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研究成果の刊行物

インフルエンザ診療マニュアル 2010−2011年シーズン版

Manual for Influenza in the 2010–2011 Influenza Season

日本臨床内科医会インフルエンザ研究班　班　長　河合　直樹
独立行政法人国立病院機構九州医療センター　名誉院長　柏木征三郎

はじめに

昨年大流行した新型AH1N1（以下，新型）は当初2010−2011年シーズンも流行の中心と予想され，日本臨床内科医会（日臨内）発行のインフルエンザ診療マニュアルも2010−2011年版（第５版）も新型中心に作成された[1]。しかし現在は新型，Ａ香港型，Ｂ型の混合流行の様相を呈しており，以下に記載した新型と，第４版までの季節性を併せて参照して流行に対処していただきたい。

昨シーズンの新型の流行について

図１のように，例年の季節性とは異なって昨年の新型は９月以降，全国的な大流行となり，11月末頃にピークを打ち，今年初めにはほぼ流行が収まった。また今年春頃まで，季節性はＢ型以外のＡソ連型，Ａ香港型はほとんど検出されなかった。新型は一部小児等で重症・緊急搬送例（ウイルス肺炎，脳症，心筋炎等）があったが，大部分は軽症であった。

迅速診断

キットの診断能は，新型では季節性よりも当初は低いと報告されたが，日臨内の検討ではほぼ季節性と遜色なかった（感度88.5％，特異度83.7％，精度86.9％）。また陽性ライン出現までの時間や陽性ラインの濃さ（クロマトリーダー測定値）はウイルス量と良好に相関した。なおキットにより鼻かみ鼻汁検体の保険適応の有無や判定時間等は若干異なる。

ワクチン

筆者らの研究によるワクチンの有効率（発生予防効果）はシーズンで異なり（Ａ型で20.5〜78.6％），原因としてワクチン株と流行株のマッチングや接種後の抗体価上昇の良否などの関与が示唆された。2009年の国産新型ワクチンは従来の季節性と同様のスプリットワクチンだが，有効率は約70％と比較的良かった（**図２**）。この理由としては新型流行株の変異が少なくワクチン株とのマッチングが良好で，かつ新型でも抗体獲得率が比較的高いことが考えられた（日臨内データで成人１回接種後の40倍以上の抗体獲得率67.5％）。なお抗体獲得率としては輸入のアジュバント付加ワクチン［乳濁Ａ型インフルエンザHAワクチン（H1N1株）：アレパンリックス］の方がさらに高かった（同抗体獲得率95％）。

抗インフルエンザ薬

2008−2009年シーズンのＡソ連型ではオセルタミビルリン酸塩（以下，オセルタミビル）耐性のため，同薬投与開始後の解熱時間は前年よりも著明に延長したが[2,3]，新型では解熱時間が24.0時間と本薬の有効性が高かっ

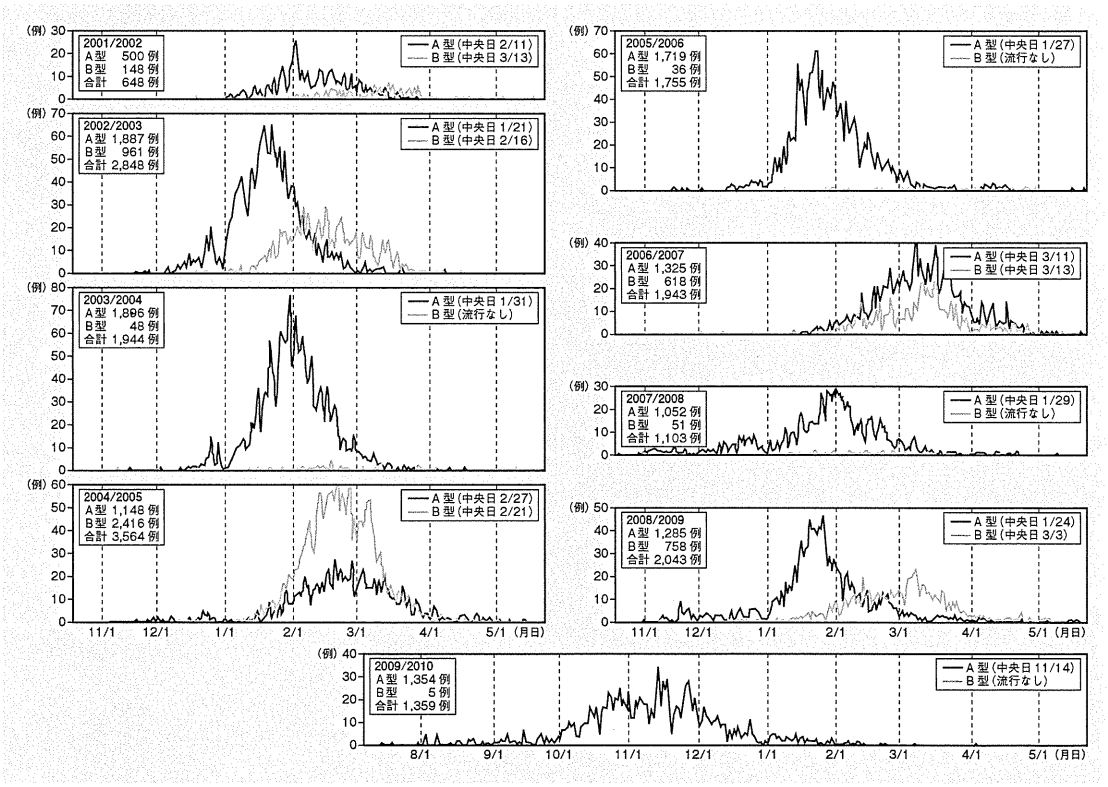

図１　過去９シーズンにおけるＡ型，Ｂ型別の発症日[1]

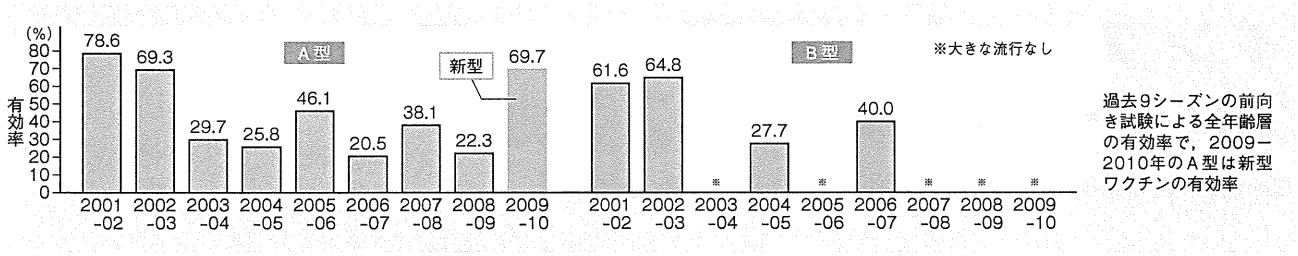

図2　A，B型インフルエンザに対するワクチンの有効率[1)]

表1　ノイラミニダーゼ阻害薬の種類

	オセルタミビル	ザナミビル	ペラミビル	ラニナミビル
剤形（対象年齢）	カプセル（Cap：成人・小児≧37.5kg*） ドライシロップ（DS：1歳以上）	吸入薬（成人，小児**）	点滴注射薬（成人，小児）	吸入薬（成人，小児）
用法・用量	Cap：1回1Capを1日2回5日間 DS：1回2mg/kgを1日2回5日間	1回10mg（5mgブリスターを2個）を1日2回5日間	成人は300mg，小児は10mg/kg（上限は600mg）を15分以上かけて単回投与（重症化する恐れのある場合は1日1回600mgまで可）	10歳以上：1回40mgを1回のみ（2容器吸入） 10歳未満：1回20mgを1回のみ（1容器吸入）
予防投薬の適用（ただし自費）	あり	あり	なし	なし（治験中）
副作用	胃腸障害等	まれ	下痢等	まれ***
耐性ウイルス	A香港型，新型とB型は低頻度。 Aソ連型はほぼ100%耐性。	まれ	H275Y変異株における感受性低下の報告あり	まれ***

