Challenging Cases (part 2)

DR MICHAEL HOLT
LOWERRE FELLOW, DIVISION OF MYCOBACTERIAL AND RESPIRATORY INFECTIONS
Just read the signs…

WARNING

Crocodile Safety
DANGER
Crocodiles inhabit this area. Attacks cause death.

WARNING

CAUTION

Today’s Stingers
Marine Stingers
Crocodiles
Submerged Objects
Sharks
Tidal

WARNING

Achtung

Warning

Recent crocodile sighting in this area.

WARNING

Strong Current

Power Craft Launch & Retrieval Area
Keep Clear

WARNING

Strong Shores

DANGEROUS SHOREBREAK

Standing waves off-shore break. DO NOT go out.

WARNING

Bluebottles

MARINE STINGERS ARE PRESENT
IN THESE WATERS DURING THE SUMMER MONTHS

MARINE STINGERS

STRONG CURRENT

MARINE STINGERS

POWER CRAFT LAUNCH & RETRIEVAL AREA

KEEP CLEAR

MARINE STINGERS

SHARKS

TIDAL

MARINE STINGERS

TIDAL
Disclosures

- Investigator in Insmed studies without compensation
Off-Label Drug Use

- This presentation includes discussion of off-label drug use
Learning Objectives

- Treatment of cavitary MAC lung disease
- Treatment of macrolide-resistance MAC lung disease
- Treatment of *M. abscessus* lung disease
- Alternative drugs for some cases of drug intolerance
Case 1
57-YEAR-OLD FEMALE
Case 1 – HPI

- Incidental diagnosis of LUL cavity on chest x-ray March 2016 for CAP
- Bronchoscopic fluid culture positive for “MAC” March and August 2016
- Treatment started September 2016: azithromycin, ethambutol, rifampin and IV amikacin
- ADRs:
  - IV amikacin - tinnitus and ear discomfort
  - Inhaled amikacin 500mg BID - dysphonia and ear fullness
  - Rifampin - nausea and arthralgia
  - Rifabutin - fevers and chills
- Mainstay of treatment was daily azithromycin and ethambutol
Case 1 – Other History

PMHx/PSHx
- NHL
  - 1999 – CHOPx4, XRTx28 to T8 vertebra
  - 2007 – relapse & allogeneic SCT
  - Off immunosuppression since 2008
  - Bronchiolitis obliterans (�)
  - Hypogammaglobulinemia

Social Hx
- Retired computer analyst
- Never smoker

Medications
- Azithromycin
- Ethambutol
- Fluticasone/salmeterol inhaler
- Clobetasol oral paste
- Loteprednol ophthalmic suspension
- Cyclosporin ophthalmic emulsion
- Topical estrogens
- IVIg
Case 1 – Examination

- SaO2 94% room air
- BMI 20kg/m²
- Afebrile
- Normal breath sounds
Case 1 – Workup at NJH

- **PFTs**
  - FEV1 1.45L (53 %pred)
  - FVC 2.23L (63 %pred)
  - FEV1/FVC(%) 65
  - DLCO 85 %pred
  - DL/VA 111 %pred

- **Labs**
  - Normal/negative autoimmune screen, Ig's, vitamin D, α-1-antitrypsin
  - Normal renal function

- **Modified barium swallow**
  - Normal

- **Esophagram**
  - Normal

- **EKG**
  - QTc 418ms

- **Audiogram**
  - Essentially normal
Case 1 – Workup at NJH

- Induced sputa
  - 9/2017: M. intracellularre, smear negative
  - 11/2017: M. intracellularre, smear negative

<table>
<thead>
<tr>
<th>Drug</th>
<th>MIC</th>
<th>Interpretation</th>
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<tbody>
<tr>
<td>Clofazimine</td>
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<tr>
<td>Rifabutin</td>
<td>&lt;=0.25</td>
<td>S</td>
</tr>
<tr>
<td>Moxifloxacin</td>
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<td>R</td>
</tr>
<tr>
<td>Amikacin</td>
<td>32.0</td>
<td>R</td>
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<td>Clarithromycin</td>
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<td>S</td>
</tr>
<tr>
<td>Rifampin</td>
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<td>S</td>
</tr>
<tr>
<td>Ethambutol</td>
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<td>S</td>
</tr>
<tr>
<td>Rifampin (+ Eth)</td>
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<td>S</td>
</tr>
<tr>
<td>Ethambutol (+ Rif)</td>
<td>0.625</td>
<td>S</td>
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</table>
Case 1 – Audience Response Item

