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Treatment for NTM: when how....and what next?

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University hospital, Amiens, France
First step = To diagnose NTM disease

- One NTM positive sample ≠ NTM disease
- NTM are normally non-pathogenic for humans
- = environment
- ATS/IDSA Criteria for definition of cases

ATS/IDSA criteria, Griffith et al, AJRCCM 2007
Isolement ≠ Infection

- Clinical criteria
  - Pulmonary symptoms
- Radiological criteria
  - Nodular or cavitary pacities, multifocal bronchiectasis with multiple small nodules
- Bacteriological criteria
  - At least 2 positive sample with positive culture Or 1 bronchial wash
  - Or 1 bronchoalveolar lavage
  - Or positive biopsy with granuloma and one positive sputum
- Appropriate exclusion of others diagnosis

Griffith ATS/IDSA, AJRCCM 2007
Isolement ≠ Infection

- **Clinical criteria**
  - Pulmonary symptoms

- **Radiological criteria**
  - Nodular or cavitary pathology, multifocal bronchiectasis with multiple small nodules

- **Appropriate exclusion of others diagnosis**

* Griffith ATS/IDSA, AJRCCM 2007*
• Radiological criteria
  • Nodular or cavitary pacities, multifocal bronchiectasis with multiple small nodules

• Appropriate exclusion of other diagnosis

Isolement ≠ Infection

• Bacteriological criteria
  • At least 2 positive samples with positive culture or 1 bronchial wash or 1 bronchoalveolar lavage or positive biopsy with granuloma and one positive sputum

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• Radiological criteria

• Nodular or cavitary pacities, multifocal bronchiectasis with multiple small nodules

Griffith ATS/IDSA, AJRCCM 2007

Griffith ATS/IDSA, AJRCCM 2007
• Appropriate exclusion of others diagnosis

Griffith ATS/IDSA, AJRCCM 2007
Second step = to decide a treatment

- NTM disease is not synonymous of systematic treatment!
- Treatment according to severity of the disease
- Need of biomarkers to decide initiation treatment....
Third step: to choose the drugs

- More than 150 NTM....
- 4 main NTM specie or complex in Europe
  - *M. avium* complex
  - *M. xenopi*
  - *M. kansasii*
  - *M. abscessus* complex
- Multidrug therapy: at least 3 antibiotics
- 12 months after sputum conversion
- Clinical, radiological and bacteriological follow-up
- Drug susceptibility testing?
- Often a key drug for each main NTM
Fourth step: to decide to stop

- Endpoints for the management not officially defined:
  - Sputum conversion without relapse (for clinical trials)
  - Clinical and radiological improvement (for patient in clinical practice)
- No biomarkers available
- Classically = 12 months after sputum conversion...
  - Only expert opinion
- No current consensus for treatment duration
  - if there is no sputum conversion
  - Or if relapse under treatment
  - Despite clinical improvement
M. AVIUM COMPLEX
M. avium complex

• 3 diseases = 3 different managements

Hot tub Lung (Hypersensitivity disease)

+  

=  

No antibiotics  
MAC exposure avoidance  
Sometimes steroids
**M. avium complex**

- 3 diseases = 3 different managements

Lady Windermere Syndrome (nodular bronchiectatic disease)

Airway clearance ++++

Sometimes antibiotics
**M. avium complex**

- 3 diseases = 3 different managements

Cavitary disease

[Image of a cartoon character smoking a cigarette with cavities represented by bubbles.]

[Image of a CT scan showing cavities in the lungs.]

[Image of an electron micrograph of M. avium.]

[Image of a CT scan showing consolidation in the lungs.]

= Antibiotics
In vitro data

• MAC Susceptible to Macrolides
• Antibiotics MIC alone higher than maximum serum concentration
• Synergism between rifampicin and ethambutol
• No known breakpoints for drugs except for macrolides.
And in humans?

- Systematic review of studies of MAC treatment
- Classification according to the antibiotics combination received:
  - Treatment without rifampicin, without ethambutol and without macrolides =
    - Cure in 32% of cases
  - Treatment with rifampicin, and ethambutol but without macrolides
    - Cure in 38% of cases
  - Treatment with macrolides = (included macrolides monotherapy)
    - Cure in 59% of cases

Field, Chest 2004

- In many studies with clarithromycin containing regimen, sputum conversion rate = 70-80%

Tanaka, Am J Respir Crit Care Med 1999
Griffith, Clin Infect Dis 2000
And in humans?

