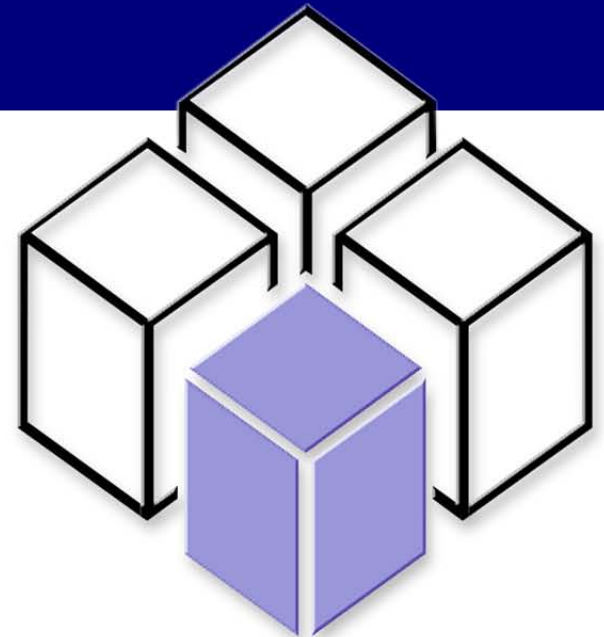


A Review of Clinical Experience in the Treatment of Severe 2009 H1N1 Influenza with Intravenous Peramivir Under an Emergency Investigational New Drug (IND) Program in the US

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**XII International Symposium on Respiratory Viral Infections, March 11-14, 2010
Chinese Taipei**



Background and Methods

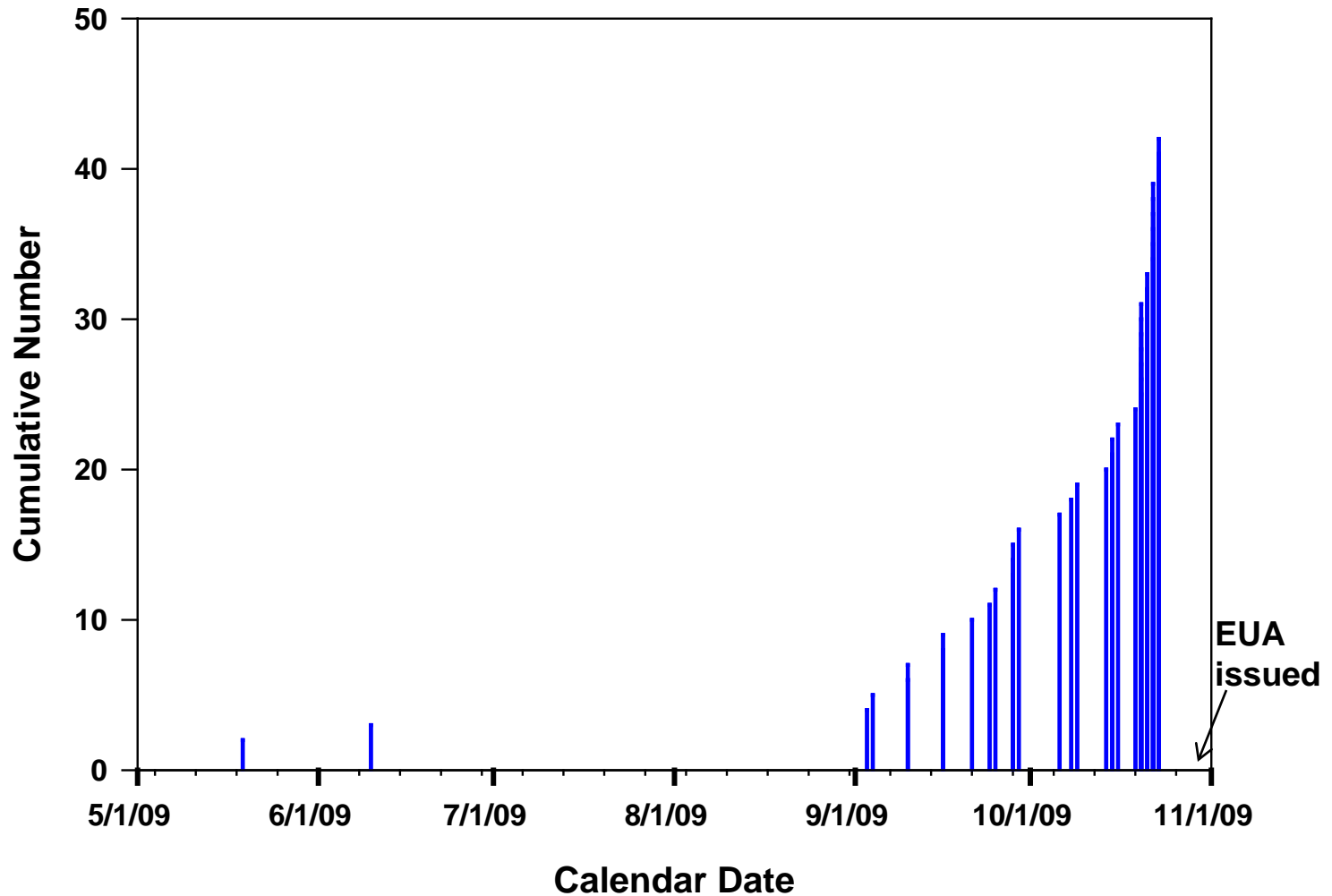
■ Background:

- Peramivir, is an investigational NAI in Phase 3 trials for treatment of influenza in hospitalized patients,
- During the 2009 H1N1 US emergency IV peramivir was made available under the FDA Emergency IND (EIND) regulations,
- Prior to the US FDA Emergency Use Authorization (10/23/09), peramivir was requested for 42 patients in the US under the EIND procedure.

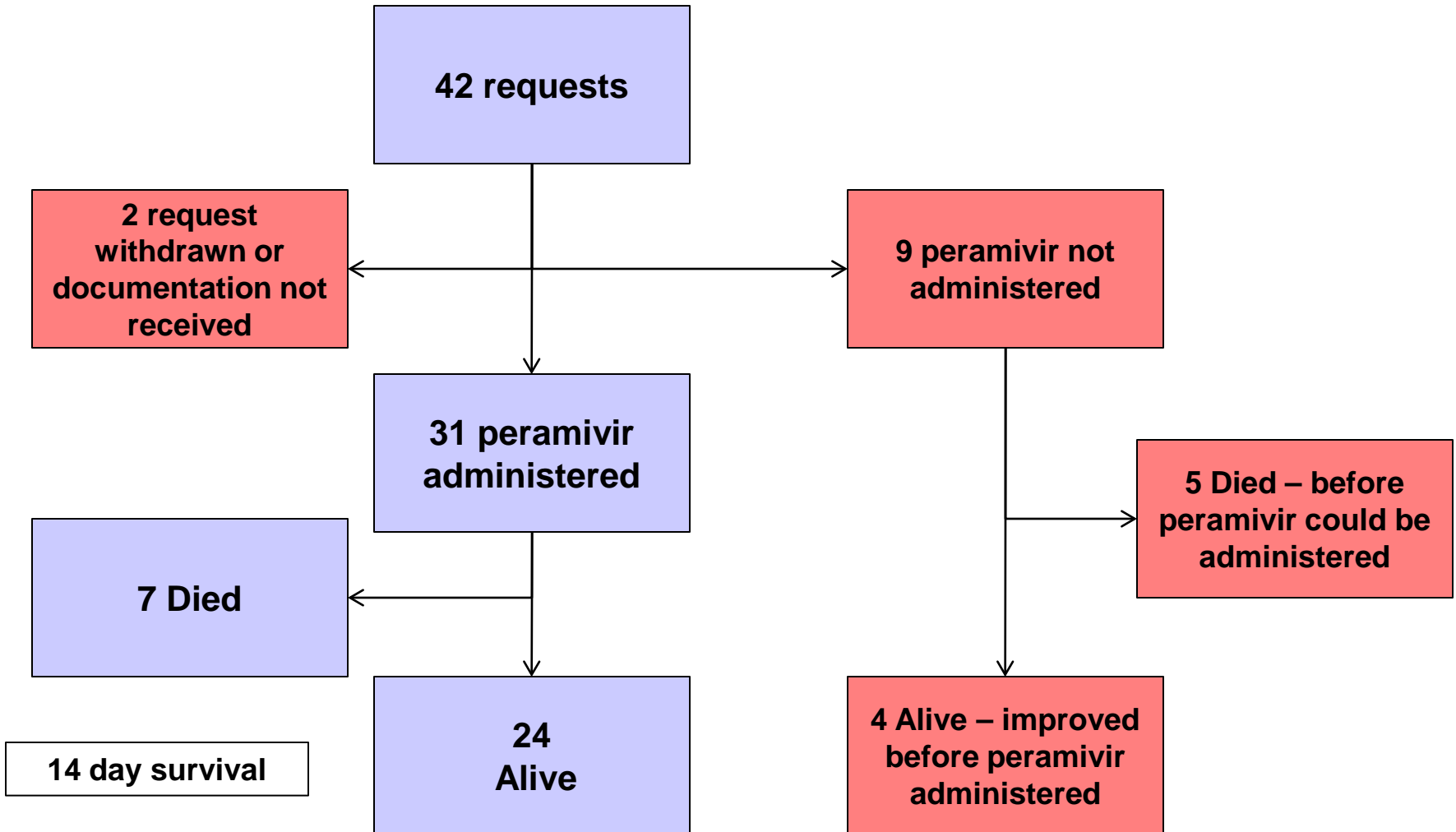
■ Methods:

- Clinical data including demographics, medical history, clinical severity information and outcome data were provided as part of the E-IND approval and follow-up process in each case,
- Peramivir drug levels were measured on request in some cases.

Great majority of EIND requests were received after 09/01/09



Peramivir i.v. E-IND series: May-October 2009



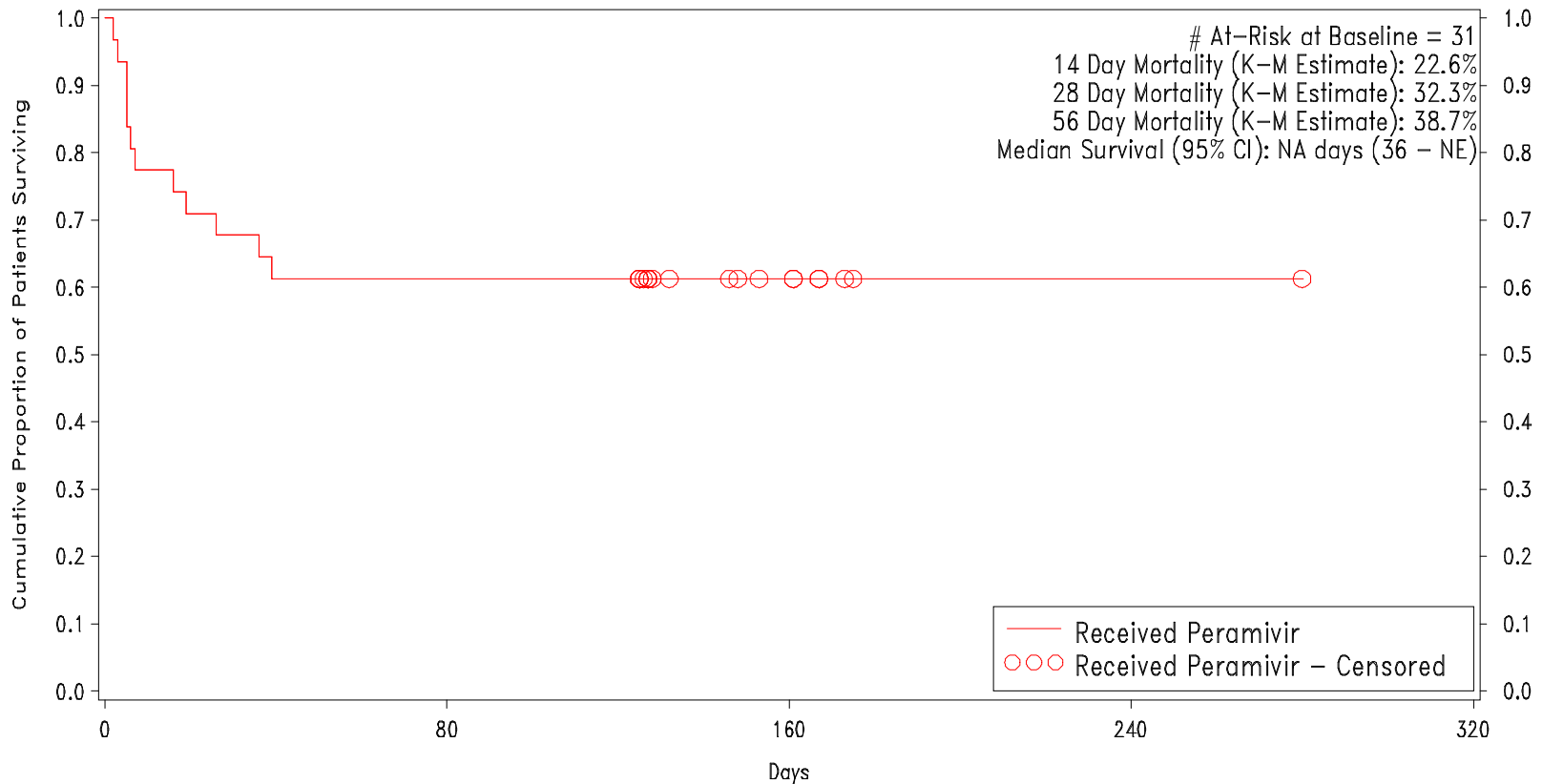
Peramivir i.v. E-IND patients: demographics and risk factors for severe disease

Parameter	Summary Information	Number with data
Age in years, median (min, max)	23.5 (0.3, 76.9)	31
Children defined as age ≤ 18 years, n/N (%)	11/31 (35%)	31
Sex (N)	13F, 18M	31
Race (N)	28 White, 2 African-American, 1 Asian	31
Ethnicity (N)	7 Hispanic, 24 Non-Hispanic	31
Body mass index [BMI] in kg/m^2 , median (min, max)	28 (12.5, 50.0)	31
Obesity defined as BMI ≥ 30 kg/m^2 , n/N (%)	11/31 (35%)	31
COPD or Asthma, n/N (%)	6/31 (19%)	31
Prior corticosteroids, n/N (%)	4/31 (13%)	31
Pregnant or post-partum	3/13 (23%)	13
Cancer, n/N (%)	2/31 (7%)	31
Diabetes, n/N (%)	2/31 (7%)	31
Solid organ transplant, n/N (%)	2/31 (7%)	31
Hematopoietic stem cell transplantation, n/N (%)	1/31 (3%)	31

Severity of illness in peramivir E-IND patients

Parameter	Summary Information
Pneumonia with respiratory failure, n/N (%)	31/31 (100%)
Mechanical ventilation required, n/N (%)	30/31 (97%)
High frequency oscillatory ventilation	6/30 (20%)
ECMO	7/30 (23%)
Vasopressor support required, n/N (%)	16/31 (52%)
Acute renal failure, n/N (%)	12/31 (39%)
Dialysis required, n/N (%)	9/31 (29%)
CRRT (CVVH/SLED/CAVHD)	7/9 (78%)
Acute heart failure, n/N (%)	6/31 (19%)
Liver failure	4/31 (13%)

Peramivir i.v. E-IND patients: Survival status through 56 days (K-M Estimate) N= 31



