Influenza Antivirals for Pandemic H1N1: Overview

22 February, 2010

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Conflict of Interest Declarations- FG Hayden

- No financial COI since 2006
- Unpaid adviser (sometimes with access to confidential information) for Abbott, Adamas, Alios, Biocryst, Crucell, Nexbio, GSK, Inhibikase, Kirin, Respivert, Roche, Toyama, 3V Biosciences, Vaxinnate since 2008

Table R1: Use of antivirals for treatment of influenza

Population	Pandemic (H1N1) influenza virus 2009	Multiple co-circulating influenza A sub-types or viruses with different antiviral susceptibilities	Sporadic zoonotic influenza A viruses including H5N1
Mild to moderate uncomplicated clinical presentation			
At-risk[a] population	oseltamivir or zanamivir (04)	Zanamivir, or oseltamivir plus M2 inhibitor[b] (10)	oseltamivir or zanamivir
Otherwise healthy[c]	Need not treat (03)	Need not treat (09)	oseltamivir
Severe or progressive clinical presentation[d]			
At-risk[a] population	Oseltamivir (01) (zanamivir should be used where virus is known to be resistant to oseltamivir, or if oseltamivir unavailable) (02)	oseltamivir plus M2 inhibitor[b], or zanamivir (05,06, 07)	oseltamivir plus M2 inhibitor
Otherwise healthy[c]			

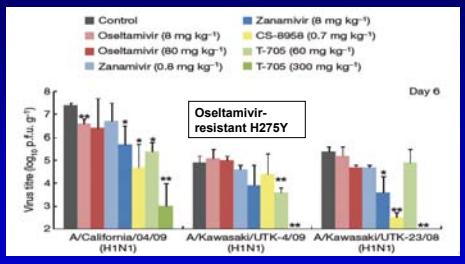
a Infants and children aged less than 5, the elderly (>65 years), nursing home residents, pregnant women, patients with chronic co-morbid conditions such as cardiovascular, respiratory or liver disease, diabetes, and those with immunosuppression related to malignancy, HIV infection or other diseases.
b Amantadine should not be used in pregnant women (recommendation 12).
c All those not covered by the at-risk definition above.
d See section 2 Case Description. Would include all patients requiring hospitalization.

WHO Guidelines for Pharmacological Management of Pandemic (H1N1) 2009 Influenza and other Influenza Viruses, August 09

Antivirals for Pandemic H1N1: *Outline*

- Therapeutic effectiveness of current agents
  - Pandemic H1N1
  - Hospitalized seasonal influenza patients
  - H5N1 illness
- Antiviral resistance (H275Y in N1)
- New antiviral agents and approaches
  - Clinical development candidates
  - Combinations

Activity of Neuraminidase Inhibitors and T=705 against Pandemic H1N1 Virus in Mice



- Treatments initiated at 1 hr post infection

Itoh et al. Nature published online 2009

Oseltamivir Treatment of Pandemic H1N1 Illness, Vietnam, May - July 2009

- 292 pandemic H1N1 rtRT-PCR positive patients
  - Oseltamivir (75 mg bid in adults) until negative
  - All mild illness, 1 with infiltrates
- Viral RNA detection from URT in 14% on day 5 and longer in 7% (up to day 12-14)
  - All culture negative after day 5
- Oseltamivir susceptibility testing
  - 3 who were RNA+ > 5 days had resistant virus with H275Y mutation on days 5, 6, and 11.

Hien TT et al. ProMED 8 August 2009 and 11 October 09

Risk Factors for Prolonged Pandemic H1N1 RNA Detection

- 350 pts with mild-moderate illness
- Early oseltamivir therapy was key variable.

Cao et al. NEJM 2009

Table 4. Risk of Viral Shedding for More Than 5 Days.*

Variable	Viral Shedding for More Than 5 Days (N=350)	
	Odds Ratio (95%CI)	P Value
Age		0.02
<14 yr	1.94 (1.13–3.31)	
≥14 yr	1.00	
Sex		0.02
Male	1.69 (1.07–2.66)	
Female	1.00	
Fever		0.82
Yes	1.10 (0.50–2.41)	
No	1.00	
Cough, sore throat, or sputum production		0.09
Yes	1.58 (0.93–2.70)	
No	1.00	
Interval from symptom onset to oseltamivir therapy		<0.001
>48 hr	4.46 (2.58–7.72)	
≤48 hr	1.00	