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Tanaka, Am J Respir Crit Care Med 1999
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Macrolides= treatment
CORNERSTONE

• The only one drug with breakpoints and in vitro/in vivo correlation
  • Macrolides resistant- MAC= FAILURE
  • Susceptible strain (MIC 0,25-4 µg/ml) = SUCCESS

  Wallace, AJRCCM 1996
  Dautzenberg, Chest 1995
  Griffith, CID 1996
  Rubin, Chest 2004

• Clarithromycin vs Azithromycin ?
  • Efficacy : Clarithromycin > Azithromycin
  • Toxicity : Clarithromycin > Azithromycin
  • Drug Interactions Clarithromycin > Azithromycin (cytochrome P450)

  Dunne M et al. CID 2000
  Ward TT et al. CID 1998
  Brown BA et al. CID 1997
MAC: others drugs....

• Rifampicin vs Rifabutin?
  • Same efficacy
  • Drug toxicity Rifabutin > Rifampicin
  • Drug Interactions Rifampicin (cytochrome P450) > Rifabutin

• Fluoroquinolones?
  • In vitro: Moxifloxacin > Ciprofloxacin
  • Mice CLA > MXF

• Aminosides?
  • Only for the most severe cavitary forms
  • Maybe in the future by nebulization
    Kobashi Respir Med 2007

• In vitro synergism between amikacin and clofazimine
  Van Ingen J et al, AAC 2012

• Others with less evidence of efficacy and toxicity risk
  • clofazimine, cycloserine, ethionamide and capreomycin
    Koh AAC 2013
    Heifets AAC 1996
MAC: ATS guidelines

- ATS/IDSA 2007: Macrolides + Ethambutol + Rifamycin ± aminoglycosids
  - Clarithromycin 500 mg x 2 per day
  - Ethambutol 15 mg/kg /d
  - Rifabutin 300 mg /D or rifampicin 600 mg/d
- Others possibilities: Azithromycin 250 mg/d, Moxifloxacin 400 mg

ATS/IDSA, Griffith et al, Am J Respir Crit Care Med 2007
M. KANSASII
## MK: In vitro data

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</tr>
<tr>
<td>Ethambutol</td>
<td>≤ 5</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>≤ 0,25</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>2-8</td>
</tr>
<tr>
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<td>≤ 0,025</td>
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10 à 50 X MIC of MTb
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Rifampicin resistant strain = in vivo Failure

10 à 50 X MIC of MTb ≤ 0,25

10 à 50 X MIC of MTb = Rifampicin resistant strain
MK: Treatment

1. ONE KEY DRUG = RIFAMPICIN
Why? No randomized studies...

**Association WITHOUT rifampicin**

- 6-months sputum conversion = 52-81%
- Short term relapse = 10%

  - Jenkins Conf of Chemotherapy 1960
  - Pezzia Rev Infect Dis 1981

**Association WITH rifampicin**

- 4-months sputum conversion = 100%
- Short term relapse = 1%

  - Pezzia Rev Infect Dis 1981
  - Ahn Rev Infect Dis 1981
  - Ahn Rev Infect Dis 1983
  - Banks, thorax 1983

Rifampicin resistant strain = Main failure factor
MK: Treatment

2. Rifampicin in combinaison with 2 others drugs
   To limit resistant strains selection
Treatment: companion drugs

• Ethambutol?
  • Possible synergism with rifampicin
    
    banks, Thorax 1984; BTS Thorax 1994

• Isoniazid?
  • INH+RIF+EMB vs RIF-EMB: no difference
    
    BTS, Thorax 1994
  • ATS Guidelines: INH+RIF+EMB

• Clarithromycin?
  • In vitro susceptibility
  • In vivo efficacy
    
    shitrit, chest 2006, griffith CID 2003

• Others drugs?
  • In vitro susceptibility: moxifloxacin, linezolid
    
    alcaide AAC 2004
So,

- Rifampicin = cornerstone of the *M. kansasii* treatment
- Same regimen
  - *Since 25 years*…
  - RMP+ EMB+ INH
  - 9 months ? Or 12 months after sputum conversion ?
    
