Lactate Dehydrogenase as a Biomarker for Prediction of Refractory *Mycoplasma pneumoniae* Pneumonia in Children

BS NGUYỄN THỊ NGỌC DIỄM

KHOA NỘI 3

Introduction

- **Mycoplasma pneumoniae (MP)**: one of the most prevalent pathogens causing CAP in children (40% CAP,18% require hospitalization)

- **Mycoplasma pneumoniae pneumonia (MPP)** :

 +usually self-limited

 +sometimes various pulmonary and extra-pulmonary complications

 +the host's immune response >> direct microbial damage

- **Refractory Mycoplasma pneumoniae pneumonia (RMPP):**

 +clinical and radiological deterioration /macrolide antibiotic therapy >=7 days

 +steroid administration is reported to be effective in this situation

→ **to recognize RMPP early ?**

Does LDH predict RMPP?

1. Clinical implications of interleukin-18 levels in pediatric patients
with MPP. Tomohiro Oishi et al 2011

2. Management of RMPP: Utility of measuring serum lactate dehydrogenase level. Norikazu Inamura et al 2014

3. Lactate Dehydrogenase as a Biomarker for Prediction of RMPP in Children Aizhen Lu MD PhD et al 2015

4. The Clinical Characteristics and Predictors of RMPP. Yuanyuan Zhang et al 2016

Clinical implications of interleukin-18 levels in pediatric patients with *Mycoplasma pneumoniae* pneumonia

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Mai Matsuo · Jun Negishi · Takayuki Kaneko · Shinya Tsukano ·
Tetsuo Taguchi · Makoto Uchiyama**

METHODS
- admitted to the Niigata Prefectural Shibata Hospital
- from 8/ 2006 to 2/ 2008, n = 23

RESULTS
-IL-18 levels :abnormally elevated, Relationship between IL-18 values and severity
-the correlation between **IL-18 and LDH**: statistically significant ($r2= 0.64$)
/other clinical parameters: WBC, NEU, CRP, -AST, -ALT: not significant
→ the usefulness LDH levels : measures of the severity of pediatric MPP

Original article

Management of refractory *Mycoplasma pneumoniae* pneumonia: Utility of measuring serum lactate dehydrogenase level

Norikazu Inamura [a], Naoyuki Miyashita, MD, PhD [b,*], Shunji Hasegawa [c], Atsushi Kato [a], Yoko Fukuda [a], Aki Saitoh [a], Eisuke Kondo [a], Hideto Teranishi [a], Tokio Wakabayashi [a], Hiroto Akaike [a], Takaaki Tanaka [a], Satoko Ogita [a], Takashi Nakano [a], Kihei Terada [a], Kazunobu Ouchi [a]

METHODS

-4 /2010 to 11/ 2012

-admitted Kawasaki Medical School Hospital and Yamaguchi University Hospital

- 20 pediatric patients MP (+)
- 5 RMPP / 15 GMPP (control group)

RESULTS

Laboratory findings of 20 pediatric patients with *M. pneumoniae* pneumonia.

Laboratory findings[a]	Refractory group		Control group	*p*-Value	
	At admission	At initiation of steroid use		At admission *vs* control	At initiation of steroid use *vs* contr
WBC (/μL)	4610 (2840−7460)	5370 (2000−13500)	5700 (3720−12210)	0.0887	0.7600
CRP (mg/d/L)	1.2 (0.5−6.3)	1.3 (0.3−3.5)	1.4 (0.3−6.7)	0.9652	0.5412
TP (g/dL)	6.8 (5.9−7.4)	6.9 (5.4−7.6)	7.2 (6.4−8.0)	0.0887	0.3155
LDH (IU/L)	331 (280−680)	571 (299−3606)	292 (208−395)	0.1266	0.0129
ALT (IU/L)	12 (9−16)	25 (13−44)	11 (7−33)	0.9203	0.0143
AST (IU/L)	29 (23−55)	41 (25−159)	26 (16−55)	0.5157	0.0404
IL-2 (pg/mL)	0 (0−3.0)	0 (0−1.6)	2.6 (0−3.7)	0.2317	0.1263
IL-4 (pg/mL)	0 (0−3.9)	0 (0−6.5)	0 (0−3.5)	0.2479	0.4237
IL-6 (pg/mL)	16.2 (12.9−81.7)	12.9 (7.3−28.6)	23.1 (7.1−135.6)	0.6169	0.0887
IFN-γ (pg/mL)	90.5 (15.3−613)	15.3 (9.8−42.6)	45.6 (9.7−121.1)	0.6171	0.0663
TNF-α (pg/mL)	0 (0−0)	1.9 (0−23.6)	0 (0−16.3)	0.6056	0.1097
IL-10 (pg/mL)	6.1 (2.6−10.1)	9.1 (2.6−24.1)	6.0 (2.8−40.8)	0.4237	0.5147
IL-18 (pg/mL)	483 (300−682)	579 (351−1680)	365 (237−610)	0.4235	0.0402