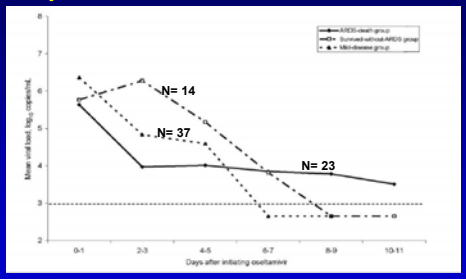
Detection of Infectious Pandemic H1N1 Virus

- 53 adults aged 17-24 yrs with pH1N1 illness
- Median duration of illness = 5.6 days (1-11)
- Isolation of pH1N1 virus > 5 days and after Sx resolution.

Witkop et al. Am J Prev Med 2009

	Samples collected (*n*)	Culture positive (*n*)	Proportion culture positive (*n*)
Temperature ≥100°F	53	46	87
Temperature <100°F	106	31	29
<24 hours symptom free or symptomatic	101	61	60
≥24 hours symptom free	58	11	19
Day from symptom onset (including day of symptom onset)			
1st (day of symptom onset)	7	6	86
2nd	21	20	95
3rd	23	20	87
4th	10	7	70
5th	22	9	41
6th	11	4	36
7th	29	7	24
8th	16	2	13
9th	13	1	8
10th–14th	20	0	0

Nasopharyngeal pH1N1 Viral RNA Levels in Hospitalized Patients Given Oseltamivir



- Slower decline in viral shedding was observed in all severe patients compared to mild disease.

To et al. CID 50: , 15 March 2010

Antiviral Use in Pandemic H1N1 Hospitalizations, April - June 2009, USA

Patient group	No. with data	Percent treated*	Median days from illness onset (range)	Percent treated ≤ 48 hr
Hospitalized	268	75%	3 (0 to 29)	39%
ICU admission	65	86%	6 (0 to 24)	23%
Fatal case	19	90%	8 (3 to 20)	0

*188 oseltamivir, 19 zanamivir; 27 oseltamivir + adamantane

Jain et al. NEJM, published 8 October 2009

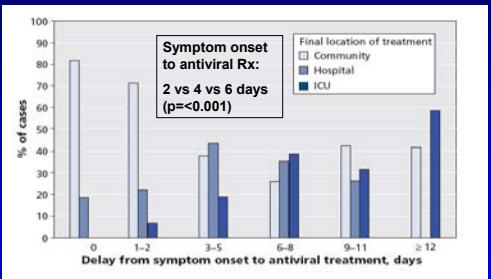
Table 4. Characteristics of Hospitalized Patients Who Were Not Admitted to an Intensive Care Unit (ICU) and Survived and Patients Who Were Admitted to an ICU or Died.*

Jain S, et al. NEJM. 2009 Oct 8. [Epub]

Characteristic	Patients Who Were Not Admitted to an ICU and Survived (N = 205)	Patients Who Were Admitted to an ICU or Died (N = 67)
Age		
Median — yr (range)	19 (21–80)	29 (1–86)
<18 Yr — no. (%)	98 (48)	24 (36)
Shortness of breath — no. (%)	104 (51)	58 (87)
Neurocognitive disorder — no. (%)	11 (5)	9 (13)
Neuromuscular disorder — no. (%)	10 (5)	9 (13)
Pneumonia seen on chest radiography on admission — no./total no. (%)	51/182 (28)	49/67 (73)
Antiviral treatment — no./total no. (%)		
Any — no./total no. (%)	144/203 (71)	56/65 (86)
≤2 Days after onset of symptoms — no./total no. (%)	62/139 (45)	13/56 (23)
Days from onset of symptoms to initiation — no. (range)	3 (0–29)	5 (0–24)
Antibiotic treatment — no./total no. (%)	144/195 (74)	62/65 (95)
Corticosteroid treatment — no./total no. (%)	57/183 (31)	29/56 (52)

* For all variables listed here, the comparisons between hospitalized patients who were not admitted to an ICU and who survived and patients who were admitted to an ICU or died were significant on bivariate analysis (P<0.05). The chi-square test was used to compare categorical variables, and the Wilcoxon rank-sum test was used to compare continuous variables. For additional clinical characteristics of the patients, see Table 2 in the Supplementary Appendix.

Days of Illness to Treatment and Outcomes, Manitoba, April – September 2009 (N = 795)



Zarychanski et al. Canadian Med Asso J, 21 January 2010

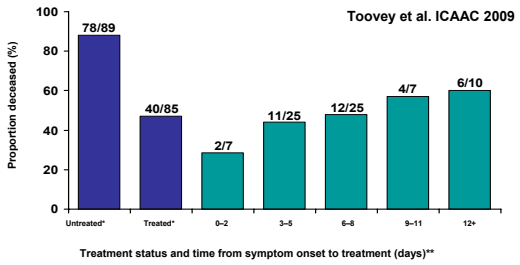
Oseltamivir Treatment in Hospitalized Patients with Season Influenza

Location, seasons	Patients	% Fatal cases: Oseltamivir	% Fatal cases: No Oseltamivir	Odds ratio (95% CI)
Toronto, 2005-06	Adults	3.9% (4/103)	10.1% (22/219)	0.21 (0.06-0.80)
Thailand, 2004-06	Adults + Children	1.6% (5/318)	13.0% (17/131)	0.14 (0.04-0.44)
Hong Kong, 2004-05	Adults	2.2%* (5/232)	5.6%** (7/124)	0.26 (0.08-0.87)

McGreer et al. CID 405:1568, 2007
Hanshaoworakul et al. PLOS ONE 4:e6051, 2009
Lee et al. CID 46:1323, 2008

* Oseltamivir ≤ 96 hrs after illness onset
** No oseltamivir or treated >96 hrs after onset

Case Fatality Rate by Time From Symptom Onset to Treatment With Oseltamivir



*1 patient has unknown survival and is excluded (untreated with any antiviral)
**Of 85 patients who received oseltamivir as treatment, 11 are excluded due to missing treatment start dates or symptom onset dates

Enteric absorption and pharmacokinetics of oseltamivir in critically ill patients with pandemic (H1N1) influenza

Robert E. Ariano PharmD, Daniel S. Sitar PhD, Sheryl A. Zelenitsky PharmD, Ryan Zarychanski MD, Amarnath Pisipati MSc, Stéphane Ahern MD, Salmaan Kanji PharmD, Jordi Rello MD, Anand Kumar MD

- 41 critically ill adults with suspected or confirmed pH1N1 who were admitted for ventilatory support
  - Plasma oseltamivir levels before gastric administration of the drug and at 2, 4,6, 9 and 12 hrs after the fourth or later dose.
- Oseltamivir was well absorbed enterically, and dosage of 75 mg twice daily achieved plasma levels that were comparable to those in ambulatory pts.

CMAJ 2010. DOI:10.1503/cmaj.092127

Characteristics of Antiviral Resistant Human Influenza Viruses- February 2010

Feature	Seasonal A(H3N2)	Seasonal A(H1N1)	Pandemic A(H1N1)	Avian A(H5N1)
Resistance (mutation)	M2I (S31N)	Oseltamivir (H275Y)	M2I (S31N)	M2I (S31N)*
Efficient H2H transmission	Yes	Yes	Yes	No
Virulence	Yes	Yes	Yes	Yes
Genetic stability	Yes	Yes	Yes	Yes
Competes with wild type	Yes	Yes	NA	NA

*Varies by clade.

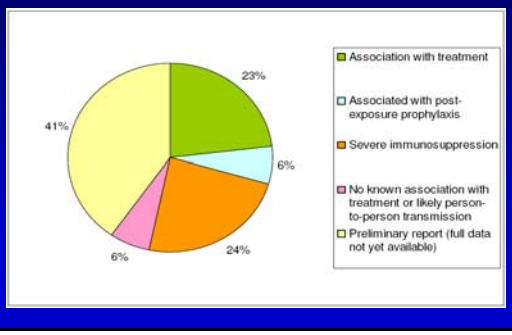
Influenza Antiviral Resistance, 2008-2009: *General Comments*

- In vitro resistance to M2Is (S31N) or oseltamivir (H275Y in N1) is high-level and confers clinical resistance (i.e., lack of in vivo effectiveness).
- M2I cross-resistance to entire M2I class, whereas NAI resistance is drug, influenza virus, and mutation specific.
  - Zanamivir inhibitory for N1 viruses with H275Y
- Recent resistant variants show no obvious reductions in virulence or transmissibility.
  - Outbreaks in healthcare facilities
  - Severe, sometimes fatal illness in at-risk patients

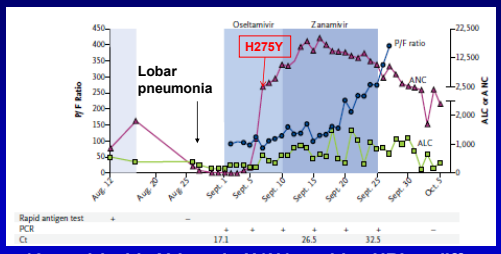
Oseltamivir Resistance in Pandemic H1N1

- Most sporadic, geographically dispersed detections
  - Clusters but no sustained community spread to date
  - 190 among >15,000 tested to 6 Jan 2010
  - All with H275Y mutation; no reassortment with seasonal H1N1
- Treatment - especially in immuncompromised hosts receiving prolonged therapy
- Those failing PEP (75 mg once daily)
- Non-drug recipients
- Most mild, self-limited illnesses
  - Except children and immunocompromised hosts

Oseltamivir Resistance in Pandemic H1N1, WHO Reports to 17 Feb 2010 (N=248)



IV Zanamivir for Oseltamivir-Resistant Pandemic H1N1 in Immunocompromised Host



- 10 yo girl with ALL and pH1N1 positive URI → diffuse pneumonia and mechanical ventilation → recovery

Gaur et al. NEJM, published online 23 December 2009

Oseltamivir-Resistant Pandemic H1N1 Cluster, Vietnam, July 2009

- Cluster of 7 oseltamivir-resistant pH1N1 cases (all H275Y) linked to a 42-hr train journey in July
  - 6/10 seated in same carriage had RT-PCR+ illness (2 others non-symptomatic; 2 no follow-up).
  - 1 with RT-PCR+ illness in another carriage
  - No prior oseltamivir or exposure, but all 7 given oseltamivir Rx for illness
- Most viral RNA negative by day 6 of illness
  - One positive to day 9 of illness with H257Y

Mai et al. NEJM, publisehd 7 January 2010

Clusters of Oseltamivir-Resistant Pandemic H1N1 in Immunocompromised Hosts

- Duke University Hospital, Oct - Nov 09
  - 4 adults aged 43 - 67 years, all severely immuno-compromised status; 3 fatalities
  - Same ward with illness onsets in a 2-week period
  - H275Y mutation identified in 3 before oseltamivir Rx
- University Hospital of Wales, Cardiff, Nov 09
  - 8 patients with underlying haematological malignancies; no fatalities
  - H275Y treatment-induced in 2 cases
  - At least 4 patients contracted the resistant virus through person-to-person transmission.

http://www.dukehealth.org/health_library/news/cdc_confirms_four_new_cases_of_oseltamivir_tamiflu_resistant_h1n1;http://www.hpa.org.uk/web/HPAwebFile/HPAweb_C/1259152327913; http://194.74.226.162/web/HPAwebFile/HPAweb_C/1259151913699

Oseltamivir Antiviral Resistance: *Comments*

- Oseltamivir-resistant pandemic H1N1 2009 viruses are transmissible and can replicate and cause illness in healthy people in the absence of selective drug pressure.
  - Capable of causing severe illness and fatalities in high risk patients, especially immunocompromised hosts
- Dual M2 and NAI resistance in some pH1N1 isolates
  - If suscepted or proven oseltamivir resistance, zanamivir is drug of choice
  - Inhaled zanamivir (Relenza) for PEP or early therapy
  - Intravenous zanamivir for serious illness

Investigational Anti-Influenza Agents

- NA inhibitors (NAIs)
  - Peramivir (IV)
  - Zanamivir (IV)
  - A-315675 (oral)
- Long-acting NAIs (LANIs)
  - CS8958/R-118958 (topical)
  - Flunet® (topical)
- Conjugated sialidase
  - DAS181 (topical)
- Protease inhibitors
- Cationic airway lining modulators (iCALM)
- HA inhibitors
  - Cyanovirin-N
  - Sialyl-glycopolymer
  - Arbidol (oral)
- Polymerase inhibitors
  - Ribavirin (oral, IV, inhaled)
  - Viramidine (oral)
  - siRNA (IV, inhaled)
  - T-705 (oral)
- Antibodies (anti-HA, NA, M2)
- Interferons

Selected Investigational Anti-Influenza Agents in Clinical Development- January 2010

Agent	Target	Sponsor	Route	Development phase
Zanamivir	NA	GSK	IV	Phase 2 + eIND
Peramivir	NA	Biocryst, Shionogi	IV	Phase 3 + EUA (licensed Japan)
Laninamivir (CS-8958)	NA	Biota, Daiichi-Sankyo	Inhaled	Phase 3
Favipiravir (T-705)	Polymerase	Toyama	Oral	Phase 2 → 3
DAS181	HA receptor	Nexbio	Inhaled	Phase 1 → 2

Comparative Pharmacology of Neuraminidase Inhibitors in Adults

Drug	Route	Dose	Cmax (ng/ml)	Cmin (ng/ml)	Plasma T1/2 (hrs)
Oseltamivir	PO	150 mg q 12 hr	~380-600	~280	6-10
Zanamivir	IV	600 mg q 12 hr	32-39,700	340-490	1.5-2
Peramivir	IV	600 mg	~43,800	~70	8-21

NA Inhibitor Resistance Profiles

NA mutation	NA type/ subtype	Susceptibility in the NAI assay (fold Δ)			
		Oselt	Zana	Peram	CS-8958
E119V	A/N2	R (>50)	S (1)	S (1)	S (1)
R292K	A/N2	R (>1000)	S (1-25)	R (40-80)	S (1)
H275Y	A/N1	R (>300)	S (1)	R (80->100)	S (2)
D198N	B	R (9)	I (9)	S (5)	?*

Mishin et al. AAC 49:4516, 2005; Wetherall et al. AAC 41:742, 2003; Yamashita et al. AAC 53:186, 2009

*IC50 value ~ oseltamivir and zanamivir in 1 study

Summary of Recent Antiviral Clinical Trials

- Uncomplicated influenza
  - Peramivir: single IV dose (300 or 600 mg) superior to placebo and comparable to 5 days of oseltamivir in adults
  - Laninamivir (CS-8958): single inhaled doses of 20 mg or 40 mg comparable to 5 of day oseltamivir in adults and children
  - Favipiravir (T-705): higher doses comparable to oseltamivir in adults
- Hospitalized adults
  - Peramivir: multiple IV doses comparable to oseltamivir in hospitalized adults (phase 2)

Combination Antiviral Therapies in Influenza

Combinations Evaluated in Animal Models	Combinations Tested or Under Evaluation in Humans	Future Considerations for Use in Combinations
Amantadine + ribavirin	Amantadine + oseltamivir*	Other NAI (peramivir, laninamivir
Amantadine + oseltamivir	Oral rimantadine + nebulized zanamivir	Polymerase inhibitor (favipiravir)
Rimantadine + oseltamivir	Oseltamivir + zanamivir	Sialidase inhibitor (DAS181)
Oseltamivir + ribavirin	Oseltamivir + T-705*	Antibody therapies
Oseltamivir + T-705	Amantadine + ribavirin + oseltamivir	Interferons
Amantadine + interferon + thymosin alpha		Immunomodulators

* Pharmacokinetic and safety study only

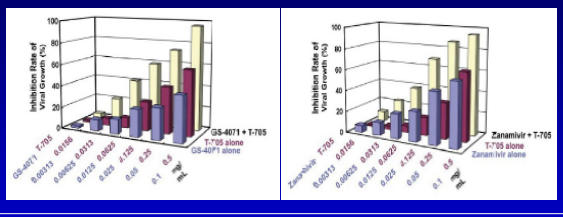
ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, May 2009, p. 2120–2128 Vol. 53, No. 5
0066-4804/09/$08.00+0 doi:10.1128/AAC.01012-08

Effects of Double Combinations of Amantadine, Oseltamivir, and Ribavirin on Influenza A (H5N1) Virus Infections in Cell Culture and in Mice[▽]

Donald F. Smee,* Brett L. Hurst, Min-Hui Wong, Kevin W. Bailey, and John D. Morrey
Institute for Antiviral Research, Department of Animal, Dairy, and Veterinary Sciences, Utah State University, Logan, Utah

- If virus M2 inhibitor susceptible, then synergistic interactions in vitro and ↑ survival in mice when combined with oseltamivir or ribavirin.
- If virus M2 inhibitor resistant, no benefit to use in combination with oseltamivir or ribavirin.
- Oseltamivir and ribavirin show primarily additive interactions in vitro and in murine model.

T-705 and NAI Combinations In Vitro



- In mice the oral combination of T-705 and oseltamivir showed dose-related additive to synergistic survival benefits for H1N1, H3N2, and H5N1 viruses

Smee et al. Antiviral Res 83:A37, 2009

Meta-Analysis: Convalescent Blood Products for Spanish Influenza Pneumonia: A Future H5N1 Treatment?

Thomas C. Luke, MD, MTMH; Edward M. Kilbane, MD, MPH; Jeffrey L. Jackson, MD, MPH; and Stephen L. Hoffman, MD, DTMH

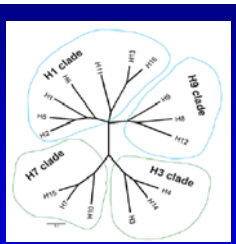
17 October 2006 | Volume 145 Issue 8 Annals of Internal Medicine

- Literature review for reports of using convalescent blood products in treating pneumonia patients hospitalized in 1918-20
  - 8 studies; total of 336 treated patients
  - 1,219 controls received supportive care
  - None blinded, randomized, or placebo-controlled
- Overall mortality reduced from 37% to 16% (difference 21%; 95% CI, 15% - 27%).
  - Benefit if treated ≤ 4 days after pneumonia Dx

OPEN ACCESS Freely available online PLoS one

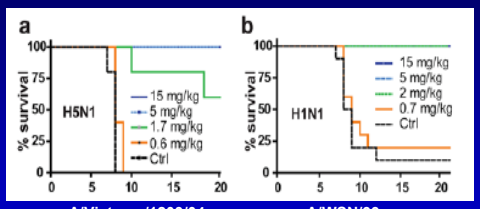
Heterosubtypic Neutralizing Monoclonal Antibodies Cross-Protective against H5N1 and H1N1 Recovered from Human IgM+ Memory B Cells

- Panel of 13 moAbs recovered from combin-atorial display libraries
- Binding to hydrophobic pocket region in the stem domain of different HA subtypes within H1 and H9 clades



Throsby et al. PLoS ONE 12:e3942, 2008

Anti-Influenza Activity of Human MoAb CR6261 in Mice

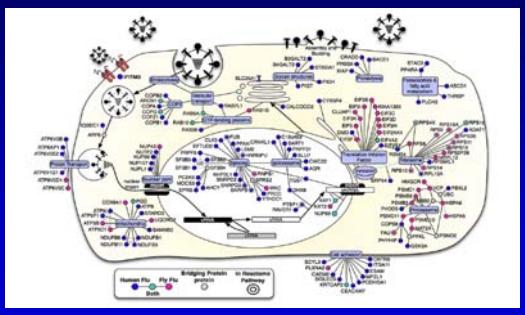


A/Vietnam/1203/04 A/WSN/33

- Dose-related prophylactic effect against lethal challenge
- Therapeutic effect up to 4 days p.i.

Throsby et al. PLoS ONE 12:e3942, 2008

Influenza A Virus Host Cell Interactions



Brass et al. Cell 139:1243, 2009

NIAID Influenza Antiviral Development Workshop: New Generation

Division of Microbiology and Infectious Diseases (DMID),
National Institutes of Allergy and Infectious Diseases (NIAID),
National Institutes of Health (NIH),
Department of Health and Human Services (DHHS)
and
Biomedical Advanced Research and Development Authority (BARDA),
Office of the Assistant Secretary for Preparedness and Response, DHHS
Natcher Building, NIH Campus
Bethesda, Maryland 20892

March 26-27, 2009

Antivirals for Pandemic H1N1 Influenza

- Resistance to adamantanes but susceptibility to multiple NAIs + investigational drugs
  - Sporadic isolates resistant to oseltamivir (H275Y)
- Delayed time to treatment observed in severe and fatal illnesses
- Antiviral therapy especially important for:
  - Patients with progressive illness or pneumonia
  - Patients with underlying medical conditions
  - Pregnant patients
- Important progress in development of IV therapies, agents with novel actions, and combinations