How would you treat this patient?
A. Continue azithromycin and ethambutol
B. Continue azithromycin and ethambutol; re-trial IV amikacin; evaluate for surgery
C. Azithromycin, ethambutol, clofazimine; re-trial inhaled amikacin; evaluate for surgery
D. Azithromycin, ethambutol and moxifloxacin
E. Azithromycin, ethambutol and moxifloxacin; evaluate for surgery
Case 1 – Audience Response Item

How would you treat this patient?

A. Continue azithromycin and ethambutol
B. Continue azithromycin and ethambutol; re-trial IV amikacin; evaluate for surgery
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D. Azithromycin, ethambutol and moxifloxacin
E. Azithromycin, ethambutol and moxifloxacin; evaluate for surgery
Case 1 – Outcome

- Treated with daily azithromycin, ethambutol, clofazimine and nebulized amikacin
- Unfortunately, did not tolerate amikacin
- VATS LUL resection after 8 weeks of therapy
- Will continue drug therapy for 12 months of negative cultures (so far, negative cultures in January and March 2018)
Case 1 – Teaching Points

- Recommended treatment for cavitary MAC is three-drug oral therapy, plus a parenteral aminoglycoside and consideration of surgery.\(^1\)

- Clofazimine is a safe and efficacious alternative to rifampin, and exhibits in vitro synergy with amikacin against MAC and \(M. \text{abscessus}\).\(^2,3,4\)

- Inhaled amikacin (parenteral preparation) is rarely tolerated at doses above 250mg daily.\(^5\)

- Beware amikacin “resistance” – MIC can be overcome with IV therapy and inhaled amikacin is efficacious up to MIC of 64mcg/mL.\(^6\)
Case 2
82-YEAR-OLD FEMALE
Case 2 – HPI

- Good health until first pneumonia 20 years earlier
- Several pneumonic illnesses and a diagnosis of bronchiectasis
- Persistent symptoms for several years:
  - chronic cough, purulent sputum and streaky hemoptysis
  - fatigue/weakness
  - weight loss of 15lbs in 3 years
  - dyspnea
Case 2 – HPI

- Sputum samples smear- and culture-positive for “MAC” 2014-2017
- CT 2010 – nodular bronchiectasis in RUL, RML and lingula
- CT 2012 – RUL cavity
- Prior antibiotic therapy with azithromycin and a rifamycin
- Most recently, 12 months of intermittent three-drug therapy (azithromycin, ethambutol & rifampin) until August 2017
- All treatment episodes well-tolerated
Case 2 – Other History

- **PMHx/PSHx**
  - Osteoporosis
  - Vitamin D deficiency
  - Vascular disease (CAD, CVD)
  - Dyslipidemia

- **Medications**
  - Umeclidinium bromide/vilanterol inhaler
  - Albuterol inhaler
  - Guaifenesin

- **Social Hx**
  - Retired school teacher
  - Never smoker
Case 2 – Examination

- BMI 17.97kg/m² (weight 46.8kg)
- SaO₂ 93% RA
- Afebrile
- Scattered wheeze and right upper zone crackles
Case 2 – Workup at NJH

- **PFTs**
  - FEV1 1.25L (73 %pred)
  - FVC 1.86L (80 %pred)
  - FEV1/FVC (%) 67
  - DLCO 53 %pred
  - DL/VA 87 %pred

- **Labs**
  - Pre-albumin 10.7 (20.0-40.0)
  - CRP 5.97 (0.0-0.4)
  - 25-hydroxyl-Vit D 18.83 (20.0-100.0)
  - Normal renal function

