Guidelines for Treatment of Respiratory Infections due to Nontuberculous Mycobacteria

Miguel Santin
Department of Infectious Diseases
Bellvitge University Hospital-IDIBELL
University of Barcelona
msantin@bellvitgehospital.cat

ESGMYC Recommendations for Mycobacterial Infections
Disclosures

Alere™ provided the participating centres with blood-collecting tubes for the OPTIMIST clinical trial, of which I am the promoter.
NTM-PD

- Emerging infection
- Poor response to chemotherapy (surgery)
- Guidance for management (expert opinion)

(BTS 1999, ATS/IDSA 2007)
Outline

- Management of NTM-PD
- The GRADE Approach
- ATS/IDSA/ERS/ESCMID Guidelines
M. avium complex

Pre-Macrolide

- Response: 27-30% with RMP (BTS)

Macrolide

- Very active (resistance in monotherapy!)
- Response: 60%-65% (multi-D macrolide-based regimens)
M. avium complex
The Guidelines say...

<table>
<thead>
<tr>
<th></th>
<th>Nodular /bronchiectasis</th>
<th>Fibrocavitary</th>
<th>Macrolide-R</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-Duration: 12 months CN (A, II)</td>
<td>-Duration: 12 months CN (B, II)</td>
<td></td>
</tr>
<tr>
<td><strong>van Ingen (2013)</strong></td>
<td>-Daily macrolide-RE (+/- AS)</td>
<td>-Alternative: macrolide-CloE</td>
<td></td>
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<tr>
<td></td>
<td>-Duration: &gt;12 months CN</td>
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</tbody>
</table>

 ATS/IDSA. Am J Respir Crit Care Med 2007;175:367-416
**M. kansasii**

-Treatment of MK-PD resembles that of MTb

-Response:
  -Pre-RMP: 50%-80% (high relapse rates)
  -93%-98% with RMP-based regimens*

-*In vitro* activity of Clarithromycin and Moxifloxacin

-Successful experience with Clarithromycin**

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**M. kansasii**

The Guidelines say...

<table>
<thead>
<tr>
<th></th>
<th>RMP-Susceptible</th>
<th>RMP-R</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ATS/IDSA (2007)</strong></td>
<td>- Daily HRE&lt;br&gt;- Duration: 12 months CN&lt;br&gt;(A, II)</td>
<td>- Three-drug regimen including: macrolide, moxi, and EMB, STX or streptomycin&lt;br&gt;(A, II)</td>
</tr>
<tr>
<td><strong>van Ingen (2013)</strong></td>
<td>- Daily HRE (+/- AS)&lt;br&gt;- Duration: &gt;12 months CN&lt;br&gt;- Alternative: macrolide-RE</td>
<td>---</td>
</tr>
</tbody>
</table>

M. abscessus

- Resistance to anti-tuberculous drugs
- Susceptible to Clarithromycin (untreated)
- Amik (90%), Cefox (70%), Imipen (50%), Linez and Tigec
- Treatment recommendations based on in vitro tests
- Surgery improves cure rates (57% vs 28%)*

*Jarand J 2011
**M. abscessus**

The Guidelines say...

|                | -Control symptoms and progression: Periodic multi-D therapy *(C, III)* |

Koh WJ (2011) (Clarithro, Cipro, Doxi, Amik, Cefoxitin)
- 12 months CC: **25%** *M. abscessus* vs. **88%** *M. massiliense*

Harada T (2012)
- 12 months CC: **31%** *M. abscessus* vs. **50%** *M. massiliense*

Park J (2017) (Clarithro, Cipro, Doxi, Amik, Cefoxitin/Imipenem)
- 12 months CC: **26%** *M. abscessus* vs. **82%** *M. massiliense*
**M. abscessus**  
The Guidelines say...

|                 | - Control symptoms and progression: Periodic multi-D therapy (*C, III*) |

| van Ingen (2013) | **M. abscessus** subsp. *abscessus* and subsp. *bolletii*  
|                  | - Three or four of: Amik, Cefox, Imipen, Tigec, Linez (intensive phase). **Duration:** >12 months CN  
|                  | **M. abscessus** subsp. *massiliense*  
|                  | - Macrolide + two of: Amik, Cefox, Imipen, Tigec, Linez (intensive phase) **Duration:** >12 months CN |

*ATS/IDSA.* Am J Respir Crit Care Med 2007;175:367-416  
*van Ingen.* Expert Rev Anti Infect Ther 2013;11:1065-77
M. xenopi

- Co-morbidity frequent

- Cure at 5 years:
  - BTS Trial (2001): 24% (RE), 10% (HRE) alive and cured
  - BTS Trial (2008): 12% (Cipro.), 18% (Clarithro.) alive and cured
  - Andréjak C (France 2009): median survival 16 months (69% dead at 3 years). Cure: 21%

- van Ingen J (Netherlands 2008): 26% culture conversion
**M. xenopi**

The Guidelines say...

| **ATS/IDSA (2007)** | - The optimal treatment and duration of M. Xenopi-PD has not been well established  
- Daily RE-Clarithromycin  
- Duration: 12 months CN |
|----------------------|------------------------------------------------------------------|
| **van Ingen (2013)** | - Daily RE-macrolide (+/- quinolone)  
- Alternative: RE-quinolone  
- Duration: 12 months CN |
ATS/IDSA/ERS/ESCMID Guidelines

