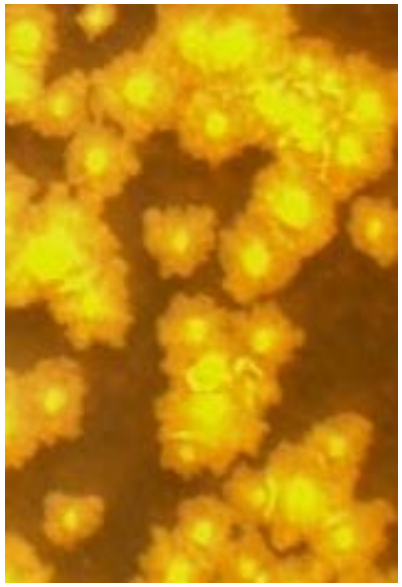
What Else Is There?
Adjunctive Therapies



Charles L. Daley, MD
National Jewish Health
University of Colorado

Conflict of Interest Disclosures

- Research grant
  - Insmed: Phase II multicenter randomized placebo controlled clinical trial of inhaled liposomal amikacin in pulmonary NTM infections
- Advisory Board:
  - Insmed
  - Johnson and Johnson

What is an adjunct?

- **Noun** – A thing added to something else as a supplementary rather than an essential part: computer technology is an **adjunct to** learning

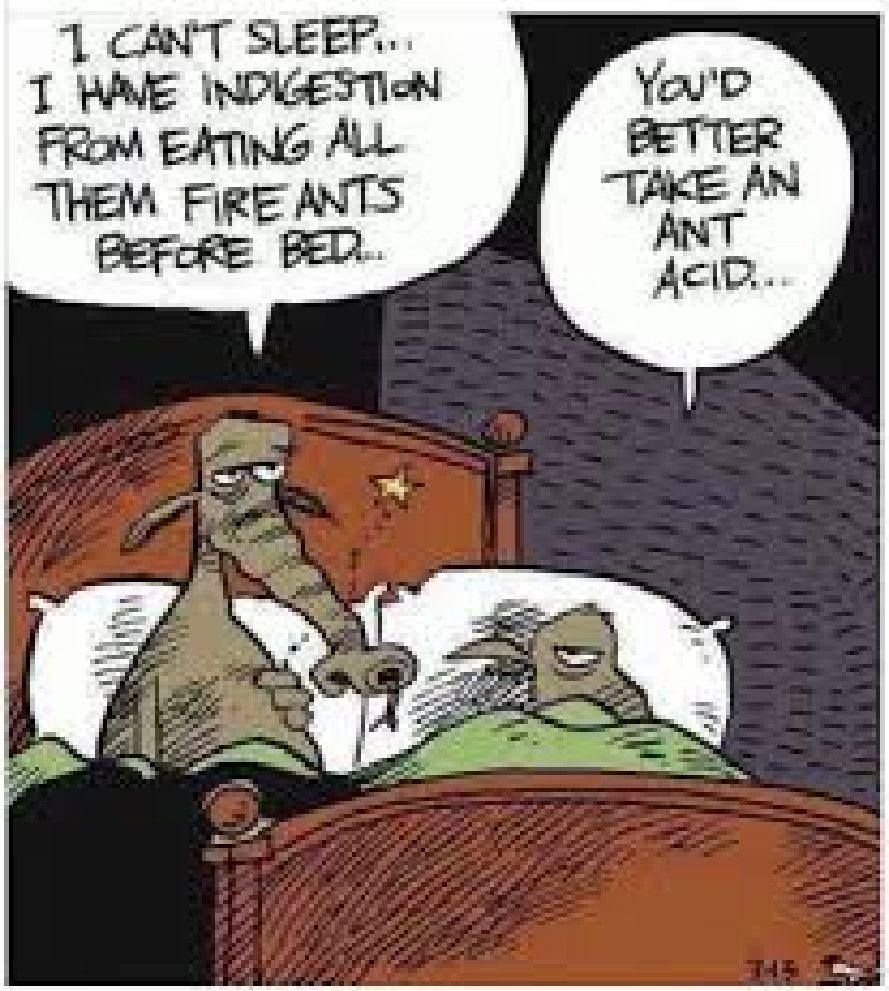
- **Adjective** – connected or added to something, typically in an auxiliary way: **adjunct** therapies include immunotherapy

New Oxford American Dictionary

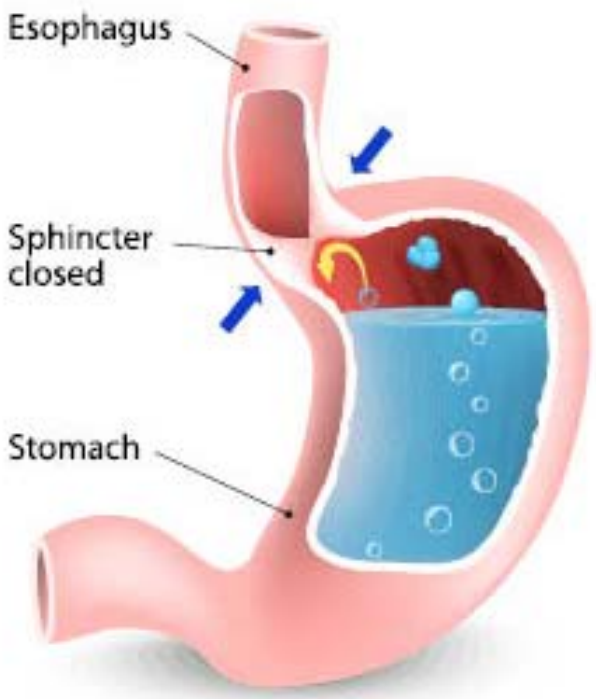
What Else Is There?
Adjuvant Therapies

- Airway clearance
- Treatment of comorbidities
- Nutritional support
- Immunotherapy
- Surgical resection

Gastroesophageal Reflux Disease
GERD



GERD



Healthy

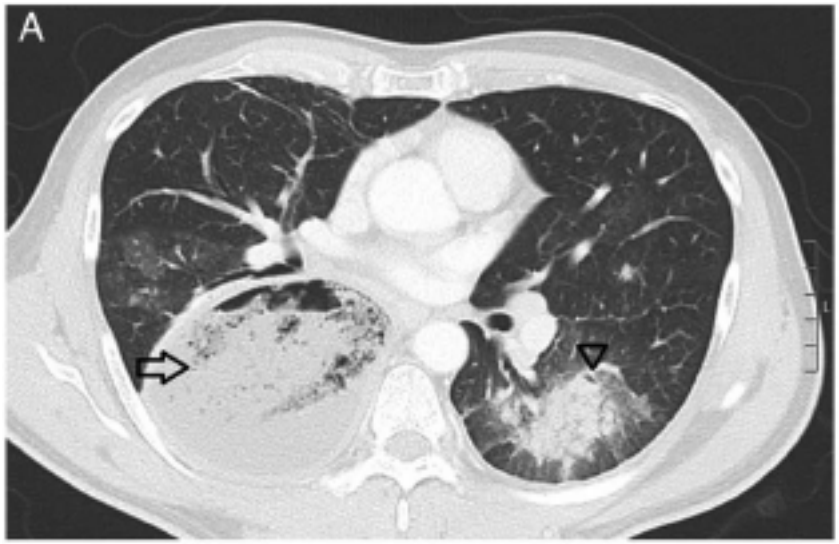
GERD

GERD

- Prevalence: 10-20% in Western populations and < 5% in Asia
- Asymptomatic GERD is common in patients with lung disease and associated with worse outcomes
  - 62% in asthma, 75% in idiopathic pulmonary fibrosis patients
- Diagnosis is often based on a trial of therapy – not accurate
- The best diagnostic test for detecting both acid and non-acid reflux is a 24-hr esophageal impedance pH test

Association of Esophageal Disorders and NTM

- *M. fortuitum* associated with achalasia in a report from 1970 with other reports to follow
- Most reports describe an association between rapidly growing mycobacteria and esophageal disease



Banerjee R, et al. Br J Dis Chest 1970;64:112
Varghese G, et al. Thorax 1988;43:151
Hadjiliadis D, et al. May Clin Proc 1999;74:45
Griffith DE, et al. Am Rev Respir Dis 1993;147:1271
Sunwoo BY. Thorax 2017;72:485

Prevalence of Clinically Diagnosed GERD in Patients with MAC

- 58 patients with MAC pulmonary disease and 58 controls with lung disease without MAC
- Subjects were given a DeMeester questionnaire to assess for GERD symptoms
- Results:
  - 44.2% of MAC patients had GERD vs 27.6% of controls ($p = 0.019$)
  - 15.5% of MAC patients were suspected to be aspirating vs 5.2% of controls ($p = 0.032$)