- **Modified barium swallow**
  - Mild dysphagia

- **Esophagram**
  - Moderate gastroesophageal reflux

- **Audiogram**
  - Severe high frequency hearing loss

- **EKG**
  - QTc 436ms
Case 2 – Workup at NJH

- Induced sputa
  - 10/2017: 3-4+ *M. intracellulare*
  - 12/2017: 2+ *M. intracellulare*
  - 12/2017: 2+ *M. intracellulare*
  - 12/2017: 3+ *M. intracellulare*

<table>
<thead>
<tr>
<th>Organism</th>
<th>M. intracellulare</th>
</tr>
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<tbody>
<tr>
<td>Antibiotic</td>
<td>MIC</td>
</tr>
<tr>
<td>1_Rifampin (RIF)</td>
<td>2</td>
</tr>
<tr>
<td>2_Ethambutol (EMB)</td>
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<tr>
<td>3_EMB/RIF Combo Effect</td>
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<tr>
<td>4_Rifampin (Combo Assay)</td>
<td>0.5</td>
</tr>
<tr>
<td>5_Ethambutol (Combo Assay)</td>
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<td>Amikacin</td>
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</tr>
<tr>
<td>Ciprofloxacin</td>
<td>&gt;16</td>
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<tr>
<td>Clarithromycin</td>
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<tr>
<td>Clzfazimine</td>
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</tr>
<tr>
<td>Linezolid</td>
<td>16</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>2</td>
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<tr>
<td>Rifabutin</td>
<td>&lt;=0.25</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>64</td>
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<tr>
<td>X Compliance Statement</td>
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</table>
Case 2 – Audience Response Item

How would you manage this patient?

A. Daily rifampin, ethambutol and moxifloxacin
B. Daily rifampin, ethambutol and moxifloxacin, plus surgical resection of the RUL
C. Daily rifampin, ethambutol and clofazimine, plus IV amikacin
D. Treat vitamin D deficiency, dysphagia, reflux and nutritional state
E. C & D
Case 2 – Audience Response Item

How would you manage this patient?

A. Daily rifampin, ethambutol and moxifloxacin
B. Daily rifampin, ethambutol and moxifloxacin, plus surgical resection of the RUL
C. Daily rifampin, ethambutol and clofazimine, plus IV amikacin
D. Treat vitamin D deficiency, dysphagia, reflux and nutritional state
E. C & D
Case 2 – Outcome

- Patient desired medical treatment due to significant symptoms
- Not a surgical candidate due to age, condition and distribution of disease – aims of therapy to control symptoms and limit progression
- Treated with clofazimine, ethambutol and rifampin daily, plus IV amikacin (twice weekly)
- Plan to transition from IV to inhaled amikacin (thrice weekly) after 2 months
- Co-morbidities addressed
Case 2 - Outcome

- Review 8/2018
  - Culture-positive but smear-negative
  - Radiological progression of some cavities
  - Unfortunately, no clinical improvement with IV amikacin, and some interval high-frequency hearing loss
  - Plan to continue therapy as salvage, with consideration of IV amikacin intermittently for worsening of symptoms
Case 2 Teaching Points

- Omission of ethambutol is a risk factor for macrolide resistance\textsuperscript{7,8}

- The combination of surgery and prolonged IV amikacin provides the best chance of culture conversion in macrolide-resistant MAC (79\% vs 5\%)\textsuperscript{8}

- Core regimen for macrolide-resistant MAC is IV amikacin, ethambutol and a rifamycin (consider clofazimine, bedaquiline)

- Fluoroquinolones do not improve outcomes in refractory disease due to macrolide resistance\textsuperscript{7,9}
Case 3
33-YEAR-OLD FEMALE
Case 3 – HPI

- Recurring bouts of projectile vomiting in infancy (?achalasia)
- 2-3 childhood episodes of pneumonia, treated with antibiotics
- Hyperemesis gravidarum in 2003 with secondary pneumonia & diagnosis of bronchiectasis
- Annual exacerbations of bronchiectasis until 2015
- 2015: hemoptysis, *M. abscessus* on sputum culture
- Increasing respiratory symptoms and exacerbation frequency thereafter
Case 3 – HPI

- Current symptoms: cough, green sputum & intermittent hemoptysis, night sweats and fatigue, dyspnea and wheeze
- Good airway clearance regimen
- Bronchoscopy early 2017: M. abscessus on BAL
- Treatment-naïve
Case 3 – Other History

