use antibiotic which covers the broadest of the common microbes.
      - Amoxicillin/clavulanic acid and doxycycline.
Bronchiectasis Exacerbations

Complications of Prolonged or Recurrent Episodes
Followed 2,572 patients with bronchiectasis from 10 centers in Europe. Categorized by baseline exacerbation frequency.

Frequent exacerbations were the strongest predictor of future exacerbation frequency, suggesting a consistent phenotype.

Figure 2. Exacerbation frequency during follow-up and the association with exacerbations in the previous year.

Am J Respir Crit Care Med, 2018

Published in: James D. Chalmers; Stefano Aliberti; Anna Filonenko; Michal Shteinberg; Pieter C. Goeminne; Adam T. Hill; Thomas C. Fardon; Dusanka Obradovic; Christoph Gerlinger; Giovanni Solgia; Elisabeth Operschall; Robert M. Rutherford; Katerina Dimakou; Eva Polverino; Anthony De Soyza; Melissa J. McDonnell; Am J Respir Crit Care Med 1971410-1420.
DOI: 10.1164/rccm.201711-2202OC

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Patients with frequent exacerbations at baseline had worse health status as measured by the SGRQ.
Figure 4. Follow-up hospitalization rates and annual survival in groups on the basis of baseline exacerbations.

Am J Respir Crit Care Med, 2018

Published in: James D. Chalmers; Stefano Aliberti; Anna Filonenko; Michal Shteinberg; Pieter C. Goeminne; Adam T. Hill; Thomas C. Fardon; Dusanka Obradovic; Christoph Gerlinger; Giovanni Sotgiu; Elisabeth Opschersall; Robert M. Rutherford; Katerina Dimakou; Eva Polverino; Anthony De Soyza; Melissa J. McDonnell; Am J Respir Crit Care Med' 1971410-1420.
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Complications of Bronchiectasis Exacerbation

- Increased rate of cardiovascular events in the 91 day period after an exacerbation.
  - Myocardial Infarction
  - Stroke.

Complications of Bronchiectasis Exacerbation - Summary

- Frequent exacerbations were the strongest predictor of future exacerbation frequency.
- Patients with frequent exacerbations at baseline had worse health status as measured by the SGRQ.
- Patients with two or more exacerbations per year at baseline have an independent increase in mortality risk.
- The number of hospital admissions is significantly greater for those with three or more exacerbations in the previous year than those with 2 or less.
- There is an increased rate of MI and stroke in the 91 days following an exacerbation.
Bronchiectasis Exacerbations
SUPPRESSIVE OR INHALED THERAPIES
You are seeing a 28 year old patient with bronchiectasis for follow up. They have a history of staphylococcus aureus colonization of the airways. They have had 4 bronchiectasis exacerbations requiring antibiotics in the last 12 months.

Which of the following would be the most appropriate next step in management?

A. Azithromycin daily.
B. Roflumilast daily.
C. Inhaled budesonide twice daily
D. Inhaled colistin daily
E. Inhaled DNase
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How to Prevent Exacerbations

- Our patient used many of the known interventions:
  - Long term macrolides.
  - Nebulized hypertonic saline.
  - Long term inhaled anti-pseudomonal.

- Additional Interventions to consider:
  - Pulmonary rehabilitation
  - High frequency chest wall oscillation.
Stepwise management.

**Step 1**
- Treat underlying cause
- Airways clearance techniques +/- pulmonary rehabilitation
- Annual influenza vaccination
- Prompt antibiotic treatment for exacerbations
- Self-management plan

**Step 2**
- If 3 or more exacerbations/yr despite Step 1*
  - Physiotherapy reassessment and consider mucociliary treatment

**Step 3**
- If 3 or more exacerbations/yr despite Step 2*
  - 1) If *Pseudomonas aeruginosa*, long term inhaled anti-pseudomonal antibiotic or alternatively long term macrolide
  - 2) If other Potentially Pathogenic Microorganisms, long term macrolides or alternatively long term oral or inhaled targeted antibiotic
  - 3) If no pathogen, long term macrolides

**Step 4**
- If 3 or more exacerbations/yr despite Step 3*
  - Long term macrolide and long term inhaled antibiotic

**Step 2**
- If 5 or more exacerbations/yr despite Step 4*
  - Consider regular intravenous antibiotics every 2-3 months

*Consider this step if significant symptoms persist despite previous step, even if not meeting exacerbation criteria

Antibiotics are used to treat exacerbations that present with an acute deterioration (usually over several days) with worsening local symptoms (cough, increased sputum volume or change of viscosity, increased sputum purulence with or without increasing wheeze, breathlessness, haemoptysis) and/or systemic upset. The flow diagram refers to three or more annual exacerbations.
How to Prevent Exacerbations

- Long term macrolides:
  - 3 randomized, placebo controlled showed that long term (6-12 months) macrolides vs placebo reduced bronchiectasis exacerbations frequently.

- Patients with Pseudomonas colonization and 3 or more exacerbations per year:
  - Inhaled tobramycin, aztreonam, colistin
  - Conflicting data

- Ongoing phase 3 trial:
  - ASPEN: Efficacy of Brensocatib in reducing pulmonary exacerbations in Participants With Non-Cystic Fibrosis Bronchiectasis.
Bronchiectasis Exacerbations

CHALLENGES & UNCERTAINTIES
What Triggers an Exacerbation?
What Triggers an Exacerbation? Viruses?

Nasopharyngeal swabs were tested with rPCR for several respiratory viruses in bronchiectasis patients experiencing an exacerbation and compared to those in a stable state.
- Bronchiectasis Exacerbations decreased significantly during the COVID pandemic, as shown in this graph.

Figure 1. Absolute number of patients experiencing 0, 1, 2, and 3+ exacerbations per year during the 3 years of observation (n = 147 total patients for each year).

Am J Respir Crit Care Med, 2021
Published in: Megan L. Crichton; Amelia Shoemark; James D. Chalmers; Am J Respir Crit Care Med 204:857-859.
DOI: 10.1164/rccm.202105-1137LE
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Lag-specific relative risks (RRs; 95% CI) for bronchiectasis exacerbations associated with a 10 μg·m⁻³ increase in particles with a 50% cut-off aerodynamic diameter of 10 μm (PM10) and nitrogen dioxide (NO2). 

- 10 μg·m⁻³ increase in air pollutant concentrations resulted in an increase in the relative risk of bronchiectasis exacerbations.

Pieter C. Goeminne et al. Eur Respir J 2018;52:1702557
Microbiome in Bronchiectasis

- A reduction in microbiome diversity, particularly one associated with dominance of Pseudomonas, is associated with greater disease severity, higher frequency and severity of exacerbations.

- Effect of antibiotics on microbiome diversity?
Uncertainties in Bronchiectasis Exacerbation Management

- 90 patients from the Bronchiectasis Clinic at the Royal Infirmary of Edinburgh, UK requiring IV antibiotics.
- Randomized to be in group receiving 14 days vs Bacterial Load Guided Group.
  - In the BLGG, antibiotics were stopped early if the bacterial load was $<10^6 \text{ CFU} \cdot \text{mL}^{-1}$ on day 7 or on day 10 (if not $<10^6 \text{ CFU} \cdot \text{mL}^{-1}$ on day 7)
- 88% of participants in BLGG stopped antibiotics at day 8.

RESULTS

- Nonsignificant trend for increased clinical improvement by day 21 in the 14-day group
- Time to next exacerbation was 27.5 days (12.5–60 days) in the 14-day group and 60 days (18–110 days) in the in BLGG

Pallavi Bedi et al. Eur Respir J 2021;58:2004388
**Figure 4.** Overview of a comprehensive approach to bronchiectasis management. AAT = α1-antitrypsin; ATS/IDSA = American Thoracic Society/Infectious Diseases Society of America; IgG = immunoglobulin G; HRCT = high-resolution computed tomography; NTM = nontuberculous mycobacteria. *A 2-week course is suggested.

Am J Respir Crit Care Med, 2013
https://www.atsjournals.org/doi/abs/10.1164/rccm.201303-0411CI
Published in: Pamela J. McShane; Edward T. Naureckas; Gregory Tino; Mary E. Strek; Am J Respir Crit Care Med 188:647-656.
DOI: 10.1164/rccm.201303-0411CI
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Bronchiectasis Exacerbations

Summary

- Definition of a Bronchiectasis Exacerbation
- Antibiotic treatment of an exacerbation based on microbiology
- Mortality, quality of life and other complications increased with exacerbations
- Strategies to reduce rate of exacerbations
- Uncertainties/Challenges:
  - Viruses
  - Air pollution
  - Long term effect of antibiotics on the microbiome
Bibliography


Evidence is primarily based on expert consensus and recent guidelines recommend antibiotic durations of approximately 14 days:


Bacterial load-guided therapy is feasible in most exacerbations requiring intravenous antibiotics. There was a nonsignificant trend for increased clinical improvement by day 21 with 14 days of antibiotics compared with bacterial load-guided therapy. However, paradoxically, there was a prolonged time to next exacerbation in the BLAGG.


AIRWAY CLEARANCE

Jeff Tarnow, RRT, RCP
Bronchiectasis and Pulmonary NTM Clinical Program
Lung Health Center, UCSF
I have no Conflicts of Interests or any Financial Disclosures
OUTLINE

- Discuss PEP and Oscillating PEP
- Order of Inhaled Medications
- Compressors and Nebulizers
- High Frequency Chest Wall Oscillation (HFCWO)/Vest
“Getting secretions out of the respiratory tract has been likened to getting ketchup out of a Bottle: Turn it upside down, thump it on the Back several times, and a splash of desired Materials usually appears”
BREAKING THE CYCLE: AIRWAY CLEARANCE

Proximal Airways

- Cough Augmentation
  - Cough assist
  - Insufflation/Exsufflation
  - Non-invasive ventilation (NIPPV)
  - Air stacking
  - Glossopharyngeal breathing (GBP)

- Flow Acceleration
  - Venturi

Distal Airways

- High Frequency Chest Wall Oscillation
- Positive Expiratory Pressure
- Breathing Exercises
  - Active Cycle (ACBT)
  - Autogenic Drainage

Conventional

- Manual
- Position

PEP
- Pari PEP
- Thera PEP
- Mask

OPEP
- Flutter
- Acapella
- Aerobika
- Lung Flute

Hillrom: Monarch, Conventional
Electromed: Smartvest
Philips: InCourage

Adapted from Belli et al, 2021. Front Med; 8:544826
BREAKING THE CYCLE: AIRWAY CLEARANCE

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  - Electromed: Smartvest
  - Philips: InCourage

- OPEP
  - Flutter
  - Acapella
  - Aerobika
  - Lung Flute

- Cycle (ACBT)
  - Manual
  - Position

Average Time for Treatment: 2 hours a day!

Adapted from Belli et al, 2021. Front Med; 8:544826
PERCUSSION AND VIBRATION

Hand positioned 3 inches from chest (2)

Strike chest in waving movement (1)
ALTERNATIVES TO PDP&V

- Positive Expiratory Pressure (PEP)
- Oscillating PEP
- High Frequency Chest Wall Oscillation (HFCWO)
- Volara System: Oscillation & Lung Expansion
AIRWAY CLEARANCE

- Decrease sputum production with low risk\(^1\)
- No one therapy shown to be improved from other
- Patient dependent

OSCILLATING PEP
(FLUTTER® VALVE/AIRPHYSIO
ACAPELLA CHOICE® ACAPELLA®)
PEP & ACAPELLA

Can ONLY be cleaned
NOT Sterilized

Can be Sterilized
but will corrode
Can cause air trapping as flow decreases
Simplified concept of different expiratory maneuvers:
Airway-mucus plug-alveolus

A) PEP: No airway compression; airway dilated away from mucus plug

B) FET: Forced expiratory technique.
Risk of early airway closure downstream of mucus plug

C) AD: Autogenic drainage.
Attempt to keep compressed segment upstream of mucus plug
### INHALED MEDICATIONS

#### Bronchodilators
- Can be done In-Line, and okay to wear vest
- Pretreatment Options
  - Albuterol/Levoalbuterol MDI
  - Ipratropium – *is drying*
  - Nebulized – *takes longer*
- Take long-acting bronchodilators AT VERY END OF REGIMEN

#### Mucolytics
- Can be done In-Line, and okay to wear vest
- Options
  - Hypertonic Saline: Preferred is 7% - 3% if hyperactive airways
  - NAC/Mucomyst:
    - *Not yet shown to be beneficial*
    - *Do not use with hyperactive airways*
    - *Must draw from a vial*
  - Dornase: Harmful in those without cystic fibrosis
    - Increase exacerbations (relative risk 1.35), increase decline in FEV1 (decline of 1.7% vs 3.6%)

#### Antibiotics
- Separate nebulizer
- Options
  - Tobramycin
  - Aztreonam
  - Colistin: must draw from vial
  - Amikacin

---

GENERIC COMPRESSOR & NEBULIZER

Compressor has small motor will burn out quickly; Not meant for multiple treatments a day

Nebulizer can ONLY be cleaned NOT sterilized
PREFERRED: CAN BE CLEANED, STERILIZED, AND CONNECT TO AEROBika

- PRONEBmax
- PARI
- Ombra
- Aeroclipse XL
PORTABLE MESH NEBULIZERS

- EFlow
- PariTrek S
- Philips Innospire
OPTIMAL SETUP
HIGH FREQUENCY CHEST WALL OSCILLATION (HFCWO)
BAXTER/HILL-ROM

- Developed by Dr. Warwick
- Vest comes in 25 sizes
- Programmable controls
- Treatments last 30 min. QD/BID
- Can give bronchodilators before/during
BAXTER/HILL-ROM MONARCH
ELECTROMED/SMARVEST

- Also developed by Dr. Warwick
- Vest comes in various sizes
- Programmable controls
- Can give bronchodilators before/during
- Is another option but bladder is less efficient
- Treatments last 30 min. QD/BID
- Weighs 3.3 pounds
PHILIPS RESPIRTECH/INCOURAGE

- Also developed by Dr. Warwick
- Can obtain a customizable garment
- Program is easy to use
- Treatments are similar (QD/BID, with or without nebulization)
WRAPS
BAXTER HILL-ROM/VOLARA

- Oscillation and Lung Expansion
- Easy to use, can nebulize concurrently
- Not covered by medicare!
CONCLUSION

- Airway treatment focuses on etiology, treatment of infections, and airway clearance
- Time consuming and must adjust to patient
- Preferred is Aerobika/oscillatory PEP with active cycling breathing and huff cough
- Add in positional changes focused on patients disease pattern
- Always encourage Exercise
- High frequency chest well oscillation (HFCWO/Vest) has multiple options
- If all else fails or pending patient, consider other options such as manual percussion, vibration (ex. Tuning forks)
CYSTIC FIBROSIS: SCREENING AND HETEROZYGOUS PATIENTS

Alyssa A. Perez, MD MEd and Vicki Jue, PharmD
UCSF Adult Cystic Fibrosis Program
March 7th, 2024
RELEVANT FINANCIAL DISCLOSURES

- We have the following relationships with ACCME defined ineligible companies:
  - None

- We WILL discuss off-label use and/or investigational use of any drugs or devices.
CASE

- 58F with history of mild bronchiectasis and pulmonary nodule
  - MAC diagnosed in 2018 via biopsy of pulmonary nodule
  - Not treated due to minimal symptoms

- Referred to CF clinic at our center in 2023
CF REVIEW OF SYSTEMS?

- Respiratory symptoms
- HEENT
- GI symptoms
- Liver
- Weight
- Fertility
- Microbiology history
- Family History
- Genetic testing

- +Cough, + x1 hemoptysis, +bronchiectasis, normal spirometry, no h/o recurrent infections
- No sinusitis or nasal polyps
- No h/o SBO, constipation, oily stool, GERD, pancreatitis, normal fecal elastase + vitamin ADEK
- Normal LFTs
- Never underweight
- No issues getting/staying pregnant
- +MAC, no pseudomonas, no Burkholderia
- Daughter w/ CF (DelF508/C524X) s/p LTx
- 1 disease causing mutation: DelF508
CF CARRIER, CFTR RELATED DISORDER, OR CF DISEASE?

- 1 known disease-causing mutation
- +Bronchiectasis
- +MAC
- Normal lung function
- No other signs/symptoms of CF on ROS

- CFTR dysfunction?
CFTR RELATED DISORDER VS CYSTIC FIBROSIS DISEASE

CFTR related Disorder (CFTR-RD)

• *Single organ manifestation of CF
• **CFTR dysfunction in CFTR-RD range**
  o In CFTR-RD range in 2 different functional tests (sweat, NPD, ICM)
  o 1 CFTR variant + CFTR dysfunction in 2 functional tests
  o 2 CFTR variants known to reduce CFTR function (at most 1 CF-causing variant)

• **Exclusion of CF:**
  o CF clinical manifestations
  o +Newborn screening
  o +Sibling with CF
  o Positive sweat chloride (> = 60 mmol)
  o 2 CF disease causing mutations

Cystic Fibrosis Disease

• Symptoms of CF (multi-organ)
• Elevated sweat chloride ( > = 60 mmol/L)
  o = Evidence of CFTR dysfunction in the CF disease causing range
• *2-disease causing variants in the CFTR gene

NEXT STEPS IN EVALUATION?

• Sweat Chloride
  • 56 mmol/L (intermediate)

• Genetic Testing
  • DelF508
  • Heterozygous for 7T/9T alleles
DIAGNOSIS?
CFTR RELATED DISORDER (CFTR-RD)

- Single organ involvement (lungs)
- 1 disease causing mutation identified
- CFTR dysfunction present but not at threshold for CF diagnosis
- Does not meet diagnostic criteria for CF disease
GENETIC TESTING FOR CYSTIC FIBROSIS

- Low threshold to send genetic testing in bronchiectasis evaluation

- Our practice is to send Invitae Cystic Fibrosis Test (+ sweat chloride)
  - Invitae
    - CF Test analyzes CFTR gene: CF, CAVD, hereditary pancreatitis
    - +/- PCD Panel: 42 genes
  - Blueprint

- If high suspicion for CF but only 1 mutation identified, we consider:
  - Mutation Analysis Program (MAP)
  - Next generation sequencing (whole exome sequencing)
OVERVIEW OF CFTR MODULATORS

- 2011: Ivacaftor, G551D
- 2015: Lumacaftor/Ivacaftor, homozygous DelF508
- 2018: Tezacaftor/Ivacaftor, homozygous DelF508

- 2019: Elexacaftor/Tezacaftor/Ivacaftor "The Triple"
  - Approved for single copy of DelF508
CFTR MODULATORS IN CFTR-RD

- Off label
- May have benefit
- How to get them?
TRANSITIONS OF CARE

**Definition of Transitions of Care**

- Per CMS, Transitions of Care (TOC) is the movement of a patient from one setting of care (hospital, ambulatory primary care practice, ambulatory specialty care practice, long-term care, home health, rehabilitation facility to another\(^1\)

**Challenges include:**

- Prescription errors
- Unable to fill medications
- Lack of communication between health care providers
- Lack of patient understanding of disease state, medications, and follow-up required
- Hospital readmission
OBTAINING AUTHORIZATION PULMONARY MEDICATIONS

Checklist includes:

- Provider’s progress notes - rationale for needing the medication
- ICD-10 codes
- Genetic mutation testing
- Necessary baseline labs, i.e., liver panel, CK, creatinine etc.
- Baseline pulmonary function tests (PFTs)
- Cultures
- Medications tried and failed
- Allergies to medications
- Primary literature support for non-FDA approved indications
- Results from participating in studies
PHARMACY TOC ACTIVITIES

TOC activities include:
- Confirm medication insurance coverage
- Follow-up on medication coverage at preferred pharmacy
- Submit medication Prior Authorizations (PAs)
- Submit medication Letters of Appeals (LOAs)
- Submit patient written LOAs
- Follow-up on copays
- Assist with copay cards, grants, Patient Assistant Programs (PAPs), Community Benefit Program (CBP)/340B, etc.
- Assist with authorization for medications administered in clinic
- Standardize documentation in the electronic system
TOC PHARMACY TECHNICIAN

Utilize pharmacy technician to practice at the top of their license:

- Expediting medication access by assisting with all TOC activities except LORs
- Updating patients on status via electronic chart messaging or phone call
- Reconnecting patient info back to providers as needed for further follow-up
6/2020-2023
Provider grant to support pharmacist every other Mon to see patients/TOC activities

2020-2023
Funding by Pharmaceutical Services, UCSF Ambulatory Pharmacy and Pulmonary Clinic for a Cystic Fibrosis (CF) pharmacy technician every Tue & every other Wed

2023-2024
Funding by UCSF Ambulatory Pharmacy and Pulmonary Clinic for a Pulmonary pharmacy technician to cover Bronchiectasis and CF clinic every Tue and Wed
PHARMACIST'S ROLES IN TOC ACTIVITIES

- Precept the pharmacy technician/learner
- Suggest and adjust doses
- LOAs
- Monitor side effects
- Patient education
Patient started on ETI
- Developed a rash necessitating dose reduction
- Now on reduced dose: 1 orange tab in AM, 1 blue tab in PM
- Improvement in cough and chest congestion
CONCLUSIONS

- Diagnosis of CFTR-RD is not straightforward
  - Refer to CF center
  - Send genetic testing + sweat chloride

- There may be benefit to using CFTR modulators in CFTR-RD

- Takes a team to get these medications for our patients!

- Recommendations for initiation of CFTR modulators:
  - Start slow – at reduced dose
  - Older / CFTR-RD patients may not require full dose ETI to have benefit
QUESTIONS?
Motile Ciliopathies

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Associate Director for Translational Research,
Center for Excellence in Pulmonary Biology,
Stanford University
Presenter Disclosure Slide

• Research Support: NIH (NHLBI, NIDDK), CF Foundation, CF Research Institute, mCHRI (Stanford)

• Support for Clinical Trials by the Pharmaceutical Industry: Vertex, Eloxx, Insmed, Respirion, Clarametyx, Aztra-Seneca

• Ad hoc consultatnships and advisory boards: Vertex

• Corporate activity: Alentar Biosciences, MCC Therapeutics, laterion, Al-rway
When Cilia Go Bad: Defects and Ciliopathies

Fliegauf M et al Nat Rev 2007
Ciliary Axoneme Cross-sectional Structure
Primary Ciliary Dyskinesia (PCD)
(Inmotile Cilia, Kartagener’s Syndrome)

- Product of defective ciliary function
- Recurrent and/or chronic Infections of the respiratory tract: recurrent Pneumonia, chronic atelectasis, bronchiectasis, chronic sinusitis, chronic otitis media.
- Male Infertility, ectopic pregnancy
- ~50% situs inversus (Kartagener).
- Estimated Prevalence U.S.A.: ~1:15,000
- Definitive Diagnosis: Demonstrating consistent structural defects in ciliary apparatus
- From a Genetic perspective, heterogeneous disorder (usually recessive), growing list of genes associated.
Classic PCD: Clinical features

- Chronic rhinorrhea
- Chronic secretory otitis media, often with hearing loss
- Chronic sinusitis
- Recurrent URI/LRI since early childhood
- Chronic bronchitis leading to bronchiectasis
- Male infertility
Traditional Diagnostic Tools

  - Obtained by nasal scrape or bronchial brush
  - Normal structural appearance by EM not enough to rule out PCD
- Ciliary Beat Frequency in freshly isolated cells.
  - High-Speed Video Microscopy (HVM) at specialized centers can be of value for difficult cases.
Abnormalities in Cilia Structure which **can be** Identified by EM

- Complete or partial absence of the ODA
- Combined ODA and IDA defects
- Microtubular disorganization defects
- Isolated IDA should not be made by single EM alone (false positive)
- Only a small set of radial spoke defects

Leigh, 2009
Abnormalities in Cilia Structure which can NOT be Identified by EM

- Defects of nexin link components
- Central Pair components
- Ciliary biogenesis defects
- Defects caused by DHAH11 gene mutations
- Some Radial Spoke head proteins

Leigh, 2009
Difficulties with HSVM

- Protocol differ among centers
- Objective methods to distinguish cilia beat pattern
- PCD variants may be misinterpreted as normal
- Changes due to inflammation
Immunofluorescence

- Fluorescent antibodies staining to ciliary
- Electron Tomography (shorter outer dynen arms, partial structures)
Development of Clinical Diagnostic Criteria for PCD

- 703 patients referred for PCD suspicion
- 241 (34%) Confirmed Diagnosis
- 253 (36%) Alternative Diagnoses
- 209 (30%) Probable Diagnosis

Leigh M. et al, ATS 2012
Development of Clinical Diagnostic Criteria for PCD

5 Clinical Criteria identified:

- Unexplained Neonatal Respiratory distress.
- Chronic Productive cough with early life onset.
- Chronic nasal congestion with early life onset.
- Recurrent Otitis first two years of life.
- Laterality defect.

4 or more present = 97% specificity
Distinguishing features of PCD: Neonates and infants

- Neonatal respiratory distress, especially in term infants, with no obvious cause (tachypnea, TTN, “wet lung”, atelectasis)
  - ~75% of those with confirmed PCD
- Rhinitis – neonatal onset, persistent (“born with a cold”)
- Situs inversus
- Heterotaxy syndromes including congenital heart disease
ATS Diagnostic Algorithm for Suspect PCD

At least 3 of the 4 key clinical features for PCD
- Unusual mucociliary clearance
- Dysnasal speech
- Repeated respiratory infections
- Spontaneous pneumothorax

If present, proceed with PCD testing.