Thomson RM, et al. Chest 2007;131:1166

Prevalence of GERD in Patients with NTM Pulmonary Disease

- 58 patients with nodular bronchiectatic NTM pulmonary disease in South Korea
  - 27 with MAC, 31 with *M. abscessus*
- Ambulatory 24-hr esophageal pH monitoring
- Results:
  - Prevalence of GERD was 26%
  - Only 27% had symptoms of GERD
  - GERD was associated with more extensive disease

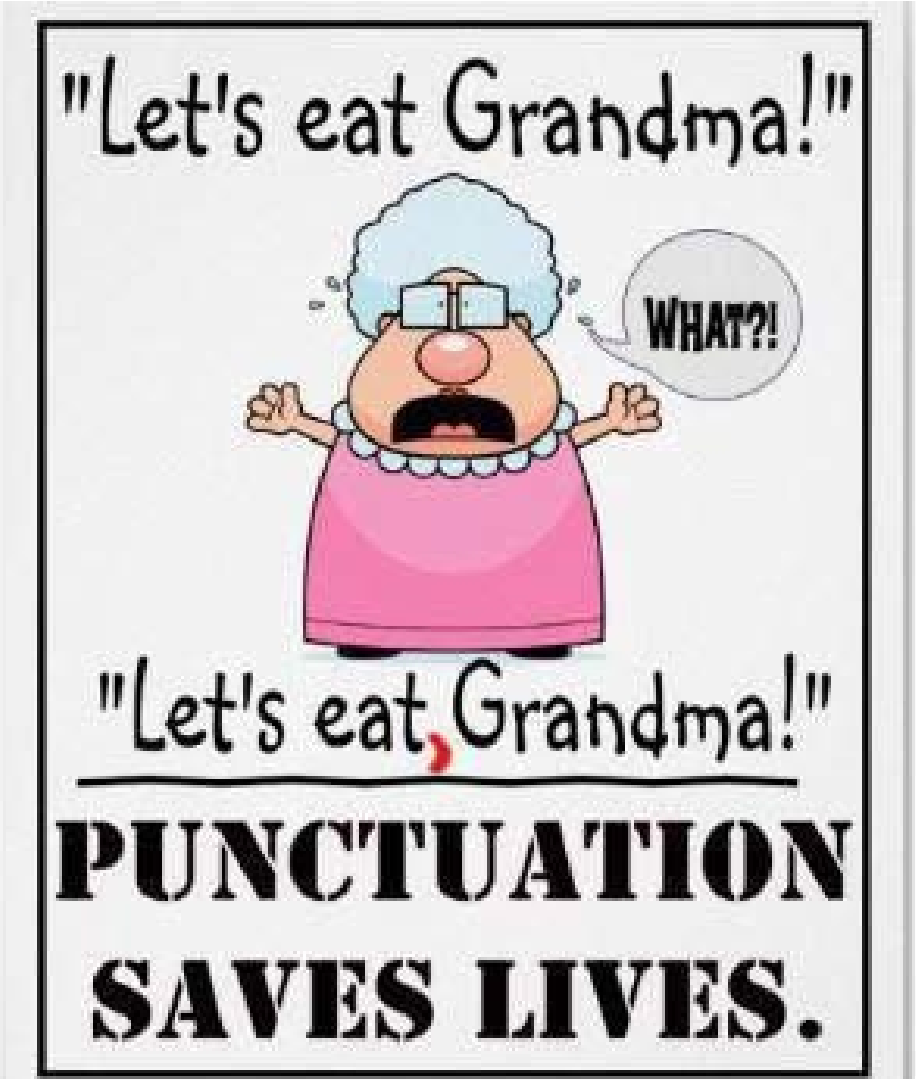
Koh WJ, et al. Chest 2007;131: 1825

Management of GERD

- Lifestyle modifications
  - Elevation of the head of the bed
  - Not eating 2-3 hours before bed
  - Avoidance of trigger foods
  - Only weight loss and elevation of the head of the bed associated with improved pH-metry/symptoms

- Antacid treatment
  - H2 receptor antagonist and/or proton pump inhibitors
- Fundoplication

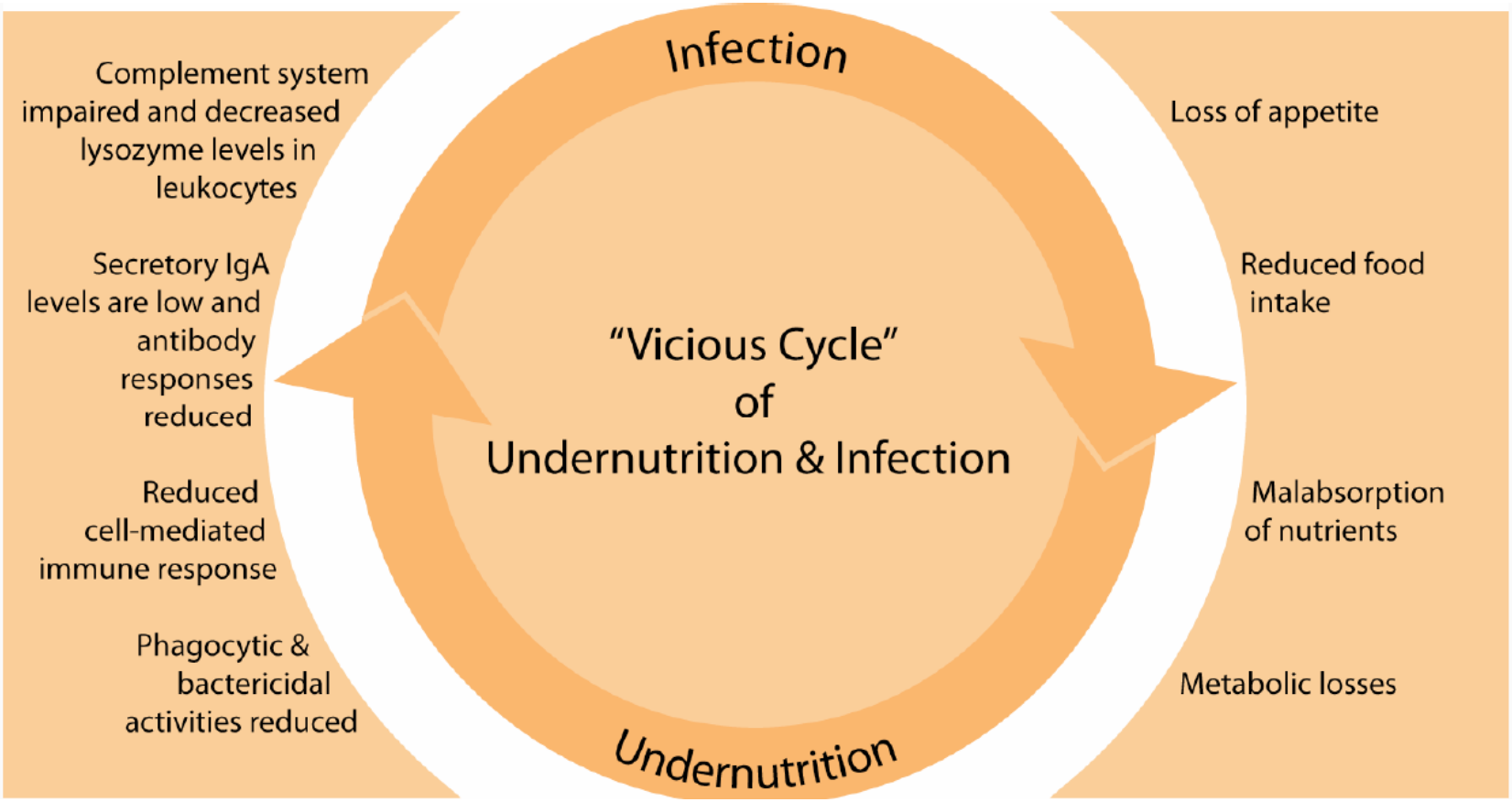
Nutrition


"Let's eat Grandma!"
WHAT?!
"Let's eat, Grandma!"
PUNCTUATION
SAVES LIVES.

