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Universitair Medisch Centrum Rotterdam

Sophia Kinderziekenhuis

Mycoplasma pneumoniae does treatment help?

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7th Danish Paediatric Infectious Diseases Symposium

September 26-27th 2014, Korsør Danmark

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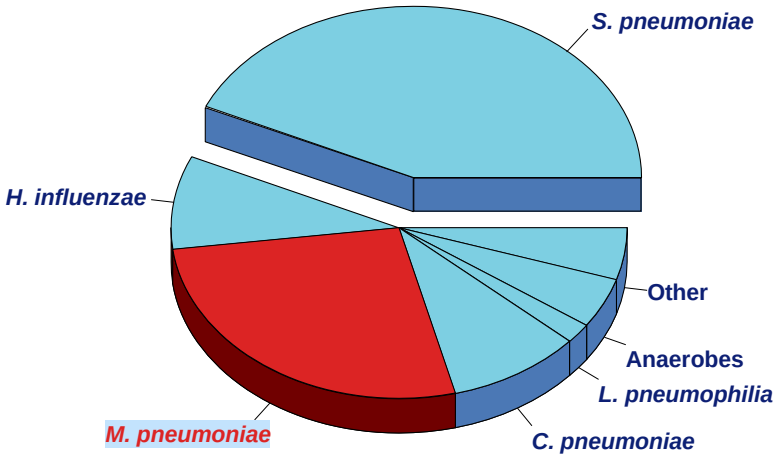
Community-acquired pneumonia: known etiology



~85% of these cases in children **≤14 years** of age

15-40% of hospitalizations because of CAP in children

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Mycoplasma pneumoniae: does treatment help?

- *Mycoplasma pneumoniae* short introduction
- Case Rick:
  - Clinical signs and symptoms
  - Diagnostics
  - Therapeutics
- Does treatment help?

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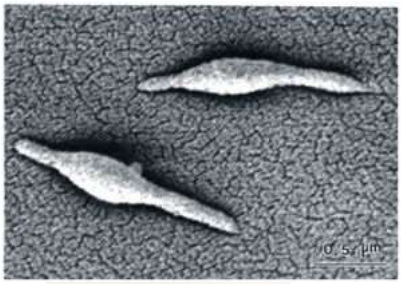
Mycoplasma pneumoniae



- *1944 Eaton's agent*
- *Thought to have evolved from gram-positive bacteria*
- Genome 816 kbp (± 1/3 genome *S. pneumoniae*)
- Smallest self-replicating organism
- *"Minimalist cell"*
- *Lack a cell wall and still maintain cell rigidity*

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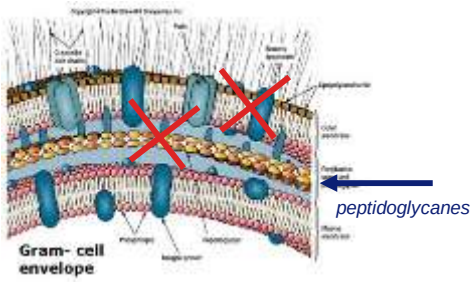
Why is *M. pneumoniae* called atypical ?

Not sensitive to betalactam antibiotics or cefalosporines

Mycoplasmata lack a cell wall

M. pneumoniae



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Rick, 4 years old

- No medical history
- Coughing since 1-2 weeks, not feeling too well
- 3-4 days fever 38-38.5 °C, vomiting, malaise
- Physical examination:
  - mild tachypnea,
  - left basal crepitations on lung auscultation

Rick, 4 years old

- White blood cell count 5800/ul with 45% neutrophils.
- CRP 48 mg/L
- Chest X-ray

`Numerous studies have shown that chest radiography findings lack precision in defining the etiology of childhood pneumonia. There is no single test that reliably distinguishes bacterial from non-bacterial causes.`

McIntosh K et al. N Engl J Med. 2002

Wilkins TR et al. Radiol Technol. 2005

Lynch T et al. Plos one 2010

When to think of *Mpn*? Radiology

Radiology

Chest X-ray:

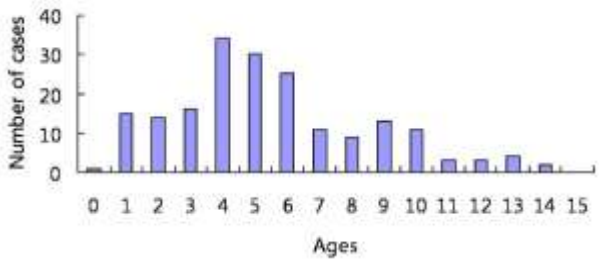
- Bilateral, diffuse, reticular
  - Lobar: 38%
  - Interstitial: 36%
  - Lobar en interstitial: 27%
  - Pleura effusion: 14%

Scan J Respir Dis 1978:179-89

When to think of *Mpn*? Age

***M.pneumoniae* pneumonia also < 5 years!**

1083 patients admitted because of LRTI: 191 *Mpn* infection



You-Sook Youn et al. B*MC Pediatrics* 2010, 10:48doi:10.1186/1471-2431-10-48

Incidence rates of acute Mycoplasma pneumoniae infection on the basis of serological and PCR findings.

Positive rest result, diagnosis	Proportion (%) of patients with infection, by age group			
	2–4 y	5–7 y	>7 y	All
Serological				
Acute bronchitis	12/62 (19.3)	8/34 (23.5)	9/17 (52.9)	29/113 (25.6)
Wheezing	12/53 (22.6)	4/15 (26.6)	7/14 (50.0)	23/82 (28.0)
Pneumonia	42/209 (20.0)	53/123 (43.0)	47/86 (54.6)	142/418 (33.9)
All	66/324 (20.4)	65/172 (37.8)	63/117 (53.8)	194/613 (31.6)
PCR				
Acute bronchitis	8/62 (12.9)	6/34 (17.6)	6/17 (35.3)	20/113 (17.7)
Wheezing	7/53 (13.2)	3/15 (20.0)	4/14 (28.6)	14/82 (17.1)
Pneumonia	33/209 (15.8)	36/123 (29.3)	39/86 (45.3)	108/418 (25.8)
All	48/324 (14.8)	45/172 (26.2)	49/117 (41.9)	142/613 (23.2)
Serological and/or PCR				
Acute bronchitis	14/62 (22.5)	10/34 (29.4)	12/17 (70.5)	36/113 (31.8)
Wheezing	12/53 (22.6)	5/15 (33.3)	7/14 (50.0)	24/82 (29.2)
Pneumonia	43/209 (20.5)	56/123 (45.5)	51/86 (59.3)	150/418 (35.8)
All	69/324 (21.3)	71/172 (41.3)	70/117 (59.8)	210/613 (34.3)

Principi N et al. Clin Infect Dis. 2001;32:1281-1289

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When to think of *Mpn*? Clinical signs and symptoms

Clinical symptoms and signs for the diagnosis of *Mycoplasma pneumoniae* in children and adolescents with community-acquired pneumonia (Review)

Wang K, Gill P, Perera R, Thomson A, Mant D, Harnden A

THE COCHRANE COLLABORATION®

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2012, Issue 10

http://www.thecochranelibrary.com

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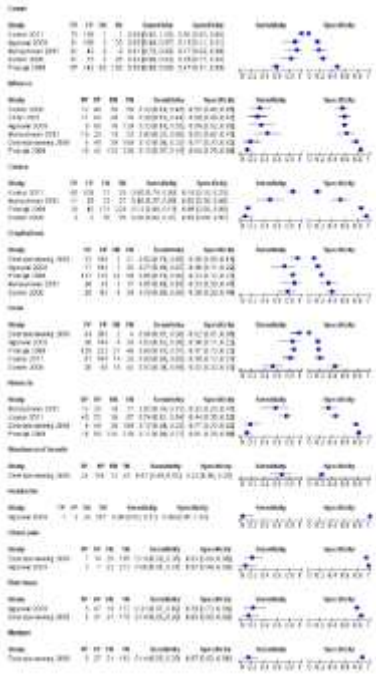
Forest plot of tests:

1. *Cough*
2. *Wheeze*
3. *Coryza*
4. *Crepitations*
5. *Fever*
6. *Rhonchi*
7. *Shortness of breath*
8. *Headache*
9. *Chestpaint*
10. *Diarrhoea*
11. *Myalgia*



Only statistical significant indicator of Mpn: Absence of wheeze

Chestpain doubles chance of Mpn

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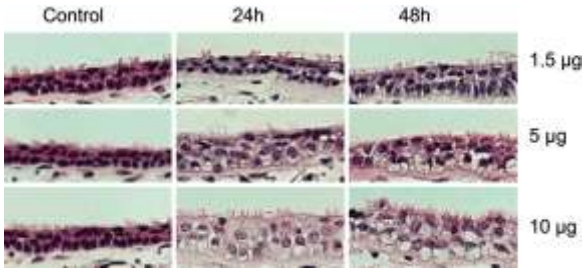
Persistent hacking cough: CARDS toxin

- First publication in 2006
- Pertussis like toxin
- Virulence factor? Strain dependent?



Kannan TR, Baseman JB. *Proc Natl Acad Sci USA 2006;103:6724–6729*

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Rick, 4 years

- *M. pneumoniae* serology:
  IgM weak positive
  IgG negative
- Nasopharyngeal washing:
  - *M. pneumoniae* PCR positive
  - viral panel PCR: negative
- Bloodcultures: negative

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Who thinks this is a
Mycoplasma pneumoniae pneumonia
because PCR is positive?

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Diagnosis of *Mycoplasma pneumoniae* infections

1. Serology
   - Retrospective diagnosis (fourfold increase of IgG)
   - Unreliable in immunocompromised patients and young children

2. Culture
   - Time consuming (2-6 weeks), labor intensive, insensitive

3. PCR
   - Fast, sensitive, specific

M. pneumoniae colonies

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Does asymptomatic carriage with *Mycoplasma pneumoniae* exist?

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OPEN ACCESS Freely available online

PLOS | MEDICINE

Carriage of *Mycoplasma pneumoniae* in the Upper Respiratory Tract of Symptomatic and Asymptomatic Children: An Observational Study

Emiel B. M. Spuesens[1,2*], Pieter L. A. Fraaij[3,4], Eline G. Visser[1], Theo Hoogenboezem[5], Wim C. J. Hop[5], Léon N. A. van Adrichem[6], Frank Weber[7], Henriette A. Moll[3], Berth Broekman[8], Marjolein Y. Berger[9], Tineke van Rijsoort-Vos[10], Alex van Belkum[10,11], Martin Schutten[4], Susan D. Pas[4], Albert D. M. E. Osterhaus[4], Nico G. Hartwig[1], Cornelis Vink[2], Annemarie M. C. van Rossum[1]

1 Department of Paediatric Infectious Diseases and Immunology, Erasmus MC-Sophia, Rotterdam, The Netherlands, 2 Laboratory of Paediatrics, Erasmus MC-Sophia, Rotterdam, The Netherlands, 3 Department of Paediatrics, Erasmus MC-Sophia, Rotterdam, The Netherlands, 4 Department of Virology, Erasmus MC, Rotterdam, The Netherlands, 5 Department of Biostatistics, Erasmus MC, Rotterdam, The Netherlands, 6 Department of Plastic Surgery, Erasmus MC, Rotterdam, The Netherlands, 7 Department of Anaesthesiology, Erasmus MC, Rotterdam, The Netherlands, 8 General Practitioners Cooperative, Rotterdam, The Netherlands, 9 Department of General Practice, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands, 10 Department of Medical Microbiology and Infectious Diseases, Erasmus MC, Rotterdam, The Netherlands, 11 Microbiology R&D, BioMérieux, La Balme-les-Grottes, France

May 2013 | Volume 10 | Issue 5 | e1001444

Main objectives:
1. Determine the existence of asymptomatic carriage of *M. pneumoniae*
2. Differentiate carriage from respiratory tract infection (RTI) based on bacterial load

What was done?
405 asymptomatic children, 321 children with RTI 3 mos - 16 years between 2008-2011. Mpn PCR and serology, bacterial and viral testing on (nasal)pharyngeal washings and swabs.