Yes

No

PCD unlikely

Access to NBD testing (with chemiluminescence device and standardized protocol) at specialty center
AND Cooperative patient, 15 years old, capable of performing VFT testing maneuver

Yes to both

(preferential pathway)

No to either

Extended genetic testing panel

Extended genetic testing panel

Diagnosis of PCD

- Unusual mucociliary clearance
- Dysnasal speech
- Repeated respiratory infections
- Spontaneous pneumothorax

Diagnosis of PCD

- Unusually low 11β-HSD1 activity
- Absent ciliary cilia to daily sputum

Electron microscopy of ciliated structure

- Normal ciliary structure
- Inadequate samples or insufficient analysis

Unknown

Consider repeat TEM or referral to PCD specialty center

Diagnosis of PCD

- Identified ciliary structural defect

Diagnosis of PCD
Nasal nitric oxide levels are low in PCD
(age $\geq$ 5 years)
nNO in Pediatric Patients (>5 yrs) with Confirmed PCD

Disease Specific cut-off:
< 77 nL/min
Sens. 0.98
Spec. >0.999

Leigh M et al, 2013
Genes associated with PCD

<table>
<thead>
<tr>
<th>Defect</th>
<th>Gene</th>
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<tbody>
<tr>
<td>ODAs or ODA docking complex (ODA-DC)</td>
<td>DNAH5 [MIM 603335]</td>
</tr>
<tr>
<td></td>
<td>DNAH9 [MIM 618300]</td>
</tr>
<tr>
<td></td>
<td>DNAH11 [MIM 603339]</td>
</tr>
<tr>
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<td>CCDC114 [MIM 615038]</td>
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<td>CCDC151 [MIM 615956]</td>
</tr>
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<td>DNAI1 [MIM 610062]</td>
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<td>DNAI2 [MIM 605483]</td>
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<td>NME8 [MIM 607421]</td>
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<td>ARM4 [MIM 615408]</td>
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<td>TTC25 [MIM 617092]</td>
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<tr>
<td>Combined ODA and IDA Deficiency</td>
<td>ODAD1 [MIM 615067]</td>
</tr>
<tr>
<td></td>
<td>ODAD2 (ARM4) [MIM 615451]</td>
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<tr>
<td></td>
<td>SPAG1 [MIM 603395]</td>
</tr>
<tr>
<td></td>
<td>DNAAF1 [MIM 613190]</td>
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<tr>
<td></td>
<td>DNAAF2 [MIM 612517]</td>
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<td></td>
<td>HEATR2 [MIM 614864]</td>
</tr>
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<td></td>
<td>DNAAF3 [MIM 614566]</td>
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<td>DXYC1C [MIM 608706]</td>
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<td>ZMYND10 [MIM 607070]</td>
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<td></td>
<td>LRRC6 (DNAAF11) [MIM 614930]</td>
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<td></td>
<td>C21orf59 [MIM 615494]</td>
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<td>PIH1D3 [300991]</td>
</tr>
<tr>
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<td>CFAP298 [MIM 615500]</td>
</tr>
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<td>CFAP300 [MIM 618063]</td>
</tr>
<tr>
<td></td>
<td>CCDC103 [MIM 614677]</td>
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<tr>
<td>Nexin-Dynein regulatory complex</td>
<td>CCDC39 [MIM 613798]</td>
</tr>
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<td>CCDC40 [MIM 613799]</td>
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<td></td>
<td>CCDC65 [MIM 611088]</td>
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<td>DRC1 (CCDC164) [MIM 615288]</td>
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<tr>
<td>Radial Spokes</td>
<td>RSPH1 [MIM 609314]</td>
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<td>RSPH3 [MIM 616481]</td>
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<tr>
<td></td>
<td>RSPH4A [MIM 612647]</td>
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<tr>
<td></td>
<td>RSPH9 [MIM 612648]</td>
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<tr>
<td>Central Pair</td>
<td>HYDIN [MIM 610812]</td>
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<td>STK36 [MIM 607652]</td>
</tr>
<tr>
<td></td>
<td>DNAJB13 [MIM 617091]</td>
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<tr>
<td>Normal Ultrastructure</td>
<td>SPEF2 [MIM 610172]</td>
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<tr>
<td></td>
<td>FOXJ1 [MIM 602291]</td>
</tr>
<tr>
<td></td>
<td>GAS2L2 [MIM 618449]</td>
</tr>
<tr>
<td></td>
<td>GAS8 [MIM 616726]</td>
</tr>
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<td></td>
<td>LRRC56 [MIM 618254]</td>
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<td></td>
<td>CCDC65 [MIM 6151504]</td>
</tr>
<tr>
<td></td>
<td>CFAP221</td>
</tr>
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<td></td>
<td>OFD1</td>
</tr>
<tr>
<td>Oligocilia</td>
<td>MCIDAS</td>
</tr>
<tr>
<td></td>
<td>CCNO [MIM 615872]</td>
</tr>
<tr>
<td>Syndromic</td>
<td>RPGR (MIM 312610) – X linked</td>
</tr>
<tr>
<td></td>
<td>OFD1 (MIM 300170) – X linked</td>
</tr>
<tr>
<td></td>
<td>Cri-du-chat (5p)</td>
</tr>
</tbody>
</table>
Global prevalence of having autosomal recessive PCD is at least 1:7,554!!

1:9,906 in African or African American; 1:10,388 in non-Finnish European; 1:14,606 in east Asian; 1:16,309 in Latino
PCD: Ultrastructural defect and Lung Function Trajectory

A

FEV₁ (percent predicted)

Age (years)

B

FEF₂₅−₇₅ (percent predicted)

Age (years)
Clinical Criteria Based PCD Diagnosis

- **Neonatal respiratory distress**
  - yes: Supplemental O2 requirement ≥ 1d
    - yes: Meconium aspiration
      - yes: Sensitivity: 57% Specificity: 89%
      - no: Sensitivity: 57% Specificity: 89%
    - no: Sensitivity: 81% Specificity: 68%
  - no: Term gestation
    - yes: Year-round
      - yes: Wet cough
        - yes: Began ≤ 6m of age
          - yes: Sensitivity: 74% Specificity: 60%
          - no: Sensitivity: 62% Specificity: 74%
        - no: Began ≤ 6m of age
          - yes: Sensitivity: 74% Specificity: 60%
          - no: Sensitivity: 62% Specificity: 74%
      - no: Sensitivity: 97% Specificity: 17%
    - no: Sensitivity: 97% Specificity: 17%
- **Chronic cough**
  - yes: Sensitivity: 97% Specificity: 17%
  - no: Year-round
    - yes: Wet cough
      - yes: Began ≤ 6m of age
        - yes: Sensitivity: 74% Specificity: 60%
        - no: Sensitivity: 62% Specificity: 74%
      - no: Sensitivity: 97% Specificity: 17%
    - no: Sensitivity: 97% Specificity: 17%
- **Chronic nasal congestion**
  - yes: Sensitivity: 97% Specificity: 19%
  - no: Year-round
    - yes: Sensitivity: 97% Specificity: 17%
    - no: Sensitivity: 97% Specificity: 17%
- **Situs inversus totalis**
  - yes: Sensitivity: 46% Specificity: 92%
  - no: Other laterality defects
    - yes: Sensitivity: 53% Specificity: 85%
    - no: Sensitivity: 53% Specificity: 85%
## Neonatal Cohort: Characteristics of study participants

<table>
<thead>
<tr>
<th></th>
<th>Overall (n = 123)</th>
<th>ODA (n = 51)</th>
<th>ODA/IDA (n = 19)</th>
<th>IDA/CA/MTD (n = 34)</th>
<th>Normal EM (n = 10)</th>
<th>Isolated CA (n = 5)</th>
<th>Oligocilia* (n = 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age at diagnosis, year, mean (SD)</strong></td>
<td>4.24 (3.90)</td>
<td>5.07 (4.48)</td>
<td>3.39 (3.40)</td>
<td>2.86 (3.12)</td>
<td>5.75 (2.93)</td>
<td>6.40 (3.29)</td>
<td>2.88 (1.44)</td>
</tr>
<tr>
<td><strong>FEV₁ z-score at enrollment, mean (SD)</strong></td>
<td>−1.46 (1.56)</td>
<td>−0.95 (1.45)</td>
<td>−1.35 (1.60)</td>
<td>−2.38 (1.50)</td>
<td>−1.18 (1.41)</td>
<td>−1.61 (0.79)</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Clinical features, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laterality defect</td>
<td>60 (48.8%)</td>
<td>29 (56.9%)</td>
<td>9 (47.4%)</td>
<td>16 (47.1%)</td>
<td>6 (60.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Neonatal respiratory distress</td>
<td>99 (80.5%)</td>
<td>40 (78.4%)</td>
<td>17 (89.5%)</td>
<td>29 (85.3%)</td>
<td>8 (80.0%)</td>
<td>3 (60.0%)</td>
<td>2 (50.0%)</td>
</tr>
<tr>
<td><strong>Exposure variables, median (range)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>neonatal-LOS, d, median (range)</td>
<td>9 (1 to 90)</td>
<td>8 (1 to 35)</td>
<td>10 (1 to 21)</td>
<td>11.5 (1 to 90)</td>
<td>7 (1 to 14)</td>
<td>10 (1 to 12)</td>
<td>7.5 (1 to 17)</td>
</tr>
<tr>
<td>SuppO₂, d, median (range)</td>
<td>5 (0 to 180)</td>
<td>5 (0 to 90)</td>
<td>5 (0 to 180)</td>
<td>8.5 (0 to 180)</td>
<td>0 (0 to 10)</td>
<td>0 (0 to 9)</td>
<td>5 (0 to 180)</td>
</tr>
</tbody>
</table>
Neonatal Respiratory distress by ultrastructure group
(with associated genes listed in order of prevalence)

<table>
<thead>
<tr>
<th></th>
<th>ODA (n=213)</th>
<th>ODA/IDA (n=90)</th>
<th>IDA/MTD (n=87)</th>
<th>DNAH11 (n=38)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DNAH5, DNAI1, CCDC103, DNAI2, CCDC114, ARMC4</td>
<td>DNAAF4, SPAG1, DNAAF3, DNAAF1, DNAAF5, LRRC6, ZMYND10, DNAAF2, CFAP300, CFAP298, PIH1D3</td>
<td>CDC40, CDC39</td>
<td>HYDIN, RSPH1, RSPH4A, CCNO, CCDC164, CFAP221, NEK10, RPGR, CCDC65, FOXJ1, CFAP57, GAS2L2, OFD1, RSPH3, RSPH9</td>
</tr>
<tr>
<td>Age, median, y (IQR)</td>
<td>11.8 (6.4, 27.3)</td>
<td>12.9 (2.7, 28.4)</td>
<td>11.3 (3.9, 23.7)</td>
<td>12.4 (5.6, 24.6)</td>
</tr>
<tr>
<td>Sex, female (%)</td>
<td>115 (54.0%)</td>
<td>48 (53.3%)</td>
<td>55 (63.2%)</td>
<td>28 (73.7%)</td>
</tr>
<tr>
<td>Race, white (%)</td>
<td>179 (84.0%)</td>
<td>68 (75.6%)</td>
<td>72 (82.8%)</td>
<td>25 (65.8%)</td>
</tr>
<tr>
<td>Respiratory distress</td>
<td>70.2%</td>
<td>75.9%</td>
<td>81.0%</td>
<td>36.8%</td>
</tr>
</tbody>
</table>

Barber et al, ATS 2022
Association between NICU LOS but not Supplemental oxygen with lung function later in life in PCD

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Sample Size</th>
<th>Regression Coefficient (per day)</th>
<th>95% CI</th>
<th>SE</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>NICU-LOS</td>
<td>n = 123</td>
<td>-0.27</td>
<td>-0.53 to -0.01</td>
<td>0.13</td>
<td>0.04</td>
</tr>
<tr>
<td>SuppO(_2)</td>
<td></td>
<td>0.07</td>
<td>-0.01 to 0.16</td>
<td>0.04</td>
<td>0.09</td>
</tr>
</tbody>
</table>

Wee et al, Ann ATS 2022
Chest Xray
(week 2 of life)
**Situs distribution by ciliary ultrastructural group**

<table>
<thead>
<tr>
<th>Ciliary ultrastructure</th>
<th>SS (n=286)</th>
<th>SIT (n=215)</th>
<th>SA (n=58)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ODA defect (n=242)</td>
<td>96 (39.7%)</td>
<td>113 (46.7%)</td>
<td>33 (13.6%)</td>
</tr>
<tr>
<td>ODA/IDA defect (n=96)</td>
<td>40 (41.7%)</td>
<td>43 (44.8%)</td>
<td>13 (13.5%)</td>
</tr>
<tr>
<td>IDA/MTD defect (n=96)</td>
<td>52 (54.2%)</td>
<td>36 (37.5%)</td>
<td>8  (8.3%)</td>
</tr>
<tr>
<td>DNAH11 (n=43)</td>
<td>19 (44.2%)</td>
<td>20 (46.5%)</td>
<td>4  (9.3%)</td>
</tr>
<tr>
<td>Normal/near normal/other (n=82)</td>
<td>79 (96.3%)</td>
<td>3  (3.7%)</td>
<td>0</td>
</tr>
</tbody>
</table>

Barber et al, Ann ATS In Press
Therapeutic Landscape

• Current SOC guidelines focused on symptom control:
  • ACT, Episodic Abx, chronic macrolides
• Disease modifying therapies in the horizon in the form of mRNA therapies:
  • ReCode: Targets DNAI1 gene defects – Phase I NCT05737485
  • Ethris GmbH: Targets CCDC40 gene defects – pre clinical
MAC Lung Disease

Alicia A. Mirza, MD
Clinical Assistant Professor
Stanford University

MAC-LD = *Mycobacterium avium* complex lung disease
RELEVANT FINANCIAL DISCLOSURES

• I have the following relationships with ACCME defined ineligible companies:
  • None

• I WILL NOT discuss off-label use and/or investigational use of any drugs or devices.
Case

70-year-old female
Diagnosis of asthma, HL
BMI 22
Retired teacher, nonsmoker
Shortness of breath with occasional cough for a few years
Meds: ICS/LABA, statin
Developed scant hemoptysis
Next Step?

