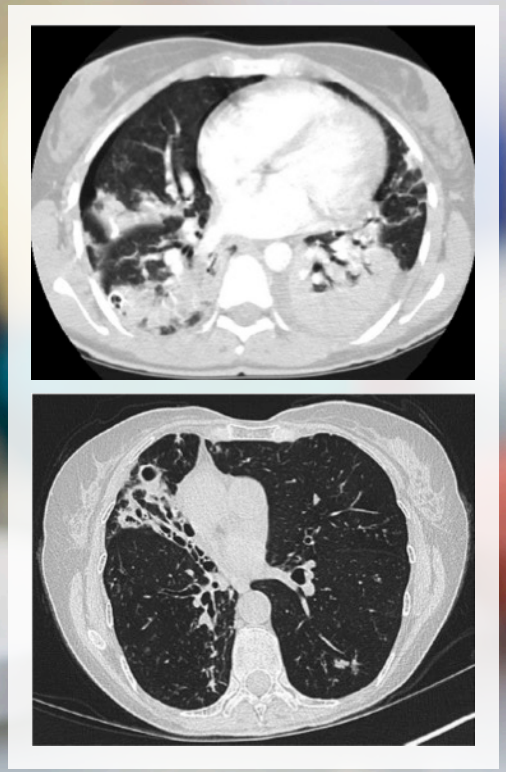


NTM Lung Infections

Nontuberculous Mycobacteria (NTM)

Where does it comes from?

- More than 150 species recognized
- Acquired by inhalation from environment
- Water thought to be the main source
- Patient to patient transmission

Who is at risk?

- Underlying lung disease and/or genetic predisposition
- Cystic Fibrosis patients
- COPD (chronic obstructive pulmonary disease)
- Immunosuppressive therapy
- Elderly population



* Data: www.ntmfacts.com, FDA

Cystic Fibrosis Phase 2a Results: Bacteriology

	CF Infections		CF MABSC
Bacteria	P. Aeruginosa	Other	NTM
N	6	3	2
Length of treatment	9 days	9 days	21 days
% decrease from baseline	62%	60%	99%

- Confidence gained from CF Infections study
- NTM targeted due to positive previous data and ability to directly measure benefit to an NTM patient
- Given difficulty in treating MABSC, AIT opted for a longer treatment period
- Given our success in treating MABSC in CF patients, we believe we can treat MABSC regardless of co-morbitity

Notes
- CF Infections data generated in 2014
- CF MABSC data generated in 2016
- % decrease from baseline of bacterial load calculated at end of treatment period
- No treatment related SAEs

MABSC in CF patients

Compassionate treatment Case 1 & Case 2

Case 1 Background

- 19 year old female
- Rapid progressive changes in CT scan and deterioration in pulmonary functions tests
- Positive NTM – since July 2009

Case 2 Background

- 13 year old female
- Hospitalized for side effects of linezolid
- Positive NTM – since May 2014

Treatment regimen:
Long exposure of high dose of Nitric Oxide

Compassion Treatment Results*

Significant changes in clinical symptoms and bacteriology**:

1. Change in lung function
2. Dramatic reduction in NTM colony forming units (CFU)
3. Increase in distance in the 6 minute walk test
4. Reduction in inflammation
5. Publication pending

* Cases were treated at Rambam Medical center as a compassion treatment. AIT supplied the device and protocol.
** Some of the changes do not appear in both cases

Current Standard of Care for NTM

TABLE 6. COMMON SIDE EFFECTS AND TOXICITIES OF DRUGS USED FOR THERAPY OR PROPHYLAXIS OF NONTUBERCULOUS MYCOBACTERIAL DISEASE
Am J Respir Crit Care Med Vol 175. pp 367–416, 2007

DRUG	MAJOR SIDE EFFECTS/TOXICITY	MONITORING PROCEDURES
Isoniazid	Hypersensitivity (fever, rash) Hepatitis Increased serum levels of phenytoin (Dilantin) Peripheral neuropathy related to pyridoxine deficiency	Clinical symptoms Clinical symptoms; periodic ALT or AST determinations, especially in first 3 mo of therapy Monitor serum levels Clinical symptoms
Ethambutol	Optic neuritis (loss of red/green color discrimination, loss of visual acuity)	Discontinue drug immediately with subjective visual loss; periodic and symptomatic testing for red/green color discrimination and visual acuity (monthly if receiving 25 mg/kg/d); ophthalmology evaluation for symptomatic patients
Rifampin, rifabutin	Orange discoloration of secretions and urine; staining of soft contact lenses Gastrointestinal disturbance (nausea, vomiting) Hypersensitivity (fever, rash) Hepatitis Increased hepatic metabolism of numerous agents, including birth control pills, ketoconazole, quindine, prednisone, oral hypoglycemics (sulfonylureas), digitalis, methadone, warfarin, clarithromycin, and protease inhibitors "Flu-like" syndrome, thrombocytopenia, renal failure	None Clinical symptoms Clinical symptoms Clinical symptoms; AST or ALT determination based on symptoms Monitor clinical status and appropriate serum levels when possible Clinical symptoms; platelet count, serum creatinine as indicated
Rifabutin only	Polymyalgia, polyarthralgia, leukopenia, granulocytopenia, anterior uveitis (rifabutin with clarithromycin)	Clinical symptoms; periodic WBC counts
Streptomycin, amikacin, tobramycin	Vestibular/auditory toxicity (dizziness, vertigo, ataxia, tinnitus, hearing loss)	Clinical symptoms including changes in hearing, ability to walk, dizziness; periodic hearing tests in high-risk patients or those with auditory/vestibular symptoms; periodic amikacin serum levels
Azithromycin, clarithromycin	Gastrointestinal disturbance (nausea, vomiting, diarrhea) Decreased hearing Hepatitis	Clinical symptoms Clinical symptoms Periodic alkaline phosphatase, AST and ALT for first 3 mo
Clarithromycin only	Inhibited hepatic metabolism of several agents, including rifabutin, some protease inhibitors	Monitor clinical status and appropriate serum levels when possible