Patients who have not died are censored at the last date of contact

Peramivir i.v. E-IND patients: Risk factors for mortality

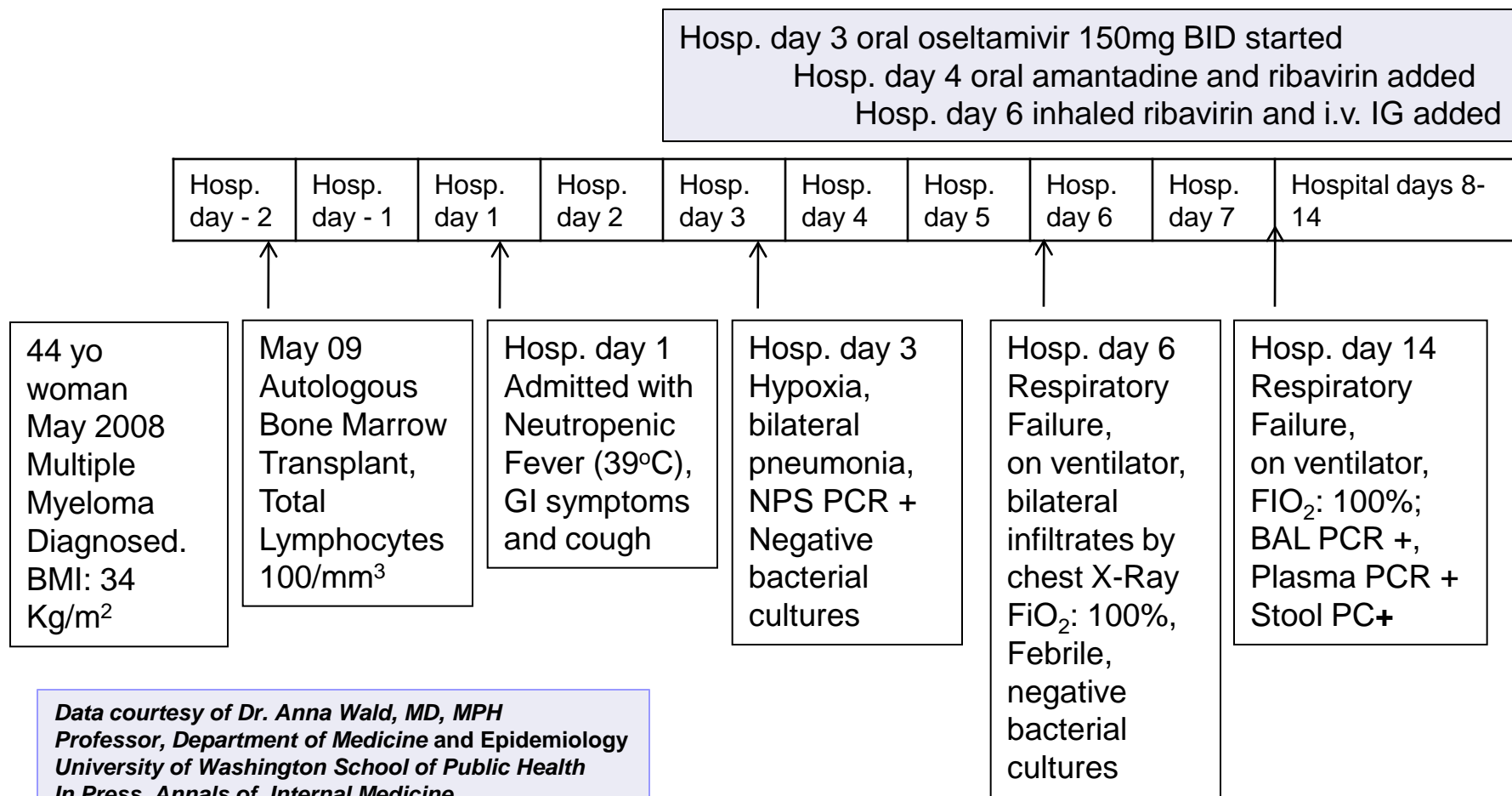
Parameter	Alive	Dead	P value*
Age (years) – Median (min - max)	26 (0.3-52)	34 (5.8-77)	0.25
< 18 years – n (%)	7/19 (37%)	4/12 (33%)	0.84
BMI – Median (min - max)	28.3 (12.5-44.2)	26.7 (15.9-50)	0.50
Sex (M/F, %F)	12/7 (37%)	6/6 (50%)	0.03
Pregnant or post-partum – n	3	0	N/A
Immune-compromise/Cancer/Lung Disease – n/N (%)	7/19 (37%)	6/12 (50%)	0.47
Vasopressor support needed	8/19 (42%)	8/12 (67%)	0.65
APACHE II Score** – Median (min - max)	20.0 (5.0, 36.0)	21.5 (16.0, 38.0)	0.13
Duration of illness before peramivir use (days)– Median (min - max)	12.0 (4.0, 27.0)	15.0 (8.0, 30.0)	0.35
Mean duration of hospitalization (days)	43	21	
Duration of hospitalization before peramivir use (days) – Median (min - max)	5.0 (1.0, 25.0)	15.0 (8.0, 30.0)	0.29
Duration of oral/inhaled NAI use before peramivir use (days) – Median (min - max)	4.0 (2.0, 23.0)	4.5 (2.0, 16.0)	0.92

*Calculated with logistic regression, **Calculated from data obtained when peramivir was requested

Rapid clinical deterioration is a consistent feature.