- PMHx/PSHx
  - Nil

- Family History
  - Nil significant

- Social Hx
  - Medical assistant
  - Never smoker

- Medications
  - Benzonatate
  - Albuterol nebs PRN
  - Dornase alfa
Case 3 – Examination

- BMI 25.56kg/m²
- \textit{SaO2} 90% room air
- Right mid-zone crackles
Case 3 – Workup at NJH

- **PFTs**
  - FEV1 1.73L (58 %pred)
  - FVC 2.47L (69 %pred)
  - FEV1/FVC(%) 70
  - TLC 100 %pred
  - RV 143 %pred
  - DLCO 71 %pred
  - DL/VA 100 %pred

- **Labs**
  - Normal/negative autoimmune screen, sweat chloride test, Ig's, vitamin D, α-1-antitrypsin
  - Normal renal function

- **MBS**
  - Normal

- **Esophagram**
  - Normal

- **EKG**
  - QTc 379ms

- **Audiogram**
  - Normal
Case 3 – Workup at NJH

- Sputum cultures
  - 8/2017: *M. abscessus*, smear negative
  - 11/2017: *M. abscessus*, smear negative
  - 11/2017: *M. abscessus*, smear negative
  - 11/2017: *M. abscessus*, smear negative
- Subspecies *abscessus* (erm41, hsp65)

### Organism Sensitivity Table

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>MIC</th>
<th>INT</th>
</tr>
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<tbody>
<tr>
<td>Amikacin</td>
<td>16</td>
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<tr>
<td>Augmentin</td>
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<td>TR D1</td>
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<td>Azithromycin</td>
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<tr>
<td>Cefepime</td>
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<td>Ciprofloxacin</td>
<td>8</td>
<td>R</td>
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<tr>
<td>Clarithromycin</td>
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<td>I D1</td>
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<td>Doxycycline</td>
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<td>Gentamicin</td>
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<tr>
<td>Imipenem</td>
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<tr>
<td>Kanamycin</td>
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<td>Linezolid</td>
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<td>Minocycline</td>
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<tr>
<td>Trimethoprim/Sulfamethoxazole</td>
<td>&gt;4/76</td>
<td>* D3</td>
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</table>
Case 3 – Audience Response Item

How would you treat this patient?

A. Azithromycin, ethambutol, rifampin and IV amikacin
B. IV amikacin and cefoxitin, with oral clofazimine and bedaquiline; evaluate for surgery
C. IV amikacin and imipenem, with oral clarithromycin and moxifloxacin; evaluate for surgery
D. Inhaled amikacin with oral azithromycin, clofazimine and bedaquiline
Case 3 – Audience Response Item

How would you treat this patient?

A. Azithromycin, ethambutol, rifampin and IV amikacin

B. IV amikacin and cefoxitin, with oral clofazimine and bedaquiline; evaluate for surgery

C. IV amikacin and imipenem, with oral clarithromycin and moxifloxacin; evaluate for surgery

D. Inhaled amikacin with oral azithromycin, clofazimine and bedaquiline
Case 3 – Outcome

- Induction therapy with IV amikacin & cefoxitin, plus oral clofazimine & bedaquiline
- Did not tolerate cefoxitin (rash) or carbapenem (rash) so IV tigecycline substituted
- RMLobectomy and RLL medial segmentectomy occurred after 8 weeks of therapy
- Will complete 4 months of IV treatment and then transition to inhaled amikacin, continuing clofazimine and bedaquiline
- PCD workup: two variants of unknown significance in DNAH1 and one in DNAH5
Case 3 – Teaching Points

- Treatment of *M. abscessus* complex involves induction therapy with 2 IV agents and an active oral agent for 2-4 months, followed by maintenance or intermittent therapy, depending on goals of treatment.

- Subspeciation important: subspecies *abscessus* and *bolletii* possess functional erm(41) genes, which confer inducible macrolide resistance; rates of sputum conversion without relapse significantly higher for *massiliense* than *abscessus*.

- Surgery significantly associated with culture conversion without relapse (NJH data).

- Bedaquiline appears safe and efficacious for MAC and *M. abscessus*.
Thank You – Questions?
References