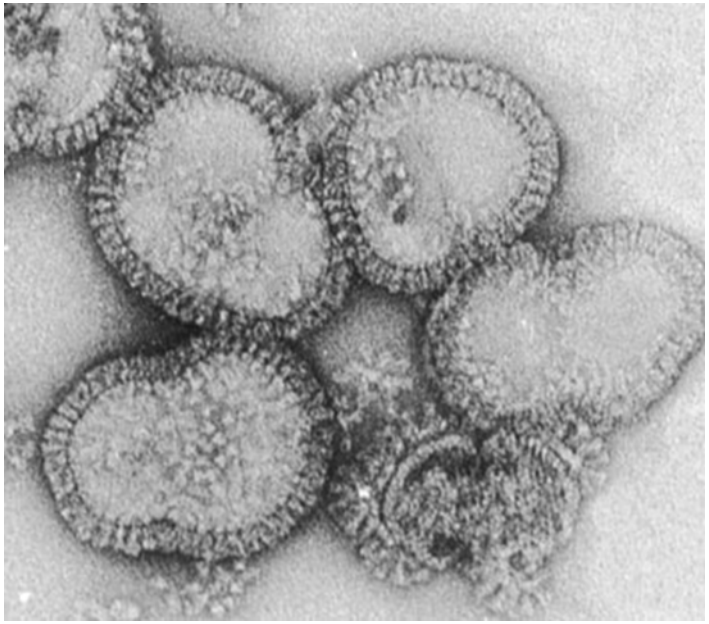
Avian Influenza A (H7N9): Clinical Management



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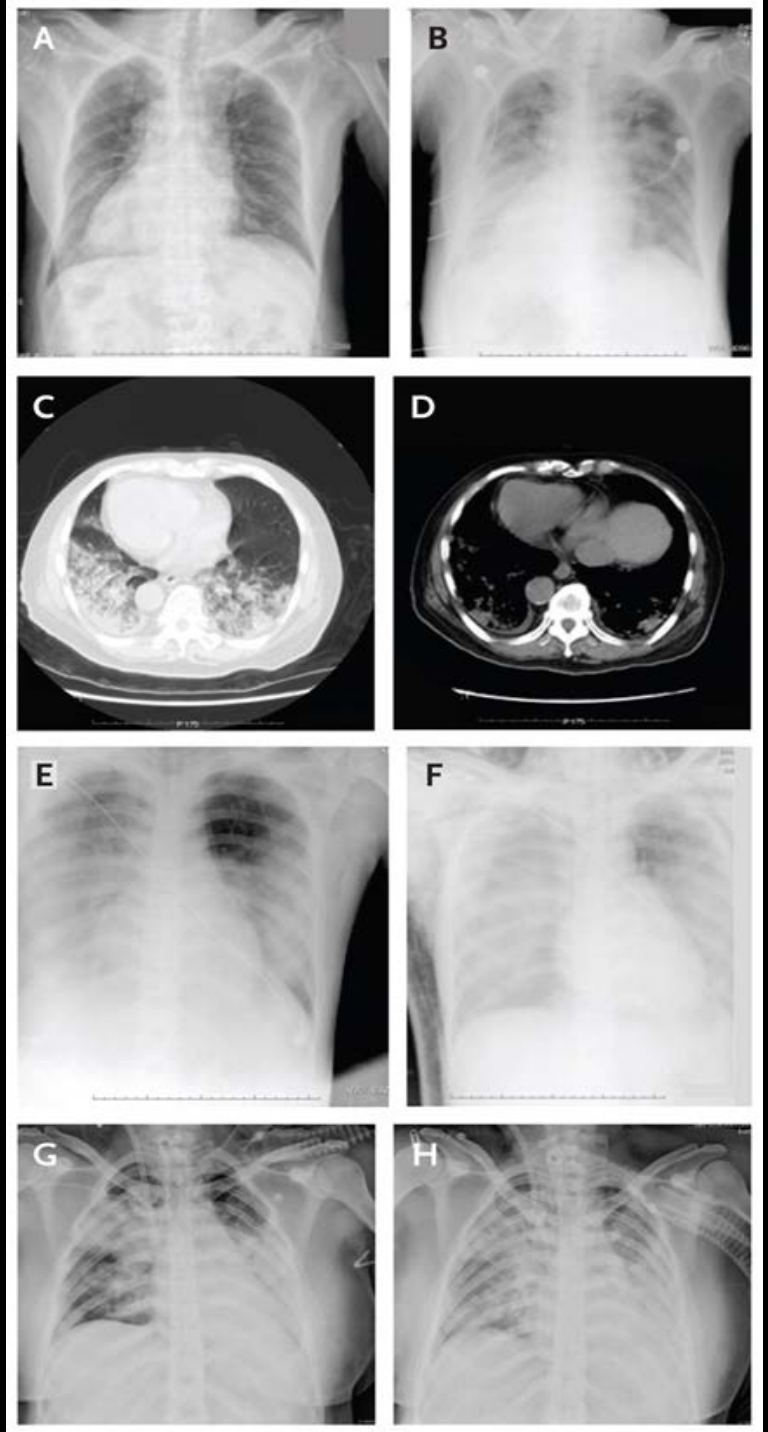
Initial symptoms: non-specific, similar to most other causes of ILI, CAP