いずれもA，B型に有効で，発症48時間以内に開始。＊10歳以上の未成年においては，原則使用不可。＊＊本剤を適切に吸入投与できると判断された場合に限る。ただし4歳以下の安全性は確立していない。＊＊＊まだ十分なエビデンスは得られていない。

文献1）より一部改変

た。またザナミビル水和物（以下，ザナミビル）はオセルタミビル感受性・耐性のAソ連型，新型のいずれでも有効性が高かった[3)]。

本邦で諸外国よりも新型の死亡率が低かったのは，抗インフルエンザ薬の有効率が高くかつ早期投与されたためと考えられる。なお新しい抗インフルエンザ薬として2010年1月にペラミビル水和物（以下，ペラミビル），9月にラニナミビルオクタン酸エステル水和物（以下，ラニナミビル）が承認された。これら新薬を含めたノイラミニダーゼ阻害薬の比較を**表1**に示すとともに，治療薬の現状の要点を記す。

1．オセルタミビル

内服薬でA型に比しB型では若干有効性が低く[4,5)]，10歳以上の未成年では原則使用禁止措置が続いている。2008－2009年シーズンにAソ連型ではH275Y変異の耐性化が進み，特に小児では有効性が低下したが，新型はH275Y変異はあまりみられず，有効性が高い。

2．ザナミビル

吸入薬で，ウイルス増殖部位の気道系に直接かつ迅速に作用して，全身への影響や耐性ウイルスの報告は少ない。患者アンケート調査の結果でも，吸入器の操作や吸入は小児でも比較的容易である。本薬は新型やH275Y変異のAソ連型を含め，いずれの型・亜型にも有効であり，B型でも解熱時間は他の亜型とほぼ同等であった[3,6)]（**図3**）。

3．ペラミビル

点滴注射用の長時間作用型ノイラミニダーゼ阻害薬で，成人は300mg（小児は10mg/kg，上限600mg）を15分以上かけて単回投薬するが重症化の恐れがある場合は1日1回600mgまでの使用や反復投与が可能。H275Y変異株で本薬の感受性低下が報告されていることには留意が必要だが，経口や吸入の困難例，ハイリスク・重症例等では使用意義が高い。

4．ラニナミビル

純国産で吸入型の長時間作用型ノイラミニダーゼ阻害薬。発症後，1回の投与で気管や肺に長時間貯留し，5日間投与のオセルタミビルと同等の薬効を示す。オセルタミビル耐性ウイルスにも有効だが，入院重症例では使用経験が少ない。

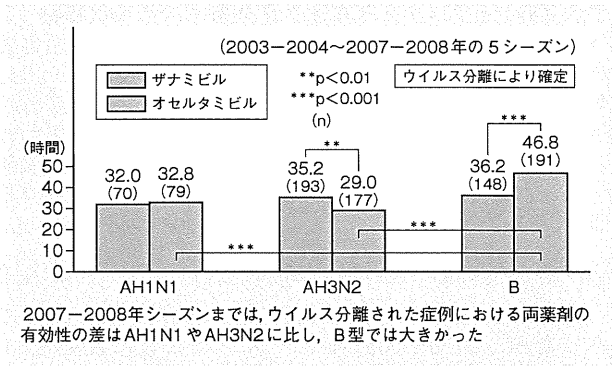

図3　2007－2008年シーズンまでの各ウイルス型におけるザナミビルとオセルタミビル投与開始後の解熱時間の比較[1)]

5．その他の治療薬

1）アマンタジン塩酸塩（M2蛋白阻害薬）

A型のみ有効で，オセルタミビル耐性Aソ連型には有効だが，A香港型や新型は耐性型のため無効とされている。

2）ファビピラビル（RNAポリメラーゼ阻害薬）

現在開発中の経口薬で，ウイルスのRNAポリメラーゼを選択的に阻害する新規作用メカニズムを有し，ノイラミニダーゼ阻害薬との併用や耐性化対策にも有用と思われる。

おわりに

本稿は『インフルエンザ診療マニュアル2010－2011年シーズン版』を抜粋したが，詳細は同マニュアル（日本臨床内科医会事務局，電話：03-3259-6111で入手可能）を参照されたい。[共同研究者：池松秀之，岩城紀男，廣津伸夫]

(文　献)
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インフルエンザ診療マニュアル 2011－2012年シーズン版

Manual for Influenza in the 2011-2012 Influenza Season

日本臨床内科医会インフルエンザ研究班　班　長　河合　直樹
九州大学先端医療イノベーションセンター　特任教授　池松　秀之
独立行政法人国立病院機構九州医療センター　名誉院長　柏木征三郎

はじめに

2009年に初めて出現し同年秋に大流行した新型AH1N1（以下，H1N1 2009）は2010－2011年シーズンには季節性と同じ冬期に流行し，このシーズンはH3N2（香港型）やB型も流行する混合流行であった。また2010－2011年シーズンは従来のオセルタミビルリン酸塩（以下，オセルタミビル）とザナミビル水和物（以下，ザナミビル）に加えてペラミビル水和物（以下，ペラミビル）とラニナミビルオクタン酸エステル水和物（以下，ラニナミビル）の４種類のノイラミニダーゼ阻害薬（NAI）が初めてフルシーズン使用された。2011－2012年シーズンも引き続きH1N1 2009やH3N2等の流行が予想され，治療も上記のNAI４剤が中心になると思われる。日本臨床内科医会（日臨内）のインフルエンザ診療マニュアルもこれらNAIの比較を含めて2011－2012年版（第６版）が発行された[1]。ここではその要点を述べる。

インフルエンザの流行状況

2009－2010年シーズンはH1N1 2009単独の流行であったが，2010－2011年シーズンはこれにH3N2，B型が加わった混合流行であり（**図１**），流行ピークは１～３月であった。また20歳未満（特に小児）ではH3N2やBの流行が目立ったが，成人はH1N1 2009が流行の主体であった[2]。2011－2012年シーズンもA型ではH1N1 2009とH3N2の両亜型が引き続き流行する可能性が高い。

迅速診断

2010－2011年シーズンに日臨内解析（以下，本研究）により培養，PCRと比較して検討したキットの陽性試験予測率はA型89.7％，B型96.7％と高く，キットの診断能は良好であった。現在H1N1 2009に特異的な抗体を用いた診断キット，H1N1 2009とH3N2の鑑別キットなども利用可能である。

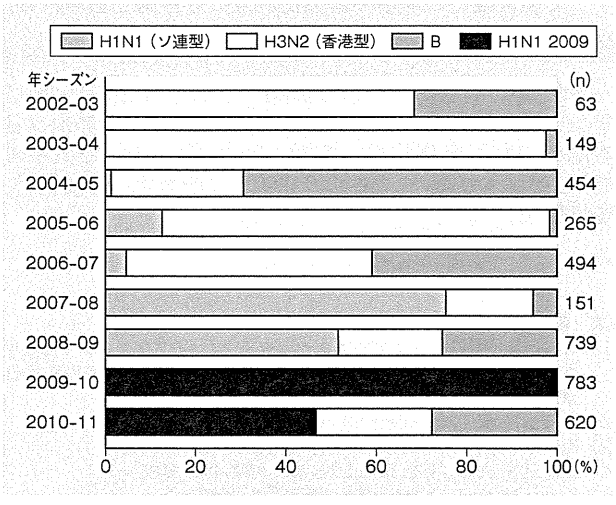

図１　過去９シーズンのインフルエンザの型・亜型別頻度[1]

