

Antiviral agents

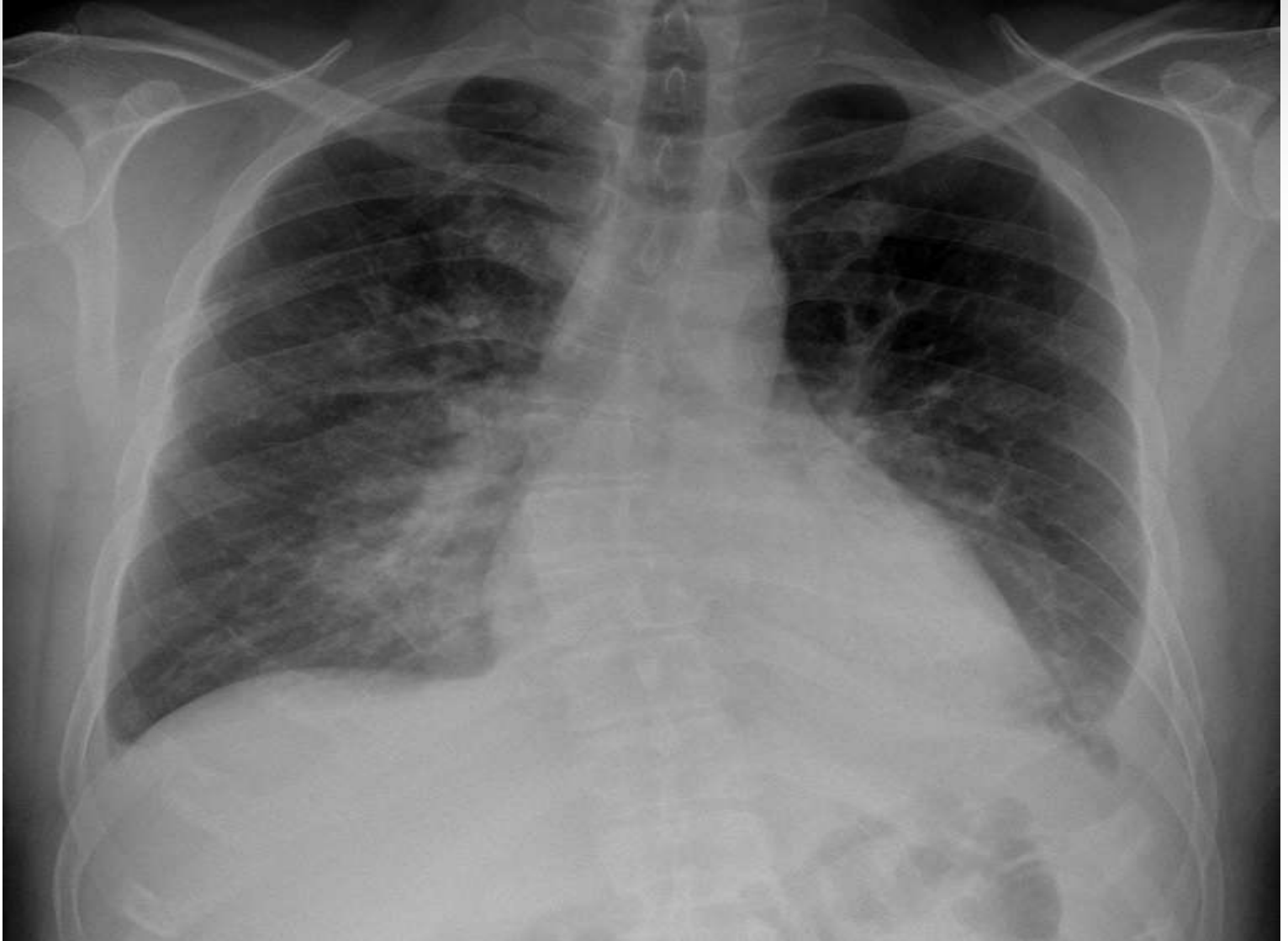
Jordi Rello

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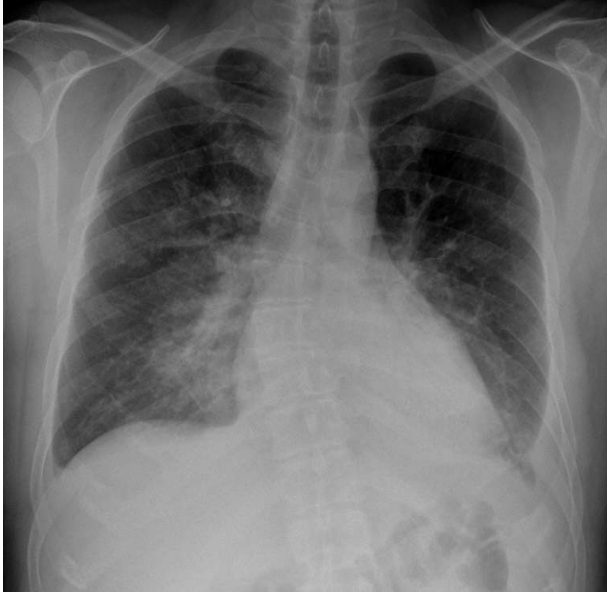
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37-yr old patient with Fever, Respiratory Failure and Rash



