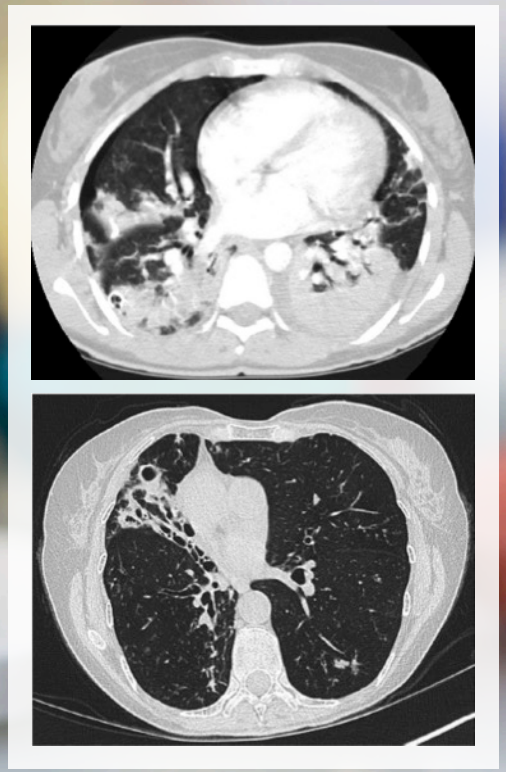


NTM Lung Infections

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

MABSC in CF patients

Compassionate treatment Case 1 & Case 2

Case 1 Background

- 19 year old female
- Carrying Delta F508, 3196C>T, and 3209G<A.
- FEV1: 65%
- Rapid progressive changes in CT scan and deterioration in pulmonary functions tests
- Positive NTM – since July 2009
- Background therapy of azithromycin, amikacin, minocycline, moxifloxacin and clofazimine
- Treatment Regimen:160 ppm NO 5x/day for 5 days, then 47 treatments over the next 21 days

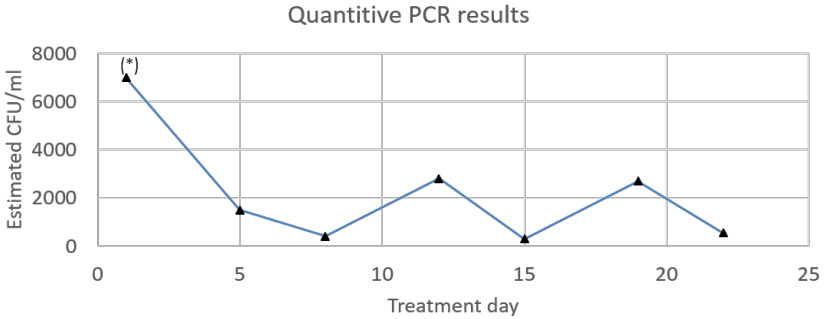
Case 2 Background

- 13 year old female
- Homozygote for Delta F508
- FEV1: 50%
- Hospitalized for side effects of linezolid
- Positive NTM – since May 2014
- Background therapy of azithromycin, amikacin, meropenem and moxifloxacin
- Denied Kalydeco due to M. abscessus*
- Treatment Regimen: 160 ppm NO 5x/day for 14 days, then 3x/day for the next 7 days

*M. abscessus was eradicated after AIT treatment and this patient qualified for a Kalydeco trial tx.

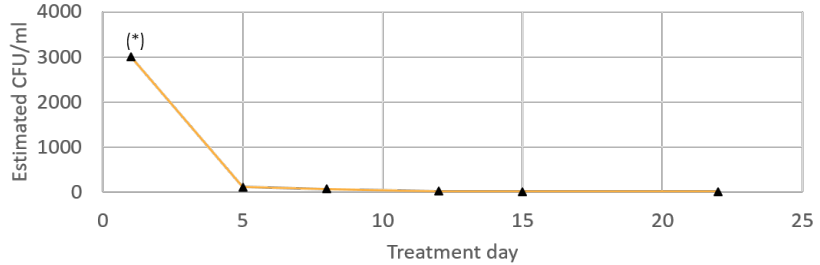
CF MABSC Compassionate Treatment: Bacteriology

MIC-01



- After 1 week at a regime of 5 treatments per day, a 2 log decrease in MABSC was observed.
- MABSC values increased with decrease in number of treatments per day.