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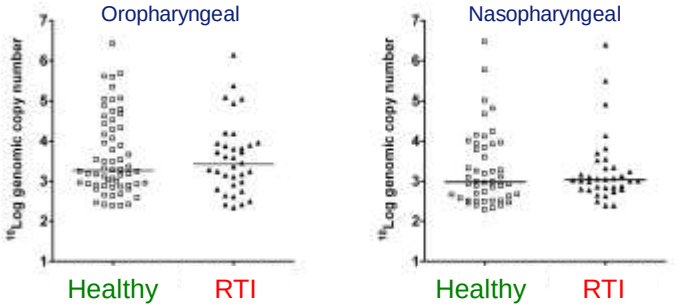
Results PCR

What is the prevalence of *M. pneumoniae* in children?

	Healthy (n = 405)	RTI (n = 321)	P-value
M. pneumoniae PCR			

Chi square 2.546

Is there a difference in bacterial load?



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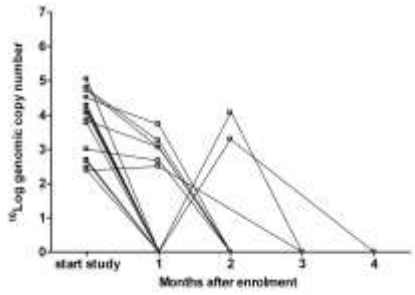
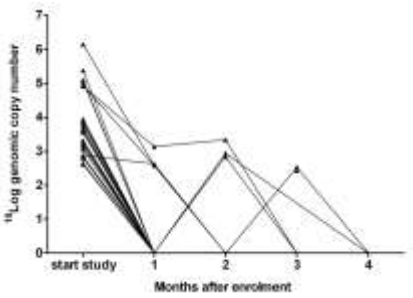
Results follow-up study

What is the 'natural course' of a positive PCR for *M. pneumoniae*?

Healthy



RTI



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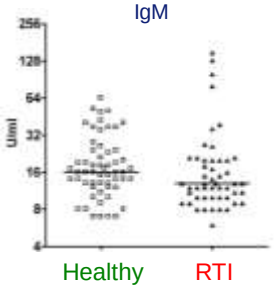
Results serology

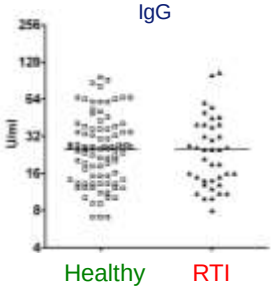
	Healthy	RTI	P-value
Anti-*M. pneumoniae* IgM		26 (9.2%)	
Anti-*M. pneumoniae* IgG		40 (14.2%)	

No difference in antibody levels

IgM



IgG



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Is *M. pneumoniae* a pathogen?

RESPIRATORY DISEASE IN VOLUNTEERS INFECTED WITH EATON AGENT; A PRELIMINARY REPORT

By R. M. Chanock, D. Ripkind, H. M. Kravetz, V. Knight, and K. M. Johnson

National Institute of Allergy and Infectious Diseases, National Institutes of Health

Communicated by Robert J. Huebner, April 18, 1961

Recent epidemiologic studies have provided evidence that the filterable agent first described by Eaton in 1944 was associated with human respiratory disease[1–4] A controlled field study among Marine recruits suggested that the Eaton agent caused a spectrum of disease including febrile respiratory illness and atypical pneumonia.[3] In the same Marine recruit population a double blind controlled study indicated that demethylchlortetracycline was effective in the therapy of pneumonia associated with Eaton infection.[4] During the course of these studies 14 strains of the agent were recovered in monkey kidney tissue culture.[4]