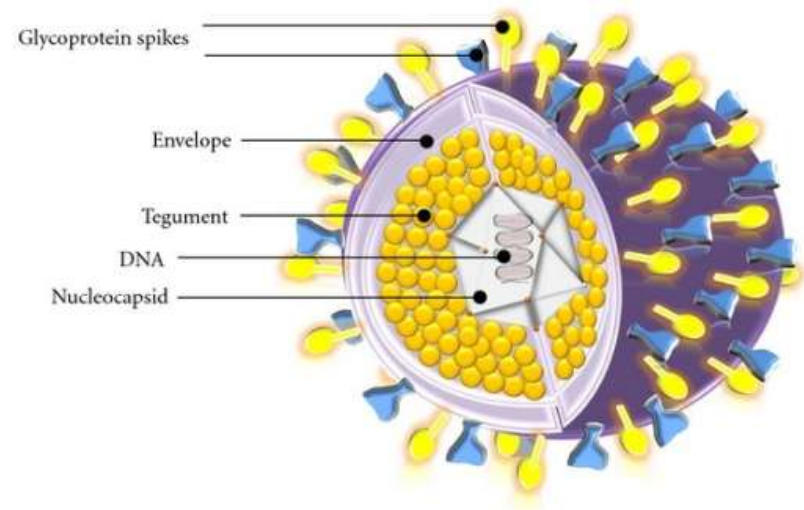
37-yr old patient with Fever, Respiratory Failure and Rash



Introduction

- *“Viral infections are common causes of respiratory tract disease in the outpatient setting but much less common in the intensive care unit” (Nicholas Stollenwerk, Critical Care 2008)*
 - Influenza, VZV/HSV, CMV, RSV : common
 - SARS, hemorrhagic fever, Hantavirus : rare
- Few drugs available outside HIV when compared to antibiotics
- Very little use in the ICU outside Influenza
- Effective against a very limited group of diseases
- Targets for antiviral drugs are various points of viral reproduction

HSV



HSV reactivation in lower respiratory tract

- 764 ICU patients, 361 tested for HSV in LRT
- HSV isolated in LRT of 58 patients(16%)
(Bruynseels, Lancet 2003)

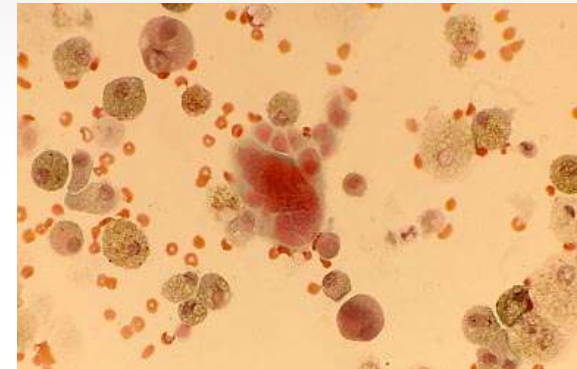


- 201 patients ventilated for ≥ 5 days with suspected VAP
- HSV isolated in LRT of 129 patients (64%)
(Luyt, AJRCCM 2007)



HSV bronchopneumonitis

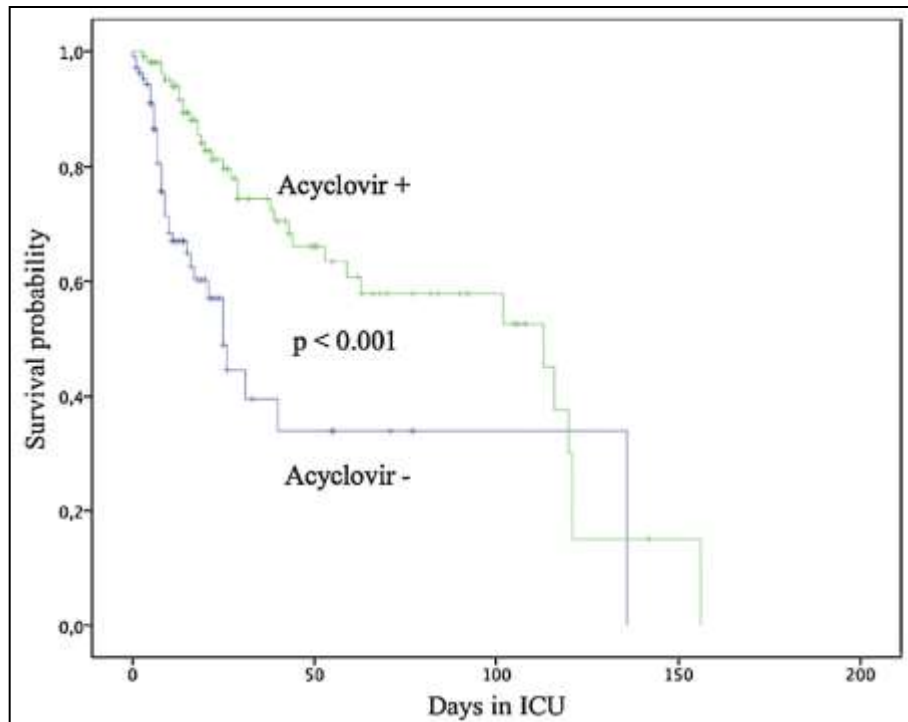
- HSV bronchopneumonitis in 42/201 (21%) patients ventilated for ≥ 5 d with suspected VAP
 - Clinical suspicion
 - HSV detection
 - HSV-specific nuclear inclusions
- 23 (55%) had oral-labial lesions



	HSV bronchopneumonitis				p
	Yes n = 42		No n = 159		
Total duration of MV, d	36.7	27.5	30.0	27.1	0.03
VAP episodes/patient, n	1.5	1.0	1.1	1.1	0.03
ICU length of stay, d	40.1	27.8	32.1	28.1	0.01
In-hospital mortality, n (%)	20 (48)		66 (42)		0.5

HSV treatment

- Single center, retrospective analysis
- 212 patients HSV +: 106 who received Acyclovir and 106 “controls”



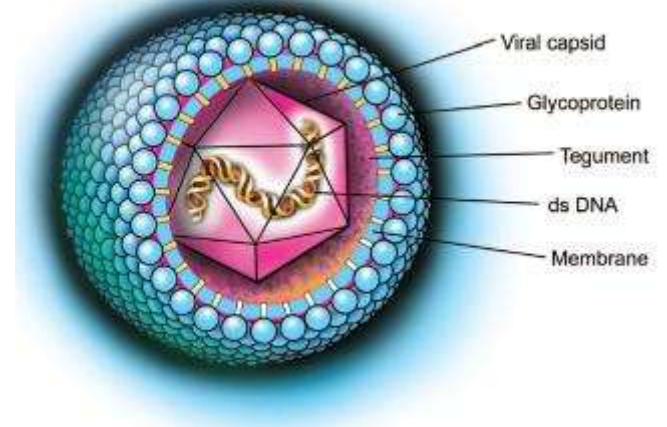
Comparison of the estimated treatment effect of acyclovir on mortality using univariable and multivariable COX regression and propensity score-matched COX-regression survival analysis.