High index of suspicion and alertness to epidemiological link is imperative



- Chest radiographs (patient's heart is on the right side) of Patient 1 is shown in Panels A and B . Mild ground-glass opacity was observed on day 6 (Panel A). Bilateral ground-glass opacity and consolidation were clearly seen on day 9 (Panel B). A computed tomographic scan of the chest of Patient 1, obtained on day 7 (the day of admission), is shown in Panels C and D. Substantial bilateral ground-glass opacity and consolidation can be seen.
- Chest radiographs of Patient 2, obtained on day 7 and day 13 after the onset of illness are shown in Panels E and F, respectively. Bilateral ground-glass opacity and consolidation can be seen on day 7, and white lungs on day 13.
- Chest radiographs of Patient 3 on day 7 and day 13 after the onset of illness are shown in Panels G and H. Bilateral ground-glass opacity and consolidation can be seen on both day 7 and day 13.

The NEW ENGLAND JOURNAL of MEDICINE

Antiviral therapy

Susceptibility to antivirals

- M2 inhibitors (amantidine, rimantidane) **X**
- Neuraminidase inhibitors (NAI):
  - Genotypic marker of resistance (R294K) reported in some isolates
  - Phenotypic test: susceptible to NAI

NAIs (1)

Oseltamivir (Tamiflu®)

- 75mg BD po in adults and children aged 13 or above; weight based dosage adjustment in children aged 12 or below
- Dosage adjustment in renal impairment
- Prolonged course +/- higher dose may be considered in:
  - severe cases
  - immunocompromised patients (e.g. haematological malignancy)

NAI (2)

Inhaled zanamivir (Relenza®)

- For treatment in adult and children ≥ 7 year old: 10mg (2 inhalations) BD for 5 days.
- No dose adjustment for patients with mild to moderate or severe renal impairment.
- Data on inhaled zanamivir in patients with severe influenza is lacking
- Use of Zanamivir diskhaler® requires coordination and is potentially problematic in the very young and elderly.

Intravenous NAI

Two agents: peramivir and zanamivir (solution form)

- Both are unregistered drugs in Hong Kong
- Zanamivir solution is only available on a compassionate use basis for the treatment of serious influenza illness through GlaxoSmithKline Ltd.

Intravenous NAI (2)