As a further step in assessing the etiologic role of Eaton agent in respiratory disease, tissue culture grown material was administered to volunteers in an attempt to reproduce the natural disease. This approach was made possible by the availability of an effective therapeutic [illegible] and [illegible] of the agent. This communication will present a [illegible] study while subsequent reports will [illegible]

TABLE 1

INFECTION OF VOLUNTEERS WITH EATON AGENT*

Fluorescent antibody titer prior to challenge	Type of illness	No. of volunteers	Fourfold or Greater Rise in Antibody** Eaton (fluorescent)	Cold agglutinin	Strep. MG agglutinin
less than 1:10	Pneumonia†	3	3	3	1
	Otitis media‡	11	11	7	2
	Febrile upper respir. illness	2	2	1	0
	Afebrile upper respir. illness	4	4	1	0
	None	7	7	0	0
	Total	27	27	12	3
1:10 or greater	Otitis media	1	1	0	0
	Afebrile upper respir. illness	6	4	0	0
	None	18	12	0	0
	Total	25	17	0	0

Rick, 4 years

- 20/4 hospital admission because of pneumonia left basal
- 21/4 increasing oxygen requirement, bronchospastic, crepitations
- 22/4 PICU admission because of respiratory insufficiency
- Physical examnination: no facial mimic, problems swallowing, areflexia, hypotonia of all extremities

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Rick, 4 years

Guillan-Barré syndroom after *M. pneumoniae* infection: molecular mimicry?

Anti-Gal-C antibodies in GBS subsequent to Mycoplasma infection: evidence of molecular mimicry
Kusunoki et al. Neurology. 2001

Cross-reactive anti-galactocerebroside antibodies and Mycoplasma pneumoniae infections in Guillain-Barré syndrome. Ang CW et al. J Neuroimmunol. 2002

Acute motor axonal neuropathy after Mycoplasma infection: evidence of molecular mimcry
Susuki et al. Neurology. 2004

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Pulmonary and extra-pulmonary complications of *Mpn* RTI

- **Pulmonary**
  - ARDS
  - Asthma exacerbation
  - Bronchiectasis
  - Bronchiolitis obliterans
  - Hyperlucent lung syndrome
  - Interstitial fibrosis
  - Lung abscess
  - Pleuritis,pulmonary embolism
  - Pneumatocele,pneumothorax
- **General**
  - Skin rashes
  - Erythema multiforme
  - Maculopapular eruptions
  - Vesicular eruption
  - Toxic epidermolysis
  - Erythema nodosum
  - Arthritis
  - Nausea/vomiting/diarrhea
- **Hematologic**
  - Hemolytic anemia
  - Diffuse Intravascular Coagulation
  - Thromboembolism
- **Cardiac**
  - Pericarditis
  - Myocarditis
- **Nephrologic**
  - Glomerulonephritis
  - IgA nephropathy
- **Neurologic**
  - Encephalitis
  - Meningitis
  - Poliomyelitis-like syndrome
  - Guillan-Barré syndrome
  - Brain-stem syndrome
  - cerebellar ataxia
  - Psychosis

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Rick, 4 years

- Treatment
  - Ventilator
  - Antibiotics: cefuroxim and clarithromycin
  - Neurological: methylprednisolon and prednison and morfin
- After 3 weeks discharge from PICU
- 2 weeks later discharge to revalidation center

Treatment of *M. pneumoniae* in children

- Macrolide (azithromycin, erythromycin, clarithromycin)

>8 years:

- Tetracyclines (doxycycline)
- Fluoroquinolones (levofloxacin, moxifloxacin, ciproxin)
- Duration?

Mycoplasma pneumoniae
does treatment help?

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Does treatment help?

Antibiotics for community-acquired lower respiratory tract infections secondary to *Mycoplasma pneumoniae* in children (Review)

Meiholland S, Gavranich JB, Gillies MB, Chang AB

THE COCHRANE COLLABORATION®

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2012, Issue 10

http://www.thecochranelibrary.com

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Does treatment help?