	Acyclovir –		
	OR	95%CI	p
ICU mortality			
Unadjusted model ^a	2.67	1.64–4.34	<0.001
Multivariable model	3.21	1.95–5.26	<0.001
BAL subgroup	8.42	2.47–28.66	<0.001
Airways subgroup	2.93	1.61–5.34	<0.001
Propensity score-matched (quintiles) ^a	3.19	1.79–5.69	<0.001
In-hospital mortality			
Unadjusted model ^a	3.42	2.23–5.26	<0.001
Multivariable model	4.02	2.60–6.22	<0.001
BAL subgroup	7.56	2.69–21.25	<0.001
Airways subgroup	4.29	2.48–7.40	<0.001
Propensity score-matched (quintiles) ^a	3.55	2.16–5.85	<0.001

^a BAL and airways.

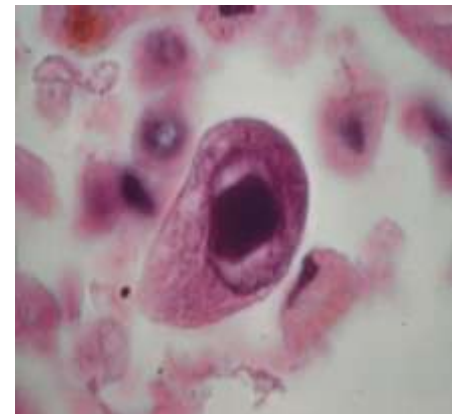
Traen, Journal of clinical virology 2014

CMV



Background

- CMV reactivation in **blood**
 - 30% of seropositive patients
 - Diagnostic using PCR
 - After 4-12 d in ICU
 - Associated to CMV disease ?
- **Pulmonary** CMV infection
 - 5 - 30%
 - Diagnostic using histology/cytology
 - After 21 d of MV

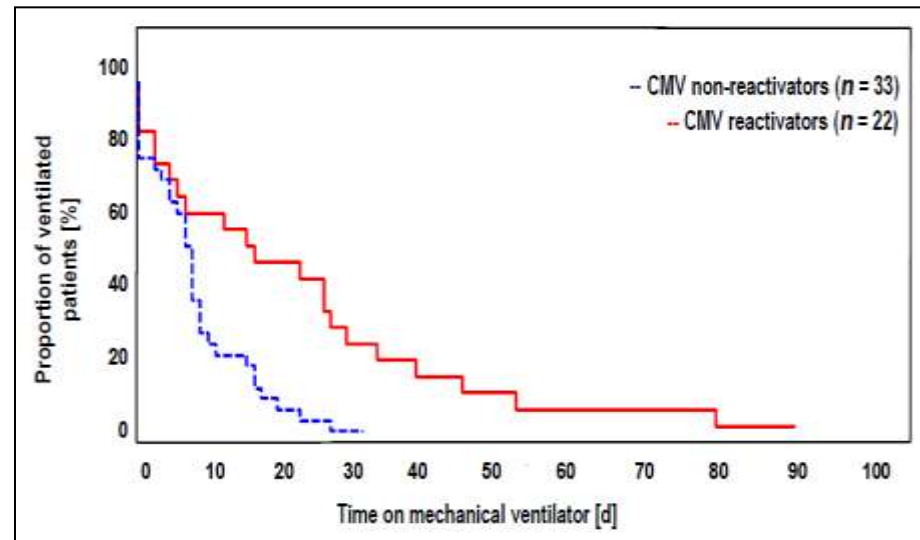
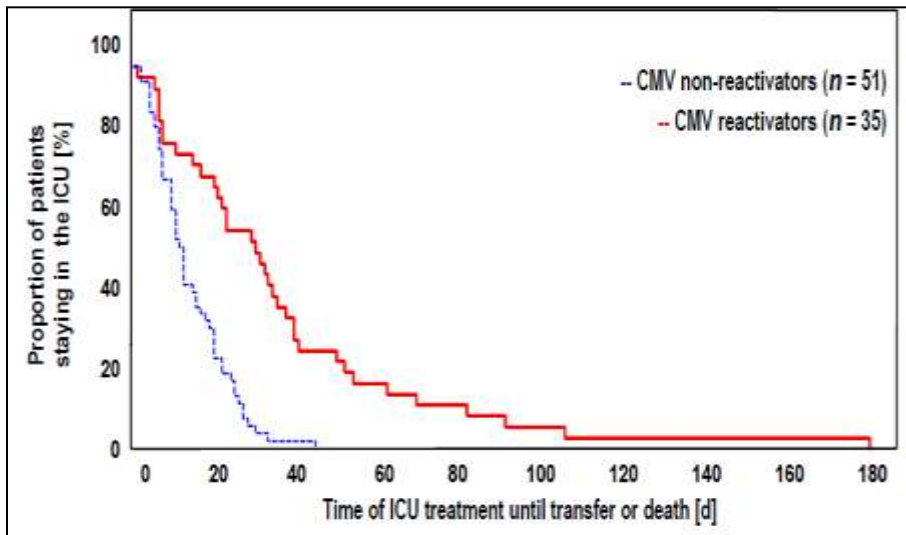