ワクチン

H1N1 2009一色の流行であった2009－2010年の本研究ではH1N1 2009単価ワクチンの有効率は70％前後と高かった。しかし2010－2011年シーズンはH3N2，Bのワクチン接種後の抗体価上昇はやや悪く（本研究でワクチン接種後の40倍以上のHI抗体価保有率はH1N1 2009が62.2％，H3N2が40.5％，Bが37.8％），H1N1 2009が流行の主体であった成人以外の有効性はやや低かったが，安全性は従来同様高かった。なお2011－2012年シーズンのワクチン株は前シーズンと同じだが小児の接種量が変更されており留意が必要である。

抗インフルエンザ薬

2008－2009年シーズンにH1N1（ソ連型）はH275Y変異のためほぼ100％オセルタミビル耐性型となり同薬の有効性が特に小児で低下したが[3]，H1N1 2009の出現とともにH1N1（ソ連型）は消えている。2010－2011年シーズンの本研究でA型の有効性はペラミビル以外の３剤はほぼ同等であった（**図２**）。またB型では各薬剤ともにA型よりも有効性が低いが，その中ではザナミビルがやや有効性が高い傾向がみられた（**図２**）。A亜型別の有効性は各NAIともにH3N2よりもH1N1 2009の方が高い傾向にあった[1]。NAI以外のアマンタジン塩酸塩はH3N2，H1N1 2009とも耐性型のため推奨されず，RNAポリメラーゼ阻害薬のファビピラビルも現時点で未承認である。以下，NAI４剤について**表１**で比較するとともに要点を記す。

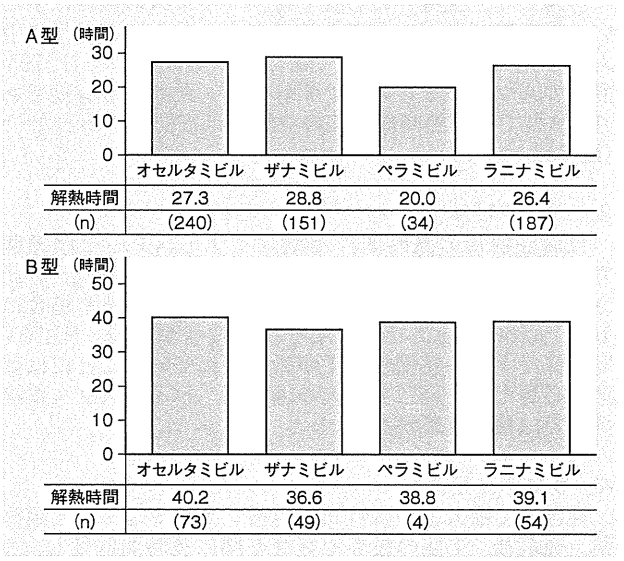

図２　迅速診断のA型およびB型における抗インフルエンザ薬別の平均解熱時間[1]

表1　ノイラミニダーゼ阻害薬の種類

	オセルタミビル[1]	ザナミビル[2]	ペラミビル	ラニナミビル
剤形（対象）	内服薬 Cap：成人・小児≧37.5kg DS：1歳以上	吸入薬 （成人，小児）	点滴注射薬 （成人，小児）	吸入薬 （成人，小児）
用法・用量	Cap：1回1Cap（75mg） DS：1回2mg/kg （1回最高用量は75mg） 1日2回 5日間内服	1回10mg （5mgブリスターを2個） 1日2回 5日間吸入	成人：300mg（2バイアルまたは1袋） 小児：10mg/kg（1バイアルまたは1袋） 単回点滴または複数回点滴[3]	10歳以上：40mg（20mgを2容器） 10歳未満：20mg（20mgを1容器） 単回吸入のみ
予防投薬の適用	1CapまたはDS2mg/kg （1回最高用量75mg）	1日1回10mg （5mgブリスターを2個）	未承認	未承認
副作用	胃腸障害等	まれ	下痢	まれ
耐性ウイルス	H1N1ソ連型はほぼ100％耐性 H1N1 2009は低頻度	まれ	H275Y変異株での感受性低下報告あり	まれ

その他の注意事項　1）10歳以上の未成年においては，原則使用不可
2）4歳以下の安全性は確立していない
3）合併症等により重症化する恐れのある患者では600mg（4バイアルまたは2袋）まで可。なお本薬は腎排泄のため，腎機能障害患者では投与量の調整を要する

文献1）より一部改変

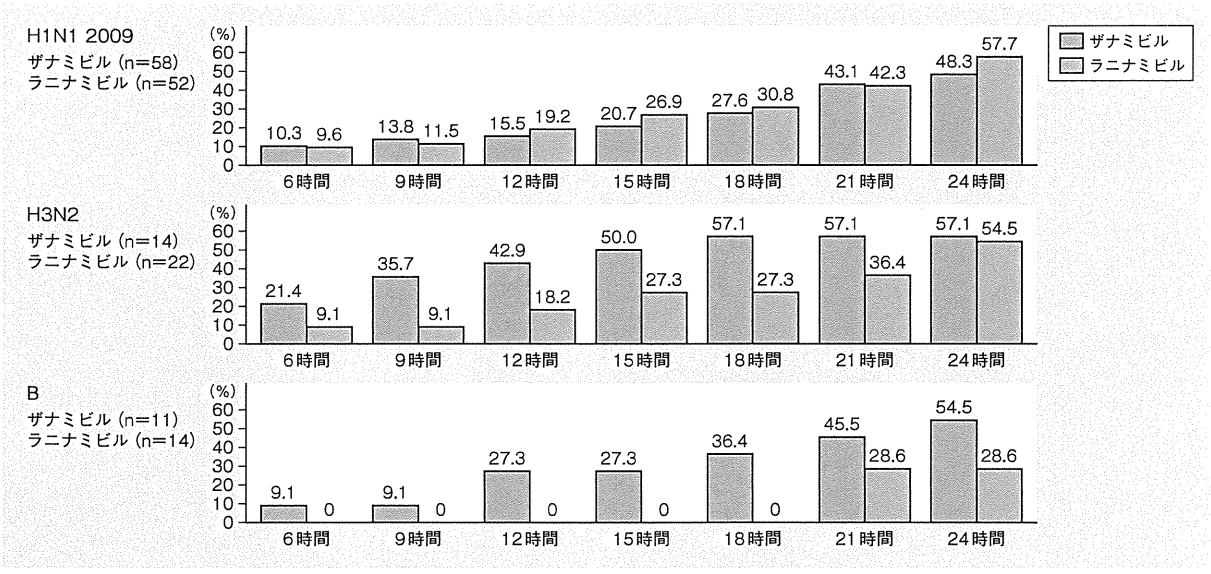

図3　ザナミビルとラニナミビル投与開始3時間ごとの解熱症例率[1]

1．オセルタミビル

内服薬で10歳以上の未成年ではハイリスク者を除いて原則使用禁止。H1N1 2009もH275Y変異が起きると本薬の有効性低下が懸念されるが，現状では耐性化率が1～2％と低く有効性は高い。2010－2011年も吸入困難な4歳以下の小児を中心に10歳未満で最もよく使用された[1,2]。

2．ザナミビル

吸入薬で全身への影響や耐性ウイルスの報告は少なく，H275Y変異を含めいずれの型・亜型にも有効で安全性も高い。患者調査では，吸入器の操作や吸入も，小児でも比較的容易であった。2010－2011年シーズンの本研究では10代で最も高頻度に使われた[2]。本薬剤はプロドラッグでなく，活性物質そのものであり，高濃度でウイルス増殖部位に直接作用するため即効性が期待される。ラニナミビルとの比較研究[4]で投与開始48時間の時点では有効性に大差なかったが24時間以内の早期ではH3N2やB型で臨床効果の出現が早い可能性が示唆された（**図3**）。

3．ペラミビル

米国より導入された長時間作用型の注射薬。薬効は1回点滴でオセルタミビル5日間投与に匹敵するとされ，A，B型の他に高病原性鳥インフルエンザウイルスH5N1にも強い抗ウイルス活性を示す。成人300mg，小児10mg/kgを15分以上かけて単回投与するが重症化の恐れがある場合はともに1日1回600mgまでの使用や連日の投与が可能。H275Y変異株で感受性低下が報告されているが，経口や吸入が困難な症例等で使用する意義が高い。