MIC-02

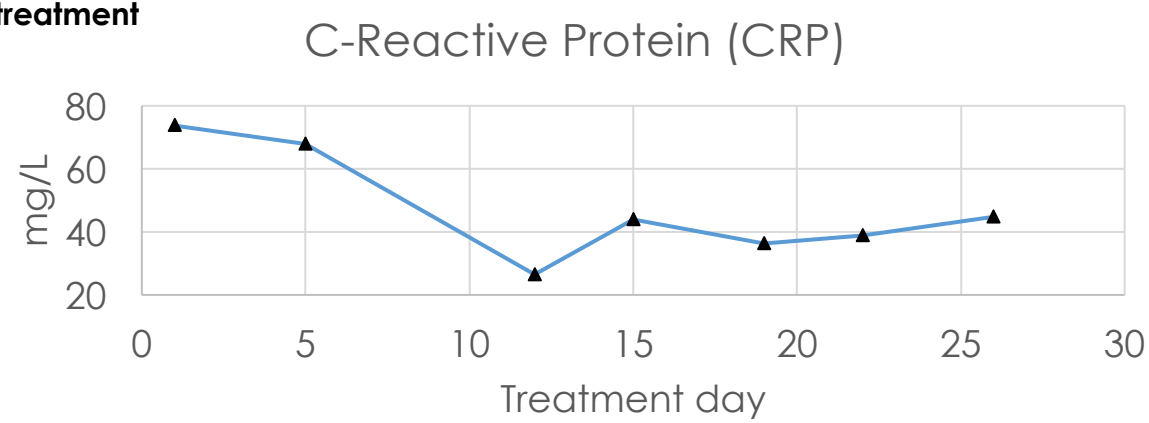


- Significant decrease in MABSC after 1 week at a regime of 5 treatments per day.

(*) First sample for both patients was taken BAL (Broncho-Alveolar), the rest of the samples were taken from sputum

CF MABSC Compassionate Treatment - Biomarker

- Elevated levels of C-Reactive Protein (CRP) marker in the blood indicates systemic inflammation
- MIC-01 had **systemic inflammation and showed decrease in CRP during NO treatment**



MIC-01 had systemic inflammation (CRP levels above 5mg/L cutoff)
MIC-02 had CRP levels below 5mg/L (not shown)

CF MABSC Compassionate Use Results Summary*

1. No adverse events reported and no treatment was prematurely discontinued
2. MABSC load in sputum was completely eradicated in patient 2 and significantly reduced in patient 1
3. Both patients experienced easier sputum production and a significant increase in sputum volume
4. Patient 1 had FEV_1 increase to 51% from 47% while patient 2 had FEV_1 decrease from 65% to 63%
5. CRP (an indicator of inflammation) was improved from 74mg/L to 45mg/L in patient 1 and was unchanged in Patient 2 (was in normal range at baseline)
6. No treatment was prematurely discontinued

* Cases were treated at Rambam Medical center as a compassion treatment. AIT supplied the device and protocol.

Nitric Oxide for NTM abscessus (NO-NTM abscessus) Phase 2 Trial Design

Single-Arm, Open-Label Trial

- Enroll 10 patients with MABSC, who are refractory to standard-of-care
- In addition to standard-of-care, Patients will receive:
  - 5 treatments of inhaled NO at a concentration of 160 ppm for 30-minutes per day for 14 days in the hospital setting
  - 3 treatments of inhaled NO at a concentration of 160 ppm for 30-minutes per day for 7 days in the ambulatory setting
- PE (primary endpoint): Safety, as measured by NO-related serious adverse events (SAEs), over the 21-day treatment period
- SE (secondary endpoints): 6-minute walk test and Mycobacterium abscessus load in sputum at day 21
- SE: Safety (specifically methaemoglobinemia and NO_2 levels) and Tolerability

Highlights

- AIT enrolled the first patient in the NO-NTM abscessus Phase 2 clinical trial on August 6, 2017
- Data will be released after the last patient reaches the end of the 21 day treatment period
- Data are expected in the fourth quarter of 2017

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.