A. Sputum cultures
B. Bronchoscopy
C. Antibiotics
D. Steroids
E. Monitor
Case

Expectorated sputum x3 grew 2/3 cultures positive for smear positive *Mycobacterium avium* complex.

AFB Culture, Respiratory

Status: Edited Result - FINAL  Visible to patient: Yes (seen)  Dx: Pulmonary Mycobacterium avium complex...

Specimen Information: Sputum, Expectorated: Resp, Lower

0 Result Notes

Culture, AFB

AFB identified as: *Mycobacterium avium complex* !

detected in liquid medium.

(by PCR/nucleic acid amplification) NOTE: This test was developed and its performance characteristics determined by Stanford Clinical Micro/Viro Lab. It has not been cleared or approved by the U.S. Food and Drug Administration. Such approval is not required for test validated by the performing laboratory.

Complex members include M. avium subspecies and M. intracellulare.
MAC:
Leading Cause of NTM Pulmonary Disease Globally

~20,000 patients from 30 countries across 6 continents

Independent Predictors of Disease Progression

**M. intracellulare**

**BMI \(\leq 20 \text{ kg/m}^2\)**

Initial fibrocavitary pattern
Does our patient have NTM lung disease?

A. Yes, sputum results, imaging, and symptoms fit the diagnostic criteria
B. Probably, but requires a bronchoscopy to confirm diagnosis
C. No, her normal BMI and lack of severe bronchiectasis means she does not have the required symptoms
Treatment of Nontuberculous Mycobacterial Pulmonary Disease: An Official ATS/ERS/ESCMID/IDSA Clinical Practice Guideline

Charles L. Daley,1,2,a Jonathan M. Iaccarino,3 Christoph Lange,4,5,6,7,a Emmanuelle Cambau,8,a Richard J. Wallace, Jr,8,a Claire Andrejak,9,11 Erik C. Böttger,12 Jan Brozek,13 David E. Griffith,14 Lorenzo Guglielmetti,8,15 Gwen A. Hutt,1,2 Shandra L. Knight,16 Philip Leitman,17 Theodore K. Marras,18 Kenneth N. Olivier,19 Miguel Santin,20 Jason E. Stout,21 Enrico Tortoli,22 Jakko van Ingen,23 Dirk Wagner,24 and Kevin L. Winthorp25
Diagnosis of NTM Disease

- Clinical
- Radiographic
- Microbiologic
Diagnosis of NTM Disease

**Clinical & radiographic** (all required)

1. Pulmonary or systemic **symptoms**

2. **Nodular** or cavitary opacities on chest radiograph or **bronchiectasis with multiple small nodules** on high-resolution computed tomography

3. Appropriate **exclusion** of other diagnoses

Diagnosis of NTM Disease

**Microbiologic:**

1. Positive culture from at least 2 separate expectorated sputum samples of the same species

2. Positive culture result from at least 1 bronchial wash or lavage

3. Transbronchial or other lung biopsy with mycobacterial histopathologic features (granulomatous inflammation or AFB) and positive culture for NTM (tissue, sputum, or BAL)

Adjustment to current medications?

A. Stop statin due to risk of hepatotoxicity
B. Add Bactrim for PJP prophylaxis
C. Stop ICS/LABA due to possible side effects
D. Add aspirin for stroke prevention
Inhaled corticosteroids predispose patients with chronic LD to NTM infections.


Do all cases of MAC-LD require antibiotic treatment?

A. Yes
B. No
The decision to treat is complex.

Consider patient:

1. comorbidities
2. prognosis
3. preferences

cavitary MAC-LD has increased mortality
### Natural History

<table>
<thead>
<tr>
<th>Year</th>
<th>Study Details</th>
<th>Progression Rate</th>
<th>Treatment Rate</th>
<th>Stable Rate</th>
<th>Spontaneous Sputum Conversion Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>2017</td>
<td>488 treatment-naïve MAC-LD pts</td>
<td>60% progressed in 3 years and got antibiotics</td>
<td>25% remained stable and untreated</td>
<td>50% of the stable patients had spontaneous sputum conversion</td>
<td></td>
</tr>
<tr>
<td>2019</td>
<td>551 pts with MAC-LD NO fibrocavitary disease</td>
<td>60% progressed &amp; got treatment within 3 years and got antibiotics</td>
<td>40% remained stable and untreated</td>
<td>50% of the stable patients had spontaneous sputum conversion</td>
<td></td>
</tr>
</tbody>
</table>

---


Which susceptibility affects the antibiotic treatment regimen?

A. Macrolide
B. Rifampin
C. Ethambutol
D. All of the above
E. None of the above
If Macrolide-susceptible

**OPT FOR:**

- A 3-drug regimen that includes a macrolide over a 3-drug regimen without a macrolide in macrolide-susceptible disease (*strong* recommendation, very low certainty in estimates of effect)

- Azithromycin-based treatment regimens rather than clarithromycin-based regimens (*conditional* recommendation, very low certainty in estimates of effect)

Antibiotic Regimen for Macrolide-susceptible MAC-LD

<table>
<thead>
<tr>
<th>No. of Drugs</th>
<th>Preferred Regimen</th>
<th>Dose</th>
<th>Dosing Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Azithromycin (clarithromycin)</td>
<td>500 mg/d (1000 mg/d) 600 mg/d (300 mg/d)</td>
<td>? mg/kg/d</td>
</tr>
<tr>
<td></td>
<td>Rifampicin (rifabutin) Ethambutol</td>
<td>? mg/kg/d</td>
<td>?</td>
</tr>
</tbody>
</table>

Nguyen M, Daley C. Treatment of Mycobacterium avium Complex Pulmonary Disease. Clinics in Chest Medicine, 2023-12-01, Volume 44, Issue 4, Pages 771-783
What factor determines 3x weekly vs daily dosing?

A. Smear positive vs smear negative
B. MAC subspecies
C. Noncavitary vs cavitary disease
D. Patient age
A thrice-weekly, 3-drug regimen, is advised for patients without cavitary disease.

Studies have demonstrated similar efficacy and better tolerance when compared with daily administration.

Antibiotic regimens for Macrolide-susceptible MAC-LD

<table>
<thead>
<tr>
<th>Type of Disease</th>
<th>No. of Drugs</th>
<th>Preferred Regimen</th>
<th>Dose</th>
<th>Dosing Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nodular-bronchiectatic</td>
<td>3</td>
<td>Azithromycin (clarithromycin) Rifampicin (rifabutin) Ethambutol</td>
<td>500 mg/d (1000 mg/d) 600 mg/d (300 mg/d) 25 mg/kg/d</td>
<td>3 times weekly</td>
</tr>
<tr>
<td>Cavitary</td>
<td>≥ 3</td>
<td>Azithromycin (clarithromycin) Rifampicin (rifabutin) Ethambutol</td>
<td>250–500 mg/d (1000 mg/d) 600 mg/d (300 mg/d) 15 mg/kg/d</td>
<td>Daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Suggest Amikacin IV (streptomycin)</td>
<td>10–25 mg/d</td>
<td>3 times weekly</td>
</tr>
</tbody>
</table>

Nguyen M, Daley C. Treatment of Mycobacterium avium Complex Pulmonary Disease. Clinics in Chest Medicine, 2023-12-01, Volume 44, Issue 4, Pages 771-783
Case

Patient started on triple drug therapy three times a week

• Azithromycin
• Ethambutol
• Rifampin
Notable side effects

1. Azithromycin
   • GI symptoms (~10%), prolonged QTc (<1%), hearing impairment/loss (post-marketing)
2. Ethambutol
   • Optic neuropathy (reduced visual acuity or impaired red/green color discrimination, post-marketing)
3. Rifampin
   - *Often chosen over rifabutin for tolerability, especially elderly*
   • GI symptoms, hepatotoxicity, hematologic, hypersensitivity
   • CYP450 inducer
   • Discoloration: teeth, urine, feces, saliva, sweat, and tears (yellow, orange, red, or brown)

Testing to consider before starting antibiotics

- Labs: CMP, CBC
- Audiology eval
- Eye exam
- ECG
Monitoring Treatment Response

• Continue treatment until culture negative for at least 2 consecutive months
• Monitor with surveillance cultures
How often do you check surveillance cultures after starting treatment?

A. Monthly starting after the 1st treatment month
B. Monthly starting after the 3rd treatment month
C. Once every three months after the 1st treatment month
D. Once every three months after the 3rd treatment month
“We recommend collecting respiratory specimens for culture every 1 to 2 months after initiation of therapy until there is sputum conversion to culture negative, which is defined as three consecutive negative sputum cultures. After that, we collect sputum every 2 to 3 months until therapy is completed with 12 months of sputum culture negativity while on therapy as determined by the date of the first negative culture”
65% to 85% microbiologic treatment success with guideline- and macrolide-based therapy

Poor adherence to guidelines by prescribers →

Survey of ~600 physicians only 13% of antibiotic regimens prescribed to patients with MAC met ATS/IDSA guidelines


Case

Patient continued to have positive cultures on TIW therapy
Refractory Disease

• Refractory = persistent positive sputum culture despite at least 6 consecutive months of standard regimen

• CONVERT trial (2018)
  • Randomized, open-label study of Amikacin liposome inhalation suspension (ALIS), a liposomal formulation of amikacin, inhaled once daily added to GBT
  • Primary endpoint: culture conversion (3 consecutive monthly MAC negative cultures by Month 6)
  • Addition of ALIS to GBT for treatment-refractory MAC lung disease \(\rightarrow\) significantly greater culture conversion by Month 6 than GBT alone, with comparable rates of serious adverse events

<table>
<thead>
<tr>
<th>Type of Disease</th>
<th>No. of Drugs</th>
<th>Preferred Regimen</th>
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<td>Daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Consider Amikacin IV (streptomycin)</td>
<td>10–25 mg/d</td>
<td>3 times weekly</td>
</tr>
<tr>
<td>Refractory</td>
<td>≥ 4</td>
<td>Azithromycin (clarithromycin) Rifampicin (rifabutin) Ethambutol Amikacin liposome inhalation suspension</td>
<td>250–500 mg/d (1000 mg/d) 600 mg/d (300 mg/d) 15 mg/kg/d 590 mg/d</td>
<td>Daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Suggest: Amikacin IV (streptomycin)</td>
<td>10–25 mg/d</td>
<td>3 times weekly</td>
</tr>
</tbody>
</table>

Nguyen M, Daley C. Treatment of Mycobacterium avium Complex Pulmonary Disease. Clinics in Chest Medicine, 2023-12-01, Volume 44, Issue 4, Pages 771-783
Summary

1. Diagnosis and Identification
   - Accurate and timely diagnosis of MAC infection can be challenging
   - IDSA/ATS Guidelines outline clinical, radiographic, and microbiologic criteria for diagnosis
   - MAC species identification is important, host factors also impact prognosis

2. Treatment Regimens
   - Involve patient in risk/benefit discussion of treatment
   - If treating, need to establish if macrolide-susceptible or not
   - Antibiotic regimen varies based on radiographic findings (nodular-bronchiectatic or cavitary)

3. Ongoing management
   - Treat for 12 months once negative culture obtained
   - There is no specific guideline about sputum culture monitoring, more often is often encouraged
   - Treatment refractory – no negative culture after 6 months of therapy, consider ALIS
   - Avoid ICS unless necessary
supplementary slides
Nontuberculous mycobacteria (NTM) –
>190 species and subspecies


http://www.bacterio.net/mycobacterium.html
The most common NTM culprits for lung disease

<table>
<thead>
<tr>
<th>Slow Growing</th>
<th>Fast Growing</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;7 days to grow in subcultures</td>
<td>Grow in &lt;7 days</td>
</tr>
<tr>
<td>Mycobacterium avium complex (MAC)</td>
<td>Mycobacterium abscessus</td>
</tr>
<tr>
<td>Mycobacterium kansasii</td>
<td></td>
</tr>
<tr>
<td>Mycobacterium xenopi</td>
<td></td>
</tr>
</tbody>
</table>

Lipid rich cell wall

- Survival and growth in diverse habitats
- Biofilm formation and persistence
- Aerosolization
- Antibiotic and disinfectant resistance

Growth requirements

- Low doubling time in culture media reduces the ability to identify these organisms in clinical and environmental samples
- Special media required to grow many of the NTM species, therefore not identified in routine laboratory cultures