4．ラニナミビル

純国産で長時間作用型の吸入薬（プロドラッグ）。発症後1回投与で気道や肺に長時間貯留し，5日間投与のオセルタミビルと同等の薬効を示す。H275Y変異型にも有効だが，入院重症例では第一選択とはなりにくい。1回完結型のため，外来患者の利便性は高く症状改善による服薬中止の心配もない。H1N1 2009では有効性が高く（**図3**），2010－2011年シーズンの本研究でも多忙な成人でよく使用された。

おわりに

本稿は『インフルエンザ診療マニュアル2011－2012年シーズン版』を抜粋したが詳細は同マニュアル（日本臨床内科医会事務局，電話：03-3259-6111で入手可能）を参照されたい。

（文　献）
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2）河合直樹，他：Clinic Magazine **38**（9）（No.506）：9-13，2011．
3）Kawai N, et al.：Clin Infect Dis **49**：1828-1835，2009．
4）池松秀之，他：日臨内科医会誌 **26**：215-219，2011．

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Original article

Clinical preparedness for severe pneumonia with highly pathogenic avian influenza A (H5N1): Experiences with cases in Vietnam

Koichiro Kudo[a,d,*], *Nguyen Gia Binh*[b], *Toshie Manabe*[a,d], *Dao Xuan Co*[b], *Nguyen Dang Tuan*[b], *Shinyu Izumi*[a], *Jin Takasaki*[a], *Dang Hung Minh*[b], *Pham Thi Phuong Thuy*[c], *Vu Thi Tuong Van*[b], *Tran Thuy Hanh*[b], *Ngo Quy Chau*[b]

[a]*National Center for Global Health and Medicine, 1-21-1 Toyama, Shinjuku-ku, Tokyo 162-8655, Japan*
[b]*Bach Mai Hospital, 78 Giai Phong, Dong Da, Hanoi, Vietnam*
[c]*NCGM-BMH Medical Collaboration Center, 78 Giai Phong, Dong Da, Hanoi, Vietnam*
[d]*Waseda University, 1-21-1 Nishi-Waseda, Shinjuku-ku, Tokyo 169-0051, Japan*

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ABSTRACT

Background: Avian influenza A (H5N1) in human presents a global pandemic threat, and preparedness is urgently required in high-risk countries.

Methods: A retrospective chart review was conducted on 8 patients with H5N1 infection (aged 2–30 years; 3 fatal) who were hospitalized in Bach Mai Hospital (BMH), Vietnam, or in affiliated hospitals with consultation by physicians in BMH between 2007 and 2010. Demographic background, chest radiographs, and clinical and laboratory data were evaluated to determine the critical issues in relation to clinical outcomes. Treatment of 4 patients with acute respiratory distress syndrome (ARDS) (2 fatal) was assessed for renal replacement therapy using continuous hemodiafiltration (CHDF), polymyxin B-immobilized (PMX) hemoperfusion, or their combination.

Results: Patients had direct contact with dead/sick poultry infected with H5N1 virus or lived in areas where H5N1 poultry outbreaks had been reported at the same time as their illness. Time to initiation of oseltamivir from symptom onset was 2–6 days for survivors and 7–9 days for non-survivors. All patients except one had infiltrative shadows on chest radiographs on admission. Patients with delayed treatment developed ARDS. Renal replacement therapy contributed to patient survival, with improvement of oxygenation and a dramatic decrease in serum cytokine levels if initiated earlier.

Conclusions: Understanding local H5N1 poultry outbreaks and chest radiography assist early diagnosis and initiation of antiviral treatment. Developing a network among local and tertiary care hospitals can reduce the time to initiation of treatment. CHDF and PMX

Abbreviations: ARDS, acute respiratory distress syndrome; ALI, acute lung injury; CHDF, continuous hemodiafiltration; PMX, polymyxin B-immobilized; IFN, interferon; IL, interleukin; TNF, tumor necrosis factor; FiO_2, fraction of inspired oxygen; PaO_2, partial pressure of oxygen in arterial blood; P/F, PaO_2/FiO_2; SOFA, Sequential Organ Failure Assessment

*Corresponding author at: Waseda University, Suite 613-6, #19 Build, 1-21-1 Nishi-Waseda, Shinjuku-ku, Tokyo 169-0051, Japan.
E-mail address: kudo@aoni.waseda.jp (K. Kudo).

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hemoperfusion are possible candidates for effective treatment of ARDS with H5N1 if applied earlier.

1. Introduction

Avian influenza A (H5N1) virus infection in human presents a global pandemic threat. To date, H5N1 infection in human has been sporadic and related to exposure to zoonotic sources of the virus [1,2]. The recent unpredictable changes in H5N1 virus in human highlight the urgent need for clinical preparedness. H5N1 outbreaks among poultry and wild birds have occurred in Japan and worldwide [3]. It is necessary to implement a high alert for H5N1 in these high-risk countries.

H5N1 infection rapidly leads to severe pneumonia and acute respiratory distress syndrome (ARDS), which are pathologically characterized as diffuse alveolar damage [4,5]. Oseltamivir treatment is recommended for H5N1 patients [6–8], and the timing of antiviral treatment is vital for achieving a positive outcome [6,9]. The development of a clinical treatment system to administer oseltamivir as early as possible is crucial for H5N1 patients. In addition, the optimal dosage and duration of oseltamivir treatment need to be clarified for H5N1 patients [10,11]. Single treatment with oseltamivir is not sufficient for most H5N1 patients. Combination therapy with antiviral agents seems to be needed for severe pneumonia [2,11]. Without appropriate treatment for pneumonia due to H5N1 infection, ARDS can develop and often leads to death [4,12]. Since 2007, 30 confirmed human cases have been reported in Vietnam to date (63.3% of mortality). Despite the relatively low incidence of human H5N1 infections globally, H5N1 infection has been occurring continuously, with a high mortality rate [1]. This has rendered it difficult to conduct clinical studies to find effective treatment strategies. It has also resulted in a small number of physicians who have the experience and knowledge to treat H5N1 patients. Therefore, additional clinical data need to be collected.

The aims of the present study were to examine the clinical backgrounds and treatment methods of patients with H5N1 infection in Vietnam and to assess how the clinical system contributed to early initiation of oseltamivir treatment, how treatment affected patient survival, and whether renal replacement therapy was effective in H5N1 patients with ARDS. Experience in treating H5N1 patients can contribute to clinical preparedness for any future pandemic deriving from highly pathogenic influenza virus infection.

2. Materials and methods

2.1. Study site and subjects

Bach Mai Hospital (BMH) is a government hospital in Hanoi, Vietnam, that has played a central role in treating H5N1 patients in northern Vietnam since 2003. BMH has developed a cooperative network for treating H5N1 patients among provincial and district hospitals in 19 provinces (Fig. 1). Within the network, medical providers can exchange scientific information relating to H5N1 infection and clinical consultations by physicians in BMH who have treated H5N1 patients. The subjects of the present study were 8 patients with H5N1 infection between 2007 and 2010 who were hospitalized and treated in BMH (2 fatal), or hospitalized in