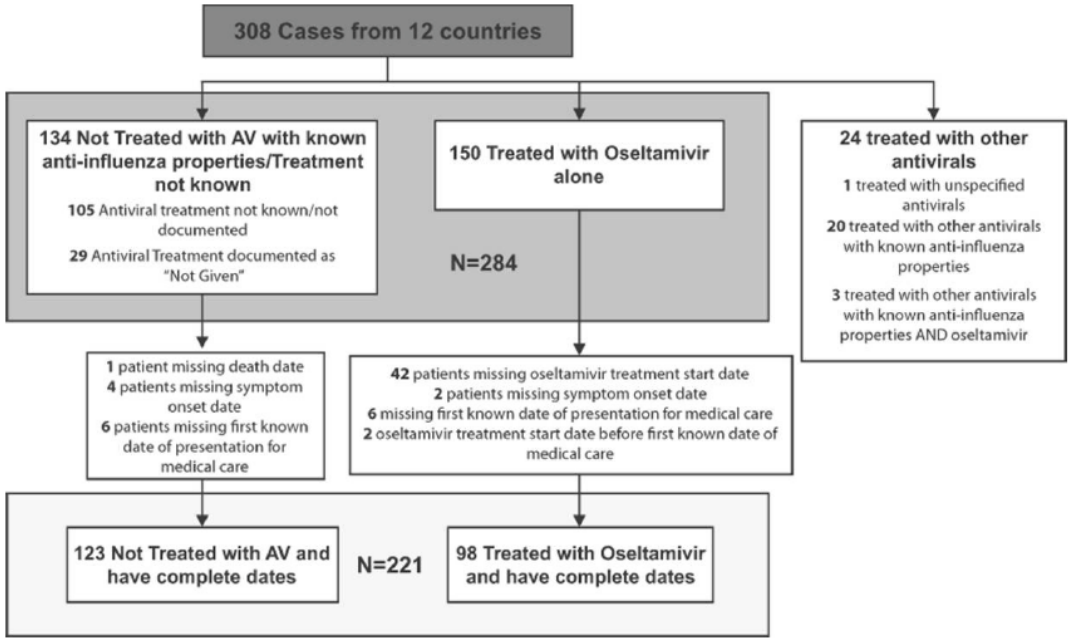
Role: as salvage therapy for hospitalized patients with severe or critical conditions due to influenza

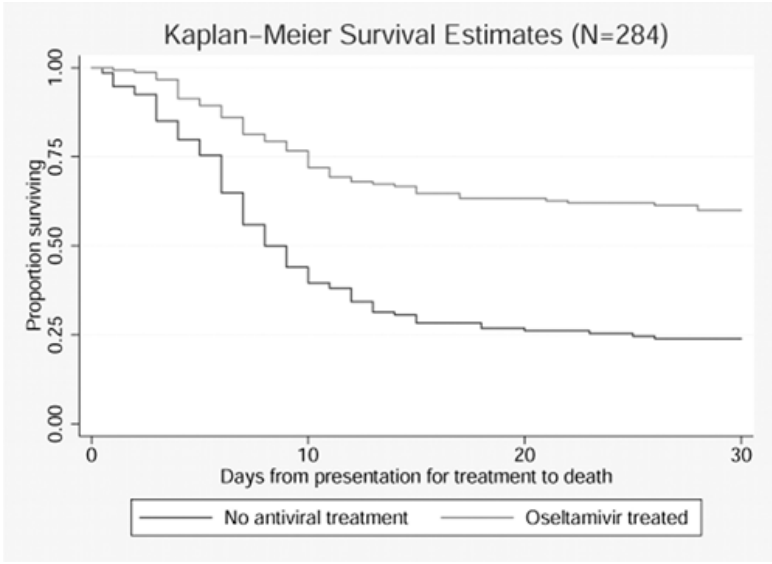
- Patient not responding to oseltamivir (iv zanamivir is preferred) , OR
- Drug delivery by a route other than IV (e.g. enteral oseltamivir or inhaled zanamivir) is not expected to be dependable or is not feasible, OR
- The clinician judges IV therapy is appropriate due to other circumstances.

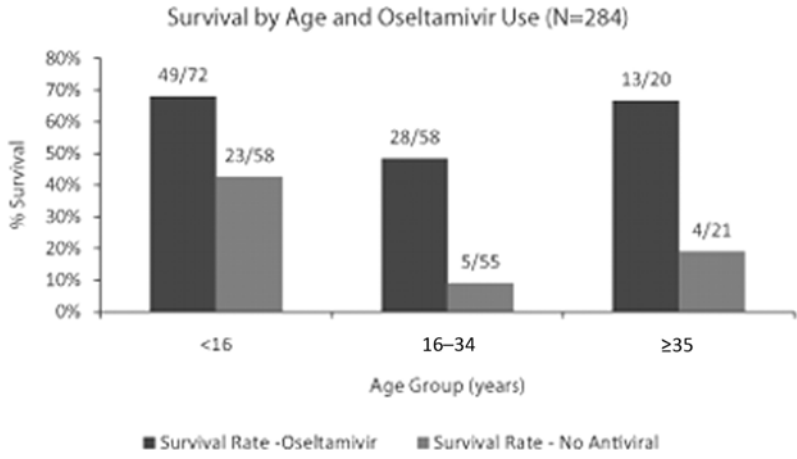
Effectiveness of Antiviral Treatment in Human Influenza A(H5N1) Infections: Analysis of a Global Patient Registry