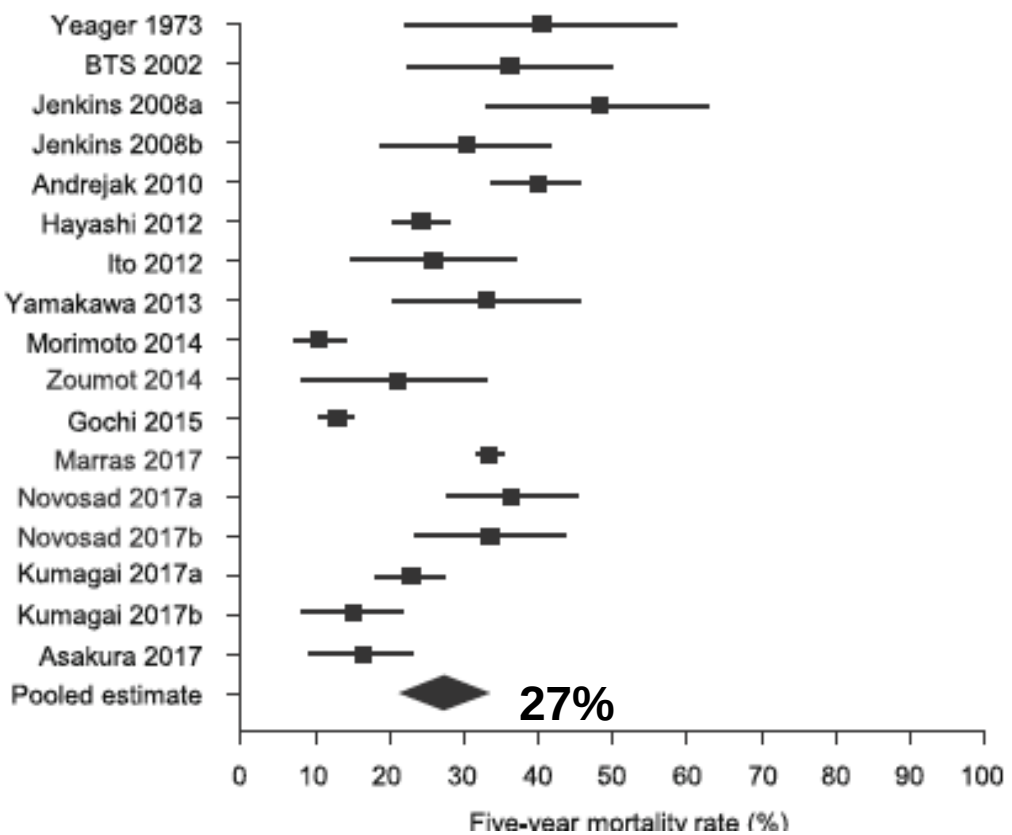
Undernutrition Leads to Deficiencies in…

- Protein
  - Deficit in amino acids needed for cell structure and metabolic function
- Calories
  - Calories derived mostly from macronutrients
    - Protein, carbohydrates, fat
- Micronutrients
  - Vitamins A, D, E, and K; B-complex, Vitamin C, iron, zinc, iodine, calcium, others

Vicious Cycle of Undernutrition and Infection



Five-year All-Cause Mortality and Risk Factors in PMAC – Systematic Review



Positive association with all-cause mortality

- Age
- Male gender
- Co-morbidities
- Cavitary disease
- High inflammatory indices
- **Low BMI (<18.5 kg/m^2)**
- **Low albumin**

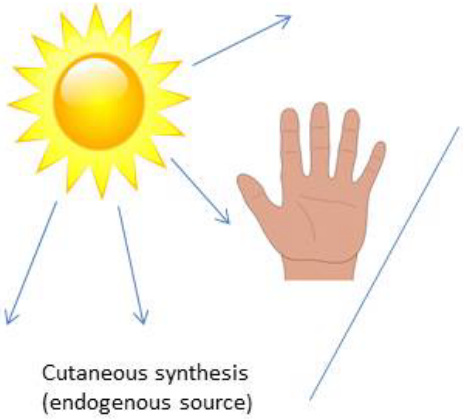
MAC-related mortality, 5-42%

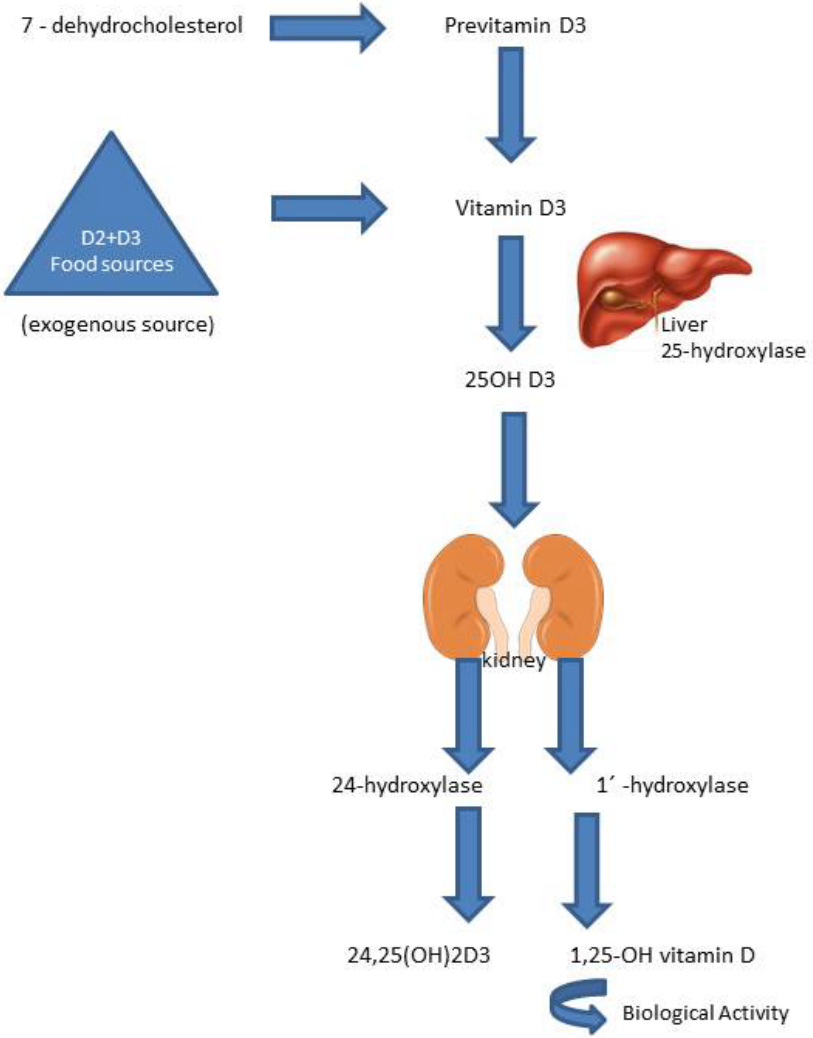
Diel R, et al. BMC Infect Dis 2018;18:206

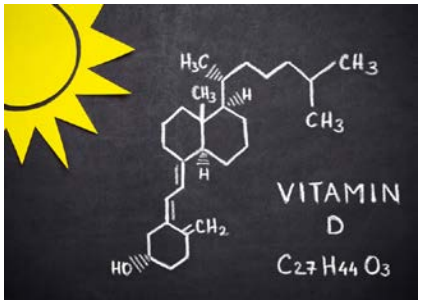
Vitamin D

- Vitamin D is a steroid hormone (not a vitamin)
- Vitamin D is a prime mediator of bone mineral homeostasis
- Also has critical role in innate immune system and bridge to adaptive immunity via autophagy
- Studies of Vit D and tuberculosis have reported mixed findings