Pulmonary CMV infection

Population	Frequency of viral detection	Clinical presentation of CMV pneumonia	Diagnostic tests
Patients with ARF and VAP (Papazian, Anesthesiology 1996)	25/86 (29%)	Diffuse interstitial pneumonia	Histology: post-mortem in 60, open-lung biopsy in 26
Surgery patients with SAPS II>40 (Heininger, Crit Care Med 2001)	7/56 (6%)	NA	Viral cultures, PCR
Unexplained ARDS (Papazian, Crit Care Med 2007)	30/100 (30%)	Pneumonia, fibrosis	Histology on open-lung biopsy. CMV (virology) in 10/30
Patients under MV (Chiche, Crit Care Med 2009)	11/242 (5%)	Pneumonia	Rapid shell-vial culture, cell culture

CMV in the ICU

- Prospective longitudinal double-blinded observational study
- 97 adult non immunosuppressed CMV-seropositive patients with new onset of severe sepsis included
- Leukocytes, plasma and tracheal secretions were examined weekly for CMV-DNA by PCR

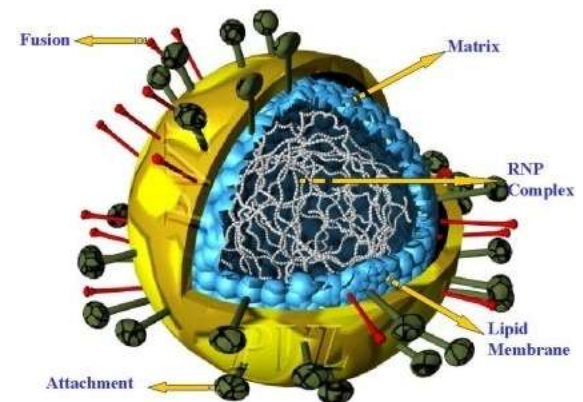


Treatment



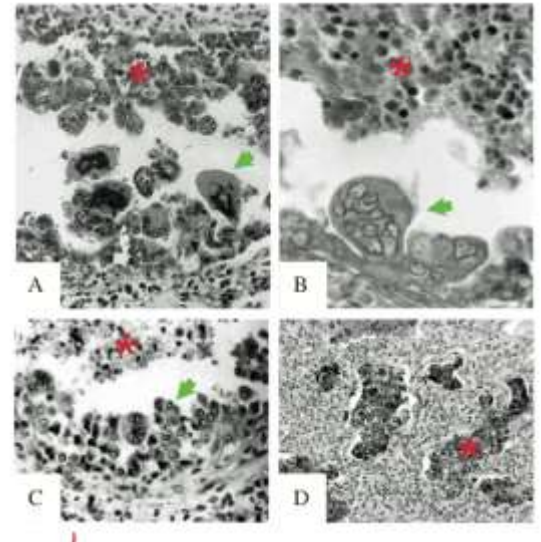
- Whether CMV is a **truly pathogen** or a **by-stander** remains to be elucidated
- **No current recommendation for treatment**
- Ganciclovir to be fully evaluated including risk/benefit ratio
- Several clinical trial (at least 2) with **Ganciclovir pre-emptive** approach ongoing
- Few promising drugs (Maribavir, Artesunate, Cyclopropavir...) in development regarding emergence of resistances

RVS



Background

- **RSV is the most commonly identified pathogen (60-80%) of LRTI in infants worldwide**
 - *RSV is the leading cause of infectious disease hospitalizations among infants and death among post-neonatal infants, besides malaria.*
 - *RSV also causes more severe and prolonged bronchiolitis compared to that caused by other etiologies.*
- 80% hospitalized RSV-infected infants <2 months being **previously healthy**