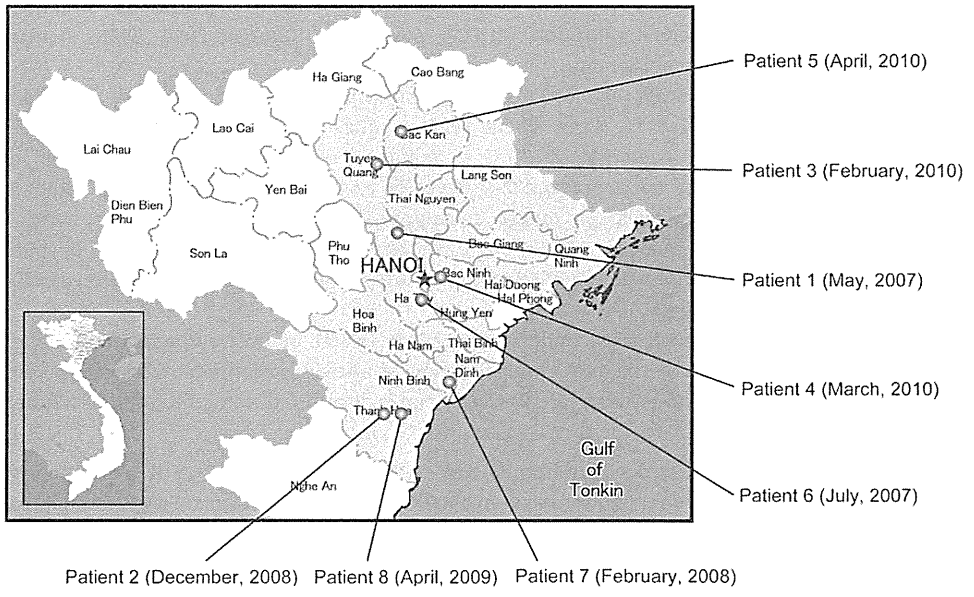

Fig. 1 – Map of Vietnam indicating the location of the study patients, as well as month and year of occurrence of H5N1 infection. Light gray area indicates the healthcare network among 19 provinces in this study.

local hospitals within the network and treated through consultations with physicians in BMH (one fatal). All patients tested positive for H5N1 virus by real-time reverse transcriptase-polymerase-chain-reaction (RT-PCR) at the National Institute of Hygiene and Epidemiology, Hanoi.

2.2. Study design

A retrospective chart review was conducted on 8 patients with H5N1 infection. Demographic background, clinical data, chest radiographs, and laboratory data were collected and assessed to determine the critical issues for treating H5N1 patients in relation to clinical outcomes. Renal replacement therapy was performed by using continuous hemodiafiltration (CHDF) [13], an absorbent column containing polymyxin B fiber (Toraymyxin/PMX, Toray Medical Co., Ltd., Tokyo, Japan) [14], or its combination, and was evaluated for treating ARDS due to H5N1 infection in 4 patients who were treated in the intensive care unit (ICU) of BMH. Partial pressure of oxygen in arterial blood/fraction of inspired oxygen (P/F) and Sequential Organ Failure Assessment (SOFA) score in 4 patients with ARDS as well as levels of serum inflammatory cytokines in a patient treated with PMX hemoperfusion were assessed at different time points during the ICU stay.

Hospital admission was defined as the time when treatment for H5N1 infection was initiated. ARDS and acute lung injury (ALI) were defined as $P/F \leq 200$ and 200–300, respectively [15].

2.3. Ethics

Ethical approvals were provided by the institutional review boards of Ministry of Health, Vietnam (No. 7998/BYT-K2DT, December 2011) and the National Center for Global Health and Medicine (No. 592, March 2011). Written informed consent was obtained from study patients or their relatives.

3. Results

3.1. General characteristics of study patients

Among the 8 patients (6 female, 2 male, aged 2–30 years) examined, four were initially treated at local hospitals and transferred and treated in the ICU, BMH. The remaining 4 patients were treated in local general hospitals (Fig. 1). The characteristics and clinical presentation on admission of each patient are shown in Table 1.

None of the patients had any underlying diseases. Two patients were chicken traders and another 2 reported cooking and eating infected (dead) poultry. One patient was a fish farmer who handled dried bird excrement as feed. The remaining 4 patients of young age (2, 8, 17, and 23 years old) had no history of direct contact with either sick or dead poultry; however, they lived in areas where H5N1 poultry outbreaks had been reported at the same time as their illness.

All patients had fever (≥ 38.0 °C) at the time of admission. Productive cough and dyspnea were common. Chest pain was observed in 5 patients. Upon admission, all patients, except Patient 5, had respiratory difficulty (median respiration rate, 30 breaths/min; range, 25–36); low oxygen saturation in arterial blood under oxygen administration with nasal, mask, or mechanical ventilation; and abnormal breath sounds (crackles) in the chest. Infiltration shadows on chest radiographs indicating pneumonia were observed at hospital admission for all patients except Patient 5. The primary laboratory tests were performed on admission (Table 1). Specific abnormalities in laboratory findings were not observed, except for tendencies toward leukopenia in peripheral blood and high levels of serum creatinine.

3.2. Clinical course and treatment of study patients

The clinical course and treatment for each patient are shown in Table 2. All patients, except Patient 5, sought primary medical assistance (primary care) in the local community before hospital admission. Time from symptom onset (fever) to primary care ranged 2–7 days. Patients were transferred to either a local general hospital or BMH, and treatment for H5N1 infection was initiated in accordance with positive results by RT-PCR. The time from primary care to hospital admission ranged 0–5 days, and total duration from symptom onset to initiation of treatment ranged 2–9 days.

ALI/ARDS was observed in all patients on admission, except Patient 5. Multiple organ failure developed in all non-survivors and 2 survivors during hospitalization. Patients 1 and 4 (survivors), who had long hospitalization, had nosocomial infections, as determined by sputum and blood cultures. Bacterial co-infection was detected in the sputum from Patient 2 on admission.

All patients were treated with oseltamivir, which is the only available antiviral agent in Vietnam. The basic dosage of oseltamivir was 150 mg/day in local general hospitals and 300 mg/day in BMH. The duration of treatment was 5–8 days, or until the patient's death. Other drug regimens and treatments included antibiotics, corticosteroids, oxygen including ventilation support, and renal replacement therapy including blood purification therapy. Between presentation to primary care and hospital admission, patients were empirically treated with antibiotics. Corticosteroids were administered to all patients with pneumonia concomitantly with oseltamivir. Antibiotics were administered during the entire treatment period.

3.3. Chest radiographs

Chest radiographs are shown upon admission (before oseltamivir administration), at the time of worst condition, and during the recovery period in Fig. 2. With Patients 6, 7, and 8 (non-survivors), consolidation shadows rapidly expanded to the entire lung fields within a few days after hospital admission (but were not critical at admission in Patients 6 and 7). consolidation shadows for survivors eventually diminished, although 2 patients exhibited exacerbated conditions after admission. Patients 1, 4, 6, and 7 developed pneumothorax during mechanical ventilation support.

Table 1 – Background and clinical characteristics of patients on admission.

Variable	Survivors					Non-survivors		
	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
General background								
Year of illness	2007	2008	2010	2010	2010	2007	2008	2009
Place treated	BMH	Province	Province	BMH	Province	BMH	BMH	Province
Age (yr)/gender (M/F)	30/M	8/F	17/F	25/F	2/F	22/F	27/M	23/F
Route of exposure to virus	Handling chickens	Ate infected chicken	Backyard poultry died 5 days before onset	Cooked and ate infected chicken	Epidemic outbreak in poultry in residential area	Fish farmer, handled bird excrement	Chicken trader, handled dead chickens	Epidemic outbreak in poultry in residential area
Underlying disease	None	None	None	None	None	None	None	None
Clinical presentation								
Body temperature (°C)	40.1	38.5	38.0	39.5	37.5	38.1	39.8	39.0
Primary signs and symptoms	Fever, dyspnea, cough, sputum, chest pain	Fever, dyspnea, cough, sputum, chest pain	Fever, dyspnea, cough, sputum	Fever, dyspnea, cough, chest pain	Fever, cough	Fever, dyspnea, cough, chest pain	Fever, dyspnea, cough, chest pain	Fever, dyspnea, cough, chest pain, diarrhea
Respiration rate (per min)	30	25	NA	30	25	36	30	36
Crackles	+	+	+	+	NA	+	+	+
SpO_2[a] under oxygen administration (L/min)	74% 8 L mask	99% 3 L nasal	92% 5 L nasal	90% 8 L mask	No oxygen	65% 100% MV	70% 9 L mask	79% 100% MV
PaO_2/FiO_2[b]	119	NA	NA	207	NA	38.4	32.8	NA
Abnormal shadow on chest radiograph[c]	Unilateral mixed	Unilateral infiltration	Bilateral mixed	Bilateral mixed	Absence of pneumonia	Bilateral mixed	Bilateral consolidation	Unilateral consolidation
APACHE score[d]	23	NA	NA	22	NA	24	32	NA
SOFA[e]	11	NA	NA	9	NA	9	10	NA
Laboratory findings[f]								
Serum creatinine (mg/dL)	1.45	0.90	NA	0.90	NA	0.82	1.12	2.68
AST (U/L)	477	145	NA	94	NA	199	171	114
ALT (U/L)	131	66	NA	12	NA	45	36	32

Table 1 (*continued*)

Variable	Survivors					Non-survivors		
	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
LDH (IU/L)	NA	101	NA	1051	NA	NA	891	NA
Leukocyte (per mm^3)	2190	2000	6100	1670	4100	5400	1320	NA[f]
Platelet (per mm^3) $\times 10^4$	8.7	2.7	NA	6.5	NA	11.9	13.6	NA

M, Male; F, female; NA, not available; MV, oxygen therapy using mechanical ventilation; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase.