Vitamin D Metabolism



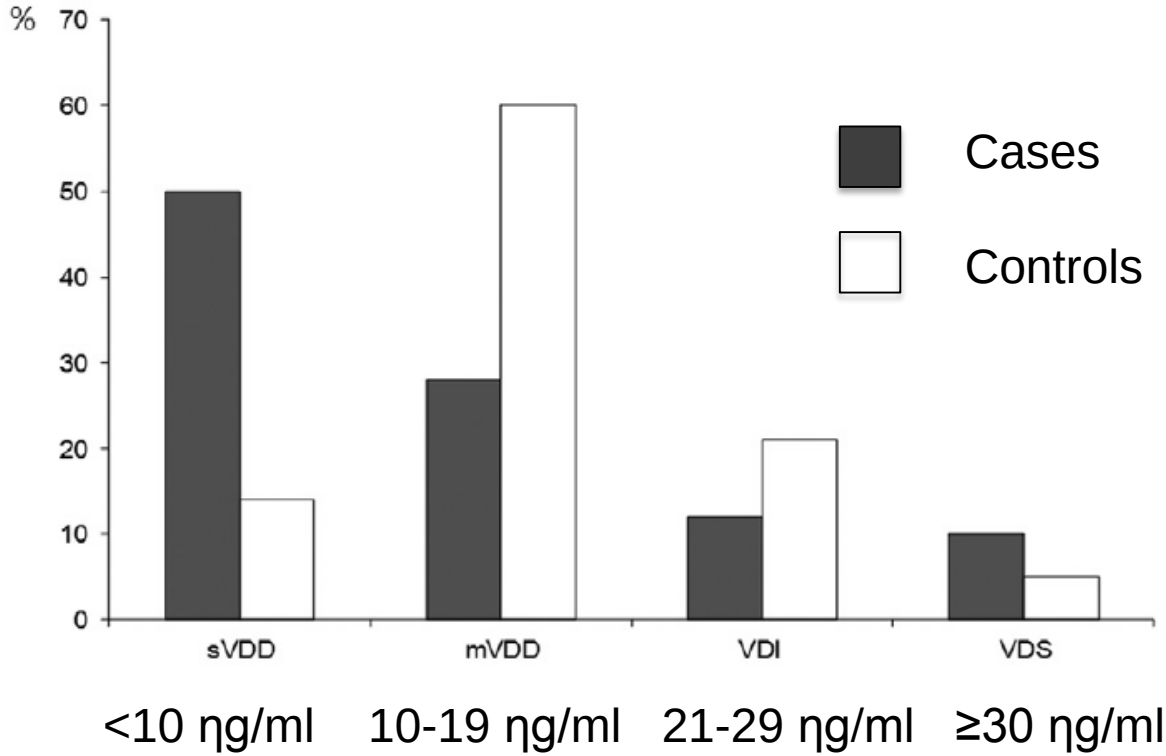




Prevalence of Vitamin D Deficiency in Cases and Controls

104 pulmonary NTM patients vs 312 controls

Assoc. of sVDD and NTM: 3.9 (1.9-8.5)



Jeon K, et al. Respirology 2013;18:93

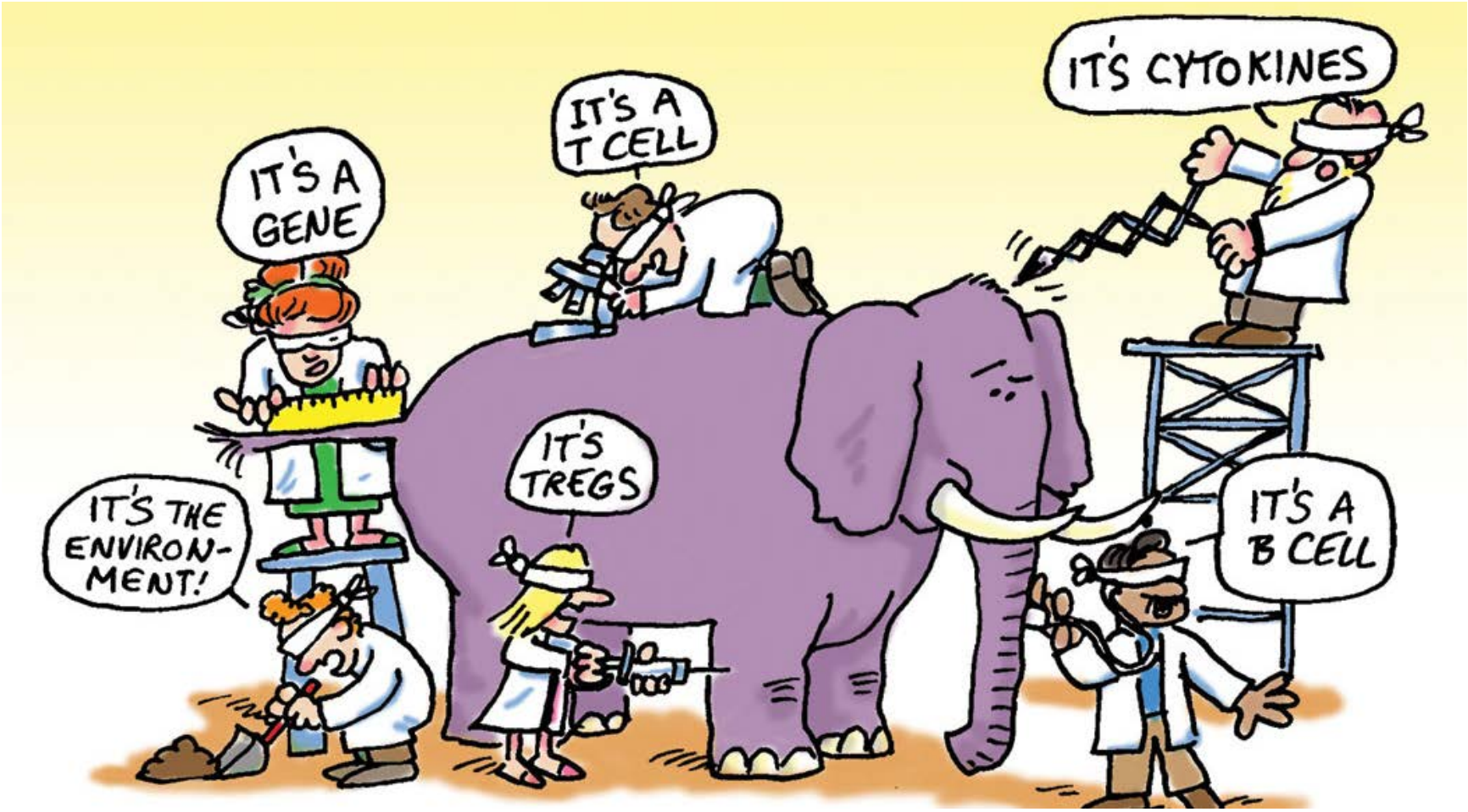
Nutritional Goals

- Protein
  - Normalize pre-albumin and increase albumin as much as possible
- Calories
  - Gain weight – get as close to ideal body weight as possible
- Micronutrients
  - Get Vit D into target range of 30-100, probably aiming for mid range
  - MVI daily – don't go crazy