Definition of abbreviations: ALT alanine aminotransferase; AST aspartate aminotransferase; WBC white blood cell.

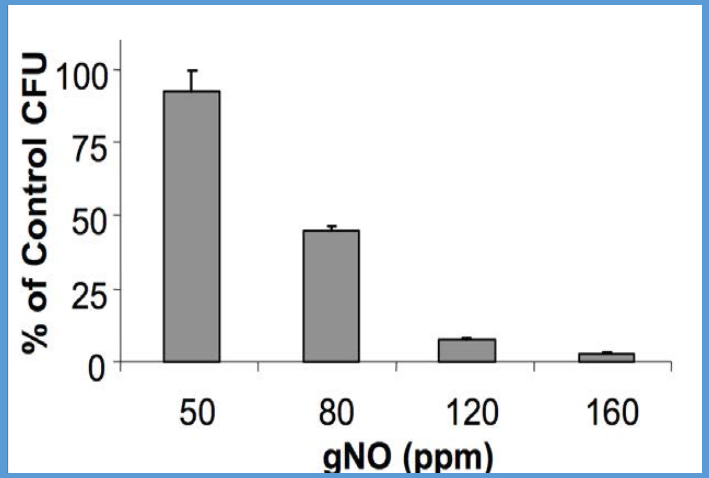
Current Standard of Care for NTM

TABLE 6. COMMON SIDE EFFECTS AND TOXICITIES OF DRUGS USED FOR THERAPY OR PROPHYLAXIS OF NONTUBERCULOUS MYCOBACTERIAL DISEASE
Am J Respir Crit Care Med Vol 175. pp 367–416, 2007

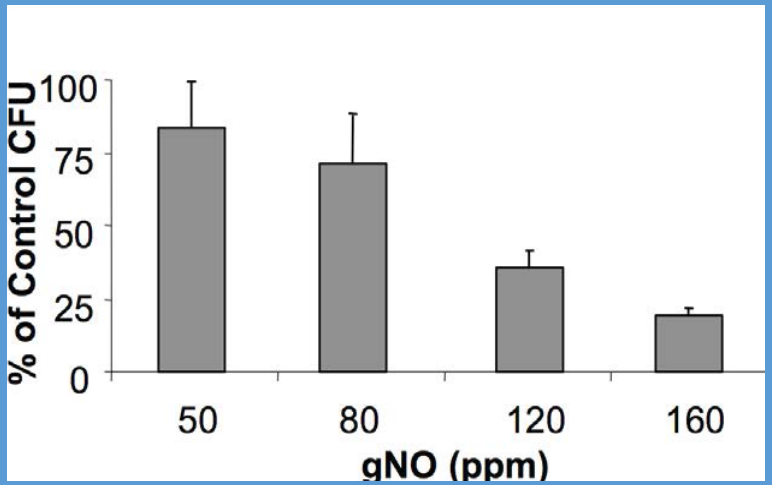
DRUG	MAJOR SIDE EFFECTS/TOXICITY	MONITORING PROCEDURES
Ciprofloxacin, Ofloxacin	Gastrointestinal disturbance (nausea, vomiting, diarrhea) Central nervous system (headache, insomnia)	Clinical symptoms Clinical symptoms
Moxifloxacin	Gastrointestinal disturbance (nausea, vomiting, diarrhea) Central nervous system (insomnia, agitation, anxiety) Musculoskeletal (tendonitis)	Clinical symptoms Clinical symptoms Clinical symptoms
Cefoxitin	Hypersensitivity (fever, rash, eosinophilia) Hematologic (anemia, leukopenia)	Clinical symptoms Periodic blood counts
Tetracyclines (doxycycline, minocycline)	Gastrointestinal disturbance (nausea, vomiting, diarrhea) Cutaneous (photosensitivity, rash, hyperpigmentation) Central nervous system (dizziness, vertigo [minocycline])	Clinical symptoms Clinical symptoms Clinical symptoms
Sulfonamides, trimethoprim/sulfamethoxazole	Gastrointestinal disturbance (nausea, vomiting, diarrhea) Hematologic (leukopenia, anemia, thrombocytopenia) Hypersensitivity (fever, rash, Stevens-Johnson syndrome)	Clinical symptoms Periodic blood counts Clinical symptoms
Imipenem	Gastrointestinal disturbance (nausea, vomiting, diarrhea) Hypersensitivity (anaphylaxis, rash) Central nervous system (seizures, confusion state) Hepatitis Hematologic (leukopenia, anemia, thrombocytopenia, pancytopenia)	Clinical symptoms Clinical symptoms Clinical symptoms Periodic hepatic enzymes Periodic blood counts
Linezolid	Gastrointestinal disturbance (nausea, vomiting, diarrhea) Hematologic (leukopenia, anemia, thrombocytopenia, pancytopenia) Peripheral neuropathy	Clinical symptoms Periodic blood counts Clinical symptoms