Culture response rates were 4.00 times higher for those with noncavitary disease compared with those with cavitary disease.
BRONCHIAL ARTERY EMBOLIZATION FROM THE IR PERSPECTIVE

David M. Hovsepian, M.D.
Clinical Professor of Radiology

7 March 2024
RELEVANT FINANCIAL DISCLOSURES

- I have NO relationships with ACCME defined ineligible companies:
- I WILL NOT discuss off-label use and/or investigational use of any drugs or devices.
OBJECTIVES

- Describe how bronchial artery embolization (BAE) is performed, including how patients are stabilized and supported in the emergency setting.
- Describe which patients are most appropriate for elective bronchial artery embolization and the ideal timing of referral.
- Understand which etiologies of hemoptysis are and are not amenable to BAE.
QUANTIFYING HEMOPTYSIS

Massive = “Major”, “Exsanguinating”, “Severe”
>100 mL to 1000 mL in 24 hours

• Quantification can be difficult
  Frequently under-reported or exaggerated
• Mortality risk is not entirely related to amount
  Airway obstruction, hypotension, blood loss

MANAGEMENT OF MASSIVE HEMOPTYSIS

Radchenko et al. J Thorac Dis 2017; (9): S1069-1086
# ANATOMIC CAUSES OF HEMOPTYSIS

<table>
<thead>
<tr>
<th>Primary vascular source</th>
<th>Pulmonary parenchymal source</th>
<th>Tracheobronchial source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arteriovenous malformation</td>
<td>Tuberculosis</td>
<td>Bronchiectasis</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>Pneumonia</td>
<td>Neoplasm</td>
</tr>
<tr>
<td>Elevated pulmonary venous pressure</td>
<td>Lung abscess</td>
<td>Bronchitis</td>
</tr>
<tr>
<td>Pulmonary artery rupture</td>
<td>Lung contusion</td>
<td>Broncholithiasis</td>
</tr>
<tr>
<td><strong>Pseudohemoptysis</strong></td>
<td>Mycetoma (“fungus ball”)</td>
<td>Airway trauma</td>
</tr>
<tr>
<td>Upper airway source</td>
<td>Idiopathic pulmonary hemosiderosis</td>
<td>Foreign body</td>
</tr>
<tr>
<td>Gastrointestinal source</td>
<td>Wegener granulomatosis</td>
<td><strong>Miscellaneous and rare causes</strong></td>
</tr>
<tr>
<td><em>Serratia marcescens</em> (gram-negative bacterium that produces a red pigment that may be mistaken for blood)</td>
<td>Lupus pneumonitis</td>
<td>Systemic coagulopathy or thrombolytic agents</td>
</tr>
<tr>
<td>Malingering</td>
<td>Goodpasture syndrome</td>
<td>Catamenial hemoptysis (pulmonary endometriosis)</td>
</tr>
</tbody>
</table>

BRONCHIAL ARTERY ANATOMY
### POSSIBLE ETIOLOGY BY HISTORY

<table>
<thead>
<tr>
<th>Finding</th>
<th>Suggested etiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticoagulant use</td>
<td>Coagulopathy</td>
</tr>
<tr>
<td>Cough</td>
<td>Bronchiectasis, COPD, foreign body, pneumonia, tuberculosis</td>
</tr>
<tr>
<td>Fever</td>
<td>Bronchitis, lung abscess, neoplasm, pneumonia, pulmonary embolism, tuberculosis</td>
</tr>
<tr>
<td>Heart disease (valvular or congestive heart failure)</td>
<td>Congestive heart failure</td>
</tr>
<tr>
<td>Immunosuppression</td>
<td>Bronchitis, lung abscess, pneumonia, tuberculosis</td>
</tr>
<tr>
<td>Recent surgery or immobilization</td>
<td>Pulmonary embolism</td>
</tr>
<tr>
<td>Smoking</td>
<td>Bronchitis, COPD, neoplasia</td>
</tr>
<tr>
<td>Sputum production</td>
<td>Bronchiectasis, COPD, pneumonia, tuberculosis</td>
</tr>
<tr>
<td>Trauma</td>
<td>Airway trauma, pulmonary embolism</td>
</tr>
<tr>
<td>Weight loss</td>
<td>COPD, neoplasia, tuberculosis</td>
</tr>
</tbody>
</table>

Indications for BAE

- > 240 mL in 24 hours ("massive hemoptysis")
- > 100 mL per day for 3 days
- > 50 mL and hemodynamic instability
- FEV1 < 40% of predicted and recurrent tsps. Of blood over multiple days
## Variant 1:

**Massive (life-threatening) hemoptysis. Initial imaging.**

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Appropriateness Category</th>
<th>Relative Radiation Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arteriography bronchial with embolization</td>
<td>Usually Appropriate</td>
<td>🌟🌟🌟🌟🌟</td>
</tr>
<tr>
<td>CTA chest with IV contrast</td>
<td>Usually Appropriate</td>
<td>🌟🌟🌟🌟</td>
</tr>
<tr>
<td>Radiography chest</td>
<td>Usually Appropriate</td>
<td>🌟</td>
</tr>
<tr>
<td>CT chest with IV contrast</td>
<td>Usually Appropriate</td>
<td>🌟🌟🌟🌟</td>
</tr>
<tr>
<td>CT chest without IV contrast</td>
<td>May Be Appropriate</td>
<td>🌟🌟🌟</td>
</tr>
<tr>
<td>CT chest without and with IV contrast</td>
<td>Usually Not Appropriate</td>
<td>🌟🌟🌟</td>
</tr>
</tbody>
</table>

[https://acsearch.acr.org/docs/69449/Narrative](https://acsearch.acr.org/docs/69449/Narrative)
**Variant 2:** Nonmassive (non–life-threatening) hemoptysis. Initial imaging.

<table>
<thead>
<tr>
<th>Procedure</th>
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</thead>
<tbody>
<tr>
<td>CT chest with IV contrast</td>
<td>Usually Appropriate</td>
<td>📘<em>pushpin stigma</em></td>
</tr>
<tr>
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</tr>
</tbody>
</table>

[https://acsearch.acr.org/docs/69449/Narrative](https://acsearch.acr.org/docs/69449/Narrative)
## ACR Appropriateness Criteria

### Variant 3:

**Recurrent hemoptysis. Initial imaging.**

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<th>Procedure</th>
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<th>Relative Radiation Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiography chest</td>
<td>Usually Appropriate</td>
<td>✰✰✰✰✰</td>
</tr>
<tr>
<td>Arteriography bronchial with embolization</td>
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</tr>
<tr>
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<td>Usually Appropriate</td>
<td>✰✰✰✰</td>
</tr>
<tr>
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<td>May Be Appropriate</td>
<td>✰✰✰✰</td>
</tr>
<tr>
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</tr>
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<td>Usually Not Appropriate</td>
<td>✰✰✰✰✰</td>
</tr>
</tbody>
</table>

[https://acsearch.acr.org/docs/69449/Narrative](https://acsearch.acr.org/docs/69449/Narrative)
CLINICAL EXAMPLE

34-year-old s/p HSCT

- Complicated post-op course
  HLH, HHV viremia, AKI
- Bronchoscopy confirmed bleeding from RLL
- CTA to define bronchial arterial anatomy
BRONCHIAL ARTERIOGRAM
GLUE EMBOLIZATION
BRONCHIAL ARTERY ANATOMY

- 9 Branching patterns (the above account for > 90%)
  Bronchial arteries typically arise at the level of the major bronchi (T5-T6)
NON-BRONCHIAL SYSTEMIC ARTERIES

• Aberrant bronchial arteries
  Arise outside of T5-T6 (major bronchi)
  Prevalence between 8 and 35%
  Arch, IMA, Thyrocervical trunk, subclavian,
  costocervical trunk, brachiocephalic,
  pericardiacophrenic, inferior phrenic,
  abdominal aorta

• Non-bronchial systemic arteries
  Enter parenchyma via pleural adhesion or
  the pulmonary ligament
  Do not parallel the major bronchi
**IMPORTANT RELATED ANATOMY**

- **Arteria Radicularis Magna**
  - "Major anterior segmental medullary artery"
  - Albert Wojciech Adamkiewicz (1850-1921)
- Typically arises from left posterior intercostal artery from T9-T12
  - Can arise from T8 to L2
- Supplies lower two-thirds of spinal cord (lumbar and sacrum)
  - Occlusion leads to paraplegia and loss of sense of pain, touch, and temperature and sphincter control.
- ~30% arises from the right
- ~25% have two \(^1,^2\)

MEDULLARY VS. RADICULAR ARTERIES

BAE FOR NON-MASSIVE HEMOPTYSIS

Gachon Medical Center
Retrospective review of 233 patients accrued from 2005-2014

Feasibility and outcomes of bronchial artery embolization in patients with non-massive hemoptysis

Jung Han Hwang, Jeong Ho Kim, Suyeong Park, Ki Hyun Lee and So Hyun Park

<table>
<thead>
<tr>
<th>Condition</th>
<th>Number (Percentage)</th>
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<tbody>
<tr>
<td>TB sequelae</td>
<td>99 (42.5)</td>
</tr>
<tr>
<td>Bronchiectasis</td>
<td>31 (13.2)</td>
</tr>
<tr>
<td>Tuberculosis destroyed lung</td>
<td>25 (10.9)</td>
</tr>
<tr>
<td>Aspergilloma</td>
<td>26 (11.1)</td>
</tr>
<tr>
<td>Fibrotic scar change</td>
<td>17 (7.3)</td>
</tr>
<tr>
<td>Active TB</td>
<td>31 (13.2)</td>
</tr>
<tr>
<td>Mycobacterium tuberculosis</td>
<td>28 (11.9)</td>
</tr>
<tr>
<td>Multidrug-resistant tuberculosis</td>
<td>3 (1.3)</td>
</tr>
<tr>
<td>Nontuberculous mycobacteria</td>
<td>8 (3.3)</td>
</tr>
<tr>
<td>Bronchiectasis without TB</td>
<td>35 (15.2)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>27 (11.6)</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>11 (4.6)</td>
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<tr>
<td>Others</td>
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Active TB

<p>| | |</p>
<table>
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<th></th>
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<tr>
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<td>22 (9.6)</td>
</tr>
</tbody>
</table>

Pre-op CT available in 95.3%
Routine use of microcatheters

<table>
<thead>
<tr>
<th>Embolic materials††</th>
<th>Count (Percentage)</th>
</tr>
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<tbody>
<tr>
<td>Gelfoam</td>
<td>42 (18.0)</td>
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<tr>
<td>PVA</td>
<td>140 (60.1)</td>
</tr>
<tr>
<td>PVA</td>
<td>99 (42.5)</td>
</tr>
<tr>
<td>PVA + Gelfoam</td>
<td>41 (17.6)</td>
</tr>
<tr>
<td>NBCA</td>
<td>34 (14.6)</td>
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<tr>
<td>NBCA</td>
<td>18 (7.7)</td>
</tr>
<tr>
<td>NBCA + PVA</td>
<td>14 (6.9)</td>
</tr>
</tbody>
</table>

Technical success
Yes                  224 (96.1)
No                   9 (3.9)

Clinical success
Yes                  219 (94.0)
No                   14 (6.0)

OUTCOMES

Median follow-up 197 days
Recurrent bleeding in 64 pts (27.5%)
Second BAE in 42 patients
  Same vessel in 5 (11.9%)
  TB sequelae most common association ($p < 0.001$)
  Aberrant bronchial artery or systemic collaterals statistically significant ($p < 0.021$)
After 2013, authors transitioned to nBCA
  Fewer rebleeding events in glue group ($p < 0.05$)
  Variety of agents used limits the study

Follow up of original cohorts (126 pts)

Patients with episodic massive (> 300 mL within 24 hours) hemoptysis or recurrent non-massive hemoptysis

Takeda et al. Respiration 2020; 99: 961-969
TECHNIQUE AND RESULTS

Pre-op CT available in all patients
Routine use of microcatheters and coils (no other agents)
- Recurrence in 19 patients (17.9%)
- Massive: non-massive 4:15
- No significant correlations

Second BAE in 13 patients
- Recanalization (12), collaterals (6), new arteries (4) and/or all of the above

Takeda et al. Respiration 2020; 99: 961-969
Hemoptysis control

Recurrence-free rate at 1, 3, and 5 years
- Tech Success: 93.5%, 85.6%, and 84.1%
- Tech Failure: 71.4%, 71.4%, and 57.1%

Takeda et al. Respiration 2020; 99: 961-969
69 BAE Procedures
9 patients lost to follow-up
100% Technical success
162 BA, 19 NBSA
92% Clinical success
2 lobectomy, 2 medical, 1 death from continued hemoptysis
No major complications

47 Patients conservatively treated
Assignment according to hospital records

- Antibiotics, correction of hypoxemia, blood products, hemostatic drugs (pituitrin, phentolamine)
MORPHOLOGIC TYPES OF BRONCHIECTASIS

**Fig. 2** Computed tomography images of the three types of bronchiectasis. **A** Columnar bronchiectasis (white arrows); **B** Varicose bronchiectasis (white arrows); **C** Cystic bronchiectasis (white arrows).