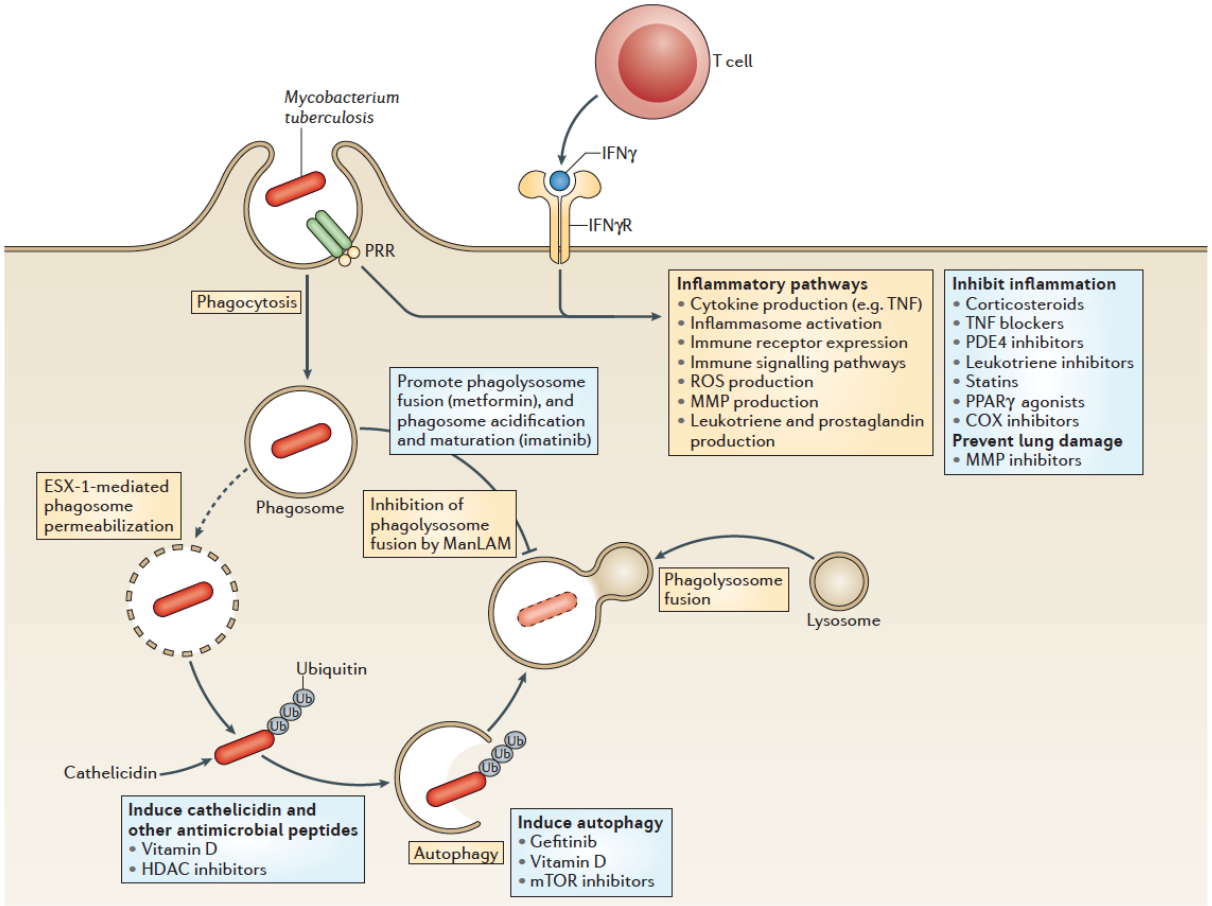
Consult with a Dietician

Host Directed Therapy

Immunotherapy



Targets of Host-Directed Therapy for *M. tuberculosis*



Wallis RS, et al. Nature Rev 2015;15:255

Immunotherapy

- BTS sponsored randomized controlled trial of patients with pulmonary NTM evaluating *M. vaccae* vaccination
  - no difference in outcomes compared with placebo

Jenkins PA et al. Thorax 2008;63:627
Lam PK, et al. AJRCCM;2006;173;1283
Milanes-Virelles MT, et al. BMC Infect Dis 2008;8:17

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Immunotherapy

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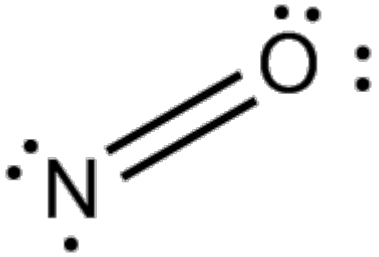
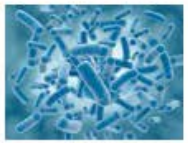
  - no difference in outcomes compared with placebo
- InterMune sponsored randomized controlled trial of inhaled interferon-gamma in patients with refractory pulmonary MAC
  - No difference compared with placebo, so trial terminated
- Randomized controlled trial of IM interferon gamma in predominantly MAC pulmonary disease performed in Cuba
  - Composite score (symptoms, radiology, microbiology) better in those receiving inhaled interferon-gamma (72%) compared with placebo (36%) (p=0.37)

Jenkins PA et al. Thorax 2008;63:627
Lam PK, et al. AJRCCM;2006;173;1283
Milanes-Virelles MT, et al. BMC Infect Dis 2008;8:17

Nitric Oxide



Nitric Oxide

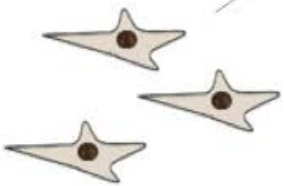


ANTIBACTERIAL

APOPTOSIS

CELL PROLIFERATION

ANGIOGENESIS

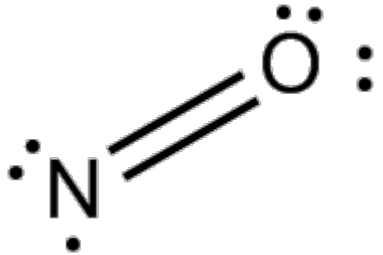


IMMUNE RESPONSE

CARDIOVASCULAR HEMOSTASIS

NEUROTRANSMISSION

Nitric Oxide

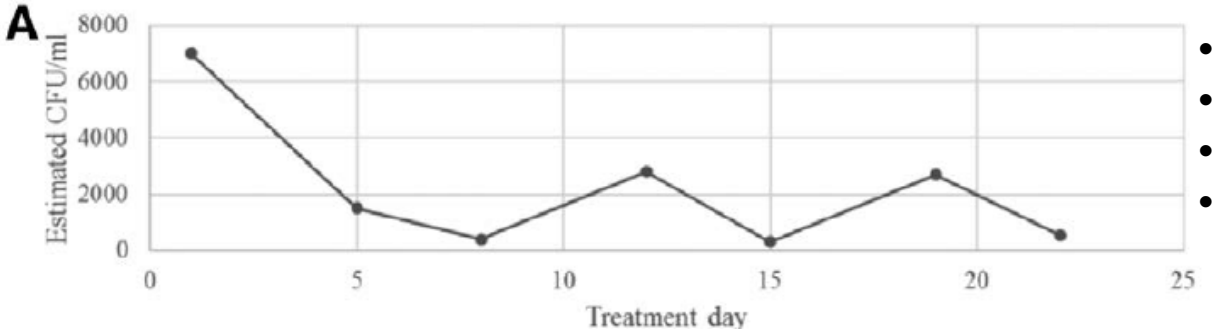


- Hydrophobic, free-radical, nanomolecular gas
- Essential part of innate immune system
- Up-regulated by inducible NO synthase (iNOS) during inflammatory conditions/infections
- In vitro, ex vivo, and animal models show potent antimicrobial affects
- Potential adverse reactions include binding of NO to hemoglobin ⟶ methemoglobin

Inhaled NO for *M. abscessus*

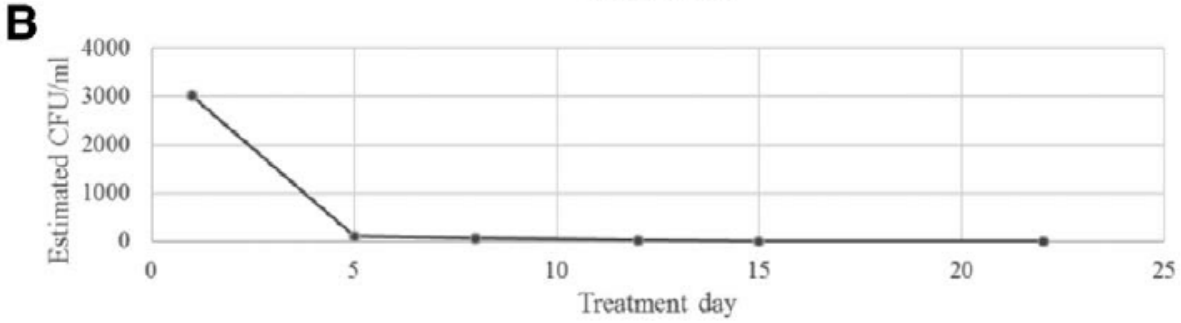
Compassionate use intermittent 30 min treatments NO 160 ppm 3-5 times/day over ≈3 weeks added to failing antibiotic regimen

- Patient 1 – 19yo progressive *M. abscessus* for 7 years, failed multiple treatment regimens, FEV1 100→50%



- Improvement in well-being
- FEV1 went from 47% to 51%
- No adverse reactions
- MetHb 4.5%

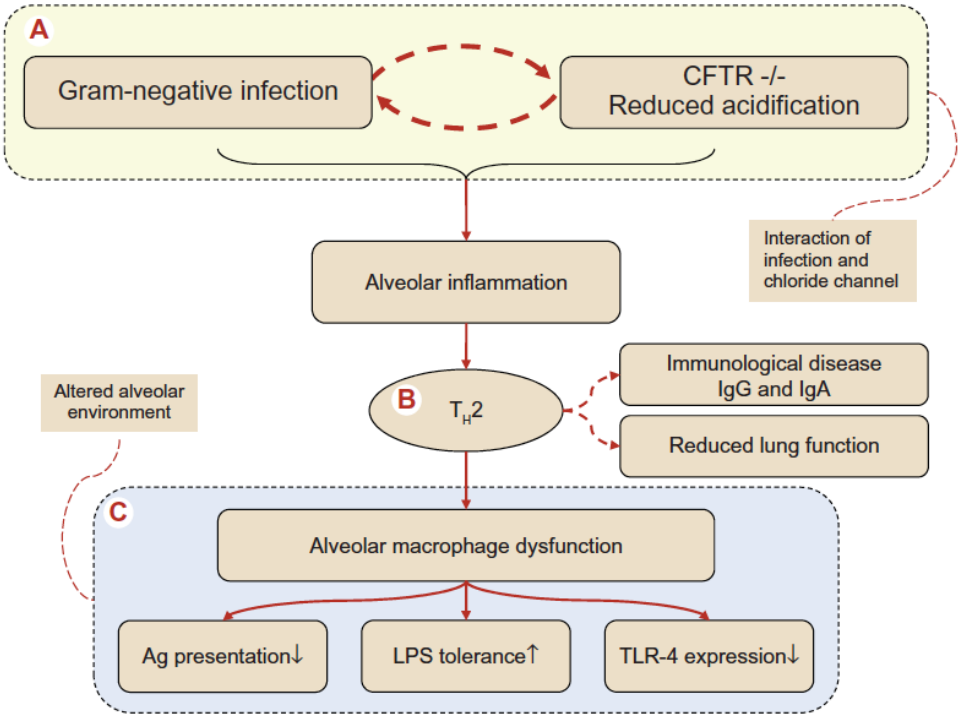
- Patient 2 – 13yo progressive M. abscessus for 2 years, failed treatment, FEV1 110-65%, subacute deterioration