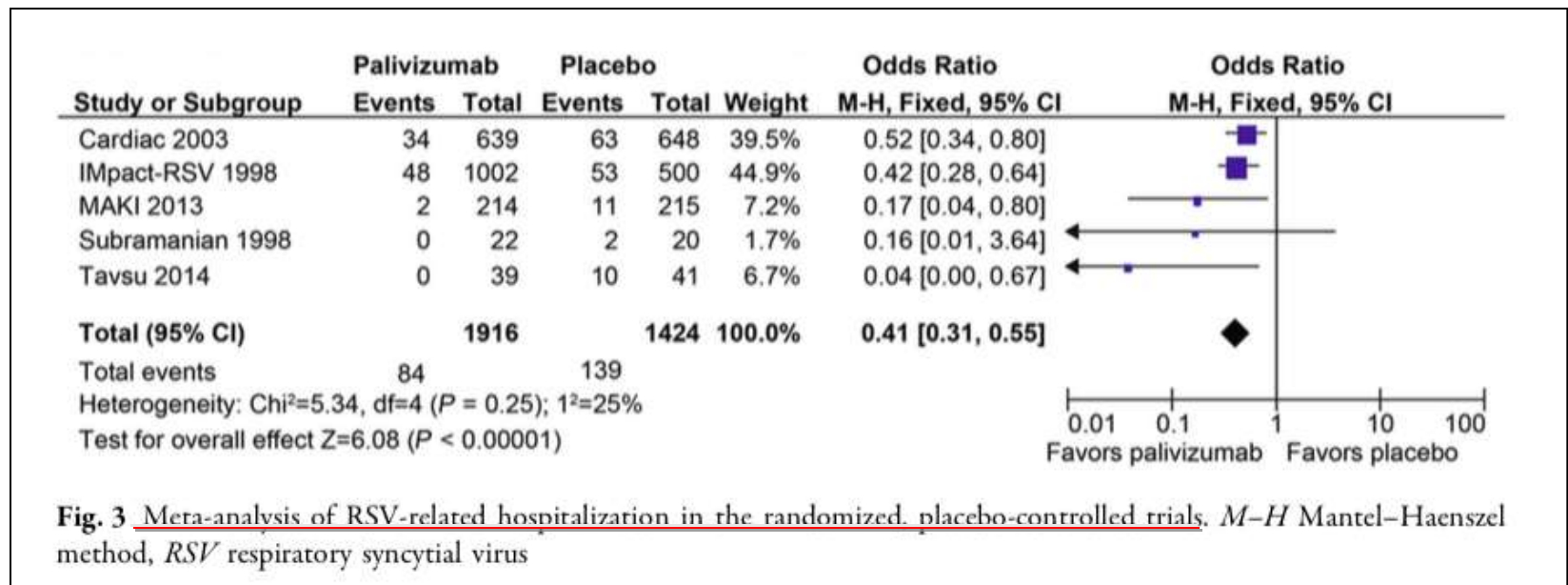


VRS in the pediatric ICU

- VRS-LRTI is the most frequent cause of non-elective PICU admission for mechanical ventilatory support in infants during the winter season.
- 734 children <2 years admitted to the hospital with VRS bronchiolitis
 - **22% admitted to the ICU** (high flow cannula, NIV)
 - **10% intubated** and MV
 - Very young age, prematurity, underlying cardiopulmonary disease and immunodeficiency, more likely to be admitted to PICU with severe disease
 - » Sala et al. J Asthma 2014 pp. 1-5
- High incidence of pulmonary bacterial co-infection in children with severe RSV bronchiolitis, increasing severity of respiratory illness
 - » Thorburn K et al. Thorax 2006; 61:611-615.

RVS Treatment

- **Absence of medical treatments. Mainly supportive.**
- ***Prevention: the most effective approach against severe RSV... but no vaccine!***
 - *Avoiding contact.*
 - ***Palizumab:*** Humanized murine monoclonal antibody directed against the surface RSV fusion protein.



Palizumab

- Cost-effective in the prevention of acute infection in high-risk patients (*passive immunoprophylaxis*)
 - ✓ **Prematurity, chronic lung disease in infants born preterm and/or hemodynamically significant congenital heart disease**
 - Resch B et al. *Pediatr Infect Dis J* 2012; 31:e1-e8.
- IM 15 mg/kg, monthly (**5 doses** during RVS season)
- **Off-label use of prophylactic palizumab in infants and young children with underlying severe respiratory disease**
 - Gaboli M et al. *Pediatr Pulmonology* 2014; 49:490-502