[a] Oxygen saturation measured by pulse oximeter.

[b] PaO_2/FiO_2 ratio. PaO_2: partial pressure of oxygen in arterial blood (mmHg); FiO_2: fraction of inspired oxygen. Measured after the initiation of mechanical ventilation.

[c] Bilateral or unilateral lung abnormal shadow on chest radiograph. Mixed, abnormal shadows represent both infiltration and consolidation.

[d] APACHE II score: Acute Physiology and Chronic Health Evaluation score. Score range, 0–71; higher range indicates more severe disease.

[e] SOFA: Sequential Organ Failure Assessment. Score range, 0–24; higher values indicate more severe disease.

[f] Normal ranges were as follows: leukocyte count, 5000–10,000; platelet count ($\times 10^4$), 15–45; AST level, <37 U/L; ALT level, <41 U/L; LDH, 105–333 IU/L; serum creatinine, 0.7–1.2 mg/dL.

3.4. *Evaluation of renal replacement therapy including PMX hemoperfusion for ARDS due to H5N1 infection*

As a therapy for ARDS, renal replacement therapy and/or blood purification therapy were applied to Patients 1, 4, 6, and 7, who were treated in BMH, where CHDF/PMX treatments were provided. The *P/F* ratios for Patients 1, 4, 6, and 7 were <100 at the time of the initiation of renal replacement therapy (Table 3). Patient 1 (survivor) and Patient 7 (non-survivor) were treated with CHDF, and the time from ARDS onset to CHDF was <20 h in Patient 1 and >27 h in Patient 7. Patient 6 (non-survivor) was treated with PMX hemoperfusion, and the time from ARDS onset to PMX was >24 h. Patient 4 (survivor) was treated with PMX hemoperfusion followed by CHDF, and the time from ARDS to the initiation of sequential therapy was 10–15 h.

The available data for the sequential therapy with PMX hemoperfusion and CHDF in Patient 4 were assessed both with oxygenation and the measurement of five kinds of serum cytokine levels (interleukin [IL]-6, IL-8, interferon [IFN]-γ, IL-1β, tumor necrosis factor [TNF]-α) (Fig. 3). Immediately after ICU admission, the respiratory condition of Patient 4 rapidly deteriorated and the *P/F* ratio decreased to 43. PMX hemoperfusion was applied sequentially using 3 columns at a flow rate of 100 mL/min for 3 days. The *P/F* ratio increased to 128 at 24 h and to 203 at 3 days after the initiation of PMX hemoperfusion. Among the 5 serum cytokines examined, levels of IL-6, IL-8, and IFN-γ markedly decreased at 24 h after initiation of PMX hemoperfusion, whereas significant elevation of IL-1β and TNF-α was not observed at the time of initiation of PMX hemoperfusion (Fig. 3). Patient 4 was treated with CHDF after PMX hemoperfusion for 4 days. The patient was extubated and discharged 23 days after symptom onset. No serious adverse events were observed during the renal replacement therapy.

4. Discussion

The present study revealed that early initiation of antiviral treatment has a strong influence on the survival of patients with H5N1 infection, and that the healthcare network can assist in providing early medical intervention. Renal replacement therapy including PMX hemoperfusion, especially sequential therapy with PMX and CHDF, can be offered to treat H5N1 patients with ARDS. However, the timing is also crucial for a positive outcome.

Most human cases of avian influenza (H5N1) occur through direct or indirect contact with poultry or contaminated environments [16–18]. Previous reports from Vietnam, Thailand, Indonesia, and Cambodia have presented a relationship between human cases of H5N1 infection and a history of contact with sick and/or dead poultry [4,17,19]. In the present study, among 8 patients admitted to hospitals within the network (Fig. 1), some had direct contact with infected poultry because of their work or life habits. Others had no history of direct contact, but H5N1 outbreaks in poultry around these patients' residential areas were reported at the same time as their illness. An association between infection in wild birds and H5N1 outbreaks among poultry

Table 2 – Clinical course and treatment of study patients.

Variable	Survivors					Non-survivors		
	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
Clinical time course								
Days from onset to primary care[a]	3	3	3	3	2	4	4	7
Days from onset to hospital admission[b]	6	6	4	5	2	7	9	8
Days from onset to treatment[c]	6	6	4	5	2	7	9	8
Days hospitalized	26	13	10	23	10	5	3	2
Days from onset to death	–	–	–	–	–	12	12	10
Clinical progression of organ dysfunction								
Respiratory failure on admission	ARDS	ALI	ALI	ARDS	None	ARDS	ARDS	ARDS
MOF (days from admission)	+ (day 1)	None	None	+ (day 1)	None	+ (day 1)	+ (day 1)	NA
Bacterial infection[d]								
On admission	ND	*Streptococcus pneumoniae*	ND	ND	ND	ND	ND	ND
During hospitalization (Days from admission)	*Acinetobacter* (day 4) *P. cepacia* (day 7) *P. aeruginosa* (day 11)	ND	ND	*Acinetobacter* (day 5)	ND	ND	ND	NA
Treatment								
Oseltamivir (duration: days)	300 mg/day (8)	150 mg/day (5)	150 mg/day (5)	300 mg/day (8)	75 mg/day (6)	300 mg/day (5, to death)	300 mg/day (3, to death)	150 mg/day (2, to death)
Corticosteroid (duration: days)	Hydrocortisone 300 mg/day (6) 200 mg/day (1)	Methylprednisolone 40 mg/day (1)	Methylprednisolone 80 mg/day (1)	Methylprednisolone 500 mg/day (4) 250 mg/day (2)	None	Hydrocortisone 300 mg/day (5)	Hydrocortisone 200 mg/day (3)	Hydrocortisone 200 mg/day (3)

Table 2 (*continued*)

Variable	Survivors					Non-survivors		
	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
Antibiotic	100 mg/day (1) Cephalosporin, Aminoglycoside	Cephalosporin, Aminoglycoside	Cephalosporin	125 mg/day (1) Cephalosporin, Carbapenem, Fluoroquinolone	Cephalosporin	Carbapenem, Macrolide	Carbapenem, Macrolide, Aminoglycoside	Cephalosporin, Aminoglycoside, Tetracycline
Oxygen therapy (duration: days)	MV (8) Nasal cannula (5)	Nasal cannula (2)	Nasal cannula (1)	MV (7) Nasal cannula (3)	None	MV (5)	MV (3)	MV (2)

ARDS: P/F <200; ALI, P/F ≤300; MOF: ARDS with oliguria in Patient 1, hypotension and coagulopathy in Patient 4, hypotension and coagulopathy in Patient 6, hypotension in Patient 7.
ARDS, acute respiratory distress syndrome; P/F, partial pressure of oxygen in arterial blood/fraction of inspired oxygen ratio; ALI, acute lung injury; MOF, multiple organ failure; NA, not available; ND, not detected; MV, mechanical ventilation.
[a] Time interval from symptom onset to local healthcare organization (primary care).
[b] Time interval from symptom onset to local general hospital or tertiary care hospital.
[c] Time interval from symptom onset to initiation of treatment for H5N1.
[d] *Acinetobacter*, *Pseudomonas*, and *Streptococcus pneumoniae* were detected in sputum; *Sepacia* was detected in blood culture.

has been reported [20]. The main period of occurrence of H5N1 poultry outbreaks is around the *Tet* holiday (Lunar New Year) festival in January or February [21]. The distribution, trading, and consumption of chickens increase dramatically during this period [22] because chicken is a traditional dish for the celebration of *Tet*. Thus, the risk of H5N1 infection in humans increases around that time [21]. Illness in the study patients tended to be concentrated around the *Tet* festival. Therefore, understanding H5N1 poultry outbreaks and traditional habits, festivals, and celebrations that increase chicken consumption can aid in prediction of the time of occurrence of human H5N1 infections. It may also assist physicians' decision making for diagnosis and treatment if patients with pneumonia are presented.

