

Postpandemic H1N1 influenza infection in ICU: Are we any wiser now?

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Since report of first two cases of human infection with a novel influenza A (H1N1) virus in the United States in April 2009 by Centers for Disease Control and Prevention, there were various studies (single center case series to multicenter) from across the globe published in the second half of 2009 itself, describing clinical and epidemiological characteristics of H1N1 confirmed critically ill patients. While most patients with H1N1 had a self-limited respiratory illness and were in younger age group (30s–40s years), there were many having severe influenza syndrome causing dyspnea or respiratory distress requiring ICU admission. Rapid progression to severe acute respiratory distress syndrome (ARDS), even in few hours in healthy young patients, leads to high case-fatality rate (15–40%). Highest mortality was reported from Mexico City hospitals, which faced early burden (March–May, 2009) and were unprepared for this epidemic.^[1]

In current issue of Indian Journal of Critical Care Medicine, Wiesen *et al.* compared clinical characteristics and outcome of H1N1 influenza confirmed ICU patients presented during 2013–2014 (postpandemic) with 2009–2010 (pandemic).^[2] In postpandemic group, patients were older (but certainly not elder) and were having higher prevalence of pulmonary and cardiac disease. This study highlighted still high mortality (41%) in the post pandemic group at their tertiary referral study center, though patients were having worse PaO₂/FiO₂ ratio during 1st week of mechanical ventilation and more patients needed vasopressors at admission, despite there were higher utilization of rescue therapies in form of prone ventilation, inhaled vasodilator therapy, extracorporeal membrane

oxygenation (ECMO), and even one patient underwent bilateral lung transplantation in the postpandemic group.

H1N1 virus mainly targets lower respiratory tract, and histopathological studies revealed features of diffuse alveolar damage including edema, hyaline membrane inflammation, and fibrosis. Extrapulmonary complications such as myocarditis, encephalopathy, increase creatine phosphokinase, and acute kidney injury have also been reported. Histologic examination of kidney shows presence of acute tubular necrosis, myoglobin pigment, and disseminated intravascular coagulation.

There are many risk factors for increased severity or complicated H1N1 influenza illness that have been identified in various studies. A systematic review and meta-analysis by Mertz *et al.* concluded that level for evidence is low for “any risk factor.”^[3] However, their result showed that elderly people, pregnant female in late

Access this article online

Website: www.ijccm.org

DOI: 10.4103/0972-5229.169323

Quick Response Code:



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How to cite this article: Gurjar M. Postpandemic H1N1 influenza infection in ICU: Are we any wiser now?. Indian J Crit Care Med 2015;19:633-5.

stage of pregnancy, postpartum period, obesity (body mass index >30), and presence of chronic underlying medical conditions, including immunosuppression, were at high risk for worse outcome; while age <18 years, certain ethnic group, or any sex were not associated with higher mortality.

As a severity assessment tool, pneumonia-specific scores including pneumonia severity index (PSI) score, CURB-65 score, and PIRO-CAP score have not shown good predictive ability for outcome, i.e., ICU mortality (area under the receiver operating characteristic curve for PSI, 0.72; CURB-65, 0.67; and PIRO-CAP, 0.64) in patients with H1N1 influenza at the time of ICU admission.^[4]

The current recommendation of oseltamivir therapy is to start within 48 h of onset of influenza symptoms and dosage is 75 mg twice daily for 5 days; as viral load has been found undetectable at 6 days after early oseltamivir initiation in mild cases. World Health Organization (WHO) recommends higher dose in critically ill patients, such as 150 mg twice daily for adults, and longer duration of treatment until clinical improvement or sequentially negative results for virus in respiratory tract is achieved. Zanamivir is the treatment of choice for all patients, where oseltamivir resistance is demonstrated or highly suspected. Recently, McQuade and Blair reviewed 6 studies regarding treatment with oseltamivir outside of labeled recommendation (i.e., effects of administering oseltamivir 48 h or more after the onset of influenza symptoms, administering the drug at double the standard dose, or continuing the therapy for more than 5 days) and found that ICU patients showed improved survival among those who received oseltamivir no later than 5 days after symptom onset and patients may also get benefit from extended treatment duration.^[5] On the basis of pharmacokinetic study of oseltamivir in patients requiring continuous venovenous hemodiafiltration (CVVHDF) for acute kidney injury and ECMO, it was found that oseltamivir dosages should be considered to decrease with monitoring of drug plasma level in patient who are on CVVHDF; while ECMO, *per se*, have not shown any impact on the pharmacokinetic of oseltamivir.^[6]

In a retrospective study from dataset of Korean Society of Critical care Medicine H1N1 Collaborator, treatment outcome of the triple-combination antiviral drugs with different mechanism of action (amantadine, ribavirin, and oseltamivir) was found comparable to that of oseltamivir monotherapy.^[7] While reviewing data set from the European Society of Intensive Care Medicine H1N1 registry, it was found that early use

of corticosteroid was not significantly associated with mortality when analyzed after adjusting for severity and potential confounding factors; but was associated significantly with increased likelihood of developing hospital-acquired pneumonia.^[8]

On the basis of positive experimental studies, recently, a randomized controlled trial has evaluated the effect of hyperimmune intravenous immunoglobulin (H-IVIG, fractionated from convalescent plasma from patients recovered from H1N1 2009 infection) and result showed that the use of H-IVIG in critically ill H1N1 patients within 5 days of symptoms onset was associated with reduced mortality.^[9]

As per Extracorporeal Life Support Organization, centers in Australia and New Zealand had highest experience in utilization of ECMO for severe ARDS due to H1N1 infection.^[10] Indications for ECMO uses are progressive lung failure (PaO₂ <80 on FiO₂ 1.0) and/or shock (hypotension on two vasoactive drugs) despite optimal treatment. Review of ESLO H1N1 registry data revealed that outcome is better if ECMO is instituted early after intubation (72% survival when ECMO started within 6 days of intubation versus 31% when patient have been intubated for 7 days or longer).^[10]

H1N1 infection may have bacterial pneumonia as co-infection at presentation, it is essential to diagnose and treat bacterial infection also, for better outcome. In a meta-analysis (of 6 studies) by Pfister *et al.*, increase in serum procalcitonin level was found a reasonably accurate marker for detection of bacterial pneumonia (i.e., co-infection with H1N1), but they also concluded that normal/low level of procalcitonin should not be considered as a stand-alone marker to rule out of co-infection of bacterial pneumonia in patients with confirmed H1N1.^[11]

In a study by Linderman *et al.*, it was found that H1N1 virus acquired several mutations in recent years, but does not change antigenic properties of the virus, which explains for high susceptibility of H1N1 viruses to middle-aged adults during the 2013–2014 influenza season.^[12] These findings also suggest that currently available vaccine strains (without mutation) might be less effective. Because of changes in circulating strains, WHO expert committee has recommended changes for 2 of 3 strains in the trivalent vaccines of influenza vaccines for the Northern hemisphere during 2015–2016.^[13]

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