    Jenkins, Thorax 1994

- In case of drug toxicity or resistant strain : clarithromycin or moxifloxacin
- Same outcome than TB when correct regimen
M. XENOPI
In vitro and in vivo data

- In vitro data: MIC higher than maximum serum concentration
- Lower MIC for clarithromycin and moxifloxacin
- No correlation between in vitro susceptibility and in vivo efficacy
- Murine model with intravenous infection
  - 9 different CLA containing regimen and 1 INH-RIF-EMB
  - CLA containing regimen >INH-RIF-EMB

Lounis AAC 1996

- Murine model with Nebulisation infection
  - EMB-RIF + MXF vs CLA and EMB-RIF-AMK +MXF vs CLA
  - No difference between CLA and MXF regimen
  - Superiority of AMK regimen

Andréjak JAC 2012
In vivo data: clinical studies

- Two randomized studies
  - 42 patients (20 and 22): INH-RMP-EMB vs RMP-EMB: no difference, mortality 69%
    Jenkins et al, Respiratory Med 2003
  - 34 patients (17 and 17): RMP-EMB-CLA vs RMP-EMB-CIPRO: no difference
    Jenkins et al, Thorax 2009

- One review (48 studies)
  - 188 patients with MX infection
  - Higher success rate in fluoroquinolones regimen
  - No difference between regimen with and without macrolides
    Varadi et Marras, Int J Tuberc Lung Dis 2009
Which treatment?

• ATS guidelines: CLA + RMP + EMB with MXF as alternative to one the drug
• Optimal treatment unknown
• CaMoMy study
  • Randomized study in France
  • CLA+EMB+RMP vs MXF+EMB+RMP
  • Main objective: 6 months sputum conversion rate in general
  • Secondary objectives: Comparison of the 2 regimens in term of efficacy, drug toxicity and outcome
  • Ongoing study
M. ABSCESSUS COMPLEX
Three subspecies

- *M. abscessus stricto sensu*
- *M. massiliense*
- *M. boletii*

- With differences of prognosis: better outcome with *M. Abscessus massiliense* in comparison to *M. abscessus stricto sensu*.
- With difference in susceptibility: inducible resistance with *M. abscessus stricto sensu*. 
• In vitro:
  • Clarithromycin (erm gene),
  • Amikacin, β lactamin and penems : cefoxitin and imipenem
  • Linezolid et glycylcyclin
  • Clofazimine, ciprofloxacin

• 107 patients
  • 42 different combinaisons, a mean of 4,6 ATB with an IV duration treatment of 6 months
  • Sputum conversion in 71%, 48% without relapse

• One objective: to improve symptoms

• Often an induction phase with injectable drugs and oral drugs until smear conversion followed by a continuation phase with orally available drugs
  • Injectable drugs (IP): amikacin and cefoxitin or imipenem
  • Others drugs (given throughout the treatment): macrolides or clofazimine (for macrolides resistant strains), linezolid, tigecyclin/tetracyclin, eventually ciprofloxacin

Wallace, Antimicrob Agents Chemother 1991,
Nash, Antimicrob Agents Chemother. 2009,
Peloquin, Clin Infect Dis 2004,
Brown, Antimicrob Agents Chemother 1992,
Others

• *M. szulgai*
  • Clinical and radiological presentation close to *M. tuberculosis*
  • Susceptibility to antituberculous drugs
  • Susceptibility to macrolides and fluoroquinolones
  • Treatment based on drug susceptibility

• *M. malmoense*
  • Mainly in North Europe
  • No correlation between in vitro data and clinical success
  • Combinaison of rifampicin, ethambutol and clarithromycin
In conclusion (1)

- Treatment is long and difficult

- Three challenges
  - To decide to start a treatment
  - To decide with which drugs to treat
  - To decide to stop the treatment

- Need of discussion and coordination with physicians with experience usually in collaboration with national reference centers
In conclusion (2)

- **MAC**
  - Key drug = clarithromycin
  - Associated with EMB-RIF
  - Alternative in case of toxicity or resistant strain: amikacin, moxifloxacin, clofazimin

- **M. xenopi**:
  - Clarithromycin + ethambutol + rifampicin
  - Alternative: moxifloxacin, Amikacin

- **M. abscessus**:
  - Intensive phase: amikacin + imipenem or cefoxitin + Drugs of the continuation phase
  - Continuation phase (at least 3 drugs): clarithromycin (if macrolide susceptible), linezolid, ciprofloxacin, clofazimine, tigecycline/tetracycline

- **M. kansasii**
  - Key drug = rifampicin
  - Associated with ethambutol and isoniazid
  - Alternative: clarithromycin, moxifloxacin
Thanks for your attention