1-, 2-, and 3-year hemoptysis-free survival rates higher in BAE group

5 Patients in the conservative group died due to recurrent hemoptysis vs. 1 in the BAE group

Cystic type more likely to have recurrent hemoptysis vs. columnar or varicose ($p<0.028$) bronchiectasis for both groups

Consider surgical management in this group?

Retrospective review

485 patients from Jan 2005 – Dec 2008
  406 patients had 3-year follow-up

403 had pre-op CT
  Bleeding focus identified in 367

67 had pre-op FOB
  Bleeding focus identified in 41

NBCA VS. PARTICLES

Fewer same-vessel recanalizations with nBCA
Overall complication rates similar (34.1% vs. 31%)
Major complication rates the same 0.3% vs. 0%

Overall 1, 3, and 5-year hemoptysis-free survival rates
77%, 68%, and 66% for PVA and
88%, 85%, and 83% for nBCA
\((p = .01)\)

1, 3, and 5-year hemoptysis-free survival rates for bronchiectasis
79%, 71%, and 69% for PVA and
100%, 95%, and 95% for nBCA
\((p = .01)\)

Bronchial artery embolization for treatment of hemoptysis is safe and effective
  • Similar outcomes for massive, submassive, and intermittent

Hemoptysis-free survival rates are lower for hemoptysis due to MAC or CPA
  • More aggressive disease, more recruits (especially NBSC’s)

Higher hemoptysis-free survival rates for bronchiectasis using nBCA
  • Cylindrical and varicose types >> Cystic bronchiectasis
նկարազարդիչներ
CTD-Associated Bronchiectasis and airways disease

Jonathan Graf, MD
Professor of Medicine, UCSF
Division of Rheumatology, Zuckerberg San Francisco General

C-STAIR
Center for Study of Advanced Immunotherapeutics in Rheumatic Diseases
Relevant Disclosures

• None
Pulmonary Complications of Collagen Vascular Diseases

<table>
<thead>
<tr>
<th>Table I. — Thoracic manifestations of connective tissue diseases.</th>
<th>RA</th>
<th>PSS</th>
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<th>PM/DM</th>
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<th>RP</th>
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<td>Follicular bronchiolitis/LIP</td>
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<td>+</td>
<td>+</td>
<td>+++</td>
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<tr>
<td>Alveolar hemorrhage</td>
<td>+</td>
<td>+</td>
<td>+++</td>
<td>+</td>
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<tr>
<td>Aspiration pneumonia</td>
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<td>+</td>
<td>++</td>
<td>+</td>
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<tr>
<td>Tracheobronchial WT/Stenosis</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+++</td>
<td>+</td>
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<tr>
<td>Bronchiectasis</td>
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<td>++</td>
<td>+</td>
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<tr>
<td>Obliterative bronchiolitis</td>
<td>++</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nodules</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PAH</td>
<td>+</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>++</td>
<td>+</td>
<td>++</td>
<td></td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diaphragm dysfunction</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td></td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UIP</td>
<td>Usual Interstitial Pneumonia</td>
<td>RA</td>
<td>Rhumatoid Arthritis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSIP</td>
<td>Non Specific Interstitial Pneumonia</td>
<td>PSS</td>
<td>Progressive Systemic Sclerosis</td>
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<td></td>
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<tr>
<td>OP</td>
<td>Organizing pneumonia</td>
<td>SLE</td>
<td>Systemic Lupus Erythmatosus</td>
<td></td>
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<td></td>
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<tr>
<td>DAD</td>
<td>Diffuse Alveolar Damage</td>
<td>PM/DM</td>
<td>Polymyositis/Dermatomyositis</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>LIP</td>
<td>Lymphocytic Interstitial Pneumonia</td>
<td>MCTD</td>
<td>Mixed Connective Tissue Disease</td>
<td></td>
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<tr>
<td>WT</td>
<td>Wall thickening</td>
<td>SJOS</td>
<td>Sjögren’s syndrome</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PAH</td>
<td>Pulmonary Arterial Hypertension</td>
<td>RP</td>
<td>Relapsing Polychondritis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Follicular Bronchiolitis

• Can be seen in many CVD’s including rheumatoid arthritis and Sjogren’s syndrome

• Hyperplasia of bronchiole-associated lymphoid tissue

• Lymphocytic proliferation and extra nodal lymphoid follicles with germinal center formation around the bronchioles that leads to narrowing of the airway lumen

RA-associated Follicular Bronchiolitis

- Clinically manifests as:
  - Progressive obstructive disease
  - Dyspnea
  - Reduction in FEV₁

- HRCT findings can be non-specific but often feature:
  - Centrilobular nodules
  - Hyperinflation
  - Mosaic perfusion
  - Air-trapping

- Biopsy is often only way to confirm diagnosis

- Clinical response to immunosuppressives such as corticosteroids and possibly macrolides
RA-associated Obliterative Bronchiolitis

- RA most common CTD associated with OB

- RA-OB often a clinical diagnosis in setting of significant airflow obstruction not believed to be due to COPD (e.g. no smoking hx)

- HRCT often shows bronchial wall thickening +/- pulmonary infiltrates with lobular areas of decreased attenuation and mosaic perfusion
  - Air-trapping can be dynamic and seen on expiratory images

RA-associated Obliterative Bronchiolitis

- Concentric fibrosis of bronchial wall + narrowing of the lumen
- +/- inflammatory infiltrates
- Poorer response to immunosuppression compared to FB
- Poorer prognosis
- Therapy combination of bronchodilator and immunomodulatory therapies +/- macrolides
- Early referral for lung TXP if indicated

72 YO female non-smoker with history of seropositive destructive RA. She is currently treated with methotrexate and etanercept with partial disease response. However she has continued to have frequent cough, sputum production, and fatigue. Her CT is shown to the right:
RA-associated Bronchiectasis

- Irreversible damaged and dilated bronchi
  - Primary airway disease or secondary to fibrotic ILD with traction
  - Damage often vicious-cyclical result of long-term damage to airways leading to thickening, dilation, increased mucous production, and often recurrent infection

- Prevalence of bronchiectasis as high as 31% in unselected RA patients screened with HRCT\(^1\)

- Prevalence of symptomatic bronchiectasis is 2-12%\(^2\)

\(^1\)Wilczynska et al. Resp Care 2013;58:694-701
Overall Prevalence of Bronchiectasis in RA: Meta-analysis of 36 studies


Fig. 2.
Forest plot and random effects meta-analysis for prevalence of bronchiectasis among patients with rheumatoid arthritis in all studies (n=36).
RA-associated Bronchiectasis: Clinical Presentation

- Chronic cough
- Frequent (even daily) sputum production. Worse in AM.
- Frequent respiratory infections
- Rhinosinusitis
- Fatigue
- Occasional mild hemoptysis
- Dyspnea
RA-associated Bronchiectasis: Clinical Associations

- Patients with RA-bronchiectasis had higher disease activity than those with RA alone
- Seropositivity (RF and anti-CCP) associated with bronchiectasis
- Higher autoantibody titers strengthen association with bronchiectasis

RA-Bronchiectasis: Significant Morbidity and Mortality

- Taiwanese cohort study 2006-2017
- 10,000+ patients bronchiectasis
- 343 with RA
- Primary outcome: respiratory failure or death
- Severe exacerbations: ED visit or hospitalization

RA-Bronchiectasis: Significant Morbidity and Mortality

• Up to 30% mortality at 3 years post diagnosis, especially for patients in whom RA diagnosis predates diagnosis of bronchiectasis

• Mortality primarily from pulmonary infections, CVD, and RA-related complications

RA-Bronchiectasis Treatment

• All patients with clinically significant RA and bronchiectasis should be co-managed by pulmonologists, rheumatologist, and respiratory therapists (pulmonary rehab program)

• Rule out other causes of bronchiectasis and recurrent sinopulmonary infections if indicated
  • CVID
  • B-cell depleting and other immunotherapies (If lgs low, consider IvIg)
  • Consideration of CFTR gene testing

• Vaccination against pneumococcal, influenza and other respiratory viruses

• Consideration of prophylactic antibiotics (e.g. macrolides) in setting of frequent (>3/year) or severe (hospitalization for Iv Abx) infections

• Consideration of inhaled corticosteroids/LABA
Debate: Choice of RA treatments in patients with Bronchiectasis

Infections
Bronchitis and bronchiectasis flares
Worsening cycle of Bronchiectasis

Suppression of disease activity
Potential reduction in airway inflammation
Reduced airway remodeling
Risk of Lower Respiratory Tract Infection and RA Treatment

Geri et al. BMC Infectious Diseases 2011, 11:304

Table 2 Lower respiratory tract infections in bronchiectasis concomitant to inflammatory diseases, according to the rheumatic disease-modifying treatment

<table>
<thead>
<tr>
<th></th>
<th>All treatments</th>
<th>Non-biologic DMARDs</th>
<th>Biologic DMARDs</th>
<th>Etanercept</th>
<th>Adalimumab</th>
<th>Infliximab</th>
<th>Abatacept</th>
<th>Rituximab</th>
</tr>
</thead>
<tbody>
<tr>
<td>N periods of treatment of the rheumatologic disease</td>
<td>98</td>
<td>40</td>
<td>58</td>
<td>19</td>
<td>4</td>
<td>12</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>Total N infections</td>
<td>93</td>
<td>16</td>
<td>77</td>
<td>13</td>
<td>3</td>
<td>34</td>
<td>23</td>
<td>4</td>
</tr>
<tr>
<td>N patient-years of follow-up</td>
<td>194</td>
<td>98</td>
<td>96</td>
<td>33</td>
<td>1</td>
<td>30</td>
<td>17</td>
<td>12</td>
</tr>
<tr>
<td>N infections per patient-year, mean (SD) [95% CI]</td>
<td>0.8 (1.4)</td>
<td>0.2 (0.5)</td>
<td>1.2 (1.6)</td>
<td>0.8 (1.4)</td>
<td>2.3 (2.1)</td>
<td>1.9 (1.6)</td>
<td>1.9 (1.9)</td>
<td>0.3 (0.7)</td>
</tr>
</tbody>
</table>

Table 3 Predictive factors of respiratory tract infections in multivariate logistic regression

<table>
<thead>
<tr>
<th></th>
<th>Odds Ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacteriologic colonisation</td>
<td>7.4 (2.0-26.8)</td>
<td>0.002</td>
</tr>
<tr>
<td>Treatment with biologics (vs non biologic DMARDs)</td>
<td>8.7 (1.7-43.4)</td>
<td>0.008</td>
</tr>
</tbody>
</table>

- No general guidelines:
- Treat RA regardless of bronchiectasis
- Caution use of biological DMARDs
  - Known NTM
- Perhaps favor macrolide use
RA-Bronchiectasis Pathogenesis

Winifred Emery as Lady Windermere, 1892
RA-Bronchiectasis pathogenesis: Infection hypothesis

• Chronic and/or recurrent airway infection drives airway inflammation, damage, mucous plugging, and susceptibility to further infection

• Immunosuppressive therapy may predispose to airway infection

• Intrinsic disease-specific factors in airways may contribute to airway colonization and infection (chronic airway inflammation with mucous production)

• Sputum cultures in Taiwanese cohort positive most often for NTM and Pseudomonas both overall and in those patients with a severe exacerbation over 3 year follow up

<table>
<thead>
<tr>
<th>Microbiology</th>
<th>General</th>
<th>N (%)</th>
<th>Severe</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NTM</td>
<td>40 (22.1)</td>
<td>NTM</td>
<td>37 (17.5)</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>26 (14.4)</td>
<td>NTM</td>
<td>18 (8.5)</td>
<td></td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>19 (10.5)</td>
<td>Negative</td>
<td>17 (8.1)</td>
<td></td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
<td>14 (7.7)</td>
<td>Stenotrophomonas</td>
<td>15 (7.1)</td>
<td></td>
</tr>
<tr>
<td>Fungus</td>
<td>12 (6.6)</td>
<td>Fungus</td>
<td>11 (5.2)</td>
<td></td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>9 (4.9)</td>
<td>Acinetobacter baumannii</td>
<td>10 (4.7)</td>
<td></td>
</tr>
<tr>
<td>Streptococcus pneumonia</td>
<td>8 (4.4)</td>
<td>Staphylococcus aureus</td>
<td>10 (4.7)</td>
<td></td>
</tr>
<tr>
<td>Klebsiella pneumoniae</td>
<td>6 (3.3)</td>
<td>E. coli</td>
<td>9 (4.3)</td>
<td></td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>4 (2.1)</td>
<td>Klebsiella pneumoniae</td>
<td>9 (4.3)</td>
<td></td>
</tr>
</tbody>
</table>

RA-Bronchiectasis pathogenesis: Genetic Predisposition Hypothesis

- Family-based association study
- Proband with both RA and DB and one affected first-degree relative with RA and/or DB
- All un/affected subjects and interviewed DNA examined
- HRCT on all RA and those with at least 2 symptoms DB

RA-Bronchiectasis pathogenesis: Genetic Predisposition Hypothesis


- 5+ fold increased odds of having CFTR gene mutation in RA with DB vs RA alone
- Driven mostly by mutations in cluster “C” mutations
- DB risk driven mostly by cluster “A” mutations
- Suggests possible genetic mechanism linking RA and an extraarticular manifestation
RA-Bronchiectasis pathogenesis: RA-related Autoimmunity Damages the Airways Hypothesis


- Antibodies to citrullinated proteins are a hallmark of autoimmune response in RA

- Seropositive patients, whether they have early RA or are asymptomatic have more airway abnormalities on HRCT than antibody negative controls
Antibody Responses to Citrullinated and Noncitrullinated Antigens in the Sputum of Subjects With Rheumatoid Arthritis and Subjects at Risk for Development of Rheumatoid Arthritis

M. Kristen Demoruelle,1 Emily Bowers,1 Lauren J. Lahey,2 Jeremy Sokolove,3 Monica Parniske,4 Nickie L. Seto,4 Michael H. Weisman,3 Jill M. Norris,5 Mariana J. Kaplan,4 V. Michael Holers,1 William H. Robinson,2 and Kevin D. Deane1

Objective. The location and mechanisms involved in the initial generation of autoantibodies to citrullinated and noncitrullinated proteins/peptides during the natural history of rheumatoid arthritis (RA) development is incompletely understood. This study sought to explore individual antibody responses to citrullinated and noncitrullinated proteins/peptides in the sputum and associations with neutrophil extracellular traps (NETs) in subjects at risk for the future development of RA.

