



Teikyo-Harvard Program 特別企画2014

2014年 **1**月 **19**日(日) 13:00 – 18:00

帝京大学板橋キャンパス 本部棟2F 臨床大講堂

同時開催:ハーバード特別講義公開授業

13:00 – 15:00

Trends in Quality of Healthcare
and Asian Infectious Diseases

ADC

鈴木和男/帝京大学 アジア国際感染症制御研究所 所長
Kazuo Suzuki, Asia International Institute of Infectious Disease
Control, Teikyo University, Director-General

主催 帝京大学 共催 Harvard Club of Japan

Program

Introduction to Symposium I

Mr. Yoshihito Okinaga

The President, Teikyo University, Tokyo, Japan.

1. Introduction to infection-induced severe pulmonary diseases such as ARDS

Kazuo Suzuki, PhD

Asia International Institute of Infectious Disease Control, Teikyo University, Tokyo, Japan.

2. Bacterial identification in septic shock children in Viet Nam National Hospital of Pediatrics

Dien Tran Minh, MD, PhD

National Hospital of Pediatrics, Hanoi, Vietnam

3. Severe ARDS cases due to influenza infection in Vietnamese children - From the cases in PICU of NHP-Hanoi -

Shoji Kawachi^{1,2}, Noriko Nakajima², Hiroyuki Nunoi⁴, Kazuo Suzuki^{2,5},
Nguyen Trung Thuy³, Tran Minh Dien³, Liem Thanh Nguyen³

¹National Center for Global Health and Medicine, Tokyo, Japan, ²National Institute of Infectious Diseases, Tokyo, Japan, ³National Hospital of Pediatrics, Hanoi, Vietnam, ⁴Miyazaki University, Miyazaki, Japan, ⁵Teikyo University, Tokyo, Japan

4. Pathological study of Severe ARDS cases in NHP-Hanoi

Noriko Nakajima¹, Yuko Sato¹, Hideki Hasegawa¹, Hoang Ngoc Thach², Nguyen Trung Thuy², Tran Minh Dien², Nguyen Thanh Liem², Le Thanh Hai², Shoji Kawachi³, Kazuo Suzuki⁴

¹National Institute of Infectious Diseases, Tokyo, Japan ²National Hospital of Pediatrics, Hanoi, Vietnam ³National Center for Global Health and Medicine, Tokyo, Japan ⁴Teikyo University, Tokyo, Japan

ABSTRACT

1. Introduction to infection-induced severe pulmonary diseases such as ARDS

Kazuo Suzuki, PhD

Asia International Institute of Infectious Disease Control, Teikyo University, Tokyo, Japan.

Since the outbreak of highly pathogenic avian H5N1 influenza virus infection in humans in 2003, the WHO has reported a mortality rate of about 60%. Drs. Liem, Kawachi and Nakajima *et al* (1,2) have reported that many H5N1-infected patients develop acute respiratory distress syndrome and died. In the case of the influenza pandemic that occurred in 2009, infected pneumocytes in some patients showed severe respiratory failure similar to that seen for H5N1 infection. H5N1 infection cases have resulted in death at the National Hospital of Pediatrics Hanoi (3). In addition, Dr. Thuy (4, 5) has reported evidences of cytokine storm in spacemen of the patients and culture of lung epithelial cells under JSPS-RONPAKU program.

On the other hand, drug candidate for severe influenza-induced pneumonia has been found by ours group using screening from a macrolide compound library which has been established in Prof. Sunazuka's lab in Kitasato Univeristy. One of them, LM-A3, which has been found by Dr. Sugamata *et al.* (6) , showed the highest survival rate (80.9%) and induced alleviative effects on lung pathology and viral proliferation in model mice we established (7). These observations provide valuable evidences for knowledge of mechanisms of leukocytes infiltration from blood to lung lavage passing thorough lung endothelium-endothelium barrier with active/potential molecules along viral activity.

Based on our previous research, we will focus to pulmonary diseases induced with infection of influenza virus and *M. tuberculosis*. Then, JST is supporting our research by JST e-ASIA joint research project among Japan-Vietnam-Philippines with Dr. Kato's team on *M. tuberculosis*.