Case One

Clinical history and course prior to peramivir administration

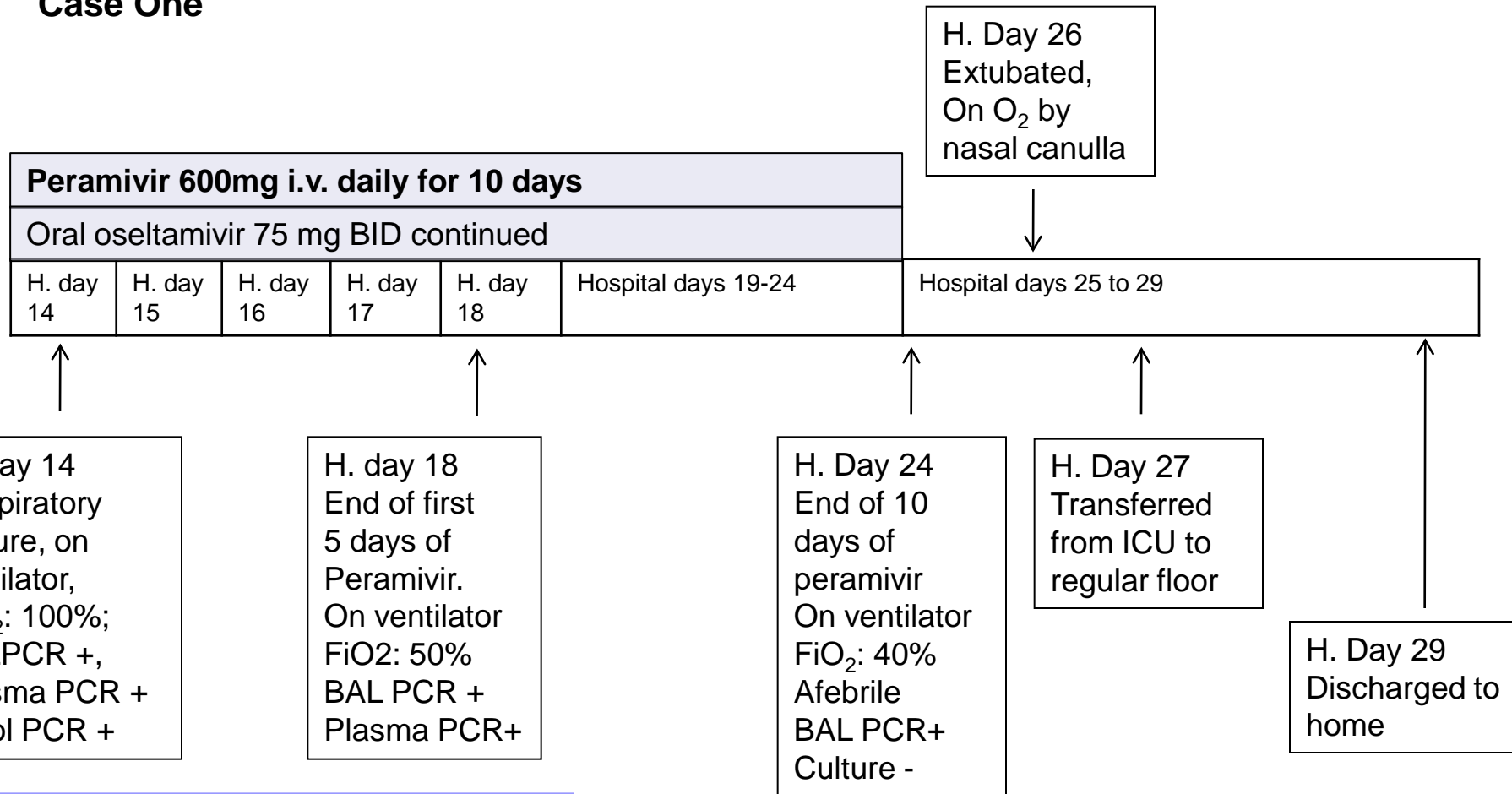


Case one – CXR at peramivir start



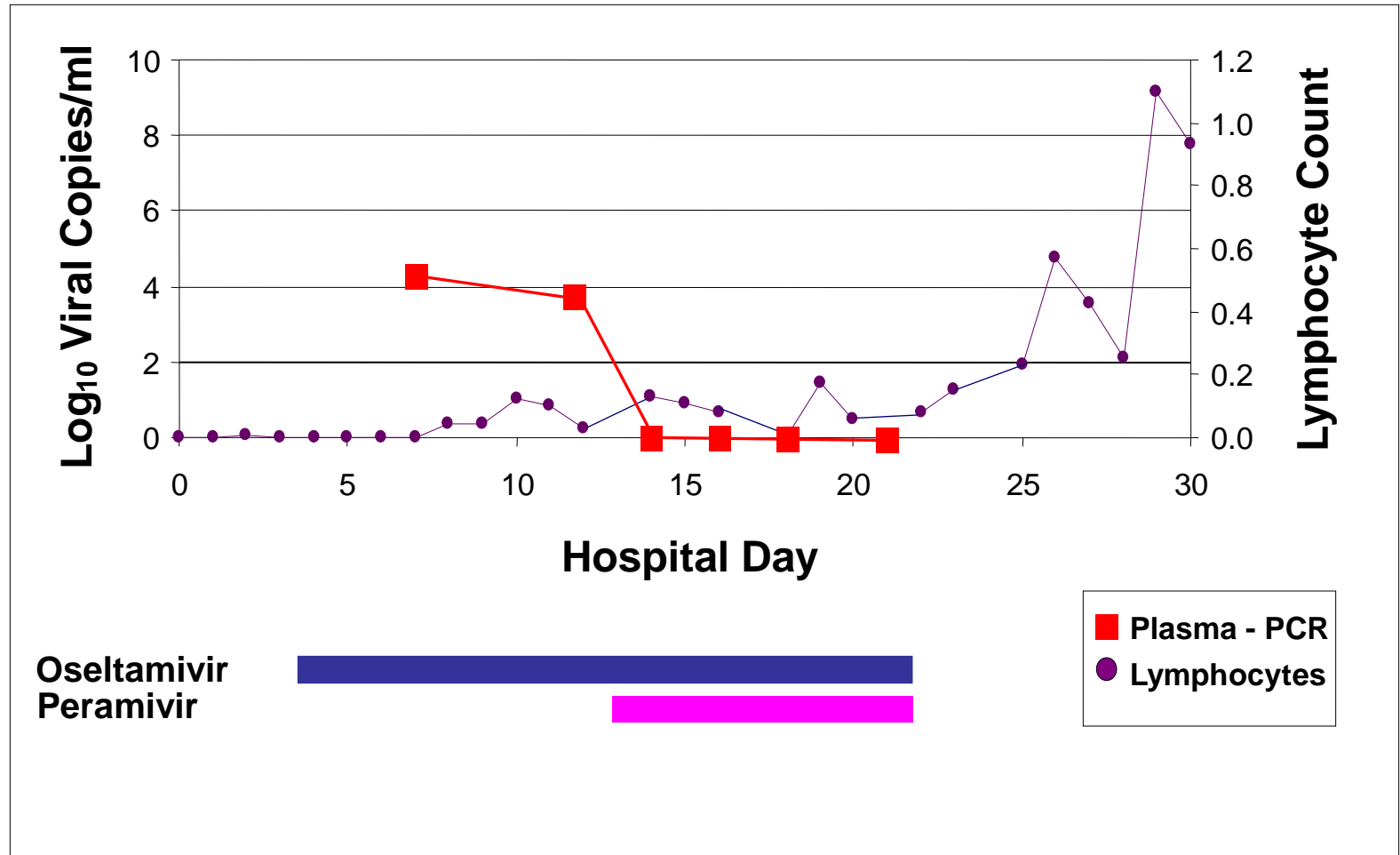
The patient's clinical course improved after administration of peramivir 600mg i.v. daily. Therapy was continued for 10 days.

Case One



Data courtesy of Dr. Anna Wald, MD, MPH
 Professor, Department of Medicine and Epidemiology
 University of Washington School of Public Health
 In Press, *Annals of Internal Medicine*

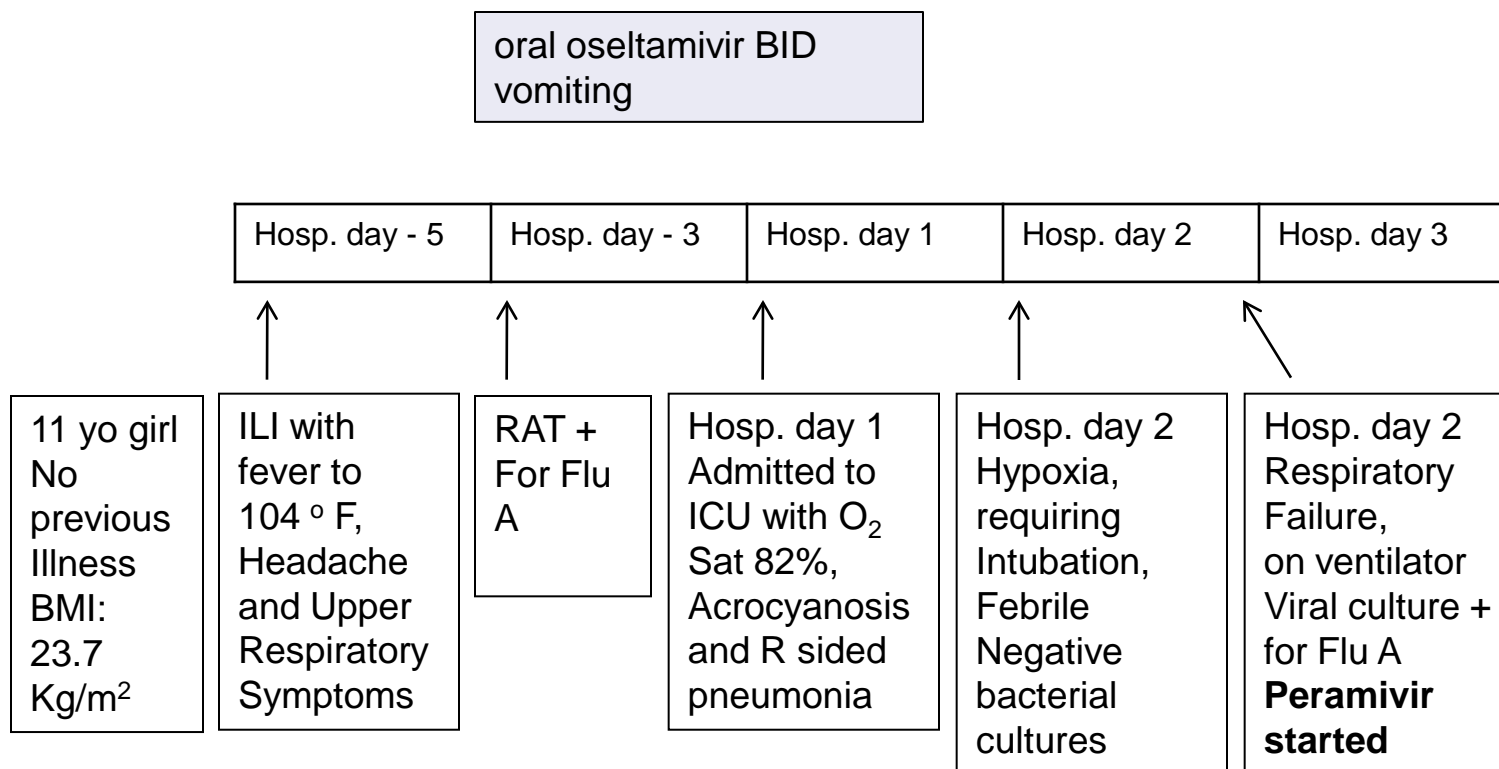
Case one - Patient improved with IV peramivir before lymphocyte recovery



Representative case in a previously healthy 11 year old girl.

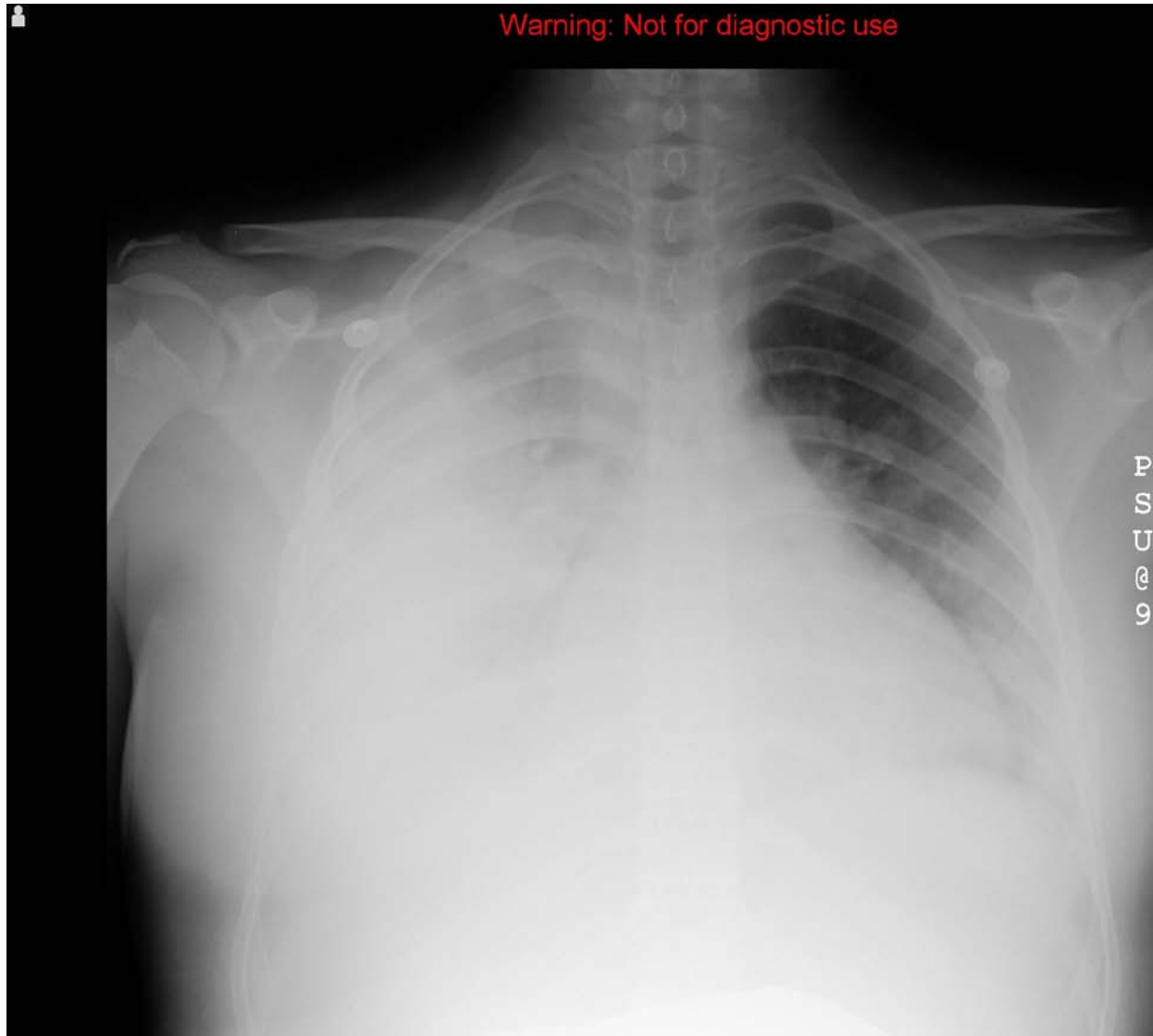
Case Eight

Clinical history and course prior to peramivir administration



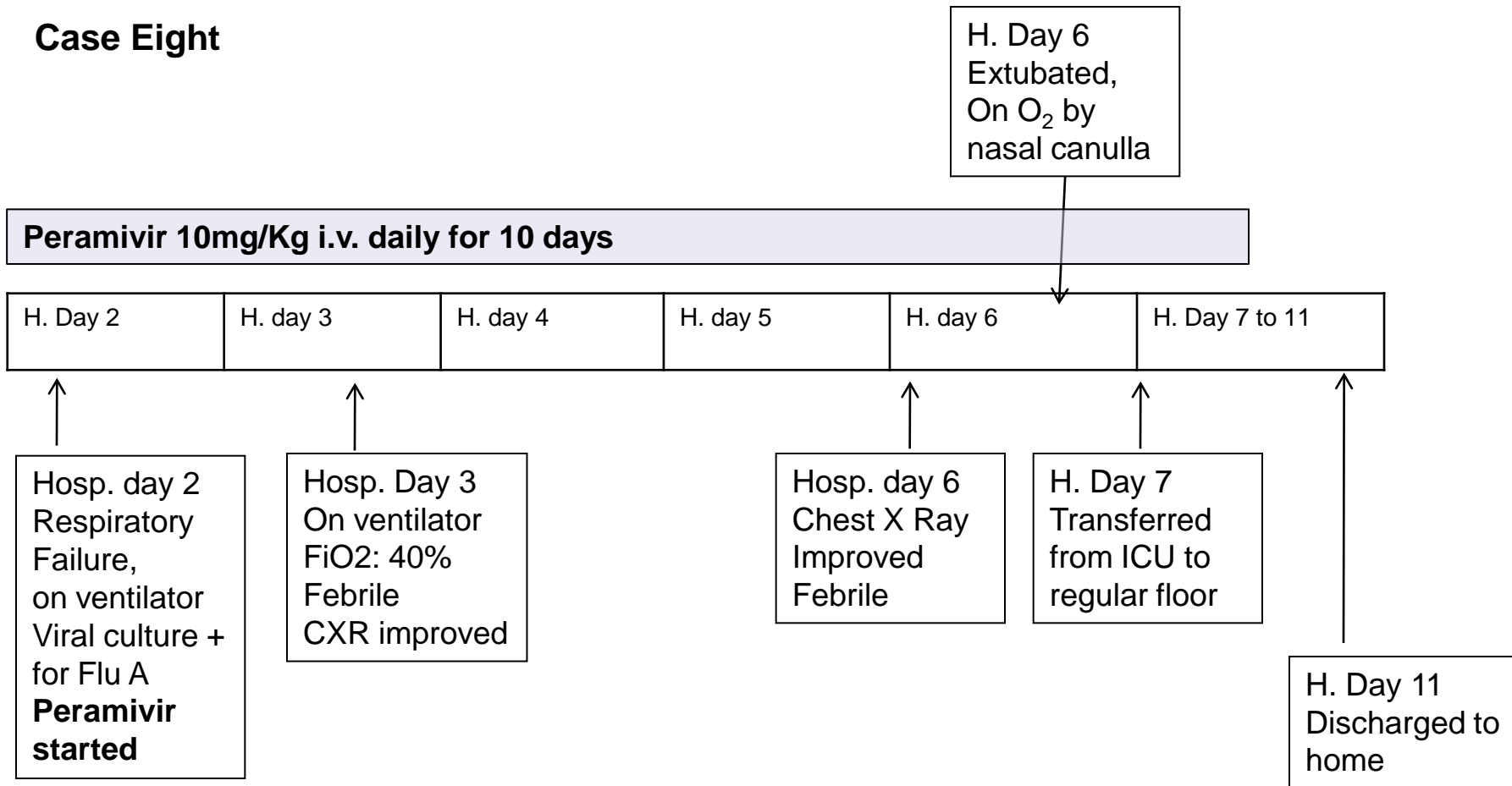
Data courtesy of Dr. Robert Armstrong, MD
San Jose California

Case eight - Admission CXR



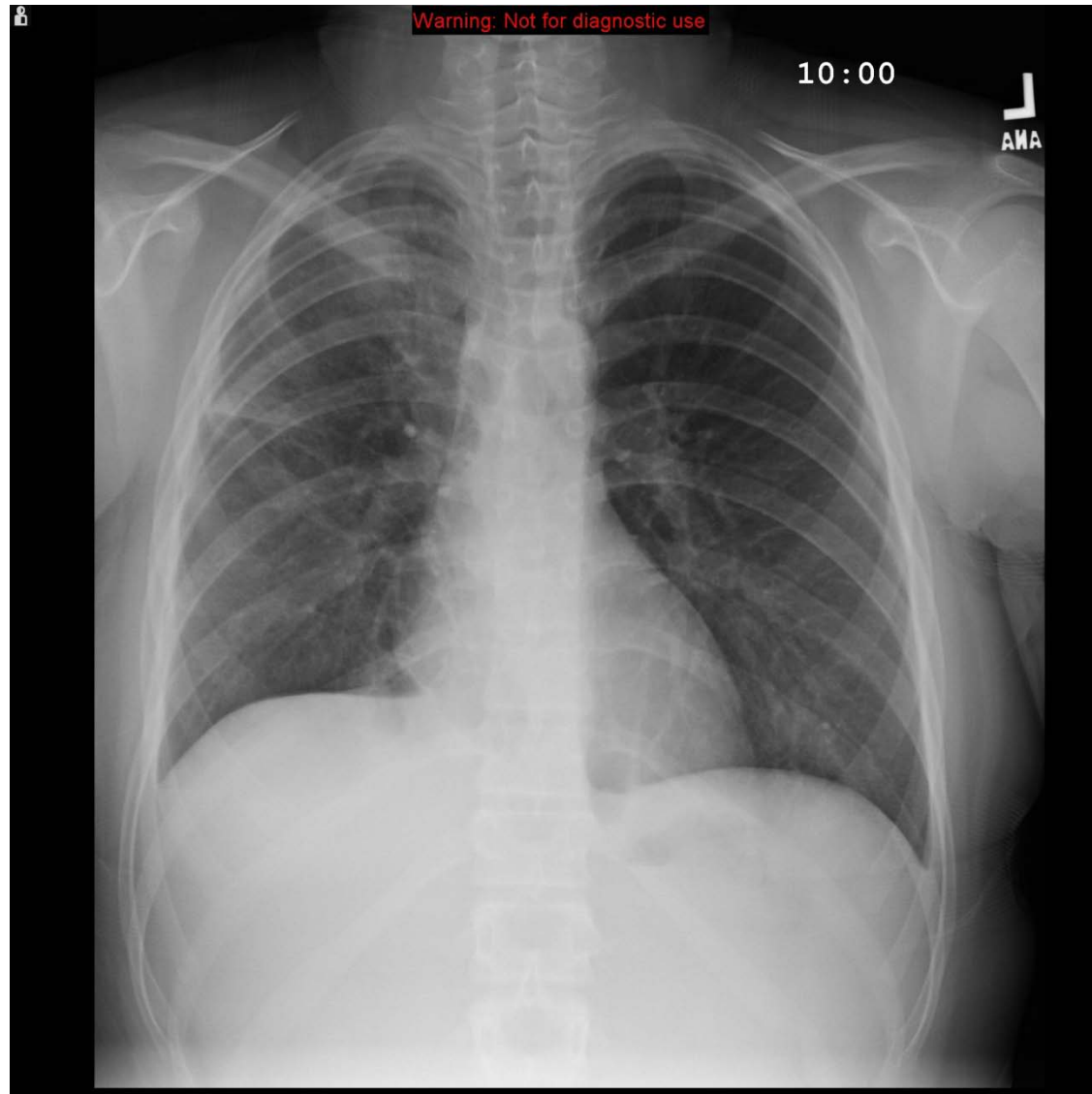
The patient's clinical course improved after administration of peramivir 10mg/Kg i.v. daily. Therapy was continued for 10 days.

Case Eight



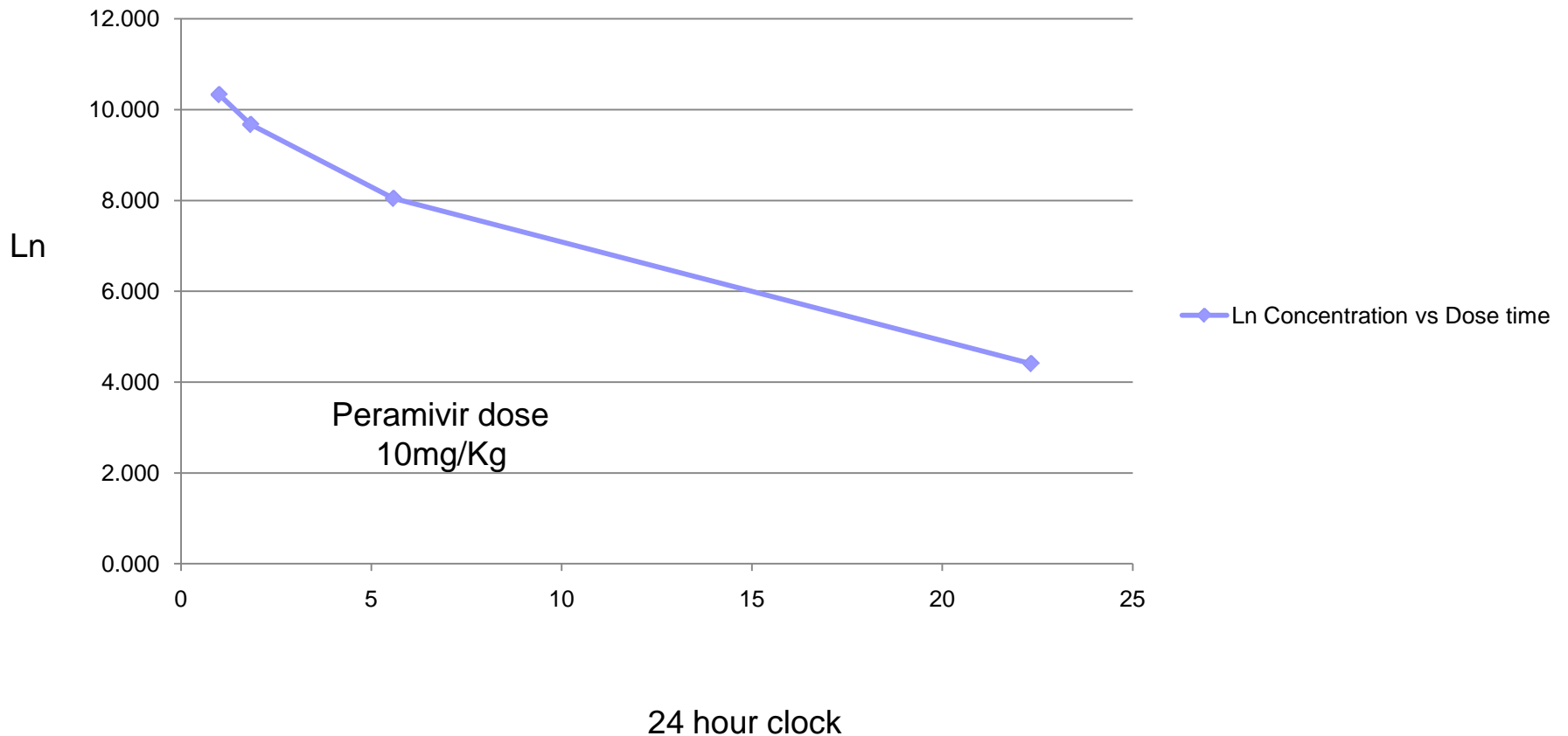
Data courtesy of Dr. Robert Armstrong, MD
San Jose California

Case eight - Chest radiograph on Discharge



Sparse peramivir PK sampling results in Case 8, an 11 year old girl, administered peramivir on a mg/kg weight basis

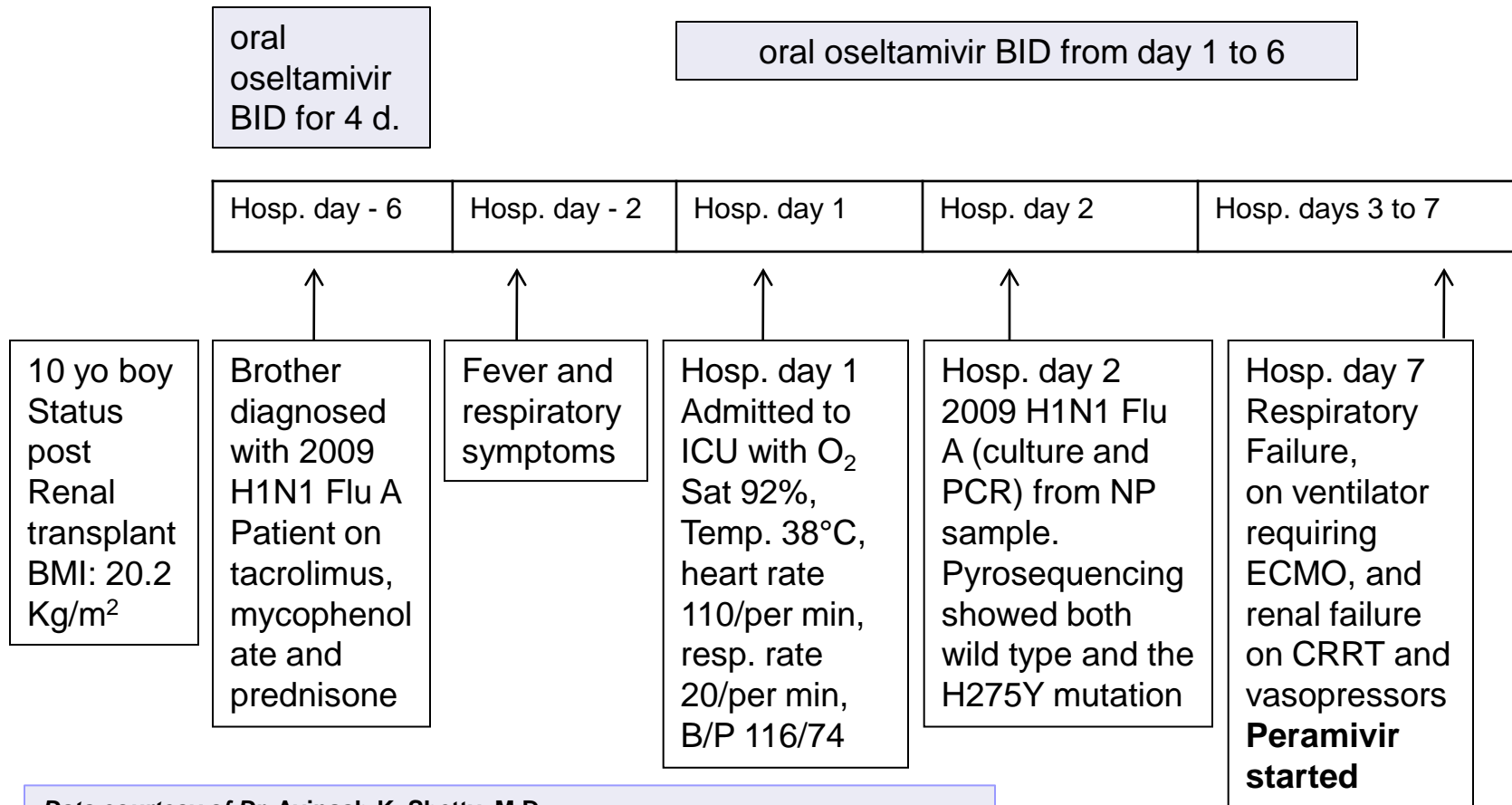
Ln Concentration vs Dose time



Oseltamivir-resistant 2009 H1N1 influenza pneumonia in a 10 year old boy post renal transplant treated with intravenous peramivir

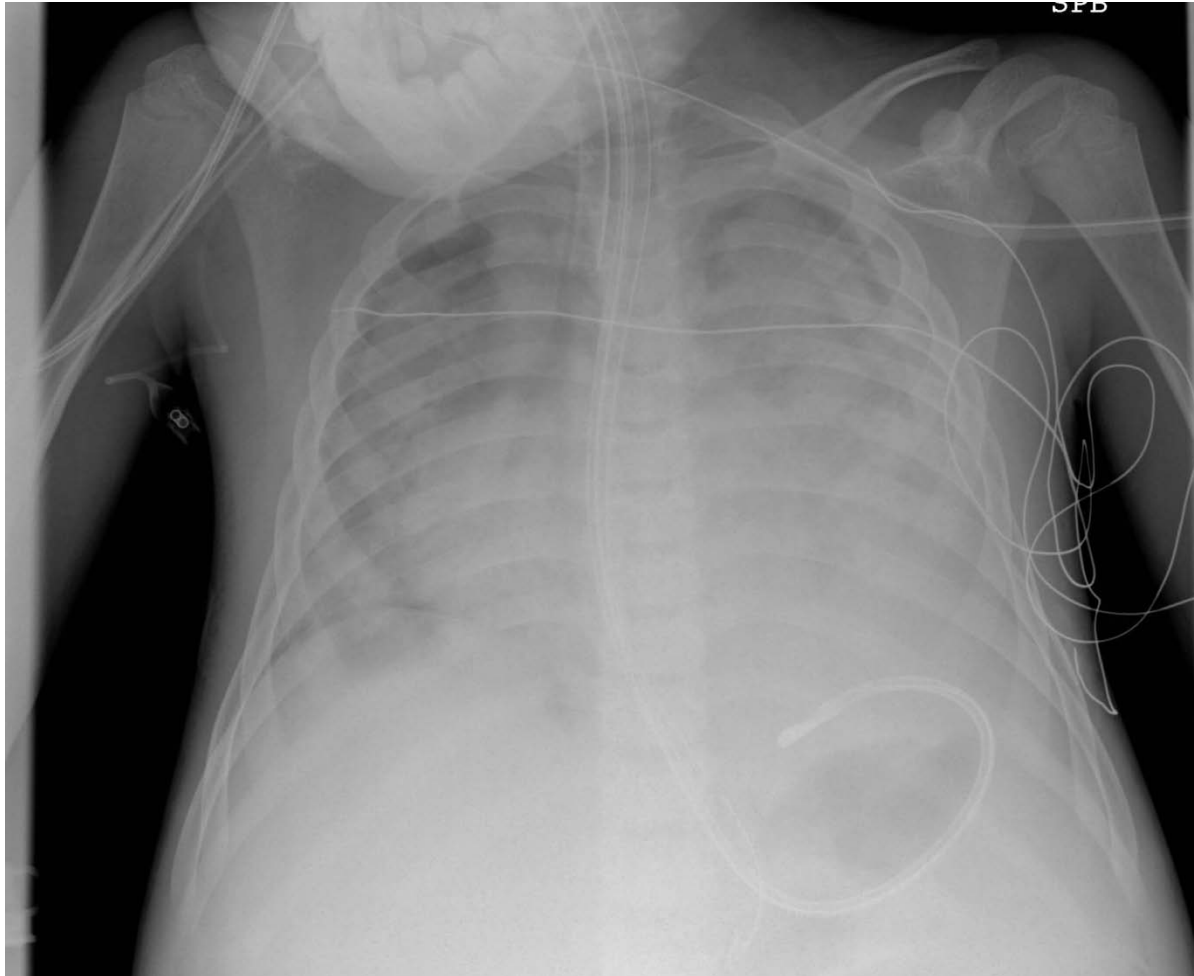
Case Ten

Clinical history and course prior to peramivir administration



Data courtesy of Dr. Avinash K. Shetty, M.D.,
 Pediatric Infectious Diseases,
 Wake Forest University Health Sciences and Brenner Children's Hospital,
 Winston-Salem, NC

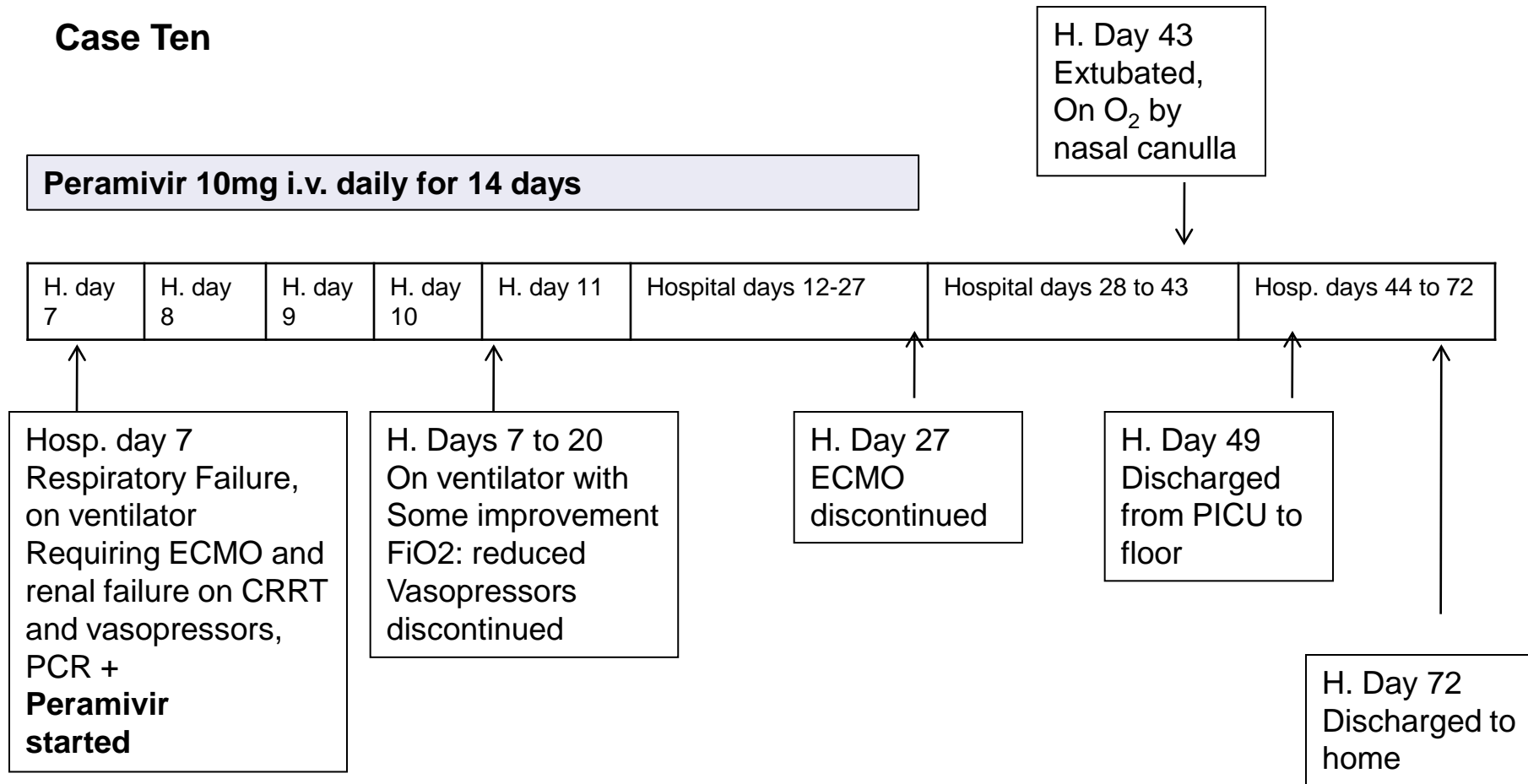
Case ten - Chest X ray on peramivir start.



The patient's clinical course improved after peramivir 10mg/Kg i.v. daily, adjusted by renal function. Treated for 14 days.

Case Ten

Peramivir 10mg i.v. daily for 14 days



Data courtesy of Dr. Avinash K. Shetty, M.D.,
Pediatric Infectious Diseases,
Wake Forest University Health Sciences and Brenner Children's Hospital,
Winston-Salem, NC

Conclusions

- Fifty eight percent of critically ill patients in this series were previously healthy.
- 2009 H1N1 disease in EIND cases: almost all had rapidly progressive viral pneumonia requiring ventilatory support.
- In almost all cases, the disease process progressed despite administration of oral antiviral medications.
- Peramivir treatment was delayed 1 to 15 days after hospital admission.
- Peramivir was generally well tolerated by these critically ill subjects.



Acknowledgements

- All participating investigators and patients who contributed to the EIND series

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- Back-up slides

Primary cause and timing of mortality for 12 patients who died

Primary cause of death	Days after hospitalization	Days after peramivir start
Pneumonia, Respiratory failure	53	38
Pneumonia, Multi-organ failure	16	15
Pneumonia, Sepsis, Encephalitis	11	4
ARDS, Multi-organ failure, Sepsis	5	3
Uncontrollable hemorrhage, DIC, Sepsis	33	18*
Bacterial pneumonia, Heart, Multi-organ failure	6	4
Pneumonia, Respiratory failure	15	15
Multi-organ failure, Sepsis, DIC	37	35*
Pneumonia, ARDS, MODS	6	4
Myocardial infarction, MODS, ARDS	11	2
Viral & Bacterial Pneumonia, ARDS	19	6
Pneumonia, Respiratory failure, CNS insult	34	25

*Medical support withdrawn per family request.

Sparse peramivir PK sampling results in Case 8, an 11 year old girl, administered peramivir on a mg/kg weight basis

Plasma Concentration (second dose)