Methods. Serum and sputum samples were obtained from 41 RA-free subjects who were considered at risk for the development of RA based on familial or serologic risk factors, from 26 subjects classified as having RA, and from 22 healthy control subjects. Samples were evaluated using a bead-based array for IgG reactivity to 29 citrullinated proteins/peptides and 21 noncitrullinated proteins/peptides. Cutoff levels for antibody positivity were established in a separate control group. NET levels in the sputum were measured using sandwich enzyme-linked immunosorbent assays that quantitate DNA-myeloperoxidase and DNA-neutrophil elastase complexes.

Results. In at-risk subjects, antibody responses to the citrullinated forms of fibrinogen, apolipoprotein E, and fibronectin were highly prevalent. The most citrulline-specific antibodies in the sputum of at-risk subjects were those to fibrinogen, vimentin, and peptides of fibrinogen A and apolipoprotein A1. Patterns of sputum autoantibody positivity differed between at-risk subjects and subjects with RA. In at-risk subjects, increasing sputum NET levels significantly correlated with several citrullinated and some noncitrullinated antibody reactivities.

Conclusion. These findings suggest that sputum antibody reactivity to particular citrullinated and noncitrullinated proteins/peptides is specific for RA and for subjects at risk of RA, and the association of these proteins/peptides with NETs may be a key feature of early RA-related autoimmunity in the lung. These results further support the hypothesis that the lung plays a role in early RA-related autoimmunity.

Citrullination is the posttranslational modification of peptidylarginine to peptidylcitrulline that is catalyzed through peptidylarginine deiminase (PAD) enzymes (1). Citrullination is a normal physiologic process that can be up-regulated during inflammation (2).
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Methods. Serum and sputum samples were obtained from 41 RA-free subjects who were considered at risk for the development of RA based on familial or serologic risk factors, from 20 subjects classified as having RA, and from 22 healthy control subjects. Samples were evaluated using a bead-based array for IgG reactivity to 29 citrullinated proteins/peptides and 21 noncitrullinated proteins/peptides. Cutoff levels for antibody positivity were established in a separate control group. NET levels in the sputum were measured using sandwich enzyme-linked immunosorbent assays that quantitate DNA–myeloperoxidase and DNA–neutrophil elastase complexes.

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Hallmark of RA-associated Autoimmunity: Auto-reactivity to Peptides that Contain Citrulline

Deiminase removes amino group

<table>
<thead>
<tr>
<th>Peptide sequence</th>
<th>Antibody recognition</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESSRDGSRHPRSHD</td>
<td>No</td>
</tr>
<tr>
<td>ESSRDGS\textit{cit}HPRSHD</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Preclinical autoimmunity in RA: appearance of anti-CCP antibodies and RF prior to onset of arthritis

Nielen et al Arth Rheum 50: 380, 2004
Sputum autoantibodies in RA patients and those at high risk for developing RA


Sputum specific anti-citrullinated protein antibodies (ACPA) in RA patients vs. controls

Sputum positive ACPA in at RA-at risk vs healthy controls, **regardless serum ACPA +/-**
Quantifying RA risk based upon genetics and environmental exposure

Malmstrom, Klareskog et al. Nat Rev Immunol 2017
Mucosal hypothesis: Generation of Local Followed Later by Systemic Autoimmunity

Summary

- Airways disease is a common manifestation of CTD systemic autoimmune diseases and is often overlooked compared to recognized parenchymal ILD

- Follicular bronchiolitis, Obliterative Bronchiolitis, and Bronchiectasis most commonly encountered RA and Sjogren’s syndrome

- No guidelines to manage RA in setting of bronchiectasis
  - Caution using biological DMARDs (esp anti-TNF) in setting of NTM
Summary Continued

• Several overlapping theories for why bronchiectasis is more commonly associated with RA: RA disease activity may drive pathogenesis of bronchiectasis

• However, pathogenesis of RA may actually begin in the lung. And airways inflammation may be site of initial autoimmune response
Lady Windemere’s Contemporary: Renoir
Mycobacterium abscessus

Mohamed Fayed MD, FCCP
Associate clinical professor
UCSF Fresno
Pulmonary critical care division
RELEVANT FINANCIAL DISCLOSURES

- No financial disclosure
- I WILL discuss off-label use of some drugs.
Objectives

- Case
  - Diagnosis
  - Therapy plan
    - None pharmacological plan
    - Pharmacological plan
Case

- 73 year-old presents with symptoms of 1 years
  - Worsening cough overtime
  - More short of breath with exertion
  - weight about 20lbs in the past 6 months
  - Non smoker, history of hypertension, osteoporosis and depression
What work up do you like to obtain

A. PFT and chest x-ray
B. PFT and CT scan
C. No need for work up, just inhaler
D. CT scan only
Clinical symptoms are suggestive of malignancy, chronic infection, airway disease

- PFT
- CT scan
▪ Clinical symptoms of chronic infection
  • Yes
▪ Radiological symptoms of chronic infection
  • Yes
▪ Next step?
<table>
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<tr>
<th>Culture Type</th>
<th>Date</th>
<th>Range</th>
<th>2023 10/11</th>
<th>2023 10/10</th>
<th>2023 10/9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Culture AFB</td>
<td>10/11/23</td>
<td>No range</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Culture Fungal-Most Source</td>
<td>10/11/23</td>
<td>No range</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Culture Respiratory w/ Gra...</td>
<td>10/10/23</td>
<td>No range</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other Micro Tests</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mycobacterium avium intracellular...</td>
<td>10/11/23</td>
<td>Not Detected</td>
<td>Not Detected</td>
<td>Not Detected</td>
<td>Not Detected</td>
</tr>
<tr>
<td>Mycobacterium species</td>
<td>10/11/23</td>
<td>Not Detected</td>
<td>Detect...</td>
<td>Detect...</td>
<td>Detect...</td>
</tr>
<tr>
<td>Mycobacterium tuberculosis comp...</td>
<td>10/11/23</td>
<td>Not Detected</td>
<td>Not Detected</td>
<td>Not Detected</td>
<td>Not Detected</td>
</tr>
</tbody>
</table>
Acid-Fast Bacillus (AFB) Identification with Reflex to Susceptibility

ARUP test code 0060997

Source: Respiratory

Body Site: Sputum Induced

Free Text Sources: See ESP

Final Report

Mycobacteroides (Mycobacterium) abscessus Group
A T28C substitution or truncation in erm(41) gene was detected. This indicates a non-functional erm(41) gene (ie. no inducible resistance). Resistance to clarithromycin could occur due to other acquired mechanisms. Correlate results with phenotypic susceptibility.

Identification by MALDI-TOF
This test was developed and its performance characteristics determined by ARUP Laboratories. It has not been cleared or approved by the U.S. Food and Drug Administration. This test was performed in a CLIA-certified laboratory and is intended for clinical purposes. This assay cannot differentiate members of the M. abscessus group.
# Susceptibility Results

**Organism:** Mycobacteroides (Mycobacterium) abscessus Group

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Interpretation</th>
<th>MIC (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin</td>
<td>SUSCEPTIBLE</td>
<td>16</td>
</tr>
<tr>
<td>Cefoxitin</td>
<td>INTERMEDIATE</td>
<td>32</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>RESISTANT</td>
<td>&gt;=8</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>RESISTANT</td>
<td>8</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>RESISTANT</td>
<td>&gt;=16</td>
</tr>
<tr>
<td>Imipenem</td>
<td>RESISTANT</td>
<td>32</td>
</tr>
<tr>
<td>Linezolid</td>
<td>SUSCEPTIBLE</td>
<td>8</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>RESISTANT</td>
<td>&gt;=8</td>
</tr>
<tr>
<td>Tigecycline</td>
<td></td>
<td>0.06</td>
</tr>
<tr>
<td>Trimethoprim/Sulfamethoxazole</td>
<td>RESISTANT</td>
<td>4/76</td>
</tr>
</tbody>
</table>
Diagnosis

What are the criteria of non tuberculous mycobacterium (NTM) lung disease

A. It is a clinical diagnosis
B. It needs microbiological evidence
C. It needs radiological evidence
D. All of the above
Table 2. Clinical and Microbiologic Criteria for Diagnosis of Nontuberculous Mycobacterial Pulmonary Disease

<table>
<thead>
<tr>
<th>Clinical</th>
<th>Pulmonary or Systemic Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiologic</td>
<td>Nodular or cavitary opacities on chest radiograph, or a high-resolution computed tomography scan that shows bronchiectasis with multiple small nodules</td>
</tr>
<tr>
<td>and</td>
<td>Both Required</td>
</tr>
<tr>
<td>and</td>
<td>Appropriate exclusion of other diagnoses</td>
</tr>
<tr>
<td>Microbiologic</td>
<td>Positive culture results from at least two separate expectorated sputum samples. If the results are nondiagnostic, consider repeat sputum AFB smears and cultures</td>
</tr>
<tr>
<td>or</td>
<td></td>
</tr>
<tr>
<td>or</td>
<td>Positive culture results from at least one bronchial wash or lavage</td>
</tr>
<tr>
<td>or</td>
<td>Transbronchial or other lung biopsy with mycobacterial histologic features (granulomatous inflammation or AFB) and positive culture for NTM or biopsy showing mycobacterial histologic features (granulomatous inflammation or AFB) and one or more sputum or bronchial washings that are culture positive for NTM</td>
</tr>
</tbody>
</table>
Clinical symptoms

- Recurrent bronchitis
- Recurrent pneumonia
- Fatigue
- Weight loss
Radiology

- Nodular or cavitary opacities on chest imaging
  - Computed tomography scan that shows bronchiectasis with multiple small nodules
Microbiology

- Identification
  - 2 separate sputum or
  - One BAL or bronchial wash or
  - One lung biopsy
Microbiology

Macrolide susceptibility

- Susceptibility-based treatment for macrolides
  - For macrolides, a 14-day incubation and/or sequencing of the \textit{erm(41)} gene should be performed to evaluate for potential inducible macrolide resistance.
Microbiology
Macrolide susceptibility

- Mutational resistance:
  - Isolate determined to be phenotypically susceptible at 3–5 days of incubation in culture.
  - Isolate determined to be phenotypically resistant at 3–5 days of incubation or sequencing identifies 23S rRNA (rrl) gene mutation known to confer resistance.

- Inducible resistance:
  - Functional erm(41) gene—Isolate determined to be resistant after 14 days of incubation or sequencing identifies functional gene sequence.
  - Nonfunctional erm(41) gene—Isolate determined to be susceptible after 14 days of incubation or sequencing identifies truncated sequence or C28 mutation (in subspecies abscessus).
Microbiology

Amikacin susceptibility

- Resistance to amikacin high MIC (>64 μg/mL)
- Amikacin is an important drug used for treatment of *M. abscessus* pulmonary disease.
  - Resistance to amikacin IV or amikacin liposome inhalation suspension (ALIS)
  - Mutation (A1408G) in the 16S rRNA (*rrs*) gene that has been associated with a high MIC (>64 μg/mL) and previous exposure to amikacin
Microbiology
Other drugs

▪ IV drugs
  • Cefoxitin
  • Imipenem
  • Tigecycline

▪ Oral drugs
  • Linezolid
  • Doxycycline
  • Ciprofloxacin and moxifloxacin
  • Clofazimine
Microbiology
Sub-species

▪ *M. abscessus* subsp. *massiliense*
  • Nonfunctional *erm(41)* gene
  • *M. abscessus* subsp. *massiliense* develops mutational macrolide resistance with a mutation in the 23S rRNA gene

▪ *M. abscessus* subsp. *abscessus* and subsp. *bolletii*
  • Functional *erm(41)* gene
  • *M. abscessus* subsp. *abscessus* C28 sequevar isolate does not exhibit inducible resistance to macrolides
New nomenclature!