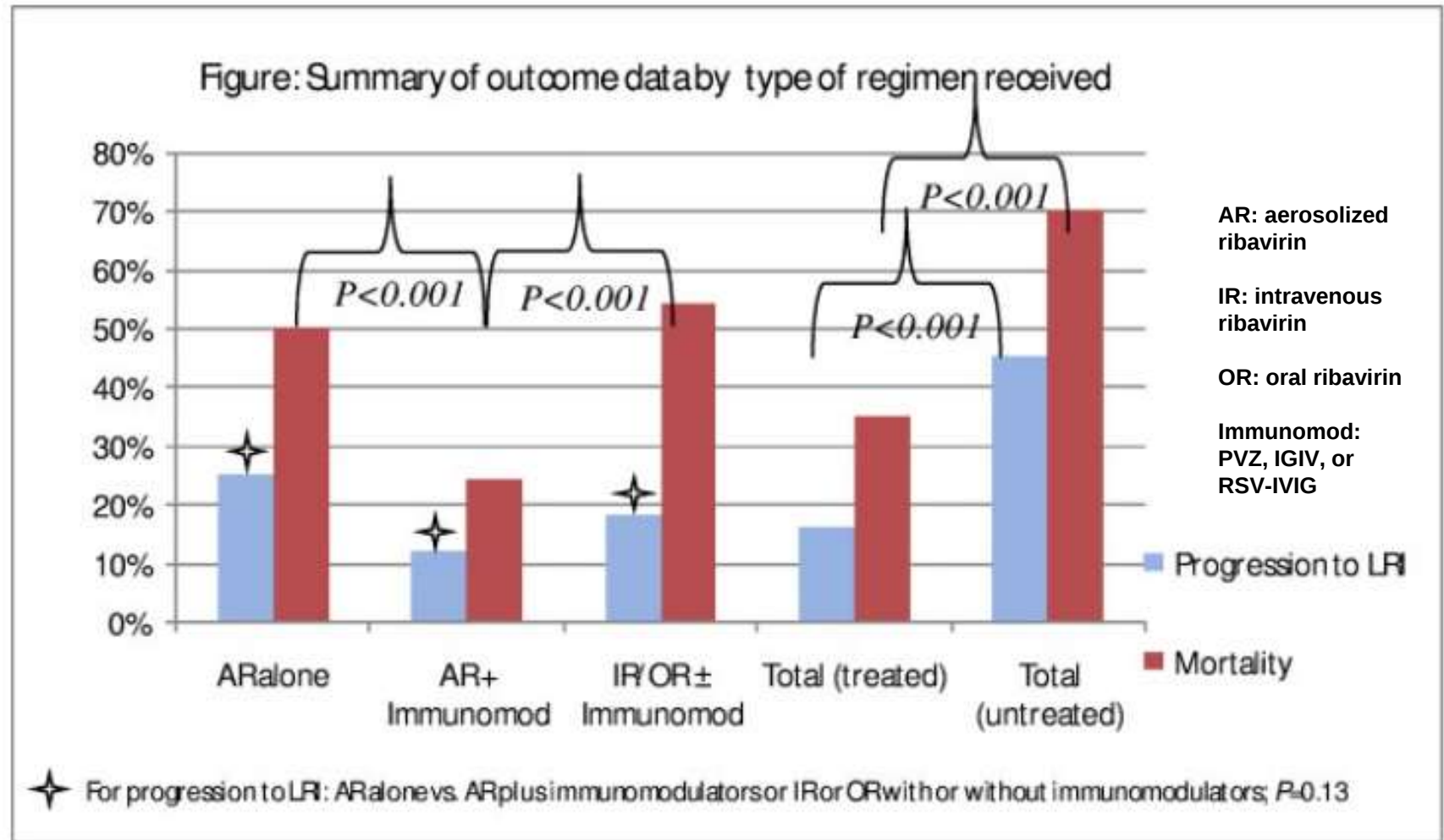
RVS in immunocompromised patients

- Children with higher RSV **genomic load** have more severe bronchiolitis
» Hasegawa et al. J Pediatr Dis 2014 pp
- **Lymphocytopenia** is a predictor of progression to LRTI, not only in the pediatric population but also in adult HSCT recipients and patients with leukemia
» Torres HA et al. Haematologica 2007; 92:1216-23
- Although neutropenia has not been conclusively established to be an independent risk factor for the development of LRTI, *it may be considered to play a role in the development of bacterial co-infections/super-infections.*

Off-label RVS treatment

- **Ribavirin:** low efficacy, carcinogenic & teratogenic potential
 - **Aerosolized:** *risk for health care workers, high costs (appropriate equipment)*
 - **Systemic** ribavirin: *effective in HSCT patients, “low” side effects*
 - » Gueller S et al. Transpl Infect Dis 2013; 15(4):435-40
 - » Casey J et al. Bone Marrow Transplant 2013; 48(12):1558-61
- **RBV + IV Polyclonal immunoglobulines** (standard and RSV-specific)
- **IV Palizumab**, *coadjuvant, preemptive?*
 - » Santos RP et al. Pediatrics 2012; 130 (6):1695-9.
- **IV palizumab and ribavirin combination**
 - » Chávez-Bueno S et al. Pediatr Infect Dis J 2007; 26(12):1089-93
 - » Chemaly RF et al. J Pediatr Hematol Oncol 2014; 36 (6):e376-81

RVS management in adult recipients of HSCT



Systematic Review. Shah JN and Chemaly RF. *Blood* 2011, 117 (10):2755-2763.

Desafios: de H5N1 a H1N1



Flexibilidad

“Prepare for the worst, hope for the best” (WHO)

Burden of Influenza

- Global burden of seasonal influenza: ~1 billion cases, with 3-5 million severe cases and up 300,000 to 500,000 deaths annually
- A/H1N1pdm09: 61 million US cases by April 2010 (20% population), with about 275,000 hospitalizations, and 12,500 deaths (CDC)
- Since 2010: **seasonal H3N2 and influenza B co-circulating with A/H1N1pdm09**
- **Risk factors different between seasonal and H1N1 pdm09**
 - H1N1pdm09 hospitalizations: <10% in elderly (>90% for seasonal flu)
 - H1N1pdm09 mean age for deaths ~ 38 yrs (76 yrs for seasonal flu)
 - 5 times more deaths in those <50 years than for seasonal flu
- H5N1 avian influenza continues to be a serious public health threat. Over 600 cases worldwide with case fatality rate ~60%

Influenza Antivirals

- Adamantanes (M2 ion channel inhibitors)
 - Prevent virus from entering cell
 - Effective against influenza A only, **but not active against current A/H3N2 or A/H1N1pdm2009 viruses**
 - Amantadine, Rimantidine
- Neuraminidase inhibitors
 - Bind to the neuraminidase enzyme active site and blocks removal of sialic acid, preventing release and spread in respiratory tract
 - Improved safety and resistance profiles compared to adamantanes
 - Effective against influenza A and B
 - Zanamivir: Inhaled (Relenza)
 - **Oseltamivir: Oral (Tamiflu)**
 - Peramivir: IV (Rapiacta, approved in Japan and South Korea)
 - Laninamivir: Inhaled (Inavir, approved in Japan)

Antiviral susceptibility (2012)

	Oseltamivir	Zanamivir	M2 Inhibitors
Pandemic A (H1N1) 2009	Susceptible*	Susceptible	Resistant
Seasonal A (H3N2)	Susceptible	Susceptible	Resistant
Influenza B	Susceptible	Susceptible	Resistant
Avian Influenza A (H5N1)	Susceptible	Susceptible	Variably resistant

*Sporadic isolates resistant to oseltamivir have been reported

Clinical resistance to Oseltamivir

- Rapid development of widespread oseltamivir resistance in seasonal A H1N1 strain during **2008-09**
 - Virtually 100% seasonal H1N1 viruses were oseltamivir resistant
 - Virus contained the **H275Y mutation**. Considered to be a spontaneous mutation and **not in response to drug pressure**
 - H275Y mutation also confers resistance to peramivir but fully **susceptible to zanamivir**
 - H1N1 seasonal variant much less in circulation after emergence of H1N1pdm2009
- Currently circulating H1N1, H3N2 and B strains are sensitive to neuraminidase inhibitors
 - Background level of oseltamivir resistance in H1N1pdm2009 virus remains low globally (**approximately 1%**); mainly due to H275Y mutation

Clinical resistance to Zanamivir

- Rare reports of zanamivir resistance
 - No cases of zanamivir resistance reported in over 5,000 patients with influenza treated in clinical studies
 - In 1998, 1 case of drug-selected resistance reported in immunocompromised child with influenza B
 - **3 reports of critically ill patients with pH1N1**
 - All immunocompromised patients
 - 2 patients had been treated with IV zanamivir, 1 with IH zanamivir
 - 2 patients I223R mutation detected during oseltamivir and before zanamivir treatment
 - No evidence of clinical clone with both mutations

