# Impact of Early Oseltamivir Treatment on Critically Ill Patients with 2009 Pandemic Influenza A


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## Background
- Pandemic AH1N1 surfaced late March 2009 and caused >18000 deaths per WHO reports
- Oseltamivir (Tamiflu) is a neuraminidase inhibitor used for the treatment of influenza in patients >1 year who have been symptomatic for no more than 2 days
- Jefferson et al (2014) did a systematic review of clinical study reports and RCTs to describe potential benefits and harms of oseltamivir in non-ICU patients.
- It shows that in prophylactic studies, oseltamivir reduces proportion of symptomatic influenza. In treatment studies, however, it modestly reduces the time to first alleviation of symptoms; but causes nausea, vomiting, and increases risk of renal and psychiatric syndromes
- Observational studies have reported that initiation of antiviral therapy <48hrs of illness onset was associated with reduced duration and intensity of clinical symptoms
- However, these observational studies only had a few ICU patients as subjects
- It had been unclear whether Oseltamivir has an impact on mortality in Critically Ill patients with 2009 H1N1

## Purpose
To investigate the relationship between the timing of antiviral administration and intensive care unit (ICU) mortality; and to determine whether early administration of oseltamivir affects the duration of mechanical ventilation (MV) and ICU length of hospital stay (LOS)

## Study design
- Prospective, Observational, cohort study of ICU patients
- 148 ICUs in Spain from April to December 2009

## Patient Population
- N= 657 patients
  - **Inclusion:**
    - Fever (> 38C)
    - Respiratory symptoms (cough, sore throat, myalgia, flu-like illness)
    - Acute respiratory failure requiring ICU admission
    - Microbiological confirmation of 2009 H1N1 infection
  - **Exclusion**
    - Children <15 yo
    - Patients with HCAP
  - Confirmed Case- acute respiratory illness with laboratory confirmed 2009 H1N1 infection identified by RT- PCR or viral culture
  - Effective antiviral therapy- received >4 doses of antiviral therapy after admission

## Intervention
- Nasopharyngeal swab, Lower respiratory secretions were obtained in intubated patients on admission
- Real time PCR (RT-PCR) was performed in accordance to CDC guidelines
- Oseltamivir was administered orally or by NGT at doses 150mg/24hr or 300mg/24hr, at discretion of physician
- 300 mg/24hr doses usually for obese and morbidly obese patients
- Groups:
  - **Early Treatment (ET)**- received treatment within 2days after onset of symptoms
  - **Late Treatment (LT)**- received treatment >2days after onset of symptoms
Multivariate analysis confirmed that early oseltamivir administration was independently associated with better survival rates (OR for death 0.44; 95% CI 0.21-0.87).

Baseline Characteristics

- Most patients are young (Mean age 44.7 +/- 14.6 years) and male
- APACHE II score 13.9 +/- 7.1; SOFA 5.6 +/- 3.6
- In MV patients:
  - ET and LT groups are comparable in age, severity of illness, number of quadrants infiltrated in CXR, vasoactive drugs due to shock, prone ventilation, high dose oseltamivir regimen
  - Asthma more frequent in ET

Results

- Patients with LT received a higher number of antibiotics than ET
- MV lasted 3 days longer in LT than in ET (13 vs 10 days, p=0.01)
- Both ICU and Hospital LOS higher in LT than ET (34.3% vs 21.5%; 95% CI 1.06-3.41)
- Higher ICU mortality in LT (23.1% vs 15.9, p=0.06)
- Early oseltamivir therapy was more frequently administered in survivors than in non-survivors (23.6% vss 13.9%, p=0.02)
**Conclusion**
- Large, multicenter trial (N=657, 148 hospitals)
- Observational, non-interventional, subjects were self-selected; Selection bias cannot be ruled out
- Propensity scores were calculated to reduce potential bias
- Clinical resolution endpoints not studied
- Safety endpoints not studied
- Mean duration of therapy is 10 days
- Excluded patients who received <4 doses, who have higher APACHE II and SOFA Scores
- Mean APACHE II and SOFA Scores for the general population studied are not really high mortality patients (~20% mortality)
- Early oseltamivir administration was associated with favorable treatment outcomes (mortality benefit, ICU LOS, MV duration) among critically ill ventilated patients with 2009 H1N1 virus infection
- ET is associated with a 3 day reduction in MV duration and 7 day reduction in Hospital LOS
- For mechanically ventilated patients in ICU, there is a mortality benefit, and decrease in total ICU LOS and MV duration for patients who had ET of oseltamivir.

**References**
3. Tamiflu package insert