Although the time to seeking healthcare reflects patients' knowledge about disease, socioeconomic difficulties, historical habits, and the healthcare system in each country, most of the previous studies in Vietnam documented a median duration from symptom onset to hospitalization for 6 days [4,23–25]. The WHO summarized 42 cases of H5N1 infection that were reported to the WHO in 2010, the median duration between symptom onset and hospital admission was 4 days (range 0–12) [26]. The present study observed a median of 6 days (range 2–9) from symptom onset to hospitalization (Table 2). The range was 2–6 days in survivors and 7–9 days in non-survivors. Based on the findings of the present study, it appears that 6 days is the critical period for patient survival. However, there were two distinct reasons that led to delayed initiation of oseltamivir treatment from symptom onset. In the present study, the average intervals from symptom onset to first access to primary care and from primary care to initiation of antiviral administration were 3.6 days (range 2–7) and 2.3 days (range 0–5), respectively (Table 2). Providing proper education to motivate people towards early access to healthcare and developing a network among the different healthcare settings that enables the transfer of H5N1 (suspected) patients from primary to tertiary care can shorten the total time interval to initiation of oseltamivir treatment [27,28]. In addition, waiting to receive a positive RT-PCR result for H5N1 virus leads to delayed diagnosis. All patients, except Patient 5, had infiltrative shadows on their chest radiographs on admission (Fig. 2). If a patient had a contact history with infected poultry or an H5N1 poultry outbreak around their residential area, he/she had the opportunity to receive early oseltamivir treatment even if the PCR result had not been obtained.

Variable symptoms and signs of the early stage of illness have been reported [4,12,17,18,23,24,29]. In the present study, lower respiratory tract symptoms were predominant at the early stage of disease. High fever, along with cough, was present in all study patients at the beginning of illness. This indicated that the viral infection began in the lower respiratory tract in most patients in the present study. At the time of hospital admission, all patients, except Patient 5, had already developed pneumonia. Patients who did not receive any treatment for >7 days from symptom onset (non-survivors) and in whom focal or unilateral shadows on chest radiographs were observed on admission rapidly progressed to severe conditions with bilateral and diffuse shadows (Fig. 2). In contrast, patients who received oseltamivir treatment by ≤6 days from symptom onset (survivors) did not experience rapid progression (Fig. 2).

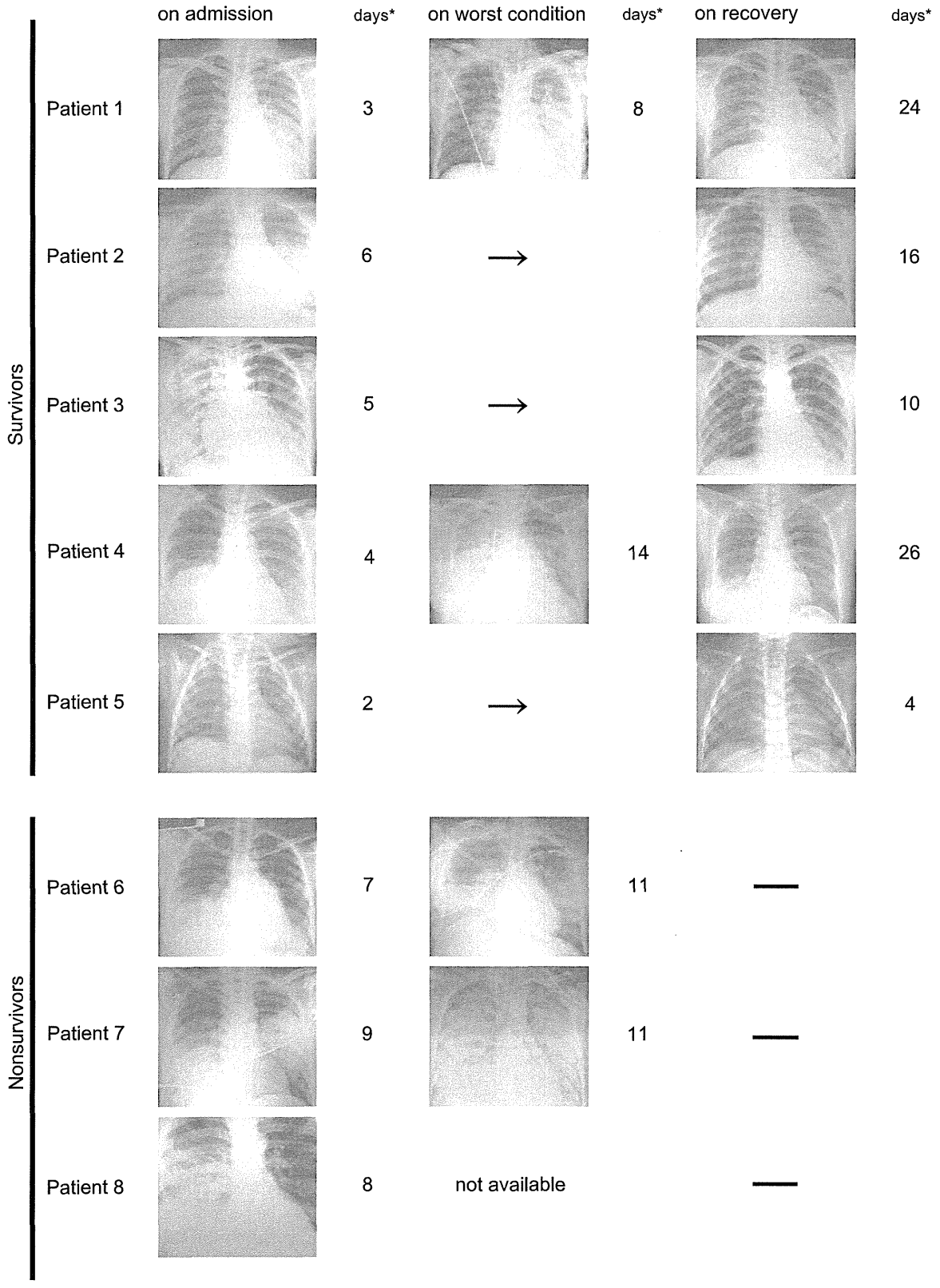

Fig. 2 – Chest radiographs of each patient upon admission (before oseltamivir administration), at the time of worst condition, and during the recovery period. All patients except Patient 5 had extensive consolidation shadows in unilateral or bilateral lung fields on admission. Patient 1: subcutaneous and mediastinal emphysema was observed (day 8). Patient 4: consolidations were observed all over the right lung and pneumothorax in the right thorax (day 14). Patient 5: no obvious shadows were observed on admission (day 2). *The number of days from symptom onset.

Table 3 – Condition of patients treated with renal replacement therapy.