- Improvement in well-being
- FEV1 went from 65% to 63%
- No adverse reactions
- MetHb 4.7%

Yaacoby-Bianu. Pediatr Infect Dis J 2017

Alveolar Macrophage Dysfunction in Cystic Fibrosis



Heslet L, et al. J Inflamm Res2012;5:19-27

Granulocyte Macrophage Colony Stimulating Factor (GM-CSF)

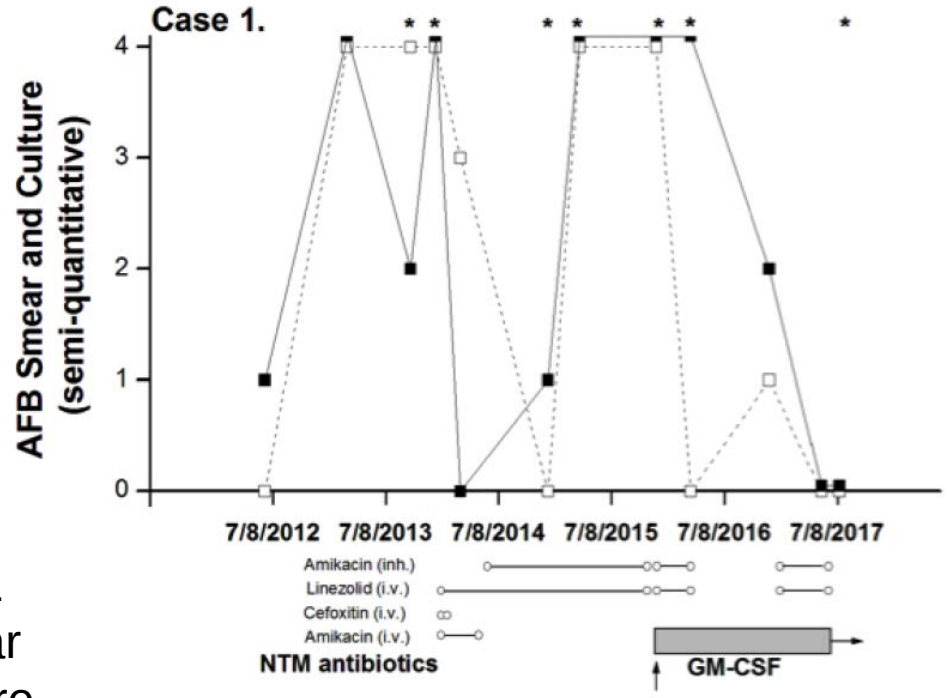
- Alveolar Macs from GM-CSF -/- mice exhibit defective phagocytosis, bacterial killing and reduced H_2O_2 production
- GM-CSF knockout models of *M. abscessus* infection are more susceptible than wild-type mice

Ballinger MN, et al. AJRCMB 2006;34:766
De Groote MA, et al. J Antimicrob Chemother 2014;69:1057

Inhaled Granulocyte-Macrophage Colony Stimulating Factor for *M. abscessus*

Case 1 – 10 y/o delta 508 homozygous female with 3.5 year history of *M. abscessus*

- Aerosolized GM-CSF, 250 µg twice daily added to antibiotics and given on alternate weeks