The Journal of Infectious Diseases

Wiku Adisasmito,[1] Paul K. S Chan,[2] Nelson Lee,[2] Ahmet Faik Oner,[3] Viktor Gasimov,[5] Faik Aghayev,[6] Mukhtiar Zaman,[7] Ebun Bamgboye,[8] Nazim Dogan,[4] Richard Coker,[10] Kathryn Starzyk,[9] Nancy A. Dreyer,[9] and Stephen Toovey[11]







Effectiveness of Antiviral Treatment in Human Influenza A(H5N1) Infections: Analysis of a Global Patient Registry

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Treatment initiation from symptom onset, days	Oseltamivir treatment, survived/total (%)	No antiviral treatment, survived/total (%)	Difference in survival, %	Relative risk	95% CI	*P*
0–2	15/18 (83)	19/95 (20)	63	4.17	2.65–6.55	<.001
3–5	15/31 (48)	32/117 (27)	21	1.77	1.11–2.83	.032
6–8	16/32 (50)	31/108 (29)	21	1.74	1.10–2.75	.031
9–11	3/8 (38)	30/70 (43)	−5	0.88	0.34–2.23	.797
⩾12	3/9 (33)	29/45 (64)	−31	0.52	0.20–1.34	.105
Any time	52/98 (53)	29/123 (24)	29	2.25	1.56–3.25	<.001

NOTE. Relative risk of survival by interval from symptom onset and first dose of oseltamivir, compared with risk of survival of individuals who presented for medical care during the interval, were alive in the interval, and did not receive any antiviral treatment during the interval. CI, confidence interval.

Antiviral treatment can reduce mortality; the earlier the better.

Other potential antiviral therapy

- Binding site inhibition: recombinant sialidase fusion protein (Fludase®)
- RNA dependent RNA polymerase inhibitor: Favipiravir

Convalescent blood products

Convalescent Plasma Therapy in H5N1 Disease

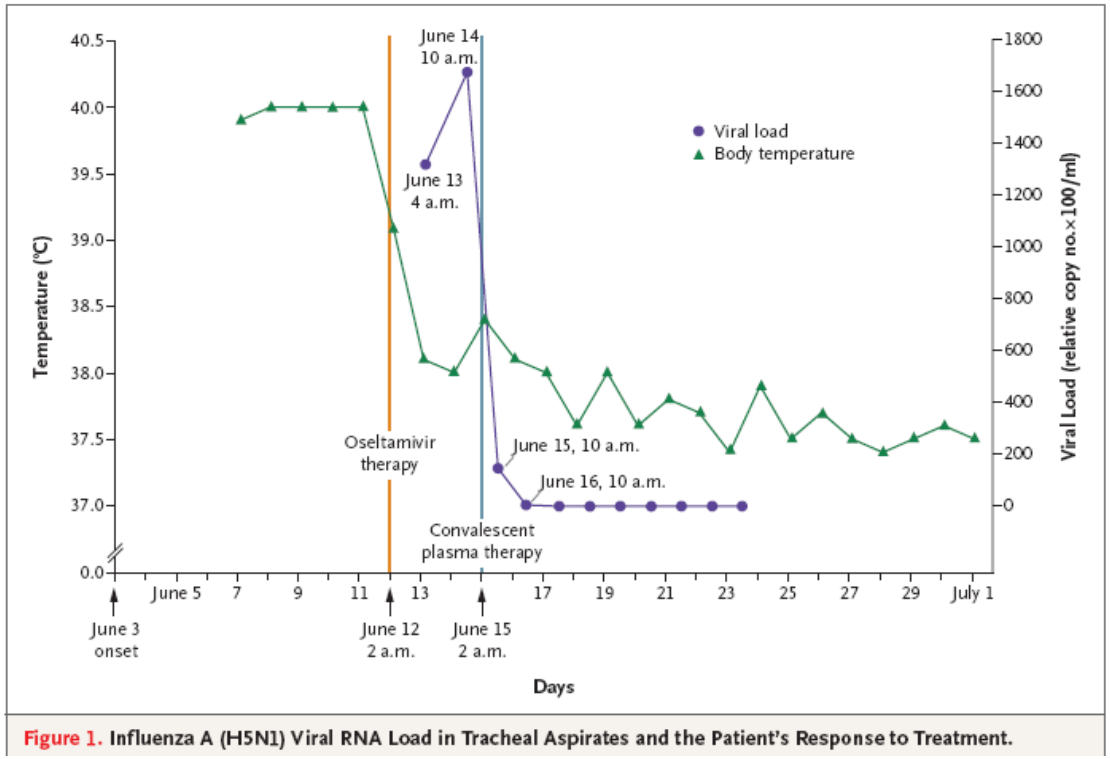


Figure 1. Influenza A (H5N1) Viral RNA Load in Tracheal Aspirates and the Patient's Response to Treatment.

- Case report of 31 yo male who presented with 4 day Hx of fever, cough, and sputum
  - CXR on day 6 showed LLL pneumonia
  - Tracheal aspirate flu A(H5N1) +ve by RT-PCR and culture
  - Oseltamivir 150 mg bid started day 9 of illness but progressive bilateral pneumonia
  - Convalescent plasma infusions from H5 survivor (200 ml X 3) on days 12-13
    - Plasma neutralizing ab titer of 1:80
  - Hospital discharge on day 30

Relative contributions of exogenous plasma, endogenous immune responses, and oseltamivir ?

Zhou et al. NEJM 357:1450, 2007

Hyperimmune Intravenous Immunoglobulin Treatment: A Multicentre Double-Blind Randomized Controlled Trial for Patients with Severe A (H1N1)pdm09 Infection

Ivan F. N. Hung; Kelvin K. W. To; Cheuk-Kwong Lee; Kar-Lung Lee; Wing-Wa Yan; Kenny Chan; Wai-Ming Chan; Chun-Wai Ngai; Kin-Ip Law; Fu-Loi Chow; Raymond Liu; Kang-Yiu Lai; Candy C. Y. Lau; Shao-Haei Liu; Kwok-Hung Chan; Che-Kit Lin; Kwok-Yung Yuen

▸ Author and Funding Information

Chest. 2013. doi:10.1378/chest.12-2907

Article

Need to collect convalescent plasma from survivors; won't be a/v as therapy at initial stage

Abstract

Abstract

Background Experience from influenza pandemics suggested that convalescent plasma treatment given within 4 to 5 days of symptom onset might be beneficial. However, robust treatment data is lacking.

Methods This is a multicentre prospective double-blind randomized controlled trial. Convalescent plasma from patients who recovered from the 2009 pandemic influenza [A(H1N1)pdm09] infection was fractionated to hyperimmune intravenous immunoglobulin (H-IVIG) by CSL Biotherapies, Australia. Patients with severe A(H1N1)pdm09 infection on standard antiviral treatment requiring intensive care and ventilatory support were randomized to receive H-IVIG or normal IVIG manufactured before 2009 as control. Clinical outcome and adverse effects were compared.

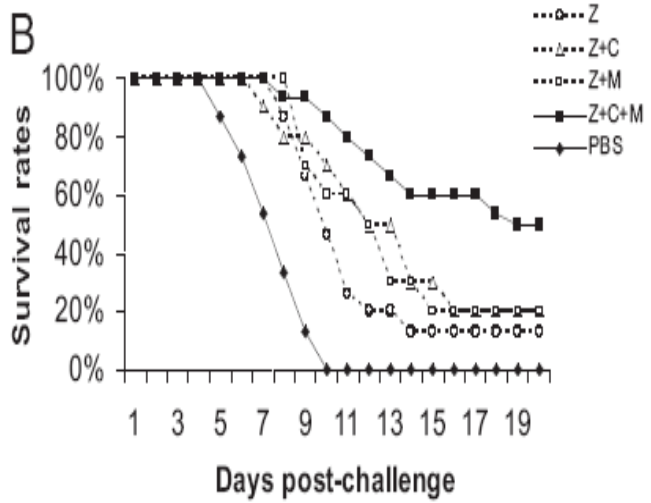
Results Between 2010 and 2011, thirty-five patients were randomized to receive H-IVIG (17 patients) or IVIG (18 patients). One defaulted patient was excluded from analysis. No adverse event related to treatment was reported. Baseline demographics and viral load before treatment were similar between the two groups. Serial respiratory viral load demonstrated that H-IVIG treatment was associated with significantly lower day 5 and 7 post-treatment viral load when compared to the control (p=0.04 and p=0.02 respectively). The initial serum cytokine level was significantly higher in the H-IVIG group but fell to similar level 3 days after treatment. Subgroup multivariate analysis of the 22 patients who received treatment within 5 days of symptom onset demonstrated that H-IVIG treatment was the only factor which independently reduced mortality [OR:0.14, 95% CI, 0.02-0.92; p=0.04].

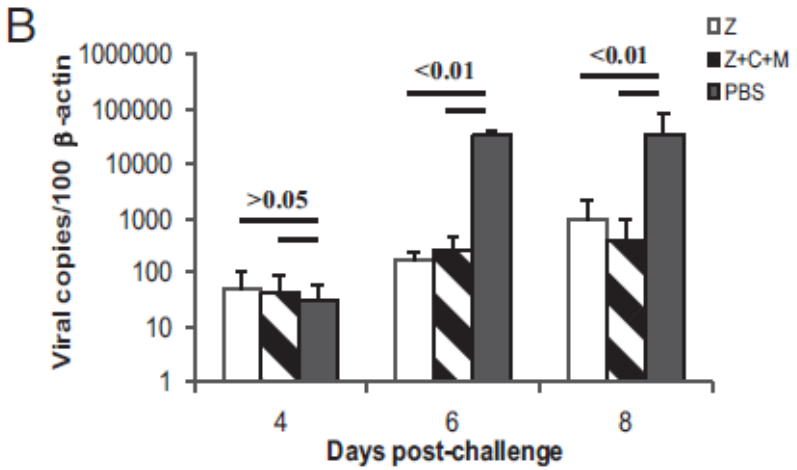
Conclusions Treatment of severe A(H1N1)pdm09 infection with H-IVIG within 5 days of symptom onset was associated with a lower viral load and reduced mortality.ClinialTrials.gov (NCT01617317)

Immunomodulators

Delayed antiviral plus immunomodulator treatment still reduces mortality in mice infected by high inoculum of influenza A/H5N1 virus

Bo-Jian Zheng*†‡, Kwok-Wah Chan§, Yong-Ping Lin§, Guang-Yu Zhao§, Chris Chan§, Hao-Jie Zhang‡, Hong-Lin Chen*†‡, Samson S. Y. Wong*†‡, Susanna K. P. Lau*†‡, Patrick C. Y. Woo*†‡, Kwok-Hung Chan*†‡, Dong-Yan Jin¶, and Kwok-Yung Yuen*†‡‖

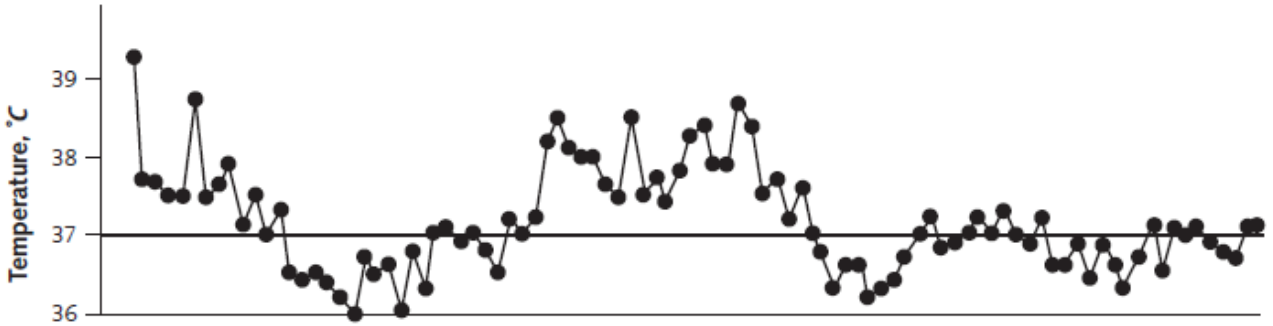




- Comparison of
  - monotherapy with i.p. zanamivir (ZNV),
  - ZNV, celecoxib, mesalazine, or gemfibrozil in various combinations
  - triple regimen of ZNV + celecoxib + mesalazine in mice
- ↑ survival with ZNV + celecoxib + mesalazine
- Even if the viral replication had been suppressed in the mice treated with antiviral, levels of cytokines and chemokines were still similar to the untreated mice, which were significantly higher than those in the mice receiving combination therapy

High dose N-acetylcysteine

Figure. **Temperature chart.**



	7/15	7/16	7/17	7/18	7/19	7/20	7/21	7/22	7/23	7/24	7/25	7/26	7/27	7/28	7/29	7/30
CRP	183			38.8		11.7	11.3	11.5	132		101		27.4	20.0	16.5	15.0
H1	+							+	+	+	+	–	±	±	–	–
Mx	+							+	–	–	+	–	–	–	–	–
M	PCV	PCV	PCV	VC	VC	CPAP	CPAP	CPAP	PCV	PCV	PCV	VC	CPAP	CPAP	CPAP	NC
FIO_2	1.0	0.7	0.6	0.4	0.4	0.35	0.4	0.5	0.85	0.5	0.4	0.35	0.35	0.35	0.35	4L
PEEP	18	18	18	15	12	10	10	13	16	15	13	10	8	8	8	0
NO	20	20	0	0	0	0	0	0	0	0	0	0	0	0	0	0
			HDNAC							HDNAC						

CPAP = continuous positive airway pressure; CRP = C-reactive protein (mg/L); H1 = polymerase chain reaction for human swine influenza A H1 gene; HDNAC = high-dose *N*-acetylcysteine (100 mg/kg per day); M = ventilator mode; Mx = polymerase chain reaction for influenza A virus matrix gene; NC = nasal cannula (O_2 L/min); NO = nitric oxide (ppm); PEEP = positive end-expiratory pressure; PCV = pressure-controlled ventilation; VC = volume-cycled ventilation.

Ann Intern Med 2010, 152:687-688

Clinical Experience Suggests No Role for Corticosteroids in A(H5N1) Treatment

•Vietnam	Survival		
	Steroid Rx	No steroids	P-value
Hanoi[a]	12/29 (41%)	29/38 (76%)	0.008
Published cases[b]	3/19 (16%)	10/15 (66%)	0.007

[a] Cao T, Liem NT. N Engl J Med 2008; 358: 261

[b] Emerg Infect Dis 2005; 11: 201; N Engl J Med 2004; 350: 1179; N Engl J Med 2006; 355: 2186-94.

Other points of note in clinical management

- Ix for other causes of ILI & CAP
- Empiric antibiotics to cover bacterial causes of CAP & secondary bacterial infections:
  - β-lactam/β-lactamase inhibitor combination OR 3rd generation cephalosporin + macrolide
  - Respiratory fluoroquinolones for patient withβ-lactam allergy

- Close monitoring: symptoms & signs, blood tests and chest radiographs
- Liaise with ICU early in patients with features of end-organ failure

Bring Home Message

1. Antivirals:
   - NAI
   - Give treatment early
   - Prolonged duration +/- higher dose in selected cases
2. Convalescent blood product: may help, but only a/v in later phase of epidemic
3. Immunomodulators:
   - limited data to address its usefulness
   - Avoid use of high dose steroid solely for viral pneumonia
4. Work-up for other causes of ILI/ CAP and empiric antimicrobial therapy to cover other DDx and secondary bacterial infection
5. Supportive treatment: monitor for and liaise with ICU early for end-organ failure

Stay tuned to the IC/ ID Training Portal for updated info

Intranet: http://icidportal.home/sites/en/webpages/h7n9.aspx
Internet: http://icidportal.ha.org.hk/sites/en/webpages/h7n9.aspx