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4. Phung TTB, Luong ST, Kawachi S, Nunoi H, Nguyen LT, Nakayama T, Suzuki K. IL-12 and myeloperoxidase (MPO) in Vietnamese children with acute respiratory distress syndrome and induced avian influenza (H5N1) infection. *J Infect.* 2011; 62: 104-108.
5. Phung TTB, Sugamata R, Uno K, Aratani Y, Ozato K, Kawachi S, Nguyen LT, Nakayama T, Suzuki K. Key role of RANTES (regulated upon activation normal T-cell expressed and secreted), nonstructural protein1 and myeloperoxidase in cytokine storm induced by influenza virus PR-8(A/H1N1) infection in A549 bronchial epithelial cells. *Microbiol Immunol.* 2011;55(12):874-884.
6. Sugamata R, Sugawara A, Nagao T, Suzuki K, Hirose T, Yamamoto K, Oshima M, Kobayashi K, Sunazuka T, Akagawa KS, Omura S, Nakayama T, Suzuki. Leucomycin A3 (LM-A3), a 16-membered macrolide antibiotic, inhibits Influenza A virus infection and disease progression. *J. Antibiotics* 2003; in press.
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2. Bacterial identification in septic shock children in Viet Nam National Hospital of Pediatrics

Dien Tran Minh, MD, PhD

National Hospital of Pediatrics, Hanoi, Vietnam

Objectives: To define the kinds of bacteria in pediatric septic shock patients.

Subjects and methods : a prospective descriptive study of 102 cases suffered from septic shock at the National Hospital of Pediatrics, during 3 years from 2006 to 2008, diagnostic criteria for septic shock as the International Pediatric Sepsis Consensus Conference 2002 (IPSCC 2002), identified the bacteria by blood culture before using antibiotics and culture body fluids, bacterial identification and do the antibiogram.

Results: The rate of positive blood cultures was 14.7 %, a positive blood culture is not related to outcome (survival/non-survivor). Of the 58 stains of bacteria isolated from blood and body fluids, rate of Gr (+) is 38 %, Gr (-) is 59 %, with 2 cases of *Candida albicans* infection. Image bacteria were: *Klebsiella pneumoniae* (22.4 %), and others prospectively are (17.2 %) of *S. aureus*, *Pneumococcus*, *E.coli*, *H.influenza* are 12,1 %, 10.3 % , 8.6 % , 6.8 %. On the antibiogram result, the Gr negative bacteria are resistant to nearly all of antibiotics, especially, the third - generation cephalosporins, *S.aureus* are sensitive to almost antibiotics.

Conclusions: The rate of positive blood cultures in children with septic shock is 14.7 %, Gr negative bacteria have 59 %, and 38 % of Gr positive. The Gr negative bacteria are nearly resistant to all of antibiotics.

Current data including viral infection and Acinetobacter in NHP will be presented in this symposium.

Keywords: *Pediatric septic shock, bacteria, antibiotic resistance.*

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3. Severe ARDS cases due to influenza infection in Vietnamese children - From the cases in PICU of NHP-Hanoi -

Shoji Kawachi^{1,2}, Noriko Nakajima², Hiroyuki Nunoi⁴, Kazuo Suzuki^{2,5},
Nguyen Trung Thuy³, Tran Minh Dien³, Liem Thanh Nguyen³

skawachi@hosp.ncgm.go.jp

¹National Center for Global Health and Medicine, Tokyo, Japan, ²National Institute of Infectious Diseases, Tokyo, Japan, ³National Hospital of Pediatrics, Hanoi, Vietnam, ⁴Miyazaki University, Miyazaki, Japan, ⁵Teikyo University, Tokyo, Japan

ARDS associated with A(H5N1) avian influenza virus infection develops severe ARDS [*JID* 2009, Kawachi, *et al*], and with other types of influenza, severe ARDS sometimes occurs among children. It is an urgent mission to elucidate the mechanism of influenza-ARDS and to make a therapeutic strategy. For this purpose, we have been co-operating the prospective study for severe ARDS with National Hospital of Pediatrics–Hanoi (NHP-Hanoi) from October 2007. 102 patients were diagnosed as severe ARDS matched in the criteria of prospective study during 2007/10-2013/3. In 8 patients among 102, the influenza viruses were detected from NPA/TLF samples with PCR; A(H5N1) (3), A(H1N1)pdm09 (4), H3N2 (1) and before 2007/10, 10 H5N1-ARDS patients were admitted in PICU of NHP-Hanoi. We analyzed the clinical data in totally 18 cases of influenza associated ARDS (influenza group). In 22 cases other viruses were detected (not-influenza group): CMV(13), Rhinovirus(8), Adenovirus (5), RSV(5), Measles (1). Significant differences were observed in pH and PaCO₂(ABGA) and also AST/ALT values, white blood cells and platelets counts in the serum. Survival probability analysis showed the differences between groups (p=0.0023 by log-rank test, p=0.0013 by Wilcoxon test) resulting longer survival days in not-influenza group (Influ: 14, not-Influ: 31 days).