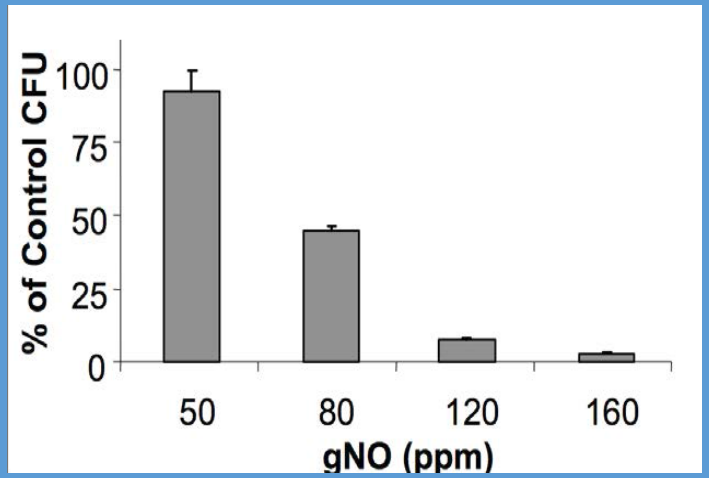
Current Standard of Care for NTM

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

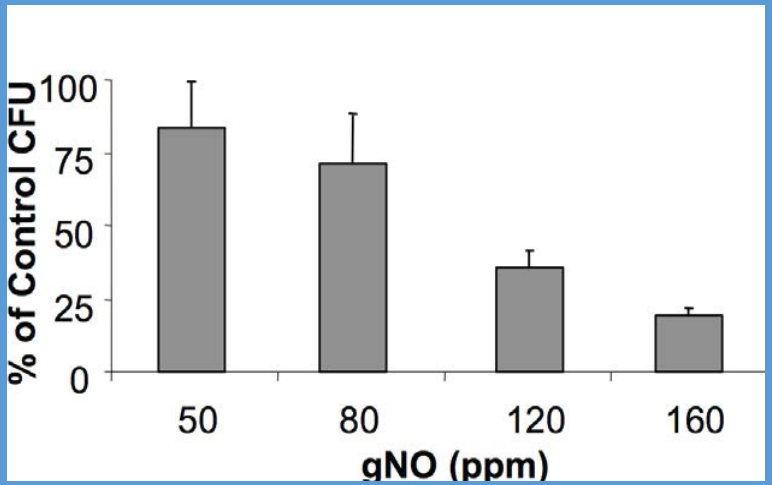
DRUG	MAJOR SIDE EFFECTS/TOXICITY	MONITORING PROCEDURES
Ciprofloxacin, Ofloxacin	Gastrointestinal disturbance (nausea, vomiting, diarrhea) Central nervous system (headache, insomnia)	Clinical symptoms Clinical symptoms
Moxifloxacin	Gastrointestinal disturbance (nausea, vomiting, diarrhea) Central nervous 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



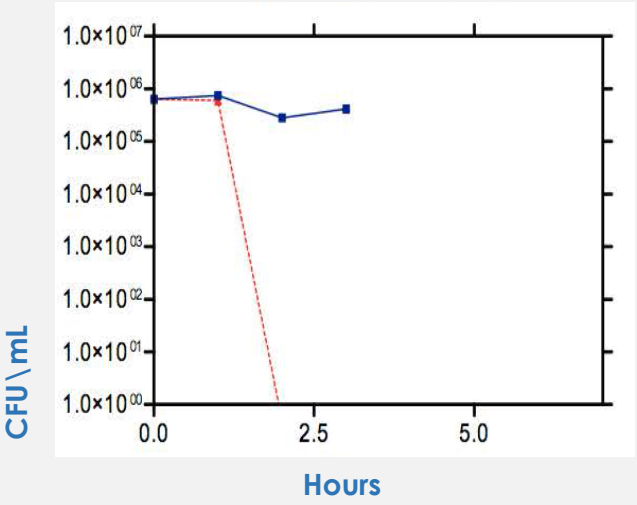
P. aeruginosa at 50, 80, 120 and 160 ppm

- 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

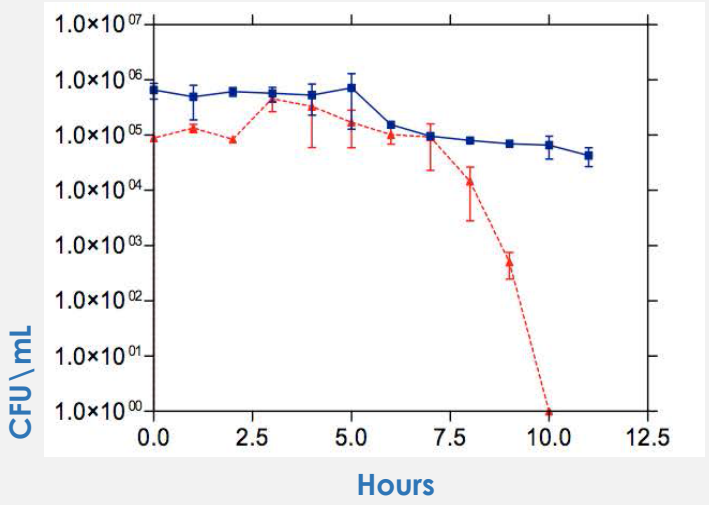
Chart 1:B Streptococcus



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