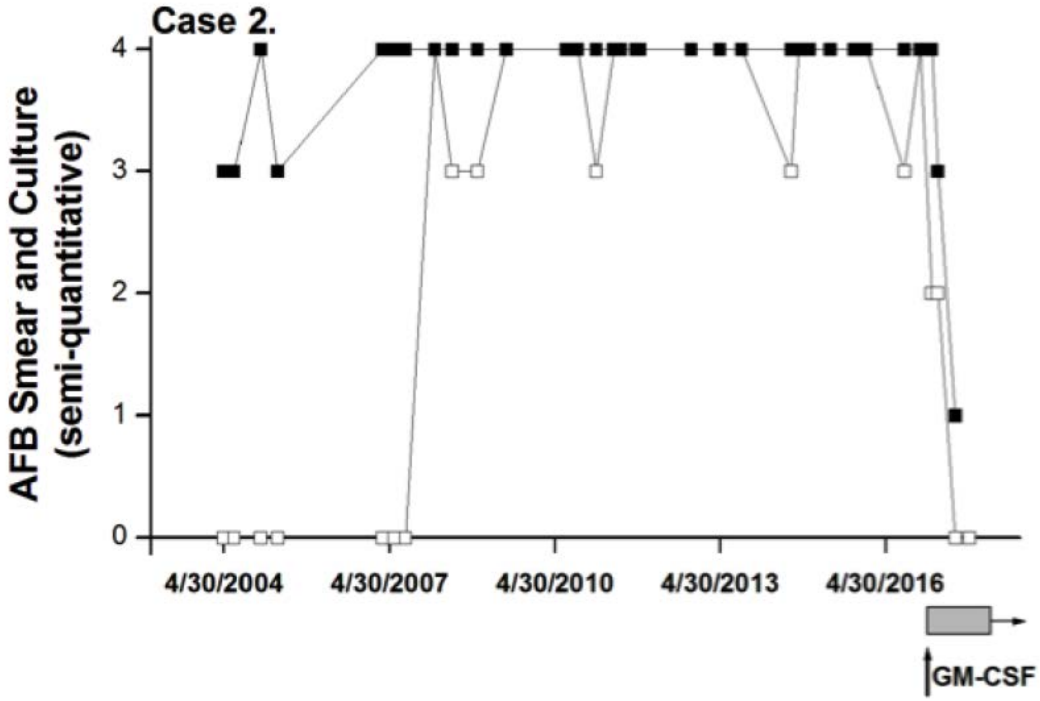
* BAL
□ Smear
■ Culture

Scott JP, et al. Eur Respir J 2018. epub

Inhaled Granulocyte-Macrophage Colony Stimulating Factor for *M. abscessus*

Case 2 – 25 y/o delta 508 homozygous male with 13 year history of *M. abscessus*

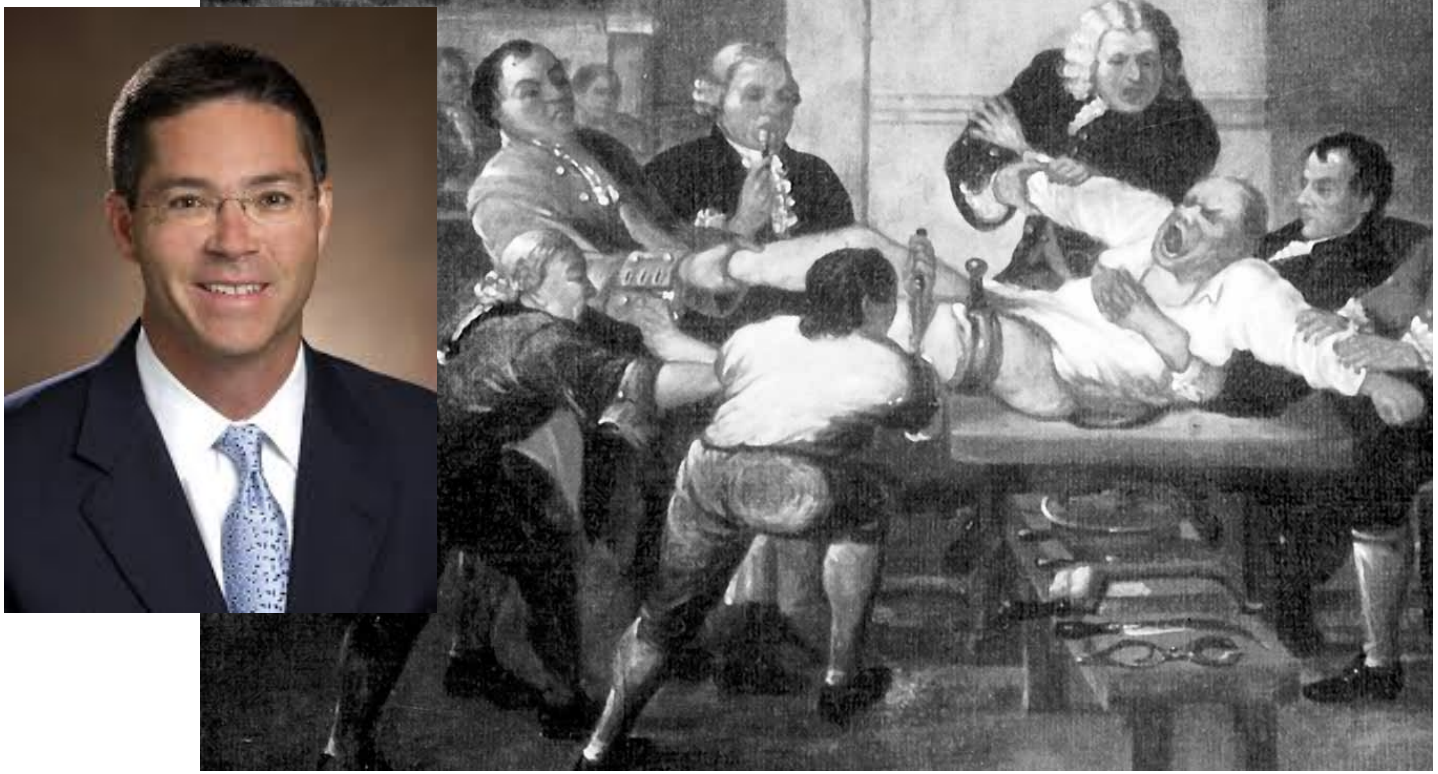
- Aerosolized GM-CSF, 250 µg twice daily added to antibiotics and given on alternate weeks



After six months of GM-CSF, smears became negative

Scott JP, et al. Eur Respir J 2018. epub

Surgery



Who Should Have Surgical Resection?

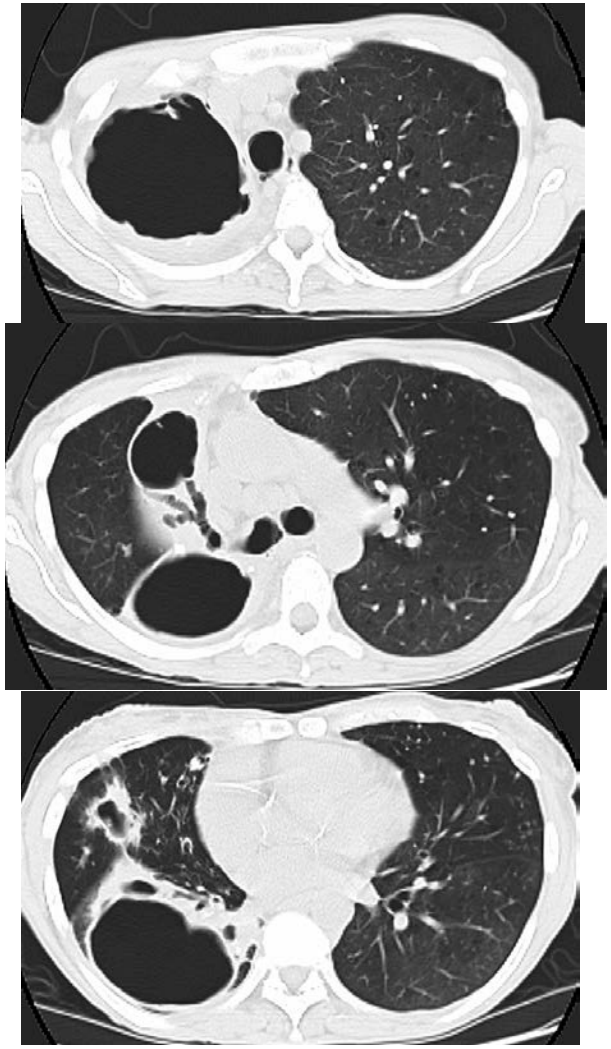
Indications

- Resistant organisms
  - Macrolide resistant MAC,
  - M. *abscessus* subspecies *abscessus*
  - Other difficult to treat NTM
- Treatment failures
- Focal pulmonary disease
  - Focal cavitary disease
  - Focal bronchiectasis
- Complications (e.g., hemoptysis)

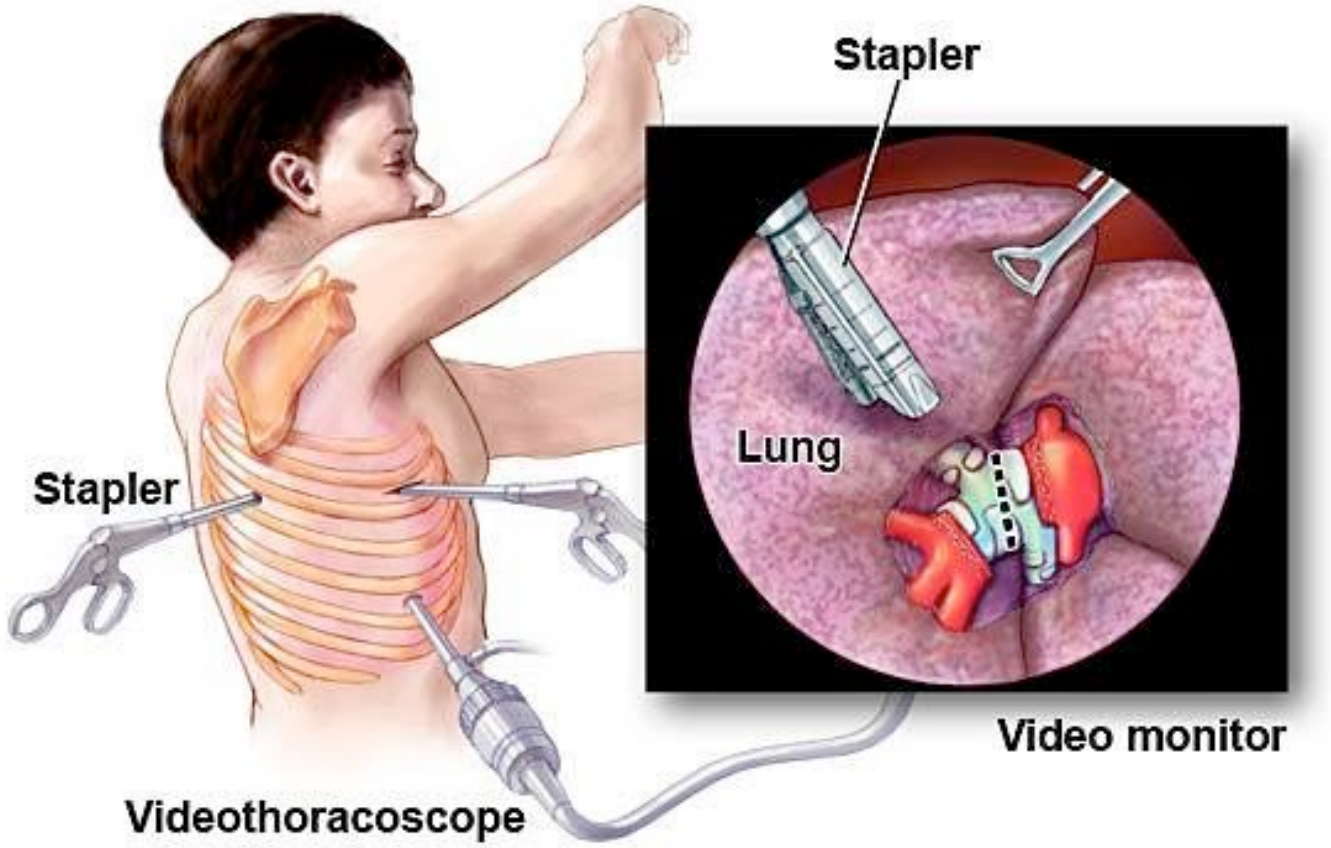
Contraindications

- Inadequate lung function
- Pulmonary hypertension
- Malnutrition
- Other serious co-morbidities

What Does Focal Disease Mean?