Mulholland et al. Cochrane Database of Systematic Reviews 2010;7

- No RCT's on effectiveness of antibiotics on Mpn LRTI
- Small proportions with *Mpn* infection in studies comparing macrolides with amoxycilline/clavulanate
- Dose and type of ab differed between studies
- Application of diagnostic criteria differed between studies
- Inclusion criteria differed between studies
- Outcome measures differed between studies

⇨

Need for RCT on efficacy of antibiotics for the treatment of childhood LRTI due to *Mpn*

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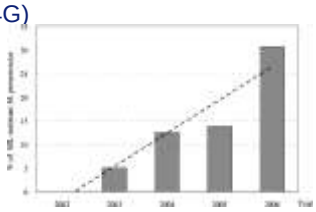
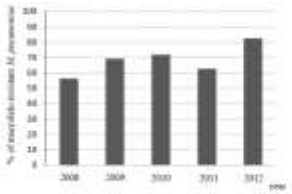
Rapidly emerging macrolide resistance *Mpn*

pointmutations in 23S rRNA (A2063G and A2064G)

- High percentages in Asia
  - Japan
    - 2007: ~ 43%
    - 2008: ~ 40%
    - 2012: 50-93%
  - China
    - 2008/2009: 60-90%
- Outside Asia:
  - Israel (30%)
  - Italy (26%)
  - France (~ 10%)
  - USA (8%)
  - Germany (3%)
  - The Netherlands (0%)



Morozumi, M. et al. 2008. Antimicrob. Agents Chemother. 52(1):348-350



Kawai et al. 2013 Antimicrob. Agents Chemother. online ahead of print

Morozumi et al., 2010, 2010, Liu et al. 2010, Cao et al. 2010, Averbuch et al. 2011, Dumke et al. 2010, Spuesens et al. 2012, Chironna et al. 2011, Wolff et al. 2008

Macrolide resistant *Mpn* in a 2011 outbreak among Japanese children

Table 2. Characteristics of Japanese Children With *Mycoplasma pneumoniae*–Associated Pneumonia From January to December 2011

Variable	Total	Macrolide-Susceptible *M. pneumoniae*, n = 26	Macrolide-Resistant *M. pneumoniae*, n = 176	*P* Value
Sex, male/female	106/96	15/11	91/85	.58
Inpatients/outpatients (%)	136/66	19/7 (73.1)	117/59 (66.5)	.50
Days from onset (range)	6 (2–15)	6 (3–12)	6 (2–15)	.67
Median age, years (range)	8 (1–14)	5 (1–13)	8 (1–14)	
≤1 (%)	6 (3.0)	3 (11.5)	3 (1.7)	.03
2–5	52 (25.7)	12 (46.2)	40 (22.7)	.01
≥6	144 (71.3)	11 (42.3)	133 (75.6)	.001

Table 3. Time to Defervescence After Initiation of a Secondary Agent and Duration of Antibiotic Use in Macrolide-Resistant *Mycoplasma pneumoniae*–Associated Pneumonia[a]

Time to Defervescence, Hours	Macrolides[b] (n = 13)	Minocycline (n = 52)	Doxycycline (n = 16)	Tosufloxacin[c] (n = 13)	*P* Value[d]
0–24	4 (30.8)	30 (57.7)	13 (81.3)	4 (30.8)	.03
25–48	2 (15.3)	17 (32.7)	1 (6.3)	5 (38.5)	.13
49–72	3 (23.1)	3 (5.8)	2 (12.5)	3 (23.0)	.98
>72	4 (30.8)	2 (3.8)	0	1 (7.7)	
Duration of administration, days (range)	6 (3–10)	5 (2–7)	3 (3–7)	5 (2–7)	

[a] Patients receiving a steroid together with an antimicrobial agent are not included.
[b] Clarithromycin (n = 8) or azithromycin (n = 5) was used.
[c] Includes 1 patient given levofloxacin.
[d] Minocycline or doxycycline vs tosufloxacin.