-At admission: no significant

-At the initiation of steroid use: serum **LDH**, ALT, AST and IL-18 levels **significantly higher** in RMPP

The correlation between IL-18 and LDH: statistically significant
→ **LDH** instead of IL-18 as a predictor of RMPP
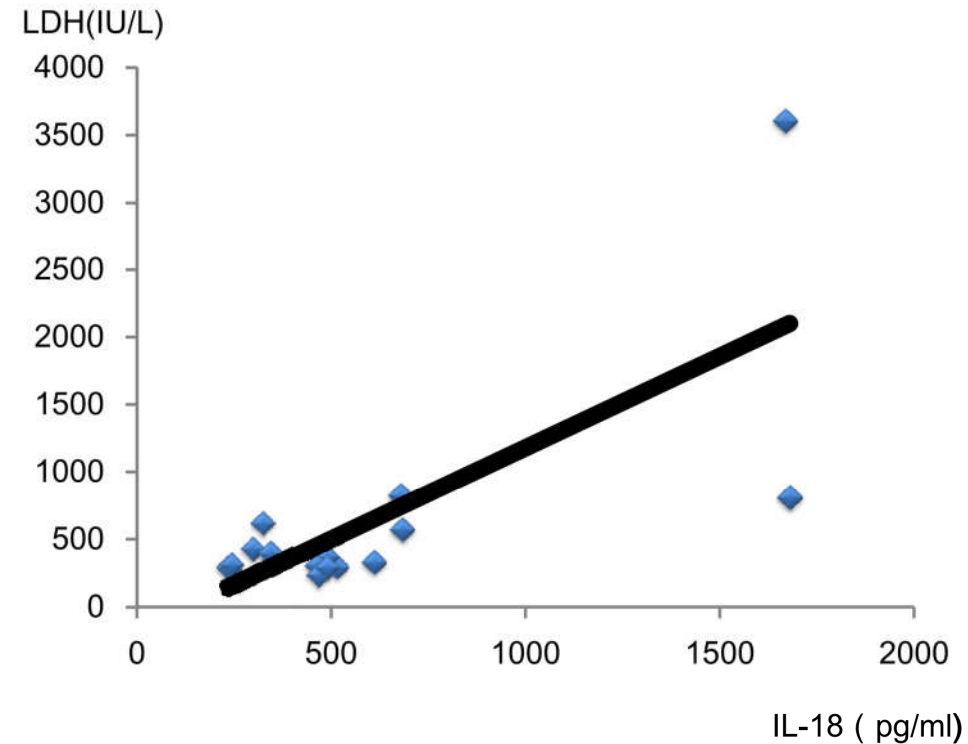
Fig. 1. Correlation between serum values of IL-18 and LDH levels. A significant relation was found between serum values of IL-18 and LDH values.

$$(r^2 = 0.504, p = 0.0433)$$

- the serum LDH cut-off level / the initiation of steroid therapy: **412 IU/L** (ss 80%, sp 100%)