インフルエンザによる重症 ARDS 症例の検討

–ベトナムハノイ国立小児病院 PICU における Study : 2005-2013 より–

河内正治^{1,2}、中島典子²、布井 博幸⁴、鈴木和男²、

Nguyen Trung Thuy³, Tran Minh Dien³, Liem Thanh Nguyen³

¹ 国立国際医療研究センター、² 国立感染症研究所、³ National Hospital of Pediatrics, Hanoi, Vietnam、
⁴ 宮崎大学、⁵ 帝京大学

インフルエンザによる severe ARDS は、最終病理像は肺胞の広範囲な障害 (DAD ; Diffuse Alveolar Damage) であるが、死亡に到るまでが数日から 2 週間と急速に進行し死亡することが特徴で [*Moderen Pathol* 2013, Nakajima, *et al*]、このときの死亡原因は ARDS による呼吸死であると考えられる。現在までにハノイ国立小児病院(NHP-Hanoi)PICU にて、ARDS に対する先行的研究によって得られたインフルエンザ症例は 18 例で、他のウイルスに起因する症例が 22 例であった。今回は NHP-Hanoi における H5N1 を含むインフルエンザ症例と他のウイルス性肺炎を主因とした severe ARDS の症例集計結果を提示し比較検討して報告する。

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4. Pathological study of Severe ARDS cases in NHP-Hanoi

Noriko Nakajima¹, Yuko Sato¹, Hideki Hasegawa¹, Hoang Ngoc Thach², Nguyen Trung Thuy², Tran Minh Dien², Nguyen Thanh Liem², Le Thanh Hai², Shoji Kawachi³, Kazuo Suzuki⁴

¹National Institute of Infectious Diseases, Tokyo, Japan ²National Hospital of Pediatrics, Hanoi, Vietnam ³National Center for Global Health and Medicine, Tokyo, Japan ⁴Teikyo University, Tokyo, Japan

We examined the lung pathology of fatal cases of severe ARDS in NHP-PICU. The ARDS induced by influenza virus infection is generally classified as severe ARDS with P/F ratio < 100 and the patients die due to respiratory failure. First, we show the results of histopathological study of lung tissues with highly pathogenic avian H5N1 influenza virus (H5N1) infection, and then, those with non-influenza virus infection. **Methods:** Formalin-fixed paraffin-embedded lung tissues were analyzed with several methods as follows: Immunohistochemistry for viral antigens, proinflammatory cytokines and chemokines, double immunofluorescence staining with cell marker proteins, real time quantitative reverse-transcription polymerase chain reaction methods for viral RNA and cytokine/chemokine mRNA. **Results:** H5N1 infected lung tissues showed a spectrum of histopathological changes of diffuse alveolar damages (DAD). Myeloperoxidase (MPO)-positive and/or CD68 (clone KP-1)-positive neutrophils and monocytes/macrophages infiltrated prominently in the alveolar septa and alveolar spaces. Viral antigen-positive cells were mainly alveolar epithelial cells and monocytes/macrophages. The expression levels of TNF- α , IL-6, IL-8, RANTES and IP-10 were correlated with H5N1-RNA copy numbers. Double immunofluorescence staining revealed that TNF- α , IL-6, IL-8 and IP-10 were expressed in epithelial cells and/or monocytes/macrophages. In particular, IL-6 was also expressed in endothelial cells. As for pathological study of ARDS cases with non-influenza virus infection, some were revealed to be CMV systemic infection and others were diagnosed aspergilosis. **Conclusions:** Pathological study clarified not only the pathogen which caused ARDS but also the local inflammatory responses in the lung. H5N1 infected alveolar epithelial cells and injured them directly. Marked accumulation of neutrophils and monocytes/macrophages suggested neutrophil-mediated lung injury. The expression levels of cytokines and chemokines suggested local uncontrolled inflammatory responses induced by H5N1 infection. These factors may work together and cause ARDS.

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