Outcome	Patient 1 Survived	Patient 4 Survived	Patient 6 Died	Patient 7 Died
Renal replacement therapy				
Method	CHDF[a]	PMX/CHDF[b]	CHDF[a]	PMX[c]
Days from symptom onset	7	6	10	10
APACHE II score[d] on ICU admission	23	22	24	32
Time from occurrence of ARDS[e] to treatment (h)	<20	10–15	>27	>24
MOF[f] at the time of initiation of treatment	Yes	Yes	Yes	Yes
P/F ratio[g] from the initiation of treatment				
At the time of initiation	65	43	38	47
1 day	119	128	47	53
2 days	102	162	43	39
3 days	130	203	NA	NA
SOFA[h]				
At the time of initiation	10	13	11	9
1 day	8	10	12	13
2 days	7	11	NA	NA
3 days	7	11	Death	Death

ARDS, acute respiratory distress syndrome; NA, not available due to patient's death.
[a] Continuous hemodiafiltration.
[b] Sequential therapy with PMX hemoperfusion (3 columns, for 3 days) and CHDF.
[c] Polymyxin B fiber column.
[d] APACHE II score [20].
[e] ARDS was considered to be present if PaO_2/FiO_2 <200.
[f] MOF: ARDS with oliguria in Patient 1, shock and coagulopathy in Patient 4, shock and coagulopathy in Patient 6, shock in Patient 7.
[g] P/F: PaO_2/FiO_2 ratio; PaO_2: partial pressure of oxygen in arterial blood (mmHg); FIO_2: fraction of inspired oxygen.
[h] SOFA, Sequential Organ Failure Assessment.

Streptococcus bacterial infection was detected in one patient at the time of admission. Nosocomial bacterial infections were found in 2 survivors. Secondary bacterial infection was not detected in non-survivors. All non-survivors had developed ARDS at the time of hospital admission and were dead within 2–5 days following admission. It was not clear if secondary bacterial infection developed between the onset of illness and death under treatment with multiple antibiotics. Antibiotics were administered to all patients. However, once viral infection has been diagnosed, antibiotics administration should be limited appropriately to reduce the incidence of nosocomial bacterial infections, which are partly caused by the large amount or variety of antibiotics.

Although the WHO recommends against administering systemic corticosteroids, except for septic shock with adrenal insufficiency [6–8], systemic corticosteroids were administered to survivors and non-survivors in the present study, with the exception of the patient without pneumonia. The dose of corticosteroids for survivors and non-survivors did not differ significantly, whereas the time to initiation of corticosteroid treatment from symptom onset was later in non-survivors than in survivors. The results suggest that corticosteroid treatment did not negatively affect survivors who received oseltamivir earlier and who had less severe pneumonia than the non-survivors did. Therefore, the timing appears to be crucial for obtaining clinical benefits from corticosteroid treatment of H5N1 patients. However, further investigations and discussions are required.

Four out of 8 patients developed ARDS and received renal replacement therapy using CHDF, PMX hemoperfusion, or both sequentially in the ICU at BMH (Table 3). PMX column is a medical device initially developed to bind blood endotoxin in sepsis caused by gram-negative bacilli [14]. PMX hemoperfusion can effectively improve the P/F ratio and mortality rate [14,30,31]. Furthermore, a report on an animal model indicated that PMX hemoperfusion could improve the oxygenation associated with non-endotoxic lung injury and reduce the serum level of IL-8 [32]. Hypercytokinemia is thought to be one of the main causes of severe pneumonia associated with influenza (H5N1) virus infection [5,6,33]. PMX hemoperfusion and CHDF can both reduce plasma cytokine levels [30,31] and absorb activated neutrophils [34,35]. In addition, PMX hemoperfusion improves hemodynamics [31,36,37]. There has been no report on H5N1 patient who was treated with PMX. Some successful cases of ARDS with influenza A(H1N1)pdm09 infection treated with PMX have been reported in Japan [38,39], including evaluation of blood cytokine levels [40]. In the present study, Patient 4 was treated with PMX columns and sequential CHDF (Fig. 3). At 24 h after initiation of PMX hemoperfusion, levels of IL-6, IL-8, and IFN-γ in the peripheral blood had markedly decreased, with improvement of the P/F ratio. We believe that the improved P/F ratio was a reflection of decreased serum cytokine levels, which resulted in suppression of the inflammatory mechanism for ARDS in the lungs by PMX hemoperfusion.

The previous reports have indicated that early initiation of PMX hemoperfusion in patients with ALI and in patients with abdominal septic shock improves pulmonary oxygenation [35,41]. In the present study, patients treated with PMX hemoperfusion within 20 h from the time of ARDS onset

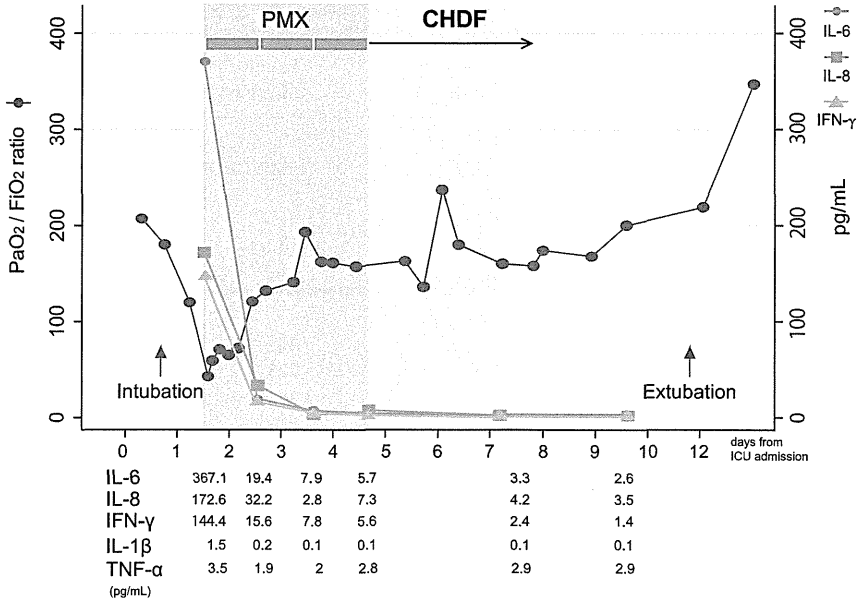

Fig. 3 – Clinical course of Patient 4 receiving sequential therapy with PMX and CHDF. The P/F ratio increased from 43 to 128 at 24 h and to 203 after 3 days, and serum levels of IL-6, IL-8, and IFN-γ markedly decreased 24 h after initiation of PMX hemoperfusion. No significant elevation in IL-1β and TNF-α was observed at the time of initiation of PMX hemoperfusion. Sequential CHDF maintained and improved the respiratory conditions of the patient.

survived, but those treated after 24 h died (Table 3). It was suggested that the early initiation of PMX hemoperfusion is also crucial for the survival of patients with ARDS caused by H5N1 infection. In addition, sequential CHDF maintained and improved respiratory conditions in patients. PMX/CHDF treatment appears to be a candidate for treating ARDS with H5N1 infection if applied early in the illness. To date, PMX columns are only commercially available in Japan and Europe [14,30,31]. Single treatment with CHDF can also contribute to survival if PMX is not available (as in Patient 1). The results were obtained from four patients, including evaluation of blood cytokine levels in one patient, thus further investigation of the effect of PMX/CHDF on the treatment of H5N1 patients with ARDS is required.

The present study was limited by the small study population of only eight patients. However, our experiences with these cases in Vietnam could contribute to clinical preparedness for severe pneumonia with highly pathogenic avian influenza A (H5N1).

5. Conclusions

Careful monitoring of local H5N1 poultry outbreaks, creating a healthcare network, and using chest radiographs can reduce the time to medical intervention for early diagnosis and early initiation of antiviral treatment. Renal replacement therapy using sequential therapy with PMX hemoperfusion and CHDF are possible candidates for treating ARDS due to H5N1 infection if applied early.

Conflict of interest

The authors have no potential conflict of interest.

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