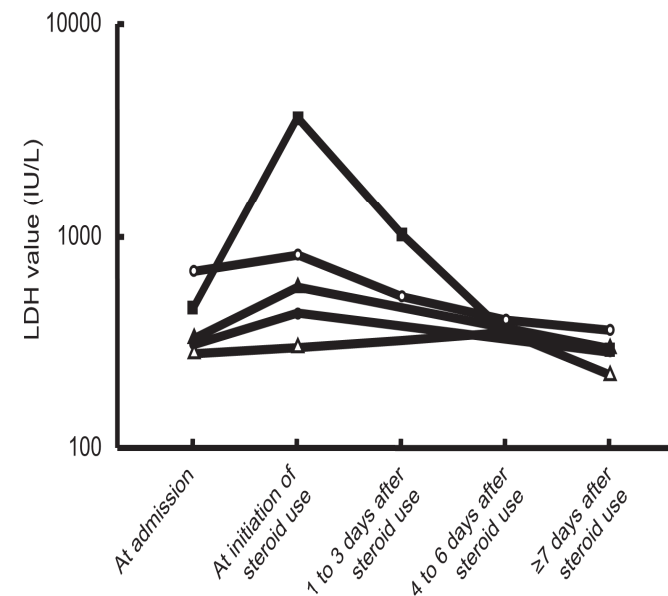- serum LDH levels : useful marker for the evaluation of therapeutic efficacy in RMPP

Fig. 2. Serum values of lactate dehydrogenase in 5 pediatric patients with refractory *M. pneumoniae* pneumonia at five points before and after steroid treatment.

Lactate Dehydrogenase as a Biomarker for Prediction of Refractory *Mycoplasma pneumoniae* Pneumonia in Children

Aizhen Lu MD PhD, Chuankai Wang, Xiaobo Zhang MD PhD, Libo Wang MD, and Liling Qian MD PhD

METHODS

-a prospective cohort study
-children with *MPP* admitted to the Children's Hospital of Fudan University
-September 2012 to August 2013
→n= **653**, 2 groups:RMPP group(300) and GMPP group (353)

Results

Table 1.   Comparison of Laboratory Findings on Admission for the Refractory and Usual *M. pneumoniae* Pneumonia Groups

Laboratory Test	Refractory *M. pneumoniae* Pneumonia Group	Usual *M. pneumoniae* Pneumonia Group	P
Creatine kinase, IU/L	116 ± 1,266 (13–986, 74)	89 ± 70 (2–825, 72)	.85
Creatine kinase MB, IU/L	35.7 ± 35.7 (9–189, 24)	30.2 ± 21.0 (6–230, 25)	.40
LDH, IU/L	449 ± 258	304 ± 78.1	< .01
HBDH, IU/L	357 ± 233	249 ± 69.3	< .01
Alanine aminotransferase, IU/L	23.2 ± 42.8 (1–394, 11.5)	12.4 ± 18.2 (1–219, 8.5)	< .01
Aspartate aminotransferase, IU/L	30.1 ± 28.7 (1–242, 21)	21.9 ± 20.7 (2–249, 18)	< .01
White blood cells, × 10^9/μL	8.62 ± 3.81 (2.1–28.9, 7.85)	8.23 ± 3.99 (1.8–43.9, 7.86)	< .01
Neutrophils, %	61.9 ± 15.0 (12.9–90.7, 63.7)	51.7 ± 17.1 (1.1–85.8, 54.0)	< .01
Lymphocytes, %	28.8 ± 13.5 (3.6–75.7, 27.0)	39.3 ± 16.3 (3.40–91.2, 35.6)	< .01
Platelets, × 10^9/μL	315 ± 125 (88–936, 299)	320 ± 116 (24–710, 315)	.23
C-reactive protein, mg/L	31.4 ± 39.1 (7–161, 7)	15.5 ± 20.5 (7–161, 7)	< .01
ESR, mm/h	40.8 ± 23.4 (6–125, 36)	28.2 ± 20.0 (0–102, 21)	< .01

Table 2. Logistic Regression Analysis of Associated Factors in Refractory *M. pneumoniae* Pneumonia