Early Oseltamivir treatment in pandemic H1N1

- **Early (≤ 48 hrs) treatment** associated with
 - ↓ duration of viral detection, fever, **symptoms**
 - ↓ risk of **pneumonia** (OR 0.12, 95% CI 0.08- 0.18)
 - ↓ risks of **death in severely ill** (OR 24.2, 95% CI 12 - 49) or ICU admit/death in hospitalized
 - ↓ risks of ICU admission (6% vs 31.5%) and mortality (0.5% vs 14.5%) in **pregnant women**
 - ↓ risks of hospitalization, ICU admit (8% vs 22%), and death (1% vs 6%) in **SOT recipients**

Cao, NEJM 2009 - Li, Chest 2010 - Kumar , Lancet ID 2010 - Siston, JAMA 2010 - Jain , NEJM 2009

Delayed Oseltamivir treatment in pandemic H1N1

Location	No. treated	Outcomes
USA (Siston, JAMA 2010)	115 pregnant women	↓ ICU (18 vs 46%) and death (5 vs 25%) risks if treated on day 3-4 vs >4
Mexico (Dominguez-Cherit, JAMA 2009)	44 ICU	↑ survival (OR 7.4; 95% CI, 1.8-31.0)
Argentina (Farias, ICM 2010)	147 pediatric ICU	↓ mortality if ≤ 1 day after hospital admit (OR 0.20; 95% CI, 0.07-0.54)

Other findings in Oseltamivir and Zanamivir

- Oral **oseltamivir**
 - **Adequate NG absorption** in most critically ill patients
 - **No dose alteration** for obesity (< 200 kg)
 - Altered dosing regimens for premature infants, neonates, renal replacement therapies
- **Nebulized zanamivir**
 - Reports of **bronchospasm** in serious pH1N1 illness
 - Risk for **obstruction** of ventilator filters (lactose carrier in commercial formulation)

Antivirals Combinations

OPEN ACCESS Freely available online

PLoS one

Triple Combination of Amantadine, Ribavirin, and Oseltamivir Is Highly Active and Synergistic against Drug Resistant Influenza Virus Strains *In Vitro*

Jack T. Nguyen^{1*}, Justin D. Hoopes², Minh H. Le¹, Donald F. Smee², Amy K. Patick¹, Dennis J. Faix³, Patrick J. Blair³, Menno D. de Jong⁴, Mark N. Prichard⁵, Gregory T. Went^{1*}

- Triple regimen highly synergistic against amantadine- and oseltamivir-resistant influenza A viruses
 - Synergy of the triple combination was significantly greater than that of any double combination tested
- Dual NAI combos showed additivity to antagonism

Nguyen, PLOSone 2010

Oseltamivir and inhaled Zanamivir in seasonal Influenza

	O + Z n=157	O n=141	Z n=149	P value O+Z/O	P value O+Z /Z
Mean (SD) viral load Δ day 0 to 2 (log10 cgeq/ μ L)	2.14 (1.54)	2.49 (1.52)	1.68 (1.68)	0.060	0.01
Day 2 influenza RT-PCR < 200 cgeq/ μ L (%)	46%	59%	34%	0.02	0.02
Duration of symptoms in days (median, IQR)	4 [2.5-14]	3 [2-7]	4 [2.5-14]	0.01	0.96

Rationale for intravenous antiviral development

- Emergence of widespread oseltamivir resistance in 2008/09 seasonal H1N1 strain and of H1N1pdm2009 highlighted need for parenteral agent with unique resistance profile
- No antiviral agents with proven efficacy for severe influenza
- No IV antiviral agents with full marketing approval for severe influenza (except peramivir in Japan and South Korea)
- **Unmet need for IV formulation** in patients who:
 - Are non-responsive to approved treatments
 - Unable to take oral medication or inhaled medication (e.g. ET tube, impaired GI function, diarrhea, ventilator use, inadequate inhalation, etc)
 - Resistance to oseltamivir (or peramivir, adamantanes)
 - Are severely ill and require reliable delivery through IV route

Others NAI clinical trials

- Uncomplicated influenza
 - **Peramivir: single IV dose** (300 or 600 mg) superior to placebo and comparable to 5 days of oseltamivir in adults (*NB: not superior for resistant H1N1*)
 - **Laninamivir: single inhaled doses** of 20 mg or 40 mg comparable to 5 days of oseltamivir in adults and children (*NB: superior for resistant H1N1 in children*)
- Hospitalized adults
 - **Peramivir:** multiple IV doses (200 or 400 mg) comparable to oseltamivir in hospitalized adults

Intravenous Zanamivir in hospitalized adults with influenza

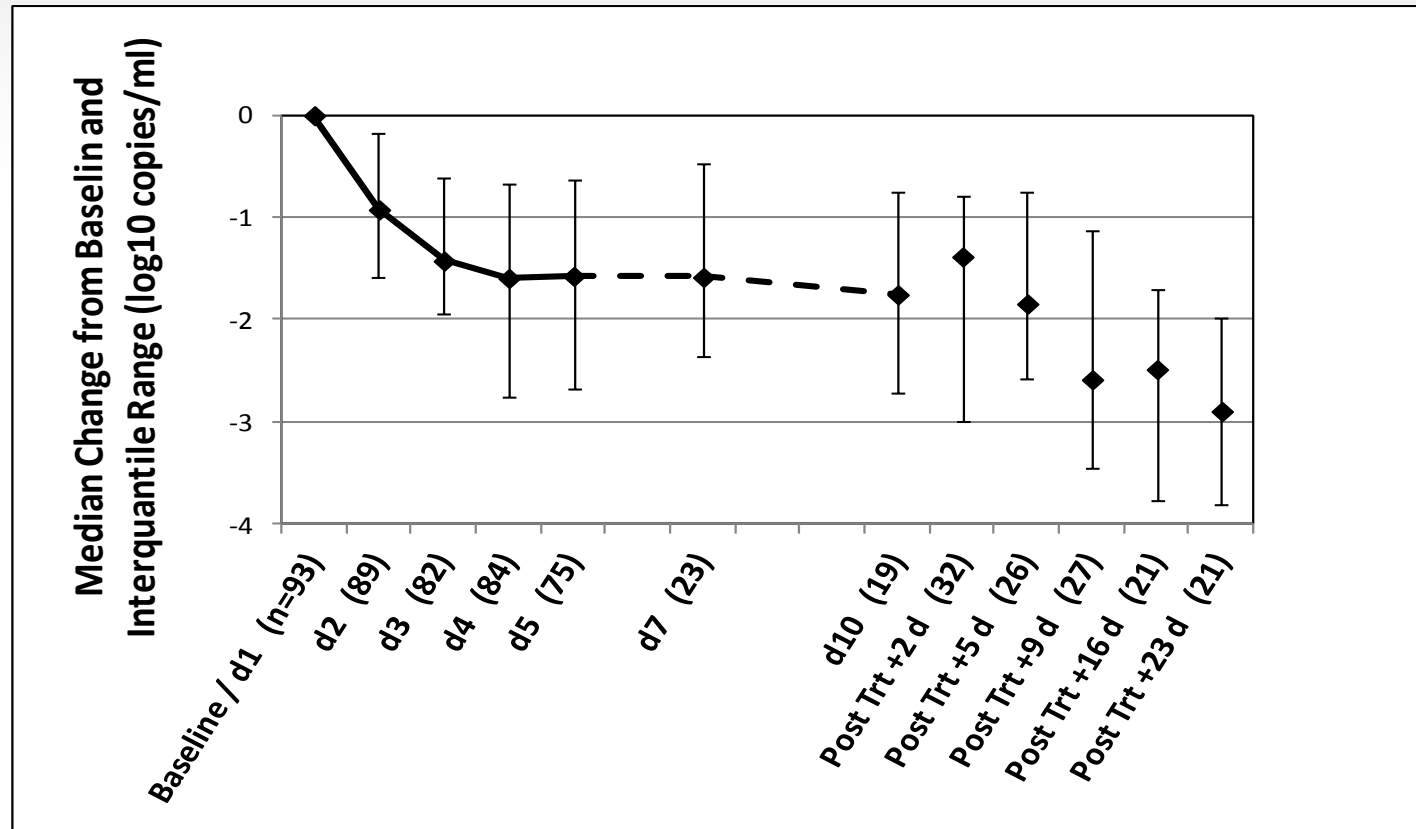
- Multicenter **open-label, single-arm Phase II study** : IVZ 600 mg twice daily for 5 days (extend up to 10 days)
- 130 adult subjects enrolled (November 2009 to September 2011)
- 87 subjects received IVZ for 5 days or less; 43 subjects received IVZ for 6-10 days (80% of subjects received oseltamivir prior to study entry)
- **14- and 28-day mortality**: 13% and 17% (respiratory failure, sepsis, pneumonia, multi-organ failure [No deaths related to zanamivir])

	Zanamivir ≤5 days (N=87)	Zanamivir >5 days (N=43)	Total N=130
Duration of hospitalization (Days) n Median [Min, Max]	87 9 [1, 83]	43 24 [6, 133]	130 15 [1, 133]
Duration of ICU Stay (Days) n Median [Min, Max]	68 8 [1, 67]	40 18.5 [3, 104]	108 11.5 [1, 104]

Marty, JID 2014

We would like to thank all investigators and study personnel involved in Study 14422076.

Intravenous Zanamivir in hospitalized adults with influenza



qPCR viral load determination in subjects positive at baseline

Marty, JID 2014

Intravenous Zanamivir in hospitalized adults with influenza

	Zanamivir ≤5 days (N=87)	Zanamivir >5 days (N=43)	Total N=130
Ventilation status at baseline^a			
ECMO ^a , n (%)	2 (2)	1 (2)	3 (2)
Endotracheal mechanical ventilation, n (%)	34 (39)	26 (60)	60 (46)
Ventilation status at any time during study			
ECMO, n (%)	2 (2)	2 (5)	4 (3)
Endotracheal mechanical ventilation, n (%)	39 (45)	35 (81)	74 (57)

Marty, JID 2014

Therapeutic antibodies

- Recent advances enabling the cloning of human Ig G genes have proven effective for discovering monoclonal antibodies with therapeutic potential
- Few candidates from numerous antibody-secreting plasma cells or plasmablasts
- Some antibodies elicit robust in vivo synergism when combined with oseltamivir
- Influenza-infected patients could benefit from antibodies treatment
- **Human RCTs coming**

Conclusions

- Medical needs for more effective therapy of severe influenza
 - Antiviral combinations in immunocompromised or seriously ill patients ?
 - Role of immunomodulatory interventions
- Antiviral drug choices and clinical use increasingly complicated by antiviral resistance issues
- Progress in development of intravenous NAIs and novel antivirals, including therapeutic antibodies
- If clinical course remains severe or progressive, despite ≥ 5 days of treatment, **should be continued until virus infection is resolved or clinical improvement**
- If oseltamivir unavailable or resistance suspected, treat with zanamivir

... OTHER VIRUSES

- Rhinovirus / Enterovirus : Pleconaril
- Human Adenovirus: Cidofovir
- Metapneumovirus: Rivabirin
- Varicella Zoster: Aciclovir

- Measles
- Hantavirus
- MERS-CoV



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