Video-assisted Thoracic Surgery
VATS



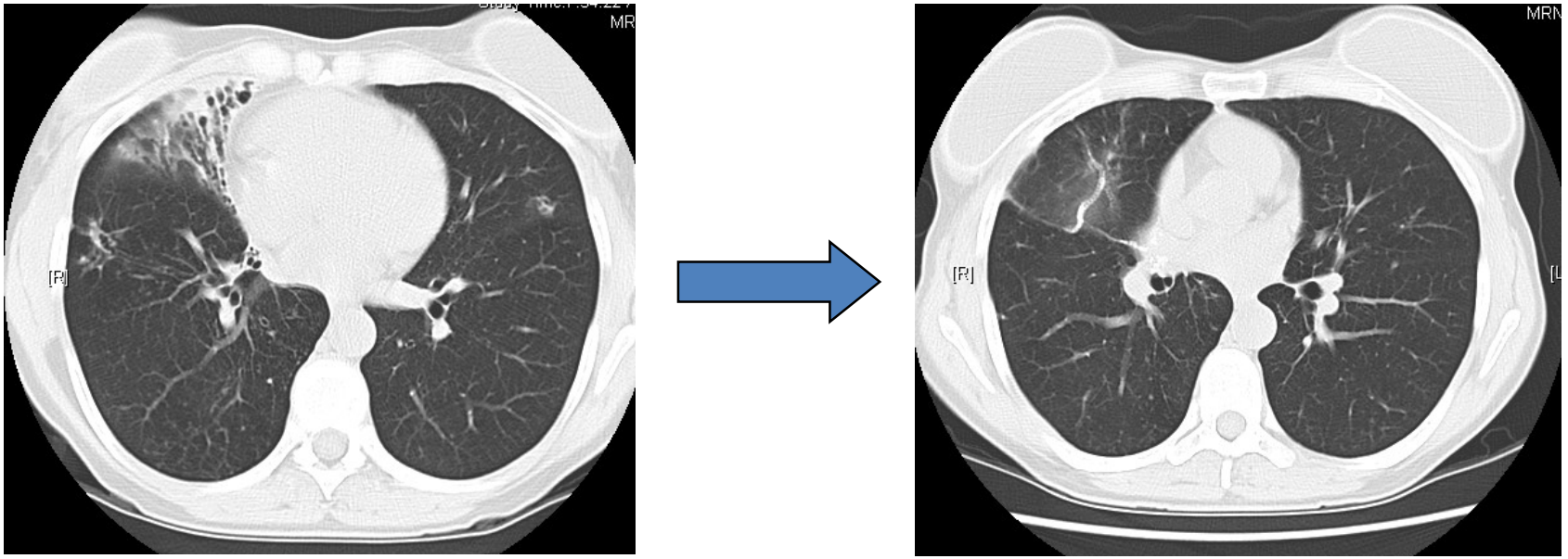
Outcomes in Surgical Studies Macrolide Era

Study, Year	N	Species	Complications	Operative Mortality	Post-Op Mortality	Conversion	Relapse
Nelson, 1998	28	MAC	32%	0	7%	88%	4%
Shiraishi, 1998	33	MAC	24%	0	6%	94%	6%
Shiraishi, 2002	21	MAC	29%	0	4.8%	100%	9.5%
Watanabe, 2006	22	MAC	0	0	0	100%	0%
Mitchell, 2008	265	NTM	11.7%	2.6%		NA	NA
Koh, 2008	23	NTM	35%	0	9%	91%	0%
Yu, 2011*	134	NTM	7%	0	0	84%	16%
Kang, 2015	70	NTM	21%	0	1%	81%	0%

* All video-assisted thoracoscopic surgery (VATS)

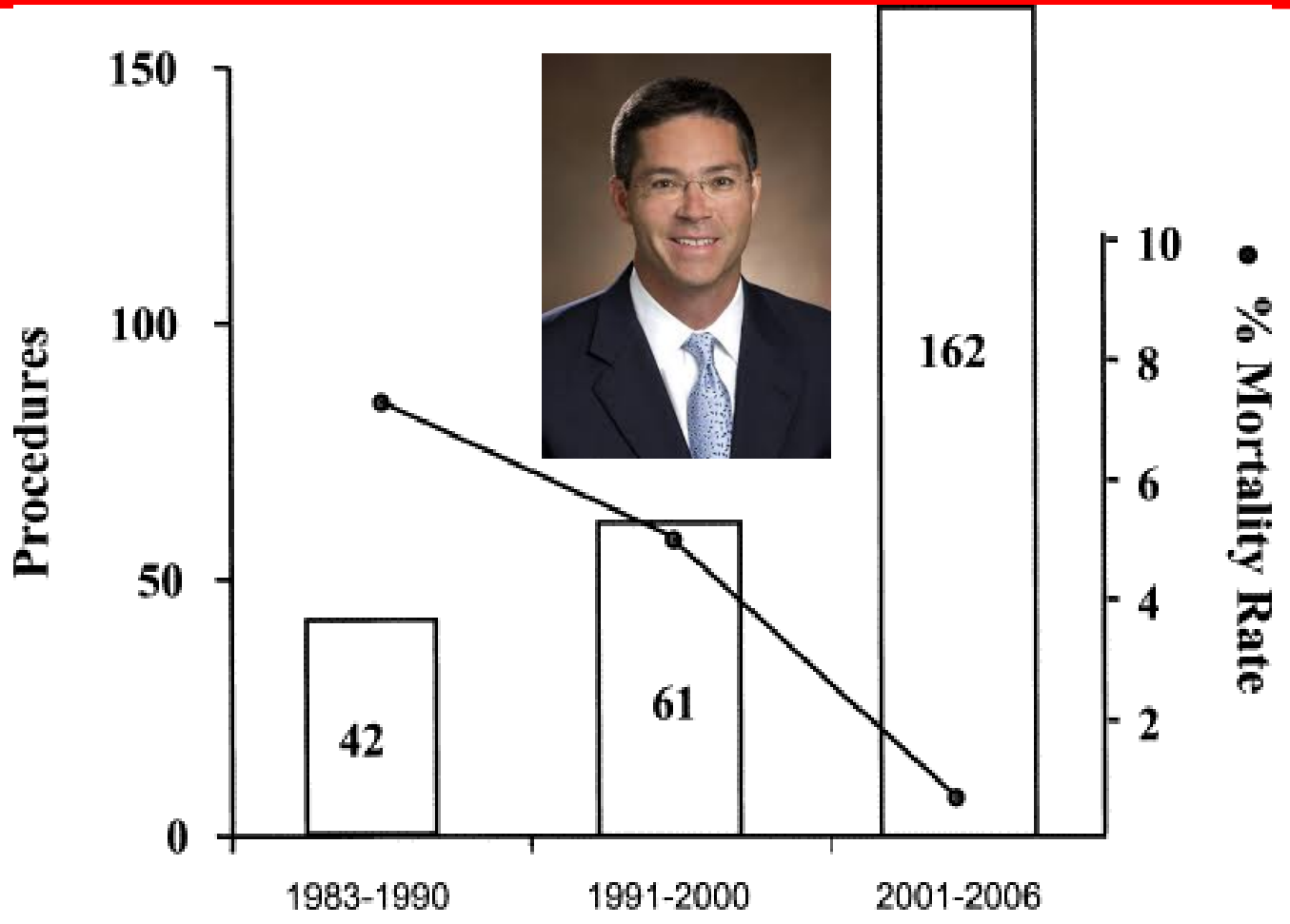
Treatment of *M. abscessus*
Surgery

56 year old Caucasian woman who developed hemoptysis in December 2004. Grew MAC and M. *abscessus.*



	Treatment Success
Jeon, 2009	58% (med) vs 88% (med+surg)
Jarand, 2011	39% (med) vs 65% (med+surg)

Case Volume and Operative Mortality, 1983-2006



Mitchell JD, et al. Ann Thorac Surg 2008;85:1887-93

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Adjuvant Therapies

- Airway clearance – not an adjunct, an essential component of therapy

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- Airway clearance – not an adjunct, an essential component of therapy
- Treatment of comorbidities - not an adjunct

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- Treatment of comorbidities - not an adjunct
- Nutritional support – not an adjunct

What Else Is There?
Adjuvant Therapies

- Airway clearance – not an adjunct, an essential component of therapy
- Treatment of comorbidities - not an adjunct
- Nutritional support – not an adjunct
- Immunotherapy – yes, an adjunct and exciting new area of focus

What Else Is There?
Adjuvant Therapies

- Airway clearance – not an adjunct, an essential component of therapy
- Treatment of comorbidities - not an adjunct
- Nutritional support – not an adjunct
- Immunotherapy – yes, an adjunct and exciting new area of focus
- Surgical resection – sometimes an adjunct and sometimes essential

Thank You!

The Maroon Bells, Aspen, Colorado