- Mycobacterial species into the five described clades
  1. *Mycobacterium* emended gen corresponding to "*Tuberculosis-Simiae*" clade, which includes all of the major human pathogens
  2. *Mycolicibacterium* gen. nov, corresponding to the "*Fortuitum-Vaccae clade"
  3. *Mycolicibacillus* gen. nov, corresponding *Triviale clade*
  4. *Mycolicibacter* gen. nov corresponding *Terrae clade*
  5. *Mycobacteroides* gen. nov. corresponding *Abscessus-Chelonae*
M. abscessus, M. abscessus subsp. abscessus, M. abscessus subsp. boletii, M. boletii subsp. massiliense, M. chelonae, M. chelonae subsp. chelonae
M. Immunogenum, M. salmoniphilum, M. franklinii, M. saрапaulense

Mycobacteroides gen. nov. ("Abscessus-Chelonae" Clade)


Mycobicibacter gen. nov. ("Terra" Clade)

M. trivialis, M. koreensis, M. parakoreensis

Mycobicibacillus gen. nov. ("Triviale" Clade)


Emended Genus Mycobacterium ("Tuberculosis-Simiae" Clade)
We believe the new nomenclature has the potential to cause confusion and provides no benefits to the field of clinical mycobacteriology. Accordingly, in this editorial, we aim to provide clinicians involved in the management of patients with NTM disease state of the art information about rules regulating the nomenclature of prokaryotes and that, in spite of this recent publication, the currently used nomenclature of NTM can remain unchanged.
Management

- None pharmacological therapy
  - Exposure reduction
Management

- None pharmacological therapy
  - Airway clearance
Management

- Pharmacological therapy

- Improvement of symptoms

- Medication side effect
Macrolide susceptibility

Mutational Susceptible

Inducible Susceptible

Initial phase
IV plus oral therapy for at least 4 weeks

IV drug (1-2 drugs)
- Imipenem
- Cefoxitin
- Tigecycline
- Amikacin

Oral drugs (2-3 drugs)
- Linezolid
- Doxycycline
- Ciprofloxacin
- Moxifloxacin
- Clofazmine

Continuation phase 2-3 oral drugs for 12 month after negative culture
<table>
<thead>
<tr>
<th>Macrolide Susceptibility Pattern</th>
<th>Mutational(^a)</th>
<th>Inducible(^b)</th>
<th>No. of Drugs(^c)</th>
<th>Preferred Drugs</th>
<th>Frequency of Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Susceptible</td>
<td>Susceptible</td>
<td>Initial phase ≥ 3</td>
<td>Parenteral (choose 1–2)</td>
<td>Amikacin</td>
<td>Daily (3 times weekly may be used for aminoglycosides)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Imipenem (or Cafoxitin)</td>
<td>Tigecycline</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Oral (choose 2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Azithromycin (clarithromycin)(^d)</td>
<td>Clofazimine</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Clofazimine</td>
<td>Linezolid</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Oral/inhaled (choose 2–3)</td>
<td>Azithromycin (clarithromycin)(^d)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Clofazimine</td>
<td>Linezolid</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Inhaled amikacin</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Macrolide susceptibility

Mutational Susceptible

Inducible resistant

Initial phase
IV plus oral therapy for at least 4 week

IV drug (2-3 drug)
- Imipenem
- Cefoxitin
- Tigecycline
- Amikacin

Oral drugs (2-3 drugs)
- Linezolid
- Doxycycline
- Ciprofloxacin
- Moxifloxacin
- Clofazmine

Continuation phase 2-3 oral drugs for 12 month after negative culture
<table>
<thead>
<tr>
<th>Mutational</th>
<th>Inducible</th>
<th>No. of Drugs</th>
<th>Preferred Drugs</th>
<th>Frequency of Dosing</th>
</tr>
</thead>
</table>
| Susceptible| Resistant  | Initial phase ≥ 4 | *Parenteral (choose 2–3)*  
Amikacin  
Imipenem (or Cefoxitin)  
Tigecycline  
*Oral (choose 2–3)*  
Azithromycin (clarithromycin)*  
Clofazimine  
Linezolid | Daily (3 times weekly may be used for aminoglycosides)                                                                 |
|            |           | Continuation phase ≥ 2 | *Oral/inhaled (choose 2–3)*  
Azithromycin (clarithromycin)*  
Clofazimine  
Linezolid  
Inhaled amikacin |
Macrolide susceptibility

Mutational resistant

Inducible Susceptible/resistant

Initial phase
IV plus oral therapy for at least 4 week

IV drug (2-3 drug)
- Imipenem
- Cefoxitin
- Tigecycline
- Amikacin

Oral drugs (2-3 drugs)
- Linezolid
- Doxycycline
- Ciprofloxacin
- Moxifloxacin
- Clofazmin

Continuation phase 2-3 oral drugs for 12 month after negative culture
<table>
<thead>
<tr>
<th>Mutational(^a)</th>
<th>Inducible(^b)</th>
<th>No. of Drugs(^c)</th>
<th>Preferred Drugs</th>
<th>Frequency of Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resistant</td>
<td>Susceptible or resistant</td>
<td>Initial phase ≥ 4</td>
<td>Parenteral (choose 2–3) Amikacin Imipenem (or Cefoxitin) Tigecycline Oral (choose 2–3) Azithromycin (clarithromycin)(^9) Clofazimine Linezolid</td>
<td>Daily (3 times weekly may be used for aminoglycosides)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Continuation Phase ≥ 2</td>
<td>Oral/inhaled (choose 2–3) Azithromycin (clarithromycin)(^9) Clofazimine Linezolid Inhaled amikacin</td>
<td></td>
</tr>
<tr>
<td>Drug</td>
<td>Daily Dosing</td>
<td>Thrice Weekly Dosing</td>
<td>Hepatic Impairment</td>
<td>Renal Impairment</td>
</tr>
<tr>
<td>-----------------------</td>
<td>-------------------------</td>
<td>----------------------</td>
<td>---------------------</td>
<td>-----------------------</td>
</tr>
<tr>
<td><strong>Oral</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Azithromycin</td>
<td>250–500 mg per day</td>
<td>500 mg per day</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>500–750 mg twice per day</td>
<td>N/A</td>
<td>N/A</td>
<td>250–500 mg dosed at intervals according to CrCl</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>500 mg twice per day</td>
<td>500 mg twice per day</td>
<td>N/A</td>
<td>Reduce dose by 50% if CrCl &lt; 30 mL/min</td>
</tr>
<tr>
<td>Clofazimine&lt;sup&gt;a&lt;/sup&gt;</td>
<td>100–200 mg per day</td>
<td>N/A</td>
<td>Caution in severe hepatic impairment</td>
<td>N/A</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>100 mg once to twice a day</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>15 mg/kg per day</td>
<td>25 mg/kg per day</td>
<td>N/A</td>
<td>Increase dosing interval (eg, 15–25 mg/kg, 3 times per week)</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>5 mg/kg up to 300 mg per day</td>
<td>N/A</td>
<td>Caution</td>
<td>N/A</td>
</tr>
<tr>
<td>Linezolid</td>
<td>600 mg once or twice per day&lt;sup&gt;b&lt;/sup&gt;</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>400 mg per day</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Rifabutin</td>
<td>150–300 mg per day (150 mg per day with clarithromycin)</td>
<td>300 mg per day</td>
<td>Caution</td>
<td>Reduce dose by 50% if CrCl &lt; 30 mL/min</td>
</tr>
<tr>
<td>Rifampicin (rifampin)</td>
<td>10 mg/kg (450 mg or 600 mg) per day</td>
<td>600 mg per day</td>
<td>Caution</td>
<td>N/A</td>
</tr>
<tr>
<td>Trimethoprim/ sulfamethoxazole</td>
<td>800 mg/160 mg tab twice daily</td>
<td>N/A</td>
<td>Caution</td>
<td>Reduce dose by 50% if CrCl &lt; 5–30 mL/min</td>
</tr>
</tbody>
</table>
## Parenteral

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dosage Details</th>
<th>Monitoring</th>
<th>Dosage Adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin (IV)</td>
<td>10–15 mg/kg per day, adjusted according to drug level monitoring&lt;sup&gt;a&lt;/sup&gt;</td>
<td>N/A</td>
<td>Reduce dose or increase dosing interval (eg, 15 mg/kg, 2–3 times per week)</td>
</tr>
<tr>
<td>Cefoxitin (IV)</td>
<td>2–4 g 2–3 times daily (maximum daily dose is 12 g/day)</td>
<td>N/A</td>
<td>Reduce dose or increase dosing interval</td>
</tr>
<tr>
<td>Imipenem (IV)</td>
<td>500–1000 mg, 2–3 times per day</td>
<td>N/A</td>
<td>Reduce dose or increase dosing interval</td>
</tr>
<tr>
<td>Streptomycin (IV or IM)</td>
<td>10–15 mg/kg per day, adjusted according to drug level monitoring</td>
<td>15–25 mg/kg per day, adjusted according to drug level monitoring</td>
<td>Reduce dose or increase dosing interval (eg, 15 mg/kg, 2–3 times per week)</td>
</tr>
<tr>
<td>Tigecycline (IV)</td>
<td>25–50 mg once or twice per day&lt;sup&gt;b&lt;/sup&gt;</td>
<td>N/A</td>
<td>25 mg once or twice daily per day in severe hepatic impairment</td>
</tr>
</tbody>
</table>

## Inhalation

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dosage Details</th>
<th>Monitoring</th>
<th>Dosage Adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin liposome inhalation suspension</td>
<td>590 mg per day</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Amikacin, parenteral formulation</td>
<td>250–500 mg per day</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

---

<sup>a</sup> Adjust dose according to clinical response and drug level monitoring. If no drug level monitoring, dosing interval should be reduced to 2–3 times per week.

<sup>b</sup> This dosage may need to be adjusted based on the severity of hepatic impairment.

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Monitoring drug side effect

- Every 1-2 month CBC/CMP on oral therapy
- Monthly audiogram/vestibular monitoring on IV aminoglycosides
- Weekly creatinine on IV aminoglycosides
- Frequent evaluation of balance, tinnitus, fullness
- Caution with fluoroquinolone related tendinopathy
Sputum collection

- After initial phase
  - Culture conversion
- After therapy completion
  - Ensure culture conversion
- During therapy
  - Depends!
  - Every 2-3 month!
Back to the case

- Tolerated IV Tigecycline for 4 weeks
- Tolerated inhaled Amkiacin for 3 weeks
- Currently on 2 oral drugs
  - Linezolid
  - Azithromycin
  - Waiting for Clofazmine
Acid-Fast Bacillus (AFB) Identification with Reflex to Susceptibility
ARUP test code 0060997

Source: Respiratory

Body Site: Sputum Induced

Free Text Sources: See ESP

Final Report

Mycobacteroides (Mycobacterium) abscessus Group

A T28C substitution or truncation in erm(41) gene was detected. This indicates a non-functional erm(41) gene (i.e. no inducible resistance). Resistance to clarithromycin could occur due to other acquired mechanisms. Correlate results with phenotypic susceptibility.

Identification by MALDI-TOF

This test was developed and its performance characteristics determined by ARUP Laboratories. It has not been cleared or approved by the U.S. Food and Drug Administration. This test was performed in a CLIA-certified laboratory and is intended for clinical purposes. This assay cannot differentiate members of the M. abscessus group.
## Susceptibility Results

**Organism:** Mycobacteroides (Mycobacterium) abscessus Group

<table>
<thead>
<tr>
<th>Drug</th>
<th>Interpretation</th>
<th>MIC (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin</td>
<td>SUSCEPTIBLE</td>
<td>16</td>
</tr>
<tr>
<td>Cefoxitin</td>
<td>INTERMEDIATE</td>
<td>32</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>RESISTANT</td>
<td>8</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>RESISTANT</td>
<td>&gt;=8</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>RESISTANT</td>
<td>&gt;=16</td>
</tr>
<tr>
<td>Imipenem</td>
<td>RESISTANT</td>
<td>32</td>
</tr>
<tr>
<td>Linezolid</td>
<td>SUSCEPTIBLE</td>
<td>8</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>RESISTANT</td>
<td>&gt;=8</td>
</tr>
<tr>
<td>Tigecycline</td>
<td></td>
<td>0.06</td>
</tr>
<tr>
<td>Trimethoprim/Sulfamethoxazole</td>
<td>RESISTANT</td>
<td>4/76</td>
</tr>
<tr>
<td>Mutational</td>
<td>Inducible</td>
<td>No. of Drugs</td>
</tr>
<tr>
<td>------------</td>
<td>----------</td>
<td>--------------</td>
</tr>
<tr>
<td>Resistant</td>
<td>Susceptible or resistant</td>
<td>Initial phase ≥ 4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Continuation Phase ≥ 2</td>
</tr>
</tbody>
</table>
- Patient was placed on IV Tigecycline and inhaled Amikacin
- Oral azithromycin and linezolid
  - Will add clofazimine
• Thank you!