Okada et al. CID 2012

Clinical efficacy of macrolides

Kawai et al. Antimicrob. Agents Chemother. 2013

188 children with *Mpn* pneumonia (culture and PCR positive):

33% < 5 years old

150 macrolide resistant (10% hospitalized)

38 macrolide sensitive (0% hospitalized)

Macrolide sensitive

TABLE 4 Clinical efficacies of macrolides against MS *M. pneumoniae* pneumonia

Treatment group (no. of patients) or parameter	No. (%) of patients whose fever disappeared within 48 h after antibiotic administration	Avg no. of days of fever after antibiotic administration
AZM[a] (16)	14 (88)	1.62
CLR[b] (22)	22 (100)	1.04
P value	0.333	0.058

[a] AZM, azithromycin.
[b] CLR, clarithromycin.

Macrolide resistant

TABLE 5 Clinical efficacies of macrolides, minocycline, and tosufloxacin against MR *M. pneumoniae* pneumonia

Treatment group (no. of patients) or parameter[a]	No. (%) of patients whose fever disappeared within 48 h after antibiotic administration	Avg no. of days of fever after antibiotic administration
AZM (27)	11 (41)	3.06[b]
CLR (23)	11 (48)	3.15[b]
TFX (62)	43 (69)	2.31
MIN (38)	33 (87)	1.83
P value for:		
AZM vs CLR	0.698	0.869
AZM vs TFX	0.017	0.062
AZM vs MIN	0.0002	0.002
CLR vs TFX	0.067	0.081
CLR vs MIN	0.001	0.008
TFX vs MIN	0.047	0.152

[a] AZM, azithromycin; CLR, clarithromycin; MIN, minocycline, TFX, tosufloxacin.
[b] Antibiotic changed to TFX or MIN at the second visit for 10 patients in the AZM group and 13 in the CLR group.

Correlation between decrease in bacterial load and clinical improvement

In ML-R more rapid decrease bacterial load with minocyline than with tosufloxacin

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Macrolide resistance associated with disease severity?

Zhou et al AAC 2014: 206 children

- Prolonged clinical symptoms
- Increase in extrapulmonary manifestiations (29% vs 10%)

Cardinale et al J Clin Microbiol 2013:

- Prolonged clinical symptoms
- No increase in extrapulmonary manifestations

Clinical impact of ML-R *Mpn* infection

Conclusions:

- Prolonged fever and coughing in ML-R *Mpn* infection
- Prompt cessation of fever after initiation of fluoroquinolon/tetracyclines
- Difference in severity of disease?
- No clear evidence (yet) of more complications in ML-R *Mpn* infection
- Correlation between decrease in bacterial load and clinical improvement
- A significant number of cases treated with ineffective antibiotics have similar outcomes to those observed in patients with ML-S *Mpn* infection
- Debate on inflammatory effect of ML

Suzuki et al. Antimicrob Agents Chemother. 2006; Kawai et al. Respirology 2012; Matsubara et al. J Infect Chemother. 2009; Cardinale et al. J. Clin. Microbiol. 2013; Kawai et al. Antimicrob. Agents Chemother. 2013 Hsieh et al. Ped Infect Dis J 2012; Shen et al. Pediatr. Pulmonology 2013; Oishi et al. Emerg. Infect. Dis. 2012; Principi et al. J Antimicrob Chemother 2013, Myiashita et al. Antimicrob. Agents Chemother. 2013, Cardinale et al. J Clin Microbiol 2013, Zhou et al. Antimicrob. Agents Chemother. 2014

Take home messages

***Mycoplasma pneumoniae*: does treatment help?**

Yes, cessation of fever and shorter duration of coughing.
Prevention of severe infection???

Debate: effect of reduction of bacterial load and/or anti-inflammatory effect of macrolides

- **Also < 5 years of age frequent cause of lower respiratory tract infection**
- **Current diagnostic methods do not discriminate between asymptomatic carriage and infection**
- **Clinical suspicion when subacute, persistent coughing, no reaction to amoxicillin**
- **Think of macrolide resistance if no reaction to macrolides in children with high suspicion of *M.pneumoniae* infection.**

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