Relevant Factor	B	SE	Wald	*P*	Odds Ratio	95% CI for OR	
						Lower	Upper
Age	0.014	0.004	10.197	.001	1.01	1.00	1.02
LDH	0.009	0.001	33.821	< .001	1.01	1.00	1.01
ESR	0.020	0.007	8.081	.004	1.02	1.00	1.03

LDH = lactate dehydrogenase
ESR = erythrocyte sedimentation rate

- serum LDH (odds ratio of 1.01, 95% CI 1.00–1.01, $P < 0.001$)
→significant risk factors for RMPP / on admission

-The optimal cutoff of **LDH** for predicting RMPP: **379 IU/L**
ss: 48%, sp 85.8%, ppv74.2%, npv 65.9%

The Clinical Characteristics and Predictors of Refractory *Mycoplasma pneumoniae* Pneumonia in Children

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METHODS

-Retrospective analysis
-admitted to Children's hospital, Zhejiang University School of Medicine - January 1, 2011 and December 31, 2014

→n= 634, divided into two groups: GMPP (489 patients) and RMPP (145 patients)

RESULTS

Table 2. Laboratory characteristic of GMPP and RMPP patients.

Laboratory information	GMPP (n = 489)	RMPP (n = 145)	*P*-value
White blood cell (×10^9/L)	8.22 (6.27~10.56)	7.60 (5.71~9.90)	0.106
Neutrophil, %	56.7 (43.4~65.6)	73.1 (65.3~78.5)	0.000
C-reactive protein (CRP), mg/L)	6 (1~14)	36 (13~90)	0.000
Lactatedehydrogenase (LDH), IU/L	366 (310~459)	537 (419~666)	0.000
Prealbumin (PAB), g/L	0.12 (0.10~0.16)	0.08 (0.06~0.11)	0.000
Total Immunoglobulin (Ig), g/L			
IgG	9.36 (7.24~11.20)	8.96 (7.56~11.32)	0.823
IgA	0.85 (0.51~1.31)	1.20 (0.77~1.54)	0.000
IgM	1.54 (1.11~2.18)	1.66 (1.16~2.43)	0.138
Subpopulations of T lymphocytes, %			
CD3$^+$	61.48 (54.52~69.69)	61.97 (55.68~71.64)	0.243
CD4$^+$	33.97 (28.26~39.29)	34.26 (27.12~39.99)	0.909
CD8$^+$	21.16 (16.43~25.34)	22.63 (17.40~27.99)	0.040
Cytokines, pg/ml			
Interleukin 2 (IL-2)	2.6 (1.7~3.7)	2.5 (1.8~3.5)	0.883
IL-4	2.8 (2.2~3.4)	2.9 (2.2~3.5)	0.929
IL-6	9.7 (4.7~24.9)	34.2 (14.3~87.3)	0.000
IL-10	4.2 (3.1~6.1)	6.7 (4.7~10.0)	0.000
Tumor necrosis factor alpha (TNF-α)	2.9 (2.0~4.1)	3.0 (1.9~4.7)	0.866
Interferon gamma (IFN-γ)	7.9 (4.6~12.2)	16.3 (8.3~49.3)	0.000

Table 5. Stepwise logistic regression analysis for the related factors predicting the RMPP.

Variable	B	S.E.	Wald	P-value	OR	95%CI	
						Lower	Upper
C-reactive protein (CRP) ≥16.5mg/L	0.705	0.330	4.570	0.033	2.023	1.060	3.861
Lactatedehydrogenase (LDH) ≥417IU/L	0.782	0.319	5.998	0.014	2.185	1.169	4.084
Interleukin 6 (IL-6) ≥14.75pg/ml	0.839	0.333	6.341	0.012	2.314	1.204	4.446

- the cut-off values for **LDH** in differentiating RMPP from GMPP **:417IU/L**
- the sensitivity and specificity : **79.7%** and **65.0%**

SUMMARY

- Many study indicates that serum LDH was elevated in RMPP: serum LDH can be used as a **biomarker** for **predicting refractory RMPP** and determining candidates who may benefit from corticosteroid therapy during the early stages of hospitalization

- However, the present study is limited by the small sample sizes of the component studies.

Thank you for your attention!