GRADE system
Grading Recommendations Assessment Development Evaluation
## Certainty of Evidence/Strength of Recommendation

<table>
<thead>
<tr>
<th>Certainty of Evidence</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Further research is very unlikely to change our confidence in the estimate of effect.</td>
</tr>
<tr>
<td>Moderate</td>
<td>Further research is likely to have an important impact on our confidence in the effect and may change the estimate.</td>
</tr>
<tr>
<td>Low</td>
<td>Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.</td>
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<tr>
<td>Very low</td>
<td>Any estimate of effect is very uncertain.</td>
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<table>
<thead>
<tr>
<th>Strength of Recommendation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Strong</td>
<td>The Guideline Development Group is confident that the desirable effects of adherence to the recommendation outweigh the undesirable effects.</td>
</tr>
<tr>
<td>Conditional (weak)</td>
<td>The Guideline Development Group concludes that the desirable effects of adherence to the recommendation probably outweigh the undesirable effects.</td>
</tr>
</tbody>
</table>
Formulate question
Select outcomes
Rate importance

PICO
Outcome: Critical
Outcome: Critical
Outcome: Important
Outcome: Not important

Evidence synthesis/systematic review/HTA

Recommendation/Decision

Panel

https://gradepro.org/guidelines-development#develop-tuts
Example of PICO question:

In patients with MAC pulmonary disease (P), should a two-drug macrolide-based regimen (I) be used instead of a three-drug regimen (C) to achieve prolonged culture conversion (O)?
ATS/IDSA/ERS/ESCMID Guidelines

• **21 PICO Questions**

• **Outcomes:** Cure, Death, Recurrence, Culture conversion, Adverse reactions, Serious adverse event, QoL, Resistance

• **Evidence:** Low to very low certainty
ATS/IDSA/ERS/ESCMID Guidelines
PICO Questions

• MAC

– Should 3 drugs w/ macrolide vs. 2 drugs w/ macrolide be used for MAC?
– Should 3 drugs with macrolide vs. 3 drugs without macrolide be used for MAC?
– Should Azithromycin vs. Clarithromycin be used for MAC?
– Should daily macrolide-based regimen vs. 3 times weekly regimen be used for MAC?
– Should Parenteral vs. No parenteral agent be used for MAC?
– Should Inhaled antibiotics vs. no inhaled antibiotics be used for MAC?
– Should <12 months vs. >12 months be used for MAC?
ATS/IDSA/ERS/ESCMID Guidelines

PICO Questions

- **M. kansasii**
  - Should <12 months vs. >12 months be used for M. kansasii?
  - Should INH vs. no INH be used for M. kansasii?
  - Should daily regimens vs. 3 times weekly regimens be used for M. kansasii?
  - Should Fluorquinolone vs. no Fluoroquinolone be used for M. kansasii?
  - Should Parenteral vs. No parenteral agent be used for M. kansasii?

- **M. xenopi**
  - Should <12 months vs. >12 months be used for M. xenopi?
  - Should Two vs. Three drugs be used for M. xenopi?
  - Should a FQ-containing regimen vs. regimens without a FQ be used for patients with newly diagnosed pulmonary M. xenopi?
  - Should Parenteral vs. no parenteral agent be used for M. xenopi?
ATS/IDSA/ERS/ESCMID Guidelines.

PICO Questions

• **M. abscessus**
  - Should **two drugs** vs. **three drugs** be used for *M. abscessus*?
  - Should **Macrolide** vs. **No macrolide** be used for *M. abscessus*?
  - Should **shorter therapy** vs. **longer therapy** be used for *M. abscessus*?

• **NTM-PD (all species)**
  - Should **any treatment** vs. **watchful waiting** be used for *NTM*?
  - Should **empiric treatment** vs. **culture-based treatment** be used for *NTM*?
  - Should **Surgery** vs. **No surgery** be used for *NTM*?
### ATS/IDSA/ERS/ESCMID Guidelines

### The Panel

<table>
<thead>
<tr>
<th>Charles Daley (ATS) (Chair)</th>
<th>Emmanuelle Cambau (ESCMID)</th>
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<tbody>
<tr>
<td>David Griffith (ATS)</td>
<td>Erik Böttger (ESCMID)</td>
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<tr>
<td>Ted Marras (ATS)</td>
<td>Lorenzo Guglielmetti (ESCMID)</td>
</tr>
<tr>
<td>Kenneth Olivier (ATS)</td>
<td>Miguel Santin (ESCMID)</td>
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<tr>
<td>Richard Wallace (ATS)</td>
<td>Christoph Lange (ERS)</td>
</tr>
<tr>
<td>Steven M. Holland (IDSA)</td>
<td>Claire Andrejak (ERS)</td>
</tr>
<tr>
<td>Gwen Huitt (IDSA)</td>
<td>Dirk Wagner (ERS)</td>
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<tr>
<td>Kevin Winthrop (IDSA)</td>
<td>Jakko van Ingen (ERS)</td>
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<td>Jason Stout (IDSA)</td>
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<table>
<thead>
<tr>
<th>Methodologists (GRADE)</th>
<th>Ad hoc expert</th>
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<tbody>
<tr>
<td>Jan Brozek</td>
<td>Enrico Tortoli</td>
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<tr>
<td>Jon Iaccarino</td>
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British Thoracic Society Guidelines for the Diagnosis and Management of Non-tuberculous Mycobacterial Pulmonary Disease (NTM-PD)

Available at:
