Extending clinical management of SARI during interpandemic time to address severe influenza in pandemics

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I have no financial relationships with commercial interests to disclose

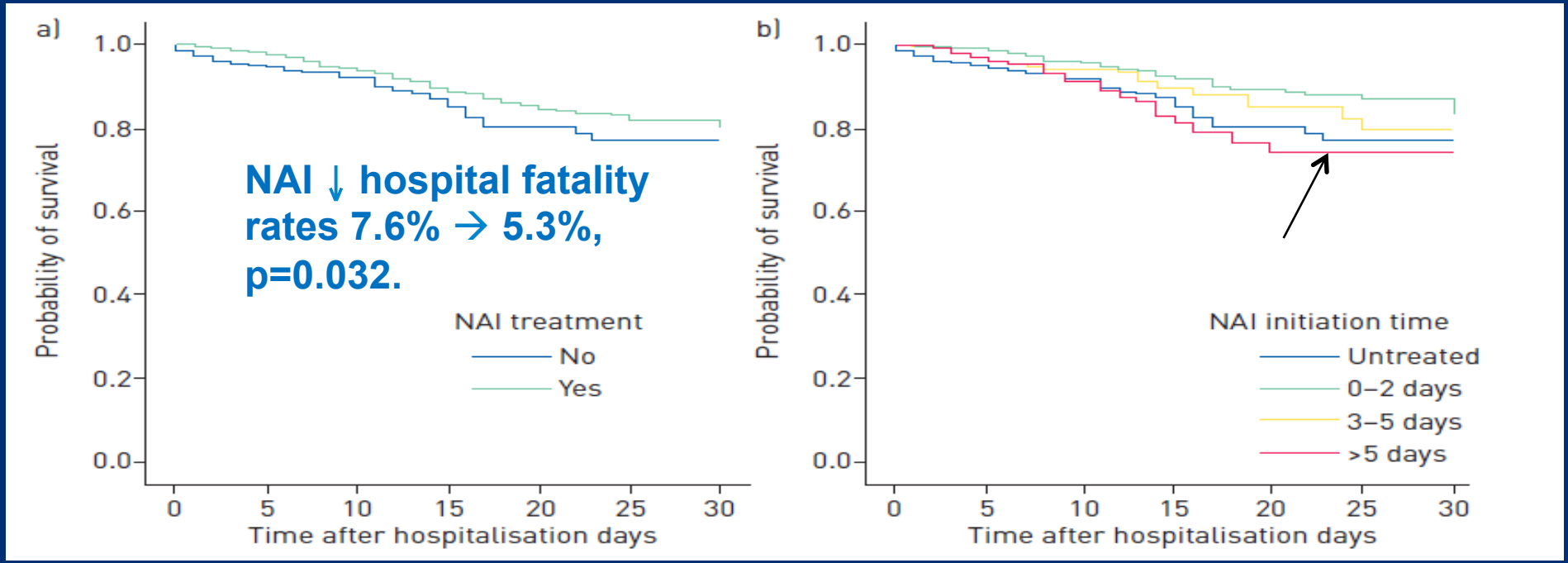
- Neuraminidase inhibitors & limitations
- Need for new antiviral therapy
- Role of immuno-modulating agents with highlights on caution with steroid, NSAID+ macrolide, etc.
- ARDS treatment including role of noninvasive ventilation, ECMO, prone ventilation, low tidal vol, etc.
- Infection control and prevention measures during aerosol-generating procedures
- Pneumococcal vaccines

N=2649 adults hospitalized with influenza in HK, Singapore & Beijing in 2008-2011

Flu A/H3N2 (>45.8%), Flu B (11.1%), A(H1N1)pdm09 (36.3%)

NAI reduced risk of deaths in adults hospitalized with influenza, adj HR 0.28, 95% CI 0.19–0.43

Best survival when NAI started ≤2 days (adj HR 0.20, 95% CI 0.12-0.32), & still beneficial starting within 3-5 days (adj HR 0.35, 95% CI 0.21-0.58). Lee N, et al. ERJ 2015



Benefit of early initiation of neuraminidase inhibitor treatment to hospitalized patients with avian influenza A (H7N9) virus

Zheng S, et al. CID 2018

- N=160 with confirmed H7N9 infection in Zhejiang were divided into **3 groups** according to NAI starting time:
- 3/20 (15%) patients for whom NAI was administered *within 2 days* **died** vs 12/52 (23.1%) who received treatment *between 2–5 days* vs 33/88 (37.5%) patients who were treated *after 5 days* (*P*<0.05).
- The median **durations of viral shedding** from NAI therapy initiation was 4.5 days [(IQR): 3–9] for patients who started NAI *within 2 days*, which was shorter than that for those who started NAI *between 2–5 days* (7.5 days ,IQR: 4.25–12.75) or *after 5 days* (7 days, IQR: 5–10) (*P*<0.05).

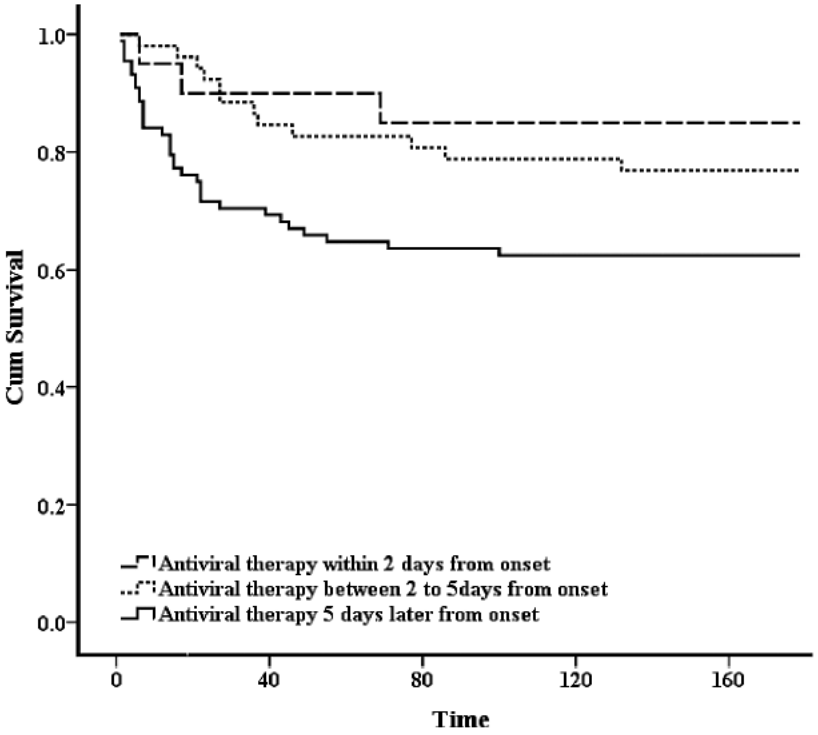


Figure 1. Kaplan-Meier survival curves according to the time of illness at initiation of antiviral treatment.

MAJOR ARTICLE

A Prospective Intervention Study on Higher-Dose Oseltamivir Treatment in Adults Hospitalized With Influenza A and B Infections

N. Lee,[1,2] D. S. C. Hui,[1,2] Z. Zuo,[3] K. L. K. Ngai,[4] G. C. Y. Lui,[1] S. K. Wo,[3] W. W. S. Tam,[5] M. C. W. Chan,[4] B. C. K. Wong,[1] R. Y. K. Wong,[1] K. W. Choi,[1] W. W. Y. Sin,[1] E. L. Y. Lee,[1] B. Tomlinson,[1] F. G. Hayden,[6] and P. K. S. Chan[2,4]

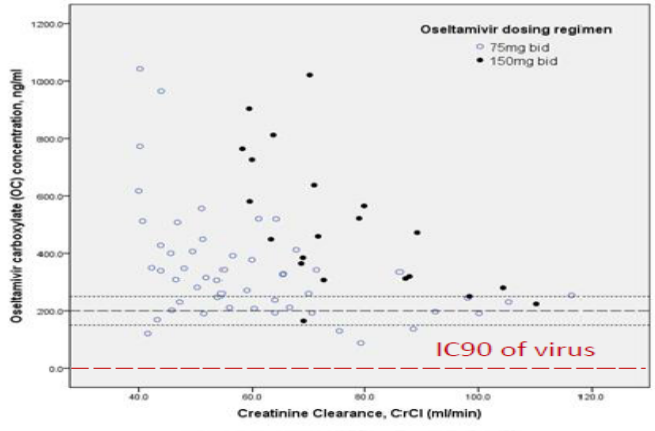
Clinical Infectious Diseases 2013;57(11):1511–9

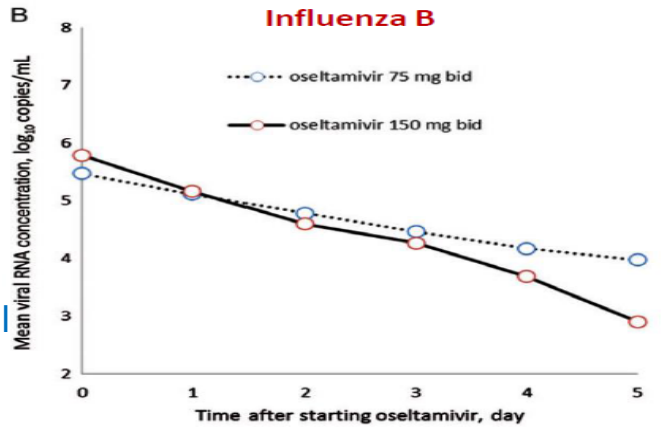
(n=155)

No advantage of double-dose (150mg bid) oseltamivir over conventional dosage (75mg bid) in influenza A (H3N2, pH1N1)

Improves viral clearance in influenza B

~40% PCR+ at treatment end; therapy >5 days may be necessary in severe cases





RCT (n=326, 75.5% children. SE Asian ID network): no differences in viral clearance & other endpoints between standard dose vs double dose.
(Farrar J. BMJ 2013)*

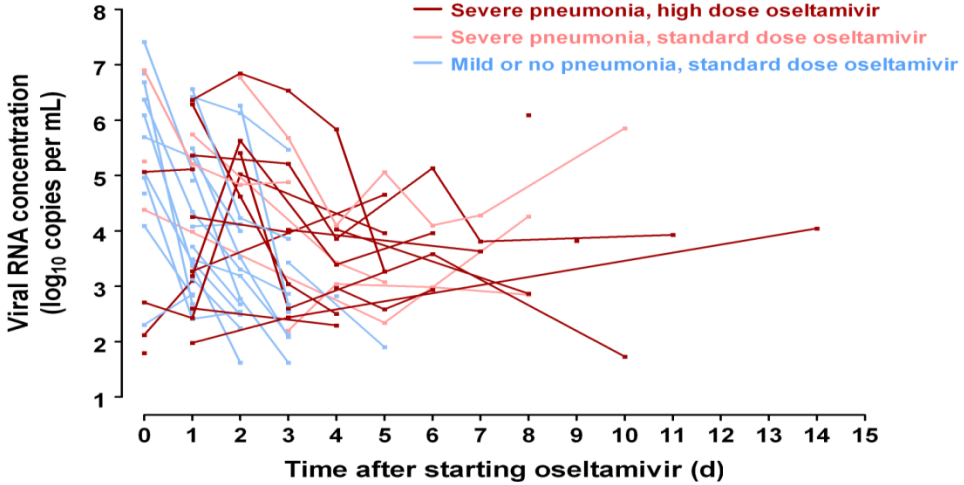
Kumar A. Canadian ICUs. RCT, Oseltamivir 225mg bd vs 75mg bd. 7/9 (78%) on triple dose were PCR negative vs 1/9(11%) on standard dose on D5. ICAAC 2013

5-day treatment course may be insufficient for influenza pneumonia

Table 2. Virologic and Clinical Outcomes

Outcome	Active Comparator Arm (n = 70)	Standard Therapy Arm (n = 87)	*P* Value	150 mg bid Recipients (n = 41)	75 mg bid Recipients (n = 114)	*P* Value	Subgroup 75 mg bid Recipients, CrCl >60 mL/min[a] (n = 49)	*P* Value[a]
Virologic[b]								
PCR negativity at day 5, %	39.7	43.3	.677	44.7	40.2	.634	47.5	.807
Culture negativity at day 3, %	88.2	94.7	.229	90.0	92.2	.739	95.5	.418
Culture negativity at day 5, %	98.6	98.7	>.99	100.0	98.1	>.99	100.0	>.99
Clinical								
Duration of hospitalization, d, median (IQR)	6.0 (3.0–8.0)	4.0 (3.0–6.5)	.138	5.0 (3.0–7.8)	5.0 (3.0–7.0)	.943	4.0 (3.0–6.0)	.300
Duration of oxygen therapy, d, median (IQR) [c]	3.0 (1.3–5.8)	3.0 (1.0–5.0)	.704	3.0 (1.0–6.5)	3.0 (1.0–5.0)	.789	3.5 (3.0–5.0)	.662
Duration of fever >37.5°C, d, median (IQR)[c]	1.5 (0.0–3.0)	1.0 (1.0–2.0)	.982	2.0 (0.0–3.0)	1.0 (1.0–2.0)	.482	2.0 (1.0–2.0)	.785
ICU admission, %	0.0	2.3	.503	0.0	1.8	>.99	2.0	>.99
Death, %	1.4	1.1	>.99	2.4	0.9	.460	2.0	>.99
ICU admission or death, %	1.4	3.4	.629	2.4	2.6	>.99	4.1	>.99

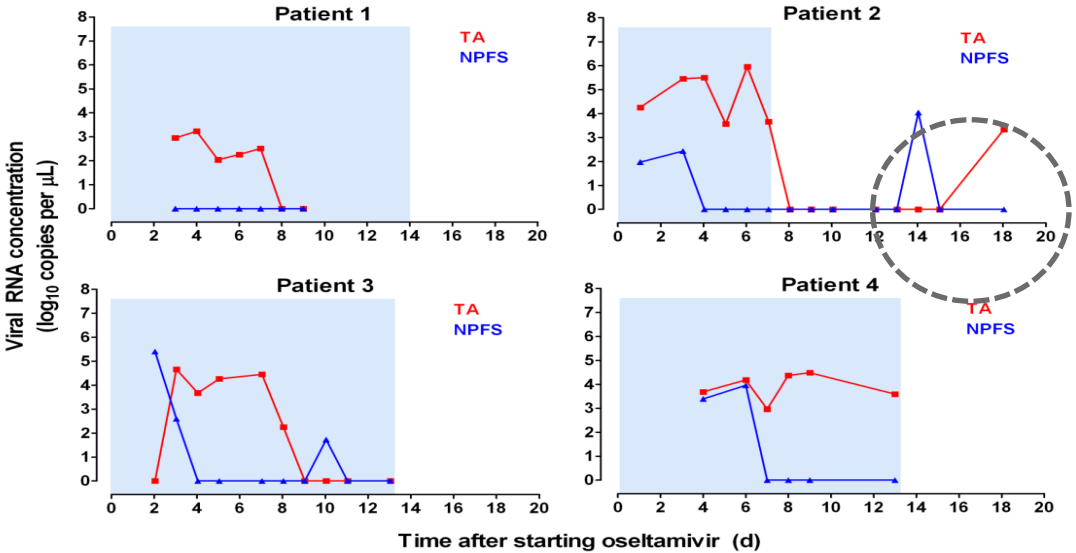
Lee N, et al. *CID* 2013



Patients with severe pH1N1 pneumonia exhibited slower viral clearance with oseltamivir treatment, esp in the LRT [duration of RNA-positivity after antiviral initiation, median(IQR): NPFS, 6.0(3.0-8.0) days; tracheal aspirate, 11.0(7.8-14.3) days; vs milder-illness group NPFS, 2.0(1.0-3.0) days, $p<0.01$]. Lee N et al. *Antiviral Ther 2011*

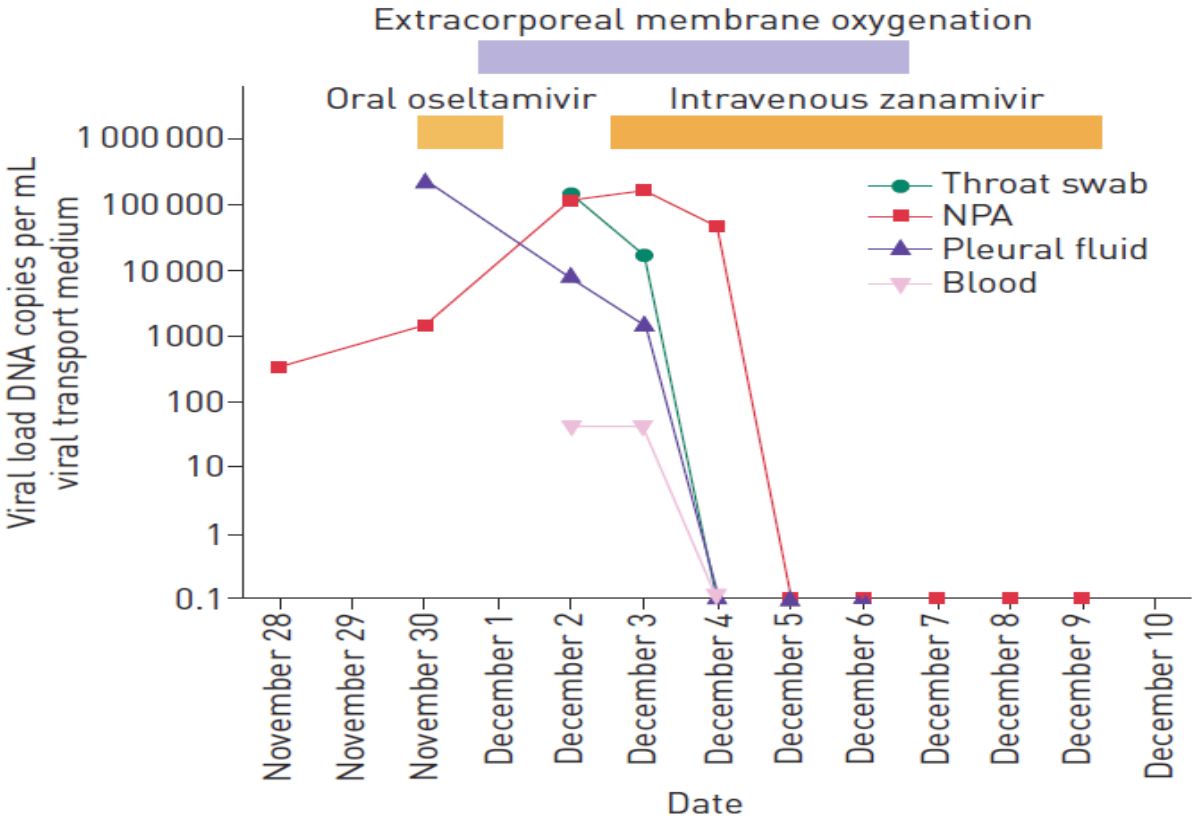
Longer duration in the lower respiratory tract and lung

Relapse possible if antiviral stopped prematurely
→ at least 10 days with monitoring
-- WHO. *NEJM* 2010



Severe influenza A H7N9 pneumonia with rapid virological response to intravenous zanamivir

Ho PL, et al. ERJ 2014



17 Nov 2013: 36-yr-old Indonesian female domestic helper travelled to Shenzhen & visited a live poultry market.
23 Nov: fever, malaise & cough.
27 Nov: CXR RLL pneumonia with progression to pleural effusion despite oseltamivir 28 Nov. ARDS & rhabdomyolysis.

A unique PA L336M mutation, associated with increased polymerase activity, was found. To KK. J Infect 2014

FIGURE 1 Temporal changes in H7N9 viral load after intravenous zanamivir therapy. NPA: naso-pharyngeal aspirate.

Antiviral resistance in H7N9 viruses

- All H7N9 viruses have adamantane resistance M2 mutation S31N
- Of 314 LPAI H7N9 viruses, 18(5.7%) isolates have reduced sensitivity to NAIs including N292K (n=15) and I222R (n=1). *(Shu YL. ISIRV AVG meeting June 2017)*
- R292K associated with adverse clinical outcome *(Hu et al. Lancet 2013).*
- Of 28 human HPAI H7N9 isolates, 7(25%) have mutations that reduce sensitivity to NAIs. Of these 5(18%) have NA 292K mutations; 1(4%) each has E119V or H274Y *(Yang et al. J Virol 2017)*

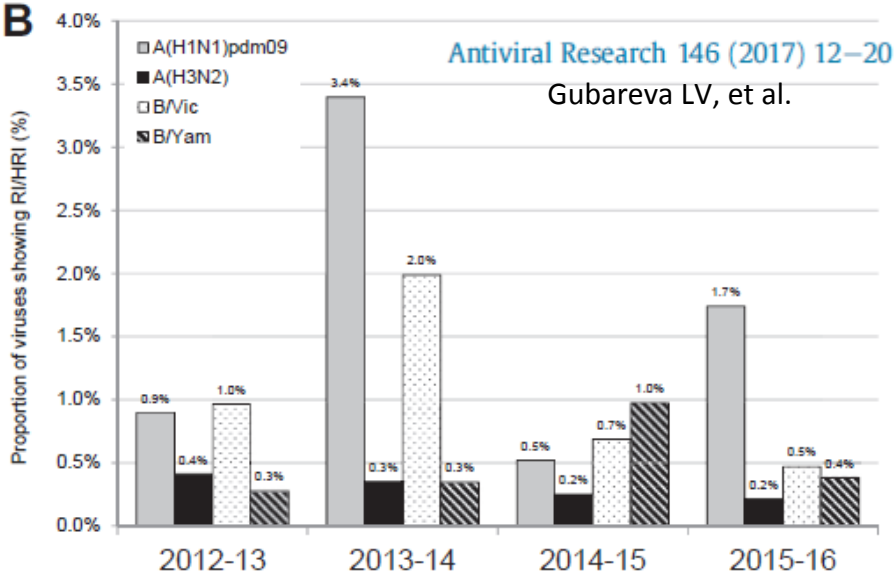
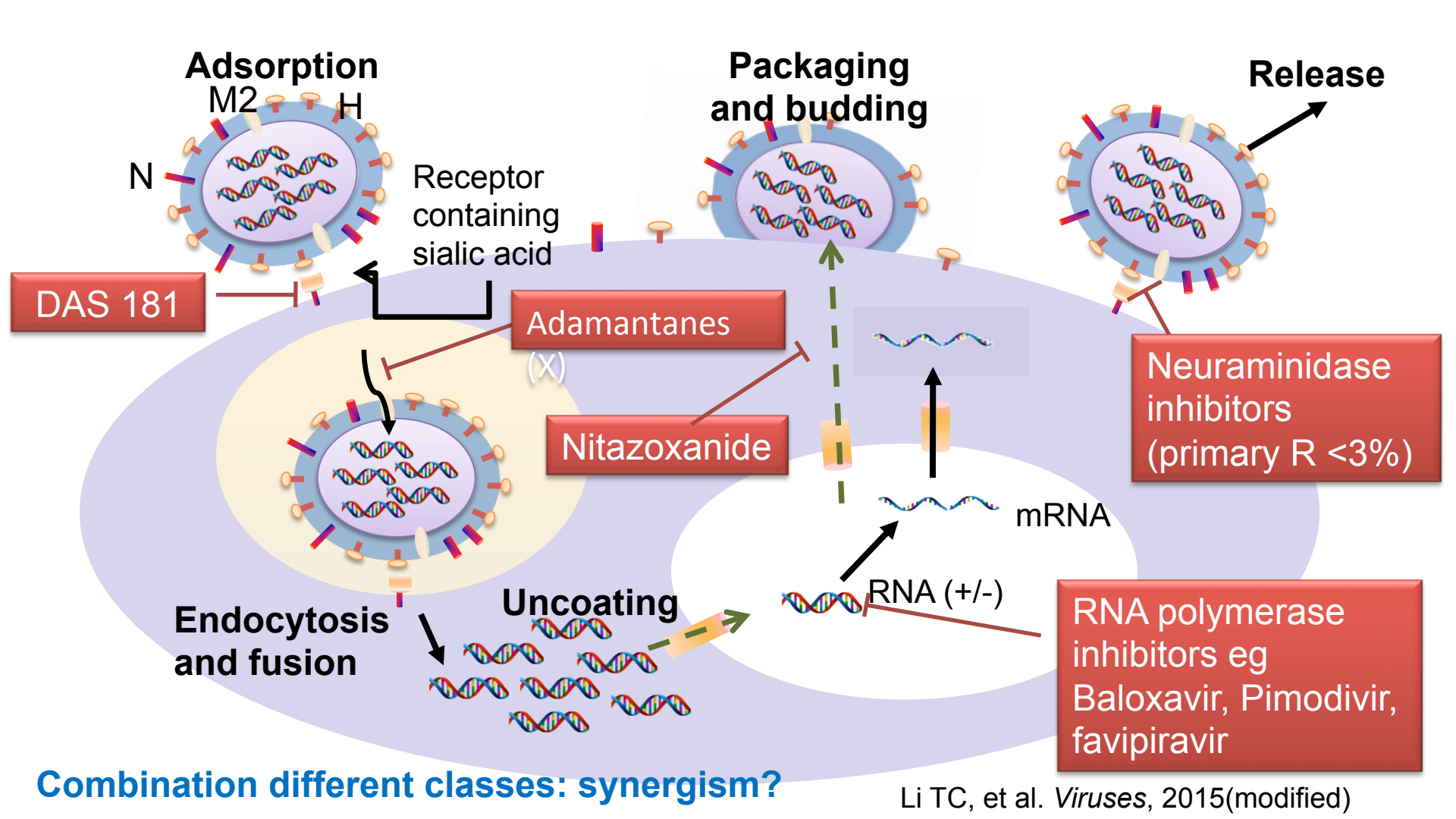


Fig. 2. A) Number of viruses tested in the neuraminidase inhibition assays (NAI assay) over the 2012–2016 period. B) Proportion of viruses showing RI or HRI by neuraminidase inhibitors (NAIs) over the 2012–2016 period. Data compiled from the global studies reporting on viruses isolated during 2012–13 (Meijer et al., 2014), 2013–14 (Takashita et al., 2015b), 2014–15 (Hurt et al., 2016), and 2015–16 (current study). B/Yamagata-lineage haemagglutinin:B/Victoria-lineage neuraminidase reassortants are included in the proportion and number of B/Victoria-lineage viruses.



Combination different classes: synergism?

Li TC, et al. *Viruses*, 2015(modified)

Efficacy of oseltamivir-peramivir combination therapy compared to oseltamivir monotherapy for *Influenza A* (H7N9) infection: a retrospective study

Yan Zhang, Hainv Gao, Weifeng Liang, Lingling Tang, Yida Yang, Xiaoxin Wu, Liang Yu, Ping Chen, Shufa Zheng, Huilin Ou and Lanjuan Li*

Table 5 Baseline information and in-hospital mortality

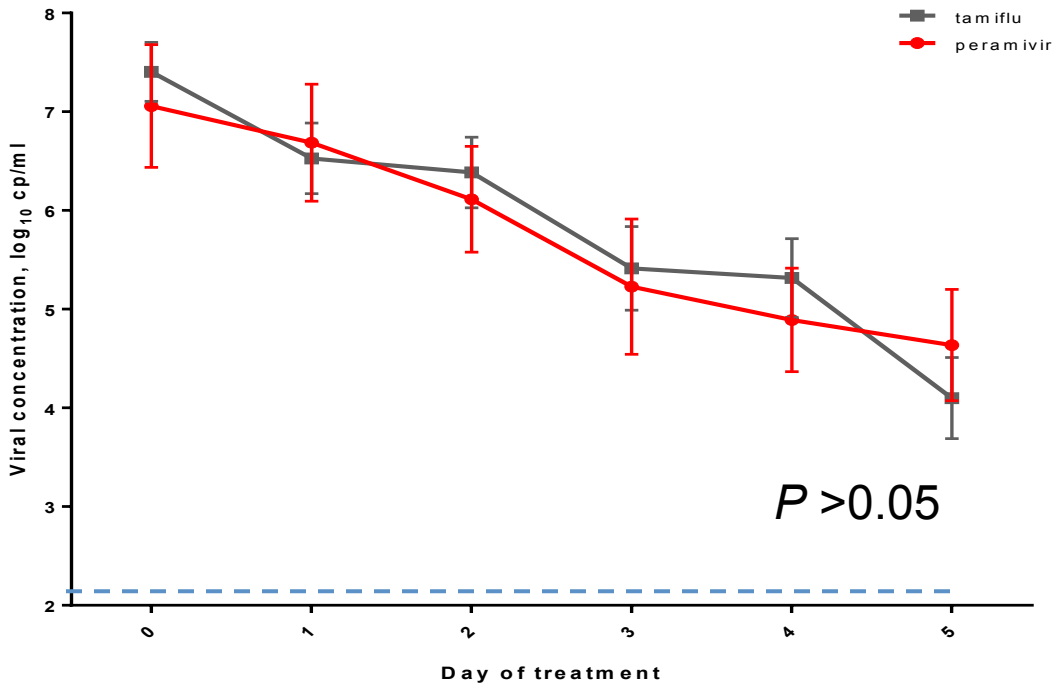
Zhang *et al. BMC Infectious Diseases* (2016) 16:76

Patients	Characteristics	O+P group	O group	*P* value
all patients included in the study *n* = 82		*n* = 39	*n* = 43	
	Age (years): mean (SD)	56.51(13.86)	59.74(14.71)	0.53
	No. of male (%)	27(69.23 %)	29(67.44 %)	1.0
	Time from symptom onset to NAIs administration (days):median(IQR)	7.00(5.00,8.00)	5.00(4.00,7.00)	0.16
	APACHE II score: mean(SD)	19.05(8.41)	21.09(8.33)	0.86
	Viral load(log10 /ul) at day 0: median(IQR)	3.34(3.06, 4.45)	3.53(2.84, 5.07)	0.08
	Mortality(%)	17(43.59)	11(25.58)	0.11

O oseltamivir monotherapy, *O+P* oseltamivir-peramivir combination therapy, *IQR* interquartile range, percentile 25 – percentile75

In adults with seasonal flu A mainly H3N2 virus infection in 2008/09, the oseltamivir-zanamivir combo appeared less effective than oseltamivir monotherapy, and not significantly more effective than zanamivir monotherapy. Duval X, et al. PlosMed 2010

Longitudinal viral RNA changes with IV *peramivir* or *oral oseltamivir* treatment in adults hospitalized for influenza



Peramivir (n=16) *vs* *Oseltamivir* (n=32)

- matched baseline characteristics [Lee N, et al, *Clin Infect Dis* 2013]
- no significant difference in viral load changes
- >2.5 log reduction after 5 days
- >40% remained PCR positive

Lee N, ….Hui DS. Int J Antimicrob Agents. 2016;48(2):215-9.

Oseltamivir, amantadine, and ribavirin combination antiviral therapy versus oseltamivir monotherapy for the treatment of influenza: a multicentre, double-blind, randomised phase 2 trial

- **80/200 (40·0%) of participants in the combination group had detectable virus at day 3 vs 97/194 (50·0%) (mean difference 10·0, 95% CI 0·2–19·8, p=0·046) in the monotherapy group.**
- **No benefit in multiple clinical secondary endpoints, such as median duration of symptoms (4·5 days in the combination group *vs* 4·0 days in the monotherapy group; p=0·21). *Beigel JH, et al.***

Lancet Infect Dis 2017; 17: 1255–65

TCAD no better than oseltamivir in a retrospective pH1N1 Korean critical care study in 14-D and 90-D mortality. Kim WY, et al. AAC 2011

Baloxavir Marboxil for Uncomplicated Influenza in Adults and Adolescents

Baloxavir marboxil is a selective inhibitor of influenza cap-dependent endonuclease. It has shown therapeutic activity in preclinical models of influenza A and B virus infections, including strains resistant to current antiviral agents.

Single-dose baloxavir was without evident safety concerns, was superior to placebo in alleviating influenza symptoms, and was superior to both oseltamivir and placebo in reducing the viral load 1 day after initiation of the trial regimen in patients with uncomplicated influenza. Evidence for the development of decreased susceptibility to baloxavir after treatment was also observed. (Funded by Shionogi; JapicCTI number, 153090, and CAPSTONE-1 ClinicalTrials.gov number, NCT02954354.)

N Engl J Med 2018;379:913-23.

Any benefits in patients at higher risk for flu complications (eg extreme age, pregnancy, chronic co-morbid illness)? Any benefits for Rx beyond 48 hrs after illness onset? PK/PD data to inform appropriate dosing and whether additional doses are beneficial in severe flu? Can combo Rx of baloxavir & oseltamivir provide greater benefit vs oseltamivir alone? Any role in Rx of NAI resistant virus infection? *Uyeki T. Editorial. NEJM 2018*

Corticosteroids as adjunctive therapy in the treatment of influenza (Review)

Rodrigo C, Leonardi-Bee J, Nguyen-Van-Tam J, Lim WS
Cochrane Database of Systematic Reviews 2016, Issue 3. Art. No.: CD010406.

On meta-analysis, corticosteroid Rx was associated with ↑ in mortality (OR 3.06, 95%CI 1.58 to 5.92). Pooled subgroup analysis of adjusted estimates of mortality from 4 studies found OR 2.82, 95% CI 1.61 to 4.92.

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Control	Corticosteroid therapy			
Mortality	141 per 1000	334 per 1000 (206 to 493)	OR 3.06 (1.58 to 5.92)	1915 (13 studies)	⊕◯◯◯ very low[a]
Hospital-acquired infection	See comment	See comment	Not estimable	619 (3 studies)	⊕◯◯◯ very low[b]
Critical illness (composite outcome including death and intensive care unit admission)	See comment	See comment	Not estimable	322 (2 studies)	⊕◯◯◯ very low[c]
Mechanical ventilation	See comment	See comment	Not estimable	377 (2 studies)	⊕◯◯◯ very low[d]

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **OR:** odds ratio

High-dose corticosteroids associated with increased mortality & longer viral shedding in pts with influenza A (H7N9) viral pneumonia.

TABLE 5. Outcomes From 65 Propensity Score–Matched Patient Pairs

Outcome	All			Low-to-Moderate Corticosteroid Dose			High Corticosteroid Dose		
	Corticosteroid, *n* = 65	Control, *n* = 65	*p*	Corticosteroid, *n* = 39	Control, *n* = 39	*p*	Corticosteroid, *n* = 26	Control, *n* = 26	*p*
Mortality,[a] *n* (%)				(25–150mg/d methylpred)			(> 150 mg/d methylpred eqv)		
30-d mortality	19 (29.2)	8 (12.3)	0.019	9 (23.1)	6 (15.4)	0.508	10 (38.5)	2 (7.7)	0.021
60-d mortality	27 (41.5)	10 (15.3)	0.002	14 (35.9)	6 (15.4)	0.057	13 (50.0)	4 (15.4)	0.022
Nosocomial infections,[a] *n* (%)									
HAP	17 (26.2)	18 (27.7)	1.000	10 (25.6)	12 (30.8)	0.804	7 (26.9)	6 (23.1)	1.000
HAP complicated by bacteremia, *n* (%)	7 (10.8)	3 (4.6)	0.289	3 (7.7)	1 (2.6)	0.625	4 (15.4)	2 (7.7)	0.625
Nosocomial bacteremia or candidemia, *n* (%)	4 (6.2)	2 (3.1)	0.625	0 (0.0)	1 (2.6)	1.000	4 (15.4)	1 (3.8)	0.250
Invasive pulmonary aspergillosis or mucormycosis, *n* (%)	4 (6.2)	4 (6.2)	1.000	2 (5.1)	1 (2.6)	1.000	2 (7.7)	3 (11.5)	1.000
Viral shedding (d)[b]	14 (12–17)	12 (11–15)	0.027	13 (10.3–16)	12 (10.5–15)	0.252	15 (13.5–20)	13 (10.8–15.3)	0.039

Cao B, et al. Crit Care Med 2016

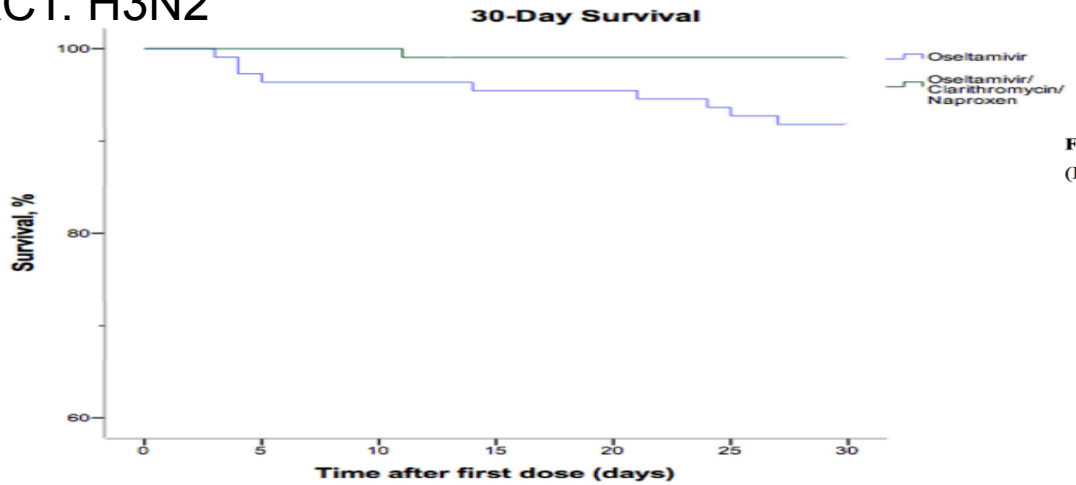
N=2649 adults hospitalized with influenza in HK, Singapore & Beijing in 2008-2011

- **Flu A/H3N2 (>45.8%), Flu B (11.1%), A(H1N1)pdm09 (36.3%)**
- Pneumonia (40.8%), respiratory failure (48.6%) , assisted ventilation(11.5%)
- Bacterial super-infections (10.8%) - *S. pneumoniae, S. aureus, H influenzae*
- 73.8% received oseltamivir; 44.5% of patients received NAI ≤2 days & 65.5% ≤5 days after onset of illness); 23.1% received systemic corticosteroids.
- Bacterial super-infections ↑ risk of death (adj HR 2.2, 95%CI 1.5–3.1)
- Systemic corticosteroids ↑ risks of super-infections (2.7% → 9.7%) & deaths (adj HR 1.7, 95% CI 1.1–2.6) when controlled for indications.

Lee N, Leo YS, Cao B, et al. ERJ 2015

Figure 2. 30-day Survival in Patients Treated With Oseltamivir/ Clarithromycin/ Naproxen Combination and With Oseltamivir alone

RCT. H3N2



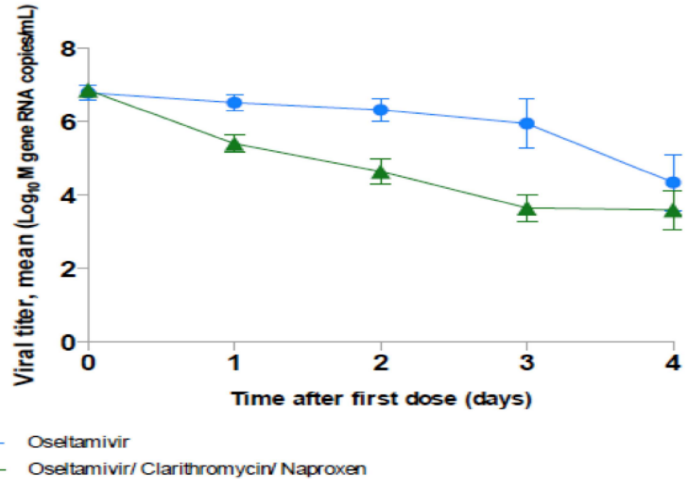
Days after first dose/ Number survived	0	5	10	15	20	25	30
Oseltamivir group (n)	110	106	106	105	105	102	101
Oseltamivir/ Clarithromycin/ Naproxen group (n)	107	107	107	106	106	106	106

Log-rank test: *P*=0.01

Triple therapy was associated with lower 30-day mortality (P=0.01), less frequent ICU/HDU admission (P<0.001), & shorter hospital-stay (P<0.0001) vs oseltamivir alone.

Figure 3. Profile Of Viral Titer After Treatment

(Error-bars represent standard error of mean)



The virus titer, PSI (day 1-3;P<0.01), & NPA specimens with NAI resistant H3N2 quasispecies ≥5% (day 1-2;P<0.01) were significantly lower in the combination Rx group. Multivariate analysis showed that combination Rx was the only independent factor associated with lower 30-D mortality (OR:0.06; 95%CI, 0.004-0.94;P=0.04). Hung IF, et al. Chest 2017

Contents lists available at ScienceDirect

Antiviral Research

journal homepage: www.elsevier.com/locate/antiviral

Review Article

Antiviral Research 150 (2018) 202–216

The role of adjuvant immunomodulatory agents for treatment of severe influenza

David S. Hui[a,*], Nelson Lee[a,b], Paul K. Chan[c], John H. Beigel[d]

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[d] Leidos Biomedical Research Inc, Support to National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, USA

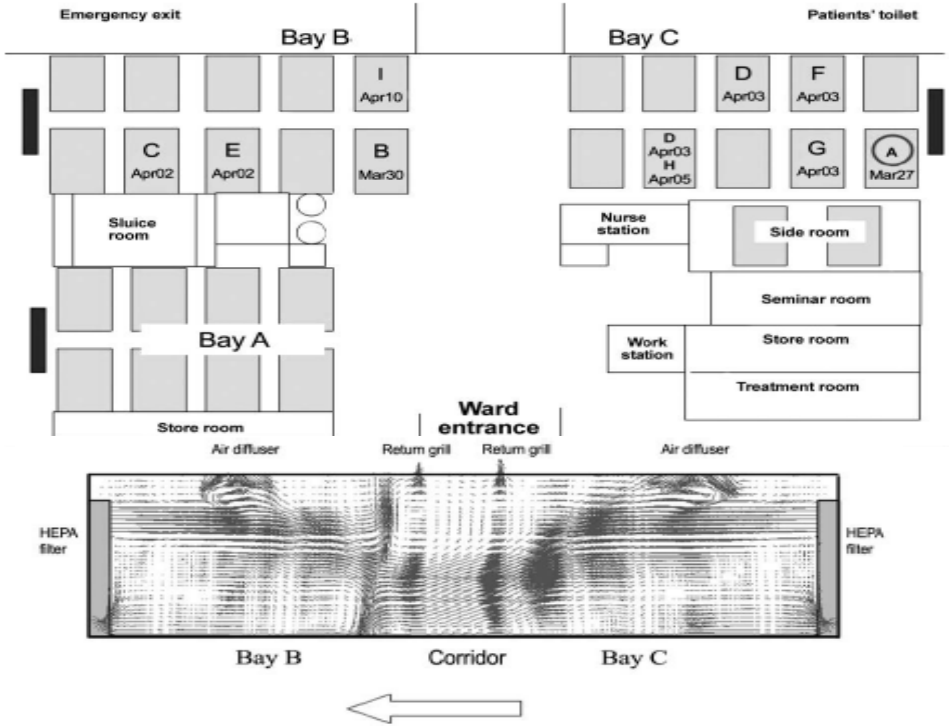
- **A severe inflammatory immune response with hypercytokinemia occurs in patients hospitalized with severe influenza.**
- **Systemic corticosteroids administered in high dose may ↑ the risk of mortality & morbidity.**
- **Passive immunotherapy such as convalescent plasma & hyperimmune globulin may be useful as an adjunctive therapy.**
- **Confirmation of the efficacy of triple therapy (oseltamivir, clarithromycin, & naproxen) would be of great interest.**
- **Other agents esp sirolimus, NAC, NTX, etc deserve more investigation by RCTs**

Possible Role of Aerosol Transmission in a Hospital Outbreak of Influenza

Clinical Infectious Diseases 2010; 51(10):1176–1183

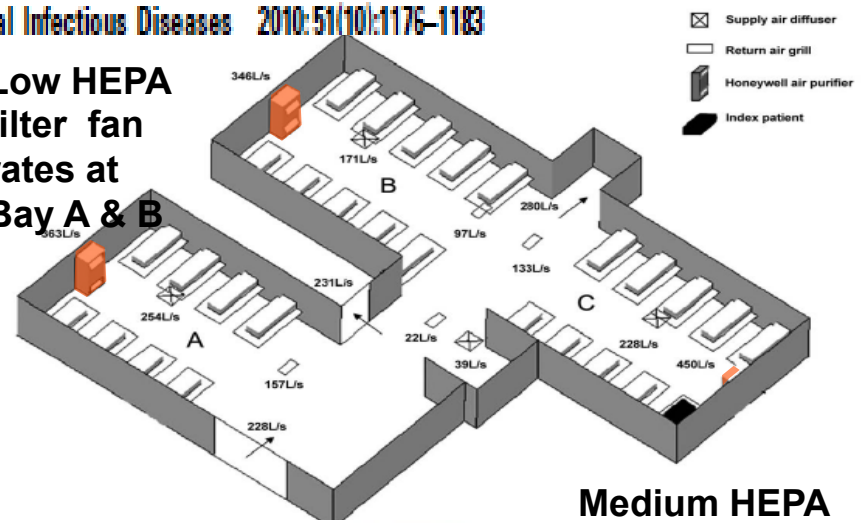
2008 ward flu outbreak: Pt A received ***non invasive ventilation*** for AECOPD but flu A+.

8 other pts infected & all isolates of H3N2 virus subtype (A/Brisbane/10/2007) & 100% identical.



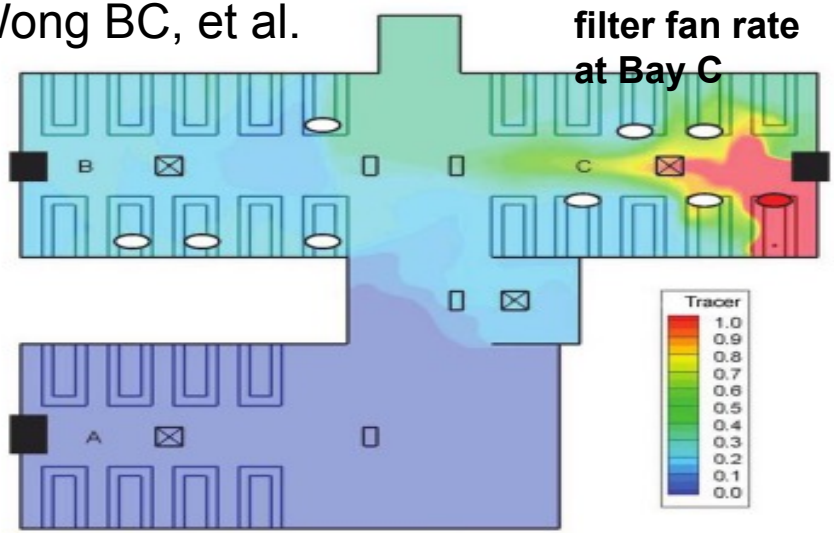
Airflow pattern at the mid-plane across the 2 high-efficiency particulate absorbing (HEPA) air purifiers in the rear bays B and C.

Low HEPA filter fan rates at Bay A & B

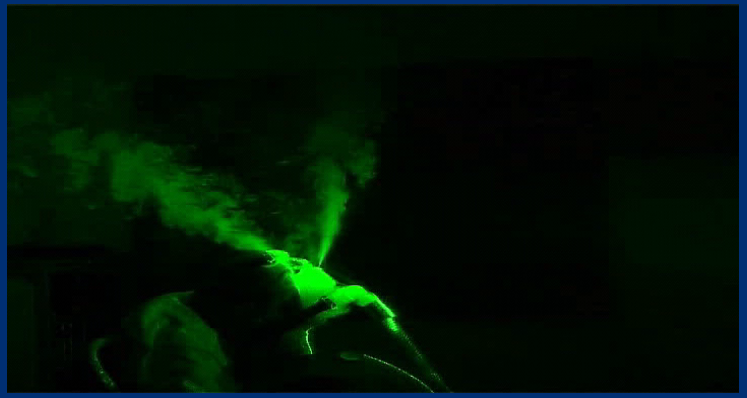


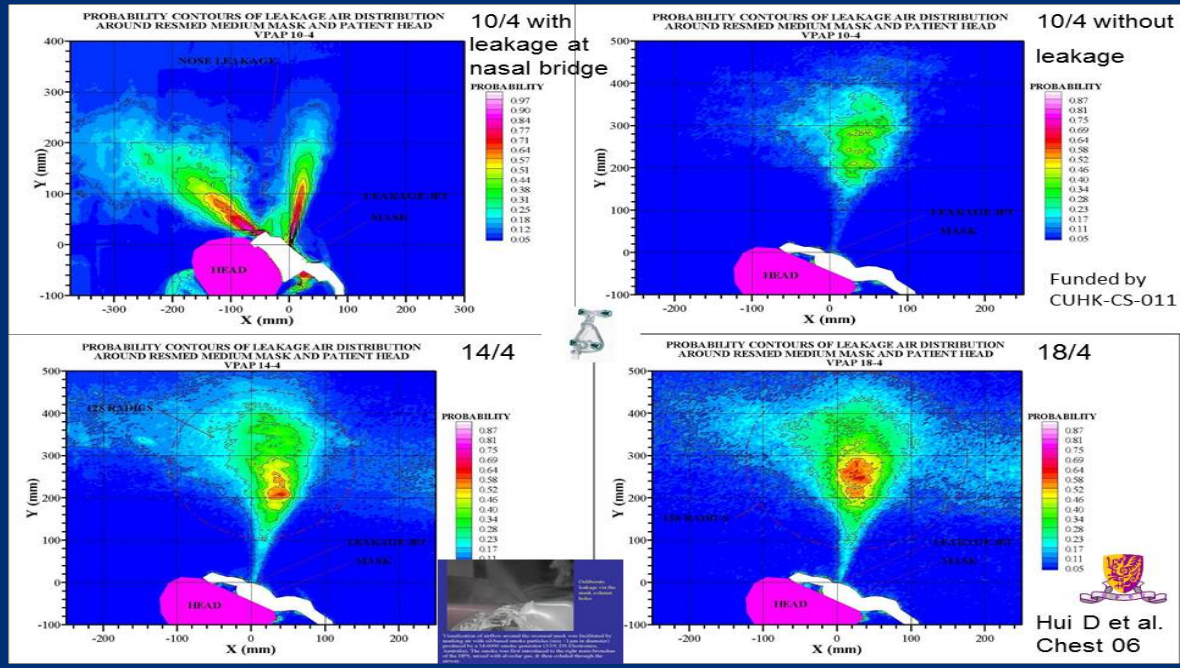
Wong BC, et al.

Medium HEPA filter fan rate at Bay C



Exhaled air dispersion from the ResMed Ultra Mirage mask during non-invasive ventilation.
Hui DS, et al. Chest 2006; 130:730-740





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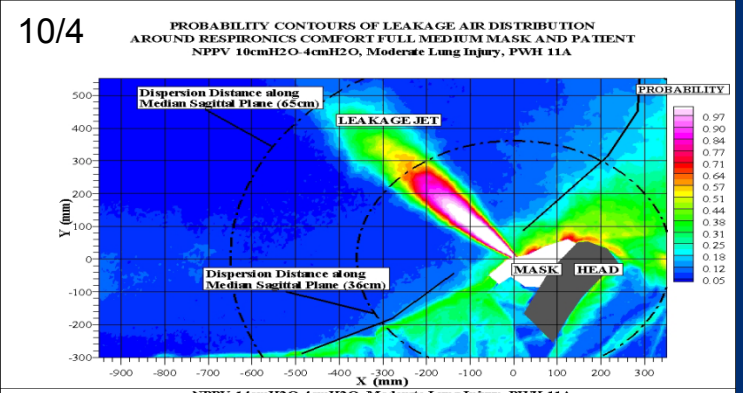

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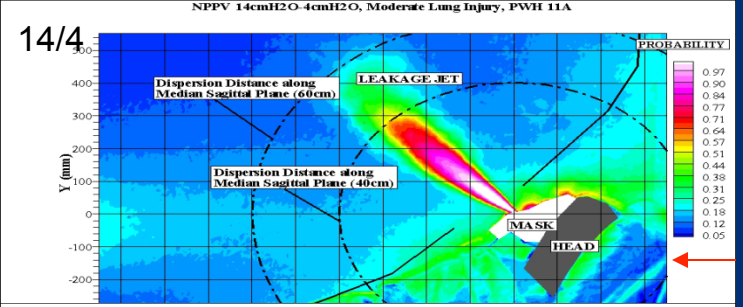

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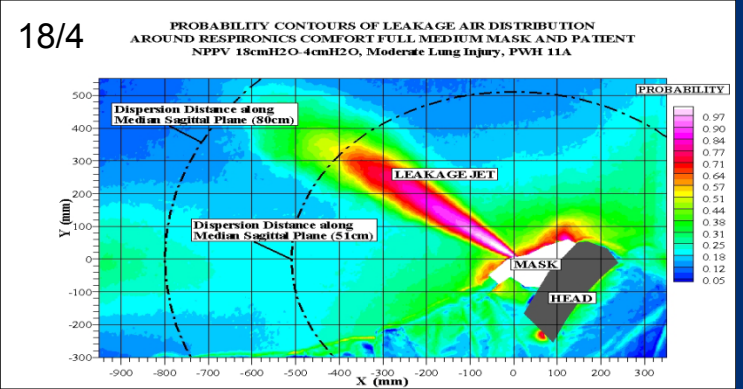
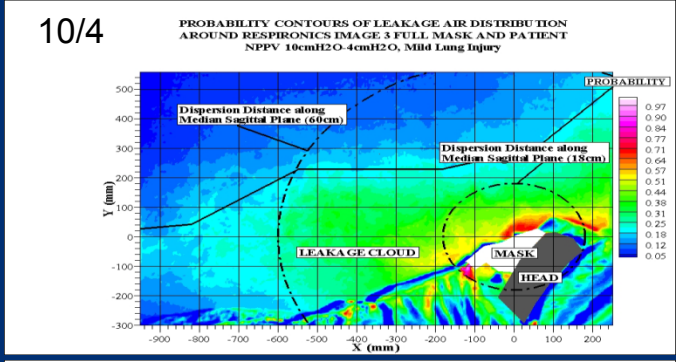


Comfort full 2 mask, HPS in mild lung injury. As IPAP increased from 10 to 18cmH20, air dispersion distances ↑ from 65 to 80cm, with more room contamination. *Hui DS, et al. Chest 2009;136:998-1005*.

Image 3 mask + a whisper swivel.

As IPAP increased from 10 to 18cmH20, air dispersion distances ↑ from 60 to 95cm, with extensive room contamination even at low IPAP.

10/4



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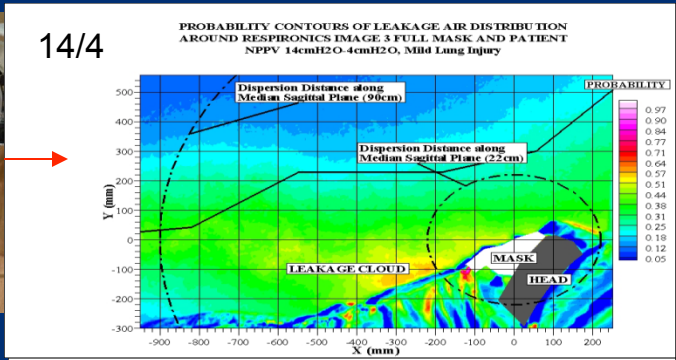

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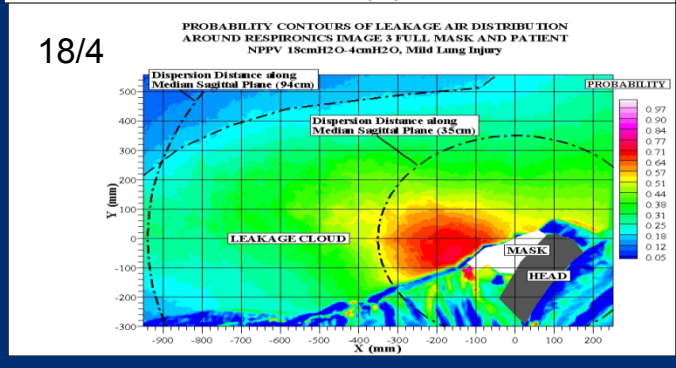

NIV for pH1N1

- 25% to 30% of pH1N1 pts were non-invasively ventilated on admission, but 70% to 86% of these pts required subsequent IMV. *(Rello J, Crit Care 2009; Ramsey CD, et al CCM 2010, Farias JA, et al. ICM 2010)*
- Beijing Chao-Yang Hosp (n=65 with pH1N1), ARDS developed in 33 and 24 were initially treated with NIV, with success in 13 (54.2%), but high death rate (8/10, 80%) in pts who subsequently received IMV *(Bai L, et al. Chest 2010).*
- NIV useful in reversing hypercapnia in pH1N1 pts with AECOPD without pneumonia *(Hui DS, et al. Chest 2010).*

On the role of non-invasive ventilation (NIV) to treat patients during the H1N1 influenza pandemic

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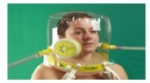
This document was officially endorsed by the ERS and ESICM in November 2009.

Table 2– Recommendations of the document endorsed by the European Respiratory Society (ERS) and the European Society of Intensive Care Medicine (ESICM)

In general, prudent isolation of the patient coupled with protective measures for care providers and other patients are the keys to limiting disease transmission
Use double-circuit tubes (or special filters for non-rebreathing devices)
Minimise leaks
Use full-face masks or helmets
Avoid heated humidification
Protect hospital personnel with standard measures (*i.e.* wearing gloves, washing hands, use of masks, negative-pressure rooms)
Discard all masks, circuits, filters and headsets immediately and safely after use according to routine infection control procedures
The routine exterior cleaning of ventilators and replacement of external filters should be sufficient to stop the spread of infection if ventilators are used on other NIV patients with H1N1



KEY WORDS: Noninvasive ventilation, pandemi

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1) Hui D, Chow BK, Ng SS, Chu LCY,Hall SD,Gin T, Sung JJY, Chan MTV.Exhaled Air Dispersion Distances During Noninvasive Ventilation via Different Respironics Face Masks *Chest* 2009 136:998-1005

2) Hui DS, Hall SD, Chan MT, Chow BK, Tsou JY, Joynt GM, Sullivan CE, Sung JJ. Noninvasive positive-pressure ventilation: An experimental model to assess air and particle dispersion. Chest. 2006130:730-40.

Exhaled Air Dispersion During Noninvasive Ventilation via Helmets and a Total Facemask

CHEST 2015; 147(5):1336-1343

David S. Hui, MD, FCCP; Benny K. Chow, PhD; Thomas Lo, MSc; Susanna S. Ng, MBChB; Fanny W. Ko, MD, FCCP; Tony Gin, MD; and Matthew T. V. Chan, MD

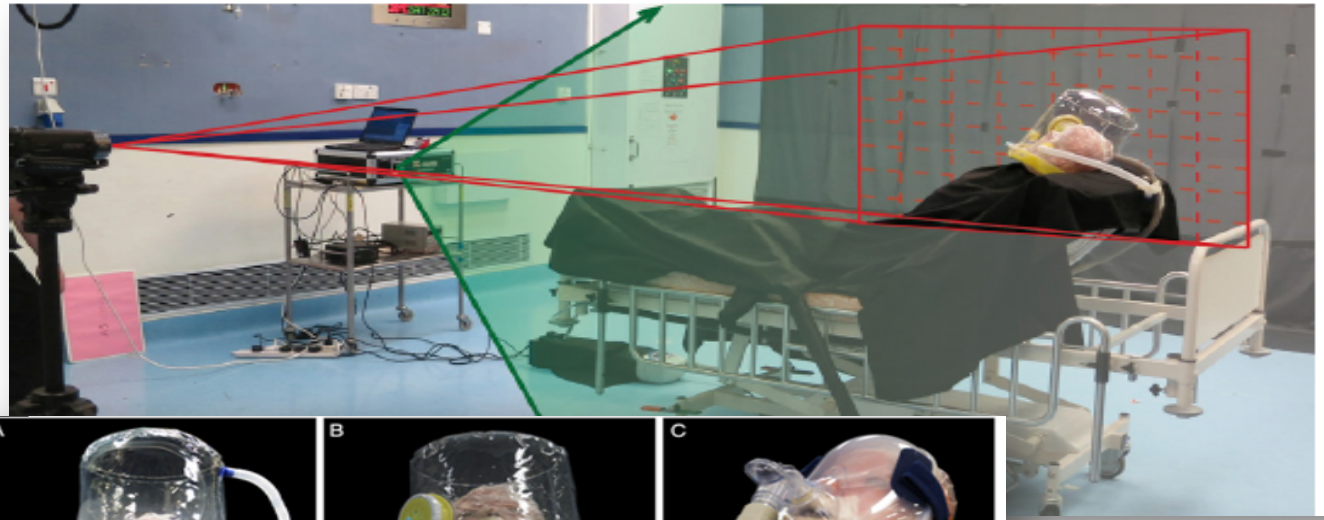
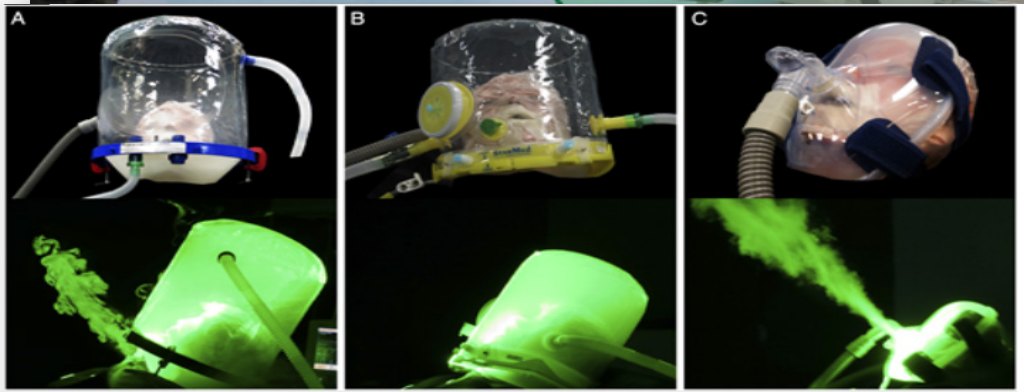
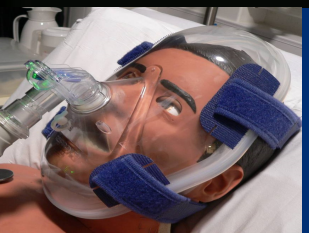


Figure 2 – *The room measured 6.1 (width) × 7.4 (depth) × 3.0 (height) m. The digital camera and the laser device were positioned along the coronal plane on the left side of the patient and along the sagittal plane of the patient at the end of the bed, respectively. Fresh air diffusers, as air inlet, were mounted on the ceiling. The negative pressure of the isolation room was produced by the air exhausts located near the floor.*

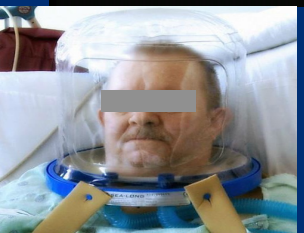


NIV via a helmet: leakage to 230mm if mask neck interface loose when IPAP ↑ from 12 to 20cmH20 while EPAP set at 10cmH20. No leakage with a good neck seal.

NIV via a total face mask: leakage up to 812mm when IPAP ↑ from 10-18cmH20 while EPAP set at 5cmH20.



NIV via a total face mask and single circuit: leakage up to 812mm when IPAP ↑ from 10-18cmH20 while EPAP set at 5cmH20. (Hui DS, et al. Chest 2015)



NIV via a helmet: leakage to 230mm if mask neck interface loose when IPAP ↑ from 12 to 20cmH20 while EPAP set at 10cmH20. No leakage with a good neck seal (Hui DS, et al. Chest 2015)

The evidence necessary to establish which AGPs are associated with transmission of respiratory pathogens are of variable quality and rigour.[6] From the available literature and incorporating UK expert opinion, the following procedures are considered likely to generate aerosols capable of transmitting respiratory pathogens when undertaken on patients with an RTI:

- intubation, extubation and related procedures; for example, manual ventilation and open suctioning
- cardiopulmonary resuscitation
- bronchoscopy (unless carried out through a closed circuit ventilation system)
- surgery and post-mortem procedures in which high-speed devices are used
- dental procedures
- non-invasive ventilation (NIV) eg bilevel positive airway pressure ventilation (BiPAP)
- continuous positive airway pressure ventilation (CPAP)
- high frequency oscillatory ventilation (HFOV)
- induction of sputum

Sukhal, *et al.*: ECMO in respiratory failure from H1N1 pneumonia – A systematic review and meta-analysis of outcome data

A systematic search of MEDLINE (1966 to April 15, 2015), EMBASE (1980 to April 15, 2015), CENTRAL, & Google Scholar for patients with severe H1N1 pneumonia & respiratory failure who received ECMO.

The **primary outcome** was all−cause mortality. **Secondary outcomes** were duration of ECMO therapy, IMV, and ICU length of stay.

Results: 13 studies included with 494 patients receiving ECMO in final review & meta−analysis. The study validity was satisfactory.

The overall mortality was 37.1% (95% CI: 30–45%) limited by underlying heterogeneity (I^2 = 65%, *P* value of *Q* statistic = 0.006). The median duration for ECMO was 10 days, IMV 19 days, and ICU length of stay 33 days.

Exploratory meta−regression identified the duration of pre−ECMO IMV in days as a moderator of mortality (coefficient 0.19, standard error: 0.09, $Z = 2.01$, $P < 0.04$, $R^2 = 0.16$).

Conclusions: ECMO therapy may be used as an adjunct/salvage therapy for severe H1N1 pneumonia with respiratory failure. Initiating ECMO early once the patient has been instituted on mechanical ventilation may result in improved survival.

2017 Annals of Cardiac Anaesthesia

Characteristic	ECMO Group (N = 124)	Control Group (N = 125)
Age — yr	51.9±14.2	54.4±12.7
Male sex — no. (%)	87 (70)	90 (72)
Immunocompromised condition — no. (%)	27 (22)	27 (22)
SOFA score†	10.8±3.9	10.6±3.5
Median time since intubation (interquartile range) — hr	34 (15–89)	34 (17–100)
Cause of ARDS — no. (%)		
Pneumonia		
Bacterial	54 (44)	58 (46)
Viral	26 (21)	20 (16)
Other	44 (35)	47 (38)
Pao_2:Fio_2 — mm Hg	73±30	72±24
PEEP — cm of water	11.7±3.9	11.8±3.7
Tidal volume — ml/kg of predicted body weight	6.0±1.3	6.1±0.9
Respiratory rate — breaths/min	30.4±4.7	31.2±4.5
Plateau pressure — cm of water	29.8±5.5	29.5±4.8
Driving pressure — cm of water	17.8±7.0	17.7±5.8
Respiratory-system compliance — ml/cm of water	25.0±11.5	25.4±10.8
Arterial blood pH	7.24±0.13	7.24±0.12
Pao_2 — mm Hg‡	69±25	68±22
$Paco_2$ — mm Hg	57±15	57±16
Prone positioning — no. (%)§	70 (56)	78 (62)
Inhaled nitric oxide or prostacyclin — no. (%)§	64 (52)	68 (54)
Recruitment maneuvers — no. (%)§	22 (18)	34 (27)
Neuromuscular blockade — no. (%)§	114 (92)	120 (96)

In an international clinical trial, patients with very severe ARDS were randomized, as indicated by one of 3 criteria:

a) Pao2/Fio2 ratio of < 50 mm Hg for > 3 hrs;

b) a Pao2:Fio2 of < 80 mm Hg for > 6 hrs; or

c) an arterial blood pH of < 7.25 with a partial pressure of arterial CO_2 of ≥ 60 mmHg for > 6 hrs;

to receive **immediate veno-venous ECMO or continued conventional treatment (control group).**

Crossover to ECMO was possible for patients in the control group who had refractory hypoxemia.

N Engl J Med 2018;378:1965-75.

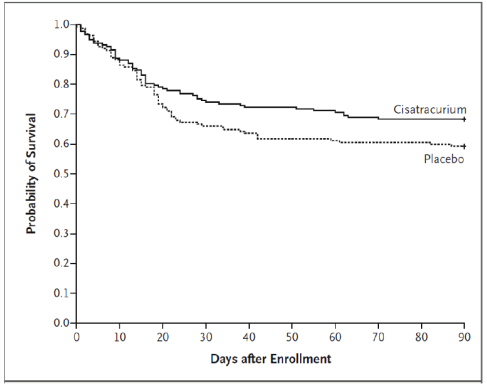
N Engl J Med 2018;378:1965-75.

End Point	ECMO Group (N=124)	Control Group (N=125)	Relative Risk or Difference (95% CI)†	P Value
Primary end point: mortality at 60 days — no. (%)	44 (35)	57 (46)	0.76 (0.55 to 1.04)	0.09
Key secondary end point: treatment failure at 60 days — no. (%)‡	44 (35)	72 (58)	0.62 (0.47 to 0.82)	<0.001
Other end points				
Mortality at 90 days — no. (%)	46 (37)	59 (47)	−10 (−22 to 2)	
Median length of stay (interquartile range) — days				
In the ICU	23 (13–34)	18 (8–33)	5 (−1 to 10)	
In the hospital	36 (19–48)	18 (5–43)	18 (6 to 25)	
Median days free from mechanical ventilation (interquartile range)§	23 (0–40)	3 (0–36)	20 (−5 to 32)	
Median days free from vasopressor use (interquartile range)§	49 (0–56)	40 (0–53)	9 (0 to 51)	
Median days free from renal-replacement therapy (interquartile range)§	50 (0–60)	32 (0–57)	18 (0 to 51)	
Prone position — no. (%)¶	82 (66)	113 (90)	−24 (−34 to −14)	
Recruitment maneuvers — no. (%)¶	27 (22)	54 (43)	−21 (−32 to −10)	
Inhaled nitric oxide or prostacyclin — no. (%)¶	75 (60)	104 (83)	−23 (−33 to −12)	
Glucocorticoids — no. (%)¶	80 (65)	82 (66)	−1 (−13 to 11)	

Among patients with very severe ARDS, 60-day mortality was not significantly lower with ECMO than with a strategy of conventional mechanical ventilation that included ECMO as rescue therapy.

More bleeding events leading to transfusion in the ECMO gp than in the control gp (in 46% vs. 28% of patients; absolute risk difference, 18% points; 95% CI, 6 to 30) as well as more cases of severe thrombocytopenia (in 27% vs. 16%; absolute risk difference, 11 % points; 95% CI, 0 to 21)

Early neuromuscular blockade for 48 hours 48 hours within onset of ARDS

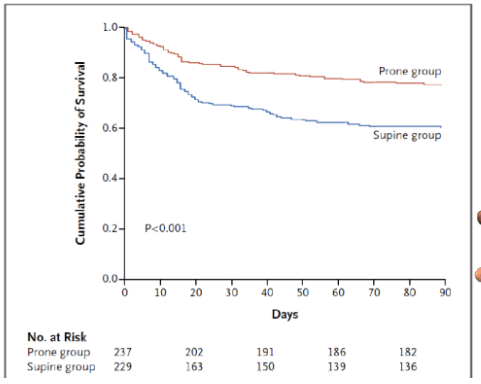


PF ratio < 150 mmHg

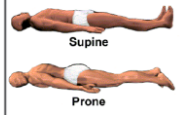
90 day mortality
31.6% vs 40.7%

NEJM 2010

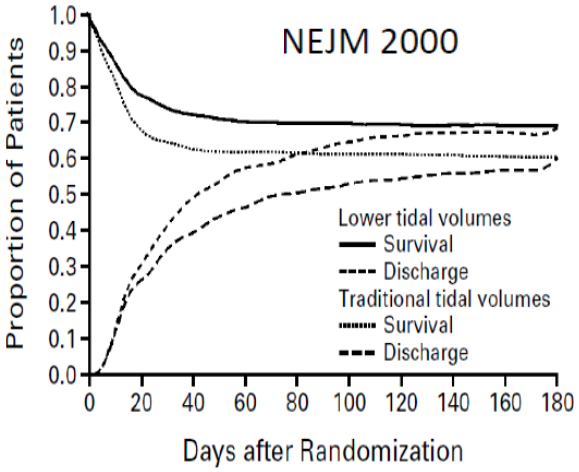
Prone positioning



PF ratio< 150 mmHg
At least 16 hours a day



NEJM 2013



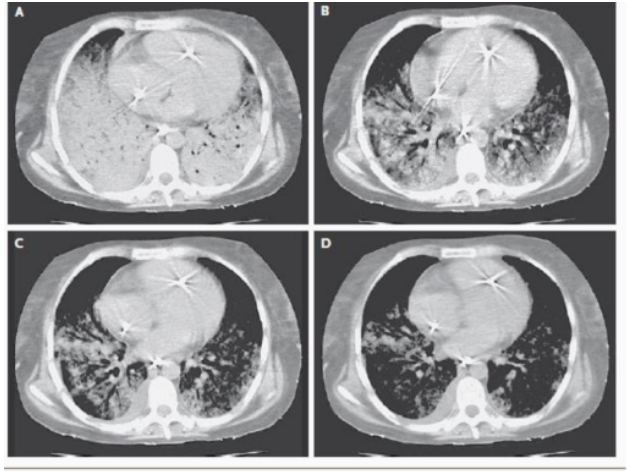
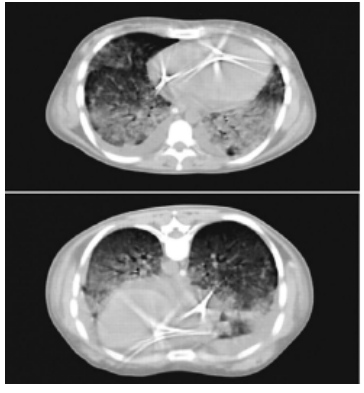


Figure 3. Effects of Recruitment Maneuvers to Promote Homogeneity within the Lung.
Panels A through D show the progressive resolution of infiltrates after application of inflations of increasing pressure. Reprinted from Borges et al.[40]

NEJM 2007



Supine

Prone

Conservative : aim CVP<4 mmHg

Liberal: CVP: 10- 14 mmHg

Table 3. Main Outcome Variables.*

Outcome	Conservative Strategy	Liberal Strategy	P Value
Death at 60 days (%)	25.5	28.4	0.30
Ventilator-free days from day 1 to day 28†	14.6±0.5	12.1±0.5	<0.001
ICU-free days†			
Days 1 to 7	0.9±0.1	0.6±0.1	<0.001
Days 1 to 28	13.4±0.4	11.2±0.4	<0.001

Bacterial Pathogens and Death during the 1918 Influenza Pandemic

N ENGL J MED 361;26 NEJM.ORG DECEMBER 24, 2009

Chien YW, Klugman KP, Morens DM.

Table 1. Culture Results for Patients during the 1918 Pandemic, According to Type of Culture and Pneumonia Status at the Time of Culture.*

Type of Culture and Population	No. of Studies	Positive Cultures	No. Positive for Pneumococci	No. Positive for Hemolytic Streptococci	No. Positive for *Staphylococcus aureus*	No. Positive for Other or Undetermined Bacteria
		no./total no. (%)				
Antemortem blood cultures						
Patients without pneumonia						
Military	5	0/323	0	0	0	0
Civilian	5	1/86 (1)	0	1	0	0
Total	10	1/409 (<1)	0	1	0	0
Patients with pneumonia						
Military	16	290/2042 (14)	238	49	2	3
Civilian	8	81/323 (25)	36	32	2	11
Total	24	371/2365 (16)	274	81	4	14
Patients with documented, subsequently fatal pneumonia						
Civilian	3	18/45 (40)	8	1	0	9
Antemortem pleural-effusion and lung cultures						
Military	5	182/224 (81)	140	55	0	10
Civilian	2	45/61 (74)	9	31	1	5
Total	7	227/285 (80)	149	86	1	15

Evidence of concurrent bacterial infection found in specimens from 22 (29%) of 77 fatal cases, including 10 caused by *S. pneumoniae. MMWR 29 Sept 2009*

Pneumococcal vaccine is important

Table 2. Clinical Features Associated with Specific Causes of CAP.

Daniel M. Musher, M.D., and Anna R. Thorner, M.D.
N Engl J Med 2014;371:1619-28.

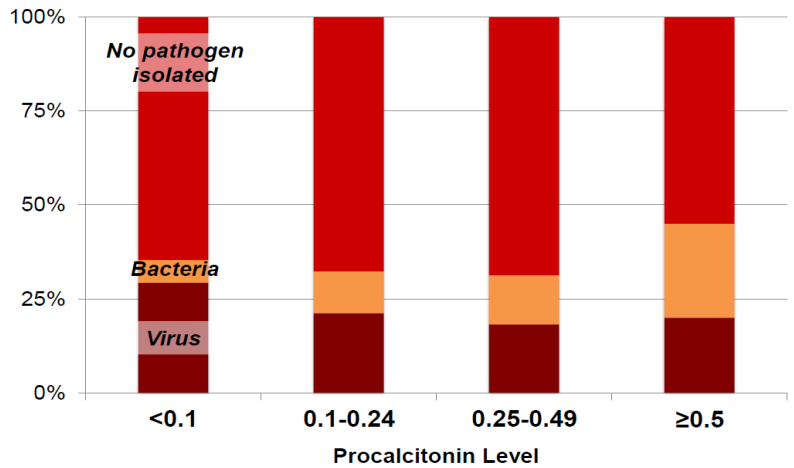
Favoring typical bacterial or legionella pneumonia

- Hyperacute presentation
- Presentation with septic shock
- Absence of upper respiratory symptoms
- Initial upper respiratory illness followed by acute deterioration (suggesting viral infection with bacterial superinfection)
- White-cell count, >15,000 or ≤6000 cells per cubic millimeter with increased band forms
- Dense segmental or lobar consolidation
- Procalcitonin level, ≥0.25 μg per liter

Clinical, radiological & lab features are unreliable to differentiating typical from atypical pneumonia!

Procalcitonin and Pneumonia Etiology

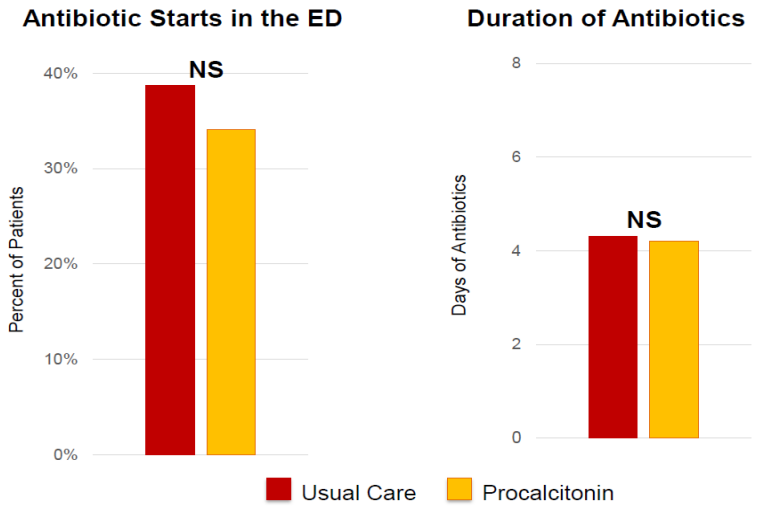
1,735 adults admitted to 5 U.S. hospitals with pneumonia



Clin Infect Dis 2017;65:183-90

Procalcitonin for ?Pneumonia

1656 patients with possible pneumonia randomized to PCT vs routine care



N Engl J Med 2018;ePub ahead of print

Summary: Treatment of SARI in the inter-pandemic period

- NAI efficacy limited by timing of Rx. Role of higher dose & longer duration requires further Ix.
- Baloxavir offers new hope but emergence of mutant viruses of concern. Role of late Rx & combo Rx for severe cases?
- Systemic corticosteroid harmful in high dose. Role of other immuno-modulating agents need further Ix (esp macrolide + NSAID, sirolimus, etc).
- Appropriate IPC needed for aerosol generating procedures.
- Role of ECMO vs other conventional Rx for ARDS
- Pneumococcal vaccine important for high risk patients.
- Development of tests based on next-generation sequencing may facilitate more accurate & timely Dx of antigenically drifted seasonal flu viruses, novel flu A viruses & viruses with known markers of antiviral resistance.

Thank You!

Cite this article as: Rochwerg B, Brochard L, Elliott MW, *et al.* Official ERS/ATS clinical practice guidelines: noninvasive ventilation for acute respiratory failure. *Eur Respir J* 2017; 50: 1602426 [https://doi.org/10.1183/13993003.02426-2016].

Question 9: Should NIV be used in ARF due to pandemic viral illness?

The use of NIV for severe acute respiratory syndrome and other airborne diseases has been assessed in several observational studies and remains controversial. These studies reported NIV failure rates of 30% and 33% [108, 109], with no evidence of viral spread to caregivers who took appropriate precautions. More recently, NIV was also used in patients with ARF due to influenza A H1N1 infection, with failure rates ranging between 13% and 77% [110–112]. However, no randomised clinical trial has assessed the efficacy of NIV in such pandemics.

Recommendation

Given the uncertainty of evidence we are unable to offer a recommendation for this question.

Justification

Despite the lack of any RCTs, the positive data from most of the observational studies and the controversial issue of possible increased risk of passing infection on to caregivers, we consider the prior recommendations against the use of NIV for pandemics as unsupportable. Although a cautious NIV trial in carefully selected patients at experienced centres, in a protected environment (*i.e.* negative pressure rooms), may be reasonable, further research is needed before a recommendation is possible.