Definition of abbreviations: ALT alanine aminotransferase; AST aspartate aminotransferase; WBC white blood cell.

Dose Response (In Vitro)*



S. aureus at 50, 80, 120 and 160 ppm



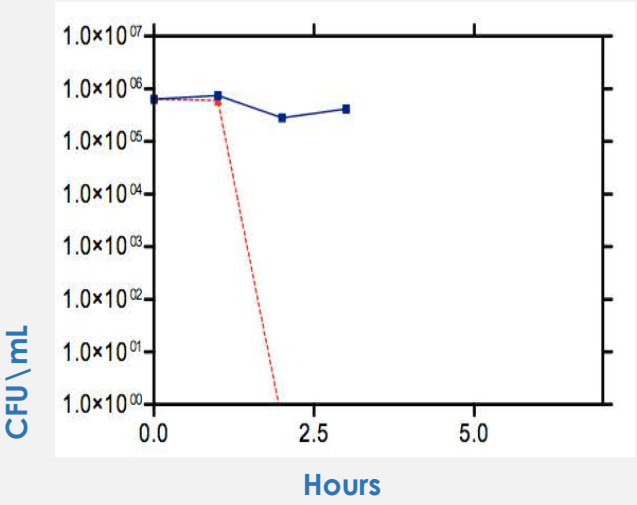
P. aeruginosa at 50, 80, 120 and 160 ppm

- 160 PPM - optimized dose for killing bacteria (measured in CFU)**
- Dose response experiments performed in two different types of bacterial strain
  - **Pseudomonas aeruginosa**: multidrug resistant (MDR) pathogen causing respiratory infection
  - **Staphylococcus aureus**: common cause of skin and respiratory infections

*~ 10 hr exposure
** Experiment was done by Pulmonox Technologies

Broad Spectrum Against Many Different Bacteria

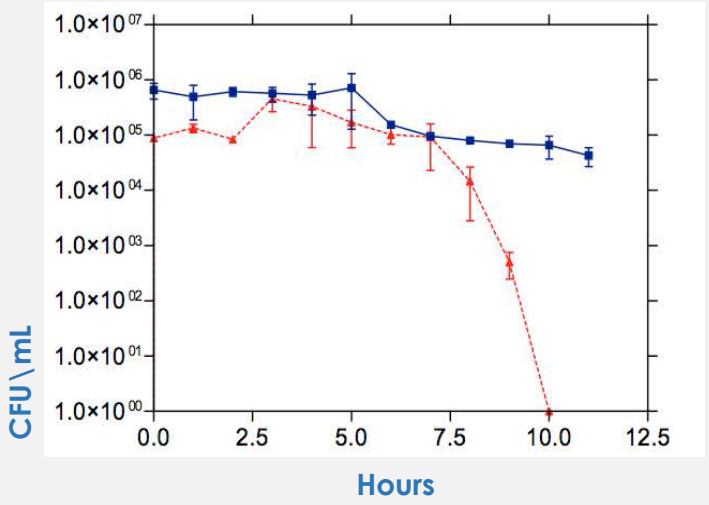
Chart 1:B Streptococcus



Additional Bacteria

1. S. aureus
2. P. aeruginosa
3. S. marcescens
4. Klebsiella
5. S. maltophilia
6. E. aerogenes
7. A. baumanii
8. MRSA
9. C. albicans
10. E. coli

Chart 2:Mycobacterium Smegmatis



- Nitric Oxide demonstrated efficacy against many different types of bacteria and viruses (in vitro)*
- Exposure time to eliminate bacteria ranged from 2hr (min) in chart 1 up to 10hr (max) in chart 2
- All of the additional bacteria mentioned below have elimination times between the min and max

* Experiment was done By Pulmonox Technologies at 200PPM exposure